UNCERTAINTY, ANXIETY, AND FEAR OF CANCER RECURRENCE

EDITED BY: Phyllis Noemi Butow, Gerald Humphris, Sophie Lebel and Joanne Shaw

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UNCERTAINTY, ANXIETY, AND FEAR OF CANCER RECURRENCE

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EDITORIAL
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Editorial: Uncertainty, Anxiety, and Fear of Cancer Recurrence

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Editorial on the Research Topic

Uncertainty, Anxiety, and Fear of Cancer Recurrence

In this topic, we sought to bring together the related topics of uncertainty, anxiety, and fear of cancer recurrence or progression (FCR). As these responses are common, can be severe, impact treatment decision making, and impact quality of life (Simard et al., 2013; Shim et al., 2018), collectively they represent key concerns for psycho-oncology.

Uncertainty is a patients' inability to determine the meaning of illness-related events, and can be a result of ambiguity (conflicting, incomplete or inadequate information); complexity (information that is difficult to understand); and unpredictability (likelihood or risk of the future outcome of the disease) (Mishel, 1988). Anxiety in cancer can arise due to existential threat, uncertainty, fear of uncomfortable tests, treatments and side-effects, and loss of meaning and coherence. Meanwhile, FCR is the fear, worry or concern relating to the possibility that cancer will come back or progress, and may relate to fear of death and dying, fear of undergoing aversive treatments again, or other issues (Lebel et al., 2016). Impacts of these constructs have been described as behavioral (e.g., increased or decreased surveillance and body-checking), cognitive (e.g., intrusive thoughts of cancer), emotional (e.g., distress), and social (e.g., inability to plan holidays for fear of a recurrence) (Lebel et al., 2016).

As Editors, we were delighted by the response to this topic, and believe this collection of papers provides the most comprehensive overview of current research in this area in the literature. The universal nature of these concerns is highlighted through contributions from researchers all around the world, including Canada, US, Australia, Europe, UK, Hong Kong and China. Topics covered are wide-ranging. New researchers to the field will find this a useful body of work with which to start familiarizing themselves with the current studies and groups globally.

Overall, we have 25 accepted papers. Two papers provided a review of the conceptualization of these or related concepts, highlighting the need to thoughtfully consider what we mean when we use terms, to define them carefully and to continue efforts to clearly articulate their similarities and differences. Maheu et al. reviewed conceptualisations of FCR, health anxiety, worry and illness uncertainty. They found all concepts were triggered by internal somatic and external cues, but that each had unique aspects also. Overall, they concluded that FCR and illness uncertainty were more likely to be triggered by cancer-specific factors, while worry and health anxiety were more trait-like. Kühne et al. reviewed conceptualisations of prognostic awareness. These authors highlighted the different aspects included under this term (such as knowledge of the chances of recovery, acknowledgment of a limited lifespan, an accurate life expectancy and knowledge of therapy goals).

Five papers reported results of systematic reviews. Anderson et al. reviewed the literature on FCR in indigenous and minority groups, identifying 19 articles. They identified some differences in the severity and correlates of FCR between cultural groups, albeit most being inconsistent. Importantly,

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their findings highlighted the need to consider cultural factors when assessing and treating FCR. O'Rourke et al. examined the small literature on factors associated with FCR in caregivers, noting relationships between age, treatment modality and illness perceptions and caregiver FCR. Stewart et al. reviewed the impact of cancer type on patients' experience of a cancer recurrence; however relevant papers addressed only breast and prostate cancer, limiting conclusions. Notably Naser et al. in a Middle Eastern sample found higher rates of depression in bladder cancer patients and anxiety in lung cancer patients. Pang and Humphris completed a review and meta-analysis of data examining the association between FCR and gender, firmly concluding that females have higher FCR than males. However, these authors noted only moderate effect sizes, suggesting that other factors are more key in determining FCR levels.

Finally, Williams et al. conducted a timely review of the cost of delivering FCR interventions. This is a critical and only newly emerging field of enquiry, which is essential if health care systems and decision makers are to be convinced of the value of funding FCR intervention programs. The review concluded that FCR is associated with greater use of healthcare resources, and can be treated cost-effectively, although additional measures and approaches are needed in future studies.

Four articles explored FCR and existential distress in novel contexts. Soriano et al. explored the impact of treatment delays caused by the COVID-19 pandemic on FCR. Women with ductal carcinoma *in situ*, lobular carcinoma *in situ*, or invasive breast cancer, whose cancer surgery was postponed due to the pandemic, completed questionnaires while they awaited their surgery or shortly after they received their delayed surgery. Reassuringly these women reported low psychosocial impacts, although as the authors noted, FCR often emerges during follow-up, thus longitudinal studies will be required to really assess the impact of COVID-19 on psychosocial cancer outcomes.

Rogers et al. focused on FCR in head and neck patients, noting that young women are particularly vulnerable to FCR and may require specialist attention. Custers et al. explored FCR longitudinally in women treated curatively with breast cancer. While a number of longitudinal studies have now been published, they still represent a small proportion of the literature. Custers et al. study highlights the often-fluctuating nature of FCR over time, and thus the importance of assessing FCR on multiple occasions in order not to miss significant morbidity and need for help. Finally, Sobota and Ozakinci explored a topic that has previously been largely ignored: fertility concerns and fear of cancer progression (FOP) in a vulnerable population, young women. This paper highlighted how FCR and FOP may be weighed up against other priorities when people make treatment decisions impacting diverse outcomes.

Two studies sought to further the growing literature on cognitive biases in FCR using experimental paradigms (dot probe tasks). Ng et al. noted attentional bias away from threat and a negative interpretation bias in women with persistent distress after breast cancer, suggesting that attention focus training, reducing threat salience or modifying threat appraisal may help this group. Similarly, Tuman et al. reported higher threat endorsement was linked to higher overall fear and mediated the relationship between experiencing somatic symptoms and FCR. As therapy which includes attention to cognitive biases has been shown to be particularly effective for FCR (Tauber et al., 2019), further attempts to understand their role, and how best to modify them, is needed.

Four papers explored personality factors associated with FCR and distress, including attachment anxiety (Graf et al.), extroversion (Alvisi et al.), and daily and pathological worry (Dinkel et al.), while Seguin Leclair et al. noted that illness beliefs and health self-efficacy can impact FCR. While some of these factors are not readily modifiable, they may represent vulnerability factors to which clinicians can be alert.

Five papers specifically explored uncertainty in cancer patients. Han et al. reported results of a qualitative study in women with ovarian cancer, noting that patients cope with, construct and maintain uncertainty in an ongoing effort to maintain hope. Bartley et al. noted a desire to reduce uncertainty in their sample of patients undergoing whole genome sequencing; patients with greater uncertainty after testing reported higher anxiety at a 12-month follow-up. Similarly, Reyes et al. explored experience of uncertainty in people with a pathogenic or likely pathogenic variant in ATM or CHEK-2, both moderate-risk cancer genes. They found that such ambiguous data was a major source of uncertainty to participants, with the potential to impact subsequent uptake of cancer risk management recommendations. These studies suggest that uncertainty is an issue that should be explored with cancer patients over time, as patients grapple with the uncertainties and realities of their disease, including the relatively new uncertainties provided by genetic and genomic results.

van Someren et al. paper nicely complements this work, by exploring how oncologists address uncertainty in audiotaped consultations. They identified seven different approaches, including explaining the reasons for and degree of uncertainty, and down-playing uncertainty. In a similar analysis of audiotaped oncology consultations with patients who have advanced cancer, Larsen et al. explored how patients expressed existential distress. They detected tentative, controlled and often indirect expressions of uncertainty about the future, uncertainty about own coping, and search for meaning. These findings emphasize the vulnerability and fear of patients in this situation, and the need for oncologists to skillfully explore patients' concerns and provide information and support where possible to address them. While not directly focusing on uncertainty, van Beusekom et al. report the co-design of communication skills training for radiologists to address distress in cancer patients, captured by the acronym KEW (Know, Encourage, Warmth).

Stepped care is emerging as a key strategy to increase access to cost-effective support and treatment for FCR (Cancer Australia, 2013). While no paper addressed this directly, three papers evaluated interventions which could complement face-to-face intensive therapy for FCR and distress. Pradhan et al. evaluated a simple online FCR booklet for women with ovarian cancer addressing FCR. While acceptable, it proved ineffective in improving FCR. Kan et al. provided acceptability data on a phone-delivered therapy supplemented by a booklet for people with high -risk melanoma. This

proved highly acceptable and was particularly effective for those with higher FCR at baseline (who perhaps had more need). Finally Zhou et al. evaluated group-delivered reminiscence therapy for cancer patients, demonstrating impact on anxiety and depression.

As this field develops, it is increasingly clear that suitable interventions are needed for different levels of FCR to ensure timely and universal access and sustainability. Further, we need to maintain a high standard of rigor in our intervention research, with attention to process as well as outcomes. To this end, Brandt et al. in this topic report on a useful fidelity tool with which to measure the extent that a manualised intervention is delivered according to instructions. Without such assessment, it is not possible to determine whether interventions are effective (or ineffective) due to the therapy content or because novel elements are introduced, or planned ones omitted.

Finally, Shaw et al. reported findings from an international Delphi study examining priorities for research in FCR moving forward. Intervention research, strategies to increase patient access to FCR treatment, evaluation in real world settings and continuing to define mechanisms of action and active components of interventions, were highlighted. These priorities nicely reflect the body of work included in this topic and suggest that the research community is working collaboratively and coherently on these issues.

A further issue cannot escape comment. Without warning, from the beginning of 2020, the world of health care has been transformed in outlook, in its delivery and response from staff and services. The impact of the COVID-19 pandemic has been an undeniable feature that threatens further to increase uncertainty, raise anxiety and possibly fears of cancer recurrence or progression. New knowledge about transmission and new variants of the virus, the likely chronic effects of long COVID and the known benefit of immunization introduces new elements of complexity. For example, long COVID has an array of presentations that may add to confusion for patients and clinical teams in identifying possible new tumors, and increase the variability of experiences of uncertainty and fears. The call for papers for this special issue did result, as mentioned previously, in a single manuscript that reported the consequence of delay due to COVID-19 on fear of recurrence. Researchers are unable to ignore the relative effects of the pandemic and will need to encompass the new working conditions for staff and patient experience in their studies to prepare bids for future resources and research activity.

In conclusion, there is much to investigate regarding anxiety, uncertainty and fear of recurrence in the context of cancer and more broadly in other diseases. We need more fruitful research to guide our understanding of the development and outcomes of these responses, how they interact, and how best to help people manage and minimize their impact on quality of life and well-being. These constructs need examination in older adult, adolescent and young adult and pediatric settings; most research to date has been in adult populations. This will require more researchers attracting funding and interest in this topic. As an international community, we need to work together to achieve these goals.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Unmet Supportive Care Needs Among Women With Breast and Gynecological Cancer: Relevance of Attachment Anxiety and Psychological Distress

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Objective: Attachment anxiety and avoidance are known risk factors for the development of unmet needs and poor well-being among patients with chronic diseases. Few studies have addressed this in individuals with cancer. We aimed to explore the relationship between supportive care needs, attachment styles and distress in women with breast and gynecological cancer.

Methods: Using a cross-sectional paper-pencil (n = 157) and online survey (n = 614), a total of 771 patients with breast or gynecological cancer completed a set of validated questionnaires. From September 2013 to January 2014, consecutive inpatients and outpatients of the university hospital Tuebingen were included in the study. Further, participants were recruited through social media, patient internet platforms, self-help group leaders and patient networks. We used the Supportive Care Needs Survey (SCNS-SF-34) with the need dimensions: health system, patient care, psychological, physical, and sexual needs, as well as the Experiences in Close Relationships-Revised Questionnaire, and the Distress Thermometer. A multiple linear regression model was used to analyze the influence of attachment styles (anxiety and avoidance) on the SCNS-SF-34 dimensions. A moderation analysis was used to explore the influence of the interaction between attachment anxiety and distress for all SCNS-SF-34 dimensions.

Results: Attachment anxiety was a significant determinant and led to higher unmet supportive care needs in all dimensions, whereas attachment avoidance was not significant. Distress did moderate the relationship between attachment anxiety and

psychological and health system needs and led to a higher unmet needs development. For the other SCNS-SF-34 dimensions, distress was not confirmed as a moderator.

Conclusion: Our findings highlight attachment anxiety as a risk factor for the development of unmet supportive care needs and potentially impaired psychological adjustment to cancer. Further studies are needed to elucidate the interactions between attachment styles, distress and supportive care needs among cancer patients.

Keywords: attachment styles, attachment anxiety, distress, psychooncology, supportive care needs, unmet needs

INTRODUCTION

The diagnosis of breast or gynecological cancer, along with the long-term invasive treatments like chemotherapy, radiotherapy, and/or surgery can lead to various psychological morbidities. The affected person can feel sad, threatened, and uncertain (Dunn and Steginga, 2000; Ahmad et al., 2015) leading to the development of high cancer-related distress (Zabora et al., 2001) and/or clinically relevant symptoms (e.g., adjustment disorder, anxiety, and depression) (Mehnert et al., 2014; Mielcarek et al., 2016). In relation to their high disease-related distress, patients – especially women with breast and gynecological cancer – can experience unmet supportive care needs during their illness (Schmid-Büchi et al., 2008; Roland et al., 2013). Unmet supportive care needs are defined as a lack of service or support that an individual perceives as necessary to reach the best possible well-being (Fitch, 2000). Younger patients, women, patients with a hereditary cancer risk or with high anxious or depressive symptoms, and patients living alone express more unmet supportive care needs and are at higher risk of poor adjustment to a cancer diagnosis and have reduced ability to cope with the demands of the disease (Ahmad et al., 2015; Faller et al., 2015; Jeppesen et al., 2015; Brédart et al., 2016; Ringwald et al., 2016). However, little is known about general trait factors associated with high levels of perceived unmet supportive care needs and poor well-being, and there is a lack of evidence regarding personality factors associated with the development of unmet supportive care needs (Faller et al., 2016).

In recent years, researchers and clinicians have begun to focus more on attachment theory as a framework for understanding adjustment to illness and disease (Nicholls et al., 2014; Nissen, 2016). Attachment theory describes the development and dynamics of relatively stable social-cognitive schemes ("internal working models"), which organize the processing of attachment-related information, influence self- and interpersonal stress regulation and guide-related behavior over the lifespan. The attachment system is activated in times of need or distress and aims at restoring a subjective sense of security (Bowlby, 1969; Mikulincer and Shaver, 2007; Ainsworth et al., 2014). Attachment in adulthood can be described by central patterns of perception, motivation, regulation, and behavior, often called "attachment styles" (Mikulincer et al., 2003; Ainsworth et al., 2014).

Individuals with a prototypically secure attachment style are confident that others will be there for them in times of need and therefore feel comfortable in seeking and receiving the help of others, but are also able to self-regulate due to the activation of self-soothing memories of the generally positive caregiving history (Mikulincer et al., 2003).

Attachment insecurity (i.e., concerning the question if others are there in times of distress) is often described in terms of attachment anxiety or attachment avoidance (Ainsworth et al., 2014). Attachment anxiety describes the attempt to adapt to this insecurity by the hyperactivation of attachment-related emotions, cognitions, and behavior, while habitually neglecting self-regulatory strategies. In particular, there is an increased fear of rejection or abandonment and heightened levels of distress when potential caregivers are unavailable or unresponsive, accompanied by increased care-seeking and interpersonal dependency (Mikulincer et al., 2003; Ainsworth et al., 2014). Attachment avoidance describes the attempt to respond to the general insecurity by downregulating attachment-related emotions, cognitions and behavior, while neglecting others' regulatory competence. Attachment avoidance often leads to a devaluation of close relationships, increased interpersonal distance, excessive focus on self-reliance and reluctance to self-disclose (Mikulincer et al., 2003; Ainsworth et al., 2014). It is important to keep in mind that insecure attachment styles are normal variants of different developmental trajectories (Mikulincer and Shaver, 2007). However, insecure attachment regulatory styles can be considered as risk factors for maladaptive behaviors when habitual attachment-related mechanisms no longer match the regulatory task, especially in the face of stress and strain. In other words, the adaptiveness of both high attachment anxiety and avoidance may break down under certain conditions (Gillath et al., 2009), influencing the perception and interpersonal modulation of stress, the psychobiological stress response, self-regulation, and health behavior, ultimately affecting health-related outcomes (Maunder et al., 2015).

The mechanism of attachment theory, often neglected in medical research, is crucial for understanding its potential impact on health behavior and disease development. Bowlby suggested that physical illness is likely to activate the attachment behavioral system due to experienced distress, unmet needs and perceived vulnerability (Bowlby, 1969). Studies in the context of chronic diseases such as cancer have demonstrated that attachment styles can predict psychological adjustment and well-being (Schmidt et al., 2002; Turner-Cobb et al., 2002; Hamama-Raz and Solomon, 2006; Porter et al., 2012; Vehling et al., 2019). It has been shown that attachment anxiety leads to higher psychological distress and increased levels of endocrine stress responses (Ehrenthal et al., 2011; Arambasic et al., 2019). Individuals with higher levels of attachment avoidance usually report lower levels of

psychological burden than individuals with higher scores of attachment anxiety (Dozier and Lee, 1995). In patients with cancer, insecurely attached individuals use less active and less positive coping strategies to manage their diagnosis of cancer and survivorship issues, such as physical and emotional consequences of the cancer treatment (Schmidt et al., 2012; Arambasic et al., 2019; Romeo et al., 2019). Moreover, related studies have shown that attachment anxiety is associated with depression (Hunter et al., 2006; Porter et al., 2012; Nissen, 2016; Scheffold et al., 2017), higher symptoms of anxiety and reduced social well-being and quality of life among cancer patients (Porter et al., 2012; Smith et al., 2018; Arambasic et al., 2019; Romeo et al., 2019). This is of special relevance as the effect of attachment anxiety on health-related outcomes (e.g., medical symptoms, overall health and bodily pain) may be moderated by the perception of social support (Stanton and Campbell, 2014; McWilliams, 2017). Insecure attachment, at the same time, is associated with lower levels of social support (Hunter et al., 2006; Nissen, 2016). Attachment security and the perceived security about the availability of others can protect from demoralization. Further, low attachment security may limit adaptive capacity to deal with illness burden and discourage morale and purpose in life with advanced cancer (Vehling et al., 2019).

However, it remains unclear how attachment insecurity and distress determine the perception of unmet supportive care needs. In previous research it was shown that distress also leads to an increased development of unmet supportive care needs in patients with cancer (Faller et al., 2017). However, it is not clear if perceived distress moderates the relationship between attachment styles and supportive care needs (that is, attachment insecurity only impacts unfulfilled supportive care needs if distress is also present) or attachment insecurity directly impacts both distress and unmet supportive care needs (van Scheppingen et al., 2011). Systematic reviews urgently call for further research focusing on attachment styles to better understand apparent inconsistencies in research into the interactions between supportive care needs and the well-being of cancer patients (Nicholls et al., 2014; Nissen, 2016).

Given the evidence gap on the pressing issues described above, the current study focuses on two key goals: (1) to define the relationship between insecure attachment styles (anxiety and avoidance) and perceived supportive care needs, and (2) to investigate the moderation effect of perceived distress on the relationship between attachment styles (anxiety and avoidance) and supportive care needs in women with breast and gynecological cancer (**Figure 1**).

MATERIALS AND METHODS

Study Design and Recruitment

In a cross-sectional approach 1172 women with either breast or gynecological cancer or both *agreed to participate in the study*. Eligibility criteria were defined as being an adult (age ≥18 years) and having sufficient German language skills to complete a set of questionnaires. The survey data were collected *via* self-report paper-pencil or self-report online questionnaires and took approximately 20 min to complete. From September 2013 to January 2014, consecutive inpatients and outpatients were approached regarding participation (paper-pencil-questionnaire at Department of Gynecology at the University Hospital Tuebingen). The research assistants asked inpatients and outpatients; after a time of consideration the patients could decide to fill in the paper-pencil or online version of the questionnaires. Patients could choose to send the paper-pencil questionnaires back with the attached envelope or hand it back immediately to the research assistants. Furthermore, breast and gynecological cancer patients were recruited *via* an electronic online survey version (Questback) of the questionnaire through social media, special patient internet platforms, self-help group leaders, patient networks (e.g., Breast Cancer Aid Germany; BRCA Network) and further cancer counseling centers. The survey was anonymous and the beginning of the questionnaire was the consent page. An incentive was not given. Of the 1172 participants (n = 243 paper-pencil and n = 929 online) assessed, 41 patients assessed online did not meet the eligibility criteria because of another cancer diagnosis. Those with incomplete data (n = 360) were excluded, resulting in a final dataset of 771 participants, of which 614 were completed online and 157 as paper-pencil questionnaires.

Procedures

The local ethics committee of the University Hospital Tuebingen approved the study protocol.

Measures

Demographic and Disease-Related Information

Demographic variables included age, gender, marital status, number, and age of children. Self-reported data on the type of cancer, time since primary diagnosis, and disease status (primary disease, metastasis, and recurrence) was also collected.

Supportive Care Needs Survey

The Supportive Care Needs Survey is a 34-item short-form version (SCNS-SF-34). We used the German version of SCNS-SF-34, which has good psychometric properties (Lehmann et al., 2012). This self-report questionnaire assesses patients' perceived type and extent of need for support in five dimensions: (1) *health system/information needs*; (2) *patient care and support needs,* (3) *psychological needs*; (4) *physical and daily living needs*, and (5) *sexual needs*. Example items are "*In the last month what was your level of need with learning to feel in control of your situation?*" or "*In the last month what was your level of need with feeling down or depressed?*". The patient ranks their needs on a five-point Likert scale, ranging from 1 to 5 (1 = no need; 2 = no need; satisfied; 3 = low need; 4 = moderate need; and 5 = high need). Summated scores for the five dimensions were first calculated and converted to scores ranging from 0 to 100 for each domain. Standardized scores were then calculated, in which higher scores indicate unmet supportive care needs within that domain.

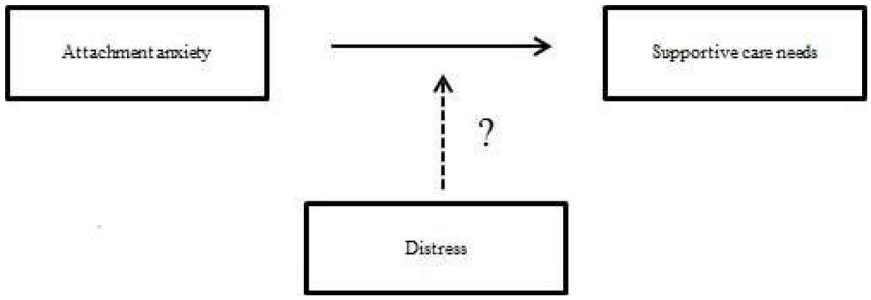

FIGURE 1 | The possible moderation of distress on the development of supportive care needs.

Experiences in Close Relationships–Revised Questionnaire

Attachment styles were measured using a brief German version of the Experiences in Close Relationships-Revised Questionnaire (ECR-RD) (Fraley et al., 2000; Ehrenthal et al., 2009). The ECR-RD assesses experiences and expectations regarding romantic relationships on two scales of attachment-related anxiety ("I often worry that my partner does not *really* love me") and avoidance ("I feel uncomfortable opening up to my partner") on a seven-point Likert-scale, ranging from 1 ("strongly disagree ") to 7 ("strongly agree"). The brief version (ECR-RD8) was developed as a screening instrument suitable for large samples in health psychology and psychosomatic medicine. Using data from several published studies on the original 36-item version, a total of eight items were extracted by means of exploratory and confirmatory factor analysis. Four items belong to the dimension "attachment-related anxiety" and the remaining four items belong to the "attachment-related avoidance" dimension. The questionnaire was furthermore evaluated in a representative sample of the German population. Its internal consistency values are good, the model fit of the confirmatory factor analysis good to acceptable, and validity was established by comparing it to measures of psychological health as well as another attachment measure (Ehrenthal et al., in preparation). The long version of the ECR-RD8 RD has been, and the short version is currently used in a wide range of studies (Ohlsson, 2013; Manes et al., 2016; Ehrenthal et al., in preparation).

Distress Thermometer

The 11-level visual analog scale of the "Distress Thermometer" (DT) is widely used to measure distress and has been validated in diverse oncology settings (Mehnert et al., 2006). Patients were instructed to "choose a number indicating how much distress they have been feeling over the past week, including today. Zero means no distress and 10 means the worst distress imaginable." A cut-off score $\geq$5 is recommended as indicative of a high distress level (Mehnert et al., 2006).

Data Analysis

Descriptive statistics, correlations, and regression analyses were performed using SPSS 21 for Windows. First, multiple linear regression models were used to explore the possible influence of attachment styles (anxiety, avoidance) on the five need dimensions of the SNCS-SF-34. The correlation matrices are shown in **Tables 1**, **2**. Due to the explorative character of our research we did not adjust the alpha-level. In a second step, a moderator analysis was conducted using the logistic path analytic model (model 1) using the SPSS PROCESS macro (Version 3.5). This moderator analysis was used to estimate the interaction between distress and attachment anxiety and their influence on the five need dimensions of the SCNS-SF-34. Lower level confidence intervals (LLCI) and upper level confidence intervals (ULCI) were calculated (Hayes, 2013). Within our models, the five need dimensions of the SCNS-SF-34 were the dependent variables, and attachment style (anxiety, avoidance), distress, and the interaction term (attachment anxiety $\times$ distress) were the independent variables (O'brien, 2007). Multicollinearity between determinants (attachment anxiety and distress) and the interaction term (attachment anxiety $\times$ distress) was prevented by using the centered scores of the component variables. Demographic variables were described using percentages and means as appropriate. Missing data were analyzed and mean missing values estimated as 8.9% for the SCNS-SF-34 questionnaire and 2.1% for the ECR-RD8 questionnaire. Missing values were imputed only if at least 80% of each questionnaire had been completed. Using the Little's MCAR test, it was confirmed that the data were missing randomly. Therefore, missing data were imputed with the expectation-maximization (EM) algorithm (Musil et al., 2002). For all statistical tests, the level of significance was set to alpha at 0.05.

RESULTS

Our final sample consisted of 771 women. The mean patient age was 50.6 $\pm$ 10.5 years (range: 25–83 years). Seventy-six percent of the sample was diagnosed with cancer for the first time and 8.3% of participants were affected by metastases. A recurrence of a previous cancer affected 9.2% of the sample. 6.1 % of patients suffered from metastases and recurrence. The frequencies of other disease-related or demographic variables are provided in **Table 3**. The mean values and standard deviations of the SCNS-SF-34, ECR-RD8, and DT are presented in **Table 4**. In the sample, significant differences in demographic variables and distress exist between the paper-pencil and online groups. The Cohen's effect

TABLE 1 | Mean, standard deviations, and correlation with attachment anxiety.

Variable	M	SD	1	2	3	4	5
1. Attachment anxiety	13.85	8.55					
2. Health system/information needs	20.51	14.10	0.288*				
3. Patient care and support needs	7.09	6.37	0.285*	0.847*			
4. Psychological needs	20.52	11.85	0.333*	0.668*	0.653*		
5. Physical and daily living needs	8.04	5.38	0.225*	0.561*	0.603*	0.674*	
6. Sexual needs	5.49	3.87	0.386*	0.751*	0.686*	0.701*	0.591*

*M and SD are used to represent mean and standard deviation, respectively. *indicates $p < 0.01$*

TABLE 2 | Mean, standard deviations, and correlation with attachment avoidance.

Variable	M	SD	1	2	3	4	5
1. Attachment avoidance	22.66	7.90					
2. Health system/information needs	20.51	14.10	0.046				
3. Patient care and support needs	7.09	6.37	−0.014	0.847*			
4. Psychological needs	20.52	11.85	0.000	0.668*	0.653*		
5. Physical and daily living needs	8.04	5.38	0.001	0.561*	0.603*	0.674*	
6. Sexual needs	5.49	3.87	0.021	0.701*	0.751*	0.686*	0.591*

*M and SD are used to represent mean and standard deviation, respectively. *indicates $p < 0.01$*

size for the paper-pencil versus online comparison was less than 0.3; therefore, we assume that these differences were not clinically relevant (data not shown).

Relationship Between Attachment Styles and Supportive Care Needs

In the first step of the analysis, a multiple linear regression model was used to explore the influence of the attachment styles (anxiety and avoidance) on each dimension of the SCNS-SF-34. Attachment anxiety was a significant determinant of all dimensions of the SCNS-SF-34, whereas attachment avoidance was not a significant determinant in our regression model (**Table 5**). For the *health system/information needs* dimension, attachment anxiety explained 6% (R^2 = 0.06) of the variance, and it was a significant determinant (β = 5.45, $p < 0.001$). For the *patient care and support needs* dimension, attachment anxiety explained 7% (R^2 = 0.07) of the variance, and attachment anxiety was a significant determinant (β = 1.31, $p < 0.001$). Over 10% (R^2 = 0.10) of the variance in the *psychological needs* dimension could be explained by attachment anxiety and it was a significant determinant (β = 1.50, $p < 0.001$). Attachment anxiety explained 5% (R^2 = 0.05) of the variance in the *physical and daily living needs* dimension and attachment anxiety was a significant determinant (β = 0.96, $p < 0.001$). For the *sexual needs* dimension, attachment anxiety explained 11% (R^2 = 0.11) of the variance and attachment anxiety was a significant determinant (β = 1.74, $p < 0.001$).

Interaction Between Attachment Anxiety and Distress

Based on conceptual considerations regarding the special impact of attachment anxiety under conditions of subjective distress, we assessed the influence of the interaction between attachment anxiety and distress on the dependent variables. The interaction effect was used as a moderator for all five need dimensions of the SCNS-SF-34 in this model. Taken together, distress as an additional determinant led to higher explanation of variance. Further, the interaction between attachment anxiety and distress became significant for the *health system/information needs and psychological needs* dimension. For the other dimensions the interaction was not significant. The results showed that distress moderates the effect and leads to higher unmet supportive care needs of the dimensions of *health system/information needs*, and *psychological needs*. These data are shown in **Table 6** and in **Figures 2**, **3**.

DISCUSSION

To our knowledge, this is the first study to address the possible determinants of attachment styles on the perception of supportive care needs among women with breast and gynecological cancer. In this sample of 771 cancer patients, we found that attachment styles, especially attachment anxiety, led to significantly higher perceived unmet needs in all supportive care need dimensions. In contrast, patients with attachment avoidance did not express higher unmet supportive care needs. We subsequently used a logistic path analytic model to better define the interaction between attachment anxiety and supportive care needs. Explained variance was higher when attachment anxiety, distress and their interaction were included as determinants in our model. We identified a significant interaction between attachment anxiety and distress within the *psychological needs*, *health system*, and *information needs* dimensions. On the other hand, for the dimensions *patient care, physical*, and *sexual needs* attachment anxiety led to a higher development of unmet supportive care needs independently of experienced distress.

TABLE 3 | Study population characteristics: sociodemographics and disease-related information.

***N* = 771**	**Mean (SD)**	**No. (%)**
Age (years)	50.6 (10.5) Range:25–83 years	
Length of time since first diagnosis and questionnaire completion	4.6 (5.1) Range:0–39 years	
Cancer diagnosis		
Breast		671 (87.0)
Gynecological		72 (9.3)
. . .Two cancer diagnosis		28 (3.7)
Disease status		
First		589 (76.4)
Metastasis		64 (8.3)
Reoccurrence		71 (9.2)
. . .Metastasis and Reoccurrence		47 (6.1)
Married/with a partner		
Yes		645 (83.7)
No		126 (16.3)
Children		
None		170 (22.0
Having children		598 (78.0))
1 child		176 (29.4)
2 children		263 (44.0)
3 children		103 (17.2)
4 children		22 (3.7)
5 children		4 (0.7)
6 children		3 (0.3)
Total number of children missing		28 (4.7)
Age of children	23.2 (11.0) Range:0–59 years	

TABLE 4 | Descriptive statistics for study variables.

***N* = 771**	**Possible range**	**Mean (SD)**
Attachment styles		
Anxiety	1–7	2.32 (1.49)
Avoidant	1–7	3.48 (1.92)
Psychological Adjustment		
Distress	0–10	5.55 (2.59)
Supportive Care Needs		
Health system/information needs	0–100	46.35 (33.63)
Patient care and support needs	0–100	35.27 (31.86)
Psychological Needs	0–100	51.18 (29.71)
Physical and daily living needs	0–100	40.12 (26.97)
Sexual needs	0–100	43.53 (33.10)

TABLE 5 | Multiple regression analysis of supportive care needs with anxious and avoidant attachment styles as determinants.

Variables	**B***	**SE†**	**β‡**	***p*-value**	R^2
Health system/ information needs					0.06
Intercept	32.80	2.85		<001	
Anxious	5.45	0.80	0.24	<**001**	
Avoidant	0.25	0.62	0.01	0.69	
Patient care and support needs					0.07
Intercept	19.16	2.69		<001	
Anxious	1.31	0.19	0.24	<**001**	
Avoidant	0.29	0.15	0.07	0.05	
Psychological needs					0.10
Intercept	34.15	2.47		<001	
Anxious	1.50	0.17	0.30	<**001**	
Avoidant	0.22	0.13	0.06	0.09	
Physical and daily living needs					0.05
Intercept	29.19	2.30		<001	
Anxious	0.96	0.16	0.21	<**001**	
Avoidant	0.15	0.13	0.04	0.24	
Sexual needs					0.11
Intercept	23.45	2.73		<001	
Anxious	1.74	0.19	0.31	<**001**	
Avoidant	0.28	0.15	0.07	0.06	

$p < 0.05$. Bold values are significant.

Our findings are in line with the attachment theory, as anxiously attached individuals have a strong motive to turn to others in times of need. Anxiously attached individuals are at the same time likely to feel uncomfortable receiving support from others and can neither focus on nor express their needs during times of distress. In particular, they are experiencing increased fear of rejection or abandonment and are thus unable to ask and seek support (Bowlby, 1969). Interestingly, in our study, the assessed supportive care needs of the patients with attachment anxiety could, for the most part, be satisfied by medical care teams, psychosocial assistants or family members. It seems likely that patients with an anxious attachment style are not able to ask or seek for support. Due to this behavior their supportive care needs remain unsatisfied. These findings resonate with the theoretical model of Maunder and Hunter, which states that less effective help-seeking behavior is problematic for insecurely attached persons (high attachment anxiety and/or avoidance) (Maunder and Hunter, 2001; Graetz et al., 2013). Moreover, securely attached individuals (less attachment anxiety and/or avoidance) may be more likely to use active and positive coping strategies to overcome their cancer-related burdens, which are predictive for a positive psychological outcome in cancer patients. It seems that active coping mechanisms, such as planning, positive reframing, acceptance techniques and social support are positive strategies that may have the potential to support post-traumatic growth in cancer patients and reduce unmet needs (Schmidt et al., 2002, 2012; Romeo et al., 2017, 2019).

According to our findings, we assumed that patients with attachment anxiety suffer from higher unmet supportive care needs due to maladaptive coping strategies. Similarly, it has been shown that patients with a hepatitis C (Ciechanowski et al., 2002), cardiovascular diseases (McWilliams and Bailey, 2010) or chronic pain (McWilliams et al., 2000; McWilliams, 2017) and attachment anxiety tend to report physical symptoms that are not explained by their underlying illness. Furthermore, Ciechanowski et al. (2003) and Schroeter et al. (2015) found that

TABLE 6 | Moderation analysis with the interaction of attachment anxiety and distress.

Variables	Coefficient	SE†	LLCI	ULCI	*p*-value	R^2
Health system/ information needs						0.14
Constant	46.90	1.17	44.60	49.19	<0.001	
Attachment anxiety	4.59	0.79	3.04	6.12	**<0.001**	
Distress	3.60	0.45	2.72	4.49	**<0.001**	
Interaction term	−0.68	0.31	−1.29	−0.08	**0.02**	
Patient care and support needs						0.14
Constant	35.70	1.12	33.49	37.90	<0.001	
Attachment anxiety	4.60	0.79	3.04	6.16	**<0.001**	
Distress	3.19	0.43	2.35	4.04	**<0.001**	
Interaction term	−0.53	0.31	−1.15	0.09	0.09	
Psychological needs						0.27
Constant	51.70	0.96	49.82	53.57	<0.001	
Attachment anxiety	4.85	0.64	3.59	6.10	**<0.001**	
Distress	4.65	0.38	3.91	5.39	**<0.001**	
Interaction term	−0.63	0.25	−1.13	−0.13	**0.01**	
Physical and daily living needs						0.21
Constant	40.09	0.89	38.34	41.83	<0.001	
Attachment anxiety	2.36	0.60	1.18	3.53	**<0.001**	
Distress	4.34	0.35	3.64	5.03	**<0.001**	
Interaction term	0.04	0.24	−0.44	0.52	0.87	
Sexual needs						0.18
Constant	43.60	1.15	41.33	45.85	<0.001	
Attachment anxiety	5.99	0.83	4.37	7.61	**<0.001**	
Distress	3.46	0.43	2.61	4.30	**<0.001**	
Interaction term	−0.09	0.31	−0.70	0.53	0.78	

$p < 0.05$. For a correct estimation of the influence of the single factors attachment anxiety and distress were centred. LLCI, Lower Level Confidence Interval; ULCI, Upper Level Confidence Interval. Bold values are significant.

ratings of insecure adult attachment are positively associated with depressive symptoms in patients with chronic pain.

In further studies it was shown that attachment anxiety interacts with higher physical and depression symptoms (Taylor et al., 2000; Kim et al., 2008; Smith et al., 2018). This could also be a possible explanation why patients with attachment anxiety may develop more unmet supportive care needs. Taylor et al. (2000) showed that patients with unexplained physical symptoms are more likely to have an insecure attachment style and psychiatric stress. This can be in line with our findings since distressed patients with attachment anxiety may suffer from higher unexplained somatic symptoms. In consequence, this may also lead to higher psychological burden and higher unmet supportive care needs.

In contrast, individuals with higher attachment avoidance develop a need for independence and self-sufficiency. This behavior might be a consequence of experiences of unresponsive parenting during childhood. Therefore, patients with attachment avoidance are uncomfortable getting close to others in times of need (Bowlby, 1969; Brandão et al., 2018). As a result, one can assume that support from others is not useful to overcome burden, even in cases of hazardous diseases such as cancer (Mikulincer et al., 2003). Attachment avoidance is also associated with a tendency to downplay threat and disease-related burden (Hunter et al., 2006). It seems likely that such attachment behavior led to disregardment of elevated unmet supportive care needs in our study.

Hamama-Raz and Solomon found that melanoma survivors with attachment anxiety experience increased distress compared to melanoma survivors with attachment avoidance (Hamama-Raz and Solomon, 2006). These findings are inconsistent with our data. Within our sample, we found that avoidantly attached patients did not differ in their distress score compared to patients with attachment anxiety. Moreover, the interaction effects of attachment anxiety and distress were not identified as significant determinants of all assessed supportive care needs suggesting that distress is not the only reason for unmet supportive care needs of patients with an insecure attachment style. This may be seen as consistent with the attachment theory, which postulates that attachment styles are internal models which are stable overtime, independent of external factors (Bowlby, 1969; Ainsworth et al., 2014). Therefore, it can be assumed that the effect of attachment anxiety on the development of supportive care needs is not significantly influenced by experienced distress. However, in our study, distress and attachment anxiety did interact with *psychological needs* and *health care needs*. A possible explanation of the interaction among *psychological needs* and *health care needs* is that the items of these two dimensions in the SCNS-SF-34 measured a similar experienced burden such as the DT. It seems that the items of both questionnaires are not selective enough. Both questionnaires measure burden in general and do not measure specific psychosocial aspects of experienced burden (Mehnert et al., 2006; Lehmann et al., 2012). For this reason, the interaction of attachment anxiety and distress led to higher unmet *psychological needs* in our study. Lehmann et al. (2012), in a validation study of the SCNS-SF-34, reported similar findings with the DT and the *psychological needs* dimension.

Taken together, we propose that insecure attachment styles, especially attachment anxiety, make it more likely that a patient will perceive a lack of support to address specific supportive care needs compared to patients with attachment security.

Additionally, attachment styles may constitute a risk factor resulting in poor well-being, independently of perceived distress among cancer patients.

Our exploratory study was based on a large sample of patients with breast cancer, gynecological cancer, or both. However, there are limitations in the sample selection and generalizability of this

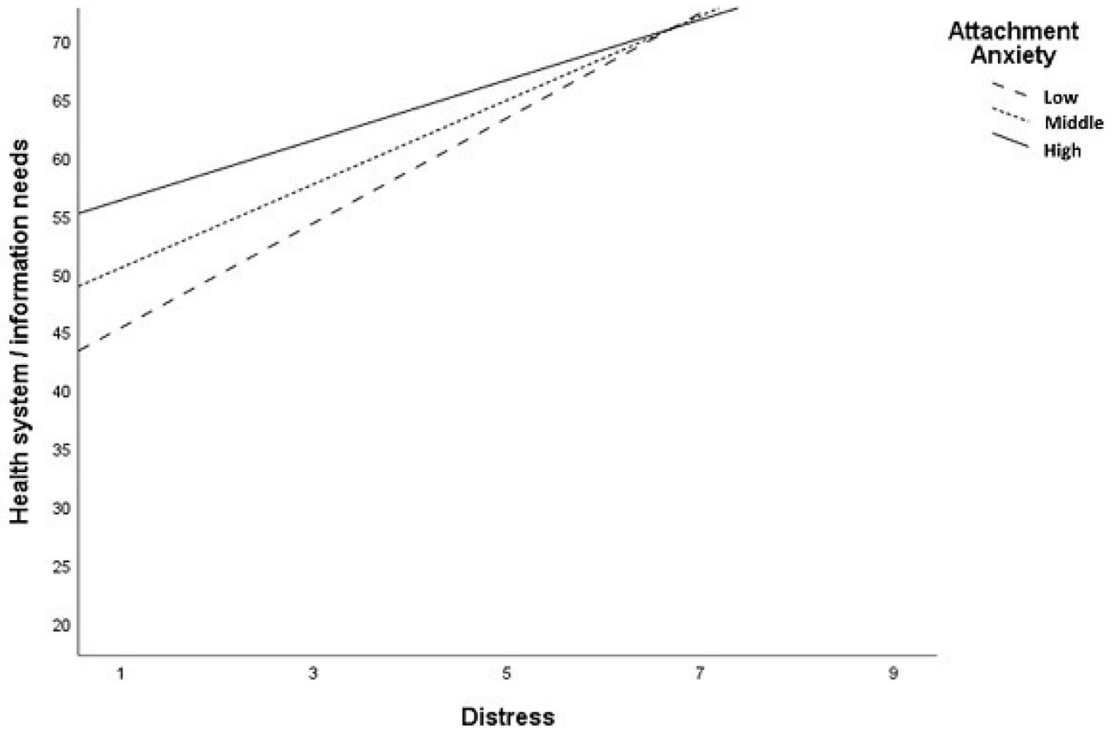

FIGURE 2 | Significant interaction between attachment anxiety and distress amoung *Health system/information needs* domain.

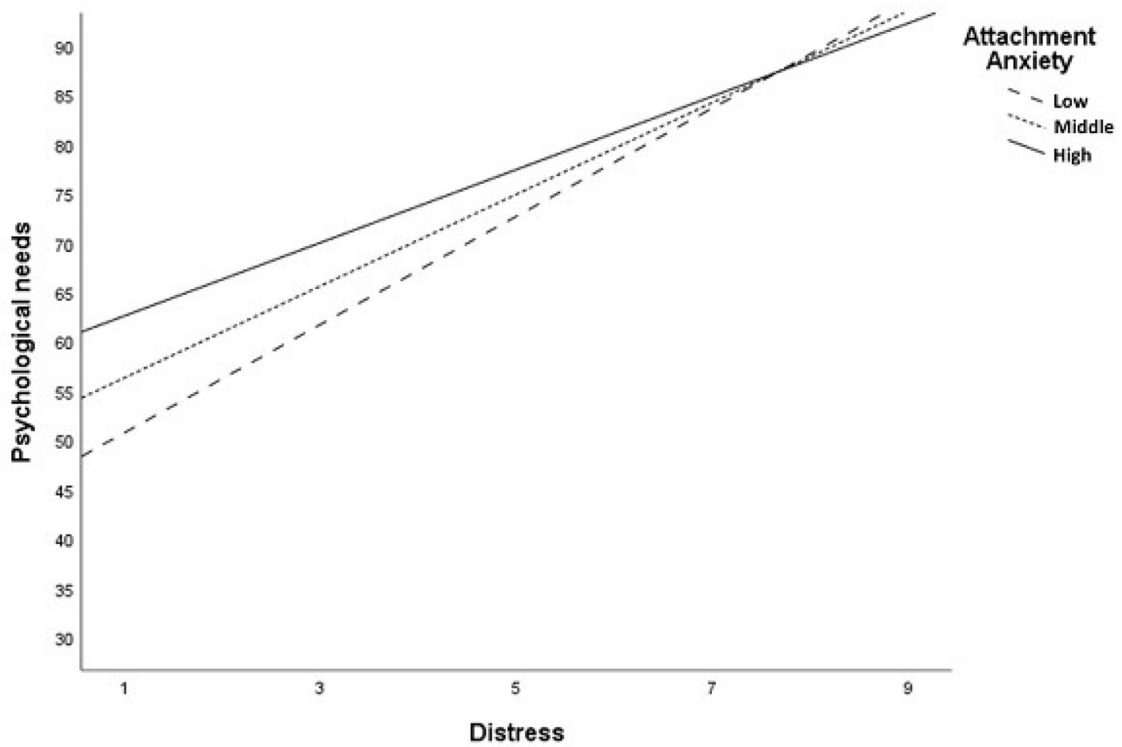

FIGURE 3 | Significant interaction between attachment anxiety and distress among *Psychological needs* domain.

study. The lack of diversity in this sample is demonstrated by the participants being predominantly younger and highly distressed. In our sample, the mean distress score was 5.55, which is higher than reported in other studies reflecting a highly burdened cohort (Dabrowski et al., 2007; Ng et al., 2017). Therefore, a recruitment bias cannot be ruled out in our study. It is important to note that mainly women with breast cancer (87.0%) participated in our survey. Although this trend has been observed in other similar studies, further studies including other tumor entities, as well as male patients, are needed. For this reason, statements concerning other tumor entities and men cannot be made at this point. Additional studies will be needed to clarify whether additional factors (e.g., depression/anxiety symptoms, relationship issues and adverse disease experiences) have a role in the development of unmet supportive care needs.

In summary, our findings showed that individuals with attachment anxiety develop higher unmet supportive care needs independent of perceived distress. Thus, this group may be at greater risk of experiencing an impaired adjustment to their cancer diagnosis. Patients with attachment avoidance may not express increased unmet supportive care needs, while still suffering from high levels of distress. Therefore, clinicians should be aware that avoidant attachment behavior can impede the identification of patients in need of psycho-oncological services (Porter et al., 2012; Maunder and Hunter, 2016). Patients with an avoidant attachment are likely to decline help and patients with an anxious attachment are, at least partly, unable to seek and ask for the required support in times of need (Turner-Cobb et al., 2002; Brandão et al., 2018). An awareness of the influence of attachment styles, especially, attachment anxiety and avoidance on the supportive care needs of patients with cancer is necessary in clinical (psychosomatic) practice. Here, we propose that an attachment style questionnaire could be added to established distress tools assessing psycho-oncological support needs since highly distressed patients often decline help in a psycho-oncological screening and therefore do not receive support (Clover et al., 2015). The use of attachment style questionnaires might help to avoid adverse psycho-social consequences, which in turn may improve the somatic course of cancer treatment (e.g., *via* adherence to medications or treatment regimens) (Shorey and Snyder, 2006; Romeo et al., 2019). By such an approach, clinicians could better understand their patients' needs and, therefore, more selectively offer the adequate psychosocial support that is most likely to satisfy the unmet supportive care needs of their patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of the University Hospital Tuebingen. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JG: conception, data acquisition, data analysis, interpretation of the results, and writing of the manuscript. FJ: conception, and contributions to the writing of the manuscript, and interpretation of the results. JE: assistance in data acquisition, conception, and contributions to the writing of the manuscript. NS, JS-K, AS, AM-T, SB, and SZ: conception, contributions to the writing of the manuscript. LM: conception, assistance in data acquisition, and contributions to the writing of the manuscript. MT: conception, data analysis, interpretation of the results, and contributions to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Not as Stable as We Think: A Descriptive Study of 12 Monthly Assessments of Fear of Cancer Recurrence Among Curatively-Treated Breast Cancer Survivors 0–5 Years After Surgery

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Purpose: Previous studies suggest one-third of breast cancer survivors (BCS) experience elevated fear of cancer recurrence (FCR) and that it remains stable. Most studies include long assessment intervals and aggregated group data. This study aimed to describe the individual trajectories of FCR when assessed monthly using both a statistical and descriptive approach.

Methods: Participants were curatively-treated BCS 0–5 years post-surgery. Questionnaire data were collected monthly for 12 months. Primary outcome was FCR [Cancer Worry Scale (CWS)]. For the descriptive approach, 218 participants were classified as low (CWS $\leq$ 13 at each assessment), high (CWS $\geq$ 14 at each assessment), or fluctuating FCR (CWS scores above and below cut-off). Latent class growth analysis (LCGA; $n = 377$) was conducted to identify trajectories over time.

Results: Around 58% of the women reported fluctuating CWS scores, 22% reported a consistently high and 21% consistently low course. Results of the LCGA confirmed the three-class approach including a stable high FCR group (13%), a low FCR group (40%), and a moderate FCR group (47%). Both the moderate and low scoring groups reported declining scores over time. Younger patients, higher educated patients, and those less satisfied with the medical treatment were more likely to belong to the moderate or high trajectory.

Conclusion: Assessed monthly, the majority of BCS report fluctuating levels of FCR. Stepped-care models should assess FCR on multiple occasions before offering tailored interventions.

Keywords: fear of cancer recurrence, individual trajectories, oncology, breast cancer survivors, Cancer Worry Scale, latent class growth analysis

INTRODUCTION

Fear of cancer recurrence (FCR) is one of the most prevalent symptoms among breast cancer survivors (BCS), with a high need for support (Armes et al., 2009; Boyes et al., 2012; Willems et al., 2016). While some degree of FCR is normal and adaptive, higher levels of FCR are associated with distress, psychological symptoms, rumination, excessive frequent bodily-checking, lower quality-of-life, and functional impairment (Simard et al., 2013). The reported prevalence of at least moderate FCR among Dutch BCS ranges between 31 and 56% (Van den Beuken-van Everdingen et al., 2008; Custers et al., 2014). Intuitively, one might expect FCR to reduce over time due to psychological adjustment and diminishing objective risk of breast cancer recurrence. However, a proportion of long-term BCS continue to experience FCR many years after their cancer diagnosis. For example in a large sample (n = 2,671) of German BCS, 17% reported moderate to high levels of fear of recurrence when surveyed an average of 8 years after diagnosis (Koch et al., 2014). While some attention has been given to studying the course and trajectories of distress (Henselmans et al., 2010; Lam et al., 2012), mental and physical functioning (Helgeson et al., 2004), and depressive symptoms (Stanton et al., 2015) among BCS, the course of FCR has received relatively little attention in the literature to date.

Synthesis of existing literature on longitudinal data of FCR in BCS is complicated by the fact that a variety of instruments have been used to assess FCR, as well as the variation in the timing and number of data collection points. Two literature reviews including studies with mixed cancer types concluded that high FCR remains stable over time (Koch et al., 2013; Simard et al., 2013). Among 22 longitudinal studies of FCR, Simard and colleagues found the majority (n = 18) reported either no change in FCR during the follow-up periods examined (3 months–6 years after end of treatment) or that there was an initial decrease of FCR with scores remaining stable thereafter. In a literature review by Koch et al. (2013) of FCR in long-term cancer survivors only two (Bowman et al., 2004; Langeveld et al., 2004) out of eight (Deimling et al., 2002; Bowman et al., 2004; Langeveld et al., 2004; Carver et al., 2006; Deimling et al., 2006a,b; Crespi et al., 2008; Skaali et al., 2009) longitudinal studies found that time since diagnosis was significantly associated with FCR, which the authors interpreted as evidence that FCR persists over an extensive period of time after the initial diagnosis without significant changes in intensity. Fifteen studies have examined the course of FCR exclusively among BCS with equivocal findings. In seven studies, FCR decreased over time (Bloom et al., 2004; Lebel et al., 2007; Armes et al., 2009; Lebel et al., 2009; Melchior et al., 2013; Halbach et al., 2016; Yang et al., 2018). Four studies (Stanton et al., 2002; Costanzo et al., 2007; Sheppard et al., 2009; Ashing et al., 2017) found that FCR remained stable over time, and two studies (Rabin et al., 2004; Dunn et al., 2015) found an initial decrease followed by stabilization. One study, which assessed FCR at multiple time points in the month prior to and after a follow-up mammography, found an increase then decrease in FCR after a good (i.e., negative) test result and increase during the month following the mammography (McGinty et al., 2016). Finally, one study reported stable levels of FCR in the first 6 months after surgery. After this period, older BCS reported decreasing levels of FCR whereas younger BCS reported an increase of FCR (Starreveld et al., 2018). It is noteworthy, however, that most longitudinal studies of FCR reported changes in FCR based on the mean of FCR scores or prevalence of high FCR (i.e., score above a cut-off on a questionnaire) aggregated at group level. Furthermore, most longitudinal studies have employed relatively large intervals between assessments.

Despite previous literature reviews concluding that high FCR remains stable over time, data on BCS are not consistent and equivocal on this issue. Furthermore, clinical experts often report that in their practice many patients with high FCR experience fluctuations in their level of FCR over time. Known triggers of FCR include internal cues such as fatigue, pain, fever, and other somatic symptoms, or external cues such as medical investigations, reminders of cancer, cancer in the media, and hearing about cancer diagnosis in a friend or relative (Lee-Jones et al., 1997; Custers et al., 2017).

To date, only three studies involving women with breast cancer have investigated trajectories of FCR using prospective data or used more than three follow-up assessments to describe the course of FCR. A study by Dunn et al. (2015) examined the trajectories of FCR of 396 women with breast cancer using monthly assessments of FCR in the first 6 months following breast cancer surgery. This study found that FCR scores declined significantly between the peri-operative period and 6 months after surgery, but that FCR scores plateau at approximately 4 months. Women with better physical health and those with higher FCR scores at baseline reported a steeper decline in FCR scores. Despite a significant decrease in mean levels of FCR over the first 6 months after diagnosis, the authors identified there was considerable variation in the individual trajectories of FCR scores with some women describing a highly fluctuating course.

One additional study has documented the course of FCR over the first 18 months after diagnosis in a cohort of cancer survivors. Savard and Ivers (2013) surveyed a mixed sample of 962 cancer survivors (48% breast cancer) scheduled to undergo surgery on FCR peri-operatively and again 2, 6, 10, 14, and 18 months later. FCR levels were found to be highest at baseline, and significantly decreased at the 2-month evaluation but remained stable throughout the remainder of the study for patients with both clinical and sub-clinical FCR. Patients with high FCR at baseline continued to display high levels at all subsequent time points, suggesting a chronic course among those with elevated FCR at baseline.

Finally, a recent study of Yang et al. (2018) examined FCR levels in a longitudinal design with breast cancer patients receiving radiotherapy (RT). Patients filled out a FCR questionnaire at their first day of treatment, and then weekly throughout the period of RT and 6–8 weeks after the end of treatment. Most women experienced a decline in fear during and after RT. However, there was considerable variation of trajectories observed. Initial level of FCR was the strongest predictor of follow-up FCR into the first 2 months of "survivorship" which, according

to the authors, tended to support the view that FCR is quite stable and already present at the start of RT.

The results of the previous studies on the course of FCR suggest that FCR scores are highest in the peri-operative period followed by an initial decrease early in the treatment trajectory. However, despite some initial decrease, it appears that individuals with elevated FCR at baseline are likely to continue to have elevated FCR over the first 18 months post diagnosis. While together these studies provide valuable insight into the course of FCR, neither they do not identify the proportion of patients with a fluctuating course of FCR nor examine the course of FCR beyond the first 18 months after surgery.

The objective of this study was to describe the course of FCR in women with breast cancer 0–5 years post diagnosis. Specific aims were to assess:

1. Whether significant differences in mean level of FCR occur when FCR is assessed monthly for 12 months (course of FCR).
2. Whether distinct classes of individual trajectories of FCR can be identified using a statistical approach.
3. The proportion of women with a low and stable FCR (henceforth called "low FCR"), high and stable FCR (henceforth "high stable FCR"), and with levels of FCR which fluctuate above and below a validated cut-off (henceforth "fluctuating FCR") using a more descriptive approach.

It was hypothesized that:

a. Mean FCR scores would fluctuate over time when assessed at monthly intervals for 12 months.
b. A higher proportion of women <3 years after surgery would have a fluctuating FCR or high FCR compared with those 3–5 years post-surgery.
c. The degree of FCR fluctuation in FCR scores would be inversely associated with time since surgery. More specifically, a moderate to large negative correlation ($r = > 0.3$) between the absolute change in FCR score and time since surgery was predicted.

Since relatively little is known about how known triggers of FCR interact with the course of FCR, this study also sought to identify the self-reported triggers of FCR experienced by women with low FCR, high stable FCR, and those with fluctuating FCR.

MATERIALS AND METHODS

Participants and Procedure

Institutional human ethics committee approval was obtained prior to commencement of the study (CMO Regio Arnhem-Nijmegen, 2012/227). Potential participants were identified by searching the institutional databases of one academic and two regional hospitals in the Netherlands for women who met the eligibility criteria for this study. Eligible participants were: 0–5 years after surgery for breast cancer; treated with curative intent and disease-free at the time of participation; and able to provide informed consent and read and write in Dutch. Eligible participants received a mailed invitation letter from their treating oncologist or surgeon explicitly stating that women both with and without elevated FCR could participate. Consenting participants received a monthly questionnaire for 12 months including demographic, medical, and psychosocial variables. Baseline questionnaires were completed in paper and pencil format, and subsequent questionnaires could either be filled in online or in paper-and-pencil form according to participants' preference. Of the 1,205 eligible women who were invited to the study, 565 (47%) were interested in receiving more information about the study and 460 (38%) consented. Study participants were compared to 539 non-responders (data of one regional hospital were not available) demonstrating that participants were significantly [$t(993{,}635) = 5.77$, $p < 0.001$] younger ($M = 56.69$, $SD = 9.6$) than non-responders ($M = 60.64$; $SD = 11.9$).

Sample Sizes

To be included in the statistical approach of class distinction (LCGA) which can handle missing data correctly, at least seven completed assessments and no more than two consecutive missing assessments were required. Therewith, longitudinal data of 377 patients were analyzed.

For the descriptive analysis in which it was not desirable to have missing data, patients with incomplete data for the Cancer Worry Scale (CWS) on any of the 12 time points were excluded resulting in a sample of 218 participants.

Measures

Clinical and Demographic Variables

Patients completed socio-demographic items assessing age, marital status, having children, education, and employment status as part of the baseline questionnaire. Clinical variables, including type of treatment and time since surgery, were self-reported in the baseline questionnaire.

Fear of Cancer Recurrence

Fear of cancer recurrence severity was evaluated using the CWS. The CWS is used in research to assess concerns about developing cancer again and the impact of those concerns on daily functioning (Lerman et al., 1991; Douma et al., 2010). The eight items of the CWS are rated on a four-point Likert scale ranging from "*never*" to "*almost always*." Scores range from 8 to 32. The CWS has been validated in Dutch women with breast cancer (Custers et al., 2014). A cut-off score of 14 or higher (sensitivity 77%; specificity 81%) has been validated in women with breast cancer indicating a high level of FCR and applied in this study (Custers et al., 2014). In this study, the Cronbach's alpha varied between 0.86 and 0.89.

Descriptive Classification of FCR Course

The course of FCR for each participant was classified using the following purpose-designed *a priori* criteria:

a. Low stable: CWS score of 13 or lower at each assessment during the 12 month assessment period.

b. High stable: CWS score of 14 or above at each assessment during the 12 month assessment period.
c. Fluctuating: CWS scores both above and below cut-off for high FCR at subsequent assessments during the 12 month assessment period.

Triggers of FCR

The 12 month questionnaire asked participants to complete a short open-ended question "*Has there been a particular situation or event that may have influenced the degree of fear that you experience now*?" immediately after completing the CWS.

Data Analysis

Absolute Change in FCR Scores (Total Delta)

To calculate the total magnitude of change in FCR scores over time, an absolute change score (delta) was calculated for each interval between months 1 to 12 in the data collection. A total absolute change score (total delta) was calculated by summation of the 11 monthly delta scores between months 1 to 12.

Identification of Classes

Following the guidelines described by Jung and Wickrama (2008), latent class growth analysis (LCGA) was conducted using MPlus to identify trajectories (classes) over time for CWS scores. MPlus' full information maximum likelihood estimation for handling missing data was applied. By estimating individual variability in outcome over time, individuals are classified into latent classes based upon similar patterns of FCR.

A single-class growth curve model, as well as a three-class model was specified. To determine the number of classes in the sample, the three-class model was compared with a two-class and four-class model, as well as a five- and six-class model. In total, the fit of six unconditional latent class models (i.e., models with no covariates) was estimated, with one to six linear trajectories. The number of trajectories was determined based on model parsimony, fit indices, and clinical interpretability. The best fitting model has significant p-values ($p < 0.05$) for the Bootstrap Likelihood Ratio Test (BLRT) and the Vuong-Lo-Mendell Ruben Likelihood Ratio Test (LMR-LRT), the smallest Bayesian Information Criterion (BIC), a higher entropy statistic (near 1.0), and higher posterior probabilities of group membership (near 1.0). The number of participants (not less than 5% of total sample) of the identified classes was considered for clinical interpretability.

Baseline Characteristics of Classes

Based on literature (Simard et al., 2013), we compared *a priori* defined baseline demographic and medical characteristics between the identified classes using univariate and multivariate logistic regression analyses. First, univariate associations of baseline characteristics (age, partnered, children, education, employment, time since diagnosis, additional treatment, and satisfaction with medical treatment) with the classes of FCR were calculated. Next, to understand the independent contribution of the baseline characteristics, multivariate logistic regression analyses were conducted.

Latent class growth analysis was performed in Mplus 7 and the logistic regression analyses in SPSS version 25.

Classification of Low, Fluctuating, or High Stable FCR: Descriptive Approach

Chi-square was used to examine difference in the proportions of women who were classified as having low and stable, fluctuating, or chronically elevated FCR by time since surgery (<3 vs. 3–5 years). Associations between absolute change in FCR (total delta) and time since diagnosis were explored using Pearson's correlation. Differences in mean delta scores between women with a low, fluctuating, and high level of FCR were assessed with one way between groups ANOVA with *post hoc* contrasts.

Triggers of FCR

Reported triggers were independently coded for themes by two researchers. Coding was initially conducted using *a priori* codes derived from the triggers subscale of the FCR Inventory (FCRI; Simard and Savard, 2009). Initial coding was discussed by the research team, and where necessary codes were adapted or new codes added, following which both raters re-coded all responses and ratings were compared to check for inter-rater agreement (87%). Any further discrepancies were resolved through discussion until consensus was achieved.

RESULTS

Participant Characteristics

Longitudinal data of 377 patients were available for the statistical approach of class distinction. Demographics and medical characteristics of these participants are shown in **Table 1**.

For the descriptive analysis, a total of 218 women with complete CWS data were analyzed. Characteristics of the $n = 377$ sample were comparable to the participants for the descriptive analysis ($n = 218$): mean age was 58 years on average at baseline (range 33–87 years, $SD = 9.4$) and patients were on average 2.8 years post-diagnosis (range 0.5–5.9 years, $SD = 1.4$). The majority of participants was married or partnered (77%) and had children (82%). Approximately half (49%) had moderate education; one quarter had low (25%) and approximately one quarter (26%) higher education. Participants received a variety of adjuvant therapies including chemotherapy (65%), radiotherapy (78%), hormonal therapy (63%), and trastuzumab (10%).

Course of FCR

For the complete sample ($N = 377$), the intercept of the CWS score generated with Mplus was 14.1 (95% CI 13.7–14.5), indicating moderate to high FCR. There was a slight decrease in CWS score (less FCR) over time (slope −0.07; 95% CI −0.09 to −0.04), equivalent to an average decrease in CWS score of −0.84 per year.

TABLE 1 | Baseline characteristics of the identified subgroups of fear of cancer recurrence (FCR).

	Total *n* = 377	Low declining FCR *n* = 149	Moderate declining FCR *n* = 177	High stable FCR *n* = 51	
Demographics					
Age, mean (SD), years*	57.6 (9.4)	58.8 (9.2)	56.2 (9.0)	58.9 (10.3)	$F(2,373) = 3,83$, $p = 0.02$
Married/partnership, *n* (%)	280 (75%)	110 (74%)	129 (74%)	41 (80%)	$X^2(2) = 0.89$, $p = 0.64$
Children, *n* (%)*	313 (84%)	116 (78%)	150 (86%)	47 (92%)	$X^2(2) = 6.26$, $p = 0.04$
Education level*					
High, *n* (%)	110 (30%)	55 (38%)	44 (25%)	11 (22%)	$X^2(2) = 10.86$, $p = 0.03$
Currently employed, *n* (%)	174 (46%)	68 (45%)	88 (50%)	18 (35%)	$X^2(2) = 3.46$, $p = 0.18$
Medical characteristics					
Time since diagnosis, mean (SD), years	2.8 (1.3)	2.8 (1.3)	2.8 (1.3)	2.6 (1.3)	$F(2,365) = 0.492$, $p = 0.61$
Additional treatment[a]					
Chemotherapy, *n* (%)	267 (71%)	107 (73%)	124 (71%)	36 (71%)	$X^2(2) = 0.23$, $p = 0.89$
Radiotherapy, *n* (%)	289 (78%)	115 (78%)	136 (78%)	38 (75%)	$X^2(2) = 0.31$, $p = 0.86$
Hormonal therapy, *n* (%)	237 (63%)	90 (61%)	119 (68%)	28 (55%)	$X^2(2) = 3.23$, $p = 0.19$
Trastuzumab, *n* (%)	45 (12%)	18 (12%)	19 (11%)	8 (16%)	$X^2(2) = 0.91$, $p = 0.64$
Psychosocial factors					
Satisfaction with medical treatment (0 not at all–4 very satisfied)*	3.4 (0.7)	3.5 (0.7)	3.3 (0.7)	3.2 (0.9)	$F(2,370) = 4,79$, $p = 0.01$

[a]*Does not sum to 100% as respondents could endorse multiple categories.*
*$p < 0.05$.

Identification of Classes: Statistical Approach

A three-class model was identified as most appropriate based on fit indices, internal reliability, and interpretability (**Table 2**). In the three-class model, compared with the two-class model, the BIC was better, but the entropy was lower. The posterior probabilities were similar for the two and three-class model. Compared with the four-class model, in the three-class model, the BIC was somewhat lower, whereas other fit indices were highly similar. In the four-class model, however, a subgroup was identified including only 10 patients, limiting clinical interpretability.

The three subgroups differed in the baseline values (intercepts) of the CWS scores. The first subgroup consisted of 149 participants and was defined as "low declining FCR," as participants reported low baseline CWS scores (intercept 10.9; 95% CI 10.5–11.3), and the slope was −0.06 (95% CI −0.09 to −0.03). The second subgroup was defined as "moderate declining FCR," as the 177 participants in this group showed moderate to high baseline CWS scores (intercept 14.9; 95% CI 14.5–15.4), and the slope was −0.09 (95% CI −0.12 to −0.05). The third subgroup was defined as "high stable FCR." For this subgroup of 51 patients, the intercept was 20.4 (95% CI 19.6–21.3), and the slope was non-significant (−0.03; 95% CI −0.13 to 0.06).

Baseline Characteristics of Classes

The results of the univariate and multivariate regression analyses comparing baseline characteristics of participants between the three FCR classes are shown in **Table 3**. Four variables (age, education, children, and satisfaction with medical treatment) were significantly different between groups in the univariate analysis and therefore selected to be included in the final model with the low declining trajectory as the reference group. The final model was statistically significant ($\chi^2 = 27.934$, $df = 8$, $p < 0.001$, Cox and Snell $R^2 = 0.074$, Nagelkerke = 0.086, and McFadden = 0.039). Age, education, and satisfaction with medical treatment remained significant predictors of FCR trajectory. Younger patients (moderate declining OR = 0.967; high stable OR = 0.994), higher educated patients (moderate declining OR = 1.954; high stable OR = 2.083), and patients less satisfied with medical treatment (moderate declining OR = 0.656; high stable OR = 0.579) were more likely to belong to the moderate declining or stable high trajectory than the low declining trajectory.

Descriptive Course of FCR

Of the 218 women with CWS scores on all 12 assessments, approximately one-fifth of the sample ($n = 45$, 20.6%) reported low FCR at each monthly assessment (CWS scores 13 or lower). A similar proportion ($n = 47$, 21.6%) consistently scored above cut-off on the CWS (high FCR) at each time point, while the majority ($n = 126$, 57.8%) reported scores which fluctuated above and below the validated CWS cut-off score for high FCR over 12 monthly assessments. No significant differences were observed in the proportion of women classified as low, fluctuating, or high CWS scores between those who were <3 years since surgery and women who were 3–5 years post-surgery ($\chi^2 = 1.68$, $p = 0.43$).

Mean CWS scores for the entire sample ranged from 13.2 to 14.8 across the assessment period (12 months).

Absolute Change in FCR Scores Over 12 Months

The median absolute change in CWS over 12 months (total delta) was 16 CWS points ($M = 17.5$, SD = 9.49, range = 0–67). There was no association between total delta and time since diagnosis.

TABLE 2 | Fit indices, entropy, and average posterior probabilities across models with different number of classes with distinct trajectories of cancer worry.

No. of classes	BIC	LMR-LRT	BLRT	Entropy	*n*	Posterior probabilities	Intercept (95% CI)	Slope linear (95% CI)
2	21117.46	0.002	<0.0001	0.968	102 (27.1%)	0.98	18.6 (17.8, 19.5)	−0.07 (−0.13, −0.004)
					275 (72.9%)	1.00	12.5 (12.2, 12.8)	−0.08 (−0.10, −0.05)
3	19868.72	0.010	<0.0001	0.950	177 (47.0%)	0.98	14.9 (14.5, 15.4)	−0.09 (−0.12, −0.05)
					51 (13.5%)	0.99	20.4 (19.6, 21.3)	−0.03 (−0.13, 0.06)
					149 (39.5%)	0.97	10.9 (10.5, 11.3)	−0.06 (−0.09, −0.03)
4	19348.81	0.014	<0.0001	0.955	61 (16.2%)	0.98	18.6 (17.7, 19.5)	−0.04 (−0.13, 0.06)
					135 (35.8%)	0.97	10.8 (10.3, 11.2)	−0.07 (−0.10, −0.03)
					171 (45.4%)	0.98	14.5 (14.1, 15.0)	−0.09 (−0.13, −0.06)
					10 (2.7%)	1.00	24.1 (22.8, 25.5)	0.05 (−0.13, 0.24)
5	18984.81	0.012	<0.0001	0.935	81 (21.5%)	0.95	15.9 (15.2, 16.7)	−0.06 (−0.14, 0.02)
					41 (10.9%)	0.98	19.5 (18.9, 20.1)	−0.05 (−0.16, 0.06)
					140 (37.1%)	0.94	13.5 (12.9, 14.1)	−0.10 (−0.14, −0.06)
					105 (27.9%)	0.97	10.3 (10.0, 10.7)	−0.06 (−0.10, −0.03)
					10 (2.7%)	1.00	24.1 (22.8, 25.5)	0.06 (−0.13, 0.24)

BIC, bayesian information criterion; LMR-LRT, vuong-lo-mendell rubin likelihood ratio test; BLRT, bootstrap likelihood ratio test; and CI, confidence interval.

TABLE 3 | Final model of baseline characteristics associated with subgroup membership for FCR, multinominal regression analysis for FCR (moderate declining worry and high stable worry vs. low declining worry).

	X^2	*p*	*B*	Wald	Exp (*B*)	95% CI
Age	7.591	0.022				
Moderate declining			−0.033	6.831	0.967	0.943–0.992
High stable			−0.006	0.111	0.994	0.959–1.030
Children	4.044	0.132				
Moderate declining			−0.432	1.898	0.650	0.352–1.200
High stable			−0.962	2.860	0.382	0.125–1.165
Education	8.161	0.017				
Moderate declining			0.670	6.947	1.954	1.187–3.215
High stable			0.734	3.538	2.083	0.970–4.475
Satisfaction medical treatment	7.603	0.022				
Moderate declining			−0.421	5.339	0.656	0.459–0.938
High stable			−0.546	5.379	0.579	0.365–0.919

A one-way between-groups ANOVA was conducted to assess differences in mean delta scores between women with a low, fluctuating, and high level of FCR. There was a statistically significant difference between the groups: $F(2, 215) = 23.96$, $p < 0.001$. *Post hoc* comparisons indicated that the mean delta scores for the stable high ($M = 21.0$, $SD = 8.5$) and fluctuating group ($M = 18.9$, $SD = 9.6$) were significantly higher compared to the stable low group ($M = 9.7$, $SD = 4.9$).

Triggers of FCR

Fifty women (23%) reported an identifiable trigger at the final assessment. Trigger themes emerging from the data were: (1) medical appointments or examinations; (2) change of medication; (3) conversations about cancer or illness; (4) seeing or hearing about someone who is ill; (5) feeling unwell (physical symptoms); (6) funerals obituaries; or (7) other. The most commonly reported triggers were seeing or hearing about someone else who is unwell (reported 16 times), hearing of a death (12 times), or personally feeling unwell or experiencing physical symptoms (8 times). Women classified as having below cut-off CWS score (low FCR) at each assessment reported fewer triggers than those with high stable or fluctuating FCR, and many categories of triggers endorsed by women with high FCR or fluctuating FCR were not endorsed at all by those classified as having low FCR (e.g., physical symptoms, funerals, or obituaries).

DISCUSSION

The main finding of this study was that more than half (58%) of BCS in the present study reported CWS scores which fluctuated above and below a validated cut-off for high FCR at each monthly assessment over 12 months, while approximately one-fifth reported high scores and one-fifth reported low scores at all time points. These findings are partly in line with those of Savard and Ivers (2013) who found among a mixed cancer survivors group that patients with clinical FCR at baseline continued to display clinical levels at all subsequent time points.

Contrary to our hypothesis that fluctuation in CWS scores would decrease over time as women were expected to adjust to their breast cancer diagnosis, we found no significant association between absolute change in CWS scores over 12 months and time since diagnosis. Nor was a significant difference observed in the proportion reporting high, low, and fluctuating course up to 3 years post-surgery compared with 3–5 years post-surgery, suggesting that fluctuation in FCR continues through the first 5 years after diagnosis. Therefore, compared to previous literature, the results of the present study suggest that high FCR may not be as stable as it has been

previously characterized. Similar to the findings of Dunn et al. (2015), our data indicated that individual fluctuation of FCR is common. Descriptive analysis of absolute change in CWS scores over 12 months and plots of individual FCR scores over time suggested that the FCR scores of those with low FCR remain relatively stable. Greater variability in FCR scores was observed in women who scored above cut-off at each monthly assessment (high and stable) and those whose scores fluctuated above and below cut-off at each monthly assessment (fluctuating). This level of variability in FCR scores seemed to be characterized by the way survivors respond to triggers of FCR as triggers were more commonly reported by women who experienced high FCR at all time points and those with fluctuating levels of FCR. This could be explained by the fact that high FCR is characterized by high levels of preoccupation and being less able to respond to triggers in an adaptive way. Although, the fluctuating group also pays attention to triggers they seem better able to adapt to and normalize accompanying feelings of FCR over time. Women with low FCR at all time points spontaneously reported fewer triggers of FCR, possibly due to less exposure to triggers, paying less attention to triggers or finding them less bothersome.

Regarding the nature of triggers, in accordance with the theoretical model of Lee-Jones et al. (1997) and Custers et al. (2017), both external (seeing or hearing about someone else who is unwell) and internal triggers (personally feeling unwell or experiencing physical symptoms) were reported. This nature of triggers might also be related to the culture in the Netherlands with a lot of media attention on (breast) cancer (e.g., breast cancer month), regular medical check-ups, national screening programs for breast cancer, and most people speaking openly about cancer.

Strength of this data was that it included assessment of triggers for current rating of FCR rather than retrospective recall of triggers as has been used in most previous studies. However, a potential limitation was that women who use avoidance-based strategies for managing FCR may also have avoided participating and or answering these questions given they were optional and less than one quarter of the sample could identify specific triggers. Research concerning triggers of FCR is currently very limited but it is of high relevance to developing evidence-based theoretical models of FCR (Fardell et al., 2016; Custers et al., 2017; Simonelli et al., 2017) and improving our understanding of the evolution of FCR.

Results of the LCGA confirmed the three-class approach including a stable high FCR group (13%), a low group (40%), and a moderate group (47%). Both the moderate and low scoring groups reported declining scores over time. The moderate group might be interpreted as fluctuating with a moderate-to-high intercept of 14.9 and a slope of −0.009 resulting in a decrease of 0.11 per year, continuing around the cut-off score. Compared with patients in the low declining FCR group, younger patients, higher educated patients, and those less satisfied with the medical treatment were more likely to belong to the moderate declining or high stable trajectory. These predictors are in line with the review of Simard et al. (2013) showing moderate to strong evidence for poor healthcare satisfaction and younger age as predictors for FCR. Findings on education as predictor for FCR remained inconclusive.

Strengths and Limitations

One of the strengths of this study is its use of a statistical (bottom-up) as well as descriptive (top-down) approach to correctly identify trajectories of FCR. Both approaches revealed three distinct trajectories of FCR, enhancing its validity and clinical interpretability. However, by interpreting the results, it is important to keep in mind that this was not an inception cohort, only linear trajectories were assessed and although the descriptive analysis was based on a validated cut-off score for high FCR, we acknowledge that the selected cut-off has not been validated against a gold-standard interview for clinical FCR. Furthermore, since participants were aware of the fact that the purpose of the study was FCR, it is plausible that there was a selection in signups for the study as confirmed by the moderate response rate of 38%. Selection bias is an aspect that should be taken into account when designing research on FCR since a proportion of survivors recognizes their FCR and expresses a need for help; whereas, other survivors cope with FCR by avoiding threat, including study questionnaires.

Implications and Future Research

Current interventions for FCR are mostly offered on the basis of a score above cut-off for high FCR on a single screening occasion (Butow et al., 2013; Van de Wal et al., 2017). An important clinical implication of the present findings is that FCR should be assessed on multiple occasions before a healthcare professional decides that new evidence-based clinical interventions for FCR are warranted. A stepped-care model with a first stage of intervention, which may include watchful waiting, psycho-education, online interventions, or other self-management approaches might be appropriate. If FCR does not dissipate after an initial waiting period or period of less intensive intervention, more intensive face-to-face interventions could be offered. Such a model has been effectively used in a hospital setting (Krebber et al., 2012, 2016) and may produce cost-savings for the health system, and help ensure that limited resources are directed to those most in need. The results of the present study also have relevance for emerging trials of FCR interventions, and raise the question whether the results observed might simply reflect the natural fluctuations in FCR over relatively short intervals (3–4 months).

There is growing interest in the use of novel research methods using very frequent assessment of symptoms (e.g., ecological momentary assessment). ESM is a method in which participants are asked to rate their situations, emotions, and reactions at random moments during the day for multiple days (Csikszentmihalyi and Larson, 2014). Compared with retrospective questionnaires which often assess constructs "over the past week," ESM offers several advantages: enhanced ecological validity because participants are assessed in their normal daily environment, minimized retrospective bias because participants' experiences are assessed in the moment, and enhanced reliability

because participants' are assessed repeatedly. Assessment of FCR using ESM might be a valuable approach for future research since frequent reassessment of FCR will provide further insights into the evolution of FCR and may prove useful in future trials evaluating FCR interventions. For researchers, the results of the present study suggest that future longitudinal studies should consider assessing FCR on multiple (>2) time-points and to consider shorter durations between assessments in order to capture potential variability. A better understanding of the evolution of FCR will help guide the implementation of evidence-based treatments for FCR.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. Requests to access the datasets should be directed to jose.custers@radboudumc.nl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Commissie Mensgebonden Onderzoek Regio Arnhem-Nijmegen. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by JC, MG, LK, WG, and JP. The first draft of the manuscript was written by JC, BT, and LK and all authors commented on previous versions of the manuscript. All authors contributed to the article and approved the submitted version.

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Supporting Patients With Untreated Prostate Cancer on Active Surveillance: What Causes an Increase in Anxiety During the First 10 Months?

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Background: The psychological burden possibly deriving from not immediately undergoing radical treatment for prostate cancer (PCa) could be a potential disadvantage of active surveillance (AS), especially in the eve of some relevant clinical exams [i.e., re-biopsy, prostate-specific antigen (PSA) test, and medical examination]. Even if it is known from the literature that the majority of PCa men in AS do not report heightened anxiety, there is a minority of patients who show clinically significant levels of anxiety after diagnosis. The present study aimed to investigate if demographic, clinical, and psychological variables at the entrance in AS (T0) were associated with the risk of developing clinically significant PCa-related anxiety 2 months before the first re-biopsy (T1) and to offer psychological support to improve quality of life (QoL).

Materials and Methods: A total of 236 patients participated in the PCa Research International: AS (PRIAS) protocol and in PRIAS-QoL study. Demographic/clinical features, health-related QoL domains, coping with cancer, PCa-related anxiety [Memorial Anxiety Scale for PCa (MAX-PC)], personality traits, and decision-making-related factors were assessed at T0. MAX-PC was also administered at T1. PCa-related anxiety at T1 was considered to be of clinical significance if the MAX-PC score was $\geq$1.5. Multivariable logistic regression coupled to bootstrap was used to detect factors associated with high levels of anxiety.

Results: The median age was 64.4 years. Fifty-six patients (24%) reported MAX-PC total score above the cutoff. Three factors were associated with a high level of PCa anxiety at T1: anxious preoccupation [odds ratio (OR) = 4.36], extraversion (OR = 1.9), and prostate-related symptoms (median OR = 0.46). Physical well-being was associated

with a low PCa anxiety subscale (median OR = 0.15); neuroticism and functional well-being were associated with PSA anxiety (median OR = 7.05 and 0.73, respectively). Neuroticism and helplessness/hopelessness were associated with fear of progression (median OR = 18.1 and 5.8, respectively).

Conclusion: Only a partial portion of the sample experienced significant levels of anxiety after 10 months. Psychological assessment should be routinely conducted to detect risk factors (i.e., anxious preoccupation, extraversion) for increased anxiety, offering tailored psychological interventions aimed at promoting interpersonal awareness and emotional well-being.

Keywords: anxiety, active surveillance, prostate cancer, coping strategies, personality traits

INTRODUCTION

Active surveillance (AS) is increasingly considered a viable alternative to radical treatment (i.e., radical prostatectomy, external beam radiotherapy, or brachytherapy) for men with a diagnosis of very low/low-risk prostate cancer (PCa). Through systematic monitoring including repeated biopsies, digital rectal examination, repeated prostate-specific antigen (PSA) tests, AS offers the advantage to reduce overtreatment and safely delay or even avoid the risk of treatment-related side effects without losing the window of curability. From the patient's perspective, it means to preserve one's own health-related quality of life (HRQoL) at least as long as the monitoring does not show evidence that treatment is needed (Klotz et al., 2015; Bokhorst et al., 2016; Marenghi et al., 2017).

On the other side, a potential disadvantage of AS could be the psychological burden possibly deriving from not immediately undergoing radical treatment for PCa. Could living with "untreated" PCa cause anxiety in patients who chose AS? The available studies focusing on the assessment of HRQoL in AS patients showed that the majority of men did not report impairing anxiety. A small but even present distress may vary from the perceptions of health and overall psychological adjustment (Klotz et al., 2015). Nonetheless, there is a minority of patients who reported significant levels of anxiety after diagnosis, for example, in the run-up to clinical exams (i.e., re-biopsy, PSA test, and medical examination) (Anderson et al., 2014; Venderbos et al., 2015; Bokhorst et al., 2016; Parker et al., 2016). Those men showed a significant decrease of anxiety over time, which may suggest a relevant impact of coping strategies during the first period on AS (Marzouk et al., 2018; Dordoni et al., 2020). Anxiety and illness uncertainty were found to be predictors of HRQoL. Hence, interventions to reduce anxiety may enhance QoL for men with PCa on AS. Although anxiety is widely recognized as a central aspect that deserves attention in the AS population, little research has been conducted on anxiety-related factors (Bellardita et al., 2015). We found only two studies reporting associated factors of anxiety during AS. Neurotic personality and a higher level of PSA both assessed at the beginning of AS were shown to be associated with PCa-specific anxiety. In another study, intolerance of uncertainty was also suggested to promote anxiety on AS (Tan et al., 2016). Further studies are needed to understand the personal, clinical, and psychosocial features associated with anxiety during AS. Coping strategies are important factors during AS, since a good adjustment to cancer might be related to HRQoL and anxiety (Bellardita et al., 2015; Dordoni et al., 2020). Coping strategies are defined as constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands (Folkman and Lazarus, 1984). Coping strategies are concerned with a person's attempts to manage stressful circumstances, along with the ascribed meaning or interpretation given to such circumstances (Dordoni et al., 2020). Moreover, after diagnosis, men may enter a phase of "*decisional conflict*" (i.e., they feel uncertain about the course of action to be taken), which may increase their distress (Steginga et al., 2004; Bangma et al., 2013; Bellardita et al., 2018). This could guide the professionals managing patients on AS in developing effective interventions for the promotion of psychosocial well-being (Parker et al., 2016).

The aim of this study was to investigate which factors might predict a high level of PCa-related anxiety during the first 10 months on AS. Anxiety is supposed to be higher during the first 10 months of AS because the first re-biopsy (generally performed at 12 months after diagnosis) may disconfirm the observational option. Such follow-up could be seen as the first "turning point" and a critical moment for patients' emotional well-being. The knowledge of variables affecting anxiety could be useful for both physicians (to offer focused psychological interventions at AS entrance) and to patients (to receive an even more "patient-centered care" aimed to prevent psychological burden during AS).

MATERIALS AND METHODS

Procedures

This research is being conducted at the PCa Program of the National Cancer Institute in Milan since September 2007, with the aim of assessing the HRQoL over time and its associated factors for patients choosing AS. It was designed as single-center ancillary research to the multicenter prospective observational "PCa Research International: AS (PRIAS) study" (Bokhorst et al., 2016), in which selected men with low-risk PCa are managed based on a standardized protocol. Men were eligible for the

PRIAS study if they had a diagnosis of PCa with a PSA <10.0 ng/ml; PSA density <0.2 ng/ml/cm^3; clinical stage T1c or T2; ≤2 positive prostate needle-biopsy cores or <15% of positive cores in a saturation biopsy (≥20 total cores); Gleason Score of 3 + 3 = 6. To be considered a candidate for AS, a patient should be fit for radical treatment (i.e., radical prostatectomy, radiation therapy, or brachytherapy). The protocol involved PSA measurements every 3 months, physical examination every 6 months, and prostate biopsy at 1, 4, and 7 years after diagnosis and annually if the PSA doubling time was <10 years. Criteria for deferred active treatment are T stage >2, cancer in more than two cores at re-biopsies, or Gleason score >6. The scientific protocol and the related informed consent were approved by the local ethical committee.

Sample

All patients with a PCa diagnosis included in the PRIAS protocol at our Institute were invited to participate in the ancillary QoL study (Ethical Commitee approved). Inclusion criteria for the study were (a) no evidence of mental disorders or cognitive impairments, (b) no evidence of physical conditions preventing the individual to read and fill in the questionnaire, (c) sufficient Italian language skill to understand the questionnaires, and (d) individual agreement with written informed consent.

Clinical/sociodemographic information was recorded at baseline. Self-report questionnaires evaluating HRQoL outcomes and other psychological variables were administered at different time points: at enrollment (T0) and 10 months after the diagnosis (i.e., about 2 months before the first re-biopsy) (T1). T0 administration was completed by patients when they signed the informed consent to enter PRIAS-QoL protocol. The follow-up questionnaires were sent by post or e-mail according to patients' preferences. If the questionnaires were not returned within 1 month, patients received a reminder.

Measures and Indicators

The anxiety specifically related to PCa was measured by the Memorial Anxiety Scale for PCa (MAX-PC) (Van Den Bergh et al., 2009) according to the Italian cultural adaptation for men in AS (Roth et al., 2003), which includes slightly modified subscales for PSA anxiety and fear of progression. Each of the 15 items is rated on a four-point Likert scale. Subscales and total score are calculated as mean values, thus ranging from 0 to 3, with 3 indicating maximum anxiety. It consists of 18 items divided into three subscales: (1) PCa anxiety, (2) PSA anxiety, and (3) fear of recurrence. The scale has been widely applied on samples of patients with PCa. Results showed that about 10% of patients report high levels of cancer-related anxiety (Roth et al., 2006).

Personality was assessed using the abbreviated form of the revised Eysenck Personality Questionnaire (EPQR-A), which consists of 24 items with two response options each (yes or no) (Alvisi et al., 2018). This tool provides three personality scales (Psychoticism, Extraversion, Neuroticism) and a control scale (Social Desirability).

HRQoL, i.e., the subjective perception about one's own well-being and the extent to which it is affected by a medical condition, was assessed through the 36-Item Short Form Health Survey (SF-36) and the Functional Assessment of Cancer Therapy–Prostate version (FACT-P). The SF-36 (Francis et al., 1992) consists of 36 items that provide two summary scores: Physical Health (PH) and Mental Health (MH). Both total scores range from 0–100, with 100 indicating the best overall health. The FACT-P (Ware and Sherbourne, 1992) includes 39 items (four-point Likert scale) that assess different HRQoL dimensions: physical well-being, social well-being, emotional well-being, functional well-being, and PCa treatment-related symptoms. Scores were normalized based on the number of items included (score range: 0–4, with scores of 3–4 indicative of high well-being).

Adjustment to cancer, i.e., the coping style adopted to adjust to the cancer diagnosis, was evaluated through the Mini-Mental Adjustment to Cancer Scale (Mini-MAC). This scale (Esper et al., 1997) includes 29 items (score range: 1–4) measuring five different coping strategies, fighting spirit, helplessness/hopelessness, avoidance, fatalism, and anxious preoccupation, with higher scores indicating a greater presence of the specific coping style.

Decisional conflict, i.e., the patients' perception of personal uncertainty about the choice of AS vs. the other feasible radical options was measured with the Decisional Conflict Scale (DCS) (Watson et al., 1994). This scale consists of 16 items with five response options (score range: 0–4): Informed, Values clarity, Support, Uncertainty, and Effective decision. Scale scores range from 0 (no decisional conflict) to 100 (extremely high decisional conflict).

Age, presence of a partner/spouse, education, and employment status were collected by an *ad hoc* survey at baseline.

Clinical data were collected from patients' medical charts: the time between diagnosis and entrance in AS, the time gap between entrance in AS and T1, PSA at diagnosis, clinical stage, and positive/total cores at the diagnostic biopsy.

Endpoints

The main endpoint of the study was PCa-related anxiety 2 months before re-biopsy at 1 year after diagnosis (T1). MAX-PC questionnaire was adopted to measure PCa-related anxiety. Clinically significance was defined by the following (Roth et al., 2003): scores ≥1.5 were considered as identifying high levels of anxiety. Total anxiety and the three specific subscales were considered as separated endpoints.

Statistical Analyses

Associations between clinically significant anxiety and individual/clinical features were evaluated through Mann–Whitney test for each of the four endpoints. Multivariable logistic regression was performed to identify factors predicting high levels of anxiety. Variable selection was based on least absolute shrinkage and selection operator (LASSO) (O'Connor, 1995); missing values were imputed through flexible multiple imputations using bootstrapping (O'Connor, 1995) (completed data for Max-PC at T1 were available for 236 patients; regarding T0, some missing data for SF-36, Mini-MAC, EPQ-R, and FACT-P questionnaires were presented—24, 13, 68, and 18, respectively—and to solve this shortcoming, they were imputed).

Bootstrap resampling (Tibshirani, 1996) (1,000 resamplings) was carried out for the evaluation of the odds ratios (ORs) of the selected variables to minimize the noise due to the particular dataset, thus trying to obtain an unbiased estimation of ORs. The performance of the resulting multivariable models was evaluated through calibration and Hosmer–Lemeshow test.

Statistical analyses were performed using MedCalc software version 12.1.4 (MedCalc Software, Mariakerke, Belgium), r-project,[1] and KNIME software (KNIME GmbH, Germany).

RESULTS

Patient Characteristics

Between September 2010 and May 2017, 449 patients were enrolled in PRIAS: 346/449 (77%) agreed to participate in the QoL study. Ninety-three (21%) refused, and 10 (2%) were excluded.

Complete data on MAX-PC at T0 and T1 were available for 236 patients. **Table 1** shows the participants' characteristics. Descriptive analyses for MAX-PC total score and subscales are reported in **Table 2**. Summary statistics for FACT-P, SF-36, EPQR-A, and Mini-MAC scores at T0 are available in the supplementary material.

Factors Predicting the Risk of Higher Anxiety

At T1, 56/236 patients (24%) reported clinically significant anxiety as measured by total MAX-PC, 35 (15%) for PCa anxiety, 72 (31%) for PSA anxiety, and 38 (16%) for fear of progression. Considering 213 patients who completed both T0 and T1 assessments, significant changes between low and high levels of score (under and above clinical threshold, respectively) between T0 and T1 were observed: 9.4% for total MAX-PC, 4.7% for PCa anxiety, 16% for PSA anxiety, and 8% for fear of recurrence (p-values < 0.001, chi-squared).

Univariate associations between MAX-PC at T1 and FACT-P, SF-36, EPQR-A, Mini-MAC, and SCD are reported in **Table 3**.

Presence of anxiety was positively associated with helplessness/hopelessness, avoidance, anxious preoccupation, FACT-P, MH, and neuroticism. Results for the four multivariable models are reported in **Table 4**.

Three factors resulted as predictors of high MAX-PC total score at T1: the EPQR-A extraversion (median OR = 1.9) and Mini-MAC anxious preoccupation (median OR = 4.36) were associated with an increased risk of anxiety, while FACT-P subscale PCa symptoms had a protective effect (median OR = 0.46).

Physical well-being at the entrance in AS was associated with PCa-related anxiety at T1 as a protective factor (median OR = 0.15). High PSA-related anxiety scores were associated with EPQR-A neuroticism subscale and to FACT-P functional well-being (median OR = 7.05 and 0.73, respectively).

Anxiety for fear of progression resulted in a two-variable model: neuroticism and helplessness/hopelessness from Mini-MAC (median OR = 0.18 and 5.83, respectively).

Calibration plots for all the models are presented in the supplementary material. **Figure 1** reports the nomogram derived from the total MAX-PC logistic model presented in **Table 4**.

[1] https://www.R-project.org/

TABLE 1 | Patients' characteristics.

	N	%
Total number of patients	236	
Socio-demographic data		
Age at diagnosis (years)	Median = 64.4	Range = 42–79
Higher education (High school)	155	66%
Employed	92	39%
Retired	138	58%
Missing	6	3%
Married or living with a partner	205	86.8%
Time between diagnosis and entrance in AS (months)	Median = 3.6	Range = 0–24.6
Time between entrance in AS and T1 (months)	Median = 6.4	Range = 0.5–9.9
PSA at diagnosis (ng/mL)	Median = 5.4	Range = 0.52–9.83
Clinical stage		
T1c	215	91%
T2a	21	9%
Biopsy at diagnosis		
1 Positive core	162	69%
2 Positive cores	74	31%

AS, Active Surveillance, PSA, Prostate Specific Antigen.

TABLE 2 | Distribution of MAX-PC (Memorial Anxiety Scale for Prostate Cancer) total and subscale scores at T0 and T1.

N = 236	Mean	SD	Median	Observed score range	*N* (%) of patients with clinically significant anxiety
T0 (*N* = 213)					
MAX-PC total score	1.2	0.4	1.1	0.4–2.5	49 (23%)
PCa anxiety	0.8	0.6	0.7	0–2.6	34 (16%)
PSA anxiety	0.9	0.8	0.7	0–3	43 (20.2%)
Fear of progression	0.8	0.5	0.8	0–2.7	28 (13.1%)
T1 (*N* = 236)					
MAX-PC total score	1.2	0.4	1.1	0.5–2.2	56 (24%)
PCa anxiety	0.8	0.6	0.7	0–2.6	35 (15%)
PSA anxiety	1.1	0.8	1	0–3	72 (31%)
Fear of progression	0.9	0.6	0.8	0–2.7	38 (16%)

SD, Standard Deviation; MAX-PC, Memorial Anxiety Scale for Prostate Cancer; PSA, Prostate Specific Antigen; N, number of patients; clinically significant anxiety: MAX-PC ≥ 1.5.

DISCUSSION

Even though clinical exams (i.e., re-biopsy, PSA test, and medical examination) may influence patients' anxiety and psychological well-being, scarce studies have investigated patients on AS' HRQoL in the run-up to clinical exams. This study offered information on anxiety levels among PCa patients in AS in

TABLE 3 | Associations between FACT-P (Functional Assessment of Cancer Therapy–Prostate), SF-36 (Short Form Health Survey-36 items), EPQR-A (Eysenck Personality Questionnaire), Mini-MAC (Mini-Mental Adjustment to Cancer Scale) and DCS (Decisional Conflict Scale) total and subscale scores at T0 and MAX-PC (Memorial Anxiety Scale for Prostate Cancer) total and subscale scores at T1 (Median scores and Mann-Whitney *p*-value).

	MAX-PC total median			PCa anxiety median			PSA anxiety median			Fear of progression median		
	Low	**High**	***p***	**Low**	**High**	***p***	**Low**	**High**	***p***	**Low**	**High**	***p***
MINI-MAC												
Fighting spirit	2.8	2.8	0.807	2.8	2.8	0.129	2.8	2.8	0.245	2.8	2.8	0.859
Helplessness/hopelessness	1.1	1.3	0.007	1.1	1.7	0.0001	1.1	1.3	0.015	1.1	1.7	<0.001
Avoidance	2.3	2.8	0.0005	2.3	3.0	0.0001	2.3	2.5	0.036	2.3	2.8	0.024
Fatalism	2.3	2.3	0.602	2.3	2.3	0.569	2.3	2.4	0.428	2.3	2.5	0.706
Anxious preoccupation	1.9	2.3	<0.0001	1.9	2.6	<0.0001	1.9	2.1	<0.0001	1.9	2.6	<0.001
FACT-P												
Physical well-being	4.0	4.0	0.11	4.0	3.9	0.007	4.0	4.0	0.497	4.0	3.9	0.005
Social well-being	2.9	2.6	0.023	2.9	2.5	0.007	2.9	2.7	0.222	2.9	2.5	0.003
Emotional well-being	3.3	3.0	<0.0001	3.3	2.8	<0.0001	3.3	3.0	<0.0001	3.3	2.8	<0.001
Functional well-being	2.7	2.4	0.0058	2.7	2.3	0.0001	2.7	2.4	0.035	2.7	2.3	0.001
Prostate symptoms	3.3	3.2	0.037	3.3	3.0	0.003	3.3	3.3	0.299	3.3	3.2	0.014
SF-36												
Mental health	52.4	48.5	0.012	52.6	45.3	0.0001	53.1	48.7	0.009	53.2	43.9	<0.001
Physical health	54.0	54.5	0.594	54.4	52.8	0.07	54.0	54.4	0.698	54.1	53.7	0.729
EPQ												
Psychoticism	0.2	0.2	0.31	0.2	0.2	0.91	0.2	0.2	0.568	0.2	0.2	0.877
Extraversion	0.7	0.5	0.931	0.7	0.5	0.841	0.7	0.5	0.366	0.7	0.5	0.306
Neuroticism	0.2	0.3	0.016	0.2	0.3	0.022	0.2	0.3	0.0007	0.2	0.5	<0.001
DCS												
Informed	25.0	25.0	0.223	25.0	25.0	0.31	25.0	25.0	0.726	25.0	25.0	0.323
Values clarity	25.0	25.0	0.877	25.0	25.0	0.729	25.0	25.0	0.774	25.0	25.0	0.719
Support	25.0	25.0	0.434	25.0	25.0	0.318	25.0	20.8	0.876	16.7	25.0	0.121
Uncertainty	25.0	25.0	0.252	25.0	37.5	0.039	25.0	25.0	0.106	25.0	37.5	0.006
Effective decision	25.0	25.0	0.196	25.0	25.0	0.167	25.0	25.0	0.54	25.0	28.1	0.062
Total decisional conflict	25.0	25.0	0.249	25.0	28.9	0.101	25.0	24.2	0.761	25.0	28.1	0.05

FACT-P, Functional Assessment of Cancer Therapy-Prostate; SF-36, Short Form Health Survey; EPQ, Eysenck Personality Questionnaire; Mini-MAC, Mini-Mental Adjustment to Cancer; DCS, Decisional Conflict Scale; MAX-PC, Memorial Anxiety Scale for Prostate Cancer. Low, patients with MAX-PC values below cut-off for clinical significance (1.5), High, patients with MAX-PC values above cut-off for clinical significance.

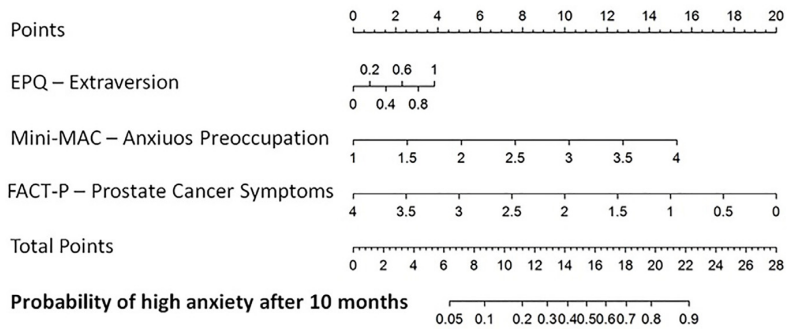

FIGURE 1 | Nomogram for the probability of having Memorial Anxiety Scale for Prostate Cancer total score >1.5 after 10 months from the diagnostic biopsy. Extraversion (continuous variable) of EPQR-A, Anxious preoccupation (continuous variable) of Mini-MAC, Prostate cancer-related symptoms.

proximity of the first clinical examination and on factors predicting anxiety. Clinicians should be aware of how patients on AS live critical moments of AS protocol (i.e., clinical exams) and of what impacts on this, so to support men preventing psychological burden from the very beginning of entrance in AS.

Our investigation confirms that only a partial portion of PCa patients on AS experience troubling levels of anxiety (24% of patients reported the MAX-PC total score above the threshold). These results are consistent with previous studies focusing on PCa-related anxiety (Roth et al., 2003; Anderson et al., 2014;

TABLE 4 | Logistic regression models for MAX-PC (Memorial Anxiety Scale for Prostate Cancer) total score, PCa anxiety subscale, PSA anxiety subscale and fear of progression subscale.

	Median coeff	% Significant coeff	Median odds ratio	10° – 90° Percentile for ORs
Endpoint: MAX-PC total ≥1.5				
Criterion: probability >0.20				
Sensitivity = 0.81, specificity = 0.66				
Hosmer-Lemeshow test, p = 0.95				
Calibration slope = 0.87, R^2 = 0.96				
Extraversion	0.64	81.6	1.9	0.74 – 4.3
Anxious preoccupation	1.47	100.0	4.4	3.0 – 6.5
Prostate symptoms	−0.77	96.4	0.46	0.25 – 0.79
Constant	−2.12			
Endpoint: PCa anxiety ≥1.5				
Criterion: probability >0.14				
Sensitivity = 0.38, specificity = 0.85				
Hosmer-Lemeshow test, p = 0.90				
Calibration slope = 1.04, R^2 = 0.89				
Physical well-being	−1.87	99.4	0.15	0.04 – 0.39
Constant	5.45			
Endpoint: PSA anxiety ≥1.5				
Criterion: probability >0.26				
Sensitivity = 0.76, specificity = 0.57				
Hosmer-Lemeshow test, p = 0.91				
Calibration slope = 0.90, R^2 = 0.85				
Neuroticism	1.95	99.8	7.05	2.9 – 16.0
Functional well-being	−0.32	89.5	0.73	0.51 – 1
Constant	−0.58			
Endpoint: Fear of progression ≥1.5				
Criterion: probability >0.08				
Sensitivity = 0.93, specificity = 0.52				
Hosmer-Lameshows test, p = 0.94				
Calibration slope = 1.06, R^2 = 0.97				
Neuroticism	2.89	100	18.1	6.4 – 57.1
Helplessness/Hopelessness	1.76	100	5.8	3.1 – 11.7
Constant	−5.17			

Coeff, coefficient; % significant coeff, percentage of coefficients >0 if mean coefficient is >0; percentage of coefficient <0 if mean coefficient <0; ORs, Odds Ratios; MAX-PC, Memorial Anxiety Scale for PCa, PCa, Prostate Cancer, PSA, Prostate Specific Antigen.

Venderbos et al., 2015; Bokhorst et al., 2016). Specifically, we here identified PSA-related anxiety as particularly relevant with up to 31% patients reporting distress when dealing with PSA testing. Anxiety indeed is a key component of such burden (Van Buuren, 2012). It is well known that PSA may be considered a "red flag" for PCa patients (Palorini et al., 2016).

Our findings also suggested that personality traits, coping strategies, and perceptions of functional well-being were associated with anxiety.

Within personality traits, the extraversion trait, i.e., indicating a talkative and lively person, who likes/enjoys meeting new people (Alvisi et al., 2018), was found to be a risk factor in predicting anxiety (Villa et al., 2017). This may seem counterintuitive. Yet we can argue that extravert men may more easily show anxiety compared to introvert men, since they are more confident in communicating their feelings (Villa et al., 2017). Such sharing could turn out to be useful, as communicating their anxiety may help them ask for emotional support.

Neuroticism (i.e., characterizing an irritable person, who is often troubled about feelings of guilt and whose mood often goes up and down) increases PCa-related anxiety (Klotz, 1997; Villa et al., 2017). Men who scored high on neuroticism were usually preoccupied about the potential progression of the disease, reacting emotionally to monitoring events (Jylhä and Isometsä, 2006). Particularly, our results revealed that neuroticism traits were associated with PSA-related anxiety and fear of progression. Men with more neurotic personalities were also previously found to have a higher chance of anxiety (Jylhä and Isometsä, 2006; Riggio and Riggio, 2002).

Helplessness/hopelessness coping strategies emerged as risk factors for anxiety (Bellardita et al., 2013; Villa et al., 2017). Such strategies refer to the perception that an individual has not enough resources and support to cope with stressful events. As a consequence, men may experience a lack of control resulting in both anxiety and little likelihood of engaging in a healthy lifestyle (Dordoni et al., 2020).

Additionally, our results showed that men who were coping with high anxious preoccupation at AS enrollment were more likely to experience overall cancer anxiety after 10 months. Coping strategies (measured through the Mini-MAC questionnaire) have shown a relevant impact on cancer patients'

emotional well-being and on men on AS' quality of life (Dordoni et al., 2020). Psychological interventions directed on problem-focused coping (i.e., strategies used in situations valuated as controllable) and emotion-focused coping (i.e., strategies used in situations in which nothing can be done) may help patients in engaging in healthier behaviors and reduce cancer-related anxiety (Bellardita et al., 2013; Dordoni et al., 2020).

PCa symptoms, physical well-being, and functional well-being had a protective effect on anxiety in our sample (see mental and physical health on FACT-P results). Men on AS usually do not report specific PCa-related symptoms; however, it is likely that those who enter AS perceiving few cancer-related symptoms take their minds off cancer, resulting in positive emotional well-being. Note that the FACT-P PCa symptoms scale in the case of men in AS is indeed measuring prostate-related symptoms mainly due to benign prostatic hyperplasia.

Finally, in the present study, no sociodemographic nor patient-related data were significantly associated with higher anxiety levels. Anderson et al. (2014) reported a limited role for sociodemographic data in explaining patients' anxiety during AS. Only a few variables such as being divorced and age have been found to impact on patients' well-being.

To monitor patients' anxiety level and prevent a potential psychological burden, a specific tool supported by clinical data was needed. For this purpose, in the present study, logistic regression model was translated into a specific prognostic nomogram, which could sustain the entire care process supporting clinicians in foreseeing patients' anxiety.

Even though our study is based on a large sample, some limitations should be acknowledged: no control group was involved, and our results could hardly be generalized to different geographic populations due to inclusion of patients enrolled in a single institution. Additionally, our multidisciplinary management, with a focus on patient engagement and shared decision-making (Eysenck and Eysenck, 1991), could further influence the generalizability of our results. Of note, compared to a mono-disciplinary approach, our multidisciplinary management provides a dedicated psychologist who offers clinical support on patients' potential anxiety.

Based on the present findings, and our 15-year experience within a multidisciplinary setting (Lazarus and Folkman, 1984; Eysenck and Eysenck, 1991; Deimling et al., 2017; Marenghi et al., 2017), psychological assessment both at the moment of diagnosis and during AS is needed to detect the risk for increased anxiety. Promoting problem-focused and emotion-focused coping and helping patients in expressing their thoughts and beliefs about cancer and AS are beneficial to the management of anxiety. A multidisciplinary clinical team including the psychologist can promote tailored information, which may help patients in better understanding the choice of AS and, in turn, reduce cancer-related anxiety over time (Eysenck and Eysenck, 1991; Magnani et al., 2012; Deimling et al., 2017). Furthermore, the prognostic nomogram may represent helpful support for the multidisciplinary clinical team because of its specificity and applicability in identifying patients who could suffer from cancer-related anxiety.

In conclusion, QoL of patients in AS is not extensively studied; we know that there are delicate moments and situations (such as PSA measurement, biopsies, and visits) that could influence patients' well-being. Furthermore, since AS is proposed to avoid the side effects of treatments, it became fundamental to understand how patients live and recognize any critical moments to help them in advance. The present study investigated predictors of anxiety in patients on AS 10 months after diagnosis. Focusing on this timing because anxiety can be critical right before the first re-biopsy (12 months after diagnosis) as it may disconfirm the observational option. An important role of personality traits (i.e., extraversion) and coping strategies (i.e., anxious preoccupation) emerged in our study as predictors of PCa-specific anxiety. Furthermore, men perceptions of physical well-being and the lack of symptoms related to PCa showed the potential to protect against clinical levels of anxiety. Finally, a prognostic nomogram was developed to predict patients' anxiety at AS entrance, aiming to identify those patients who may need psychological support.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because institutional protocol. Requests to access the datasets should be directed to dataset is not available.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Fondazione IRCCS Istituto Nazionale dei Tumori (Milan). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MA and PD: project administration, writing original draft, writing review, and investigation. MA, TR, and FB: data curation, analyses, and writing review. BA, NN, LD, TM, CM, JM, VS, ZF, and SR: data collection and writing review. VR and BL: study design, supervision, and writing review. All authors contributed to the article and approved the submitted version.

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Development and Testing of a Novel Measure to Assess Fidelity of Implementation: Example of the Mini-AFTERc Intervention

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Background: Fidelity of implementation (FOI) reflects whether an intervention was implemented in clinical practice according to the originally developed manual and is a key aspect in understanding intervention effectiveness. To illustrate this process of developing a fidelity measure, this study uses the Mini-AFTERc, a brief psychological intervention aimed at managing breast cancer patients' fear of cancer recurrence, as an example.

Objectives: To illustrate the development of an FOI measure through (1) applying this process to the Mini-AFTERc intervention, by including the design of a scoring system and rating criteria; (2) content validating the FOI measure using thematic framework analysis as a qualitative approach; (3) testing consistency of the FOI measure using interrater reliability.

Methods: The FOI measure was developed, its scoring system modified and the rating criteria defined. Thematic framework analysis was conducted to content validate the FOI measure using nine intervention discussions between four specialist cancer nurses and four breast cancer patients, and one simulated breast cancer patient. Intraclass-correlation was conducted to assess interrater reliability.

Results: The qualitative findings suggested that the Mini-AFTERc FOI measure has content validity as it was able to measure all five components of the Mini-AFTERc intervention. The interrater reliability suggested a moderate to excellent degree of reliability among three raters, r_{ICC} = 0.84, 95% CI [0.51, 0.96].

Conclusion: The study has illustrated the steps that an FOI measure can be developed through a systematic approach applied to the Mini-AFTERc intervention. The FOI measure was found to have content validity and was consistently applied, independently, by three researchers familiar with the Mini-AFTERc intervention. Future studies should determine whether similar levels of interrater reliability can be obtained by distributing written and/or video instructions to researchers who are unfamiliar with the FOI measure,

using a larger sample. Employing developed and validated FOI measures such as the one presented for the Mini-AFTERc would facilitate implementation of interventions in the FCR field in clinical practice as intended.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT03763825.

Keywords: fidelity, implementation, Mini-AFTERc intervention, breast cancer, fear of cancer recurrence

INTRODUCTION

Fear of cancer recurrence (FCR) is the "Fear, worry, or concern about cancer returning or progressing" (Lebel et al., 2016, p. 3267). FCR is a common issue that up to 97% of cancer survivors experience and, importantly, 22–87% of cancer survivors reported experiencing moderate to high FCR levels (Simard et al., 2013). The level of FCR has been associated with the time since primary surgery, the type of surgery and treatment, having symptoms of pain, fatigue, unmet needs, and age (Simard et al., 2013). This paper focused on the Mini-AFTERc intervention which aims to support breast cancer survivors in the management of FCR and was developed for patients experiencing moderate FCR levels (Davidson et al., 2018; McHale et al., 2020). This intervention is based on the cognitive-behavioral therapy approach of Leventhal's Self-Regulatory Model (Leventhal et al., 1984). Its purpose is to normalize breast cancer patients' fears and concerns by addressing the primary causes of these fears (Lee-Jones et al., 1997; Davidson et al., 2018; McHale et al., 2020). The intervention consists of 5 key components: Assessment, Family, Thoughts and Feelings, Expectation, and Return of cancer (AFTERc; **Figure 1**). The Mini-AFTERc is a structured 30 min counseling intervention, which is designed to be delivered during a single telephone conversation led by a specialist cancer nurse (SCN), who has undertaken an intervention training course and has been provided with the intervention manual.

Fidelity of implementation (FOI), also referred to as fidelity of delivery, is an important yet understudied aspect of psychological interventions. FOI has been defined as the extent to which an intervention was delivered as intended, such that the manual originally developed was adhered to, and the critical components of the intervention were present (Orwin, 2000; Century et al., 2010). FOI helps to establish internal and construct validity by providing evidence for the extent to which the implementation of the intervention followed the intervention manual (Stains and Vickrey, 2017). Additionally, FOI contributes to the establishment of external validity by increasing credibility and confidence of scientific findings for practitioners and policymakers, and aids a better understanding of what constitutes an effective intervention (Borrelli, 2011; Brownson et al., 2017). As such, conclusive statements about intervention effects cannot be made without an assessment of FOI (Borrelli, 2011).

Abbreviations: Mini-AFTERc, Assessment, Family, Thoughts and Feelings, Expectations, Return of cancer: Brief intervention; CI, Confidence Interval; FCR, Fear of cancer recurrence; FOI, Fidelity of implementation; ICC, Intraclass correlation coefficient; NHS, National Health Service; SCN, Specialist cancer nurse.

Measuring FOI enables researchers to confirm what exactly has been implemented and worked, and hence what can be replicated by research (Nelson et al., 2012). It also aids in identifying aspects of the intervention that were implemented poorly, which may guide future improvements (Nelson et al., 2012). Meta-analyses summarizing over 600 intervention studies targeting mental and physical health, highlighted that higher levels of intervention fidelity were associated with better treatment outcomes (Durlak and DuPre, 2008; Saini, 2009). These findings demonstrated that studies using structured intervention manuals and assessing FOI produced larger effect sizes than studies that did not.

Previous studies that have developed structured psychological interventions for FCR do not robustly or consistently address FOI using evidence-based measures (Lebel et al., 2014; Dodds et al., 2015; Dieng et al., 2016; Butow et al., 2017; van de Wal et al., 2017; Tomei et al., 2018). For example, the SWORD study by van de Wal et al. (2017) used a checklist for a group cognitive behavioral therapy for depression (Hepner et al., 2011), which was not developed specifically for the SWORD intervention. This checklist was developed for the Building Recovery by Improving Goals, Habits, and Thoughts (BRIGHT) and BRIGHT-2 interventions (Hepner et al., 2011). It is unclear to what extent this checklist is relevant and representative of the blended cognitive behavior therapy of the SWORD study, and whether it had been tested previously to ensure content validity. Furthermore, some of these studies do not report how FOI assessments were used to draw conclusions about the intervention, such that they have not been linked to the intervention's effectiveness. A further example is the ConquerFear study by Butow et al. (2017) which reported that clinicians completed session checklists to ensure fidelity. Additionally, a random 11% of audio recorded intervention sessions was reviewed independently by one of the study team (a clinical psychologist) and feedback was provided to clinicians where non-fidelity was identified. The authors do not report any intra-rater reliability and it is unclear whether the checklist included the core components of the intervention.

Considering the importance of assessing FOI for the robust development and implementation of psychological interventions, it is essential to consistently test and improve fidelity with which current interventions are implemented in clinical practice. As existing measures of fidelity are often generalized to allow the assessment of intervention implementation across a variety of settings and interventions (Breitenstein et al., 2010), they are not always applicable to the intervention being studied. At present, a specific measure to assess FOI of the

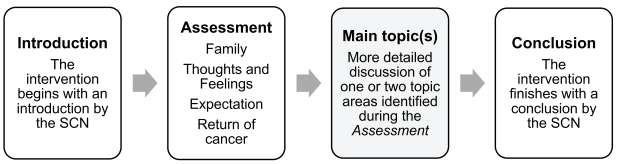

FIGURE 1 | The procedure of the Mini-AFTERc intervention.

Mini-AFTERc intervention does not exist and thus necessitates development and testing.

The AFTER intervention (Humphris and Ozakinci, 2008), on which the Mini-AFTERc was based, stressed the need to attend to the therapeutic alliance. Experience of applying this intervention in clinical practice demonstrated that users of the intervention aspired greater flexibility to follow issues that transpired in the patient interaction. Additionally, it increased the chances of the interventionist to provide acknowledgment to patient difficulties and empathize with emotional expressions. Therapeutic alliance can be defined as the collaborative and affective relationship between the therapist and patient (Bordin, 1994; Luborsky, 1994). The therapeutic alliance is regarded to be the most significant aspect in attaining positive therapeutic change (Paul and Charura, 2014). Accordingly, it is important that the interventionist understands the principles of therapeutic alliance to facilitate a strong therapeutic relationship with their client (Paul and Charura, 2014). Earlier meta-analyses including 573 studies concerning youth and adult psychotherapy demonstrated a moderate but reliable link between good therapeutic alliance and positive intervention outcome (Shirk and Karver, 2003; Karver et al., 2006; Horvath et al., 2011; Shirk et al., 2011; Flückiger et al., 2018). Furthermore, a review by Ackerman and Hilsenroth (2003) including 25 studies investigated the type of therapist characteristics and techniques that positively impact on therapeutic alliance. They reported that personal attributes such as being warm and interested, and therapist techniques such as exploration and reflection, impact positively on therapeutic alliance (Ackerman and Hilsenroth, 2003). Therefore, these aspects should be considered when rating the level of fidelity for the Mini-AFTERc intervention and possibly any intervention involved with modifying FCR levels.

Assessing FOI is essential to draw correct conclusions about the effectiveness of the Mini-AFTERc intervention (Borrelli, 2011). It allows researchers to verify that the therapeutic approach used by the SCNs during the intervention represents the defined intervention, and aids in establishing internal, construct, and external validity (Borrelli, 2011; Brownson et al., 2017; Stains and Vickrey, 2017). Particularly, as there is continued work to develop the Mini-AFTERc intervention, close attention is required to devise a bespoke measure for a major trial. Therefore, a comprehensive FOI measure representing the flexibility of the Mini-AFTERc intervention should be developed. Importantly, when defining the rating criteria, therapeutic alliance should be considered (Ackerman and Hilsenroth, 2003). Lastly, interrater reliability of the novel FOI measure, which reflects the variation among two or more raters who measure the same groups of participants, should be established to allow its use in research or clinical applications (Koo and Li, 2016).

This study aimed to develop a comprehensive FOI measure for the Mini-AFTERc intervention and act as an example to other investigators wishing to assess the effectiveness of their interventions in the FCR field. The development of the FOI measure included the design of an unambiguous scoring system and rating criteria to categorize the level of fidelity, providing researchers with a standardized way to quantify how closely the SCNs adhered to the Mini-AFTERc intervention manual. The study objectives were to:

1. Develop a Mini-AFTERc FOI measure, including the design of a scoring system and rating criteria;
2. Content validate the Mini-AFTERc FOI measure using thematic framework analysis as a qualitative approach;
3. Test the consistency of the Mini-AFTERc FOI measure using interrater reliability.

MATERIALS AND METHODS

Study Design

The qualitative study described in this paper was part of the Mini-AFTERc pilot trial (McHale et al., 2020). Thematic framework analysis was employed using an essentialist/realist approach (Terry et al., 2017) to address the study objectives. Thematic framework analysis was chosen due to its flexibility, as it can be used within most theoretical frameworks (Terry et al., 2017).

Study Objective 1: Development of the Mini-AFTERc FOI Measure, Including the Design of a Scoring System and Rating Criteria

The FOI Rating System, designed by Forgatch et al. (2005), was used to inform the development of an initial version of the Mini-AFTERc FOI measure (**Figure 2**). This rating system was selected because it was developed to evaluate the fidelity of a manualized theory-based interventions through audio-visual recordings of the intervention being delivered, which fit well with the Mini-AFTERc pilot study protocol (Forgatch et al., 2005). Initial testing of the FOI measure with a small sample of audio recorded Mini-AFTERc intervention telephone calls, collected as part of a feasibility study (Davidson et al., 2018), highlighted that clarification and refinement of content, scoring, and rating was necessary.

Identification of Components

The current iteration of the FOI measure, presented in this paper, was developed by the first author (NGB). After studying the Mini-AFTERc intervention training manual and the initial FOI measure, NGB identified that, while the FOI measure addressed some fundamental aspects of the intervention, including Mini-AFTERc knowledge, structure, follow an agenda, and overall quality, it did not address the separate four core components: *Family*, *Thoughts and Feelings*, *Expectation*, and *Return of cancer*. Missing, or lacking details, of these

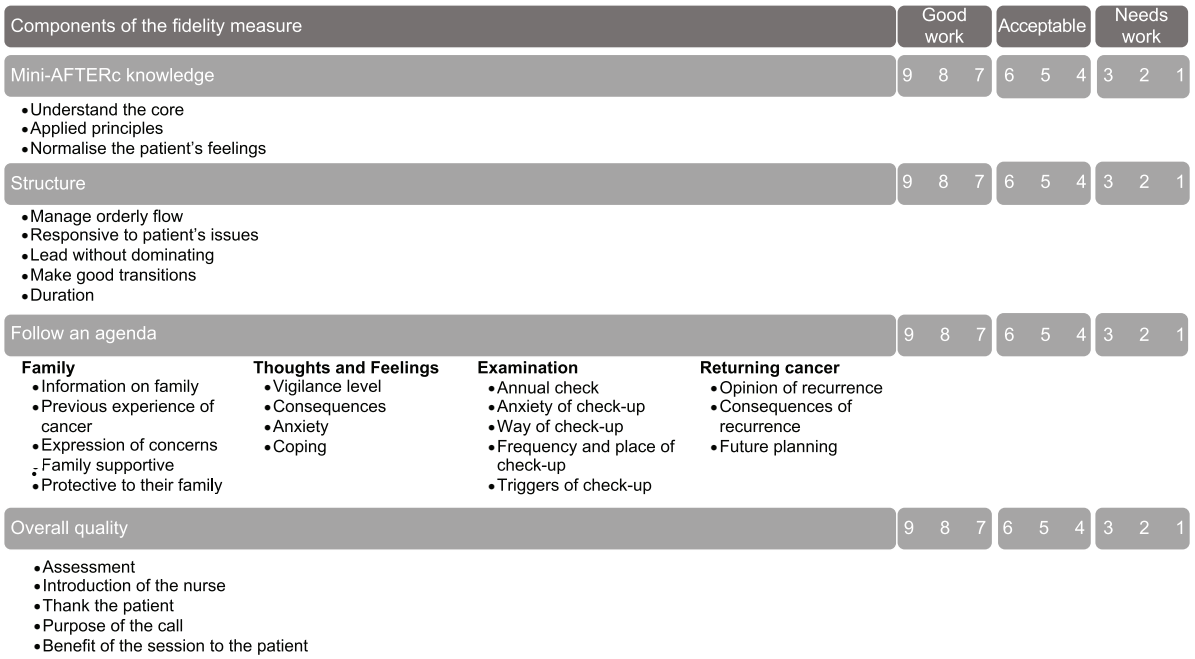

FIGURE 2 | Initial version of the Mini-AFTERc FOI measure.

essential components leads to an inability to address the intervention's flexibility and comprehensiveness, thus limiting the ability to assess properly the intervention's FOI. Hence, to allow the development of a comprehensive FOI measure specifically designed for the Mini-AFTERc intervention, the core components must be addressed separately to enable accurate scoring and rating.

Scoring of the Mini-AFTERc FOI Measure

The initial development of the FOI measure included a 9-point scoring system (**Figure 2**) which NGB redesigned to a 3-point scale. This 3-point scale of adherence was designed to reduce the ambiguity of the scoring process and allow raters to employ their discriminative abilities (Jacoby and Matell, 1971), reducing the possibility of introducing error. The possible adherences scores are as follows: (2) high adherence, (1) moderate adherence, and (0) low adherence. Adherence is defined as whether "a program service or intervention is being delivered as it was designed or written" (Mihalic, 2004, p. 2).

The intervention manual instructs that it is not feasible, within the allotted 30 min, to cover all four core intervention discussion topics in extensive detail. If it is apparent that a patient has potential issues in all four topics, the SCN should prioritize two topics and potentially offer another session. Therefore, the scoring system was designed with the expectation that only one to two core discussion topics would be the major focus of discussion during the intervention. At least half of the subcomponents must be addressed for a topic to be identified as a major focus of the intervention discussion. During the major topic discussion phase, at least half of the subcomponents had to be explicitly addressed by the SCN in at least one major discussion topic for "high adherence" to be scored, providing the SCN scored "high adherence" for all components. To reduce the possibility of scoring unfairly and/or inaccurately, high fidelity could be achieved regardless of whether half of the subcomponents of one main topic were addressed, or all subcomponents of two main topics (**Table 1**; parts 3.1–3.4).

Rating Criteria of the Mini-AFTERc FOI Measure

The decision to rate adherence as high (2) or moderate (1) was informed by principles positively contributing to therapeutic alliance (Ackerman and Hilsenroth, 2003; **Table 2** and **Supplementary File 1** for full principle definitions). If the SCN displayed personal attributes and used therapist techniques during the intervention (**Table 2**), the SCN should receive a rating indicating high adherence (2); otherwise, they should receive a rating indicating moderate adherence (1). Additionally, if the SCN did not consider the intervention's flexibility, they should receive a rating indicating moderate adherence (1); this includes adhering too strictly to the manual and not considering possible issues that had been shared previously in the interaction by the patient. A rating of 0 should be attributed to a component that is not addressed.

The researcher should rate the duration as 2 if it was within the limits of 25–35 min, 1 if it was between 20–25 and 35–40 min, and 0 if it was below 20 min or above 40 min. These limits were discussed and agreed on by the three researchers involved in this study, as duration is a key component in the design of the intervention. Lastly, no negative points should be given for flexibility; when rating the main topic of the intervention, points

TABLE 1 | Possible adherence scores for each component and total fidelity score calculation.

Part no. and components	No. of sub-components	High adherence (2)	Moderate adherence (1)	Low adherence (0)
Part 1: Introduction	4	8	4	0
Part 2: Assessment of Family	–	2	1	0
Part 2: Assessment of Thoughts and Feelings	–	2	1	0
Part 2: Assessment of Expectation	–	2	1	0
Part 2: Assessment of Return of cancer	–	2	1	0
Part 3: Topic of which specific attention is required				
Part 3.1: Family*	6	6[a]–12[b]	3[a]–6[b]	0
Part 3.2: Thoughts and Feelings*	4	4[a]–8[b]	2[a]–4[b]	0
Part 3.3: Expectations*	6	6[a]–12[b]	3[a]–6[b]	0
Part 3.4: Return of cancer*	4	4[a]–8[b]	2[a]–4[b]	0
Part 4: Conclusion	3	6	3	0
Part 5: Duration	–	2	1	0
Total fidelity score range	–	28[c]–48[d]	14[c]–24[d]	0
Level of fidelity and score range		High 28–48	Moderate 14–27	Low 0–13

**Only rate the topic if discussed in greater detail, i.e., it was the major focus of the intervention.*
[a] *Score if half of the subcomponents were addressed.*
[b] *Score if all subcomponents were addressed.*
[c] *Score if one topic with four subcomponents was discussed in greater detail, of which two subcomponents were discussed.*
[d] *Score if two topics with six subcomponents were discussed in greater detail, of which all subcomponents were discussed.*

TABLE 2 | Principles positively contributing to therapeutic alliance.

Personal attributes	Therapist techniques
• Respectful	• Exploration
• Flexible	• Reflection
• Trustworthy	• Facilitates the expression of affect
• Warm	• Accurate interpretation
• Confident	• Attends to the patient's experience
• Interested	• Supportive
• Honest	• Affirming
• Open	• Understanding
• Friendly	
• Alert	

Adapted from "A review of therapist characteristics and techniques positively impacting the therapeutic alliance" by Ackerman and Hilsenroth (2003). See ***Supplementary File 1*** *for definitions.*

should be given for any subcomponents of the main topic already discussed during the *Assessment* process.

Study Objective 2: Content Validate the Mini-AFTERc FOI Measure Using Thematic Framework Analysis

This FOI measure was tested by qualitatively analyzing the audio-recordings of the intervention discussions using thematic framework analysis (Terry et al., 2017).

Participants

A convenience sample of nine audio-recorded Mini-AFTERc intervention discussions was used to test the FOI measure. Four SCNs (A-D) from two breast cancer centers in National Health Service (NHS) Scotland, five breast cancer patients and one simulated breast cancer patient produced these nine intervention discussions. SCN A and B held the intervention with breast cancer patients 1–5. SCN C and D held the intervention with one simulated breast cancer patient, who acted out four different patient roles, resulting in breast cancer patients 6–9 (**Table 3** and **Figure 3**). The simulated breast cancer patient was a volunteer actor who works regularly with the School of Medicine at the University of St Andrews to facilitate practical and communication training with medical students. They assumed the persona of several FCR case studies, developed by GMH based on previous real clinical cases. Nine participants were chosen as this study sought sufficient complexity in the transcripts of intervention discussions to ensure all aspects of the FOI measure could be tested.

Data Collection

The Mini-AFTERc intervention was delivered through one single telephone conversation between SCNs and NHS breast cancer patients. Additionally, four simulated telephone conversation between SCNs and the simulated breast cancer patient were recorded as part of SCNs training for the Mini-AFTERc pilot trial (McHale et al., 2020). All SCNs and NHS breast cancer patients were consented to participate. The conversations were audio-recorded using Tascam DR-05X, resulting in good

TABLE 3 | Breast cancer patients' eligibility criteria.

Inclusion criteria	Exclusion criteria
Moderate FCR as defined by the FCR4 (Humphris et al., 2018)	Low (< 60th percentile) or high (> 90th percentile) FCR as defined by the FCR7 (Humphris et al., 2018)
Completed primary cancer treatment	Not yet completed their cancer treatment
Cancer-free	Not cancer-free
	Major psychological disorder(s)
	Male

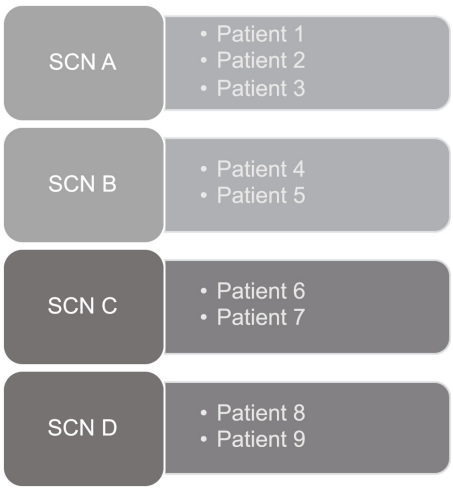

FIGURE 3 | Mini-AFTERc intervention interviews between SCNs and breast cancer patients.

audio quality. Audio-recordings were brought to the School of Medicine, University of St Andrews for storage and analysis. The data from all SCNs were included to ensure the level of fidelity was not due to a specific therapist technique used by one SCN.

Thematic Framework Analysis

Given that clearly defined themes already exist in the Mini-AFTERc intervention (**Figure 1**), a deductive, analyst-driven approach was used. This approach allows existing theoretical concepts to be brought in that provide a basis for "seeing" the data (Braun and Clarke, 2006, 2012). As the intervention's components were discussed explicitly and implicitly, the data was approached semantically and latently (Braun and Clarke, 2006, 2012). All nine audio-recorded intervention discussions were transcribed verbatim (total duration = 254.04 min). The author reviewed the transcripts against the audio-recordings several times to ensure accuracy and correct potential mistakes (Terry et al., 2017). To test the FOI measure, the transcripts were analyzed according to the thematic analysis principles outlined by Braun and Clarke (2006). This process involved familiarization with the data, such as transcribing the audio-recordings, reading and re-reading through the transcripts and taking initial notes. Data coding was completed by highlighting particular sentences or phrases in different colors to represent different codes. Lastly, the different codes were sorted into the relevant, clearly defined sub-themes and themes of the Mini-AFTERc intervention (**Figure 4**).

Ethical Considerations

Ethical approval for this study was granted for the Mini-AFTERc pilot trial by the NHS Research Ethics Committee (18/SS/0135) and the University of St Andrews Teaching and Research Ethics Committee (MD14241). All nurse and patient participants provided written consent to participate. Ethical issues were considered by removing all identifiable information from the transcripts, including patients' names, family's or friends' names, and names of locations, places, or organizations.

Study Objective 3: Testing the Consistency of the Mini-AFTERc FOI Measure Using Interrater Reliability

NGB listened to the audio-recordings available and read verbatim transcripts; two researchers, who are considered experts of the Mini-AFTERc intervention (originator and feasibility investigator: GMH and CTM, respectively) read verbatim transcripts to rate the SCNs' adherence to the intervention manual independently of each other.

Interrater reliability analysis was performed by NGB on nine transcripts using intraclass correlation on IBM SPSS Version 24 on macOS Mojave Version 10.14.1. The intraclass correlation coefficient (ICC) estimates and their 95% confident intervals (CI) were calculated based on mean-rating (k = 3; k is the number of raters), consistency, and a two-way mixed-effects model, for the total fidelity score of each of the nine transcripts. Interpretation was as follows: < 0.50, poor; 0.50–0.75, moderate; 0.75–0.90 good; > 0.90, excellent (Koo and Li, 2016; Perinetti, 2018).

RESULTS

Study Objective 1: Development of the Mini-AFTERc FOI Measure, Including the Design of a Scoring System and Rating Criteria

See **Supplementary File 2** for the full FOI measure. A description of the development process can be found in "Materials and Methods" section of this paper.

Study Objective 2: Content Validating the Mini-AFTERc FOI Measure Using Thematic Framework Analysis

The nine analyzed conversations lasted between 12:42 and 45:20 min (M = 28:18 min, SD = 9.00). The average total fidelity score across all evaluated intervention discussions was 27 (range: 19–34), reflecting moderate adherence to the intervention manual. The qualitative findings indicated that the Mini-AFTERc FOI measure has content validity as it was able to measure all five components of the Mini-AFTERc intervention: Introduction, assessment, main topic(s), conclusion, and duration. Additionally, the subject matter experts, GMH and CTM, judged the contents of the FOI measure to be relevant and representative to those of the Mini-AFTERc intervention. The qualitative findings including examples of, and explanations for, FOI ratings are presented in the following sections.

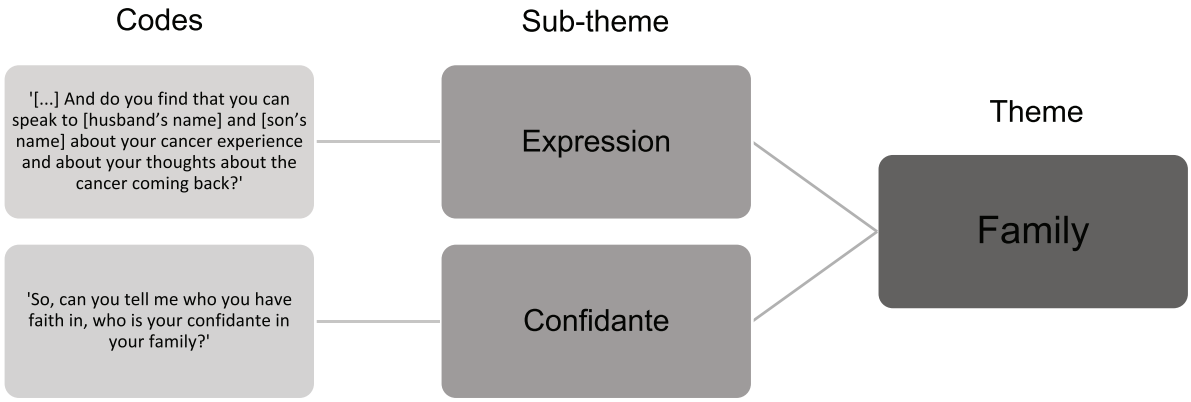

FIGURE 4 | Example of codes sorted into the relevant sub-theme and theme of the Mini-AFTERc intervention.

Introduction (Setting the Scene)

The total fidelity score ranged between 3 and 7 among SCNs out of a possible 8. SCN_D held two interventions and was rated above average, as they exhibited personal attributes such as being warm, friendly, and supportive (**Table 4**). In contrast, SCN_C held two interventions but did not receive a score above average, mostly because they did not address subcomponents b and d in both interventions held, which led to a rating of 0 for both. Additionally, SCN_C received a rating of 1 for subcomponent c, as it was unclear what questions they were referring to, and what the intervention will be about (**Table 4**).

Assessment of Which Topics Require Detailed Discussion

The SCNs' total fidelity score ranged between 4 and 8 out of a possible 8. As SCN_A had technical difficulties with the tape recording, they received an average total fidelity score of 4. All SCNs exhibited personal attributes and used therapist techniques (e.g., reflection; **Table 5**) essential for therapeutic alliance. For example, SCN_C used therapist techniques, such as exploration and facilitating the expression of affect, which reflects their high score (**Table 5, a**). In contrast, SCN_A did not attend to the patient's experience, which reflects their moderate score (**Table 5, c**).

Topic of Which Specific Attention Is Required

Each of the four components that form the main part of the intervention were present in the transcripts. The findings are presented in the following subsections.

Family

Four interventions held by two SCNs covered this component as the main topic of the intervention. The total fidelity score ranged between 5 and 11 out of a possible 12. SCNs used therapist techniques such as exploration and reflection, and had personal attributes, such as being warm, friendly and interested, which reflect their high scores (**Table 6**). For example, SCN_D reflected back the patient's words to explore whether the patient felt the need to be protective of their family members, whilst being open and interested (**Table 6, e**).

TABLE 4 | Fidelity of implementation ratings for the "introduction (setting the scene)".

Subcomponents	Supporting quotes by SCNs	FOI rating	SCN (Patient)
a. Introduction of the SCN to the patient	'Hello [patient name], it's [SCN's name], [SCN's name] one of the breast care nurses at the [place].'	2	C (7)
	'Hello. It's [SCN name].'	1	A (3)
b. The SCN thanks the patient for partaking in this discussion	'Can I first of all thank you very much for agreeing to take part?'	2	A (2)
c. The SCN tells or reminds the patient of the reason for having this discussion and what it will be about	'You filled in a questionnaire about breast cancer coming back and you rated your concerns a little bit higher. That's why we are having a chat about your concerns and hopefully we'll be able to help you answer some of the questions and kind of alleviate some of the concerns you have.'	2	B (4)
	'And um, you had received the, the, the letter about the study they're doing and um, [patient's name] had went through some paper work and some, some questions and felt this would be a good study for you?'	1	C (7)
d. The SCN gives the patient a vague indication of what they can hope to get out of this discussion	'So hopefully you know after today's conversation, hopefully we'll be able to help you, you know, feel as so you can cope with these things a wee bit, so hopefully you'll find some benefit from it.'	2	D (8)
	Not addressed	0	B (5)

TABLE 5 | Fidelity of implementation ratings for the "assessment".

Subcomponents	Supporting quotes by SCNs and patients	FOI rating	SCN (Patient)
a. Family	N: 'And do you find that you can speak to [husband's name] and [son's name] about your cancer experience and about your thoughts about the cancer coming back?'	2	D (8)
	N: 'And did you feel that you were able to talk to [friend's name] about this? Was she, was she quite supportive or did you feel you could not ask her things cause you were being protective about her?'	2	C (6)
b. Thoughts and Feelings	N: 'How about your thoughts and feelings? Do you worry about having any aches or pains? How do you manage it? [. . .] When you have sort of an ache or a pain, which is a bit different, how do you feel? How do you cope with that? How do you react?'	2	B (4)
c. Expectation	N: 'So, do you think because of these fears, are you examining yourself more?'	2	C (7)
	N: 'And hopefully when you have your mammograms and come back to the clinic, you will get that reassurance that everything's ok. When you come to the clinic for a mammogram, how does that make you feel?'	2	B (5)
	N: 'Do you?' P: 'Yes, I do. I have more time to think about it now as I live on my own, I suppose, but [friend's name] seems very good. I don't say much to my family at all. They have a hard time accepting everything. They are a bit worried that the cancer comes back, and I don't say too much to them. My sister is the only one I can [confide in]. My friends are great, but we don't actually talk about it. It's just [friend's name] that talked about it, because unfortunately [friend's name] [. . .] is going through exactly the same thing. [. . .] She is doing the radiotherapy. But hers didn't come back. It was the first time she had [cancer].' N: 'Oh, dear. Just tell me how do you feel when the annual review comes up? When your check-up comes around?'	1	A (1)
d. Return of cancer	N: 'Um, I'm just wondering about you know, if you've, how are things getting, do you feel things are getting back to normal, have you gone back to work at all? [. . .] Have you done anything you know nice like book yourself a wee holiday or anything?	2	D (9)

TABLE 6 | Fidelity of implementation ratings for the main topic "family".

Subcomponents	Supporting quotes by SCNs and patients	FOI rating	SCN (Patient)
a. Information on family	N: 'Can you explain to us who your confidante is, in whom you're going to when you're worried about things?' P: 'Any family member.' N: 'Family? What family members do you have?' P: 'Mother in law, sisters, sisters in law, friends as well.' N: 'And your daughter lives with you?'	2	A (2)
b. Previous experience of cancer	N: 'Just to go back to something you said at the beginning. You said that it was quite difficult because everybody that you knew had breast cancer.' P: 'Right.' N: 'So quite a negative experience [. . .] I think it's actually difficult to see that when you're surrounded by so many people that have had the disease come back.'	2	A (3)
c. Expression	N: 'Oki doke. And do you find that you can speak to [husband's name] and [son's name] about your cancer experience and about your thoughts about the cancer coming back?'	2	D (8)
d. Family supportive or antagonistic	N: 'I'm sure when you worry about things you probably feel that you have to protect her [daughter] a little bit. Have you got somebody that you feel you don't have to protect? A sister or your mum?' P: 'Yeah' N: 'Can you be quite open with them?' P: 'Yes.' N: 'So, it is a safe place to talk to them. And they are quite supportive?'	2	A (2)
e. Protective	N: 'Aha, ok, ok. Um, just going back a wee bit, I appreciate what you were saying about your husband [husband's name] and that's wonderful to hear how supportive he's been um, sometimes and I don't know whether this is how you feel but sometimes patients feel as though they got to put on a good face, and they've got to be positive as do their loved ones and you sometimes feel that you don't want to be a burden to people? Do you feel like that at all?'	2	D (8)
f. Confidante	N: 'So, can you tell me who you have faith in, who is your confidante in your family?' P: 'My husband.' N: 'Your husband! Do you feel that you have to protect him, or can you really go and tell him how you're really feeling?'	2	A (3)

Thoughts and Feelings

Four interventions held by three SCNs covered this component. The total fidelity score ranged between 5 and 8 out of a possible 8. All SCNs had personal attributes, such as being open and flexible, and used therapist techniques such as exploration, attending to the patient's experience and accurate interpretation during their conversation with the patient, which reflect their high scores (**Table 7**).

Expectation

Four interventions held by three SCNs covered this component. The total fidelity score ranged between 4 and 8 out of a

TABLE 7 | Fidelity of Implementation ratings for the main topic "thoughts and feelings".

Subcomponents	Supporting quotes by SCNs and patients	FOI rating	SCN (Patient)
a. Vigilance level	N: 'Are you paying more attention to symptoms or sensations in your body?'	2	C (7)
b. Consequences	N: 'So, when you, you're saying that when you get shoulder pain, sounds like you automatically get into thinking oh my goodness is it the cancer coming back.' P: 'Yes.' N: 'And is the shoulder pain there all the time?' P: 'No, no. Over the last couple of weeks, it's maybe happened maybe five times or something but just kind of, uh, it just kind of I mean it's possibly nothing to do with it at all. I suppose it just being my left, the left side of me uh, it, in kind of my more rational moments I think it's nothing to do with anything, and then when it's there I'm thinking oh my god what's this?'	2	C (6)
c. Anxiety	N: 'M hm, and before all this were you the kind of person that worried about things or is this. . .?'	2	C (7)
d. Coping	N: '[. . .] When you have aches and pains, do you phone the GP, or do you put it into a different perspective?'	2	B (5)
	N: 'M hm, and what do you do when you have these feelings? And these aches and pains? Do you do anything? Do you take any painkillers or try any exercises or?'	2	D (8)

possible 12. SCN_A showed warmth and attended to the patient's experience, which reflects their high score (**Table 8, b**). Similar skills were observed for SCN_C who demonstrated interest, attended to the patient's experience and used exploration as a therapist technique (**Table 8, c**). In contrast, although SCN_A accurately interpreted why the patient is checking themselves in the shower, they may have used exploration to further investigate whether there are any specific triggers to checking, which reflects their moderate score (**Table 8, f**).

Return of Cancer

One SCN discussed this component as the main topic of the intervention, with a total fidelity score of 6 out of 8. As the SCN addressed subcomponent a without attending to the patient's experience, they received a rating of 1; although the patient directed the conversation from *Return of cancer* toward *Family*, the SCN did not attend to the patient's experience of their mother dying from cancer and led the conversation back to the main topic *Return of cancer* (**Table 9**).

Conclusion

The total fidelity score ranged between 1 and 4 among SCNs out of a possible 6. SCN_D received a rating of 2, as they showed interest and used exploration as a therapist technique (**Table 10, c**). In contrast, SCN_C received a rating of 1 as they could have been more open and interested in the patient getting a benefit out of the intervention discussion (**Table 10, c**). Compared to other parts of the intervention, no SCN addressed all three subcomponents of the Conclusion.

Duration

The total fidelity score ranged between 0 and 2 out of a possible 2 among SCNs. SCN_A held the intervention with three patients and received different scores for the duration for each of them: 0, 1, and 2, for 12:42 min, 23:31 min, and 27:33 min, respectively. In contrast, SCN_D held two interventions with a simulated patient and received a score of 2 for both, a duration of 30:10 min and 31:40 min.

TABLE 8 | Fidelity of implementation ratings for the main topic "expectation".

Subcomponents	Supporting quotes by SCNs and patients	FOI rating	SCN (Patient)
a. Annual check-up	N: 'And have you had any further appointments recently? How do you feel before any appointments or any scans?'	2	C (6)
	N: 'And how are you feeling about the thought of not having your, for not having any hospital appointments for a wee while, how does that make you feel?'	2	D (9)
b. Anxiety over annual check-up	N: 'So how do you think you're going to feel then, when your check-up comes around? [. . .] How far away is the check, when you're going to have it?' P: 'I think probably August or September.' N: 'So this is only July, so there's quite a lot of worry before we get there, isn't it?' P: 'Yes. [. . .]'	2	A (2)
c. How do they check	N: 'You're right, you're right. But can I ask when you're, when you say you're checking yourself every day in the shower, is it your breast that you're checking, or your armpits or?'	2	C (6)
d. Checking frequency	N: '[. . .] Do you find yourself checking? Since you found your cancer came back, you're performing self-checking? [. . .] You do that quite often?'	2	A (1)
e. Public or private	Not addressed	N/A	N/A
f. Triggers to checking	N: 'Every second day?' P: 'Yeah. I just check in the shower. It's easier to check and this is how I found the other [lump].' N: 'Doing that every other day doesn't seem unreasonable since you're in the shower and its part of the routine.'	1	A (1)

TABLE 9 | Fidelity of implementation ratings for the main topic "return of cancer".

Subcomponents	Supporting quotes by the SCN and the patient	FOI rating	SCN (Patient)
a. Patient's opinion of recurrence likelihood	N: 'Do you find that this stops you from planning for the future? I mean the diagnosis of cancer stops you from doing anything?' P: 'It's a fear that makes you wonder if it's going to come back. I think a lot of that has to do with my mum dying from cancer quite young, as well. My mum was 50 when she died and I'm thinking I'm 47.' N: 'Well, it's not silly. Did you have the same type of cancer as your mum, or a different cancer?' P: 'She had ovarian cancer.' N: 'Ovarian, ok. But on a scale of 1 to 10 what do you measure your fear as? You know, worrying about coming back?'	1	B (4)
b. Likelihood changing	N: 'So, as you said, you've done everything possible to reduce the risk [. . .] of anything happening and you've taken some reassurance from that.' P: 'I mean it's still.I think it's going to come back when it's going to come back. You do have it at the back of your mind all the time.' N: 'Yeah. I can understand that [. . .]'	1	B (4)
c. Consequences of recurrence	N: 'Have you ever thought what [. . .] you know, what do you think would happen if it [cancer] did come back?'	2	B (4)
d. Future planning	N: 'Do you find that this stops you from planning for the future? I mean the diagnosis of cancer stops you from doing anything?'	2	B (4)

TABLE 10 | Fidelity of implementation ratings for the "conclusion".

Subcomponents	Supporting quotes by SCNs	FOI rating	SCN (Patient)
a. The SCN asks whether there is anything else the patient would like to discuss	'Ok was there anything else that you wanted to talk about just now [. . .]?'	2	D (8)
	Not addressed	0	B (4)
b. The SCN thanks the patient for attending the session	'[. . .] but thank you for, um, agreeing to do this [. . .] thank you [patient name], [. . .]'	2	C (7)
	'Thank you for taking part in that.'	1	B (5)
	Not addressed	0	D (8)
c. The SCN states that they hope the patient got some benefit out of this discussion and that it may have helped them a little	'M hm, and do you feel there's been anything that's been helpful with the conversation?'	2	D (9)
	'[. . .] hope you found it quite helpful.'	1	C (7)
	Not addressed	0	A (2)

Study Objective 3: Testing the Consistency of the Mini-AFTERc FOI Measure Using Interrater Reliability

A moderate to excellent degree of reliability was found among raters, average measure ICC = 0.84, 95% CI [0.51, 0.96]. The full interrater dataset and analysis can be found in **Supplementary File 3**.

DISCUSSION

This study developed and tested an FOI measure, designed specifically for the Mini-AFTERc intervention to assess and categorize adherence to the intervention manual. The findings indicate that, through the processes of development outlined, this FOI measure is a useful and practical tool to comprehensively assess the delivery of the Mini-AFTERc intervention, that it has content validity, and that it is reliable with the sample used in this study.

Mini-AFTERc FOI Measure: Scoring System and Rating Criteria

The 3-point scoring system was found to be useful in practice, as it allowed researchers to employ their discriminative abilities (Jacoby and Matell, 1971) and reduced the possibility of introducing error. Therefore, the reduced rating scheme from nine to three categories can be considered more precise and accurate compared to complex scoring systems with various response categories. Using therapist principles that positively impact on therapeutic alliance (Ackerman and Hilsenroth, 2003) as rating criteria were instructive and facilitated the rating process, allowing a more accurate distinction to be made between high and moderate adherence. Consequently, these categorical definitions for each rating point may increase consistency among prospective raters who are unfamiliar with this FOI measure.

Content Validating the Mini-AFTERc FOI Measure: Qualitative Findings

The qualitative findings indicated that the Mini-AFTERc FOI measure has content validity as it was able to measure

all five components of the Mini-AFTERc intervention: Introduction, assessment, main topic(s), conclusion, and duration. Additionally, the subject matter experts judged the contents of the FOI measure to be relevant and representative to those of the Mini-AFTERc intervention, allowing valid results to be produced. Consequently, the FOI measure's scores may be used to make important and relevant implications, suggestions, and interpretations, and also allow researchers to link the FOI results to the intervention's effectiveness and thus draw accurate conclusions. As mentioned previously, existing FCR intervention studies do not consistently address the development and testing of FOI, which may have implications for how the results of these interventions are reported and interpreted (Lebel et al., 2014; Dodds et al., 2015; Dieng et al., 2016; Butow et al., 2017; van de Wal et al., 2017; Tomei et al., 2018). Although many of these studies do employ fidelity assessment tools, they are often not comprehensively described and/or their development and implementation is not addressed. Therefore, it is unclear whether many of these fidelity tools have content validity and whether their results accurately reflect treatment fidelity. This lack of clarity may result in inaccurate application of the fidelity tools, ambiguity regarding the integrity of the tools, and inaccurate conclusions about the efficacy of the intervention. This paper provides a detailed report of how FOI was conceptualized, developed and tested for the Mini-AFTERc intervention to ensure content validity, which may provide a template for future FCR intervention fidelity assessment tools. We propose that the systematic and evidence-based development of an FOI measure, as well as transparent, detailed and replicable reporting of such measures, should be the norm within FCR intervention research, as it is within many other areas of psychological intervention research. We hope that the work detailed in this paper will have a wider impact in that it will provide a rigorous methodological and analytical template for other researchers seeking to develop bespoke fidelity measures of healthcare communication interventions. Such practices would improve clarity, reduce bias and inform and facilitate improved FOI tool development. Most importantly, robust FOI development and assessment may lead to the refinement of FCR interventions and ensure their effectiveness for clinicians and patients.

Testing the Consistency of the Mini-AFTERc FOI Measure Using Interrater Reliability

The results indicate a moderate to excellent consistency among the three raters, as per the classification from Koo and Li (2016). However, there was noticeable total fidelity score variability among raters, which may be attributable to the rating process. NGB listened to the four audio-recordings available to transcribe the data and rate the intervention discussions. In contrast, GMH and CTM rated the intervention discussions using the transcripts only. Research has reported that transcribing spoken data loses information as emotional responses or concrete events are translated into written language; this results in the loss of the fundamentals of natural speech, such as intonation and stress, which increase insights and understanding beyond the explicit content (Markle et al., 2011). As the rating process involved consideration of the principles of therapeutic alliance to differentiate between moderate and high adherence, GMH and CTM may have had less information on which to base and interpret their ratings and scorings of these principles, as opposed to NGB. This may explain some of the scoring variability.

Strengths, Limitations, and Future Research

A strength of the present study is the unambiguity of the 3-point scoring system. This allows raters to employ their discriminative abilities, increases accuracy and limits the possibility of introducing error (Jacoby and Matell, 1971) as opposed to the 9-point scoring system designed during the initial development of this FOI tool. A further strength is the variety of audio-recordings and transcripts, such that each of the core components of the Mini-AFTERc intervention was present at least once in the intervention discussions used in this study. Consequently, this allowed the FOI assessment of all core components of the intervention. Furthermore, definitions and descriptions of the measure, its scoring system, and rating criteria make the application of the FOI measure more accessible. Finally, the moderate to excellent degree of interrater reliability among the three researchers involved in this study will allow the use of the FOI measure in research or clinical applications (Koo and Li, 2016).

A potential limitation to the application of the interrater reliability finding is that the developer of the FOI measure (NGB) was involved in rating the transcripts and provided instructions and explanations face-to-face to the other two raters. Therefore, future research should establish whether similar levels of interrater reliability can be obtained with the use of written and/or video instructions, that could be distributed to researchers who are unfamiliar with the FOI measure. Furthermore, it is commonly accepted that data should be collected from a broad range of participants to obtain accurate estimates of reliability in research. However, the sample of this study was relatively small due to restricted resources. Nevertheless, this study yielded important qualitative and quantitative findings, and future research should consider replicating the current study with a larger sample of patients, SCNs, and raters.

Implications for Research and Practice

The availability of this unambiguous, content validated, and reliable FOI measure will allow confident application by individuals trained on how to employ this FOI measure. This FOI measure will allow researchers and clinicians to recognize what aspects of the Mini-AFTERc intervention work well or require improvement, and thus what aspects to emphasize in training sessions. To reduce the risk of potential liking bias, prospective researchers assessing the intervention's FOI should be independent and not work directly with the SCNs holding the intervention. Lastly, the approach taken to develop the FOI measure for the Mini-AFTERc intervention may be helpful for other investigators to consider for novel interventions in the FCR field.

CONCLUSION

This study developed and tested a novel FOI measure that considers the flexibility and comprehensiveness of the Mini-AFTERc intervention. The 3-point scoring system allowed raters to employ their discriminative abilities, thus increasing accuracy. The qualitative findings indicated that the FOI measure was able to assess all of the Mini-AFTERc intervention's core components, thus indicating that the FOI measure has content validity. The quantitative findings indicated that the FOI measure has a moderate to excellent degree of reliability with the sample used. Future research should determine whether similar levels of interrater reliability can be obtained by distributing written and/or video instructions to researchers who are unfamiliar with the FOI measure, using a larger sample. Researchers trained on using the Mini-AFTERc FOI measure may use it to understand the translation of evidence-based research of the Mini-AFTERc intervention into clinical practice. The procedures outlined provide an example for other interventionists concerned with implementing FCR management programmes.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because full transcripts of Mini-AFTERc intervention discussions, used to test the FOI measure, are potentially identifiable. The data used to calculate interrater reliability are available. Requests to access the datasets should be directed to CTM, ctm2@st-andrews.ac.uk.

ETHICS STATEMENT

This study involved human participants and was reviewed and approved by the NHS South East Scotland Research Ethics Committee 02 (18/SS/0135) and the University of St Andrews Teaching and Research Ethics Committee (MD14241). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NGB developed the FOI measure, conducted all transcription and data analysis, and drafted the manuscript. CTM and GMH collected the audio recordings. All authors contributed to the interrater reliability scoring and edited and agreed the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.601813/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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The Generalization of Conscious Attentional Avoidance in Response to Threat Among Breast Cancer Women With Persistent Distress

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Objectives: A sample of women with persistent distress following breast cancer (BC) previously exhibited attentional bias (AB) away from supraliminally presented cancer-or threat-related information, responses consistent with avoidance coping, and showed negative interpretation bias. Here, we attempt to characterize the nature of supraliminal AB and interpretation bias in that sample of women by comparing against healthy controls.

Methods: Extending our previous work, we compared AB patterns for supraliminally presented negatively valenced words and cancer-related information (CRI) assessed by modified dot-probe tasks and negative interpretation bias assessed by an ambiguous cue task between 140 BC women previously identified as featuring low-stable or persistent high anxiety and 150 age-matched non-BC healthy controls having HADS-defined low or high anxiety (HADS-anxiety scores = 8).

Results: Attentional avoidance of non-cancer-related negatively valenced words was seen among the anxious BC group, while heightened attention toward such words was seen in anxious healthy controls, $F(3, 282) = 3.97$, $p = 0.009$. However, all anxious women in both BC and healthy groups directed attention away from CRI under supraliminal conditions. Interpretation bias scores were significantly higher in BC women with high anxiety vs. healthy controls with high anxiety, $F(3, 282) = 13.26$, $p < 0.001$.

Conclusion: Women with high anxiety generalized conscious attentional avoidance responses to negatively valenced stimuli, indicating a likely hypersensitivity to potential threat in ambiguous cues and exaggerated threat perception. This may cause (or reflect) maladaptive emotional regulation. Attention focus training, reducing threat salience or modifying threat appraisal, may help women alleviate anxiety levels after BC.

Keywords: psycho-oncology, attentional bias, interpretation bias, psychological distress, breast cancer

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INTRODUCTION

Though many women with breast cancer (BC) experience stable low or transient distress, a subset, ∼10–20%, remain distressed > 5 years after diagnosis, detrimentally impacting their quality of life (Helgeson et al., 2004; Burgess et al., 2005; Henselmans et al., 2010; Lam et al., 2010, 2012). Understanding individual differences in psychological adjustment to BC helps enable accurate identification of those at high risk of persistent distress and informs better therapeutic approaches (Lam et al., 2018).

Cognitive theories of emotional disorders claim that biased attentional and interpretation processing of threat-relevant information underpins enhanced vulnerability toward developing symptoms of anxiety and/or depression by modifying information salience, which may involve an interplay between early, automatic (preconscious) and later, strategic (conscious) stages of processing (Mathews and MacLeod, 2005; Bar-Haim et al., 2007). Prior findings in emotional disorders using experimental paradigms including dot-probe tasks better capture the time-course effect of attentional bias (AB) by manipulating stimuli exposure duration. Such studies reported that individuals with anxiety often displayed facilitated preconscious (automatic) attentional allocation (bias) toward threat-related stimuli under initial subliminal exposure, which was either maintained or reallocated away from such stimuli, depending on the emotional condition, under prolonged supraliminal exposures reflecting conscious control; in depression, AB toward threat-related stimuli appeared to be confined to only supraliminal exposures, indicative of inability to disengage among depressed individuals (Mathews and MacLeod, 2005; Bar-Haim et al., 2007; Cisler and Koster, 2010).

Few studies have adopted dot-probe tasks to identify the distinct temporal nature of AB in psychological distress among cancer survivors. In the only study found on subliminal AB, subliminal bias was uncorrelated with distress among BC survivors (Glinder et al., 2007). The findings from four available studies on supraliminal AB were inconclusive, with one reporting AB away from cancer-related word stimuli (Glinder et al., 2007) among those with higher distress, one reporting no significant association of supraliminal AB with fear of cancer recurrence (Butow et al., 2015), and the others reporting that cancer patients exhibiting significant supraliminal AB toward negatively valenced facial expression experienced higher anxiety (Koizumi et al., 2018) or greater symptoms of posttraumatic stress disorder (PTSD) (Chan et al., 2013). However, due to the use of cross-sectional study design, none have examined AB in distress with reliable distress chronicity assessment.

Our previous AB study (Lam et al., 2018) sampled eligible Chinese women with BC from an ongoing longitudinal study of psychological distress trajectories following BC diagnosis. We found that women with persistent distress exhibited a bias away from supraliminally presented (1,250 ms) negatively valenced or cancer-related stimuli (avoidance) in a neutral prime condition; women with low-stable/transient distress showed a bias toward the stimuli (vigilance) (Lam et al., 2018). Such supraliminal attentional response shared the distinctive patterns of attentional avoidant expression reported in a PTSD sample (Bar-Haim et al., 2010). Intentional threat-information avoidance could impede adaptive engagement coping to manage threat, thereby enhancing psychological distress (Glinder et al., 2007; Lam et al., 2018). However, the absence of a non-BC control rendered the specificity of our findings in BC patients unclear and so warrants further investigation.

To test the specificity of these results to cancer threat, we compared patterns of AB expression in response to supraliminally exposed negatively valenced stimuli among women recovering from BC who reported persistently high anxiety and healthy women reporting high anxiety. Considering cognitive theories of emotional disorders and the findings from our previous study, we hypothesized that both groups of anxious women would exhibit conscious attentional avoidance of supraliminally presented negatively valenced stimuli (hypothesis 1). However, the personal relevance hypothesis posits that AB may be thematically specific (MacLeod and Rutherford, 1992; Pergamin-Hight et al., 2015). We therefore tested for differences in the patterns of AB for supraliminally presented cancer-related information (CRI) between both groups of anxious women, hypothesizing that the BC group would display greater consciously averted AB under this condition (hypothesis 2). In addition, schema theories of emotional disorders propose that the priming effect of AB acts via schema-driven processing (Beck, 1979; Beck and Clark, 1997). Assuming a more elaborated cancer-specific schemas in the BC sample due to their cancer experience that could be accessed and activated easily reinforcing CRI processing, we hypothesized that the BC group would display greater consciously averted AB under cancer-related prime compared with the non-BC control (hypothesis 3).

Negative interpretation bias for ambiguous information is also common in emotional disorders (Mathews and MacLeod, 2005), individuals with chronic pain (Edwards and Pearce, 1994; Pincus et al., 1996) and with chronic fatigue syndrome (Moss-Morris and Petrie, 2003). Similarly, a significant positive correlation between negative interpretation bias and anxiety was observed in our earlier study; following BC, women with persistent anxiety tended to disambiguate information in a negative, cancer-related manner, relative to their low-stable anxiety peers (Lam et al., 2018). To clarify interpretation bias in anxious BC survivors, we compared differences in negative interpretation bias between BC and healthy women with high anxiety, hypothesizing that following BC, women with high anxiety relative to their healthy counterparts would be predisposed to cancer-related interpretations of ambiguous information (hypothesis 4).

MATERIALS AND METHODS

Participants and Design

Ethical approval of this study was obtained from participating institutions (Ref: UW14-136).

A total of 140 Cantonese-speaking Chinese women previously diagnosed with and treated for non-metastatic BC {67 with persistent distress and 73 with low-stable distress [based on the

Mixture Growth Modeling (MGM) classification using the 14-item Hospital Anxiety and Depression Scale (HADS)] (Snaith and Zigmond, 1986; Leung et al., 1999)} were recruited for the original AB study (Lam et al., 2018) from an earlier ongoing longitudinal study. Of the 67 subjects demonstrating persistent distress in the ongoing longitudinal study, only 31 (46.3%) continued to report high HADS-anxiety scores (HADS-anxiety scores $\geq$ 8) on recruitment into the original AB study (Lam et al., 2018). These women also formed the BC sample for the present study. Details of the BC sample recruitment and the MGM characterization of distress trajectories are described in Lam et al. (2018).

To clarify whether the observed conscious attentional avoidance of supraliminally presented threat-related information in the original AB study defined a pattern of AB specific to persistent high anxious BC survivors (Lam et al., 2018), the current study used the data previously presented in Lam et al. (2018) and additionally included a comparison group of 150 age-matched healthy women without history of cancer or mental health problems recruited from the University of Hong Kong via bulk emailed advertisement. Potential participants were contacted by phone with a detailed explanation of the study. Using a HADS-anxiety cutoff score of $\geq$ 8 to classify high vs. low anxiety levels (Snaith and Zigmond, 1986; Leung et al., 1999), 17 (11.3%) healthy controls reported high anxiety, whereas 133 (88.7%) reported low anxiety.

Subsequent analyses compared four anxiety groups: breast cancer sample—anxious BC (N = 31) or non-anxious BC (N = 109), and healthy controls—anxious HC (N = 17) or non-anxious HC (N = 133).

Measures

Psychological Distress

The Chinese version of HADS (Snaith and Zigmond, 1986; Leung et al., 1999), including two 7-item subscales, was employed to assess anxiety and depression, respectively. Each item is rated on a four-point Likert-type scale, with higher scores indicating greater psychological distress. The HADS cutoff score of 8 was used to indicate high anxiety. Good internal consistency of each subscale was reported (anxiety, Cronbach's α = 0.89; depression, Cronbach's α = 0.85).

Attentional Bias Paradigm

Attentional bias for negatively valenced stimuli and CRI was measured by two modified dot-probe tasks (MacLeod et al., 1986) using visually presented word stimuli. The paradigm was presented on a 15.6 inch laptop using E-Prime, positioned approximately 50 cm away from the participants. The assessment was conducted in a quiet private room with minimum distraction. The dot-probe task demonstrated poor internal consistency with Cronbach's α ranging between -0.42 and 0.26, suggesting high variability in response to the individual trials of the task.

Negatively Valenced Stimuli

A word list comprised of 64 neutral (e.g., "Height"), 32 negative (e.g., "Suicide"), and 32 positive (e.g., "Happiness") two-character Chinese compound words chosen from validated word-sets based on their valence and arousal ratings (Bleiker et al., 2000; Lee et al., 2008; Leung et al., 2009) was used in this dot-probe task (see **Supplementary Materials**).

Every trial began with a fixation for 500 ms, followed by a priming condition involving a subliminal presentation (20 ms) of a two-character Chinese compound word either "breast cancer" (target prime) or "sky" (neutral prime) (Bullock and Bonanno, 2013; Lam et al., 2018) to examine the content-specific nature of AB. Following a 500 ms pattern mask, a word pair, one negatively/positively valenced and one neutral, was presented horizontally for 1,250 ms (to assess later supraliminal, strategic attentional processing) (Mogg et al., 2004; Lam et al., 2018). A probe stimulus (dot) appeared in the location of one of the paired words immediately after the offset of each word pair. Response latency for probe detection was recorded.

Faster reaction times to probes replacing negatively valenced words (congruent events) vs. neutral words (incongruent events) indicate AB toward negatively valenced stimuli (Mogg et al., 2004; Lam et al., 2018). AB scores were calculated using the following formula (Butow et al., 2015):

$$Bias\ index = \frac{[(trpl - tlpl) + (tlpr - trpr)]}{2}$$

where t = target word, p = probe location, r = right side, and l = left side. A positive bias score represents an AB toward the target stimuli, whereas a negative bias score represents an AB away from the target stimuli. Recorded reaction times from trials with errors and outliers of < 200 or > 3,000 ms, or more than 3 SD above each participants' mean reaction time, were discarded from analysis (Bradley et al., 1997; Lam et al., 2018).

Cancer-Related Information

A similar modified dot-probe task with cancer-related words (e.g., "Cancer treatment") replacing negative valenced words as target stimuli was used (Lam et al., 2018). In this second dot-probe task, 32 cancer-related two-character Chinese compound words that have been pilot-tested on BC patients and healthy women were used, and the priming condition was excluded since CRI was used as the target threat stimuli (see **Supplementary Materials**). In all other matters, the settings were the same as described above.

Ambiguous Cue Task

Interpretation bias for CRI was measured by an ambiguous cues task (Pincus et al., 1996; Moss-Morris and Petrie, 2003; Lam et al., 2018). The critical stimuli were 25 ambiguous and 25 unambiguous Chinese words (see **Supplementary Materials**). Each ambiguous word represents a pair of homophones, words that while sounding the same can have neutral or cancer-related meanings (e.g., 岩 "rock" is phonetically similar to "cancer" in Chinese). All words were presented aurally in a random order. Participants were instructed to write down the first Chinese compound word they associated the cue with after the presentation of each word. Written responses were coded by two independent raters who were blinded to the participants' anxiety status. One point was given for every cancer-related negative

interpretation. Higher total scores suggest greater negative interpretation tendency for ambiguous cues. The two coders reached 100% agreement on scoring.

Procedure

After obtaining fully informed consent, participating women completed the ambiguous cue task, two dot-probe tasks, and a set of questionnaires in that order.

Data Analysis

To compare the patterns of supraliminal AB expression for threat-related information between BC and healthy control groups, a mixed repeated measures analysis of variance was conducted with the anxiety group as the between-subjects variable (anxious BC vs. non-anxious BC vs. anxious healthy controls vs. non-anxious healthy controls) and prime condition (target vs. neutral prime) and target word (positively vs. negatively valenced) as within-subjects variables. Univariate analysis of variance was conducted to compare group differences in interpretation bias scores.

RESULTS

Sample Characteristics

Sociodemographics, except occupation ($\chi^2 = 22.38$, $p < 0.001$), did not significantly differentiate between women with BC and healthy controls. Women with BC were less likely to be retired or more likely to be unemployed than were healthy controls. Women with BC averaged 4.75 years since cancer diagnosis. Overall mean levels of anxiety ($p = 0.004$) and depression ($p = 0.002$) were higher in the BC group than in healthy controls (**Table 1**). **Table 2** presents the demographic and psychological characteristics of BC and healthy control anxiety subgroups.

Attentional Bias for Negatively Valenced Stimuli

Since occupational status differed by group, this was included as a covariate in subsequent analyses.

Repeated measures analysis of variance showed a significant main effect for groups, $F(3, 282) = 3.06$, $p = 0.029$, $\eta^2 = 0.032$, and for target words, $F(1, 282) = 4.38$, $p = 0.037$, $\eta^2 = 0.015$, and a significant three-way interaction of anxiety group × prime condition × target word, $F(3, 282) = 2.74$, $p = 0.044$, $\eta^2 = 0.028$. *Post hoc* tests showed that there was no difference in AB in response to negatively valenced words vs. positively valenced words, and anxious BC subjects showed a significant bias away [mean = −22.98, *SD* 49.03, $F(3, 282) = 3.97$, $p = 0.009$] from supraliminally presented negatively valenced stimuli only under neutral prime, whereas anxious HC subjects had a bias toward such stimuli (mean = 42.16, *SD* 105.20; **Figure 1**).

Attentional Bias for Cancer-Related Information

The observed marginal main effect for groups did not attain significance, $F(3, 281) = 2.54$, $p = 0.056$, but there was a significant main effect for target word, $F(1, 281) = 5.39$, $p = 0.021$, $\eta^2 = 0.019$, and a significant two-way interaction between anxiety group × target word, $F(3, 281) = 4.11$, $p = 0.007$, $\eta^2 = 0.042$. *Post hoc* tests indicated that, again, AB did not differ in response to cancer-related words vs. positively valenced words, and both anxious BC and anxious HC women showed AB away from supraliminally presented CRI (mean = −17.84, *SD* 52.81, for anxious BC vs. mean = −18.75, *SD* 29.89, for anxious HC, $p > 0.05$; **Figure 1**).

Interpretation Bias

Univariate analysis of variance showed a significant main effect for cancer status, $F(1, 282) = 29.69$, $p < 0.001$, and a significant two-way interaction between cancer status and anxiety status, $F(1, 282) = 4.24$, $p = 0.040$. *Post hoc* testing showed a significant difference for interpretation bias scores in anxiety groups, $F(3, 282) = 13.26$, $p < 0.001$, on stimulus ambiguity. Anxious BC group members obtained significantly higher negative interpretation bias scores (mean = 7.19, *SD* 3.20, $p < 0.001$) than did anxious HC group members (mean = 4.22, *SD* 1.89). These scores were also higher for non-anxious BC group members (mean = 6.02, *SD* 2.38, $p < 0.001$) vs. non-anxious HC members (mean = 4.60, *SD* 2.16).

DISCUSSION

This study compared supraliminal AB expression among cancer patients and healthy controls classified by distress status, in response to cancer-specific and ambiguous threat-related information, providing several new insights. First, women with BC in general reported higher HADS-anxiety scores than did healthy controls, consistent with the meta-analysis study of Mitchell et al. (2013) suggesting that long-term cancer survivors are at increased risk of anxiety compared with healthy controls.

A comparable pattern of supraliminal AB for CRI was seen in both high anxiety groups, contradicting the hypothesized thematic specificity in AB (MacLeod and Rutherford, 1992; Custers et al., 2015; Pergamin-Hight et al., 2015). Women in both high anxiety groups exhibited conscious attentional avoidance of CRI, potentially reflecting a common self-protective coping response to stimuli with high threat value. Cancer, a life-threatening disease, is often encoded in cancer schemas as a "killer" on the basis of second-hand stories, observations, and even personal life experience. The activation of pre-existing cancer schemata by relevant information might automatically present high threat warnings especially in emotionally vulnerable individuals (Beck and Clark, 1997; Clark and Beck, 1999). Schema activation involves parallel cognition and emotional processing. Primary appraisal of cancer threat as lethal and minimally controllable likely evokes aversive emotions like fear. Under such circumstances, instrumental coping attempts may be seen as ineffective, and reliance on emotion-focused coping may ensue (Folkman, 2013). One strategy is to avoid stimuli that trigger the fear response by conscious reallocation of attention away from threatening stimuli. Motivated disengagement coping responses such as avoidance to downregulate unwanted emotions

TABLE 1 | Demographic and psychological characteristics of breast cancer survivors and healthy controls.

	Overall sample (*n* = 290)	Healthy controls (*n* = 150)	BC survivors (*n* = 140)	χ^2/t	*p*-value
Demographic characteristics					
Age (years), mean ± *SD*	55.58 ± 8.21	55.35 ± 8.32	55.81 ± 8.10	0.48	0.633
Marital status, *n* (%)				0.056	0.814
Single/divorced/separated/widowed	91 (31.4%)	48 (32.0%)	43 (30.7%)		
Married/cohabiting	199 (68.6%)	102 (68.0%)	97 (69.3%)		
Education level				2.43	0.119
No formal/primary tertiary	44 (15.2%)	18 (12.0%)	26 (18.6%)		
Secondary/tertiary	246 (84.8%)	132 (88.0%)	114 (81.4%)		
Occupation status				22.34	<0.001**
Employed (full-time/part-time)	157 (54.1%)	79 (52.7%)	78 (55.7%)		
Retired	58 (20.0%)	38 (25.3%)	20 (14.3%)		
Housewife	55 (19.0%)	31 (20.7%)	24 (17.1%)		
Unemployed	19 (6.6%)	1 (0.7%)	18 (12.9%)		
Others	1 (0.3%)	1 (0.7%)	0 (0%)		
Clinical characteristics					
Time since diagnosis (years) ± *SD*	–	–	4.75 ± 1.33		
Currently receiving any cancer treatments	–	–	83 (59.3%)		
Currently receiving hormonal therapy	–	–	79 (56.4%)		
Currently receiving target therapy	–	–	2 (1.4%)		
Currently receiving chemotherapy	–	–	2 (1.4%)		
Currently receiving radiotherapy	–	–	0 (0%)		
No active treatment	–	–	57 (40.7%)		
Cancer recurrence	–	–	6 (4.3%)		
Psychological distress					
HADS-anxiety, mean ± *SD*		3.77 ± 3.50	5.14 ± 4.43	2.91	0.004*
HADS-depression, mean ± *SD*		3.09 ± 3.20	4.43 ± 3.86	3.20	0.002*

*BC, breast cancer; SD, standard deviation. *p < 0.05; **p < 0.001.*

TABLE 2 | Demographic and psychological characteristics of breast cancer and healthy control subgroups.

	Anxious BC (*n* = 31)	Anxious HC (*n* = 17)	Non-anxious BC (*n* = 109)	Non-anxious HC (*n* = 133)
Demographic characteristics				
Age (years), mean ± *SD*	52.90 ± 7.29	56.18 ± 6.82	56.64 ± 8.16	55.25 ± 8.51
Marital status, *n* (%)				
Single/divorced/separated/widowed	11 (35.5%)	7 (41.2%)	32 (29.4%)	41 (30.8%)
Married/cohabiting	20 (64.5%)	10 (58.8%)	77 (70.6%)	92 (69.2%)
Education level				
No formal/primary tertiary	4 (12.9%)	3 (17.6%)	22 (20.2%)	15 (11.3%)
Secondary/tertiary	27 (87.1%)	14 (82.4%)	87 (79.8)	118 (88.7%)
Occupation status				
Employed (full-time/part-time)	16 (51.6%)	9 (52.9%)	62 (56.9%)	70 (52.6%)
Retired	0 (0%)	3 (17.6%)	20 (18.3%)	35 (26.3%)
Housewife	5 (16.1%)	5 (29.4%)	19 (17.4%)	26 (19.5%)
Unemployed	10 (32.3%)	0 (0%)	8 (7.3%)	1 (0.8%)
Others	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)
Psychological distress				
HADS-anxiety, mean ± *SD*	11.48 ± 3.06	11.41 ± 2.83	3.34 ± 2.80	2.80 ± 2.09
HADS-depression, mean ± *SD*	9.03 ± 3.32	8.29 ± 2.87	3.12 ± 2.92	2.42 ± 2.57

BC, breast cancer; HC, healthy controls; SD, standard deviation.

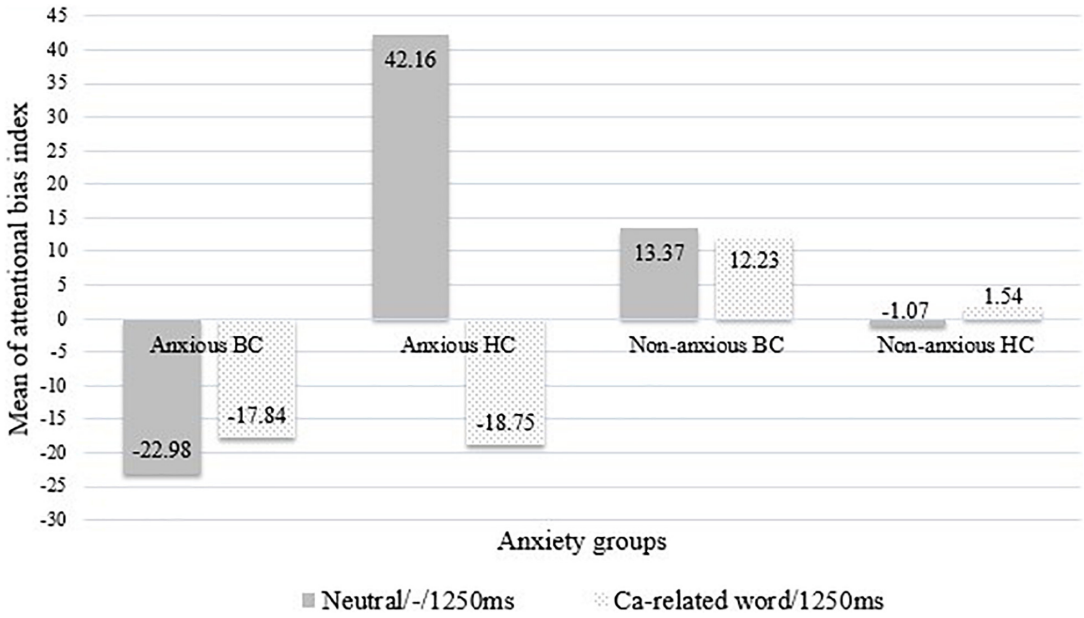

FIGURE 1 | The patterns of supraliminal attentional bias for negatively valenced or cancer-related words among anxiety groups. BC, breast cancer; HC, healthy controls. Neutral/-/1,250 ms: using supraliminally presented negatively valenced words under neutral prime in the dot-probe task. Ca-related word/1,250 ms: using supraliminally presented cancer-related words in the dot-probe task. A positive bias score represents an attentional vigilance, whereas a negative bias score represents an attentional avoidance.

(Lazarus and Folkman, 1984; Stapinski et al., 2010) might interfere with threat habituation, thereby contributing to prolonged psychological distress (Glinder et al., 2007; Mogg and Bradley, 2016; Lam et al., 2018). Substantial evidence has demonstrated the association between disengagement coping and emotional dysfunction in both cancer (Lam et al., 2012; Brandão et al., 2017; Morris et al., 2018) and non-cancer populations (Aldao et al., 2010).

Another coping approach (or perhaps later stage) is to increase threat monitoring in an attempt to reduce uncertainty and hence threat imminence, manifesting as heightened health anxiety, which features enhanced distress. Interestingly, our findings identified a generalized pattern of supraliminal AB expression responding to general negatively valenced stimuli among women diagnosed with BC with high anxiety, in comparison with healthy controls with high anxiety. Women diagnosed with BC experiencing persistently high anxiety, again, exhibited conscious attentional avoidance of negatively valenced stimuli. Conversely, healthy controls with high anxiety showed conscious attentional vigilance toward the stimuli. Theoretically, exposure to a stressful life event (e.g., cancer diagnosis) might entrain (or reinforce pre-existing) dysfunctional schemas which embody enhanced anticipation of harm or perception of loss on next encounter, further reducing the activation threshold of threat-alert signaling in emotionally vulnerable cancer patients (Lazarus and Folkman, 1984; Beck and Clark, 1997; Clark and Beck, 1999). Threat stimuli may become overgeneralized and increasingly ambiguous. As such, affected women diagnosed with BC with high anxiety relative to anxious healthy controls might become disproportionately sensitive to negatively valenced stimuli that shared only vague similarities with CRI and overestimate threat or danger arising therefrom, prompting a generalization of maladaptive conscious attentional avoidance in response to general threatening information. Comparable but non-significant patterns were also seen in both groups with high depression (a considerable overlap exists between the anxious and depressed groups). However, the observed patterns may represent comorbid anxiety (Mathews and MacLeod, 2005), which was not examined here.

Despite no observed significant difference in the mean AB score reflecting patterns of supraliminal AB for CRI or negatively valenced stimuli between both non-anxious groups (**Table 3**), non-anxious healthy controls had near-zero scores, indicative of no significant bias (Mogg et al., 2004), whereas non-anxious women in the BC group showed relatively higher positive scores representing a tendency to direct attention toward threatening information. Modified attentional focus in non-anxious women with BC (but not in non-anxious healthy controls) provided indirect support for the notion that cancer experience may lower sensitivity threshold toward potential threat. However, unlike anxious women with BC, it is likely that non-anxious BC women felt able to effectively cope with appraised threat, hence effortfully directing action to actively manage the threat itself rather than the emotion evoked by it (Folkman, 2013). The use of adaptive engagement coping as reflected in conscious attentional vigilance may facilitate disconfirmatory information processing and so modify (or reflect less) pre-existing dysfunctional schemata, resulting in psychological adaption (Wells, 2013).

Our findings also suggested that as expected, women with BC experiencing high or low anxiety relative to their healthy

TABLE 3 | Mean supraliminal attentional bias scores of the dot-probe task.

	Overall sample (*n* = 290)	Anxious BC (*n* = 31)	Anxious HC (*n* = 17)	Non-anxious BC (*n* = 109)	Non-anxious HC (*n* = 133)
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Supraliminal attentional bias using negatively valenced stimuli					
Stimulus (+ or −)/prime (BC or neutral)					
+/BC	0.42 (63.28)	−0.35 (57.48)	24.91 (84.37)	8.70 (45.19)	−9.30 (72.47)
+/Neutral	−1.87 (57.36)	7.19 (47.39)	−9.44 (81.66)	−1.28 (55.64)	−3.50 (57.63)
−/BC	8.20 (68.80)	7.15 (69.38)	28.55 (56.49)	2.96 (52.72)	10.14 (80.80)
−/Neutral*	4.55 (69.92)	−22.98 (49.03)	42.16 (105.20)	13.37 (59.48)	−1.07 (73.93)
Supraliminal attentional bias using cancer-related information					
Stimulus (Ca-related words or non−ca words)					
Ca-related words*	2.30 (43.63)	−17.84 (52.81)	−18.75 (29.89)	12.23 (43.39)	1.54 (40.62)
Non−ca words	−0.30 (48.28)	7.34 (56.58)	15.34 (68.89)	2.71 (31.66)	−6.60 (53.78)

*+ positively valenced stimuli; − negatively valenced stimuli. BC, breast cancer; Ca-related words, cancer-related words; Non-ca words, non-cancer words. *p < 0.05.*

control counterparts had a greater tendency to overinterpret ambiguous information negatively. As discussed earlier, cancer experience may elaborate pre-existing cancer schemata among cancer survivors, which in turn enhanced the retrieval of CRI during interpretation processing (Beck and Clark, 1997; Clark and Beck, 1999). Such predisposition to negative, cancer-related interpretation in cancer survivors may further reinforce the activated dysfunctional schema by negative thoughts and images, causing and perpetuating anxiety (Beck, 1979). This also provided another possible explanation for the significant difference in anxiety between cancer survivors and healthy controls. However, interpretation bias did not differ between groups with high depression, probably due to the fact that negative interpretation bias was a common feature of depressed individuals (Everaert et al., 2017).

Study Limitations

Several methodological limitations of this study merit comment. First, the BC sample was formed as a secondary analysis of our previous study (Lam et al., 2018). Second, with an average onset duration 4.75 years since diagnosis in the BC sample, distress levels may have varied over time. However, changes in attentional biases over time were less likely due to their stable, trait-like characteristics (Beck and Clark, 1997). Third, due to a single timepoint distress assessment in the healthy control sample, data were unavailable on duration of anxiety in the control group. We were only able to make a cross-sectional comparison of distress levels with the BC sample. Fourth, the small numbers of participants in high anxiety groups potentially weaken statistical power to detect smaller between-group differences (Lam et al., 2018). Fifth, the dot-probe task has been criticized as unreliable (Schmukle, 2005; Dear et al., 2011; McNally, 2018), yet the issue of reliability might be canceled out in studies comparing different samples (Schmukle, 2005). More importantly, this indirect reaction time-based method is insensitive for capturing visual temporal attention patterns (Möbius et al., 2018). The use of more direct and precise AB measurements, such as eye-tracking, should be used in future studies. Nevertheless, given its previously wide use as an AB assessment research, the use of the dot-probe task in this study enables cross-studies comparison within the narrower psycho-oncology literature (Butow et al., 2015). Sixth, the word stimuli used in the dot-probe task were not matched for the Chinese character frequency. Lastly, the reported findings are not generalizable to male or other cancer populations.

Clinical Implication

As an extension of the original study, a generalization of conscious attentional avoidance response to general threat stimuli was identified as a distinctive feature of anxious women with BC. Hypersensitivity to potential threat in ambiguous cues due to elaborated dysfunctional schema potentially predisposed this subset of affected women to utilize avoidance coping strategies, which can impair emotional regulation in a long-term. Future studies and interventions could provide AB modification through promoting active goal-oriented attention search (Mogg and Bradley, 2016; Lam et al., 2018) to focus individuals' attentional resources on the threat itself for threat habituation, or challenge pre-existing dysfunctional schema through information disconfirmatory processes to reduce threat salience, or modify threat appraisal through enhancing cancer patients' coping self-efficacy, all of which perhaps promote the use of active coping approach for better distress management. For example, provision of self-management support (SMS), which has been recently listed as a priority area for action in cancer care, including interventions to boost patients' self-efficacy and improve coping capacity, perhaps enables them in effective self-management and optimizes health outcomes (Howell et al., 2020). However, in practice, it remains challenging to ensure healthcare professionals actually offer such support. Along with already heavy workloads, a focus on biomedical aspects of disease and low confidence in discussing psychosocial aspects, little of which is included in training programs and even less in practice, with rare exceptions, means psychosocial support is often absent or minimal. A care model partnering with non-governmental organizations to provide staff coaching, and skills-based SMS workshops to cancer patient, with professional organizations

emphasizing benefits from psychosocial interventions could help to facilitate implementation in clinical populations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Ref: UW14-136). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DN completed the data collection, performed the statistical data analysis, and drafted the initial version of the manuscript. WL and RF oversaw this research study, contributed to manuscript revision, and approved the final submitted version. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Cause or Effect? The Role of Prognostic Uncertainty in the Fear of Cancer Recurrence

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Background: Fear of cancer recurrence (FCR) is an important cause of suffering for cancer survivors, and both empirical evidence and theoretical models suggest that prognostic uncertainty plays a causal role in its development. However, the relationship between prognostic uncertainty and FCR is incompletely understood.

Objective: To explore the relationship between prognostic uncertainty and FCR among patients with ovarian cancer (OC).

Design: A qualitative study was conducted utilizing individual in-depth interviews with a convenience sample of patients with epithelial ovarian cancer who had completed first-line treatment with surgery and/or chemotherapy. Semi-structured interviews explored participants' (1) understanding of their prognosis; (2) experiences, preferences, and attitudes regarding prognostic information; and (3) strategies for coping with prognostic uncertainty. Inductive qualitative analysis and line-by-line software-assisted coding of interview transcripts was conducted to identify key themes and generate theoretical insights on the relationship between prognostic uncertainty and FCR.

Results: The study sample consisted of 21 participants, nearly all of whom reported experiencing significant FCR, which they traced to an awareness of the possibility of a bad outcome. Some participants valued and pursued prognostic information as a means of coping with this awareness, suggesting that prognostic uncertainty causes FCR. However, most participants acknowledged fundamental limits to both the certainty and value of prognostic information, and engaged in various strategies aimed not at reducing but constructing and maintaining prognostic uncertainty as a means of sustaining hope in the possibility of a good outcome. Participants' comments suggested that prognostic uncertainty, fear, and hope are connected by complex, bi-directional causal pathways mediated by processes that allow patients to cope with, construct, and maintain their uncertainty. A provisional dual-process theoretical model was developed to capture these pathways.

Conclusion: Among patients with OC, prognostic uncertainty is both a cause and an effect of FCR—a fear-inducing stimulus and a hope-sustaining response constructed

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and maintained through various strategies. More work is needed to elucidate the relationships between prognostic uncertainty, fear, and hope, to validate and refine our theoretical model, and to develop interventions to help patients with OC and other serious illnesses to achieve an optimal balance between these states.

Keywords: uncertainty, fear of cancer recurrence (FCR), qualitative study, theoretical model, prognosis, ovarian cancer

INTRODUCTION

Fear of cancer recurrence (FCR) is an important cause of suffering for cancer survivors and a topic of intense interest for clinicians and researchers. Broadly defined as "fear, worry, or concern relating to the possibility that cancer will come back or progress" (Lebel et al., 2016), FCR has been measured in different ways and found to be associated with various negative outcomes including psychological distress, diminished quality of life, and higher health care utilization (Lebel et al., 2013; Champagne et al., 2018; Mutsaers et al., 2020). Several theoretical models have been developed to explain the causes and effects of FCR, and the strategies patients use to cope with it (Lee-Jones et al., 1997; Fardell et al., 2016; Simonelli et al., 2016; Curran et al., 2017; Lebel et al., 2018). These models emphasize different factors and processes, but share a common view of prognostic uncertainty as a primary cause of FCR (Crist and Grunfeld, 2013; Simard et al., 2013; Hall et al., 2018; Tauber et al., 2019). Referencing Mishel's influential Uncertainty in Illness Theory, several models construe uncertainty as a deficit state—specifically, an "inability to determine the meaning of illness-related events" (Mishel, 1988)—that provokes FCR both directly and indirectly (Fardell et al., 2016; Simonelli et al., 2016; Curran et al., 2017; Lebel et al., 2018).

This view of prognostic uncertainty as a primary cause of FCR is consistent with a vast body of research documenting the many aversive psychological effects of uncertainty (Afifi and Weiner, 2004; Han, 2013; Hillen et al., 2017b). At the same time, however, it reflects and reinforces a narrow conception of the nature, function, and beneficial effects of uncertainty. In treating uncertainty solely as a deficit state—a mere "inability" or absence of knowledge—it disregards how it also represents a form of knowledge in its own right: a metacognitive awareness of ignorance that serves the adaptive function of enabling individuals to cope with threats (Han et al., 2011). It overlooks potential beneficial effects of uncertainty, such as the maintenance of hope in the face of ignorance about the future (Babrow, 1992; Babrow and Kline, 2000; Brashers et al., 2000; Brashers, 2001). This benefit may explain why patients with serious life-limiting illness strive not only to decrease prognostic uncertainty, but to increase and maintain it in various ways—including actively avoiding prognostic information and embracing uncertainty in prognostic estimates (Fallowfield et al., 1995; Butow et al., 1997, 2002; Kutner et al., 1999; Hagerty et al., 2004, 2005; Kirk et al., 2004; Helft, 2005; Elkin et al., 2007; Hancock et al., 2007; Robinson et al., 2008; Innes and Payne, 2009; Bilcke et al., 2011; Rayson, 2013; Han, 2016). These responses suggest the need to move beyond construing prognostic uncertainty solely as a cause of FCR and other psychological states, to adopt a broader, bi-directional view that accounts for the alternative role of prognostic uncertainty as an *effect* of FCR—a consequence of patients' efforts to cope with their fear.

The overarching aim of the current study was to explore this alternative role and the potential bi-directional causal pathways that link prognostic uncertainty and FCR among patients with ovarian cancer (OC). The most lethal gynecologic malignancy and fifth leading cause of cancer deaths among United States women, OC has a high risk of recurrence and progression and OC survivors have a correspondingly high degree of FCR (Wenzel et al., 2002; Shinn et al., 2009; Roland et al., 2013; Ozga et al., 2015; Kyriacou et al., 2017; Galica et al., 2020). The experiences of OC survivors may thus yield valuable insights on the causes and effects of FCR, and the specific aim of the current study was to explore these experiences to better understand how prognostic uncertainty might represent not only an aversive cause but an adaptive effect of FCR. Appropriate to this exploratory aim, the study employed in-depth, semi-structured qualitative interviews with individual OC survivors, which allowed survivors themselves to describe their lived experiences in detail, and to account for the relationships between prognostic uncertainty and FCR in their own words. The study thus allowed us to generate testable hypotheses about these relationships and to develop a tentative, provisional theoretical model to guide future research on the relationship between prognostic uncertainty and FCR among cancer survivors.

MATERIALS AND METHODS

Study Design, Participants, and Recruitment

The study utilized individual qualitative interviews with a convenience sample of patients with epithelial ovarian or fallopian tube cancer, recruited from the Gynecologic Oncology Service of a large urban 637-bed teaching hospital. Eligible participants consisted of patients with Stage I–IV disease, determined by surgical or clinical staging after biopsy-confirmed diagnosis, who had completed first-line treatment with surgery and/or chemotherapy. In order to minimize potential psychological harms that might be caused by asking patients to discuss prognosis-related topics including the prospect of their own death, patients were excluded if they reported significant levels of cancer-specific emotional distress on routine screening using the National Comprehensive Cancer

Network (NCCN) Distress Thermometer (Holland et al., 2001) (scores $\geq$ 3). Eligible and interested patients were identified by practice staff during regularly scheduled office visits and recruited by the research team, who informed participants of the study's voluntary and exploratory nature and its overall focus on the topic of prognosis. Participants were provided a $25 (USD) incentive. We aimed for a minimum sample size of 20 based on available study resources and our prior qualitative research exploring similar themes with cancer survivors (Han et al., 2013; Hillen et al., 2017a). The study was approved by the Maine Medical Center Institutional Review Board.

Data Collection and Interview Content

From July 2018 to November 2019, individual in-person interviews, lasting approximately 45–60 min each, were conducted by trained qualitative researchers (CG, HM, PH) with no professional or personal relationships with participants. Interviews were semi-structured and followed a moderator guide developed by our multi-disciplinary research team and consisting of open-ended questions and close-ended probes designed to elicit participants' (1) prognostic understanding; (2) experiences, preferences, and attitudes regarding prognostic information; and (3) strategies for coping with prognostic uncertainty (Appendix). During the course of the study, minor revisions were made in the interview guide to clarify and further explore emergent themes. All interviews were audio-recorded with prior consent of participants, and transcribed verbatim by a professional transcription service.

Data Analysis

In-depth qualitative analysis and line-by-line software-assisted coding of anonymized interview transcripts was conducted using the qualitative analysis software program MaxQDA^{TM}. The analysis utilized an inductive, constant comparative approach aimed at minimizing preconceptions, identifying key themes and relationships between them, and generating new theoretical understandings (Glaser, 1965; Strauss and Corbin, 1998). Four investigators—a palliative medicine physician and behavioral researcher with expertise in medical uncertainty (PH), an experienced qualitative health researcher (CG), a palliative medicine physician and health services researcher (RH), and a medical sociologist (AF)—first developed a working codebook by reading eight transcripts, inductively identifying themes in participants' verbatim statements (open coding), and then categorizing emergent themes according to their content (axial coding) (Strauss and Corbin, 1998; Ryan and Bernard, 2003; Corbin and Strauss, 2014). The investigators met after coding each transcript to compare coding decisions, resolve areas of disagreement, and refine the codebook. The remaining 13 transcripts were double-coded by pairs of researchers (PH and CG, or PH and RH), who met regularly to compare new data, concepts, and themes, to resolve further disagreements, and to refine the codebook. One researcher (PH) conducted further analysis of identified themes and developed an integrative conceptual model with feedback from the research team.

RESULTS

The study sample (**Table 1**) consisted of 21 participants, most of whom reported experiencing prognostic uncertainty and FCR at some point in their illness. Their descriptions of the relationship between these phenomena suggested two different views: (1) prognostic uncertainty as a cause of FCR, and (2) prognostic uncertainty as an effect of FCR. Supporting the former view, participants described managing FCR by pursuing prognostic certainty. Supporting the latter view, participants described managing FCR by pursuing prognostic uncertainty, and further identified various strategies that they used to construct and maintain this uncertainty. These views, furthermore, were not mutually exclusive; some participants endorsed both at once.

Prognostic Uncertainty as a Cause of FCR

Consistent with prevailing theories of FCR, study participants described prognostic uncertainty as a primary cause of their fear, which they managed by pursuing prognostic certainty.

The Fear of Possibility

Study participants' accounts suggested that prognostic uncertainty was associated with higher FCR. Participants reported experiencing the greatest uncertainty and fear at the time of their initial cancer diagnosis, and during follow-up visits and diagnostic testing (bloodwork and radiologic imaging studies) for cancer surveillance. Participants' comments further

TABLE 1 | Participant characteristics.

	N	%
Age		
40–50	4	19.0
51–60	3	14.3
61–70	9	42.9
71–80	5	23.8
>80	0	0
Race		
White/Caucasian	21	100
Other	0	0
Cancer type		
Ovarian	16	76.2
Fallopian tube	5	23.8
Cancer stage		
I	3	14.3
II	1	4.8
III	14	66.7
IV	3	14.3
Months since diagnosis		
$\leq$ 12	8	38.1
13–24	4	19.0
25–36	4	19.0
37–48	1	4.8
49–60	2	9.5
>60	2	9.5

suggested that FCR originated not only from uncertainty *per se*, but from a negative bias in its perception and interpretation: a selective, pessimistic focus on worst-case possibilities, which clinical psychologists have termed a "catastrophizing" response to uncertainty (Robichaud, 2013). This bias was manifest in several study participants' tendency to equate prognostic uncertainty with worst-case outcomes including cancer recurrence, progression, and death (**Table 2**). One participant (Patient 15), for example, traced the fear she felt at the time of her routine follow-up visits both to the inability to know whether or not her illness "was going to end badly," and to an irresistible urge to imagine the worst: "every time I come here I'm panicked, just because it is scary to think that I could come back at any time and have a re-occurrence." Other participants exhibited the same pessimistic bias in describing their cancer as a "hiding," "sneaky" threat lurking "somewhere else, just waiting" to return and spread.

Restricting Possibility: The Pursuit of Certainty

Further supporting the view of prognostic uncertainty as a primary cause of FCR, participants reported managing their fear by pursuing prognostic certainty. This pursuit served the critical function of restricting future possibilities—that is, narrowing the range of potential outcomes—which made them more tolerable (**Table 2**). One participant (Patient 12) argued that reducing her prognosis to a finite "time bracket" gave her a "sense of time" that lessened her worry. Other participants (Patients 17, 21) similarly reported that by limiting the range of possible

TABLE 2 | Prognostic uncertainty as a cause of fear of cancer recurrence.

Themes	Illustrative quotes	Patient
The fear of possibility	I mean it's cancer. And cancer is sneaky. For me, you hear of cases that are positive but you also hear of cases that are negative where it wasn't supposed to come back but it did. So I think the percentages would have to be way higher, like 99%, you know. And it's just not that high. So 80—I forget what it is, 80 to 90% is great, but it's not 100% chance of it not coming back.	17
	But I have to say, just that initial diagnosis when they say, "Oh we think you possibly have ovarian cancer or you do have ovarian cancer," it's almost like a PTSD thing. So emotional, crying, fear. That fear is with me all the time. It's always like, any little thing I get now, I think, has that cancer spread? Do I have cancer somewhere else now? Because cancer always comes back . . . But just the diagnosis, knowing that they found cancer in an ovary, it's in my head. I had cancer. And that fear is in me that it's somewhere else, just waiting . . . They say, it was tiny, we got it, it was nowhere else. But in my head it was nowhere else that you looked, and what if there's one tiny little thing and it's somewhere just waiting years down the road. Because you hear people beat cancer and then 15 years down the road it's back. So I have that and I get really emotional. . . . I'm like, "I'm a nervous wreck, I'm crying because I'm scared to death."	20
	Well, now being in cancer—knowing what I know about it, you're not really in remission, it's just hiding really. It doesn't really ever go away . . . if you read the Internet, high-grade serous carcinoma almost always comes back. I'm not sure I've found anybody that it hasn't. It doesn't mean it's going to kill you. It just means it flares again. You know, your CA 125 starts going up. So they start hitting you with more chemo. Or it goes to an organ. Because now everything I have now is vital. They took out everything I didn't need. So if it goes—like it likes to go to the lungs. It likes to go to the spleen, the liver, sometimes the bowels and the bladder, sometimes the brain, yay!	21
Restricting possibility: the need for certainty	I don't believe the number absolutely. But it gives me a time bracket. So, I shan't be worried about things that are going on that I can't explain, because they're either old age or cancer. But after this point, if something different starts to happen, I will make note of it. Up until that point, I could probably drop dead in 4 years and not worry about it. But it does give me a sense of time. For me that's good.	12
	I was trying to get reassurance on—I was really looking for stats, like this percentage of people survive . . . Again, in my case just looking for reassurance like okay, for a person between the ages of 40 and 50 who have BRCA and get it caught in Stage II, what are the numbers? They're not always available. But for me it was just kind of trying to reassure myself that in general ovarian cancer is a pretty—is one of the harder ones to treat successfully in the long run. So I'm just looking for something like when she says this is curable, this is beatable, you're in a good situation, I just want to see the numbers that back that up I guess.	17
	What's my chances of dying? That's what everybody wants to know when they get cancer. But I mean, I do think it's good to know. Most of that stuff I've learned, like I said, from the Internet. But maybe it would be helpful to know, what is the likelihood that it's going to come back? When it will come back? So I'll know when to—sometimes concrete knowledge is good . . . You want to know. You don't want to live and la-la land . . . You want to be making plans. Should I be working at this point or should I be out making memories with my family? So that's what I mean. I think it kind of helps with the seriousness. Ovarian cancer is not the worst, but it's not the best. You've got a 50/50. Okay, so what makes up that 50/50? Tell me about the people that are on the bad side of 50.	21
Unrestrictable possibility	. . . let's say I'm in the 74%, who knows which side I'm on. The 74 or the 26 side. Who knows? Who knows?	3
	We think that probably based on that and study one, 40 days, you know, all this stuff, probably you're gonna be fine. If he says 60% or 80% does that really mean anything to me? No. That's bullshit. It's word filler. and so I just want to hear the real stuff. And if it's not real, just keep it to yourself.	9
	That was sufficient for me. I would have, me, if he would have said, you have 0%, I would have stuck to that. If he said you have 0 to 0.5%, that 0.5 would drive me crazy forever. I would focus. I'd still have a 0.5. This past May I was having a lot of dizziness and stuff. So anyway, long story short, I ended up in the Emergency Room and they were doing heart monitor, then they look at my history and they're like, hmm, "Well we better do an MRI on your brain and a CT scan, because you've had Ovarian Cancer." Well hello. That's what I mean by it's always there. Always there.	20

outcomes, prognostic information imposed a concrete order that enabled them to set priorities in their lives—a function they perceived as valuable regardless of how unfavorable their prognosis might have been.

Unrestrictable Possibility

At the same time, study participants acknowledged fundamental limits in the extent to which prognostic possibilities could be restricted. Participants argued that medical experts "don't really know" the prognosis of individuals (Patient 2), that statistics "are not about people" because they simply "mix together" individual lives (Patient 7), and that even precise prognostic estimates do not answer the question of their own fate (**Table 2**). Participants thus recognized that the range of their potential outcomes could never be narrowed sufficiently to include knowledge of their own personal fate; prognostic certainty was unachievable. This recognition was a source of distress for many participants; Patient 20, for example, reported that even a small "0.5%" probability of a bad outcome was enough to "drive me crazy forever." Such responses lend further support to the view of prognostic uncertainty as a primary cause of FCR.

Prognostic Uncertainty as an Effect of FCR

Yet study participants' accounts of their experiences suggested that prognostic uncertainty was not merely a primary cause but also a secondary *effect* of FCR: an adaptive response as well as an aversive stimulus, a source of hope as well as fear (**Table 3**).

The Hope of Possibility

Study participants' accounts suggested that prognostic uncertainty was associated not only with higher but lower FCR. Participants' comments further suggested that this association may have originated from a positive bias in the perception and interpretation of uncertainty: a selective, optimistic focus on best-case possibilities, which might be termed "optimizing"—in contrast to the "catastrophizing" that resulted in the fear of possibility. This opposing focus made prognostic uncertainty a source of hope as well as fear. One participant (Patient 5) viewed even the smallest possibility of a best-case outcome as a reason for hope: "even if there was a 1% chance, I was like it didn't matter," she asserted, adding that "We don't know what they can do." In a similar vein, Patient 4 focused on the possibility of "beating" her cancer, in deliberate defiance of the high likelihood that her cancer would recur. Patient 7 acknowledged the "liberating" nature of the fact that all future outcomes—both bad and good—ultimately represent mere possibilities, and affirmed how the awareness of this fact "creates a little more hopefulness" (**Table 3**). For all of these participants, in other words, prognostic uncertainty signified the possibility of not only realizing a dreaded outcome—cancer recurrence, progression, death—but averting these outcomes. Uncertainty was thus a source of not only fear but hope.

Expanding Possibility: The Pursuit of Uncertainty

Corroborating the alternative view of prognostic uncertainty as a secondary effect of FCR rather than a primary cause, study participants reported coping with their fear by increasing rather than decreasing their uncertainty. Prognostic uncertainty was a key goal for many participants, who described conscious efforts to maintain ignorance about their future as a way of expanding the range of prognostic possibilities to include desirable as well as undesirable outcomes (**Table 3**). Patient 2 put it pointedly: "I don't want to know what stage cancer it is because if I don't know, it can be anything." Patient 15 acknowledged her poor prognosis but reported actively foregoing more precise prognostic information—intentionally maintaining prognostic ignorance and uncertainty. For this and other patients, uncertainty kept prognostic possibilities open, and thus served the vital function of preserving hope in a better future.

Adaptive Effects of Uncertainty

Related to—yet independent of—its hope-preserving function, furthermore, prognostic uncertainty had other important, psychologically adaptive effects (**Table 3**). One was to prevent patients from resigning from further efforts to fight their disease; Patient 13 viewed such a response as a danger of prognostic certainty and a rationale for preserving prognostic uncertainty. Another adaptive effect of uncertainty, acknowledged by multiple study participants, was to help them focus attention on issues within their control and to disengage from issues that were not. One participant (Patient 9) viewed maintaining prognostic uncertainty as part of a general strategy "not to borrow trouble"—to let go and simply attend to the pragmatic task of "doing what I can do." Other participants affirmed that prognostic uncertainty had the added benefit of allowing them to cease thinking and worrying about their future outcomes, as Patient 15 put it—and to "trust the care I was getting."

Constructing Prognostic Uncertainty

Further supporting the conception of uncertainty as an effect rather than a cause of FCR, study participants not only pursued prognostic uncertainty by foregoing prognostic information, but actively constructed it by engaging in two strategies: (1) highlighting the indeterminacy of their personal prognosis, and (2) highlighting ambiguity in prognostic information (**Table 4**). These strategies reinforced participants' prognostic uncertainty, which further enabled them to maintain hope in a favorable outcome.

Highlighting Indeterminacy

The most commonly reported way in which study participants constructed uncertainty was by highlighting the indeterminacy of their prognosis. Nearly all participants expressed a belief in the uniqueness of individual patients, and in the inability of statistics to account for all possible determinants of their own, personal prognosis—e.g., age, medical history, family history, positive attitude, and lifestyle. These beliefs affirm long-recognized epistemological problems that limit the precision and value of all probability estimates for individuals, and engender what philosophers of statistics have called aleatory uncertainty (Hacking, 1975; Gillies, 2000). Study participants, however, embraced and highlighted this uncertainty because it allowed them to believe that prognostic estimates did not

TABLE 3 | Prognostic uncertainty as an effect of fear of cancer recurrence.

Themes	Illustrative quotes	Patient
The hope of possibility	So I am fighting cancer. Even though nothing shows on a scan right now, it doesn't mean there's not still cancer. And I'm not in denial about that, you know. I'm fighting it. You know everyone will say that; I don't know how many times I've heard, "Oh I'm so sorry." I say, "Why? I'm going to beat it." That's what I say every time. I say, "I'm beating it now."	4
	Well I mean also I feel because I'm on this new treatment, you know because, I mean my provider has straight up said, I have no idea; you're in the wilderness and we have no statistics; you're the, you're one of the like, you'll be a, you know you'll be a statistic. Like I'm part of the like, "Does this work, or does it stop working after 5 years, or does it give me another kind of cancer, or?" I mean all of those are—like it's all possibilities. So there's something really liberating in that in a way . . . Yeah, you never know, you never know. Like you could just—like I mean yes, the natural history of this disease is most people are dead within X number of years; you know you have some recurrences, they get closer together, they don't, they get resistant to treatment and then you die a terrible death, right? So yeah, so not knowing, like just being like, just having the, maybe this will work for a long time, like creates a little more hopefulness.	7
	But it was never, for me personally, it was never a question that I needed to ask. I already knew the answer and how I know, I don't know. But it was always a matter of, "Okay, I've got this. Let's get on with the treatment. And of course I'm going to survive" . . . And then he gave us that information. But it was like 41/2 years survival rate for women with III-C or greater, IV. And I looked at him and I said, "So half of the people don't make it to 41/2 years. And I said, "And half of the people live way beyond that." I said, "I'm definitely in the second category. Definitely." I said, "There's no question about that at all." And it was, it's not, and even when I was at the bottom looking up at the bottom of the barrel, it was never a point of I'm not going to get through this. It's like, "Yeah, this is hard, and this doesn't feel good. And this is the pits, but tomorrow is better. Tomorrow you will feel better. Tomorrow you will be able to do a little bit more than you did today. Don't worry about today. Tomorrow is going to be better.	14
Expanding possibilities: the need for uncertainty	. . . the first time I met with Dr. _____ I said, "I don't want to know what stage cancer it is because if I don't know, it can be anything." Do you know what I mean? So I didn't want to know that because if I knew a number, that's going to, that's going to be a scary thing. And I didn't, I didn't want to know a number. I knew it was serious; hell, I knew it was serious. I've got this big tumor; they've all told me it's an adeno something or other; it's aggressive . . . I know that, I know that that means it's stage 4. But as long as they're not telling me that, I haven't heard it.	2
	So maybe that's why I didn't want to know originally. I didn't want any, to know like, "Well this could be really bad," because I'd be thinking, "I'm not going to survive, you know" . . . I didn't ask questions that I didn't think—I mean, "Am I gonna die?" "What are my chances?" I think those are questions that a doctor can't answer with any more certainty than I can. And rather than hear him guess or not, and distort my confidence in him, only ask a question if you really want the answer.	8
	I don't want to think about it too much and if there's hope then I'm good with that. I didn't really want, and quite honestly I kind of knew that it probably wasn't gonna give me good numbers. I was at like Stage 3, so I didn't anticipate—I was just kind of grasping, kind of hoping for a positive to hang onto . . . I did get paperwork and stuff when I first, one of my first times here when they were explaining things to me, and it had statistics and stuff. And I looked at 'em once, and I couldn't look at them again because they were not helpful to me. I only wanted to hear words of encouragement and hope. And those statistics did not give me any of that . . . I didn't really want the numbers. I just wanted at that time to hear from him, "Oh, you've got this," or whatever. And it was wishful thinking on my part to even to ask. So in response to your question, no I wasn't really looking for numbers necessarily . . . If it was something that was going to give me hope and like, I can do this sort of thing, then I probably would have wanted them, but if it was anything negative I wouldn't have wanted it.	15
Adaptive effects of uncertainty	Well to finalize something that—you always have that on your mind. You're counting the days. Like say if I was told I had 3 months, you'd be living every day just counting the days away. That type of thing. And not trying to focus on getting better, or you know, prolong it or whatever.	13
	So, I'm good with that. I tend not to borrow trouble. It's really, what do I have to do now? Where do I have to be? What do I have to do? What do I have to take? And just tell me when and where to be there and I'll do my part . . . Here's where I am. I'm doing everything that I can do. Dr. ____ is doing everything that he can do. There is nothing else to be done. So I'm not doing any more.	9
	I guess the biggest thing is I am such a worrier, and I would think about it too much and those—for me, not knowing everything helped because I knew what I knew and what I was working on and that's all I could control, and beyond that I had to trust the care I was getting.	15

apply to them, and that their personal prognosis was thus alterable. Folkman (2010) referred to this cognitive reappraisal process as "personalizing the odds." As Patient 4 affirmed, "I think that certain people obviously are different. Everyone is so individual"; she went on to assert that she was "not the average Joe" and would "change the rule books" in fighting her cancer (**Table 4**). Another patient stated that she purposefully avoided seeking prognostic information because "Whatever it [prognostic estimate] says, I want to be the outlier" (Patient 5). The effort to highlight prognostic indeterminacy to preserve the possibility of beating the odds, furthermore, appeared to involve physicians as well as patients. Participants recounted how their physicians used language supporting the personal inapplicability of prognostic information—e.g., "Every patient is different" (Patient 15), and "your situation is a little different" (Patient 17). Patient 21 stated that her physician refrained from providing any prognostic estimate precisely for this reason: "And she's never—she still hasn't given me survivability odds. She just says that I am my own case. She says, 'You know it's really difficult to give that kind of definite knowledge because everybody is so individual.'" These accounts suggest that physicians played an important role in

TABLE 4 | Constructing prognostic uncertainty.

Themes	Illustrative quotes	Patient
Highlighting indeterminacy	I am a fighter. I am my mother's daughter and she's a fighter and we don't ever follow the rule book, so if the rule books say 20%, then screw that. We're going to change the rule books. And you know, and we're all like that in my, my mom's side anyway and I just, no I just never thought I was going to go down like that, and so I just was determined not to . . . you know when they told me 20%, I said, okay so somebody has to be the one that skews the odds. I said, and why can't I be that person? So that's just how I viewed it from the day he told me so. I didn't let the 20% affect me that way . . . You know that's funny because I think that certain people obviously are different. Everyone is so individual . . . But like I said, I'm not the average Joe. But I think that, so maybe I feel that maybe some doctors, hopefully they gauge out; I mean they only know you as a chart.	4
	So you've got to find yourself a different Cinderella, this shoe doesn't fit me. I'm not anywhere close to calling it quits . . . The objective point of view is, you've got all of this information coming in. Yeah, it's legit for him to say that. But then you have the part that he can't see, which is the subjective part, which says yeah, but you know what, you know better than that . . . the subjective part that they can't see and they don't know about or they can't hear, is the greater part of that equation. And that part of the equation is the part that you hang onto. And not just hang onto, but is the real part, is the missing bit of information to go into this equation to turn that answer around.	14
	There is some backing for statistics. Yeah, I'm sure there's some research behind it and stuff. I know, well, I don't know this but this is what I think. I know often times people who have ovarian cancer tend to be older, I think. And maybe the statistics have to do with them a little bit more . . . But I was just thinking that maybe the statistics have to do more with them than maybe me . . . I remember asking Dr. ___, "So am I going to be okay?" And he couldn't exactly answer that question, obviously. But he did say, "Every patient is different." He said, "I have patients that don't do well." And then he said, "I have patients that do amazing." And so he said, "I can't answer that question" . . . I think he was just honestly saying, "I don't know exactly what's gonna happen, how you're going to react to the treatment."	15
Highlighting ambiguity	I wanted to dissect the number right away. Okay, you say let's say 40%, and then I go in and I read ovarian III on the internet and it says women over 65 have a poorer prognosis than those who are under 65. Okay, I'm 72. So how many of that 40% are under 65 and how many of them are over 65? If you're in the 70's, are you telling me the 40% has all of the women who are 28 years old all the way up to 90, and I'm probably actually more like I've only got a 28%, or are you telling, you know. I wanted to dig into it but I also knew and they said they can't, they, we can't tell you; that research hasn't been done.	3
	And I had another friend who had had cancer. And they both said to me, don't look at the research numbers in terms of healing or how long you're going to live because that research was done 5 years ago at least and so many innovations have come from that since then.	5
	Yeah, because what we know today, what I knew or what they knew in September of '16 is different than what we know of what this is like in April of '19, things have happened. More drugs have come out. And that was one thing that they talked about saying, "Well these two drugs aren't for you anymore but we have this one and this one and this one. We've got an arsenal. We've got a toolbox full of drugs that we can give you" . . . Now it's open-ended. Depending on how soon you get treated, how soon you get diagnosed, see how much further information we have to give you to say, "Yeah this is a devastating diagnosis to you, but because of all the research we've done and because of all the studies that we've done, we know that at your stage, this is how long, a productive life you have. And that's hopeful.	14

co-constructing prognostic indeterminacy with patients as a means of maintaining hope in beating the odds.

Highlighting Ambiguity

Another important way in which study participants constructed prognostic uncertainty was by highlighting limitations in the reliability, credibility, or adequacy of prognostic information—features of information that produce what decision theorists have termed "ambiguity" (Ellsberg, 1961; Camerer and Weber, 1992). Ambiguity in prognostic information arises from missing or conflicting risk evidence or methodological limitations that produce imprecise, conflicting, or changing estimates, leading to what philosophers of statistics have called epistemic uncertainty. Study participants highlighted the ambiguity of prognostic information in several ways, including acknowledging the imprecision or unreliability of prognostic estimates for particular patient subgroups, due to shortcomings in empirical evidence—e.g., "research hasn't been done" (Patient 3) (**Table 4**). Other participants noted how prognostic knowledge is unstable and "changing at every moment" (Patient 21) due to ongoing scientific advances. Highlighting these ambiguities of prognostic information reinforced participants' uncertainty, further broadening the range of their possible futures to include favorable outcomes.

Maintaining Prognostic Uncertainty

Study participants described how they not only construct uncertainty by acknowledging key limitations of prognostic information, but actively maintain it by engaging in two other general strategies—relinquishing knowledge and embracing ignorance—which enabled them to both sustain hope and better tolerate their uncertainty.

Relinquishing Knowledge

A primary strategy that participants used to maintain prognostic uncertainty consisted of relinquishing prognostic knowledge and its pursuit. Several participants viewed their prognosis as a moot question given that only one course of action—to pursue treatment—offered any hope of controlling their cancer; prognostic knowledge thus served no practical purpose. In this vein, Patient 2 argued that simply knowing she had OC was enough, and that her priority was simply "to concentrate on what we can do," while Patient 4 disavowed prognostic knowledge because it would not change her "plan of care" (**Table 5**).

Other participants added that prognostic knowledge was not only practically but existentially irrelevant. Patient 18 affirmed a need to accept whatever future outcomes might lie ahead, and to simply deal with her illness one step at a time. The practical and existential irrelevance of prognostic information led these participants to relinquish prognostic knowledge and its pursuit—especially as time went on and their illnesses progressed—which had the ultimate effect of sustaining their uncertainty and making it more tolerable.

Embracing Ignorance

Yet study participants reported maintaining prognostic uncertainty by engaging in not only the negative act of relinquishing knowledge about their prognosis, but the positive act of embracing ignorance. Apart from the basic desire to maintain prognostic ignorance in order to expand the range of future possibilities to include hopeful outcomes (**Table 3**), participants also described a positive affinity for ignorance, which served other fundamental life goals. Patient 1 reported that embracing ignorance about her future provided a sense of freedom and openness that allowed her to "take it a day at a time" (**Table 5**). Patient 8 embraced ignorance about her prognosis because she "didn't want any limit" to what was possible; she believed that acknowledging a poor prognosis posed the risk of turning into a self-fulfilling prophecy. Patient 7 evocatively described this same orientation toward ignorance as a capacity for "holding some amount of the spaciousness of the unknown"—for affirming prognostic ignorance and preventing it from collapsing into premature or excessive certainty about one particular outcome or another.

DISCUSSION

This qualitative study explored the relationship between prognostic uncertainty and FCR among survivors of OC. To our knowledge it is the first study to focus on bi-directional causal pathways between these phenomena in this population, and to provide evidence of the role of prognostic uncertainty as an effect as well a cause of FCR, an adaptive response as well as an aversive stimulus. Study participants vividly described how uncertainty can not only provoke but ameliorate FCR and sustain hope in the face of an unknown and threatening future. They further reported using various strategies to cope with uncertainty and FCR, and identified several psychological processes that may mediate the relationships between uncertainty, FCR, and hope. These findings are clearly provisional given their qualitative nature; more research will be needed to confirm the causal nature and direction of the relationships identified. In the meantime, however, these findings generate testable hypotheses and provide the basis for a provisional new theoretical model that can guide future empirical research on the relationship between prognostic uncertainty and FCR among cancer survivors.

This provisional theoretical model is presented in **Figure 1**. Uncertainty occupies the center of this model, affirming both its primary importance in the lives of patients with cancer, and its fundamentally ambiguous, dual nature and function: it is at once

TABLE 5 | Maintaining prognostic uncertainty.

Themes	Illustrative quotes	Patient
Relinquishing knowledge	Believe me; hearing I've got ovarian cancer; that's enough. That's going to make my head spin. I don't need the extra 5 min on the whirligig you know. It's like, I'm getting enough information with that piece of information. And this, hmm, how do I word this? I think sometimes we do think; like we put things in numbers, in categories where really it doesn't need to be . . . so people with stage I have a greater chance of recovery, and people from stage 4 have a less chance of recovery. Does that help? Does knowing that really help? . . . Seriously, I don't think knowing those numbers helps anybody; I really don't think it helps because like I said, it, they're just numbers. And like Dr. _____ said, it's a number; you're one in a thousand and it's what it is you know . . . we've got to concentrate on what we can do.	2
	I don't know that doctors may not tell their patients how grim it is because, well like he told me; no matter what, if it was in my bones or if it was, then the course of treatment was going to be the same. I was still getting these six cycles of chemo, this chemo, no matter what the course was. Whether it was in my bones or whether it was everywhere or if it was just here . . . So in my mind, I'm thinking that he didn't give me all of that total information because it wasn't changing my plan of care . . .. It isn't going to make a difference. Because the treatment's the treatment. And what you have at the end is what you have at the end.	4
	No. I'm not worried about it because if it's gonna happen, it's gonna happen. I'm strictly like—she said to me today, "I'd like to do a CT scan, I think it's come back." Okay, let's do the CT scan. And he said, we'll start treatment again." "Okay, let's do treatment again." I've just accepted it. Is that understandable? I've accepted that I have cancer. And I've just gotta do it.	18
Embracing ignorance	So I think that's my, the way I am . . . it's like we don't need to know. We're suited to take it a day at a time and yet, I mean, it's okay to plan somewhat; I'm not saying that. Like okay, if suddenly we couldn't stay with our family, then that's okay; we kind of know, we're free, we can do this. Well there are other options you know. That's been our life . . . Yeah, we're cut out for that I guess but it's very freeing.	1
	For me, it wasn't helpful because I didn't want any limit. I watched it with my mother. I watched what limits do to people across every, any level. If you tell someone who's a quadriplegic that they can't ski and then you go up and you see them on the mountain, the kids that weren't told that they couldn't. And I just think that for me, I don't want to know; I didn't want to know what my chances were or what my odds were . . . I've watched it with friends who get diagnosed with something and they, that's what they; you know I only have 5 years, I only have, the doctor said you know I have 3–5 years and that's all they think about and I thought, "I have today. . ."	8
	I mean again, it's because I think it has to do with the, like providers holding some amount of the spaciousness of the unknown. Like here's what we can do and here's what seems to work but they don't know and I think that's something in medicine overall. Like it's about fixing; not about health . . . I mean you know you can't push it but if you hold the space, if you hold the space for it, there's an invitation also to, for us as patients to like drop a little under. I mean some people can't.	7

a cause and an effect, a source of fear and hope, and a mediating variable between these states. Conventional theories of FCR focus on the direct uncertainty-fear pathway on the right-hand side of the model. For example, the model developed by Fardell et al. (2016) identifies "lack of information" about risk of recurrence as a direct cause of FCR, while integrative models of FCR put forth by Simonelli et al. (2016) and Curran et al. (2017) construe uncertainty as a primary trigger of subsequent cognitive appraisal processes that, in turn, produce FCR. A "blended" model of FCR developed by Lebel et al. (2018) characterizes uncertainty as a primary factor that moderates the effect of internal and external triggers (e.g., physical symptoms) on perceived risk of cancer recurrence, which then leads to FCR. The common feature of all these models is that they situate uncertainty upstream in the causal pathways that lead to FCR, and do not identify uncertainty-specific negative coping processes (e.g., catastrophizing, restricting possibility) that mediate the effects of prognostic uncertainty on FCR. Most importantly, they ignore potential reverse-causal pathways by which fear might induce uncertainty, and the uncertainty construction processes (e.g., highlighting the indeterminacy of prognosis and the ambiguity of prognostic information) that might mediate this pathway.

This new model acknowledges a whole other side of the phenomenon: the critical role of prognostic uncertainty in promoting not only the fear of cancer recurrence but the hope of cancer non-recurrence. The hope-promoting function of uncertainty as a more general phenomenon has been acknowledged in conceptual models put forth by health communication theorists Babrow (1992) and Brashers (2001); however, much remains unknown about the causal pathways connecting uncertainty and hope. In the current model fear and hope are simply inverse responses to the complementary possibilities posed by uncertainty; fear manifests a focus on negative, undesirable possibilities, hope a focus on positive, desirable ones. The model is a dual-process conception that postulates a mirror-image causal pathway by which uncertainty induces hope through the mediating action of positive coping processes (optimizing, expanding possibility), as well as a reverse-causal pathway in which hope induces uncertainty through the mediating action of uncertainty maintenance processes (relinquishing knowledge, embracing ignorance).

This dual-process model thus clarifies that uncertainty is an essential source of both fear and hope, and exactly which of these states predominates at any given time is determined by how individuals balance different positive and negative uncertainty coping strategies. The degree of uncertainty that individuals experience, in turn, is determined by how they balance different uncertainty construction and maintenance strategies. In other words, uncertainty, fear, and hope are interdependent states that exist in dynamic equilibrium and influence one another through different feedback loops. Uncertainty can initiate either a self-perpetuating, vicious cycle of fear, or a similarly self-perpetuating, virtuous cycle of hope. On the one hand, prognostic uncertainty can stimulate primarily negative coping responses that promote FCR, which then stimulates uncertainty construction processes that promote even more uncertainty, which then stimulates further negative coping responses, and so on. On the other hand, prognostic uncertainty can stimulate primarily positive coping responses that promote hope of cancer non-recurrence, which then stimulates uncertainty maintenance processes that

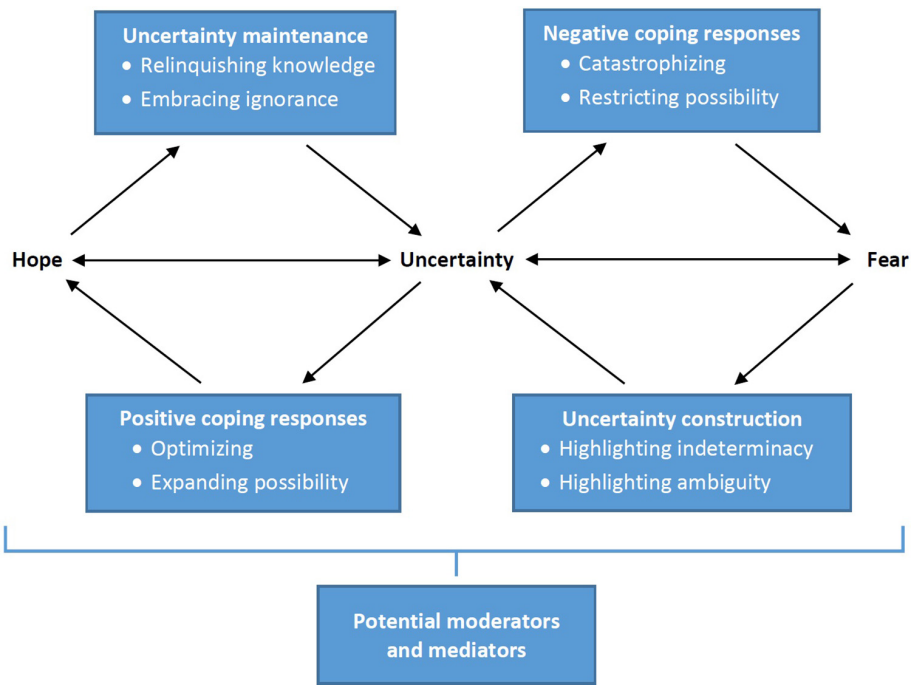

FIGURE 1 | Dual-process equilibrium model of the relationship between prognostic uncertainty, fear of cancer recurrence, and hope.

promote uncertainty, which then stimulates further positive coping responses, and so on.

More research is needed to elucidate the factors that cause patients to either enter or exit these opposing, self-perpetuating cycles, to experience more or less prognostic uncertainty, to refocus attention on either negative or positive possibilities, or to shift the balance of their psychological responses to uncertainty from fear to hope or vice versa. One important mediating factor may be physicians and physician-patient communication; our data suggest that physicians collude with patients to highlight indeterminacy and ambiguity in prognostic estimates, and thereby co-construct the prognostic uncertainty that both parties need to maintain hope. One important moderating factor may be individual differences in patients' uncertainty tolerance; past research suggests that uncertainty tolerance influences the extent to which individuals perceive uncertainty and respond to it in negative *vs*. positive ways (Hillen et al., 2017a; Strout et al., 2018; Anderson et al., 2019). These and various other factors may mediate and moderate the causal pathways connecting uncertainty, fear, and hope, and warrant further research.

Our dual-process, equilibrium model of uncertainty provides a guiding framework and set of testable hypotheses for this research. The intermediary processes connecting uncertainty and fear (negative coping responses, uncertainty construction processes) and uncertainty and hope (positive coping responses, uncertainty maintenance processes) can be measured and their effects quantified. In the meantime, our model also raises important normative questions for research on FCR, including how much prognostic uncertainty ought to be constructed and maintained, what negative and positive coping responses are appropriate, and what balance of fear and hope is optimal. Unmitigated fear clearly causes significant suffering and is maladaptive; however, the same may be true for unmitigated hope, which may lead to unrealistic expectations and a "distortion of reality "(Folkman, 2010). More research, both empirical and conceptual, is needed to determine when particular responses are not only psychologically adaptive but morally appropriate, and why.

This study had several limitations that qualify its findings and call for further research. It was conducted at a single institution using a relatively small and racially homogeneous convenience sample of female OC patients with primarily advanced-stage disease. Study recruitment was driven by available study resources rather than thematic saturation; although the repeated occurrence of key themes across the interviews suggested a high degree of thematic saturation, important themes could have been missed. Larger studies, utilizing both qualitative and quantitative methods and more sociodemographically and clinically diverse patient populations, are needed to determine the validity of our findings and theoretical model.

In spite of these limitations, our study provides valuable empirical evidence and a new theoretical model of the relationship between prognostic uncertainty and FCR—and between uncertainty, fear, and hope as more general phenomena. In this model prognostic uncertainty has a dual nature—it is both a cause and an effect, a source of fear as well as hope—and which of these natures predominates at any given time manifests a dynamic equilibrium between dual, opposing processes that promote negative vs. positive coping responses. It remains for future research to confirm our findings, to validate and refine our theoretical model, and to develop interventions that can help patients with OC and other serious illnesses to achieve an optimal balance between uncertainty, fear, and hope.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because they consist of qualitative interview data containing potentially sensitive information, and participants have not given consent for their broader use. Requests to access the datasets should be directed to the corresponding author paul.han09@gmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Maine Medical Center Research Institute IRB. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PH contributed to the conceptualization, resources, funding acquisition, supervision, methodology, investigation, formal analysis, writing – original draft, and writing – review and editing. CG contributed to the conceptualization, methodology, investigation, formal analysis, writing – review and editing, and project administration. RH contributed to the formal analysis and writing – review and editing. JL contributed to the conceptualization, resources, project administration, and writing – review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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The Relationship Between Fears of Cancer Recurrence and Patient Gender: A Systematic Review and Meta-Analysis

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Background: A significant concern for patients treated for cancer is fear of cancer recurrence (FCR). Although a common experience, some patients report high levels of FCR that are difficult to manage and result in over vigilant checking and high use of health services. There has been speculation about the relationship of FCR with gender with mixed reports from several systematic reviews.

Aims: To determine the association of FCR with gender in previous reported studies and investigate the strength of this relationship with various moderators including year of publication, type of cancer and measurement attributes of self-reported FCR instruments.

Methods: A systematic review was conducted with searches of the literature from the MEDLINE, PubMed, Embase, and PsycINFO databases following PRISMA guidelines. All the included papers were divided into two groups, namely: "pure" that comprise only of patients with cancer types that both men and women can contract and "mixed" that report on patients with a variety of cancer types. The association between gender and FCR level was assessed by meta-analysis. A meta-regression was performed to investigate the moderating effects of factors including: the year of publication, cancer type, mean age of the sample and the length of the FCR scale measurement. This review was registered with PROSPERO, ID: CRD42020184812.

Results: Finally, 29 studies were included. The *N* size of pooled participants was 33,339. The meta-analysis showed females to have an overall higher level of FCR than males (ES = 0.30; 95% CI, 0.23, 0.36). The meta-regression of moderating or control variables found little, if any, systematic variation in effect-sizes.

Conclusion: This systematic review has clarified a potentially confused pattern of previous results in understanding the relationship between gender and FCR. Women report higher levels of FCR than men and this feature is one that clinicians and researchers can factor into their practice and future studies. The effect size is moderate, hence there is ample variation in FCR level, independent of gender, that requires further investigation.

Keywords: cancer recurrence, fear, meta-analysis, gender, demographic characteristics

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INTRODUCTION

Fear of cancer recurrence (FCR), or fear of progression (FoP) has been shown to be prevalent among cancer survivors, ranging from a normal reaction to a clinically significant level (Yang et al., 2017; Borreani et al., 2020). Through a rigorous consensus-based procedure in 2016, the latest commonly accepted definition of FCR is "fear, worry, or concern relating to the possibility that cancer will come back or progress" (Lebel et al., 2016). It is commonly reported to be the most significant concern of cancer survivors and the most frequent issue they want to discuss in consultations (Spencer et al., 1999; Lebel et al., 2007; Rogers et al., 2009; Ashing-Giwa and Lim, 2011). It has also been one of the most intensively studied areas of cancer-related health worries and unmet needs (Deimling et al., 2006b; Tsay et al., 2020). High-level FCR can lead to excessive checking behaviors and psychological distress, estimated to feature in 10% of cancer patients, as well as significant effects on associated mental health constructs such as depression and quality of life (QoL) (Hodges and Humphris, 2009; Tsay et al., 2020).

Researchers have been investigating factors associated with high FCR level. Demographic characteristics, such as gender, younger age, poorer education and lower income, may predict higher FCR level. Several studies have reported that females experience higher FCR than men (Wagner et al., 2018; Götze et al., 2019; Leclair et al., 2019), while others have not found any significant association between gender and FCR (Mullens et al., 2004; Steele et al., 2007; Jeon et al., 2019), and very few studies reported higher FCR in males (Yang et al., 2019; Luo et al., 2020). To date there has been no review exclusively focusing on the gender difference of FCR. Some comprehensive systematic reviews investigated factors that influence FCR level, including gender (Crist and Grunfeld, 2013; Koch et al., 2013; Simard et al., 2013). The results of these studies were somewhat contradictory. That is, they noted either that no results were provided to show a gender difference comparison or that there appeared to be little consensus, even when gender differences were explored. For instance, in Simard's review, only 4 studies reported significant association between genders and FCR while 12 other studies reported "no significance." Hence the number of studies to examine a possible gender difference was relatively small, and none of these reviews were able to draw a definite conclusion about the role of gender.

Some cancers are gender-specific, such as ovarian, cervical, uterus and prostate cancers, which only females or males could contract. Breast cancer can be diagnosed in very few cases of men, however, in terms of its rareness it is usually regarded as a gender-specific cancer type as well. When assessing the factor of gender, many studies included both gender-specific cancer types and general cancer types, which both male and female can contract. This may produce biased gender-related results because gender-specific cancers only include patients of one gender, which may result in a mix of gender and cancer type factors and a biased gender distribution in a study sample. For example, more than half of the sample of Stephens' study (Stephens et al., 2016) are breast/uterus and prostate cancers. The former are all women, and the latter are all men. So, in this part of the sample (3,461 out of 6,099), different genders had different cancer types. It is hard to identify the exact effect level that either gender or cancer type is responsible for. This might explain for example why Simard and Savard's study found that women reported higher FCR, which included gender-specific cancer types such as breast and prostate cancers, but the association disappeared when cancer types were controlled (Simard and Savard, 2009). Moreover, gender-specific cancers may result in additional mental health related problems because these cancers are usually associated to the genital system, sexual characteristics, and hormonal differences (i.e., biological factors). It has been reported that some breast cancer patients may undergo significant mental health problems due to the negative psychological impact of the disease itself and the experience of the treatment process (Capuron et al., 2000; Ganz, 2001). Therefore, when analyzing the factor of gender, it is necessary to control cancer types and especially distinguish between gender-specific cancers and general cancers.

The reason to explore this potential gender difference with greater attention is that the clinician can use the gender classification as a potential reliable indicator of FCR. A similar remark has already been raised by Lim and Humphris in their review of FCR and patient age (Lim and Humphris, 2020). Hence, the clinician who is aware of the patient's gender (in addition to knowledge of the patient's age) may have the potential to predict somewhat the FCR in patients attending out-patient clinics. The present study therefore aims to conduct a systematic review of quantitative studies to investigate the association between gender and FCR level. Studies including gender-specific cancers and those only including cancer that can be contracted by both genders are analyzed, respectively, and compared. Furthermore, to understand the reported systematic variation of discrepancies between men and women in FCR level, we examined the possible effects of publication year, cancer type, FCR measure and mean age of the study sample.

METHODS

Protocol

The present systematic review is registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/; ID: CRD42020184812).

Literature Collection

The relevant studies (published between 01 April 2000 and 01 May 2020) were identified by searching MEDLINE, PubMed, Embase, and PsycINFO databases, adhering to The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) systematic review and meta-analysis guidelines (Shamseer et al., 2015). We also included any study known to the research team that had been submitted or in press in peer-review journals.

The key search terms were ("fear" [MESH] OR worry OR concern OR anxiety) AND ("neoplasm" [MESH] or cancer or carcinoma) AND ("recurrence" [MESH] OR "neoplasm recurrence" [MESH] OR progression OR return OR relapse OR remit) AND (gender OR male OR female OR men OR women).

Inclusion/Exclusion Criteria

Papers selected for inclusion had to (a) be published in peer-reviewed journals between 01 April 2000 and 01 May 2020; (b) be written in English; (c) be quantitative studies and (d) report the association between patient gender and FCR or fear of progression (FoP) level in their results. Qualitative studies, dissertations, editorials, conference abstracts and commentaries were excluded. In addition, studies that reported fear of recurrence of nonneoplastic or noncancerous diseases were excluded.

Data Extraction

After removing duplicate studies, the titles and abstracts of potential references were reviewed, and unsuitable ones were excluded. Then full texts were acquired and examined. The papers that completely fulfilled the inclusion criteria were conserved and recorded. Data extraction was conducted by CP and overviewed by GH. The following data were extracted for each study: (a) Authors' names, (b) year of publication, (c) sample size of the study, (d) mean age of the sample, (e) cancer types, (f) statistical data on gender and FCR/FoP association, (g) difference direction (males or females that have higher FCR/FoP), (h) FCR/FoP measure utilized (i) country of study, and (j) study design.

For papers incorporated more than one wave of valid data collection from different samples, each data collection was, respectively, extracted as independent studies in our review protocol. Where studies incorporated longitudinal waves of data collections from the same sample, we decided *a priori* to extract the association statistic from the baseline wave. The logic of selecting the first instance of patient assessment in a panel study was that it would likely have the largest sample size and hence favorable statistical power.

Based on the cancer types included in each of the study samples, all the included papers were divided into two groups. Group 1 (pure group) included studies that exclusively have cancers of one site or one system without gender-specific types. Hence the patients in this group will have contracted cancer such as head and neck cancer that affects both men and women. Whereas, group 2 (mixed group) included the studies with a number of cancer types including, or not including, gender-specific cancers, such as studies with mixed ovarian, prostate and other cancers. Although breast cancer can be contracted by men in rare cases, it is also regarded as a gender-specific type because the vast majority of the patients are women. Only one study in the mixed group does not have gender-specific cancers (Langeveld et al., 2004). Thus, in the pure group, we will be able to exclude the potential bias caused by gender-specific cancers or other various cancer types, while the studies with mixed cancer types were also analyzed so that it could be compared with the pure group to see if significant differences do exist. The cancer type will also be analyzed globally as a moderator in the following meta-regression to further investigate its possible effect on our results.

Quality Assessment

The Joanna Briggs Institute (JBI) critical appraisal checklist for analytical cross-sectional studies was modified and applied to the cross-sectional, longitudinal, and RCT studies included in the present review (Aromataris et al., 2015; Lim and Humphris, 2020). The JBI checklist was an 8-item quality assessment tool. We excluded two items for our review which were not applicable: "was the exposure measured in a valid and reliable way" and "were objective, standard criteria used for measurement of the condition." The assessment selections of "unclear" and "not applicable" were merged into one. The 6-item tool was manually applied to all 29 studies included in this review. The modified checklist is presented in the **Supplementary Material**.

Statistical Analysis

Meta-Analysis

The meta-analysis of the two groups was conducted according to PRISMA guidelines to assess the association between gender and FCR in the included studies. The effect sizes were calculated using Comprehensive Meta-analysis routines (version 2.0). The raw correlation, odds ratio, *t*-test statistics or regression coefficients were obtained from the original published papers for conversion to an effect size in the analysis.

Heterogeneity

The heterogeneity estimates the variance among included studies, demonstrating the difference between the true effect size and the observed effect size. Measures of heterogeneity include Q value (random error), T^2 (variance of effect sizes), T (standard deviation of effect sizes), and I^2 (percentage heterogeneity) (Borenstein et al., 2009). We adopted a random effects model as the results tend to be more conservative and is considered more meaningful. That is, it calculates an effect size that can be referred to as a population estimate, as opposed to a fixed effects model that is more limited in its reference to the studies included in the review. In other words the random-effects model focuses not only on the differences in the effect-size in each study but also the sampling variability (chance).

Publication Bias

A conventional approach to publication bias was performed by plotting a "funnel plot" of the selected studies. Studies that reside outside pre-specified barriers or constraints can be identified. The number and patterns of these publications in occupying outside recognized contours would alert the review researcher to results that may be biased. The formal statistical tests, namely: Eggers and Beggs for reporting small study bias were performed. We also ran a procedure known as "one study removed" to assist with the detection of a single study that may distort the overall effect size estimation. The meta-analysis was rerun repeatedly and dropping in turn each study and replacing the previous omission. The purpose of this commonly utilized approach was to identify any major study that would influence unduly the final set of included studies.

Meta-Regression

Meta-regression was used to evaluate the association between one or more independent variables and effect size. It can be compared with multiple regression because similar statistical methods are used and it is possible to assess the relationship between the

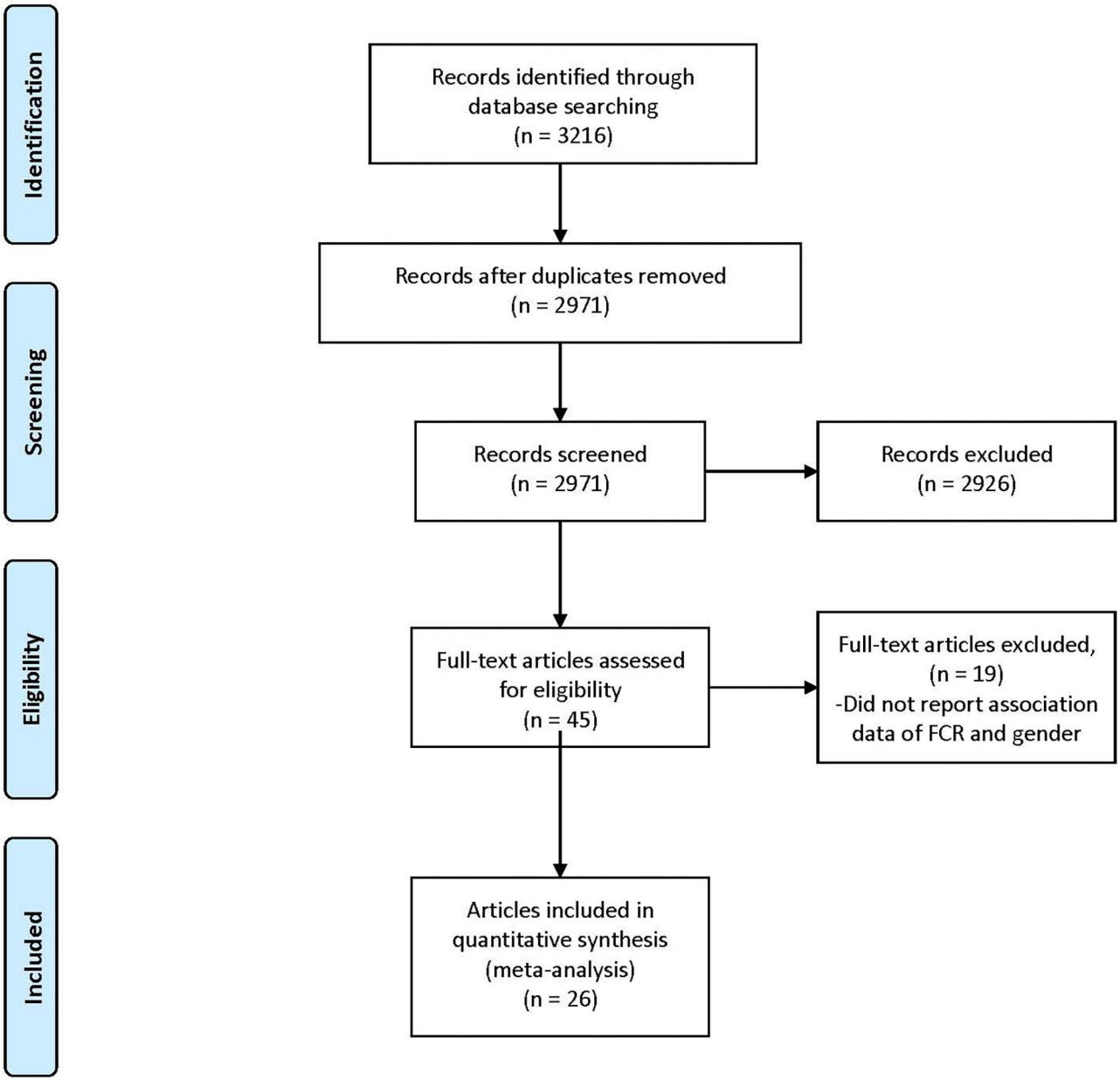

FIGURE 1 | Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram.

determined quality (or the moderator variable) and the effect size of each study (Thompson and Sharp, 1999; Higgins, 2011).

The analysis was performed adopting as the dependent variable the effect size for each study as displayed in the forest plot. With 29 studies therefore we have 29 effect sizes. We then include as independent variables the 4 moderator variables including the year of publication, cancer type, mean age of the sample and the length of the FCR scale measurement (single-item or multi-item).

The statistical results were produced by STATA15 software. The measures of heterogeneity were also generated, such as T^2, I^2, adjusted R^2, and z value. The alpha level was set to the 0.05 (double-sided).

RESULTS

Study Selection

The search process is shown in **Figure 1**. In total, 3,216 references were identified from the four databases (EMBASE, MEDLINE, PubMed, and PsycINFO). After the duplicates were excluded, the remaining 2,971 titles and abstracts were scrutinized for relevance. Preliminary screening identified 45 papers to be

relevant. The full texts were obtained, and the data regarding gender and FCR level were extracted. Finally, 26 papers were included. As described in the Data Extraction section, two included papers each incorporated two waves of data collection of different samples (Humphris et al., 2003; Deimling et al., 2006a). These four waves of data were extracted as four independent studies in the present review for analysis, entitled as Humphris[a,b] and Deimling[a,b] in **Table 1**. Additionally, one set of data was extracted from the Head & Neck 5000 study database, entitled as (Head Neck 5000 - NHS Foundation Trust, 2016[d]) and is being submitted. Hence the total number of studies for analysis is 29, out of which 15 were included in pure group and 14 were included in mixed group (**Tables 1A,B**).

Quality Assessment

Studies were all satisfactory as they were rated positively in half or more of the six criteria (**Tables 2A,B**).

Overall Effect

The N size of pooled participants was 33,339, 16,493 in the pure group and 16,846 in the mixed group. Two thirds of the included studies (66% i.e., 19 out of 29) reported that females have significantly higher FCR level. Two studies reported a higher average mean FCR score for males. These were conducted with separate samples from the Guangzhou Hospital Region (Yang et al., 2019; Luo et al., 2020). The forest plot (**Figure 2**) shows the effect sizes of the pure group and mixed group are, respectively, 0.28 (95% confidence interval: 0.24–0.32) and 0.29 (95% confidence interval: 0.18–0.40), with an overall effect size of 0.30 (95% CI: 0.23–0.36). The tests for the overall, pure, and mixed group effect size are, respectively, $z = 9.16$ ($p < 0.001$), $z = 13.90$ ($p < 0.001$), $z = 5.34$ ($P < 0.001$). With the "one study removed" analysis it was found that the minimum overall effect size reported was 0.284 demonstrating the very limited effect of any single study to influence the overall results. A classic Fail-safe *N* calculation resulted in 2,750+ studies would need to be found to bring the effect size to a not significant value ($p > 0.05$).

Heterogeneity

The overall Q value for heterogeneity is 127.75 (df = 27, $p < 0.001$), I^2 is 78%, and Tau^2 is 0.034. The Q values of the pure group and mixed group are 14.65 (df = 14, $p = 0.403$) and 105.40 (df = 13, $p < 0.001$), respectively. The difference between the two groups is significant ($p = 0.006$).

Publication Bias

The Egger and Begg tests found no consistent evidence of reporting bias ($z = -0.07$, $p = 0.94$ and $z = -0.99$, $p = 0.32$, respectively). Likewise, the funnel plots showed little evidence of consistent bias (**Figure 3**) as shown by an approximate symmetric pattern on either side of the 95% CI boundary.

Meta-Regression

A meta-regression was performed, including four moderators of the publication year (range = 2,003–2,020), cancer type (0 = pure or 1 = mixed), mean age (in years) of the sample (range = 24–74) and the length of the FCR measurement (0 = single-item or 1 = multi-item) (**Table 3**). No statistically significant effects of these moderators were found (all p levels > 0.4). In addition, we investigated the potential difference between single cancer type, such as the head and neck cancer, and the other cancers but again no reliable effect was shown ($z = -0.26$, $p = 0.79$).

DISCUSSION

The present study is the first systematic review and meta-analysis to investigate the gender difference of FCR specifically. It demonstrated a significant association between gender and FCR level, with a moderate overall effect size of 0.30 in a pooled sample of 33,339 from 29 studies, and the two groups "pure" and "mixed" reported consistent effect sizes of 0.28 and 0.29, indicating females with greater FCR levels. Only two studies from Guangzhou, China reported slightly higher FCR in males but the differences are not statistically significant (Yang et al., 2019; Luo et al., 2020). The overall effect size value stays stable with the removal of any single study. The quality assessment assured a good methodological standard for all the included studies, and no consistent bias was found.

Previously, it seems an apparent consensus among clinicians that a gender difference of FCR exists. However, there are many studies demonstrating no significant association between gender and FCR level. Some previous comprehensive systematic reviews to investigate possible determinants of FCR involved gender in their analysis (Crist and Grunfeld, 2013; Koch et al., 2013; Simard et al., 2013). However, given that gender was not the focus of their analysis, its role was not discussed in detail. The result of the present review has clarified the potentially confused pattern of previous results in understanding the relationship between gender and FCR. That is, women report higher levels of FCR than men, and this feature is one that clinicians and researchers can factor into their practice and future studies.

Possible Reasons for FCR Gender Differences

An explanation of the gender difference of FCR is likely to be multifactorial. The etiology of FCR development is complex and is poorly understood. The basis of how gender might influence FCR can be speculated upon from various sources. In general, gender differences are common and well-described in mental and psychological conditions among common people as well as cancer patients, and negative conditions are more prevalent in women than men (Faravelli et al., 2013; Salk et al., 2017; Aminisani et al., 2021). A recent study demonstrated that the frequency of psychological distress is especially high among women with colorectal cancers (Aminisani et al., 2021). Another study reported that female sarcoma patients have lower health-related quality of life (HRQoL) (Eichler et al., 2020). Specifically, first, gender differences of social and psychological indicators are associated to factors of income (Reiss, 2013), exposure to violence (Koss et al., 1995) and the division of labor by gender (Wood and Eagly, 2012). These social factors also apply to cancer patients, and women cancer patients usually need more social and mental support (Ozbayir et al., 2019). These have been explained as largely stemming from the gender inequality against women

TABLE 1A | Summary characteristics of the included studies in pure group.

References	Sample size (N)	Mean age (SD)	Caner type	Main results	Higher FCR	FCR measurement	Country	Study design
Pure								
Wagner et al. (2018)	136	54.3 (12.6)	Melanoma	Mean score (SD) Female = 32.2 (±8.4) Male = 28.5 (±8.0)	Female	FoP-Q-SF	Germany	Cross-sectional
Koch-Gallenkamp et al. (2016)	1,052	69	Colorectal Cancer	Mean score (SD) Female = 28.5 (9.6) Male = 25.6 (8.2)	Female	FoP-Q-SF	Germany	Cross-sectional
Sarkar et al. (2014)	239	50.4 (12.6)	Hematological Cancers	Multiple linear regression analysis b = 4.45	Female	FoP-Q-SF	Germany	Prospective clinical trial
Mirosevic et al. (2019)	216	62.3 (9.7)	Head and Neck Cancer	Age-adjusted univariate regressions Beta = 0.337 t = 0.502 P = 0.62	NS	CWS	the Netherlands	Cross-sectional
Humphris et al. (2003)[a]	87	58.3 (11.3)	Orofacial Cancer	Recurrence concern frequency; n (%) Male 50 (82%) Female 22 (85%)	NS	CWS	UK	Prospective (Sample 1)
Humphris et al. (2003)[b]	50	58.3 (11.4)	Orofacial Cancer	Recurrence concern frequency; n (%) Male 22 (63%) Female 10(67%)	NS	CWS	UK	Cross-sectional with follow up (Sample 2)
Borreani et al. (2020)	75	N/A	Hematological Cancer	Multiple linear regression B = 0.416 SE = 0.153 β = 0.306 t = 2.724	Female	FCRI	Italy	Cross-sectional
Fisher et al. (2016)	10969	≥65 6,772 <65 4,197	Colorectal Cancer	Binary logistic regressions; Male = 1 OR (95% CI) 1.59 (1.48, 1.72)	Female	Single question	UK	Cross-sectional
Deimling et al. (2006a)[a]	96	N/A	Colorectal Cancer	Mean (SD) Female 10.9 (3.2) Male 11.7 (3.1)	Female	4 items	USA	Cross-sectional
Mullens et al. (2004)	41	56.1	Colorectal Cancer	Women 2.08 (0.88) Men 2.07 (0.64)	NS	Single question	USA	Cross-sectional
Steele et al. (2007)	91	≤60 years 32 61–70 years 39 >70 years 20	Colorectal Cancer	Chi-square test p = 0.52	NS	Single question	UK	Cross-sectional
Rogers et al. (2010)	123	<55 years 32 55–64 years 45 65+ years 46	Head and Neck Cancer	Chi-square p = 0.86	NS	PCI	UK	Clinical cohort trial
Erim et al. (2013)	70	58.1 (15.5)	Malignant Melanoma	Multiple linear regression Z = −2.447; p = 0.014	Female	FoP-Q	Germany	Cross-sectional
Humphris et al. (2018)	53	67	Colorectal	Women 9.000 (3.406) Men 8.563 (4.071)	Female	FCR4	UK	Cross-sectional
Head Neck 5000 - NHS Foundation Trust (2016)	3195	<50 years 13.6% ≥50 years 86.4%	Head and Neck Cancer	Women 11.86 (4.05) Men 10.62 (3.90)	Female	FCR4	UK	Prospective longitudinal

The [a,b] mean to differentiate them as described in Results-Study Selection.

TABLE 1B | Summary characteristics of the included studies in mixed group.

References	Sample size (*N*)	Mean age (SD)	Caner type	Main results	Higher FCR	FCR measurement	Country	Study design
Mixed								
Götze et al. (2019)	1,002	66.7 (10.5)	Mixed	Mean (SD) Male22.1 (8.4) Female 27.4 (9.5) effect size $d = 0.593$	Female	FoP-Q-SF	Germany	Cross-sectional
van de Wal et al. (2016)	2,615	63.6 (12.9)	Mixed	Male 2.64 Female 2.84 (1.00) $t = -4.898$ effect size d = 0.19	Female	IOC-HWS	The Netherlands	Cross-sectional
Stephens et al. (2016)	6,099	<65 $n = 2{,}595$ 65 $n = 3{,}499$	Mixed	Mean(SD) Male 0.85 (1.10) Female 1.26 (1.28)	Female	CPILS	USA	Cross-sectional
Matthews (2003)	123	54.96	Mixed	Analysis of covariance, Mean(SD) Male = 5.64 (SD 3.44) Female = 5.69 (SD 3.84) $F = 0.01$ df = 1, 121	Female	QOL-F/CS	USA	Cross-sectional
Baker et al. (2005)	752	18–54 years 50% >54 years 50%	Mixed	Chi-square tests OR (95% CI) 1.5 (1.23–1.75)	Female	Single item	USA	Prospective longitudinal
Simard and Savard (2009)	600	Lung 62 (1.5) Breast 59 (0.6) Colorectal 61.6 (1.3) Prostate 69.1 (0.5)	Mixed	Correlation $r = 0.31$	Female	FRQ	Canada	Cross-sectional
Mellon et al. (2007)	207	65 (6.2)	Mixed	Point biserial correlations $r = 0.04$	NS	FRQ	USA	Cross-sectional
Langeveld et al. (2004)	400	24 (4.9)	Mixed	Mean (SD) Male 7.3 (2.7) Female 8.2 (3.0) effect sizes $d = 0.31$ $p < 0.05$ *t*-test	Female	Single item	Netherlands	Cross-sectional
Deimling et al. (2006a)[b]	321	72.3(7.5)	Mixed	Regression 1 = Female Item 1–4: $r = -0.07, -0.02, -0.02, -0.02$	Female	Four items	USA	Cross-sectional
Gemmill et al. (2010)	307	74 (8.7)	Mixed	Mean score Female 7.0 Male 7.9 $p = 0.02$	Female	HRQOL	USA	Cross-sectional
Hinz et al. (2014)	2059	62.4	Mixed	Two-way ANOVAs *d* (effect size) = 0.52	Female	FoP-Q-SF	Germany	Prospective
Mikkelsen et al. (2009)	340	59.5 (11.5)	Mixed	Positive answers number, *N* (%) Male 51 (40.8) Female 125 (58.1)	NS	Single question	Denmark	Cross-sectional
Luo et al. (2020)	996	48.04 (11.71)	Mixed	Multivariable logistic regression Female Exp (*B*) = 1.292 $P = 0.348$	Male (NS)	FoP-Q-SF	China	Cross-sectional
Yang et al. (2019)	1025	<35 years 14.2% 35–60 years 65.9% >60 years 19.9%	Mixed	*t* (df) = 1.13 (1,023)	Male (NS)	FCR7	China	Cross-sectional

Abbreviations of FCR measurements: FoP-Q, Fear of Progression Questionnaire; FoP-Q-SF, Fear of Progression Questionnaire-Short Form; CWS, Cancer Worry Scale; FCRI, Fear of Cancer Recurrence Inventory; PCI, 45-item Patient Concerns Inventory; FCR4 or FCR7, 4 or 7 item version of the Fears of Cancer Recurrence Scale; IOC-HWS, The Health Worries subscale of the Impact of Cancer scale; CPILS, Cancer Problems in Living Scale; QOL-F/CS, Quality of Life–Family/Cancer Survivor; FRQ, Fear of Recurrence Questionnaire; HRQOL, Health-related quality of life.

TABLE 2A | Quality assessment by modified Joanna Briggs tool on the included studies in pure group.

References	Item 1 inclusion criteria	Item 2 subject details	Item 3 confounds	Item 4 strategies	Item 5 measure-ments	Item 6 statistics	Overall score (6 max)
Pure group							
Humphris et al. (2003)[a]							5
Humphris et al. (2003)[b]							5
Mullens et al. (2004)							5
Deimling et al. (2006b)[b]							6
Steele et al. (2007)							3
Erim et al. (2013)							5
Sarkar et al. (2014)							6
Koch-Gallenkamp et al. (2016)							6
Fisher et al. (2016)							4
Wagner et al. (2018)							6
Humphris et al. (2018)							4
Mirosevic et al. (2019)							6
Borreani et al. (2020)							6
Rogers et al. (2010)							4
Head Neck 5000 - NHS Foundation Trust (2016)							6

Green = "Yes"; Red = "No"; Yellow = "Unclear/Not applicable." The [a,b] mean to differentiate them as described in Results-Study Selection.

TABLE 2B | Quality assessment by modified Joanna Briggs tool on the included studies in mixed group.

References	Item 1 inclusion criteria	Item 2 subject details	Item 3 confounds	Item 4 strategies	Item 5 measure-ments	Item 6 statistics	Overall score (6 max)
Mixed group							
Matthews (2003)							6
Langeveld et al. (2004)							5
Baker et al. (2005)							5
Deimling et al. (2006b)[a]							6
Mellon et al. (2007)							6
Simard and Savard (2009)							4
Mikkelsen et al. (2009)							5
Gemmill et al. (2010)							4
Hinz et al. (2014)							4
van de Wal et al. (2016)							6
Stephens et al. (2016)							6
Götze et al. (2019)							6
Luo et al. (2020)							6
Yang et al. (2019)							6

Green = "Yes"; Red = "No"; Yellow = "Unclear/Not applicable."

within society but vary widely on a cross-nation level (Salk et al., 2017). Second, women cancer patients are more inclined to express their problems and seek for help, while men patients may abstain from expressing fear or worry when suffering a negative condition because of feelings of shame (Clover et al., 2015; Anuk et al., 2019). This implies that women may tend to report higher FCR level.

The Comparison Between Groups and the Heterogeneity

Many studies with mixed cancer types included gender-specific cancers when assessing the effect of gender. This may have potential impact on the gender distribution of study samples and gender-related analysis, and lead to bias of study results. Given this concern, we divided all the included studies into "pure" and

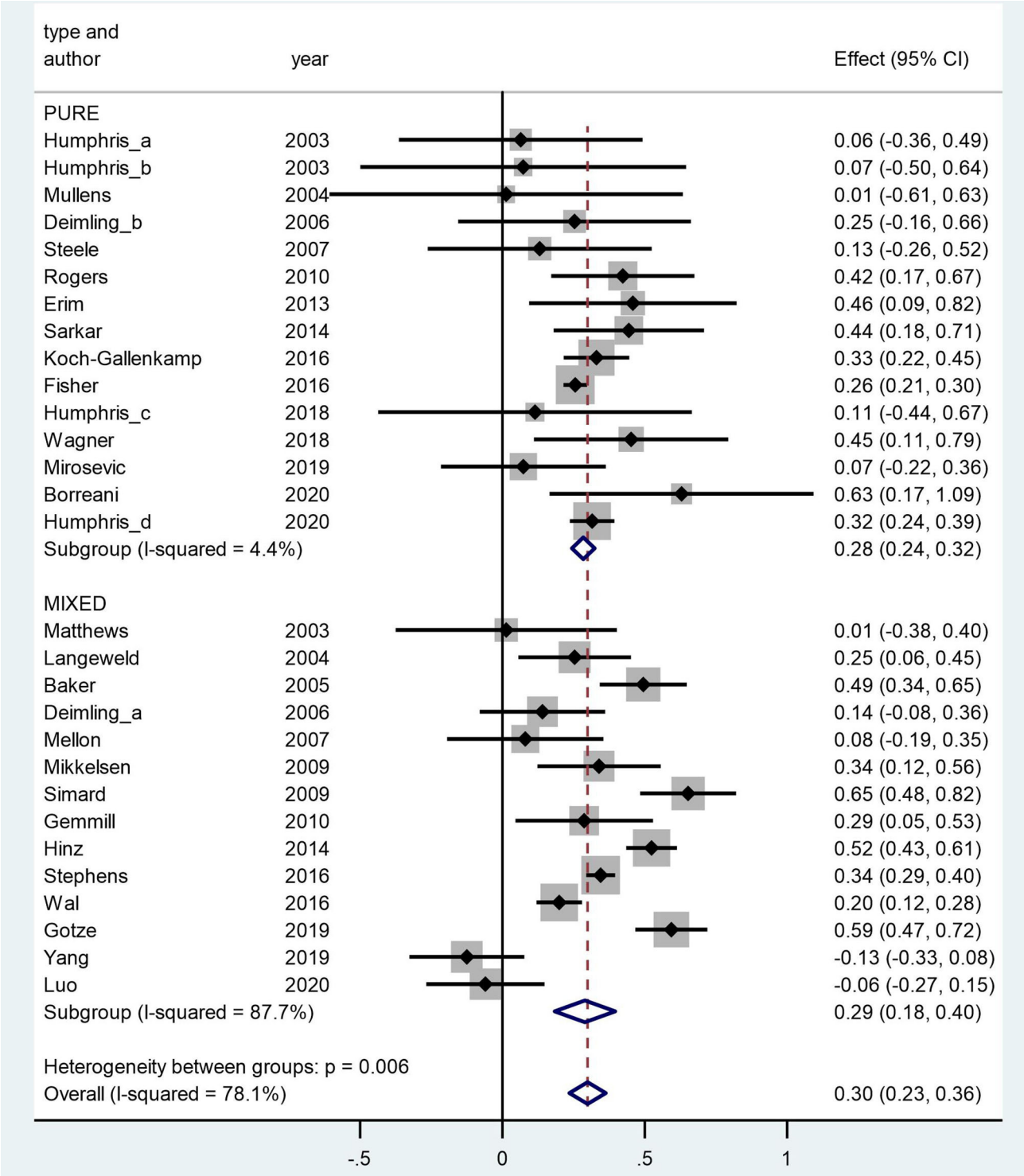

FIGURE 2 | Forest plot of fears of cancer recurrence (FCR) and gender in a random-effects model. Weights are from random-effects model.

"mixed" groups. The cancer type seems to have a very limited effect, and less than expected on effect sizes of the two groups, resulting in almost identical values (0.28 vs. 0.29). However, the heterogeneity of the mixed group is much greater than the pure group, leading the overall heterogeneity to a similarly high level. This was to be expected because studies of the mixed

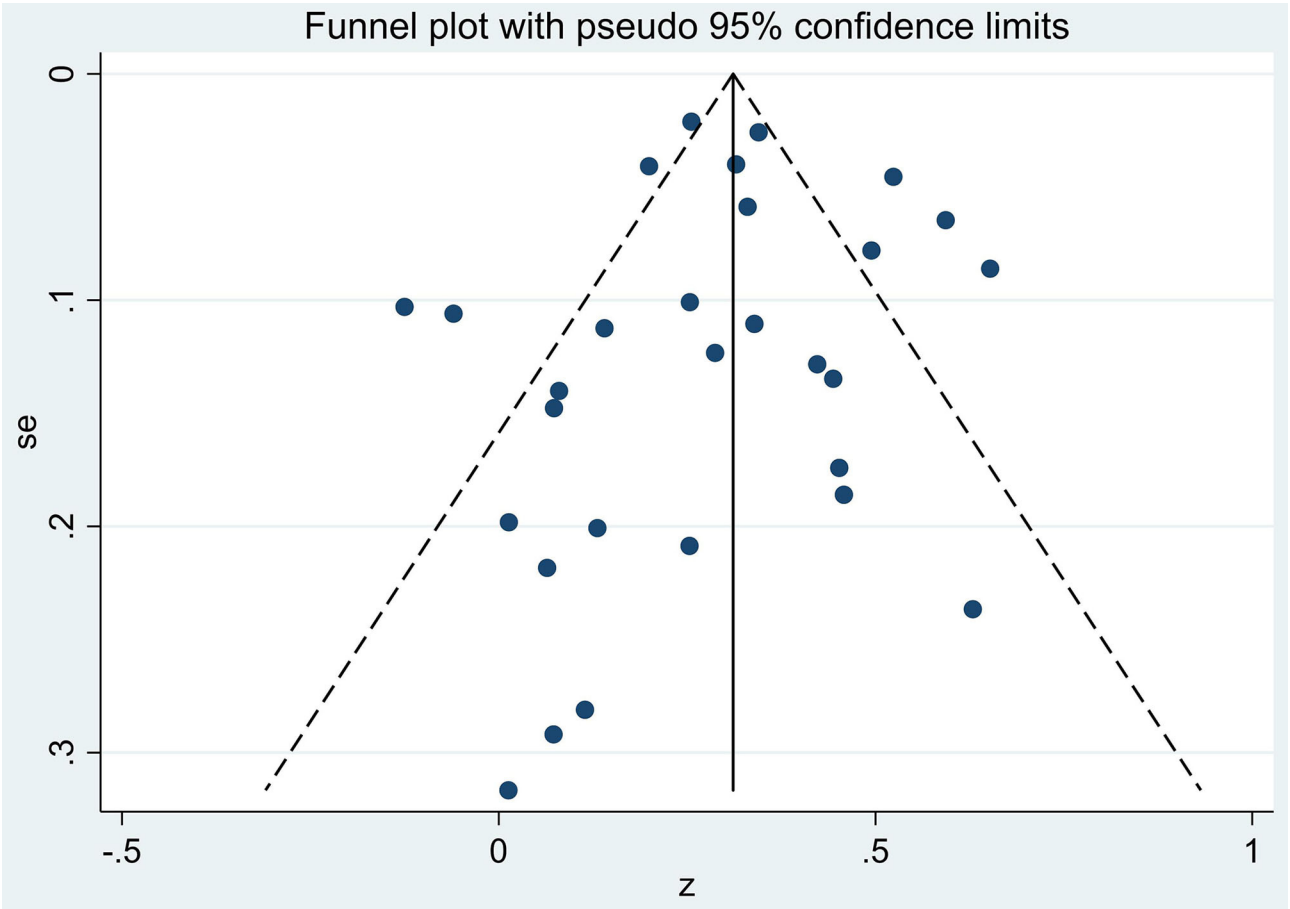

FIGURE 3 | Funnel plot of the four covariates: year of publication, cancer type, age of sample, and FCR measurement on gender by fears of cancer recurrence (FCR) association effect sizes (z).

group have more diverse samples with various types of cancer including gender-specific cancers and in addition the authors adopted more complex data analytical approaches. They also used, on inspection, a more variable set of FCR measurement tools. Most of the studies of the pure group used standardized questionnaires such as the Fear of Progression Questionnaire (FoP-Q) or the 4 item version of the Fears of Cancer Recurrence Scale (FCR4), while in the mixed group, almost all the studies used study specific FCR measures ranging from a self-defined single question, 4-item scale, to subscales extracted from various other questionnaires such as the Cancer Problems in Living Scale (CPILS), the Health Worries subscale of the Impact of Cancer scale (IOC-HWS) or Health-related Quality of Life (HRQOL). The exception to this rule were three studies that consistently used the FoP-Q short form (Hinz et al., 2014; Götze et al., 2019; Luo et al., 2020). This possible complication, may reflect itself in the observed level of heterogeneity of the mixed group as well as the overall statistics. We consider this may not influence our conclusion substantially because the heterogeneity of the pure group stays at a very low level, and the pure group possessed an almost identical effect size as the mixed group and subsequently the overall result.

TABLE 3 | Meta-regression of effect sizes by four covariates: year of publication, cancer type, age of sample, and FCR measurement on gender by fears of cancer recurrence (FCR).

Moderators	B coef	SE	*t*	*P*	95% conf. interval	
Year of publication	0.000	0.008	0.02	0.983	−0.016	0.017
Cancer type	0.005	0.088	0.05	0.957	−0.176	0.185
Age of sample	0.003	0.004	0.75	0.459	−0.006	0.012
FCR Item length	0.047	0.105	0.45	0.660	−0.170	0.264

Moderator Variables

We performed a meta-regression including four moderator variables of: cancer type, publication year, mean age of the sample and single- or multi-item FCR measurement, because these factors have potential effects on FCR level. FCR level

differs among patients with different cancer types (Crist and Grunfeld, 2013; Simard et al., 2013), which was also discussed in the gender-specific cancer relevant section in this review. In a meta-analysis about the relationship between age and FCR, the authors found the more recent the study, the strength of the effect size decreases (Lim and Humphris, 2020). Several studies demonstrated a relationship between patient age and FCR. The older the cancer patients, the lower the reported FCR level (Simard et al., 2013; Lim and Humphris, 2020). Furthermore, given that there is no consensus on the measurement tool of FCR, the methods in literatures vary from the 43-item Fear of Progression Questionnaire (FoP-Q) (Erim et al., 2013) to a single-item question like "I have fear about my cancer coming back" (Fisher et al., 2016), which generate different FCR results. However, no significant result of the moderator variables was found in the present study, demonstrating they might have less effect than expectation. But in consideration of the previous positive evidence mentioned above, these factors are still important in future studies to be explored further.

Clinical Implications

In clinical communication, clinicians play a crucial role and often occupy an important position from the patient's perspective. It has been recommended that clinicians should pay attention to the discussion of FCR with cancer patients. There are studies showing that non-mental health trained clinicians can provide effective interventions for FCR (Liu et al., 2019). But this is still challenging because non-mental health trained oncologists often have difficulties in deciding which patients need such assistance. There are tools developed to assist clinicians to be aware of cancer patients' individual needs, such as the Patient Concerns Inventory (PCI), a checklist where patients can select the items they want to discuss at a clinic, including the fear of cancer recurrence (Rogers et al., 2018). However, it may be of benefit if the more easily obtained demographic characteristics, such as gender and age, can be used as easily available indicators to help clinicians to focus on the discussion of FCR with patients at high risk. The result of this review fits our prediction and supports clinicians who consider gender as a useful indicator of FCR level. It might help clinicians to focus discussion of FCR with patients attending follow-up clinics when combine their gender with other easily obtained demographic characteristics, and help improve the efficiency of doctor-patient communication.

Strengths and Limitations

This review has a number of strengths including the systematic search for all quality studies that reported the relationship between fears of recurrence or progression with gender. In addition, this is the first study to utilize meta-analytical and meta-regression methodology to assist interpretation of a substantial pooled sample of reported investigations. However, this systematic review and meta-analysis has several limitations. First, to completely avoid the potential bias from gender-specific cancers, only papers about both-gender cancers should be included. However, only sixteen studies have met this criterion, which provides some evidence but not extensive. Therefore, we included gender-specific cancers and divided these studies into two groups ("pure" and "mixed") as outlined already with the additional analysis to study the effect of cancer types, that showed no statistical significance. Second, this review excluded papers not written in English, which may reduce its generalisabilty to some extent.

Future Directions

In the literatures on FCR so far, gender has been usually regarded as a "not-so-important" factor out of various demographic characteristics. The effect of gender should be investigated with greater consideration and authors in the FCR field are encouraged to report FCR levels by gender. When attempting to assess the factor of gender, cancer types that only a single gender can contract should be considered carefully in their interpretation when intending to investigate gender FCR differences. An argument can be voiced to exclude such cancer types in assessing gender and FCR association to avoid possible confusion. In terms of the high-level heterogeneity observed in the mixed group of this review, while the mixed group of studies may have included a wider selection of patient samples the varied measurements employed indicated that an international consensus on the FCR measurement may be helpful to reduce the number of measures and possibly strengthen consistency. In addition, authors of future studies are commended to include in their manuscript results a breakdown or association statistic of gender and FCR to assist any review update and strengthen our understanding of this key relationship.

CONCLUSION

In this systematic review of studies over the past 20 years, the previous confusing pattern of outcomes reported in the literature of the relationship between gender and FCR was clarified. Women report higher levels of FCR than men, a finding that clinicians and researchers can factor into their practice and future research with care to avoid possible stereo-typing. With only a moderate effect size, indicating that the level of FCR was somewhat variable, independent of gender, demonstrates that further study is required.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

GH conceived the study, analyzed the raw data, and reviewed and edited the original draft. CP collected

the papers, extracted the raw data and wrote the original draft. The whole study process was overviewed by GH and discussed regularly by GH and CP. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.640866/full#supplementary-material

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Using Co-design With Breast Cancer Patients and Radiographers to Develop "KEW" Communication Skills Training

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Previous work (FORECAST) has shown that concerns of breast cancer patients after finishing radiotherapy are responsive to conversations with radiographers during the treatment period. This study seeks to further understand radiographer and patient experiences, determine shared priorities for improvement in clinical interaction and develop communication guidelines and training to help radiographers support patients.

Methods: Using the principles of Experience-Based Co-Design, semi-structured interviews were held with $N = 4$ patients (videoed) and $N = 4$ radiographers, followed by feedback events ($N = 7$) to validate findings. Patients and radiographers exchanged experiences in a joint co-design session, agreed with shared priorities and generated ideas for further support. A survey was conducted for process evaluation. To scale up findings, UK-wide representatives from patient networks ($N = 8$) and radiographers and managerial staff ($N = 16$) provided consultative input utilizing an iterative, adaptive procedure.

Results: Radiographers expressed a need for support with "difficult conversations," especially those on Fear of Cancer Recurrence, and their appropriate management. Important pointers for reassuring communication were identified, including: being treated like a person, knowing what to expect, and space to ask questions. The co-design process was rated positively by both staff and patients. Thematic collation of findings and mapping these on literature evidence resulted in the "KEW" communication guidelines for radiographers: Know (Confidence; Expectations; Person), Encourage (Emotions; Space; Follow-up), Warmth (Start; Normalize; Ending). National stakeholder consultations validated and helped fine-tune the training model. The resulting training package, included: trigger videos ($n = 6$), a simulated patient scenario and interactive handouts on fears of cancer recurrence and the patient pathway.

Conclusions: The co-design process captured good practice to help standardize quality in empathic communication in the radiotherapy service. The resulting KEW: Know, Encourage, Warmth guidelines, and training package are user-centered as well as evidence-based. Supplementing single-site co-design with national consultative

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feedback allows for the development of interventions that are relevant to the clinical practice, even in detail, and helps to generate appropriate buy-in for roll out on a wider scale after evaluation.

Trial Registration: www.ClinicalTrials.gov ID: NCT03468881

Keywords: recurrence fear, psycho-oncology, radiotherapy, co-design, patient involvement, breast cancer, communication training

INTRODUCTION

While medical outcomes for people with a breast cancer diagnosis are steadily improving (Allemani et al., 2018), cancer patients' psychological needs often remain unmet (Sanson-Fisher et al., 2000). One of the most prevalent concerns relates to the possibility of the cancer coming back or progressing to other parts of the body (Fear of Cancer Recurrence), experienced by up to 86% of breast cancer survivors. At higher levels, such worries can lead to intense psychological emotional reactions, poor quality of life, and functional impairments (Simard et al., 2013).

The original FORECAST study, in which breast cancer patients' fears of cancer recurrence trajectories were mapped throughout and following their radiotherapy treatment, showed that patients are likely to experience lower levels of emotional distress after treatment if they get the space to express their concerns to their therapeutic radiographers while they are in receipt of the radiotherapy service (Barracliffe et al., 2018; Humphris et al., 2019). Although radiographers regularly encounter questions about emotional concerns both during these review sessions and at the treatment machine (Barracliffe et al., 2018), in the UK, there are no professional competencies associated with communication skills training (Azevedo et al., 2019).

A recent literature review showed that Communication Skills Training (CST) for the radiotherapy team has the potential to improve communication of staff members as well as patient outcomes such as anxiety and concerns (van Beusekom et al., 2019). There are also promising indications that training can help to improve the supportive skills of members of the radiotherapy team (Timmermans et al., 2006; Merckaert et al., 2015) and how often "emotional words" are used by patients when interacting with the trained radiotherapy team (Gibon et al., 2013; Merckaert et al., 2015).

A requirement for successful embedding of communication training in the context of radiotherapy is support from the organization and staff members who receive the training and being able to work around practical constraints within the service (Gibon et al., 2013; Liénard et al., 2016). A collaborative approach to developing such training together with relevant stakeholders can help to ensure a good fit with the day-to-day reality of the service and increase the likelihood of long-term engagement (Steen et al., 2011), a method described as co-design (Sanders and Stappers, 2008). Experience-Based Co-Design[1] is an approach to co-design in the field of healthcare that encourages an exchange of experiences between patients and healthcare staff (Donetto et al., 2014, 2015; Rohde et al., 2016) to prioritize and work out improvements for a service.

This study describes the development of a model for empathic communication in the radiotherapy setting and corresponding communication skills training for radiographers. It builds upon the findings of the original FORECAST project, but uses a co-design approach to start with an in-depth qualitative understanding of radiographer and patient experiences and of shared priorities for quality in clinical interaction, to ensure the development of a user-centered, clinically relevant intervention to support the patient pathway.

MATERIALS AND METHODS

This paper covers phases 1 and 2 of the FORECAST2 study (van Beusekom M. M. et al., 2018): a co-design process with patients and staff and development process with national stakeholders input. The work has been approved by the London-Surrey Research Ethics Committee (18/LO/0669) and the University Teaching and Research Ethics Committee (MD13914). Informed written consent was obtained from all participants. All described sessions were facilitated by a health behavior expert (MB) and/or clinical psychologist with expertise in psycho-oncology (GH). Interactive and creative tools were used, designed to foster an open exchange between patients and staff. Materials included: portable white board and markers, "sticky note" pads, colored felt pens, video camera, handouts, index cards, and feedback grids.

Experience-Based Co-design

Experience-Based Co-Design (EBCD) principles and the online EBCD toolkit[2], were used to capture how radiographers and patients with breast cancer experience the radiotherapy service, understand what helps to make a good experience and what could be further improved to support the patient experience (**Figure 1**).

Individual Interviews

First, semi-structured interviews were held (MB) with $N = 4$ radiographers (female; aged 32–48; 5–10 years or >10 years

Abbreviations: FCR, Fear of Cancer Recurrence; EBCD, Experienced-Based Co-Design; RT, radiotherapy; Pat, patient; Rad, radiographer.

[1]The Point of Care Foundation. EBCD: Experience-based co-design toolkit. Available from: https://www.pointofcarefoundation.org.uk/resource/experience-based-co-design-ebcd-toolkit/

[2]The Point of Care Foundation. EBCD: Experience-based co-design toolkit. Available from: https://www.pointofcarefoundation.org.uk/resource/experience-based-co-design-ebcd-toolkit/'

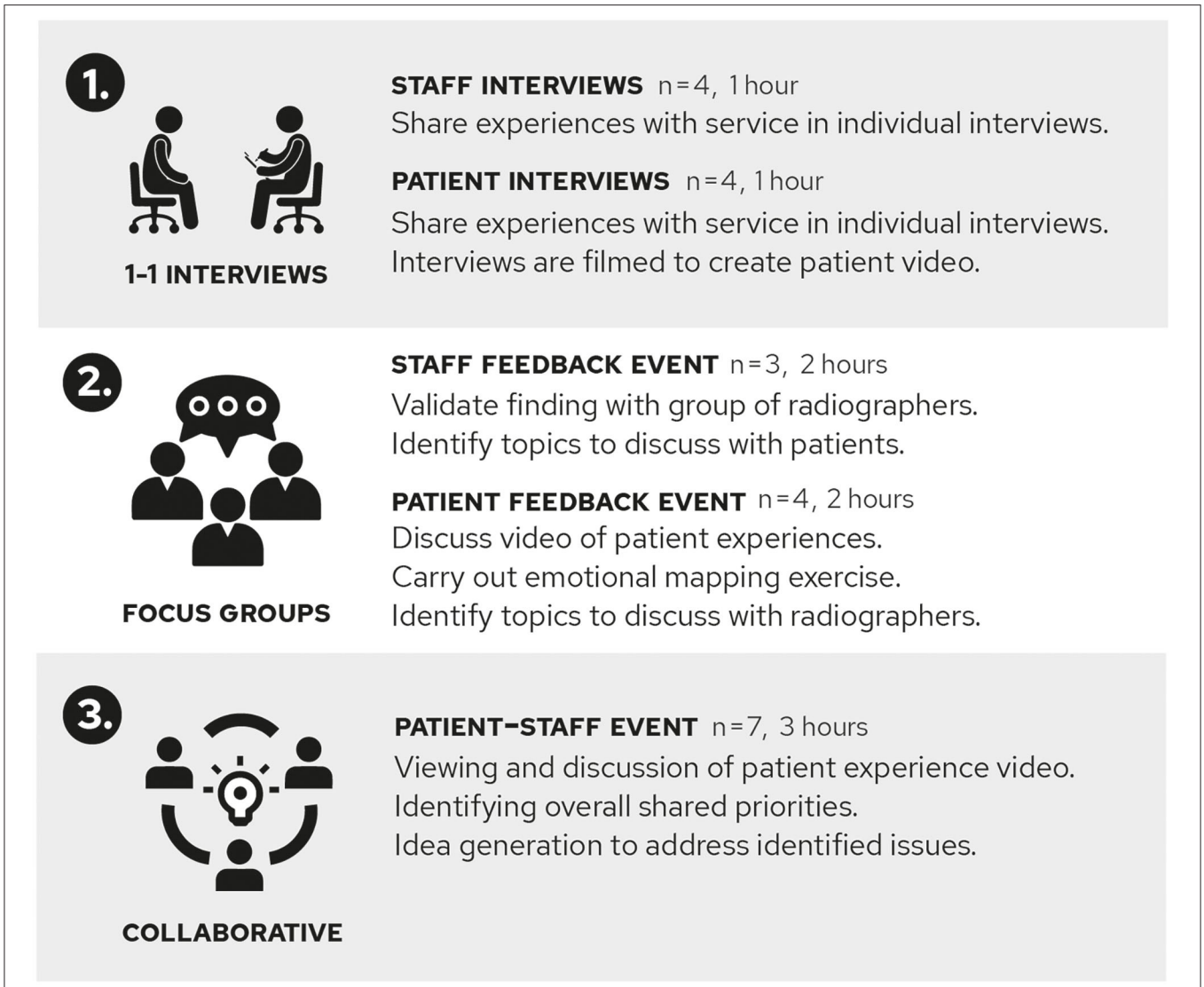

FIGURE 1 | The three steps of the Experience-Based Co-Design Approach.

experience as therapeutic radiographer) and $N = 4$ women (aged 51–70; education from secondary education to University degree; no chemotherapy; no trastuzumab), who had recently finished radiotherapy for breast cancer at a major NHS Lothian Cancer Center. Patients were recruited and consented by the Clinical Radiographer Specialist on the project team and endorsed by responsible consultant. The 30- to 60-min-long interviews were filmed and used the topic guide shown in **Table 1**. Throughout the interviews, the researcher (MB) summarized the conversations to help validate findings.

Within the study department, the on treatment review clinic is undertaken by a team of three radiographers: a lead Radiographer who specializes in breast cancer and two radiographers who work clinically and undertake breast review as part of their role. It is a radiographer-led service where the role of the radiographer can include all aspects of the breast cancer patient journey from CT planning, review, consent, follow up as well as triaging problems post-radiotherapy. Female radiographers were involved in the co-design discussions, as male radiographers do not perform breast review in the study department.

Feedback Events

To prepare for the patient feedback event, topics were collated thematically and a short video was edited using fragments from the filmed interviews to reflect patient experience. In addition, a handout was designed that listed the identified "significant moments of interaction" with the service. To aid the discussion at the feedback event, this handout included questions from Synthesized Member Checking (Birt et al., 2016) to check whether the outputs matched the participants' experience and if they wanted to change anything. After discussion of the video

TABLE 1 | Topic guide for radiographer and patient individual interviews as part of the Experience-Based Co-Design process.

Topic guide radiographers	Topic guide patients
Background of role and experiences working in the service, e.g.: can you describe a typical day's work in this service? What does a good day at work look like, and a frustrating one? What challenges do you encounter from a staff point of view?	**Treatment journey up to this point**, e.g., could you tell me a little about the first time you went in for radiotherapy treatment? What was your first impression? What stands out about meeting your radiographer for the first time?
Perceptions of the patient experience, e.g.: What do you think it is like to be a patient in this service? Which patient needs are met, which not? What are the things that really shape the patients' overall experience?	**Satisfaction with the radiotherapy service, including (1) the relationship with the radiotherapy staff and information provision**, e.g.: how satisfied have you been with the care you received during radiotherapy? How did you get on with the radiotherapy staff? Were there things that you were worried about but didn't know whether you could ask or not?
Thoughts on improving communication in the service, e.g.: how do you experience speaking with patients at the review meeting? Do you experience difficulties to talk at some length or in depth? What do you see as main priorities for improving communication with patients from the staff point of view? What do you think that patients would identify as priorities?	**… and (2) questions on the 'best and worst bits' of radiotherapy,** e.g.: what moments in the radiotherapy journey really shaped your overall experience? What were the crucial moments in talking with your radiographer?

and moments of interaction, an Emotional Mapping exercise[3] was done at the feedback event, in which the moments of interactions were mapped out across the meeting room wall on a portable whiteboard. Participants were asked to map on a high-low scale how positive or negative that interaction with the service had been in their experience and to add words denoting their emotional experience. This map was discussed as a group with the researchers (MB, GH) and priorities were discussed for what to bring to the subsequent joint event with radiographers.

Prior to the radiographer feedback session, the researchers (MB and GH) framed core insights from the staff interviews as "Insight Statements"[4] At the feedback session, these were presented on a handout with supporting quotes and discussed as a group to validate findings. Together, these "Insight Statements" were converted into "How Might We?" questions[5], which were then mapped out on the wall display. The radiographers were invited to map their priorities as a group on a high-low scale, where higher on the wall indicated the topic was considered more important. A selection was made of topics to be addressed internally and topics to bring to the co-design work.

Staff-Patient Session

At the joint staff-patient session (3 h), participants first watched and discussed the patient experience video together. Card sorting was used to translate and narrow down topics identified in the feedback sessions to shared priorities to move forward. These priorities were then presented in the context of four significant interactions of patients with the radiotherapy service. In a brainstorm carousel, radiographer-patient pairs rotated through these settings to generate ideas to address the questions raised. To round up, the outcomes were discussed as a group.

[3]The Point of Care Foundation. Running the Patient Feedback Event [Available from: https://www.pointofcarefoundation.org.uk/resource/experience-based-co-design-ebcd-toolkit/step-by-step-guide/11-running-patient-feedback-event/

[4]IDEO.org. Create Insight Statements [cited 2019 09]. Available from: http://www.designkit.org/methods/62

[5]IDEO.org. How Might We [cited 2019 09]. Available from: http://www.designkit.org/methods/3

Evaluation Co-design

The co-design process was evaluated through paper-based self-report surveys that are part of the online Experience-Based Co-Design toolkit[6], distributed to the participants at the end of the session and collected ∼1–2 weeks later via post, email or in person. The survey included seven questions about the patient experience video, discussing experiences with staff and patients, discussing priorities for the project, comfort with participation, any issues that were not discussed, and suggestions for improvements for future events. Participants could rate on a 5-point scale, from excellent to very poor, and space was provided for open-ended responses.

Scaling Up: Iterative, Consultative Development

Following the co-design session, $N = 24$ national stakeholders were involved in the consultative, iterative development of a model for empathic communication and supporting training package. The aim was to "scale up" findings beyond the single center and include a national perspective in the development of the training, to ensure it reflects the reality of the wider service.

To build the model, co-design findings were mapped onto the KEPe Warm framework, which has been shown to reduce patient distress in primary care consultations (Little et al., 2015). Several resources were consulted for good practice on the format of the supporting training, including Draper and Silverman's framework for designing communication skills teaching sessions (Draper and Silverman, 1990) and reviews on communication skills training for healthcare professionals working with people who have cancer (Moore et al., 2018) and in the radiotherapy setting specifically (van Beusekom et al., 2019).

Starting with the communication model draft and storyboards with conversation scenarios, new training materials were developed and included throughout the iterative feedback process. **Table 2** shows the number of participants providing

[6]The Point of Care Foundation. EBCD: Experience-based co-design toolkit. Available from: https://www.pointofcarefoundation.org.uk/resource/experience-based-co-design-ebcd-toolkit/

TABLE 2 | Developed training materials and number of stakeholders who provided input.

Description	Radiographer feedback*	Patient feedback*
KEW model Model for empathic communication: Know, Encourage, Warmth	*n* =12 (focus group; individual feedback–survey)	*n* = 6 (individual feedback–email/in person)
Storyboards/trigger videos Scenarios for difficult conversations between radiographers and breast cancer patients. Videos for use in training to trigger discussion on personalized strategies	*n* = 12 (focus group; individual feedback–survey)	Storyboards: *n* = 5 Trigger videos: *n* = 1 (individual feedback–email/in person)
Fear of Cancer Recurrence handout Strategies for (1) gauging concerns, (2) encouraging conversation, (3) addressing fears of recurrence. Prompt to reflect on who patients can talk with within their service	*n* = 1 (individual feedback–email)	*n* =3 (individual feedback–email/in person)
Simulated Patient Scenario Detailed background for a fictional patient receiving radiotherapy for breast cancer, to use for role-play with simulated patient	*n* = 1 (individual feedback–email)	*n* =1 (individual feedback–email)
Informed Consent form Sheet and instructions for radiographers to use with patients for training audio-recording	*n* = 2 (individual feedback–survey)	*n* =2 (individual feedback–email)
Patient Experience Exercise Sheet detailing patient interactions with the radiotherapy service and common emotions. Prompts to reflect on how to apply the KEW principles at each stage and service-specific considerations, e.g., the waiting area	*n* = 1 (individual feedback–email)	*n* =1 (individual feedback–email)

**Some stakeholders provided feedback on more than one component. For anonymity purposes, numbers have been clustered. Radiographers include: n = 10 Radiographers from SCoR and n = 2 from ECC. Patient Representatives include members from Independent Cancer Patients Voices, Yorkshire Cancer Patients Forum, and Maggie's Center.*

feedback on each component, including representatives from patient support networks ($N = 8$), who all received treatment for breast cancer, but with varying treatment journeys, radiographers ($N = 12$) and other members of the National Society and College of Radiographers (SCoR) Research Advisory Group ($N = 4$), including education providers and service managers, experienced with a wide remit of cancers. Feedback was invited in the stakeholders' preferred format, using visual drafts and feedback grids (Interaction Design Foundation), including a group session and individual interviews (max 1 h) and via email. In addition, four SCoR members in managerial roles and two SCoR radiographers provided feedback on the overall training manual. When possible, feedback was incorporated into the materials directly. In case of practical barriers or conflicting recommendations, suggestions were discussed between authors MB and GH.

RESULTS

Patient Experiences

The patient interviews and feedback session resulted in an overview of interactions with the radiotherapy service that participants felt shaped their experience in a significant way. **Figure 2** gives an overview of these interactions and a summary of what emotional states participants associated with them. Overall, participants felt mostly positive to start radiotherapy, especially after consideration of some more negative experiences leading up to this stage, such as the anxiety of waiting for the biopsy results and feeling scared about surgery. The overall ease of moving through the service and from appointment to appointment was rated highly.

However, participants also expressed to have felt some apprehension at several moments. One of those was being under the treatment machine. As a participant commented on her experience: ***"In the end, it's you and the machine, and you're never going to get to the point where you feel friendly toward this machine, although you know that it's helping you. It's a sort of bizarre experience."*** *(Patient (Pat) 4, female, age 70).*

Another moment where patients felt apprehensive was going in for the first day of radiotherapy treatment. A participant described: "***I felt quite lost actually first. And then it was fine, I met the girls who were taking me through and I just got on with it."*** *(Pat 3, female).* The waiting areas, which were rated as a relatively negative moment of interaction, also played a role in this context: ***"I think the first time coming in, it would be nice to have someone come meet you at the door. You do get kind of confused and lost if you've never dealt with this before."*** *(Pat 3, female).* The waiting areas were also described as ***"a little bit bleak. I think it could be a little more uplifting"*** *(Pat 2, female, age 70).*

Participants described some unexpected moments that left a significant impression, such as receiving the radiotherapy tattoo: ***"I'm needle-phobic and that was quite a shock. I knew I was having them, I don't know how I thought they were actually going to do it."*** *(Pat 1, female, age 51).* Also, encountering a male member of staff at the treatment machine was mentioned as a bit of a surprise: ***"There was a male, and I wasn't uncomfortable that's the wrong word, but I do prefer to have two female radiographers. You are feeling very stressed and anxious and it's a very intimate thing to do."*** *(Pat 2, female, age 70)*

The support, trust and confidence from the radiotherapy team that patients felt was rated as the most positive interaction. As a

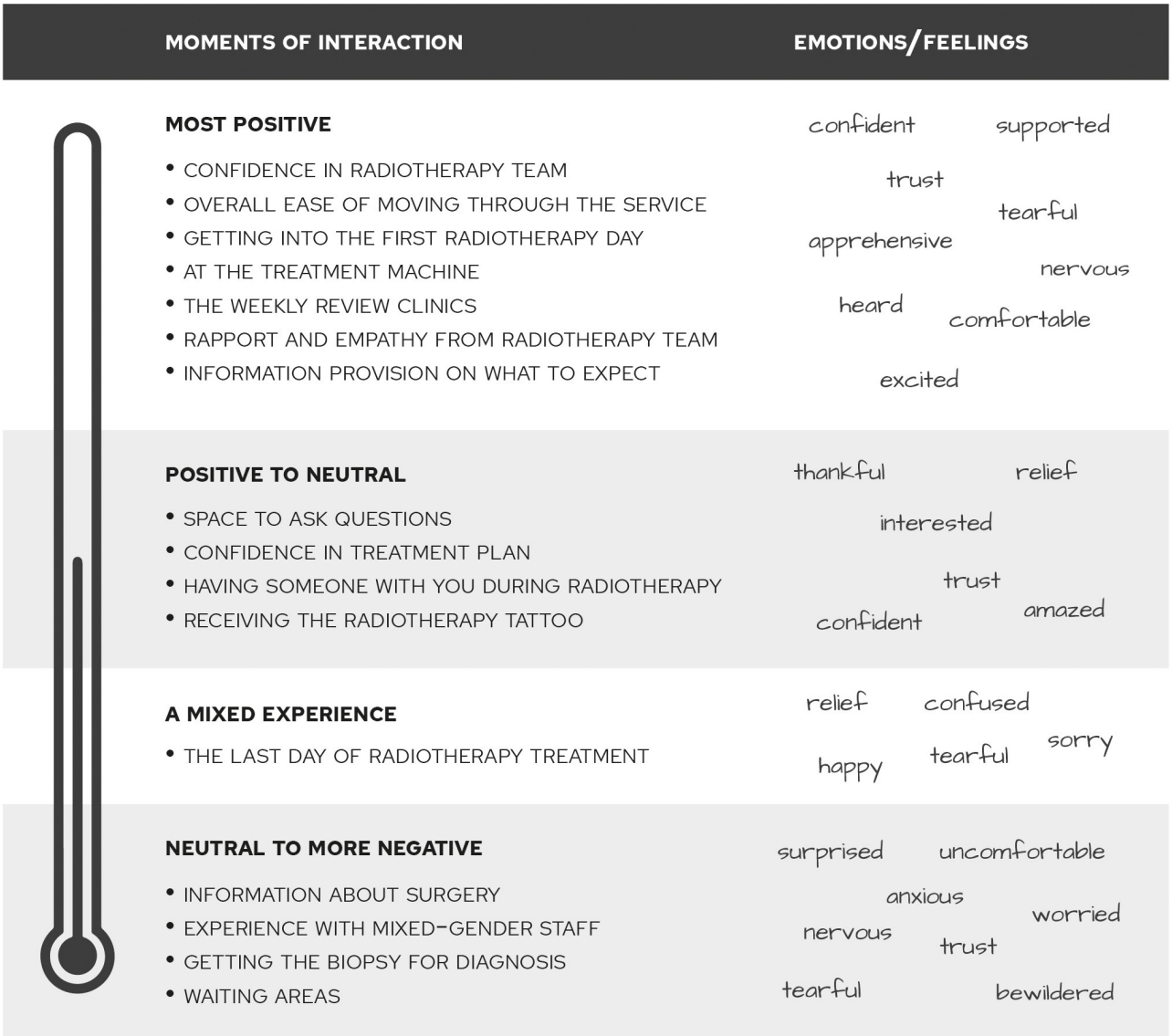

FIGURE 2 | Moments of interaction with emotion words as ranked in the patient feedback session.

participant describes: ***"You get the feeling while they are doing that that they are very much in control of what they are doing. They know exactly what's going on. And that's very reassuring. That's what you want. What you don't need when you're going through this is anyone who feels the slightest bit nervous or uncertain about what they are doing, because that immediately transfers onto you."*** *(Pat 2, female, age 70).* In the context of the rapport and empathy they experienced from the radiotherapy team, a participant emphasized the importance of ***"just being treated like an individual, rather than another patient number."*** *(Pat 4, female, age 70)*

A cluster of significant interactions focused on this type of support, including the importance feeling that there was enough space to ask questions despite the full waiting room, good information provision to establish a sense of what is going on and having the support of a partner or family member. The weekly review clinics in particular were mentioned as an opportunity for more in-depth conversations. As a participant describes: ***"[The radiographer] used the expression of radiotherapy as a sort of insurance policy, which I found very reassuring. (…) Toward the end of the second [review] I was able to ask her the key question "what would you do if this did do the worst and spread to say my bones?" (…) She talked a little bit about that with me and said that people who have cancer of the bones can still live a pretty good life. It probably would be good if there were built in more opportunities like the review where it was just you and one other person being able to talk about you as an individual."*** *(Pat 4, female, age 70).* As a result of the value of

this support, participants indicated to have experienced mixed emotions around leaving the service: while it was a relief to be finished, it was also a confusing time to have to leave this support system.

The radiotherapy review session and the role of the person leading it as "trouble shooter" was considered essential and the topic of "space to ask questions" was identified by the patient participants as a priority for co-design. As a participant described: ***"It felt possible to ask questions. It was more my awareness that these were people who were quite pressed for time and there were a lot of other people in the waiting room."*** *(Pat 4, female, age 70).*

Radiographer Experiences

The following Insight Statements relating to the radiographers' experience resulted from the radiographer interviews and feedback session, captured by six themes: (I) A good day at work, (II) Logistical barriers, (III) Supporting patients, (IV) Review Clinics, (V) Support with communication, and (VI) Team support. **Figure 3** illustrates a good and difficult working day for the radiographers.

Theme I: A good day at work

1) The RT team particularly enjoy their workday when they feel that patients leave the service feeling helped and reassured: ***"When you feel like you've helped somebody. And (…) that they leave the appointment and they're like "Oh, I feel so much better, you really reassured me about that.""*** *[Radiographer (Rad) 1]*
2) On a good day in the clinic, patient appointments are nicely spread out throughout the day: ***"… that we have enough spaces in between and a lunch break, really."*** *(Rad 2)*

Theme II: Logistical barriers

3) The heavy workload and understaffing can be tiring and feel unmanageable for the radiotherapy team: ***"Sometimes we're down to one person covering the service (…). Doing all these patients on your own for a long period isn't sustainable."*** *(Rad 1)*
4) The unpredictable patient schedule can lead to queues and consequently to frustrations for patients and radiographers feeling "on edge" because of time constraints: ***"We're at the liberty of the treatment machine. So if they are running an hour late, we are then an hour late."*** *(Rad 3)*
5) It can be particularly difficult to lead a review session when patient notes are not available before going into the clinic: ***"Quite often, the notes won't be there (…). I feel like you're at a massive disadvantage because you're going blind into a review."*** *(Rad 2)*

Theme III: Supporting patients

6) Overall, the RT team think patients are pleased with the "caring and careful" staff. Most practical/information needs are met, as well as many of the emotional needs: ***"I had about three or four different patients who all said to me (…) the staff were so caring and interested in them as a person."*** *(Rad 1)*
7) The wide range of patient needs and communication styles can be challenging to deal with, such as patients who had a complex treatment journey and who may feel angry, embarrassed or scared and challenge offers for help. Some patients may not be very talkative, while others would like to talk more than there is time available.
   - ***"She said she wasn't coping, but was unwilling to accept any help"*** *(Rad 1)*
   - ***"For some people, their fear presents as anger"*** *(Rad 4)*
   - ***"Often you are kind of having to end the conversation"*** *(Rad 3)*
8) The RT team see that on the first day and last day of treatment patients may need extra support: ***"I still think it must be very daunting and scary for them (…) not fully understanding exactly what's going to go on."*** *(Rad 3)*

Theme IV: Review clinics

9) Review clinics are essential to offer psycho-social support as the time with patients at the machine is not sufficient to cover such topics: ***"You do get more time to actually sit down (…), you can start to explore different things that are going on."*** *(Rad 2)*
10) The repeated review sessions are perceived as helpful to **build rapport** with patients: ***"You do build up a rapport with patients (…). They've maybe thought from one week to the next about what they want to ask about whatever it is."*** *(Rad 1)*

Theme V: Support with communication

11) The RT team is keen to receive communication training to boost confidence in offering (mainly psycho-social) support, in particular with questions such as: how to make a patient feel valued as a person, deal with challenging behavior, determine needs, address them concisely, prompt non-talkative patients, round up the conversation in a respectful manner, refer patients with emotional concerns, address topics such as worries about treatment or fear of recurrence. ***"The thing we're not trained for though is the emotional side. That's certainly an area that (…) I would like to (…) be able to deal with."*** *(Rad 3)*
12) The RT team support also each other with communication strategies for more challenging patient cases: ***"Say that there is a particularly difficult patient or a difficult situation with a patient, we always sit and chat about it."*** *(Rad 3)*

Theme VI: Team support

13) It is important to have the opportunity for support and decompression after difficult cases on a day-to-day basis: ***"If you can relate to that–it's been a horrible situation–then that is actually quite hard, and you can then take that home."*** *(Rad 4)*

The radiographers identified the issue of offering psycho-social support as the priority to bring to the co-design session. Items relating the logistics and workload of the service were taken forward by the radiographers to discuss and address internally.

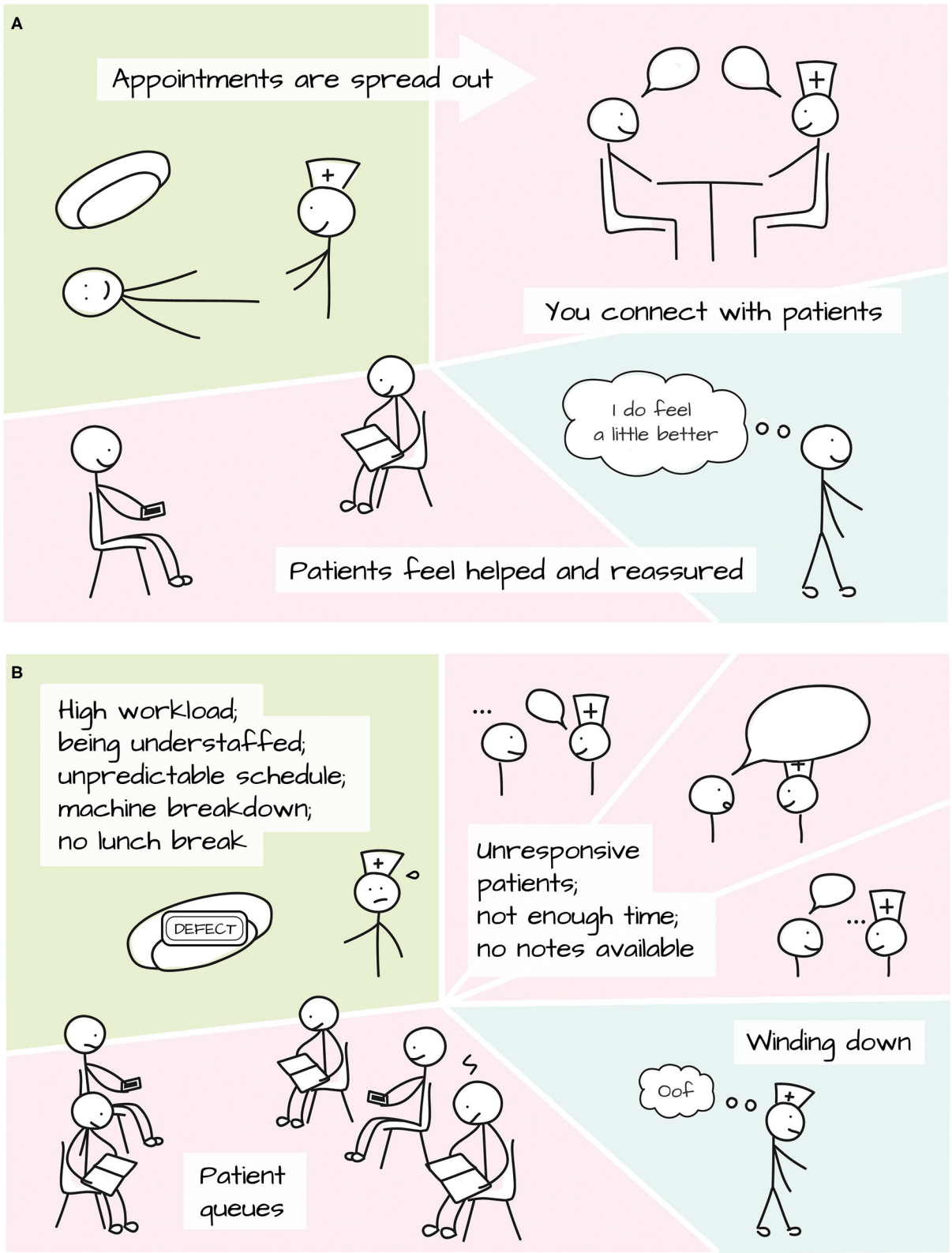

FIGURE 3 | A **(A)** good and **(B)** difficult working day for the radiographers.

Shared Priorities and Solutions

At the joint patient-staff event, after watching the patient experience video, radiographers and patients collaboratively narrowed down their shared priorities to: (I) making patients feel valued as a person, (II) addressing topics such as worries about treatment or fear of recurrence, and (III) supporting patients with space to ask questions. Additionally, it was agreed to include the (IV) less positively rated experience encountering male staff at the treatment machine and the waiting area in the brainstorm session. These themes were presented in the context of significant settings as identified: the first and last day of treatment, at the treatment machine, the review clinic, and the overall journey through the service, including the waiting area.

A recurring theme in the idea generation process (**Figure 4**) was supporting patients with knowing what to expect. For example, to reduce apprehension at the start of treatment, the group suggested to revisit the day-to-day logistics and reiterate information, including reassurances, over the first couple of visits. This was considered a helpful addition to written information and to support understanding from family members as well. Personal contact such as "***being greeted and checked you're okay***" in this context was identified as essential and could be complemented by having someone meet the patient at the reception.

Checking the patient's understanding of what is going to happen was advised to avoid catching them off-guard in a situation where they already feel vulnerable. For example, regarding the issue of being helped by a male member of staff, the group suggested it would already make a difference to simply know this in advance, before they undress for the treatment machine. Knowing what to expect was also a key theme in addressing the topic of space to ask questions. In addition to the identification of settings that provide a good opportunity for questions, such as at the treatment machine with the radiographer and at the review clinic, the group recommended indicating when time would be available if a longer conversation was not possible, for example by offering an additional appointment to respond to the patient's questions.

Next to this "deferring" strategy, "referring" to other staff was recommended as a strategy to help manage patient questions. In an ideal situation, there would be a dedicated person in the service to deal with appointment questions and provide emotional support also outside of the review clinics. A smooth "handover" was also recommended to support patients with apprehension on the last day of treatment. The group agreed that the focus should be on creating awareness of existing support services, such as the breast care nurse, Maggie's Centre programmes and counseling services. It was also suggested to have a telephone follow-up with the radiotherapy team 1 or 2 weeks after treatment completion and again after 3 months, to be able to talk with a "familiar face."

To support patients with feelings of fear or cancer recurrence during their time in the radiotherapy service, it was recommended to use positive words throughout conversations, such as "treatable" in relation to the cancer and to give reassurance about regular checks. The group also agreed on being direct in addressing this topic, for example by asking "Do you have concerns about going forward/the future?" or "What is it that bothers you most moving forward?" It was acknowledged that some patients may not want to discuss these feelings; however, staff and patients agreed that this questioning should not be limited to people with poorer prognoses.

Suggestions for the waiting area included to make it more uplifting by removing medical pictures and designing what patients would consider, in consultation, a positive and bright space. A layout was recommended that encourages conversations between patients. In addition, some distractions could be added such as perhaps a TV.

Co-design Evaluation

Evaluation of the co-design process showed that talking about and sharing the different experiences of staff and patients was rated by radiographers as "excellent" (no free responses) and by patients as "good" to "excellent." This exchange was appreciated by a patient who commented that ***"this felt worthwhile, as the needs of patients met within the realities of the radiographers' jobs. As always, time and resources are crucial"*** *(Pat 4). Two* patients noted that the patients' shared mostly positive experiences, e.g.: ***"I found this very useful, although I did feel the patients had all had similar, very positive experiences"*** *(Pat 1).*

Seeing the patient film was rated consistently by both parties as "good" to "excellent." Patient participants reported that the video represented their experiences well and enjoyed watching it: ***"The film was carefully edited, so that there was a coherent thread running through it. People clearly felt sufficiently at ease to give their ideas and experiences at each point"*** *(Pat 4)* and ***"I enjoyed hearing the other women's experiences–I thought the film was fair, well-constructed and balanced, with everyone having a say"*** *(Pat 1).* A radiographer commented that ***"what was said was what I hoped the patients thought, but it was good to hear"*** *(Rad 3).*

Discussing and deciding the priorities that would be worked on and improved was rated as "excellent" by the radiographers (no free responses) and "good" to "excellent" by patients. A patient mentioned that despite the positive tone of the experiences ***"we were still able to find areas to improve and work on"*** *(Pat 1).* A patient said that they ***"felt privileged to be part of the changes that could be made, big or small"*** *(Pat 42).* Again, the exchange between staff and patients was valued: ***"this section was focussed and useful. It was good to have a member of staff in the groups, so it was not dominated by patients' experiences"*** *(Pat 4).* With regards to the outcomes of the priorities, a patient expressed her hope that ***"perhaps this will help to create a follow-up service, required for future patients' mental health issues linked to breast cancer"*** *(Pat 2).*

Radiographers rated how comfortable they felt participating in the event and their ability to contribute their own thoughts and experiences as excellent (no free responses) and patients as "good" to "excellent." A patient participant described the atmosphere as ***"welcoming (. . .) we all got to have our say"*** *(Pat 1)* and others described their participation as ***"very positive"*** *(Pat 2)*, as well as ***"comfortable"*** and feeling ***"valued as a contributor"*** *(Pat 4).*

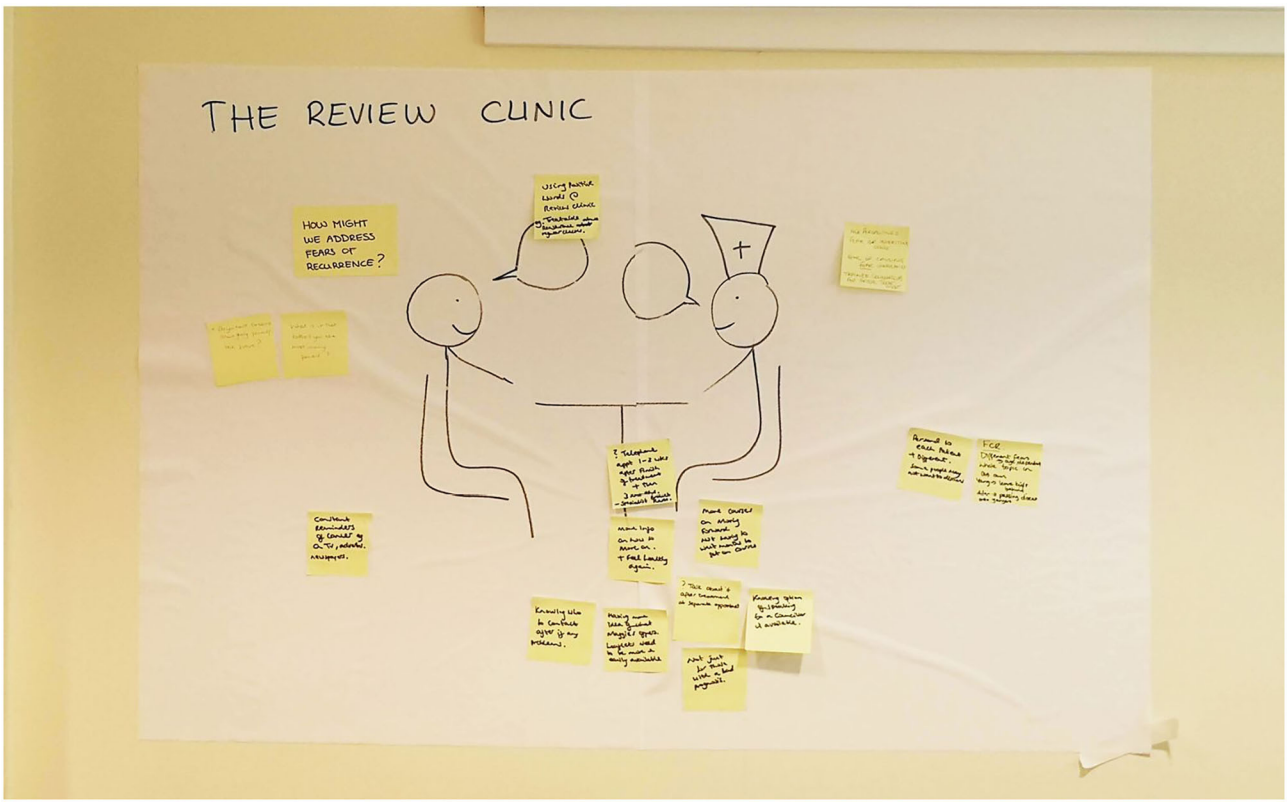

FIGURE 4 | One of the idea generation roulette "stations" at the joint staff-patient session.

Radiographers did not feel that there was anything that they did not get a chance to say that they had wanted to contribute and most patients agreed. One patient added that she would have liked to learn more about how the radiographers envisage their ideas being put into practice and whether the organization will be flexible enough to allow this: ***"communication training will take time, and will involve commitment from staff, meaning time has to be made available"*** *(Pat 4).*

Points for improvement of the co-design process were ***"more time***" *(Rad 2)* from the radiographers' point of view. With respect to the positive experiences in the room, a patient suggested that ***"it might be useful to hear from patients whose experience was less positive–it might broaden the discussion a little"*** *(Pat 1)*. Another patient mentioned that sharing experiences can sometimes ***"result in a loss of focus at points***" *(Pat 4)*. Overall, both radiographers and patients rated the organization of the co-design process as good to excellent.

KEW: Know, Encourage, Warmth

Most priorities identified in the co-design session related directly to communicative behaviours, i.e., making patients feel valued, addressing difficult topics, and providing space. Mapping these priorities and themes from the Experience-Based Co-Design process onto the KEPe Warm model (Little et al., 2015) resulted in a model for empathic communication, KEW, for Know (Confidence, Person, Expectations), Encourage (Emotions, Space, Follow-up), and Warmth (Start, Normalize, Ending), as clarified in **Figure 5**.

Feedback from national radiographer and patient representatives indicated that overall, the model was considered to be clear and concise and its components important and relevant. A radiographer commented: ***"I especially like warmth. It's a caring profession and an aspect that's important to me. Knowledge is also essential and having confidence when discussing information with patients.***" Also patients' feedback on the model was positive: ***"The KEW model accurately represents the good parts of the patient experience: the empathy, showing the person behind the patient by making social comments, giving realistic expectations and realistic timeframes."***

Some suggestions for changes could be directly included in the model, such as a radiographer's comment on the importance of a personalized approach for patients (***"No mention of individualizing/personalize as well as normalizing"***) that led to the inclusion of this topic under the subcategory "Person" within the theme "Know." A patient's remark about the risk of normalizing feelings that were *not* the usual reaction ***("Under normalize important to also insert wording to cover situations that are not the usual reaction"***), led to rephrasing of the relevant sentence under the subheading "Normalize" within the theme "Warmth."

Other feedback could be incorporated in the training manual that was developed alongside the KEW model, such as the advice

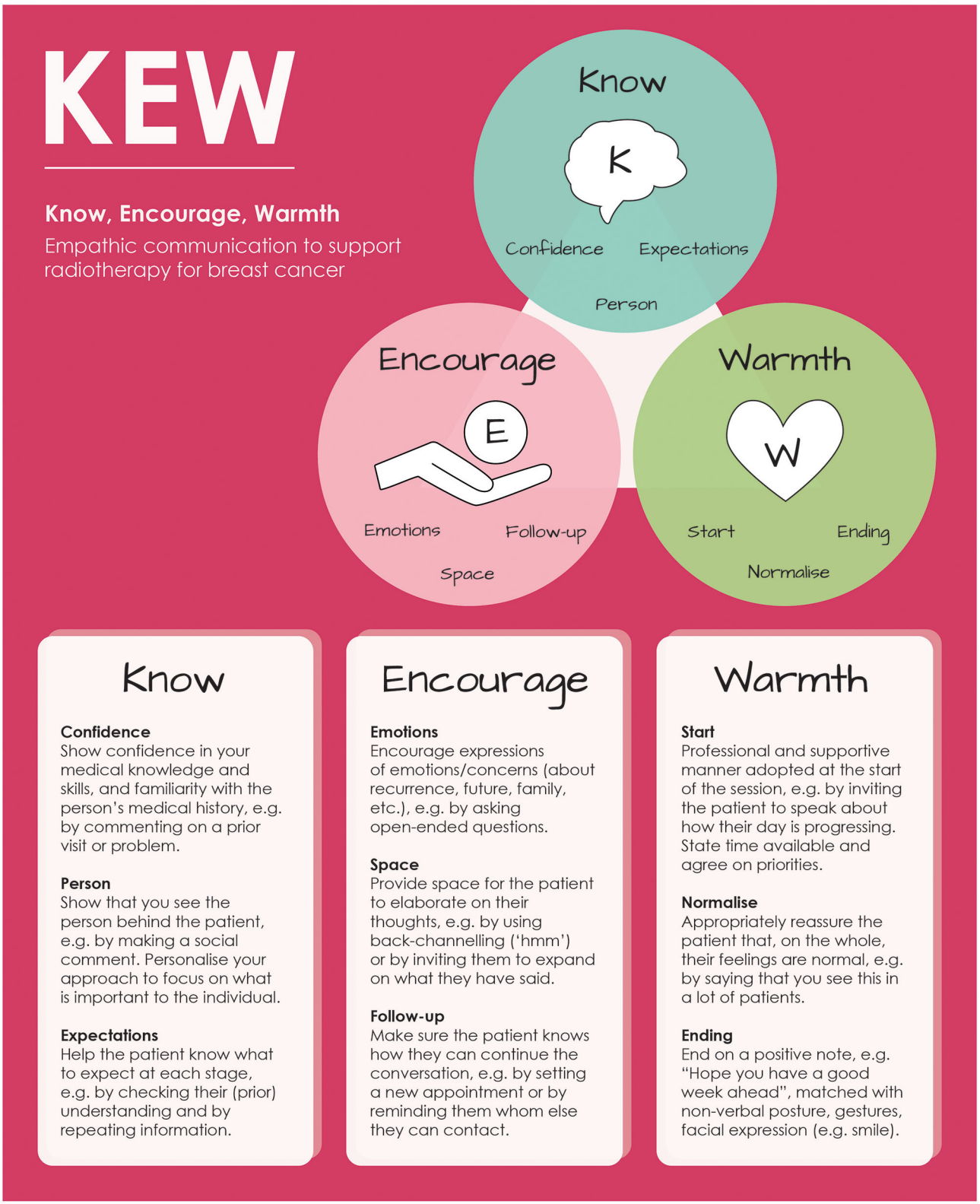

FIGURE 5 | The Know, Encourage, Warmth (KEW) model for empathic communication.

TABLE 3 | Outline of KEW training workshops.

Session 1	Between sessions	Session 2
Activation of prior knowledge *Learner- and patient centered exercise; reflection on prior knowledge* Trigger videos, handout	Audio-record two review sessions with patients	Warm-up exercise *Activation of prior knowledge* (Trigger video, handout)
Introduction of KEW model *Definition of skills* (Presentation with slides, KEW handout)		Reflection on audio-recordings *Experiential Learning, ALOBA*
Fears of Cancer Recurrence *Reflection on prior knowledge, definition of skills* (Trigger video, FCR handout)		KEW in the wider service Patient experience exercise handout)
Role play with Simulated Patient *Experiential learning, Agenda-Led Outcome Based Analysis (ALOBA)* (Scenario, handout)		
Setting personal goals		

to broaden the use of the model to be implemented throughout the radiotherapy setting and the suggestion to address barriers radiographers may experience to start potentially difficult conversations with patients. Following repeated suggestions, pragmatic advice with specific examples on how to achieve KEW strategies were included, and practice-based examples were generated in feedback rounds by asking participants to supply responses to conversation scenarios described in the storyboards. This led to a database of examples that can be used in the training by the facilitators. Another category of feedback recommended to encourage management support, which was addressed by including managerial staff in the feedback rounds and including links to national strategic cancer frameworks in the training package.

Feedback on the other training components as described in **Table 2** consisted of acknowledgment of their relevance for clinical practice and relatability to the diversity of patient experiences, with detailed suggestions on how to match the flow of medical procedures, use of language, and patient experience even more accurately. To illustrate, for the simulated patient scenario, a patient representative commented: ***"…"surgery "smooth" except for infection and redressing"–most of us as patients would think this as major not just a hiccup,"*** while a radiographer commented that ***"the time delay between biopsy and seeing the surgeon is more realistically 2 weeks."*** These changes were then made to the materials accordingly.

In consultation with radiographers, it was agreed that two half day sessions would be a suitable format for the resulting training workshops, as described in **Table 3**.

DISCUSSION

This study describes the development of a concise model for empathic communication in radiotherapy for breast cancer: KEW, for Know, Encourage, and Warmth, building on service user-experiences of radiographers and breast cancer patients. The linked communication skills training provides radiographers with theory and tools on how to provide space and foster empathic communication with patients throughout their treatment pathway, with a focus on key interactions such as the first and last day of treatment and the review clinic. The training also enables radiographers to develop personalized strategies to discuss difficult topics with patients, such as fear of cancer recurrence.

Emotionally, radiotherapy is known to consist of a series of ups and downs for patients (Humphris et al., 2019). The Experience-Based Co-Design process helped capture what factors contribute to a positive patient journey, including the support, confidence, and personable approach from the radiotherapy team to help reduce apprehension at key moments of interaction with the service. From this study, it is apparent that radiographers are keen to receive training to help increase their own confidence in how to best offer emotional support while being realistic about time constraints, to move beyond the feeling of potentially "opening a can of worms" when starting a difficult conversation.

It is already known that encouraging emotional cues and responding to these appropriately can improve quality of medical consultations (Little et al., 2015), which is reflected in existing communication training for the radiotherapy setting (Timmermans et al., 2006; Halkett et al., 2012, 2013, 2018; Hollingworth et al., 2013). The outcomes of the co-design approach suggest the need for a more encompassing approach to improving the patient experience: i.e., not only focussing on the quality of communication and information provision during a single conversation, but ensuring that patients are not "left hanging" between these formally organized interactions and are supported throughout their journey within the service by "referring" or "deferring" conversations. This integrated approach is reflected in the training programme, along with a focus on realistic and timely expectation management in patient communication, described by some as being part of the empathic process (Underhill et al., 2014). The review clinic, which in the UK patients have the opportunity to attend to discuss their treatment and general reactions with their radiographer (Cameron et al., 2008), was identified as a key opportunity for more in-depth conversations and to help the build rapport to foster the warm and personal approach to communication that helps to reassure patients.

The Experience-Based Co-Design approach was valued by patient and staff participants. The visual tools, in particular the recorded patient stories, and interactive exercises effectively triggered the partnership synergy required for successful collaboration (Lasker et al., 2001; Bate and Robert, 2007). However, this rigorous process included only a small number of, all female, patient participants who were relatively positive about their experience. As a result, the initial co-design process allowed the research team to capture good practice. To improve generalisability, the findings were scaled up using consultative input from national radiotherapy and patient representatives. The number of participants for each step were kept small for several reasons: (1) the co-design process in particular required intensive facilitation and guidance to ensure that all involved felt comfortable with their participation (2) the practical aspect of the timeline of the development process, and (3) reducing the burden for research participants–the research team aimed to encourage active participation for in-depth contributions, which is not a small ask both in terms of offering sufficient guidance and from the participant perspective. Previous experience with stakeholder-involvement showed that the iterative aspect to the development process is a key factor to target the outcome to the needs of the end-users (van Beusekom M. et al., 2018). The described process led to invaluable insights on how to take a tailored approach both with respect to patient communication and to the communication skills workshops for radiographers, to be able to reflect the diverse range of experiences and services.

The main aim of the collaborative process was not to improve a single service, but to develop a wider applicable intervention. Participants were aware of this, which may have influenced their decision-making process regarding prioritization of topics. However, the participant-led discussions included a wide range of topics, including site-specific concerns around the waiting area. This topic, along with other site-specific suggestions have been included in the training package as points of reflection for the overall patient experience. In addition, specific suggestions for improvement were also fed back to managerial staff of the service where the co-design was conducted.

Conclusions

In conclusion, the support from the radiotherapy team is a significant contributor to a positive patient experience. The Know, Encourage, Warmth (KEW) model and training offer a concise framework and tailored approach to help radiographers support breast cancer patients with emotional concerns throughout their radiotherapy journey. The use of single-site Experience-Based Co-Design in combination with consultative input from national stakeholders proved useful to capture good practice and optimize wider generalisability to help standardize quality in communication across radiotherapy services. Delivery and evaluation of the communication skills training is warranted to determine effectiveness to prepare for roll-out on a wider scale and to examine the potential for use of the framework across a range of cancer sites as well as other staff working with cancer patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by London–Surrey Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GH designed the overall study. MB developed the co-design methodology and led the data collection. JC and CB were essential in the implementation. EB and RH in the involvement of national patient and radiographer representatives. MB and GH undertook the analysis and wrote the first draft. All authors contributed to the design and assisted with the interpretation of the findings and drafts and read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Setting an International Research Agenda for Fear of Cancer Recurrence: An Online Delphi Consensus Study

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Background: Fear of cancer recurrence (FCR) is common amongst cancer survivors. There is rapidly growing research interest in FCR but a need to prioritize research to address the most pressing clinical issues and reduce duplication and fragmentation of effort. This study aimed to establish international consensus among clinical and academic FCR experts regarding priorities for FCR research.

Methods: Members of the International Psycho-oncology Society (IPOS) Fear of Cancer Recurrence Special Interest Group (FORwards) were invited to participate in an online Delphi study. Research domains identified in Round 1 were presented and discussed at a focus group (Round 2) to consolidate the domains and items prior to presentation in further survey rounds (Round 3) aimed at gaining consensus on research priorities of international significance.

Results: Thirty four research items were identified in Round 1 and 33 of the items were consolidated into six overarching themes through a focus group discussion with FCR experts. The 33 research items were presented in subsequent rounds of the delphi technique. Twenty one participants contributed to delphi round 1, 16 in round 2, and 25 and 29 participants for subsequent delphi rounds. Consensus was reached for 27 items in round 3.1. A further four research items were identified by panelists and included in round 3.2. After round 3.2, 35 individual research items were ratified by the panelists. Given the high levels of consensus and stability between rounds, no further rounds were conducted. Overall intervention research was considered the most important focus for FCR research. Panelists identified models of care that facilitate greater access to FCR treatment and evaluation of the effectiveness of FCR interventions in real world settings as the two research items of highest priority. Defining the mechanisms of action and active components across FCR/P interventions was the third highest priority identified.

Conclusion: The findings of this study outline a research agenda for international FCR research. Intervention research to identify models of care that increase access to treatment are based on a flexible approach based on symptom severity and can be delivered within routine clinical care were identified as research areas to prioritize. Greater understanding of the active components and mechanisms of action of existing FCR interventions will facilitate increased tailoring of interventions to meet patient need.

Keywords: cancer, fear of cancer recurrence, Delphi method, research priorities, international

INTRODUCTION

Early diagnosis and improved treatments for cancer have led to higher survival rates (Arnold et al., 2019). With improved survival, there are increasing numbers of people living with the fear that their cancer will recur (Koch et al., 2013). New treatments have also led to increased numbers of people with advanced disease living with uncertainty (Thewes et al., 2017). While some degree of fear of recurrence (FCR) defined as "*fear, worry, or concern relating to the possibility that cancer will come back or progress*" (Lebel et al., 2016)(pg3267) is considered normal, nearly 50% of survivors experience moderate to high levels, suggestive of clinical FCR. High levels of FCR can persist over time (Crist and Grunfeld, 2013) and negatively impact psychological wellbeing and quality of life, resulting in increased utilization of healthcare resources (Lebel et al., 2013; Simard et al., 2013; Thewes et al., 2013). FCR is one of the most prevalent and severe unmet supportive care needs reported, with Simard et al. reporting in their review that up to 79% of cancer survivors reporting FCR as an unmet need or concern (Simard et al., 2013).

For these reasons, research interest in FCR has grown rapidly, evident from a doubling of the number of publications (based on a PubMed database search conducted on June 2020) from a mean publication rate of 57 per year (2010−2014) to 108 per year (2015−2020), including the publication of 12 systematic reviews (Crist and Grunfeld, 2013; Koch et al., 2013; Simard et al., 2013; Thewes et al., 2013; Ozga et al., 2015; Fardell et al., 2016; Simonelli et al., 2017; Yang et al., 2017a,b, 2019; Hall et al., 2018; Tauber et al., 2019). These reviews summarize a broad range of research activity including identification of factors associated with FCR (Crist and Grunfeld, 2013; Ozga et al., 2015), FCR measurement (Thewes et al., 2013), FCR interventions and management (Simonelli et al., 2017; Hall et al., 2018; Tauber et al., 2019), theoretical frameworks explaining FCR (Fardell et al., 2016) and prevalence, determinants and consequences of FCR (Simard et al., 2013; Yang et al., 2017a,b, 2019) as well as different care delivery models (Liu et al., 2019) and highlight that much of the research has been focused on FCR in breast cancer or mixed cancer samples composed mainly of colon, prostate, or lung and breast cancer patients (Simard et al., 2013). However, despite the increasing volume of FCR research and progress made in areas such as FCR treatment, fundamental questions regarding assessment, optimal intervention across patient groups, and determinants of severity are still to be answered (Sharpe et al., 2017). Establishing priorities for FCR research will increase the quality and clinical utility of findings, and reduce the potential for research waste through duplication and/or fragmentation of effort, and increased co-ordination of research will enhance funding competitiveness (Cristea and Naudet, 2019; Sullivan et al., 2019).

A recent priority-setting exercise for FCR research in Australia provided guidance for local research activities (Butow et al., 2019), however, these may not generalize more broadly given differences in settings delivering psycho-oncology care internationally. Similarly, although a review of ovarian cancer-specific psychosocial research gaps identified FCR as an important area for further research—the scope and focus of the FCR agenda for this patient group was not explored (Goarin et al., 2020). Priority setting exercises have demonstrated their potential to inform research. For example, a 2 day FCR colloquium in Ottawa, Canada (Lebel et al., 2017) not only provided a consensus definition for FCR but also highlighted the need for research to standardize measurement and development of theoretically informed interventions. Fostered through the establishment of a Special Interest Group under the banner of the International Psycho−Oncology Society (FORwards), these objectives have driven FCR research to date, but have now largely been met. In this study, we aimed to build on previous priority setting exercises and gain consensus on international FCR research priorities to foster collaborative research efforts and optimize FCR outcomes for adult cancer patients.

MATERIALS AND METHODS

Study Design

A mixed methods approach was adopted to identify research priorities based on the methodology used in previous priority setting activities (Butow et al., 2019). Round 1 of the Delphi to identify research domains of potential importance, involved completion of an online survey. The survey results were presented and discussed at a focus group (Round 2) to consolidate the domains identified in round 1 prior to presentation in further survey rounds aimed at gaining consensus on research priorities of international significance to guide future collaborative research. The Delphi technique is a research methodology for establishing consensus among experts through a series of questionnaires (Keeney and McKenna, 2011) and commonly used to identify research priorities (Downing et al., 2015; Butow et al., 2019; Sullivan et al., 2019).

Participants

Participants were recruited through the International Psycho-oncology Society (IPOS) fear of cancer recurrence special interest group (FORwards). IPOS is an international multidisciplinary professional network of researchers and clinicians (n = 598 from 68 countries) established to foster clinical and research collaborations to support the psychosocial health of those affected by cancer. The FORwards special interest group is comprised of IPOS members with an interest in FCR (n = 85 from 23 countries). The broad aims of the group are to raise awareness of FCR and promote activities to improve the identification and treatment of high levels of FCR amongst cancer patients and the group has a strong focus on stimulating multi-disciplinary, international FCR research. FORwards members were emailed an invitation to participate in each phase of the Delphi, however, for the focus group, it was a requirement that members be present at the IPOS World Congress, Banff Canada since this component required face to face participation, and Banff represented an ideal opportunity when a large number of FCR experts were already present. The study was approved by the University of Sydney human ethics committee (HREC 2019/608).

Data Collection

Identification of Research Domains

Round 1

FORwards special interest group members were emailed an invitation to participate in round 1 of the Delphi—an online survey. Interested participants provided online consent prior to accessing the survey. The survey was constructed and administered using RedCap (Research Electronic Data Capture) database, a secure, web-based software platform designed to support data capture for research studies (Harris et al., 2009). The descriptive survey asked respondents to indicate what they perceived to be the three most important FCR research priorities of international significance. Survey responses were collected as free text variables and content analyzed using a conventional approach (Hsieh and Shannon, 2005) by two researchers independently (JS and PB). Any disagreements were resolved through discussion to ensure consensus. The analysis identified a list of individual items, which were grouped into higher-order themes to identify research domains. The individual items were weighted (score of 3 = first priority, 2 = second priority, 1 = third priority) and mean scores for each item were used to calculate an overall ranking of research priorities.

Round 2

The results of the survey were presented to FORwards members attending the IPOS World Congress in Banff Canada (September 2019) as part of a 90 min focus group convened specifically to review and discuss FCR research priorities. An experienced qualitative researcher (JS) conducted the focus group and two researchers documented the discussion. The results of the content analysis were presented to the focus group including each domain and associated items. The focus group followed a semi structured format with the facilitator guiding initial discussion and allowing participants to openly discuss potential research questions and priorities. All new research items generated through group discussion were included in the focus group transcript. Thematic analysis (Braun, 2012) of participant responses was conducted by two researchers independently (JS and PB) and an agreed coding scheme developed, with subsequent higher-order analysis to identify overarching themes. The transcripts were reviewed line-by-line by a single author (JS) who searched for concepts, themes, and ideas, and developed a preliminary coding scheme. Transcripts were read and coded by a second author independently (PB) who compared and discussed their individual coding choices. Any disagreements were resolved by discussion. The coding scheme was revised based on these discussions to develop a final coding structure. No *a priori* assumptions regarding priorities were made by the researchers. The researchers inductively developed two categories of descriptive themes from the data—the research priorities expressed by the participants and the rationale participants used to explain their research priorities.

Gaining Consensus for Research Priorities

Round 3

Research items generated through the item identification phase were presented to FORwards members using an online Delphi consensus methodology. Members were emailed an invitation to participate in an online consensus process and the survey was constructed and administered using RedCap. In each round, panelists indicated their agreement on the importance of each research item on a 5-point Likert scale (1 = very important to 5 = not important at all). Panelists were able to provide free text comments explaining the reasons for their rating. Consensus was defined *a priori* as 80% or more of panelists rating the item either important/very important or not important/not at all important. Panelists were also able to indicate if there were other research priorities they perceived as important, but not included.

Data from round 3.1 of the consensus process was summarized and any new items, as well as items where consensus was not reached (with percentages endorsing each response option and any free-text responses), were re-presented in a second round (i.e., round 3.2). We had an *a priori* stopping rule that no further rounds would be conducted when there were fewer than two items where consensus was achieved. In round 3.2, panelists also nominated their top three research priorities, ranking them from 1 (most important) to 3 (3rd most important). Non-responders were e-mailed up to three reminders for each round.

Statistical Analyses

Data were exported from RedCap into an excel spreadsheet and analyzed descriptively. Percentage agreement was calculated based on the number of respondents who agreed/strongly agreed or disagreed/strongly disagreed on the importance an item, divided by the total number of respondents as a percentage. SPSS Statistics 24 (IBM, Armonk NY) was used to calculate mean importance for each item. Lower mean scores indicated higher perceived priority. From round 3.2 data, the top three ranked research priorities from the total list

of research items was calculated. The individual items were weighted (score of 1 = first priority, 2 = second priority, 3 = third priority) and total scores for each item were used to calculate an overall ranking. Research domains were also ranked using Kendalls co-efficient W to assess ranking agreement among respondents.

RESULTS

Round One: Identification of Research Domains

Twenty-one (25%) FORwards members completed the online survey. The majority of respondents were psychologists (66%, n = 14), with > 10 years working in oncology (71%, n = 15). Sixty six percent (n = 14) of respondents indicated research accounted for > 50% of their time, and 81% (n = 17) indicated they were currently involved in FCR research. The survey elicited 34 individual research items across five higher order themes to identify research domains: (1) intervention research, (2) screening and measurement, (3) model and/or guideline development, (4) etiology of FCR, and (5) implementation research. The full list of research items and associated weighting is provided as **Supplementary Tables 1,2**.

Round Two: Consolidation of Research Items

Sixteen (19%) FORwards members (12 psychologists, two nurses and two psychology graduate students involved in FCR research) from nine countries participated in the focus group. Thematic analysis of the focus group discussion transcript resulted in refinement and reconceptualization of the research items identified from the survey and consolidation of 34 items across six overarching research domains: (1) intervention models (n = 8 items), (2) researching specific populations (n = 7 items), (3) definitions and mechanisms of action for FCR (n = 8 items), (4) description of FCR predictors and consequences (n = 4 items), (5) detection and screening (n = 3 items), and (6) implementation (n = 4 items). All 34 research items were presented as part of the Delphi process and are listed in **Table 2**.

Round Three: Consensus for Research Items

Participants

Twenty five (29% response rate) FORwards members participated in round 3.1 of the Delphi consensus survey and 29 (34%) participated in round 3.2. The mostly female (83%) respondents were representative of the disciplines and international regions engaged in FCR research and IPOS membership (**Table 1**).

TABLE 1 | Delphi round 3 respondent characteristics.

Variable		Round 3.1 (n = 25) N (%)	Round 3.2 (n = 29) N (%)	Proportion of IPOS membership**
Age	26–30	5 (20)	2 (7)	
	31–40	7 (28)	10 (36)	
	41–50	7 (28)	6 (21)	
	51–60	4 (16)	7 (25)	
	61–69	2 (8)	3 (11)	
	>70	0 (0)	0 (0)	
Gender	Female	20 (80)	24 (82)	478 (80)
	Male	5 (20)	5 (18)	120 (20)
Discipline	Psychology	14 (56)	17 (59)	244 (41)
	Psychiatry	1 (4)	2 (7)	80 (13)
	Nursing	1 (4)	2 (7)	40 (7)
	Social work	0 (0)	0 (0)	14 (1)
	Oncology	0 (0)	0 (0)	18 (2)
	Research	9 (36)	8 (27)	83 (14)
Country *	Australia	5 (20)		63 (11)
	Canada	4 (16)		30 (5)
	Denmark	1 (4)		7 (1)
	Japan	1 (4)		22 (4)
	Mexico	1 (4)		11 (2)
	Netherlands	3 (12)		11 (2)
	Portugal	1 (4)		2 (0.3)
	Russia	1 (4)		7 (1)
	South Korea	1 (4)		4 (0.7)
	Spain	2 (8)		3 (0.5)
	United Kingdom	2 (8)		25 (4)
	United States of America	3 (12)		93 (16)
Research role	Up to 5%	1 (4)	1 (3)	
	5–10%	3 (12)	2 (7)	
	10–15%	2 (8)	3 (11)	
	15–25%	0 (0)	0 (0)	
	25–50%	4 (16)	5 (17)	
	50–75%	4 (16)	5 (17)	
	75–100%	11(44)	13 (45)	

*Due to a programming error country was not collected in round 2.
**Only limited demographic data collected by IPOS.

Consensus Rating

Thirty-three research items were initially presented to panelists and 27 of these reached consensus (≥80% agreement). Panelists also identified 4 additional items in round 3.1, including two items conceptualized under an additional domain *Uncertainty and avoidance*. The items where consensus was not reached (n = 7) and the additional four items were re-presented to panelists in round 3.2. Consensus was reached on nine items. Two items failed to reach consensus: *Explore the underlying similarities and differences between Fear of Cancer Recurrence (FCR) and Fear of Progression (FoP)* (72.4% agreement) and *Examine the effects of FCR/P on use of alternative therapies and their costs (69% agreement)*. Thus, these two items were eliminated. In summary, given the stability across rounds, 35 individual research items were ratified by the panelists and no further rounds were conducted. **Table 2** lists individual items grouped by domain and final level of consensus for each item in ranking order.

TABLE 2 | Mean ratings and level of consensus for fear of cancer recurrence international research priorities.

Research priority	Round 3.1		Round 3.2	
Intervention models	**Mean (*SD*)***	**% agreement (n)**	**Mean (*SD*)***	**% agreement (n)**
Develop and evaluate more accessible models (low cost, online, telehealth, group, blended models of care, non-mental health delivered)	1.32 (0.56)	96 (25)		
Evaluate the effectiveness of existing interventions in real world settings (pragmatic trials)	1.48 (0.77)	92 (25)		
Develop and evaluate brief FCR/P interventions (suitable for inpatients, single session interventions at follow up appointments)	1.6 (0.71)	88 (25)		
Develop and evaluate stepped care interventions for low, sub-clinical, clinical levels of FCR/P	1.56 (0.71)	88 (25)		
Develop and evaluate early interventions for prevention of FCR/P	1.64 (0.76)	84 (25)		
Develop international collaborations for FCR/P intervention studies and evaluate cross-cultural validity of interventions	1.6 (0.87)	84 (25)		
Develop and evaluate interventions for sub-clinical levels of FCR/P	2.12 (0.78)	72 (25)	1.86 (0.74)	86 (29)
Develop and evaluate FCR/P interventions delivered in community settings (non-cancer settings)	1.92 (0.81)	72 (25)	1.79 (1.01)	86 (29)
Reaching specific populations				
Explore FCR/P in "avoidant" people (i.e., those people who manage FCR/P by avoiding health-related behaviors/follow up appointments)	1.6 (0.65)	92 (25)		
Explore FCR/P in patients having new treatments (e.g., immunotherapy, targeted therapy, etc.) on FCR/P	1.76 (0.83)	84 (25)		
Explore FCR/P in caregivers of people with cancer (parents or relatives of people with cancer)	1.72 (0.84)	84 (25)		
Explore Fear of Progression (FoP) in patients with advanced disease (for whom existential issues are more relevant)	1.76 (0.97)	80 (25)		
Explore FCR/P in survivors of childhood cancers/adolescent and young adult cancer	1.72 (0.89)	80 (25)		
Explore the prevalence of FCR/P across cancer groups	2.2 (0.91)	56 (25)	1.66 (0.86)	90 (29)
Explore how caregivers and people with cancer influence each other's FCR/P	not yet defined		1.52 (0.69)	86 (29)
Definitions and mechanisms of action				
Describe trajectories of FCR/P and identify covariates to explain any differences	1.64 (0.64)	92 (25)		
Map interventions to the different FCR/P trajectories	1.56 (0.65)	92 (25)		
Define the mechanisms of action and identify the active components across FCR/P interventions	1.28 (0.61)	92 (25)		
Refine the definitions of FCR and FoP	172 (0.89)	88 (25)		
Refine the theoretical model that explains FCR/P	1.60 (0.82)	88 (25)		
Explore the relationship between FCR/P and healthy anxiety	1.76 (0.72)	84 (25)		
Explore the underlying similarities and differences between Fear of Cancer Recurrence (FCR) and Fear of Progression (FoP)	1.88 (0.97)	76(25)	1.79 (1.01)	72 (29)
Explore the relationship between FCR/P and tolerating uncertainty more generally	1.76 (0.83)	72 (25)	1.31 (0.54)	96 (29)
Description of FCR/P predictors and consequences				
Examine the effects of FCR/P on healthcare seeking/health service utilization and associated costs	1.48 (0.59)	96 (25)		
Establish predictors of clinically significant FCR/P	1.48 (0.65)	92 (25)		
Establish predictive models for FCR/P	1.60 (0.76)	84 (25)		
Explore the impact of FCR/P on clinical outcomes (e.g., adherence to treatment)	1.64 (0.81)	80 (25)		
Examine the effects of FCR/P on use of alternative therapies and their costs	not yet defined		1.97 (0.98)	69 (29)
Detection and screening				
Develop better clinical and outcome measures of FCR/P which reflect clinical criteria for FCR/P	1.44 (0.65)	92 (25)		
Develop better FCR/P screening measures which reflect clinical criteria for FCR/P	1.36 (0.64)	92 (25)		
Establish clear clinical cut-offs for FCR/P screening measures (to guide intervention recommendations)	1.52 (0.71)	88 (25)		

(Continued)

TABLE 2 | Continued

Research priority	Round 3.1		Round 3.2	
Intervention models	**Mean (*SD*)***	**% agreement (n)**	**Mean (*SD*)***	**% agreement (n)**
Implementation				
Develop FCR/P clinical guidelines	1.50 (0.66)	92 (24)		
Develop and evaluate implementation research outcomes for FCR/P interventions	1.52 (0.79)	83 (23)		
Conduct health economic analyses of FCR/P intervention	1.83 (0.92)	75 (24)	1.24 (0.44)	100 (29)
Evaluate implementation of routine screening for FCR/P	1.78 (0.85)	74 (23)	1.24 (0.51)	97 (29)
Uncertainty and avoidance				
Explore the relationship between uncertainty and FCR/P	Not yet defined		1.59 (0.73)	86 (29)
Explore the relationship between avoidance, uncertainty and FCR/P	Not yet defined		1.59 (0.78)	83 (29)

**Mean of reported scores for each item where 1 = very important to 5 = not at all important (possible range 1–5).*

Research Priorities Ranking

The mean ranking of the seven research domains is listed in **Table 3**. Lower mean score is indicative of higher ranking of importance. Although all the priorities and related items were deemed important, *Intervention models* was identified as the highest priority (rank 3.04) and *Uncertainty and Avoidance* lowest (rank 5.04). In line with the ranked research domains, when asked to indicate their top three research items in order of importance, participants nominated two research items related to intervention models—*Develop and evaluate more accessible models* and *Evaluate the effectiveness of existing interventions in real world settings*, followed by *Define the mechanisms of action and identify the active components across FCR/P interventions* as the research of highest priority. Individual research items listed by >10% of participants as one of their top three priorities are listed in **Table 4**. Of note, although the item *Explore the underlying similarities and differences between Fear of Cancer Recurrence (FCR) and Fear of Progression (FoP)* failed to gain consensus, five panelists ranked this item as their 2nd or 3rd most important research domain.

DISCUSSION

Through the use of Delphi methods, this study developed consensus among key clinical and research stakeholders regarding aspects of FCR research that should be prioritized in future international collaborations. Based on the overall ranking of overarching themes, development and evaluation of intervention models was considered the most important focus for FCR research. In line with this, stakeholders identified development and evaluation of models of care that facilitate a greater access to FCR treatment and evaluation of the effectiveness of FCR interventions in real world settings as the two research questions of highest priority, with high levels of consensus (96 and 92%, respectively). Stakeholders also highlighted the importance of further work related to defining the mechanisms of action and active components across FCR/P interventions, ranking this research as the third highest priority.

TABLE 3 | Mean rank of overall research themes.

Research themes	Mean rank (Kendalls W)*
Intervention models	3.04
Definitions and Mechanisms of Action for FCR/P	3.25
Detection and Screening	3.64
Description of FCR/P predictors and consequences	4.00
Implementation	4.36
Reaching specific populations	4.68
Uncertainty and Avoidance	5.04

**Lower mean scores = higher perceived priority.*

The results of this priority setting exercise confirm that although the existing treatment protocols incorporating interventions delivered by specialist mental health clinicians are effective (Tauber et al., 2019), there remains a need to evaluate new service delivery models aimed at increasing accessibility. Preliminary research investigating use of online delivery and oncologist and nursing-led interventions reflects this move to more accessible alternatives (Liu et al., 2019; Cruickshank et al., 2020; Reb et al., 2020; Smith et al., 2020; Wagner et al., 2020). The focus on flexible delivery options is not surprising given increasing international efforts directed toward survivorship care models better tailored to address the needs-support gap (Carolan et al., 2018). For cancer survivors dealing with FCR, evidence-based models of care outside of the hospital-setting are perceived as a valid means of reducing the burden of distress experienced (Smith et al., 2020), although these interventions have yet to demonstrate their efficacy (van Helmondt et al., 2020).

Given FCR treatment models are currently time and resource intensive, there was also a clear support for evaluation of stepped care approaches incorporating interventions tailored to FCR severity, such that more intensive interventions (psychologist delivered face to face sessions) are reserved for patients with clinical levels of FCR who do not benefit from simpler first line approaches (online or non-mental health delivered). A stepped care approach is, however, contingent on the identification of clinical cut-offs to appropriately identify the intensity of intervention best suited to the severity of symptoms experienced. The stepped care approach to anxiety and depression screening and management as outlined in the clinical pathway for

TABLE 4 | Top three ranking for individual research topics across research themes *.

Item	Priority 1 (n)	Priority 2 (n)	Priority 3 (n)	Total No participants rating priority 1–3
Develop and evaluate more accessible models—low cost, online, telehealth, group, blended models of care, non-mental health delivered (theme 1)	6	3	5	14 (48%)
Evaluate the effectiveness of existing interventions in real world settings (theme 1)	5	1	3	9 (31%)
Define the mechanisms of action and identify the active components across FCR/P interventions (theme 3)	3	1	2	6 (20.6%)
Explore the relationship between avoidance, uncertainty, and FCR/P (theme 7)	3	0	2	5 (17.2%)
Develop and evaluate stepped care interventions for low, sub-clinical, clinical levels of FCR/P (theme 1)	2	3	0	5 (17.2%)
Explore the underlying similarities and differences between Fear of Cancer Recurrence (FCR) and Fear of Progression (FoP) (theme3)	0	2	3	5 (17.2%)
Explore FCR/P in patients having new treatments (e.g., immunotherapy, targeted therapy, etc.) on FCR/P (theme2)	1	0	3	4 (13.8%)
Develop and evaluate early interventions for prevention of FCR/P (theme1)	1	2	1	4 (13.8%)
Refine the theoretical model that explains FCR/P	0	1	3	4 (13.8%)

**Only topics listed by > 10% of participants are reported.*

identification and management of anxiety and depression in cancer (Butow et al., 2015) provides a useful framework for the development of a multi-disciplinary evidence-based guidance for FCR management. Although trials of evidence-based stepped care models have not yet been reported, a number of brief interventions among patients with low levels of FCR and interventions aimed at FCR prevention hold promise for this approach (Davidson et al., 2018; McHale et al., 2020). Prevention of FCR was also highlighted as a key area for future research. Finally, stakeholders acknowledged that efficacy of FCR interventions has been confirmed under ideal settings within randomized controlled trials targeting early stage, primarily breast cancer patients (Simonelli et al., 2017). To facilitate a greater translation of evidence into practice, they highlighted the need to conduct pragmatic trials, encompassing more diverse patient groups both in terms of disease and socio-demographic factors, conducted in routine clinical settings that reflect a diversity of cultural contexts, to ensure interventions are evaluated under real world conditions (Sanson-Fisher et al., 2019).

Despite the dissemination of a number of FCR conceptual models (Lee-Jones et al., 1997; Mellon et al., 2007; Fardell et al., 2016; Simonelli et al., 2017; Lebel et al., 2018) and exploration of relationships between FCR and related constructs [e.g., death anxiety (Sharpe et al., 2018), pain (Heathcote and Eccleston, 2017)], stakeholders reported research to better understand the mechanisms of action and active components of FCR interventions as one of their top three priorities. A number of recent studies have reported moderators and mediators of FCR in terms of patient level characteristics (Herschbach et al., 2010; Smith et al., 2018) and mechanisms of treatment efficacy (Lebel et al., 2018; Sharpe et al., 2019). A meta-analysis of FCR interventions also found that more contemporary forms of CBT aimed at modifying thought *processes* (i.e., how individuals relate to their inner experiences, rather than thought *contents*) were more effective (Simonelli et al., 2017). However, the link between cognitions and behaviors common in FCR, and individual intervention components, has not been established. Conducting comparative effectiveness studies (i.e., head to head trials) between FCR interventions may also help to better understand the relative merits of different interventions (Hulbert-Williams et al., 2018). Stakeholders confirmed such information would facilitate not only replication of findings, but also inform optimization of existing interventions in terms of treatment dose and determining where active elements can be adapted or modified in real-world settings (Rankin et al., 2019).

Understanding the mechanisms of action can also help to predict who might best benefit from available treatments. Stakeholders questioned whether the differing prognostic outcomes of disease influence the FCR trajectory for individual patients in clinically meaningful ways. Ratings indicated that stakeholders perceived that exploring potential differences across prognostic categories will inform development of interventions that better target recurrence and progression of fears across different patient groups.

An interesting finding of this study, which differs from the findings of the Australian Delphi study (Butow et al., 2019), was the support for greater research to explore the relationship between avoidance, uncertainty, and FCR. Stakeholders noted that while current conceptualizations of FCR have focused on those cognitions that drive hypervigilance, less attention has been given to patients who engage in avoidant behaviors. This patient group was of particular concern to the stakeholders as the risk of recurrence was higher due to their avoidant health behaviors aimed at reducing fear and uncertainty (Simonelli et al., 2017). The role of uncertainty, which has previously been linked with increased FCR (Lebel et al., 2018), was also highlighted as an important area of research in light of newer immune and targeted therapies which offer uncertain futures to patients with advanced disease (Levy et al., 2019).

Finally, it should be noted that two research topics proposed in the initial survey and confirmed during the focus group discussion failed to reach consensus. However both topics were conceptually similar to other items within the Delphi

where consensus was reached; for example, the item *explore the underlying similarities and differences between FCR and fear of progression* (72.4% agreement) is closely related to a number of other items within the Definitions and Mechanisms of Action theme such as refining the *definitions of FCR and FoP* and the theoretical model *that explains FCR/P* both of which reached consensus (88%). Similarly, the item *effects of FCR/P on use of alternative therapies and their costs* (69% agreement) may have been subsumed into the broader item *examine the effects of FCR/P on healthcare seeking/health service utilization and associated costs* (96% agreement).

The results of this consensus study need to be viewed in light of a number of limitations. Firstly, although all members of the FORwards special interest group were invited to participate at each phase of the research, overall participation rates were low with less than one third of members completing the Delphi study. Additionally, FORwards members are predominately from Western-culture based and OECD nations, limiting potential multicultural considerations of FCR research. Participation in the focus group was limited to only those FORwards members able to attend the IPOS World Congress. Despite the low recruitment rate, those who did participate represented key opinion leaders in the field and therefore were able to provide expert advice on the state of current international research. There was also there was limited representation of stakeholders from developing nations, although given the limited psycho-oncology services available, the findings around the need for increased FCR treatment accessibility may not have changed. A strength of this study was the international multidisciplinary participation, although there was an over-representation of psychologists. However, given that psychologists are the discipline most commonly treating FCR, their engagement with this agenda setting supports the clinical relevance of recommendations resulting from the consensus process. Finally, although the conduct of the Delphi was based on best practice methodologies, the majority of research items were rated highly, and once consensus was reached were not re-presented in subsequent rounds. Re-presenting items after consensus was reached may have provided greater differentiation of research priorities and better refined some of the lower ranked priorities. However, the high levels of consensus across a broad range of themes highlights the breadth of research questions yet to be answered. Given stakeholders were able to identify the three most important research topics to be addressed internationally and are largely consistent with the priorities identified by the Australian Delphi study (Butow et al., 2019), despite the study limitations, the findings confirm a clear direction to researchers and funding bodies about the nature of the research that should be considered in the immediate future.

CONCLUSION

The findings of this study provide a roadmap for international FCR research. Stakeholders confirmed intervention research to identify models of care that increase access to treatment, are based on a stepped care approach, and are able to deliver as part of routine clinical care as the highest priorities for future research. Greater understanding of the active components and mechanisms of action of existing FCR interventions will also facilitate greater tailoring of interventions to meet patient need.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Sydney Human Research Ethics Committee (2019/608). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JS lead the data collection and analysis. PB and HK contributed collection and analysis. JS lead manuscript development. All authors contributed to review and finalization of the manuscript, study conceptualization and design, and interpretation of results.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.596682/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Is a Brief Online Booklet Sufficient to Reduce Fear of Cancer Recurrence or Progression in Women With Ovarian Cancer?

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Background: Fear of cancer recurrence or progression (FCR/P) is a common challenge experienced by people living with and beyond cancer and is frequently endorsed as the highest unmet psychosocial need amongst survivors. This has prompted many cancer organizations to develop self-help resources for survivors to better manage these fears through psychoeducation, but little is known about whether they help reduce FCR/P.

Method: We recruited 62 women with ovarian cancer. Women reported on their medical history and demographic characteristics and completed the Fear of Progression Questionnaire-Short Form (FoP-Q-SF). They then read a booklet on FCR specifically created for Ovarian Cancer Australia by two of the authors (ABS and PB). One week after reading the booklet, 50/62 women (81%) completed the FoP-Q-SF and answered questions about their satisfaction with the booklet.

Results: More than half of the women (35/62; 56.5%) scored in the clinical range for FCR/P at baseline. Of the completers, 93% said that they would recommend the booklet to other women. Satisfaction with the booklet was relatively high (75.3/100) and more than two-thirds of women rated it as moderately helpful or better. However, FCR/P did not change significantly over the week following reading the booklet [$t_{(49)} = 1.71$, $p = 0.09$]. There was also no difference in change in FCR/P between women in the clinical vs. non-clinical range on the FoP-Q. Women high in FCR/P rated the booklet as less helpful in managing FCR/P ($r = -0.316$, $p = 0.03$), but overall satisfaction with the booklet was not associated with degree of FCR/P ($r = -0.24$, $p = 0.10$).

Conclusions: These results suggest that a simple online FCR booklet is acceptable to women with ovarian cancer and they are satisfied with the booklet, but, it was insufficient to change in FCR/P levels. These results suggest that such resources are valued by women with ovarian cancer, but more potent interventions are necessary to reduce FCR in this population.

Keywords: cancer, oncology, neoplasm, fear of cancer recurrence, fear of cancer progression, ovarian cancer, psychoeducation

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INTRODUCTION

Ovarian cancer is the leading cause of death among gynecological cancers with a 46% 5-year survival rate, as the disease is often diagnosed at an advance stage (Australian Institute of Health and Welfare, 2020). Approximately 70% of women with ovarian cancer are expected to experience recurrence of their cancer, particularly when diagnosed at later stages (Ovarian Cancer Research Alliance, 2020). Not surprisingly given this high recurrence rate, fear of cancer recurrence or progression (FCR/P) is one of the most common psychosocial concerns reported by this population (Matulonis et al., 2008; Kyriacou et al., 2017). FCR/P, defined as "fear, worry, or concern about the cancer returning or progressing" (Lebel et al., 2016, p. 3267), continues to be the most cited unmet need for ovarian cancer survivors (Tan et al., 2020). In a systematic review of FCR/P in ovarian cancer, Ozga et al. (2015) confirmed that FCR/P was prevalent amongst ovarian cancer survivors, and that women with ovarian cancer felt that there was insufficient support for managing FCR/P. Moreover, in a large prospective study of heterogeneous cancer survivors, those with advanced disease or who had experienced a recurrence had higher levels of FCR (Savard and Ivers, 2013).

Studies have identified that higher levels of FCR/P are associated with reduced quality of life (Hart et al., 2008), increased anxiety and depressive symptoms (Humphris et al., 2003; Koch et al., 2014) as well as post-traumatic stress symptoms (Mehnert et al., 2009). In addition to psychological symptoms, FCR/P is also characterized by increased healthcare costs (Thewes et al., 2012) and frequent reassurance seeking, such as through additional oncology appointments and increased medication use (Lebel et al., 2013). Therefore, individuals experiencing high levels of FCR often require specialized psychological support and intervention (Butow et al., 2018).

Despite clear evidence that high FCR/P is associated with poorer psychological outcomes and additional medical costs, specific interventions to manage FCR/P are still relatively scarce. In a meta-analysis of RCTs, Tauber et al. (2019) found over 23 controlled trials that had examined the efficacy of a psychological intervention and measured FCR, however, only 8 of these had specifically targeted FCR/P. The majority of those evaluated face-to-face interventions (e.g., ConquerFear, Butow et al., 2018) or blended interventions where treatments were administered partially online and partially face-to-face (e.g., SWORD, van de Wal et al., 2017). Both of these interventions required highly trained therapists and considerable time commitment (minimum of four sessions). In that meta-analysis, there were only two trials of a self-administered approach (i.e. minimal intervention). The study by Otto et al. (2016) found that such self-guided gratitude training interventions promoted well-being leading to a decrease in death-related FCR. The other intervention used Cognitive Bias Modification (CBM), an approach than aims to change implicit cognitive processes, such as interpreting ambiguous situations in a threatening way and preferentially attending to threatening information. The CBM approach was associated with reductions in health-related worries compared to placebo (Lichtenthal et al., 2017). One other randomized controlled trial, by Dieng et al. (2016), with melanoma survivors combined psychoeducational materials, as well as three telephone consultations with a psychologist, and found improvements in FCR/P, which were maintained at 12 month follow-up (Dieng et al., 2019). However, the telephone support still required specialist psycho-oncology skills. Given the number of survivors, and the fact that help with FCR/P remains a leading unmet psychosocial need, most services do not have the capacity to support all survivors with elevated levels of FCR/P.

Consequently, researchers are investigating other ways to increase access to information that might reduce or prevent persistent FCR/P. For example, brief interventions led by health professionals who manage the medical needs of survivors (most commonly nurses) have been developed. A recent systematic review of these approaches found that evidence to support their use is still lacking (Liu et al., 2019). Similarly, there has been interest in developing internet-delivered interventions specifically targeting FCR. Most of these are either in early stages of development (Smith et al., 2020) or currently being tested (e.g., Lyhne et al., 2020) and the only online intervention which specifically targeted FCR/P produced largely null results (van Helmondt et al., 2020).

Self-help materials have been used for other survivorship issues, including to reduce anxiety and depression and/or to improve quality of life. Cuthbert et al. (2019) identified 41 studies of self-help interventions that had been evaluated in randomized controlled trials. The results were largely mixed, with some showing short-term benefits and others showing little improvement in outcomes. None of these studies targeted FCR/P.

However, even in the absence of evidence, several non-profit organizations such as, Cancer Council Australia, National Breast Cancer Foundation, Breast Cancer Network Australia and Lymphoma Australia have developed online booklets or leaflets for addressing concerns related to cancer coming back or progressing. Whether these self-help materials attenuate FCR/P has not been the subject of research. Lynch et al. (2020) have recently completed a preliminary evaluation of a stepped care approach for survivors of melanoma who were treated with novel immunotherapies. The first step in their "FearLESS" program was a self-help intervention. Of those who scored in the sub-clinical range and were offered self-help, 90% did not feel the need for referral to individual therapy at the end of the study (Lynch et al., 2020). However, the authors did not evaluate whether changes in FCR/P were significant for those who received the self-management approach.

The evidence examining informational needs of cancer survivors suggests that most patients want to receive as much information as possible about their disease and its consequences (Shea–Budgell et al., 2014; Fletcher et al., 2017). A systematic review of 10 studies that assessed a range of patient outcomes in RCTs of educational resources specific to cancer, found that the provision of psychoeducation was associated with better outcomes for satisfaction, symptom management and anxiety and depressive symptoms (McPherson et al., 2001). However, we could not identify a purely psychoeducational resource that had been developed specifically for FCR/P which had been evaluated in terms of its acceptability and effect on FCR/P.

Therefore, we (PB & ABS) developed a simple online booklet that (a) outlined the nature of FCR/P, (b) provided information about how FCR/P becomes persistent, (c) suggested strategies (based on evidence-based treatments) that might help survivors to better manage FCR/P; and (d) provided links to where survivors can find additional help. The aims of this study were to determine whether (i) the booklet was acceptable to survivors (ii) survivors were satisfied with the booklet and would recommend it to others; and (iii) the booklet reduced levels of FCR/P.

It was hypothesized that

- Women with ovarian cancer will be satisfied with the booklet and would recommend it to other survivors.
- Women with ovarian cancer will have lower levels of FCR/P a week after reading the booklet compared to baseline.
- The booklet will lead to a greater reduction in FCR/P for women with low to mild FCR/P.

METHOD

Design

Women with ovarian cancer completed measures of FCR before and 1 week after reading an online psychoeducational booklet about FCR/P. In addition, a measure of satisfaction was given 1 week after women accessed the booklet.

Participants

Women who had been diagnosed with ovarian cancer, were over 18 years of age, and fluent in English were eligible to take part in the study. Participants were recruited online through Ovarian Cancer Australia (OCA) (see below). Ethical approval was provided by the University of Sydney's Human Research Ethics Committee (Project no.: 2018/993). Informed consent was obtained from all participants online, and they were free to withdraw from the study at any time.

Procedure

The new online FCR booklet developed by the authors was released through OCA and advertised to its members. When women indicated they would like to access the booklet, a pop-up window asked whether they would like the option of taking part in some research to evaluate the impact of the booklet on FCR/P. Women who chose not to do so, were directed immediately to the booklet, while those who indicated their interest in taking part in the research were invited to follow a link which described the study in more detail. Unfortunately, we were unable to get information from women who chose not to take part. After providing consent, participants were directed to an online questionnaire including some demographic and medical information and a measure of FCR/P[1]. On completion, women were given access to the booklet. One week later participating women were sent an email and asked to complete measures of FCR/P and satisfaction with the FCR/P booklet. We chose 1 week as a time frame because we suspected that any impact on FCR/P would be short-term, consistent with the systematic review on psychoeducational approaches (Cuthbert et al., 2019).

[1]Measures of interpretation bias and physical symptoms were included, the results of which are presented elsewhere.

TABLE 1 | List of contents in Fear of Recurrence booklet.

1. What does "cancer recurrence" mean?
2. Why are women fearful?
3. Types of fears
4. Common worry times
5. Day-to-day approaches to managing your fears
6. Carers' feelings
7. Some techniques for managing the fear of recurrence
8. Finding information online
9. Further information and support

Fear of Cancer Recurrence Booklet

The booklet was developed in conjunction with OCA and input from oncology health writer in terms of translating information from ConquerFear study suitable for women with ovarian cancer. It aims to provide information on FCR/P, which is identified as a significant survivorship issue for women with ovarian cancer (Kyriacou et al., 2017), and also suggest strategies to manage these fears. The techniques to manage FCR in this booklet were adapted from the ConquerFear program by Butow et al. (2017). See **Table 1** for the list of contents in the booklet (online link to the booklet: https://www.ovariancancer.net.au/page/94/support-resources).

Materials

Satisfaction Questionnaire

The satisfaction questionnaire has three items that assess: satisfaction with the information provided in the booklet; helpfulness for managing the concerns about cancer coming back or progressing; and whether women would recommend it to another woman diagnosed with ovarian cancer. The participants rated each item on a 10-point scale, from 1 (not at all) to 10 (completely). A higher score indicates that women are more satisfied with the booklet. Women completed this questionnaire 1 week after reading the booklet.

Fear of Cancer Recurrence/Progression

The 12-item Fear of Progression Questionnaire- Short Form (FoP-Q-SF; Herschbach et al., 2005) was administered to assess the level of FCR/P. Responses options ask how often a particular symptom of FCR/P is experienced on a five-point scale from 1 (never) to 5 (very often) (5). Thewes et al. (2012) conducted a systematic review of assessment measures for FCR/P and recommended the use of the Fear of Cancer Recurrence Inventory (Simard and Savard, 2009) and the FoP-Q-SF for assessing FCR/P. We opted to use the FoP-Q-SF because for women with ovarian cancer, many of whom have already experienced a recurrence, fear of recurrence is less relevant than fear of progression. Scores on FoP-Q-SF range from 12 to 60 and a score of 34 and above is taken to indicate a clinical level of FoP (Herschbach et al., 2010). The Cronbach's alpha for the current sample was 0.85.

Data Analysis

All statistical analyses were conducted in SPSS version 26. Preliminary analyses compared those women that completed the study vs. those who accessed the booklet but did not complete questionnaires after reading the booklet. For continuous variables, we used independent *t*-tests and for other variables we used Mann Whitney U tests (categorical variables) or Chi-square (dichotomous).

Mean scores and frequencies were examined for satisfaction ratings. For FCR/P, a paired samples *t*-test was used to compare the level of FCR/P before and after reading the booklet. Using the cut-off of 34 on the FoP-Q, we identified women with clinically significant levels of FCR/P vs. those who scored in the normal range to determine whether clinical FCR/P affected the impact of the booklet. To investigate the impact of clinical status, we conducted a mixed-model 2 (FCR/P: Clinical range vs. within normal range) x 2 (time: before vs. after reading the pamphlet) ANOVA. Finally, we conducted correlations between FCR/P and satisfaction ratings to determine whether level of FCR/P affected the satisfaction that women reported after reading the booklet.

RESULTS

Participant Characteristics

Sixty-two women diagnosed with ovarian cancer were recruited for the study. Participants had a mean age of 56.9 years. In terms of stage of disease, relatively few women had Stage I ($n = 10$; 16%), or Stage II ($n = 11$; 18%) disease, with 47% ($n = 30$) reporting Stage III and 9 (15%) reporting stage IV cancer. See **Table 2** for demographic and medical details. Of the 62 participants who commenced the study, 50 (19% attrition rate) completed the questionnaires again a week after reading the pamphlet.

Between group comparisons revealed that there was no significant difference between participants who completed the study and those who did not for age [$t_{(60)} = 1.13$, $p = 0.26$], education ($U = 216$, $p = 0.11$), cancer stage ($U = 276$, $p = 0.65$), number of children ($U = 289.5$, $p = 0.84$), marital status ($U = 284$, $p = 0.73$), cancer status [$\chi^2_{(1,62)} = 1.06$, $p = 0.33$] or employment status [$\chi^2_{(1,62)} = 0.14$, $p = 0.76$]. Likewise, there were no significant differences between participants in terms of FCR/P scores [$t_{(60)} = -0.26$, $p = 0.79$].

Satisfaction With the Booklet

Almost 75% (37/49) of the respondents rated the booklet to be relevant to people with ovarian cancer and indicated it provided the needed information about FCR/P (as indicated by ratings > 80/100). Only 1 woman indicated that the booklet was not at all relevant. More than two thirds of women (32/49) rated the booklet as at least moderately helpful (ratings > 50/100) in managing their worries about cancer coming back or progressing. Of those, 14/49 reported that it was completely helpful, and only 3/49 thought it was not helpful at all. Importantly, 93% (41/44 women) of the participants would recommend the booklet to other women.

TABLE 2 | Demographic and clinical characteristics of the sample.

	Cancer patients (*n* = 62)
Variable	**Mean**
Age	56.9 (11.64)
Time since diagnosis	3.45 (3.29)
	Frequency (percentage)
Marital status	
Married	41 (65.45%)
Widowed	2 (3.64)
Divorced	9 (14.55)
Separated	3 (5.45)
Never married	7 (10.71)
Children	
None	13 (20.97)
One	9 (14.52)
Two	32 (51.61)
More than two	8 (12.9)
Education level	
Did not complete high school	0 (0)
Completed high school	24 (38.18)
Undergraduate degree at university	22 (36.36)
Postgraduate degree at university	16 (25.45)
Employment status	
Currently employed	28 (45.16)
Currently unemployed	34 (54.83)
Stage at diagnosis	
Stage 1	10 (16.36)
Stage 2	11 (18.18)
Stage 3	30 (47.27)
Stage 4	9 (14.53)
Not known	2 (3.64)
Current cancer status	
Currently on treatment	18 (29.09)
Active disease	2 (3.64)
In remission	42 (67.27)
Cancer recurrence	
Yes	22 (36.36)
No	40 (63.64)
Surgery	
Yes	1 (1.12)
No	61 (98.88)
Treatment type	
Radiotherapy	0 (0)
Chemotherapy	46 (74.19)
Hormonal therapy	12 (19.35)
No treatment	4 (6.45)
CA-125 testing	
Yes	60 (96.23)
No	2 (3.77)
Not known	0 (0)

FCR/P Results

Self-reported outcomes on the FoP-Q indicated that, on average, women with ovarian cancer fell within the clinical range ($M = 35.58$, $SD = 8.52$). Based on the cut-off score on the FoP-Q of 34, 56% ($n = 35/62$) of the participants reported clinically significant levels of FCR/P and the remainder (44%; $n = 27/62$) reported FCR/P scores within the normal range.

Overall, significant differences were not observed in the FoP-Q scores before ($M = 35.4$, $SD = 8.59$) compared to 1 week after reading the booklet ($M = 33.94$, $SD = 9.00$) [$t_{(49)} = 1.71$, $p = 0.09$; Cohen's $d = 0.17$; 95% CI −0.22 – 0.55], indicating that the booklet did not change levels of FCR/P. In considering whether the booklet had a differential impact based on level of FCR/P, we conducted a 2 × 2 mixed-model ANOVA. Consistent with the *t*-test reported above, there was no significant main effect of time [$F_{(1,48)} = 2.69$, $p = 0.11$] on FCR/P scores. There was a significant main effect of FCR/P level indicating that women scoring in the clinical range had higher levels of FCR/P throughout the study [$F_{(1,48)} = 81.96$, $p > 0.001$]. The interaction between time and FCR/P level indicated that clinical status did not impact the effect of time on FCR/P scores [$F_{(1,48)} = 0.13$, $p = 0.72$].

Finally, we performed Pearson product-moment correlations to investigate the relationships between FCR/P and ratings of satisfaction. There was no significant correlation between ratings of satisfaction of the booklet in terms of providing sufficient information and level of FCR/P ($r = -0.24$, $p = 0.10$). However, correlations indicated that women with higher levels of FCR rated the booklet as less helpful in managing their worries about FCR/P ($r = -0.316$, $p = 0.03$).

DISCUSSION

The aim of this study was to determine whether an online booklet about FCR/P led to reductions in FCR/P and whether women were satisfied with the resource. The results demonstrated that there were high levels of satisfaction, and that most women would recommend the booklet to others. However, the booklet did not significantly improve levels of FCR/P, nor did it worsen them. The impact of the booklet on FCR did not differ for women in the clinical range for FCR/P compared to those with lower levels of FCR/P, although women with higher FCR/P rated the booklet as less helpful. Taken together, these results suggest that women believed that the booklet provided relevant information and was helpful, but the booklet was insufficient to reduce FCR/P.

These results are not entirely inconsistent with the previous literature and there are a number of potential reasons that might account for the failure to find an effect of this online resource. Firstly, Cuthbert et al. (2019) found mixed effects of self-help interventions, with some studies finding an effect and others not. They noted that very few self-help resources included specific behavior change techniques (e.g., Michie et al., 2011) and this could account for the failure of some interventions to affect change. This is true of the online resource in this study, which did not specifically include behavior change techniques.

Secondly, Cuthbert et al. (2019) described that in many self-help resources, there was an absence of a theoretical basis for the information provided. The information in the current booklet was adapted from the ConquerFear program (Butow et al., 2017), which was based on Fardell et al. (2016) model of the development of persistent FCR/P. This was the same model that was used as the first stage of the stepped care package developed by Lynch et al. (2020) for melanoma survivors who had responded to immunotherapy. However, in that study, the authors also included exercises as well as information, and there were three brief telephone conversations. Nevertheless, results on the FoP-SF-Q in the FearLESS study were similar to our results. Lynch et al. (2020) did not report the significance of their results for the 21 people that completed the self-help component, but the Cohen's d was similarly small ($d = 0.02$, 95% CI −0.59 – 0.62). Thus, even though both interventions were based on a theoretical model, neither appeared able to change FCR/P significantly and therefore this does not appear to explain the lack of effect observed here.

Thirdly, it has been suggested that some level of FCR/P is adaptive for people following cancer (Butow et al., 2018). This is because for all people who have been diagnosed with cancer, a recurrence is possible. For those in our study, with ovarian cancer, this is particularly the case since up to 70% of women with ovarian cancer will have a recurrence. According to this argument, FCR/P can provide the motivation to adhere to surveillance and therefore identify when a recurrence occurs. While this explanation cannot be excluded, it should be noted that in the Tauber et al. (2019) meta-analysis, there was no effect of cancer stage on the efficacy of interventions for FCR/P. Nevertheless, the bulk of the research on FCR/P involved patients whose cancer has been treated with curative intent and are currently disease-free. More research is needed to determine whether FCR/P is similar in patient groups with poorer prognosis to determine whether similar approaches are indicated. It may be in samples with advanced disease and high risk of relapse that distress and/or QOL are more relevant outcomes than FCR/P.

Finally, it is likely that the simple static FCR/P booklet, available in a PDF, was not sufficient to bring about change for the women who accessed it through this study who had high levels of FCR/P. FCR/P levels that were demonstrated by women in this study can be persistent and very distressing. It is perhaps unsurprising that a brief resource would not be sufficient to reduce FCR/P when one considers that even amongst the 8 available RCTs of psychological interventions with FCR as primary target, the effects were relatively small (Cohen's $d = 0.44$) (Tauber et al., 2019). However, it does pose a problem. With the increasing number of survivors, the small psycho-oncology workforce and the high levels of FCR/P, how can we meet the needs of survivors for help managing FCR?

We urgently need to focus on research that can develop cost-effective interventions that can be implemented in practice. Both the ConquerFear and SWORD studies (Butow et al., 2017; van de Wal et al., 2017) were shown to be cost effective, in that they had reasonable willingness to pay thresholds. However, we also need to consider stepped care models, such as FearLESS (Lynch et al., 2020), which have less time intensive interventions (such as self-management components that can be delivered via internet or telehealth) and/or utilize other members of the

oncology workforce. Liu et al. (2019) in their review, concluded that there was insufficient evidence to support the delivery of interventions by non-specialists. However, there have been successful applications of nurse-led approaches, or clinician-driven interventions (Humphris and Ozakinci, 2008; Davidson et al., 2018; Reb et al., 2020). This needs to be a priority for research, particularly as patients themselves are more likely to take up the offer of therapy with nurses than with psychologists or psychiatrists (Brebach et al., 2016).

Study Limitations

A number of methodological limitations are to be noted in the current study. Firstly, we did not recruit participants from clinical services and so relied on self-report regarding medical details. We did not take into account specific anxiety provoking situations such as oncology or scanning appointments. Studies have consistently shown that the time period when scan results are due can trigger significant anxiety in some patients (Feiler, 2011). This was not assessed and may have impacted the levels of FCR/P for some participants. Secondly, we are uncertain as to how much the booklet was read prior to the follow-up survey and the time was 1 week, and it might take longer for women to process apply the information, or it may have had immediate effects that tapered over time. The levels of motivation and engagement of the participants with the material could vary and could possibly provide a partial explanation for the results. Unfortunately we were unable to get data on how often women downloaded the booklet or how long they used it for. We did not have the pamphlet assessed formally by experts, which may have improved the resource and led to higher satisfaction. Further, our sample included all English-speaking participants and we were unable to get information about women that chose not to take part, therefore, the generalizability of this online resource across people from diverse backgrounds is unknown. The study would have benefitted from a formal power analysis since the study only had sufficient power to detect a moderate effect size (Cohen's $d = 0.33$). Finally, we developed a satisfaction scale for the study rather than using a previously validated scale.

Implications

Findings of the present study suggest that we need to develop brief interventions that are scalable to try and help manage the demand for support for FCR. Stepped care models, such as the FEARLESS (Lynch et al., 2020) approach are likely to be important, but we need evidence to support the efficacy of the first step. Internet-delivered approaches would be an obvious first step, however, the first of these to be trialed produced null findings (van Helmondt et al., 2020), and the only other reported intervention, iConquerFear (Smith et al., 2020) is in the process of being evaluated (Lyhne et al., 2020). In the most recent meta-analysis of treatment for FCR (Tauber et al., 2019), only two minimal interventions were identified. One of these, gratitude training improved well-being and had an impact on some aspects of FCR (Otto et al., 2016). The other intervention trailed was cognitive bias modification (CBM). CBM has been found to be effective in anxiety (Jones and Sharpe, 2017) and has shown some promise in managing some aspects of FCR/P (Lichtenthal et al., 2017). To be able to meet the growing needs of survivors to help them manage FCR/P, there is an urgent need to develop minimal interventions that are efficacious. If effective minimal interventions can be developed, they could be a useful addition to a stepped care approach in reducing FCR/P.

CONCLUSION

In conclusion, the online resource developed for women with ovarian cancer was rated as helpful. Women reported high levels of satisfaction and almost all women reported that they would recommend the resource to a friend. Despite these positive findings, the online resource did not lead to reductions in FCR/P and importantly it was those women with the highest levels of FCR/P who found the resource least helpful. Future research needs to investigate ways in which interventions can be delivered to the large number of cancer survivors who need help to deal with FCR/P.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Sydney's Human Research Ethics Committee (Project No: 2018/993). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PP, LS, and HR conceived the idea for the present study. PP wrote the first draft of the manuscript and performed the data analysis. PB and AS contributed in developing the online booklet. HR contributed to the participant recruitment. All authors discussed the results and contributed to the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Fear of Cancer Recurrence, Health Anxiety, Worry, and Uncertainty: A Scoping Review About Their Conceptualization and Measurement Within Breast Cancer Survivorship Research

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Objective: Fear of Cancer Recurrence (FCR), Health Anxiety (HA), worry, and uncertainty in illness are psychological concerns commonly faced by cancer patients. In survivorship research, these similar, yet different constructs are frequently used interchangeably and multiple instruments are used in to measure them. The lack of clear and consistent conceptualization and measurement can lead to diverse or contradictory interpretations. The purpose of this scoping review was to review, compare, and analyze the current conceptualization and measurements used for FCR, HA, worry, and uncertainty in the breast cancer survivorship literature to improve research and practice.

Inclusion Criteria: We considered quantitative, qualitative, and mixed methods studies of breast cancer survivors that examined FCR, HA, worry, or uncertainty in illness as a main topic and included a definition or assessment of the constructs.

Methods and Analysis: The six-staged framework was used to guide the scoping review process. Searches of PubMed, CINAHL, and PsycINFO databases were conducted. The principle-based qualitative analysis and simultaneous content analysis procedures were employed to synthesize and map the findings.

Findings: After duplicate removal, the search revealed 3,299 articles, of which 82 studies met the inclusion criteria. Several critical attributes overlapped the four constructs, for example, all were triggered by internal somatic and external cues. However, several unique attributes were found (e.g., a sense of loss of security in the body is observed only among survivors experiencing FCR). Overall, findings showed that FCR and uncertainty in illness are more likely to be triggered by cancer-specific factors,

while worry and HA have more trait-like in terms of characteristics, theoretical features, and correlates. We found that the measures used to assess each construct were on par with their intended constructs. Eighteen approaches were used to measure FCR, 15 for HA, 8 for worry, and 4 for uncertainty.

Conclusion: While consensus on the conceptualization and measurement of the four constructs has not yet been reached, this scoping review identifies key similarities and differences to aid in their selection and measurement. Considering the observed overlap between the four studied constructs, further research delineating the unique attributes for each construct is warranted.

Keywords: fear of cancer recurrence, health anxiety, uncertainty, worry, conceptualization, measurement, scoping review, cancer survivorship

INTRODUCTION

The psychosocial impact of a cancer diagnosis is increasingly recognized as a significant clinical issue. The most extensively assessed constructs in psycho-oncology are Fear of Cancer Recurrence (FCR), Health Anxiety (HA), worry, and uncertainty in illness (Miller, 2012; Costa et al., 2016; Lebel et al., 2016a; Strout et al., 2018; Mutsaers et al., 2019). Yet despite the rapid proliferation of psycho-oncology research, the standardized conceptualization and measurement of these four core constructs have not yet been established and they are frequently used interchangeably (Bradford et al., 2013; Jones et al., 2014; Butow et al., 2019). Further, although associations between these constructs have been established (Fink et al., 2004; Moye et al., 2014), their use as proxies for one another is not empirically supported (Consedine et al., 2004; Hirai et al., 2008). In part, this practice reflects a lack of clarity on their categorical distinctions. For example, health anxiety has been used to describe the fear and worry in response to living with a chronic illness (Asmundson et al., 2010; Lebel et al., 2020); similarly, fear and worry have also been used to characterize FCR (Lebel et al., 2016b). To further muddle the distinctions among these four constructs, uncertainty in illness has been defined as the phenomenological experience of anxiety arising from unpredictable real or unreal health issues (Grupe and Nitschke, 2013), using terms often found in the other studied constructs. While FCR has been proposed as a unique psychosocial issue (Mutsaers et al., 2019), its clinical characteristics overlap with the established diagnostic criteria for HA and are also related to worry (Commons et al., 2016).

In an attempt to clarify the nature and characteristics of FCR, a group of content experts met in 2015 to formulate a consensual definition of FCR using the Delphi method (Lebel et al., 2016b). The researchers determined that FCR is a multidimensional construct encompassing triggers, emotions, thoughts, physiological reactions, and coping strategies. They described a broad-spectrum definition of FCR as: "Fear, worry, or concern about cancer returning or progressing." (Lebel et al., 2016b). Conversely, Costa et al. proposed that although FCR is commonly recognized as a multidimensional construct, further research was required to determine the core construct of FCR, which in turn would facilitate the development of shorter, more easily decipherable FCR measures (Costa et al., 2016).

Beyond cancer and FCR, the constructs of uncertainty, worry, and HA have also been defined and applied to a variety of health, illness, and other psycho-social contexts. Mishel's widely used Theory of Uncertainty in Illness defined health and illness-related uncertainty as "the inability to determine the meaning of illness-related events, and accurately anticipate or predict health outcomes (Mishel, 1988)." In their conceptualization, Dugas et al. observe that in worry, "counterproductive beliefs, appraisals, and expectations may interfere with the individual's ability to use problem-solving behavioral skills (Dugas et al., 1995)." Lastly, HA has been conventionally conceptualized as "a multifaceted phenomenon consisting of distressing emotions, physiological arousal and associated bodily sensations, thoughts and images of danger, and avoidance and other defensive behaviors (Lang, 1985; Bradford et al., 2013)." In this approach, levels of health anxiety can vary along a continuum: on one end, HA is a healthy response and a motivation for performing positive health behaviors, whereas, on the opposite end, HA becomes pathological and dysfunctional.

In the area of measurement and assessment, there are also significant overlaps. For example, the Impact of Event Scale (Sundin and Horowitz, 2002) has been used measure both cancer-related anxiety and FCR (Thewes et al., 2001; Custers et al., 2016). Its use in FCR measurement applied the scale's sub-items such as intrusive and unpleasant thoughts to the worry that cancer could come back (i.e., FCR). Added to the psychometric confusion or "noise," some FCR instruments included items assessing other psychological constructs concerning cancer patients, such as anxiety and worry (Costa et al., 2016). In these ways, the use of the same instrument to measure multiple constructs, and the incorporation of multiple constructs within a single instrument further perpetuates the confusion of what tool is best to use to specifically measure each of FCR, worry, health anxiety, or uncertainty. Thus, both the conceptual distinctions between and the empirical clinical measurement of these constructs remain unclear.

While consensus on these distinctions has yet to be achieved, researchers do agree that distinct constructs and standardized definitions and measurements are required to effectively apply

them to clinical practice and research (Costa et al., 2016; Lebel et al., 2016b; Maheu and Galica, 2018; Butow et al., 2019). A common understanding of these constructs will help clinicians and researchers to target their care and interventions to specific cancer survivors' psychosocial needs and mental health outcomes. The identification of the core components and characteristics of the four constructs can improve measurement and screening capacity, and intervention development and implementation in the field of psycho-oncology.

The purpose of this scoping review, therefore, was to provide an overview of current use to conceptualize (i.e., characteristics, theoretical features, triggers, and correlates) and measure FCR, HA, worry and uncertainty as applied within a frequently occurring type of cancer, breast cancer. Our aim was to compare similarities and differences in how constructs have been used in research and map out existing evidence to contribute to the clarification of the application and measurement of these constructs in survivorship research, practice, and the development of interventions. The results of this review will guide future survivorship research relevant to the four different psychological concerns.

METHOD

The scoping review method applies a rigorous literature review process to investigate a body of literature on emerging or diverse topics, map out key constructs, clarify their definitions, and establish conceptual boundaries (Peters et al., 2020). Scoping review results are typically used to inform clinical decision-making and practice and provide direction for future research (Peters et al., 2020). In this review, we employed the Joanna Briggs Institute's (JBI) scoping review methodological framework, originally developed by Arksey and O'Malley (2005) and refined by Levac et al. (2010). Its six stages include the identification of the research question and relevant studies; study selection; data charting; collating, summarizing, and reporting results; and consultation (Arksey and O'Malley, 2005). Our scoping review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) checklist (Tricco et al., 2018) (i.e., refer to **Supplementary File 1** for the completed checklist). Critical appraisal and risk of bias assessment of studies are not mandatory in scoping reviews (Peters et al., 2020) and so these steps were not conducted. The scoping review protocol was registered with the Open Science Framework (OSF): (https://osf.io/78hxj/).

Stage I: Research Question and Objectives

Our research question was: "*What are the similarities and differences in the conceptualization (i.e., characteristics, theoretical features, triggers, and correlates) and measurement of the following constructs: FCR, HA, worry, and uncertainty in breast cancer survivor research*?" A sub-question was: *"How are HA, worry, and uncertainty similar to, or different from FCR?"* Our objectives were to summarize the conceptualization and empirical measurement of the four constructs in the breast cancer survivorship literature and provide recommendations to guide future survivorship interventions and research.

Stage II: Relevant Literature Identification

The search strategy followed the JBI iterative three-step process (Aromataris and Munn, 2020a): an initial search of the selected database using pre-specified keywords; a second thorough search across all included databases; and a final review of the reference lists of included studies to identify any missing studies. For the second step, only relevant articles from the initial screening were analyzed to inform the final search (Morris et al., 2016; Aromataris and Munn, 2020b). The academic librarian (FF) for the McGill Ingram School of Nursing and Affiliated Health Institution Libraries conducted the step one search in Ovid MEDLINE. These results were peer-reviewed by a second librarian (see **Appendix A: Search Strategies**); the revised search was conducted on March 11, 2020, in Ovid MEDLINE(R) ALL 1,946 onwards and CINAHL Plus with FullText (EBSCO). FF exported the search results from the Medline and Cinahl searches into EndNote X9 (Clarivate, PA, USA). Two reviewers (MS & WLT) screened results with the inclusion criteria; FF analyzed results using Yale's Medical Subject Headings [MeSH] analyzer to identify additional keywords and MeSH subject headings. The revised search was conducted on May 22, 2020, in Medline and Cinahl and was translated into APA PsycInfo 1967 onwards (second step of the search process). FF exported all results into EndNote and removed duplicates and articles already screened using a simplified method recommended by Bramer et al. (2016). Two reviewers (MS & WLT) conducted the second round of screening of results from all databases. For the third step, these reviewers screened the reference list of all relevant studies for additional relevant studies and used Google Scholar, Scopus, and the related article feature of Pubmed to identify citing articles of relevant studies. Two reviewers (AE & CM) screened these citing articles for inclusion. Reviewers hand-searched relevant therapeutic and special topic journals, contacting subject experts as needed.

Stage III: Study Selection

The team consolidated search results, removing duplicates, using Endnote and Covidence. Two reviewers (MS & WLT) screened article titles and abstracts to exclude those that did not meet the eligibility criteria. Disagreements about article eligibility were resolved by arbitration of a third reviewer (MH). For those fulfilling the eligibility criteria, the full article was retrieved. Two team members (AE & WLT) screened the full text of the articles, again excluding those not meeting the eligibility criteria. Eligibility disagreements were discussed between the two reviewers until consensus was reached or again, were arbitrated by a third reviewer (MH).

The primary inclusion-exclusion criteria were summarized in **Table 1**. Throughout the study selection process, the inclusion and exclusion criteria were refined iteratively, as the reviewers calibrated the threshold for inclusion and exclusion through discussion and consensus and with input from the entire research team. Finally, in accordance with PRISMA-ScR guidance, the

TABLE 1 | Study inclusion and exclusion criteria.

Study characteristics	Inclusion criteria	Exclusion criteria
Design	A primary quantitative or qualitative research. We included only the primary research if a secondary analysis of the same set of data was available.	Case report, protocols, reviews of the literature, and conference proceedings
Publication types	Peer-reviewed journal; the full article describing the research was available in English.	Commentaries, books, book reviews, letters to the editor, theses, opinion papers, abstracts without full-text, or articles without an English full-text.
Participants	Participants must involve women with stage 0–3 breast cancer, ductal carcinoma *in situ* and lobular carcinoma *in situ* are considered stage 0 breast cancer; participants must have completed initial treatment (chemotherapy or surgery) but could be on hormone therapy	The participants in the study had metastatic or recurrent cancer; participants were undergoing genetic testing or counseling, as this was considered to be a form of treatment.
Study concepts	Included Fear of Cancer Recurrence (FCR), Health Anxiety (HA), Worry or Uncertainty as a major concept. Fear of progression (FoP) is used interchangeably with FCR; therefore, we included the term FoP in our search and selection process.	The concepts under study included fear of disfigurement, fear of having children, fear of returning to society, etc.

study selection process with detailed reasons for study exclusions is presented in a PRISMA-ScR flow diagram (see **Figure 1**).

Stage IV: Data Extraction (Data Charting)

Based on the preliminary scoping phase, the team developed a data extraction framework that defined 18 categories (see **Appendix B "Data Extraction Instrument"**). This instrument was built into the Covidence extraction tool. Alongside standard bibliographical information (i.e., authors, title, journal, and year of publication), the design of the study, study setting, and study purposes were extracted. For each study, characteristics of the study populations, including age, marital status, ethnicity, stage of cancer diagnosis, time since the end of treatment/ time since diagnosis were also documented. For studies that validated a psychometric scale or instrument to measure one of the four constructs, we included studies with participants of mixed cancer diagnosis; in such cases, we documented the percentage of breast cancer patients if the participants consisted of mixed samples of cancer survivors. From validation studies, we also extracted information on the research question, including the definition and conceptualization framework, the assessment tool (i.e., measurements/scales/questionnaires/interview questions), details of psychometric validation of the tool, and the characteristics of any of the four constructs described in the results and discussion sections.

Questions arising during the data extraction stage were discussed by the team and disagreements were resolved through team consultations. When necessary, the categories were modified, and the data extraction instrument was revised accordingly. Four members of the team (two pairs: TE & JG, and CM & WLT) independently extracted data from each study using the data extraction feature in Covidence. To ensure inter-rater reliability, extracted data were compared. Any discrepancies in extracted data were discussed between the reviewers until consensus was reached or by arbitration of a third reviewer, as required.

Stage V: Data Analysis and Synthesis

We developed a structured approach to synthesize and collate review data by modifying and combining the principle-based qualitative analysis of Morse and Field (1995) and simultaneous content analysis procedures (Haase et al., 1993). Notably, we followed Morse and Field (1995) in aligning the purpose of the analysis with the complexity of the constructs, expanding structural features of attributes as needed. We also drew from Haase et al. (1993) simultaneous concept analysis process and we used an iterative process of examining relationships across constructs using consensus groups.

To address our research questions, two major attribute categories were formed: (1) conceptualization and (2) measurements. In order to clarify the characterization of the four constructs, we have incorporated guidance from principle-based content analysis procedure (Penrod and Hupcey, 2005) and established an expanded classification of the first category, conceptualization, resulting in 4 sub-categories: (a) characteristics, (b) theoretical features, (c) triggers, (d) correlates. We developed a standardized coding guideline (see **Table 2**) defining each of the critical attribute categories and subcategories to guide the coding process. For this review, we defined "Characteristics" as the description or statement containing defining features that aid in determining which phenomena match the construct and usually followed the key phrases such as "defined as" or "described as." "Theoretical features" we defined as the presence of specific features or indications in the theoretical model that aid in understanding the construct. We defined "Triggers" as the events or antecedents that present prior to the specific phenomenon of the construct. Finally, we defined "Correlates" as factors shown to have an association with the given construct.

The extracted data (i.e., refer to **Supplementary File 2** for the extracted data and a complete listing of the references) were analyzed according to the coding guideline. The critical attributes of the four constructs were then transferred into summaries across studies using *in vivo* coding (using a word

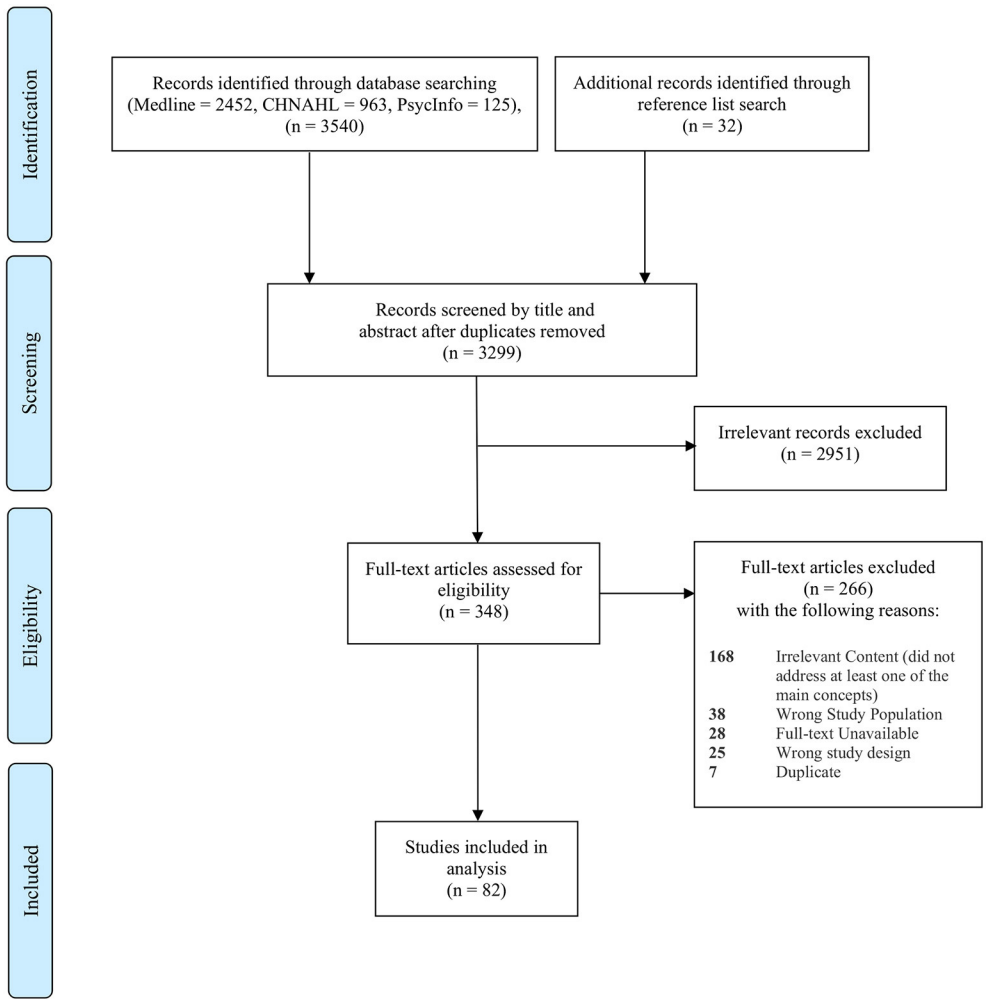

FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) selection of sources of evidence flow diagram.

or short phrase taken from that section of the data). Every textual description of a conceptualization was categorized into a single subcategory. To facilitate the consistency of categorization, one team member (WLT) carried out the initial coding procedures, and the resulting construct matrices were reviewed independently by two team members (CM & MS) (see **Tables 3**, **4** for the two construct matrices, with articles numbers reflected in **Supplementary File 2**). The review team met bi-weekly to discuss the process and results of the data synthesis, validating the synthesis methodology, auditing the decision-making trail, and providing feedback on the analysis results. Modifications to the coding procedures were made to reflect the re-examination of the preliminary results. The study characteristics and coded evidence were summarized using both qualitative and quantitative techniques and were then tabulated in an aggregate and visual form (i.e., matrix tables and bubble graphs). The tabulated summary was elaborated narratively, addressing the research questions and scoping review objectives.

Stage VI: Consultation Exercise

In this optional step, stakeholders outside the study review team are invited to provide their insights to inform and validate the scoping review findings. We asked members of the IPOS Fear of Cancer Recurrence Special Interest Group (FORwards) for feedback via a short survey. Three individuals provided a critical review, and their feedback was incorporated into our results and discussion.

RESULTS

Study Selection and Characteristics

As shown in the PRISMA-ScR flow diagram (see **Figure 1**), our search strategies initially yielded a total of 3,572 records (2,452 from Medline, 963 from CINAHL, 125 from PsyInfo, and 32 from reference and hand searches). Of these, 3,299 were screened by title and abstract after duplicates were removed. After excluding irrelevant records (n = 2,951), 348 full-text articles were retrieved and assessed for eligibility. At this stage, 266

TABLE 2 | Critical attribute categories and coding guidance for categorizing the four psychological constructs.

Critical attribute category	Critical attribute definition and coding guidance	Examples[a]
Conceptualization	Conceptualization of the four constructs is demonstrated in the following four ways: • **Characteristics.** The description or statement containing defining indicators that aid in determining which phenomena match the construct and which do not. • **Theoretical features.** The presence of specific features or indications in the theoretical model/ framework that aid in understanding the construct. • **Triggers.** The events or antecedents that are presented prior to the specific phenomenon of the construct. • **Correlates.** The factors that have been shown to have an association with the construct. Only correlates that are descriptions of primary study findings will be coded. The direction of the relationship will not be described.	**Characteristics** • "FCR is defined as the **"fear or worry that the cancer will return or progress in the same organ or in another part of the body**." [13] **Theoretical features** • "According to Leventhal's self-regulation model of illness, an individual's level of FCR is determined by his/her **illness representation through cognition and emotional processing**." [7] **Triggers** • "Uncertainty is generated when **components of illness or treatment possess the characteristics of inconsistency, randomness, complexity, unpredictability, and lack of information** in situations of importance to the individual" [41] **Correlates** • "**Social constraints** demonstrated a significant indirect effect on FCR through the mechanism of cognitive processing." [69] • "Anxiety was positively associated with **depression and symptom severity**." [8]
Measurements	• Instruments designed to determine the quantity of a variable within the concepts (i.e., **questionnaires, inventories, scales, surveys, and interviews**). Both quantitative and qualitative measurements will be documented.	• "Health anxiety is measured using the **Short Health Anxiety Inventory (SHAI)**, it demonstrates good reliability and validity and discriminates between individuals with and without hypochondriasis." [46] • "The **Mishel Uncertainty in Illness Inventory Scale-Community version (MUII)** is used to measure uncertainty. The MUII is a 33-item scale that measures an individual's clarity, understanding, and certainty regarding their illness." [63] • "FCR was assessed in a **semi structured interviews:** women described their thoughts and feelings regarding the possibility of recurrence, the nature of their fears, the circumstances under which their fears were most salient (i.e., what triggered their fears), and their efforts to cope with those fears." [77]

[a]*refer to* ***Supplementary File 2*** *for a complete listing of the references.*

records were excluded. The reasons for exclusion are as follows: irrelevant content ($n = 168$), wrong study population ($n = 38$), English full-text unavailable ($n = 28$), wrong study design ($n = 25$), and duplication ($n = 7$). A final set of 82 articles met all inclusion criteria and were included in this review (refer to **Supplementary File 2** for a complete listing of the references).

Extracted data (see **Table 5**) included the description of studies by location, sample size, and study design. The majority of studies used a quantitative, cross-sectional survey design (50.0%, $n = 41$) that had 101–500 participants ($n = 39$). Nearly 48% of the included studies were conducted in the United States ($n = 39$).

Critical Attributes Part I: Conceptualization

Characteristics

As seen in **Table 3** and **Figure 2**, 13 descriptions of characteristics were identified from the four analyzed constructs. While overlaps were found among certain study constructs, not one characteristic was found to be shared among all four constructs. Two characteristics identified with HA alone are *state* and *trait anxiety*. *Six* characteristics were identified only for uncertainty, which included: *the inability to determine the meaning or outcome of the illness; being in doubt; a state of liminality; a mismatch between one's expectation and the realistic world; a moderator between triggers and FCR;* and *a trigger of FCR*. These unique characteristics speak to the vagueness and liminality of a situation or illness outcome and could include risk of recurrence. One unique characteristic was identified for FCR: *a subset of anxiety;* the two unique descriptions for worry included: *a symptomatic consequence of anxiety* and *a type of emotional reaction*. Two characteristics were shared by both FCR and worry about breast cancer: *the concern that cancer will come back or progress,* and *a type of cancer-related worry.*

Theoretical Features

As seen in **Table 3** and **Figure 3**, 23 theoretical features were identified, 10 of which were observed in more than one construct. One feature, *excessive seeking of professional advice for reassurance*, was identified in all four constructs. FCR, HA, and worry had four additional theoretical features in common, they all involved *excessive personal checking behavior; misinterpretation of neutral bodily symptoms; adoption of avoidance-oriented coping;* and *worry, rumination or intrusive thoughts. Three* other shared features were found for FCR and HA: *being determined by illness representation; increased vigilance to somatic sensations;* and *anxious preoccupations.* In addition to the above-mentioned shared features, FCR and worry shared one unique feature: o*ngoing, persisting, and being stable overtime. Multidimensionality* was a theoretical feature observed in both FCR and uncertainty, along with the main common features

TABLE 3 | Conceptualization: number and prevalence of thematically derived critical attributes for the four constructs: article numbers reflected in **Supplementary Material**.

Critical Attribute: conceptualization subcategories	**Constructs[a]**			
	Fear of Cancer Recurrence (FCR) ***n*** **= 73**	**Health Anxiety (HA)** ***n*** **= 38**	**Worry (W)** ***n*** **= 11**	**Uncertainty (U)** ***n*** **= 15**
Characteristics = 13				
The concern that cancer will come back or progress	[3] [6] [15] [16] [30] [40] [41] [42] [46] [49] [56] [57] [58] [60] [63] [66] [67] [69] [70] [71] [72] [73] [74] [78] [81] [82] [76]	—	[61]	—
A type of cancer-related worry	[17] [30] [32] [33] [34] [41] [49] [70] [79] [81]	—	[17] [41] [61]	—
A subset of anxiety	[13] [30] [40] [46] [49] [51] [54] [67]	—	—	—
Trait anxiety	—	[6] [40] [48] [62]	—	—
State anxiety	—	[6] [40] [48] [62]	—	—
A symptomatic consequence of anxiety	—	—	[17] [54]	—
A type of emotional reaction	—	—	[61]	—
The inability to determine the meaning or outcome of the illness	—	—	—	[10] [25] [26] [52]
Being in doubt, being undecided, perceptions of vagueness	—	—	—	[29] [68]
A state of liminality	—	—	—	[75]
A mismatch between one's expectation and the realistic world	—	—	—	[80]
A moderator between triggers and FCR	—	—	—	[41]
A trigger of FCR	—	—	—	[10] [12] [25] [26] [27] [41] [52] [55] [56] [80]
Theoretical features = 23	**FCR**	**HA**	**Worry**	**Uncertainty**
Excessive seeking of professional advice for reassurance	[1] [2] [15] [21] [23] [35] [40] [41] [57] [58] [72] [76]	[49] [58]	[54]	[41]
Worry, rumination or intrusive thoughts	[3] [14] [35] [40] [51] [59] [63] [71] [72]	[73]	[10] [71]	—
Excessive personal checking behavior	[15] [27] [35] [41] [43] [46] [57] [71] [72] [75] [76]	[49] [58] [72]	[19]	—
Misinterpretation of neutral bodily symptoms	[15] [40] [46] [76]	[41]	[67]	—
Adoption of avoidance-oriented coping	[16] [30] [35] [40] [41] [51] [63] [65] [71] [72] [76]	[35] [58] [72]	[54]	—
Anxious preoccupations	[1] [3] [14] [15] [43]	[46]	—	—
Determined by illness representation	[7] [12] [24] [37] [44] [46] [65] [66] [81]	[38]	—	—
Increased vigilance to somatic sensations	[40] [46] [51]	[41]	—	—
Ongoing, persisting and stable over time	[4] [10] [22] [27] [33] [34] [57] [59] [60] [66] [72] [75] [76] [78]	—	[61]	—
Multidimensional	[9] [37] [42] [78] [82]	—	—	[9] [25] [26]
Realistic fear	[37] [43]	—	—	—
Excessive concern about the treatment adverse effects	[21] [27] [44] [64]	—	—	—
Extra reassurance serves to maintain patients' fear	[58] [73]	—	—	—
Loss of a sense of security in the body	[75]	—	—	—
Estimation of danger enhanced by threat-related stimuli	—	[13]	—	—
Unrealistic fear	—	[46] [54] [58] [72] [76]	—	—
Autonomic arousal	—	[6] [40] [62] [73]	—	—
A trend decreases over time	—	[23] [38]	—	—
Occurs among individuals without a medical problem	—	[46] [76]	—	—
Experience an anxiety/relief cycle	—	[1]	—	—
Self-focused attention	—	—	[71]	—

(Continued)

TABLE 3 | Continued

Critical Attribute: conceptualization subcategories	Constructs[a]			
	Fear of Cancer Recurrence (FCR) ***n*** **= 73**	**Health Anxiety (HA)** ***n*** **= 38**	**Worry (W)** ***n*** **= 11**	**Uncertainty (U)** ***n*** **= 15**
Perceptual state that existed on a continuum changes over time	—	—	—	[27] [29] [52] [55] [80]
Not feeling secure and safe from danger	—	—	—	[29]
Triggers = 14	**FCR**	**HA**	**Worry**	**Uncertainty**
Internal (somatic) cues such as physical symptoms	[10] [12] [23] [24] [26] [27] [33] [44] [50] [54] [65] [66] [71] [79]	[30] [44]	[17] [19]	[27] [52] [55] [64]
External cues such as medical check-ups and media	[15] [21] [23] [26] [27] [33] [46] [57] [65] [72] [77] [82]	[1]	[19]	[27] [52] [55] [64]
Attentional and interpretation bias to threat-relevant stimuli	[6] [13]	[13] [43]	[6] [71]	—
Cognitive vulnerability: intolerance to uncertainty	[6] [41] [65] [71] [79]	[27]	[41]	—
Unmet information/knowledge needs	[32]	—	—	[10] [26] [52] [64] [80]
Social constraints	[11] [69] [81]	—	—	—
Poor problem-solving skills	[31]	—	—	—
Concerns about financial consequences of treatment	[62]	—	—	—
Decision regrets with treatment	[32]	—	—	—
General health worries	—	[17] [18] [62]	—	—
Possibility of potentially negative but uncertain future events	—	—	[17]	—
Inability to interpret and manage treatment-related side effects	—	—	—	[27] [55] [68] [80]
Not being able to rely or count on someone or something	—	—	—	[29]
Complexity, unpredictability, ambiguity of illness	—	—	—	[9] [10] [25] [26] [27] [29] [41] [55] [56] [64] [68] [75] [80]
Correlates = 23	**FCR**	**HA**	**Worry**	**Uncertainty**
Younger age	[4] [8] [20] [30] [33] [37] [40] [42] [67] [78] [82]	[38] [40] [62]	[61]	—
Excessive emotional distress	[1] [3] [14] [31] [35] [43] [57] [62] [70] [78] [79]	[13] [38]	—	[10] [27] [29] [52] [56] [64] [80]
Amount of social support	[56] [69] [81]	[27] [38]	—	[55] [64] [80]
Appropriate self-protective response	[21] [39] [66] [73] [76]	—	—	[39]
Fear of death	[1] [5] [65]	—	—	[55] [56] [64]
Maladaptive hypervigilant coping	[3] [32] [35] [41] [43] [58] [73] [75]	—	—	[80]
Difficulties making plans for the future	[3] [15] [65] [70]	—	—	[29] [80]
Diminished health related quality of life	[2] [3] [11] [21] [22] [23] [33] [37] [43] [57] [60] [65] [67] [70]	—	—	[27] [64]
Threat appraisal	[50] [60] [66]	—	[61]	—
Functional impairments	[3] [7] [11] [21] [22] [37] [57] [58] [65] [67] [72] [77] [78] [79]	[58] [59]	—	—
Specific type of treatment	[42] [47] [67] [76]	[36]	—	—
Dysfunctional processing of fear	[57]	—	—	—
Chronic uncertainty	[25] [36] [39] [41] [64]	—	—	—
Level of self-efficacy	[82]	—	—	—
Cultural practices	[33] [34] [53]	—	—	—
Depressive symptoms	—	[8] [12] [58]	—	—
Associated with symptom severity	—	[8]	—	—
Associated with self-blame and shame	—	[27]	—	—

(Continued)

TABLE 3 | Continued

Critical Attribute: conceptualization subcategories	Constructs[a]			
	Fear of Cancer Recurrence (FCR) ***n*** **= 73**	**Health Anxiety (HA)** ***n*** **= 38**	**Worry (W)** ***n*** **= 11**	**Uncertainty (U)** ***n*** **= 15**
Meta-cognitive beliefs about worry	–	–	[6] [41] [54] [71]	–
Level of confidence	–	–	–	[55]
Level of anxiety	–	–	–	[9] [64]
Ability to register information	–	–	–	[25]
Short survival time	–	–	–	[10] [68] [80]

[a] *Refer to* ***Supplementary File 2*** *for a complete listing of the references.*

shared in all four constructs with *excessive seeking of professional advice for reassurance*.

Distinguishable theoretical features of each of the four psychological constructs were identified. Studies examining FCR recognized four unique theoretical features of this construct: *realistic fear; excessive concern about the treatment adverse effects; extra reassurance serves to maintain patients' fear;* and *loss of sense of security in the body*. Those investigating HA identified four distinct features: the *estimation of danger is enhanced by threat-related stimuli; unrealistic fear; autonomic arousal (apprehension, tension and nervousness); decreases over time; can occur among individuals without a medical problem,* and sometimes involves an *anxiety/relief cycle. Self-focused attention* was the single unique theoretical feature identified in the literature with worry. Unique theoretical features of uncertainty include a *perceptual state that exists on a continuum changing over time* and *not feeling secure and safe from danger*.

Triggers

A total of 14 triggers were identified from the four constructs as seen in **Table 3** and **Figure 4**. Five of these were observed in more than one construct. FCR, HA, worry, and uncertainty had two triggers in common; they are all triggered by *internal cues* (e.g., somatic/physical symptoms) and *external cues* (e.g., medical check-ups and media). For all constructs except for uncertainty, two common triggers were found such as *cognitive vulnerability (i.e., Intolerance to uncertainty*); and *attentional and interpretation bias to threat-relevant stimuli*. Both FCR and uncertainty were triggered by *unmet information/knowledge needs*.

Several distinguishing triggers of each construct were also identified. The unique triggers of FCR were *social constraints; poor problem-solving skills; concerns about financial consequences of treatment;* and *having regret about treatment decisions*. Uncertainty was specifically triggered by *unmanageable treatment side effects*; *not being able to rely on count on someone or something;* and *the complex*, *unpredictable and ambiguous nature of the illness*. A unique trigger of HA was *general health worries,* and the *potentially negative but uncertain future events* was a distinctive triggering factor for worry.

Correlates

As outlined in **Table 3** and **Figure 5**, among the 23 correlates gathered from the 82 selected papers, 15 were associated with FCR, 8 with HA, three with worry, and 11 with uncertainty. No correlates were identified with all four constructs. At most, three correlates were identified with three of the constructs: *excessive emotional distress* and *amount of social support* with FCR, HA, and uncertainty; and *younger age* with FCR, HA, and worry. Nine correlates were identified with various combinations of two constructs with FCR being reflected in all of these combinations.

Twelve correlates were identified with only one of the study constructs. Correlated only with FCR were: *dysfunctional processing of fear memory; chronic uncertainty; level of self-efficacy;* and *cultural practices*. Correlates identified with HA were *depressive symptoms, symptom severity,* and *self-blame and shame*, and worry was the only construct identified with *metacognitive beliefs about worry*. Lastly, uncertainty was the only construct linked to *level of confidence, level of anxiety, ability to register information,* and *shorter survival time*.

Critical Attributes Part II: Measurements

As presented in **Tables 4**, **6**, the construct of FCR was measured using 18 different approaches from the 73 FCR papers retained. The three most frequently used scales to measure FCR were the Concerns About Recurrence Scale (CARS) (Vickberg, 2003) used 18 times, followed by the Fear of Cancer Recurrence Inventory (FCRI) (Simard and Savard, 2009) used 17 times (8/17 times full form, and 9/17 times short forms severity subscale), and the Cancer Worry Scale (CWS) used seven times with either the 8-items (Custers et al., 2014) or the revised 6-items scale (Custers et al., 2018). Two scales were used to measure either FCR and worry: the CWS (Custers et al., 2014), and the Assessment of Survivor Concerns (ASC) scale (Gotay and Pagano, 2007). In examining the development of these scales, the CWS by Custers et al. (2014) is the only scale that was developed to specifically measure FCR, but not worry, in breast cancer survivors and contains subscales (e.g., cognition, intrusiveness, and general worry with cancer) that can also be found in the other two scales mentioned above. CWS is the only scale among the three to have a specific cut-off score that distinguishes between low and high FCR levels. As for the ASC scale, it is not specific to fear of cancer recurrence and includes broad assessments of HA. While

TABLE 4 | Measurements: number and prevalence of thematically derived critical attributes for the four constructs: article numbers reflected in **Supplementary Material**.

Critical Attribute: measurements	Constructs[a]			
	Fear of Cancer Recurrence FCR) ***n* = 73**	**Health Anxiety (HA)** ***n* = 38**	**Worry (W)** ***n* = 11**	**Uncertainty (U)** ***n* = 15**
Focus group/semi-structured interview with open-ended questions	[1] [16] [21] [27] [39] [65] [73] [75] [77]	[1] [27]	–	[27] [29] [39] [55] [68]
Cancer Worry Scale (CWS); Custers et al. (2014, 2018)	[13] [14] [15] [46] [49] [50] [76]	–	[61]	–
Assessment of Survivor Concerns (ASC) questionnaire; Gotay and Muraoka (1998)	[23]	–	[17] [23]	–
IES-cancer (measures cancer-specific distress: (a) Intrusive thoughts, and (b) Avoidance; Horowitz et al. (1979)	–	–	[63]	–
Study made 1 item "I worry about my cancer coming back or spreading" from 0 (not at all) to 4 (very much)	[3] [7] [62] [79]	–	–	–
Worry about cancer scale; Easterling and Leventhal (1989)	[2] [12]	–	–	–
Concerns about Recurrence Scale (CARS) (4 domains: worries with health, womanhood, role, and death; Vickberg (2003)	[5] [9] [11] [18] [25] [31] [40] [43] [45] [53] [57] [58] [59] [67] [69] [70] [78] [82]	–	–	–
Fear of Cancer Recurrence Inventory (FCRI) or/and	[41] [42] [67] [71] [72] [73] [74] [76]	–	–	–
FCRI- Subscales or Short Form (FCRI-SF); Simard and Savard (2009)	[6] [14] [16] [35] [44] [58] [60] [63] [69]			
Fear of recurrence questionnaire; Northouse (1981)	[8] [24] [56] [67]	–	–	–
Concerns about Recurrence Questionnaire (CARQ-4); Thewes et al. (2015)	[20] [74]	–	–	–
Visual analog scale, indicating the severity of FCR	[22] [49]	–	–	–
Fears of cancer recurrence scale (FCR7) and short form (FCR4); Humphris et al. (2018)	[30]	–	–	–
Short form of the fear of progression questionnaire (FoP-Q-SF); Mehnert et al. (2006)	[37] [51] [66]	–	–	–
Cancer Rehabilitation Evaluation Survey—Short Form (CARES-SF); Schag et al. (1991)	[47]	–	–	–
FCR-1; Rudy et al. (2020)	[63]	–	–	–
Study made 3-items means (worry about cancer coming back in the same breast, in the other breast, and to other parts of my body) on a 5-point likert-type scale	[32] [33] [34]	–	–	–
Study made items survey yes/no with FCR and fear of death; Befort and Klemp (2011)	[4]			
Study made 5-items FCR empirically derived; Xu et al. (2019)	[81]			
Depression anxiety stress scale-21; Lovibond and Lovibond (1995)	–	[6]	–	–
Hospital Anxiety and Depression Scale (HADS); Zigmond and Snaith (1983)	–	[8] [12] [13] [14] [23] [30] [31] [35] [36] [54] [59] [60] [67] [69]	–	–
State-Trait Anxiety Inventory (STAI); Spielberger et al. (1983)	–	[9] [24] [40] [44] [48] [54] [62] [79] [82]	–	–
Profile of Mood States (POMS) tension–anxiety subscale, by McNair et al. (1971)	–	[17]	–	–
Psychological General Well-being Index (PGWB); Dupuy (1984)	–	[18]	–	–
Schedule for Affective Disorders and Schizophrenia (SADS); Spitzer and Endicott (1975)	–	[27] [28]	–	–
Generalized anxiety disorder scale; Spitzer et al. (2006)	–	[35]	–	–
Numeric visual analog scale for anxiety; Johnson et al. (2016)	–	[36]	–	–
Beck Anxiety Inventory (BAI); Beck et al. (1988)	–	[38]	–	–
Health Anxiety Questionnaire (HAQ); Lucock and Morley (1996)	–	[41]	–	–
Short Health Anxiety Inventory (SHAI); Salkovskis et al. (2002)	–	[46]	–	–
The Breast Cancer Anxiety Scale (BCAS); Kash (2001)	–	[48] [62]	–	–
Profile of Mood States-short form (POMS-SF); Shacham (1983)	–	[52]	–	–
Whiteley Index-Short Form (WI-7); Conradt et al. (2006)	–	[74]	–	–

(Continued)

TABLE 4 | Continued

Critical Attribute: measurements	Constructs[a]			
	Fear of Cancer Recurrence FCR) *n* = 73	Health Anxiety (HA) *n* = 38	Worry (W) *n* = 11	Uncertainty (U) *n* = 15
Metacognitions Questionnaire-30; Wells and Cartwright-Hatton (2004)	–	–	[6] [71]	–
Why do people worry about health questionnaire; Pelletier et al. (2002)	–	–	[41]	–
Penn State Worry Questionnaire (PSWQ); Meyer et al. (1990)	–	–	[54] [58]	–
Illness Worry Scale (IWS); Robbins and Kirmayer (1996)	–	–	[67]	–
Study made 4 items worry about cancer; Easterling and Leventhal (1989)			[19]	
Uncertainty in illness scale-survivor version; Mishel (1999)	–	–	–	[9] [10] [25] [26] [41] [63] [64] [80]
Cognitive Coping Strategies Questionnaire (CSQ); Rosenstiel and Keefe (1983)	–	–	–	[52]
Telephone survey assessing uncertainty triggers; Gill et al. (2004)				[28]

[a] *Refer to* ***Supplementary File 2*** *for a complete listing of the references.*

FCR and worry shared similar tools to measure two different constructs, worry was measured using seven different approaches and uncertainty measured using four different approaches (see **Table 4**). HA and uncertainty did not have overlapping measures to other study constructs. Among the 38 HA studies, the most consistently cited scale to measure this construct was the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) with 13 mentions. Among the measures used for worry, only the PSWQ represents a trait measure (Meyer et al., 1990). Uncertainty was measured eight times using the Mishel Uncertainty in Illness scale (MUIIS) (Mishel, 1981).

DISCUSSION

This scoping review represents the first known study that has used a rigorous knowledge synthesis methodology to simultaneously examine four similarly viewed psychological constructs in the breast cancer survivorship literature: FCR, HA, worry and uncertainty in illness. This review identified the unique and overlapping conceptual components of these constructs and examined the instruments used to assess them. Findings reveal a partial overlap among the four constructs with some uniqueness in their critical attributes (i.e., characteristics, theoretical features, triggers and correlates), but less overlap in their measurement.

Critical Attributes: Conceptualization (Characteristics, Theoretical Features, Triggers, Correlates) and Measurement

This review found that the four study constructs share many attributes, which may explain in part the initial conundrum which was the catalyst for conducting this review: their frequently interchangeable use in the empirical literature (Bradford et al., 2013; Jones et al., 2014; Butow et al., 2019). In this section, we aim to bring clarity on their categorical distinctions and areas of overlap.

Overview of Unique Attributes

The principal finding of our scoping review was that the psycho-oncology literature on breast cancer yields significant attributes that delineate clear distinctions among the four constructs of interest: FCR, HA, uncertainty, and worry. Beginning with the analysis of characteristics (see **Table 3** and **Figures 2–5**), among the 13 characteristics (see **Figure 2**) identified in the 82 papers reviewed, none of the characteristics overlapped all four constructs, 11 were distinguishing characteristics, and only two were shared by two constructs (FCR and worry). Similarly, 13 (of 23) theoretical features, nine (of 14) triggers, and 12 (of 23) correlate attributes were specific to only one construct. Thus, these findings from across the four critical attributes used in our analysis—characteristics, theoretical features, triggers, and correlates—provide a fruitful point of departure for delineating key distinctions among FCR, HA, worry and uncertainty.

Characteristics attributes that were unique to FCR include *the concern that cancer will come back or progress*, *a type of cancer-related worry*, *decision regrets with treatment*, *concerns with financial consequences of treatment, hypervigilance coping, memory dysfunction, poor self-efficacy and cultural practices, difficulty in making plans for the future.* Some of these identified FCR characteristics resonate with those identified from an international Delphi survey identifying key characteristics of FCR (Mutsaers et al., 2019), with some distinctions found. That is, other FCR characteristics identified in this scoping review are *decision regrets with treatment*, *concerns with financial consequences of treatment, and cultural practices.*

Another unique trigger related to FCR and not associated with the other three constructs was for social constraints, financial worries, and treatment decision regrets (Janz et al., 2014). The findings of our review and the recent Delphi survey support the notion that FCR may likely be best assessed as a multidimensional concept (Mutsaers et al., 2019). FCR also tended to remain unchanged if not clinically addressed whereas the other constructs were observed to carry elements of change over time. In our findings, FCR was the only construct aligned

TABLE 5 | Description of studies by location, sample size, and study design ($N = 82$): article numbers reflected in **Supplementary Material**.

	Article Number[a]	*n*	(%)
Location by Country			
Australia	[6] [18] [71] [72] [73] [74]	6	7.3
New Zealand	[12]	1	1.2
Netherlands	[13] [14] [15] [16] [76]	5	6.1
Demark	[20]	1	1.2
German	[37] [51]	2	2.4
Turkey	[38] [65]	2	2.4
France	[44] [54]	2	2.4
United Kingdom	[1] [2] [28] [30] [75]	5	6.1
Thailand	[5] [8] [80]	3	3.7
Tai Wan	[21] [22] [23]	3	3.7
Japan	[31] [53] [57] [59]	4	4.9
China	[60] [81]	2	2.4
Korea	[66]	1	1.2
Canada	[40] [41] [42] [63] [67] [68]	6	7.3
United States	[3] [4] [7] [9] [10] [11] [17] [19] [24] [25] [26] [27] [29] [32] [33] [34] [35] [36] [39] [43] [45] [46] [47] [48] [49] [50] [52] [55] [56] [58] [61] [62] [64] [69] [70] [77] [78] [79] [82]	39	47.6
Sample size			
1–50	[1] [9] [16] [21] [29] [31] [36] [39] [46] [54] [55] [56] [65] [68] [70] [73] [75] [76] [77]	19	23.2
51–100	[2] [5] [6] [7] [35] [43] [44] [59] [63] [64] [81]	11	13.4
101–500	[3] [8] [10] [11] [12] [13] [15] [17] [18] [19] [20] [22] [23] [24] [25] [26] [27] [28] [30] [38] [41] [42] [45] [48] [49] [50] [53] [57] [58] [60] [61] [62] [66] [69] [71] [72] [78] [79] [80]	39	47.6
501–1,000	[4] [32] [47] [52] [67]	5	6.1
>1,000	[14] [33] [34] [37] [40] [51] [74] [82]	8	9.8
Study design			
Qualitative interviews	[1] [16] [21] [27] [28] [29] [39] [55] [65] [68] [73] [75] [77]	13	15.9
Instrumental validation	[14] [30] [42] [60] [63] [67] [74] [78]	8	9.8
Case study	[46] [54] [76]	3	3.7
Cross-sectional surveys	[4] [6] [7] [8] [9] [10] [11] [12] [13] [15] [18] [19] [20] [22] [24] [33] [34] [36] [37] [38] [40] [41] [44] [45] [48] [50] [51] [53] [56] [57] [58] [60] [62] [64] [66] [70] [71] [72] [80] [81] [82]	41	50.0
Longitudinal or prospective	[32] [47] [49]	3	3.7
Randomized controlled trials	[23] [25] [26] [35] [43] [52] [59]	7	8.5
Mixed method	[2] [69]	2	2.4
Other designs	[3] [5] [17] [31] [79]	5	6.1

[a] *Refer to* ***Supplementary File 2*** *for a complete listing of the references.*

with the attribute that "*extra reassurances serve to maintain the fear.*" Another subtle difference found between FCR and the other three constructs was the increased frequency of threat appraisal associated with FCR. This finding may reflect the literature focused on providing for exposure therapy with a specific focus on fear. In contrast, the other constructs who remain more general tend to be treated with behavioral therapy. This would be a topic to study more widely.

The correlate cultural practices was only identified with FCR (Janz et al., 2011, 2016; Momino et al., 2014). Janz et al. (J2011) and Janz et al. (2016) found higher worry of recurrence (as they named) among Latina women in comparison to White women, while African American women experienced lower worry of recurrence than White women. The authors suggested that the main factors for higher worry of recurrence among Latinas were attributed to having less information about cancer, longer delays in diagnosis, and poorer communication styles. These findings might be due to the different levels of cultural appropriateness of expressing FCR among cultures, or the availability of psychosocial oncology assessment and/or intervention in different geographic locations. However, it should be noted that an examination of FCR correlates across cultures or countries has received little empirical study. This gap illuminates an important area for expanded research, as FCR measures are translated into an increasing number of languages [e.g., Chinese (Lin et al., 2018), Dutch (van Helmondt et al., 2017), and Persian (Bateni et al., 2019), to name a few]. Scholars such as Momino et al. (2014) have illuminated key cultural differences when validating the American-developed Concerns About Recurrence Scale (Vickberg, 2003) among Japanese participants. Slight differences in the factor structure were found between American and Japanese women; in the Japanese version, they found a new

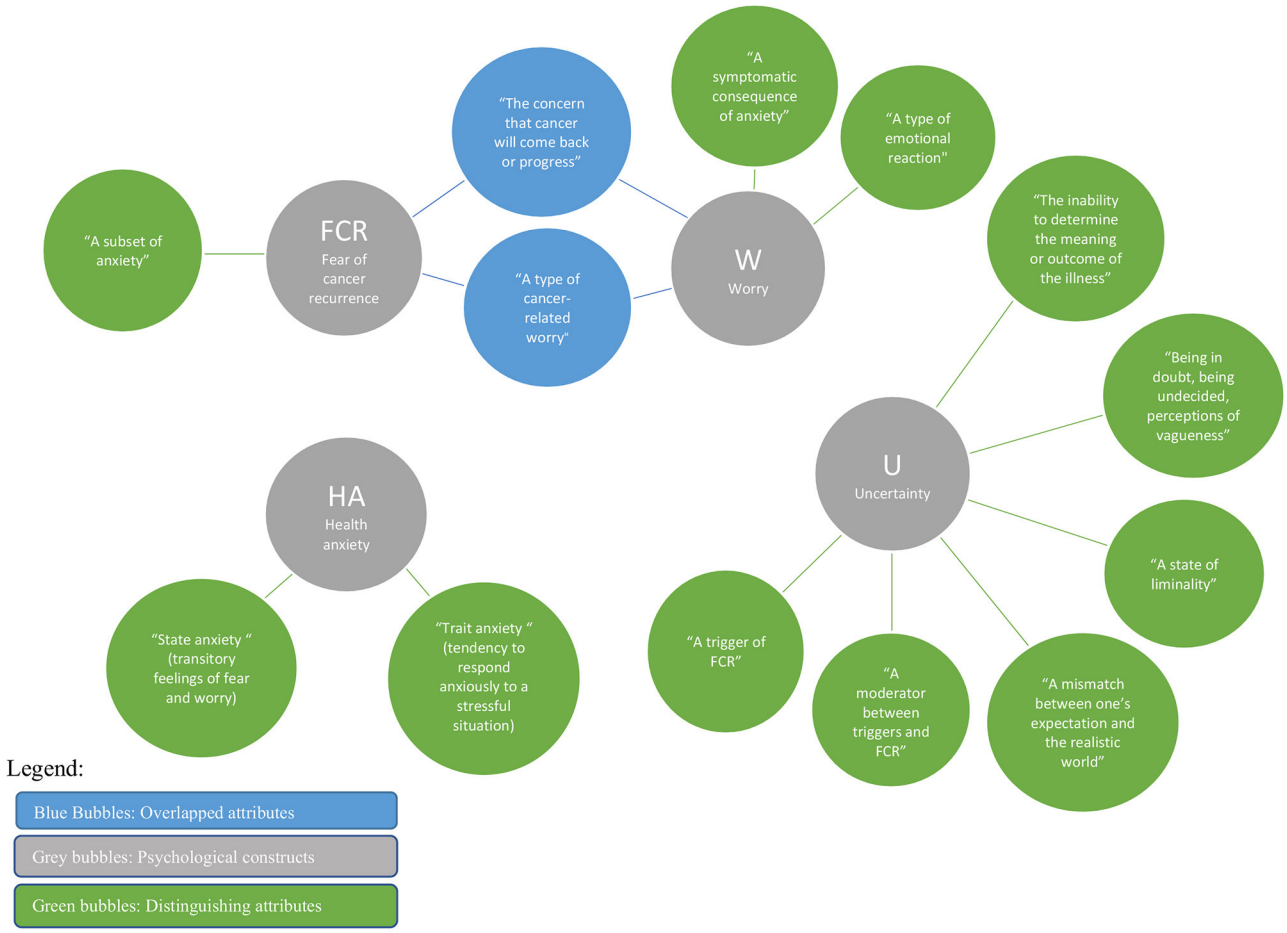

FIGURE 2 | Overlapped and distinguishing characteristics of the four constructs.

factor reflecting continuity after death widely believed to exist in this country. Collectively, these findings suggest that cultural differences impact the degree to which FCR, and perhaps other psychological problems, are experienced or displayed.

HA presented itself with six unique theoretical features that could point to a definition of HA itself (i.e., *estimation of danger, unrealistic fear, autonomic arousal, decreases over time accompanied by anxiety and relief cycle, and can be present in individuals with no known medical problem*). Even the relief cycle can also be helpful in differentiating between HA and generalized anxiety disorders, as the latter may be psychopathological conditions for which relief is unlikely to be shown (Dugas et al., 1998). However, in this review, HA was most often defined using terms such as a transient feeling to respond anxiously with fear or worry to a potential or existing health threat. Using HA as a proxy for FCR only becomes relevant if the worried thought and emotion is anchored to a context associated with FCR such as feeling of fear or worry that cancer will come back. Otherwise, HA represents a general state of worry toward one's health. Interestingly, HA was the only construct correlated with self-blame and shame and depression (Gill et al., 2004) and had distinguishing characteristics of both "*trait anxiety*" and "*state anxiety*." Previous evidence has revealed the correlation between shame proneness with maladjustment (Tangney et al., 1992) and the correlation between self-blame and major depressive disorder (Zahn et al., 2015). More specifically, it was argued that shame and guilt were similar in terms of internal attributions, but they also differ since shame had global and stable attributions while guilt had specific and unstable attributions for negative events (Tangney et al., 1992). Therefore, given these findings, it can be suggested that HA, unlike other constructs, may show characteristics of both transient distress and psychopathology depending on the level of effect on self-concept. In contrast, a recent review on the correlates of FCR found that this concept was on the whole rather stable, or perhaps could initially decrease then stabilize (Lebel et al., 2020). Worry was uniquely related to the theoretical attribute of self-focused attention. This finding can be particularly important when designing a measurement or also an intervention program, as individuals who are worriers tend to worry about themselves in specific situations, while in FCR, the situations feared are more varied (*feeling nervous prior to doctor's appointments, worrying about what will become of the*

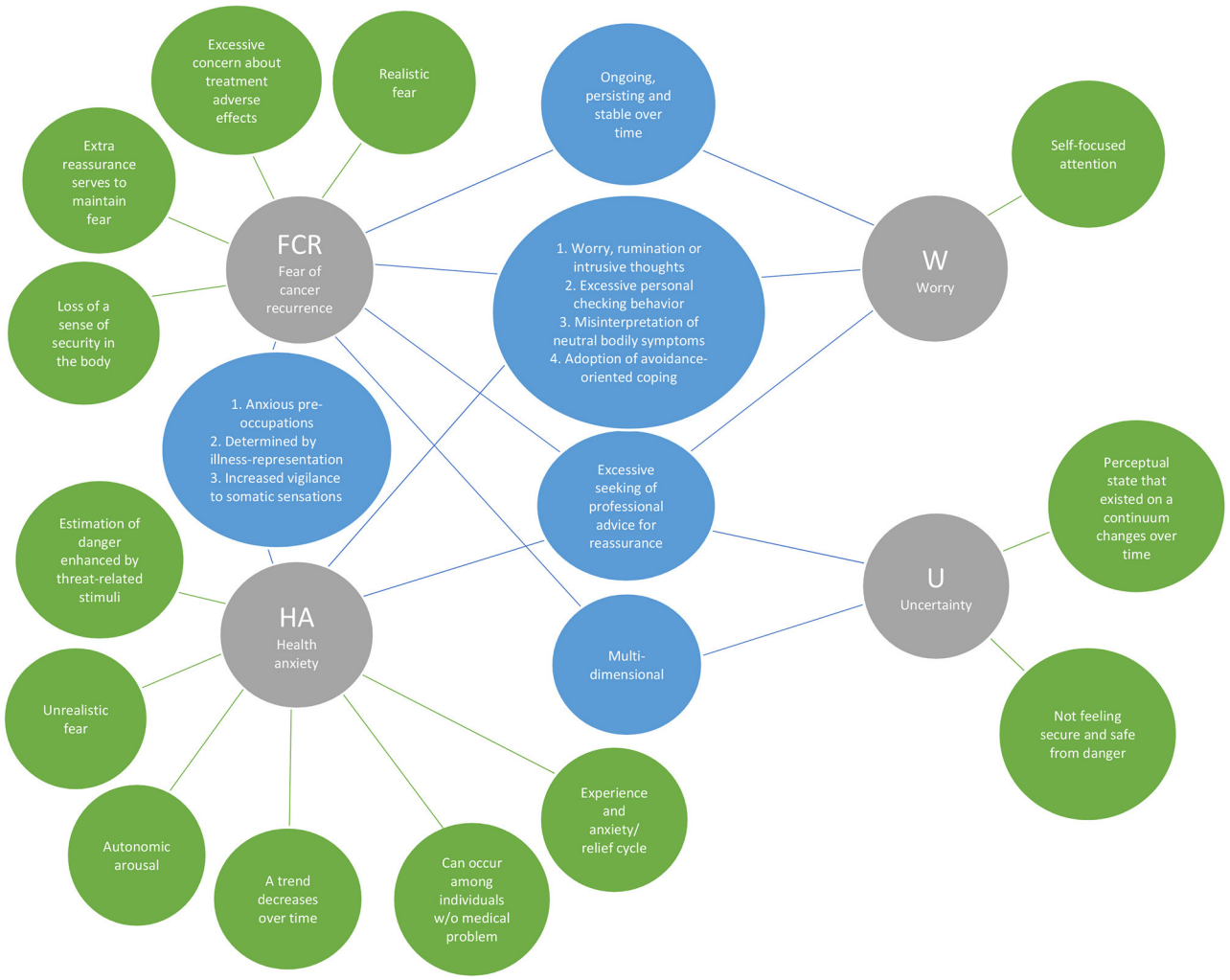

FIGURE 3 | Overlapped and distinguishing theoretical features of the four constructs.

family, being afraid of becoming less productive at work, fear of leaving the children parentless, fear of further treatment, fear of dying) (Götze et al., 2019).

Uncertainty was the only construct where its defining characteristics were existential issues aligned with the concept of uncertainty (i.e., *being unable to determine meaning of illness outcome, being doubtful, mismatch between own expectations and real world*). However, uncertainty and FCR did share overlapping triggers related to patient information needs that could be considered in designing preventative programs by providing good and sound information tailored to patient needs.

Overlapping Attributes

Among the identified theoretical features, several substantial features overlapped among the four constructs, with a majority of features being behavioral cues. For example, the increased use of and seeking professional advice for reassurance along with excessive personal checking behavior was often noted as a consequence of FCR (Janz et al., 2011, 2016); these behavioral cues, however, were found to be associated with all four constructs. Therefore, these attributes are not strong delineating characteristics.

Internal cues (e.g., somatic/physical symptoms) and *external cues* (e.g., medical check-ups and media) are identified as triggers for all four constructs. This finding was expected, perhaps related to seeking reassurance, since both internal and external cues are somatic related (Hall et al., 2017). External triggers are also related to media exposure and could be the stimuli for non-cancer specific psychological disturbance such as HA and worry, as well as cancer-specific distress including FCR and uncertainty of illness (Lemal and Van den Bulck, 2009). Furthermore, FCR, HA and uncertainty shared two overlapping triggers. First, the trigger *cognitive vulnerability to uncertainty* overlapped with the three constructs, but interestingly, not with uncertainty. This finding was perhaps due to the nature of the analytical methodology, as studies addressing the construct of

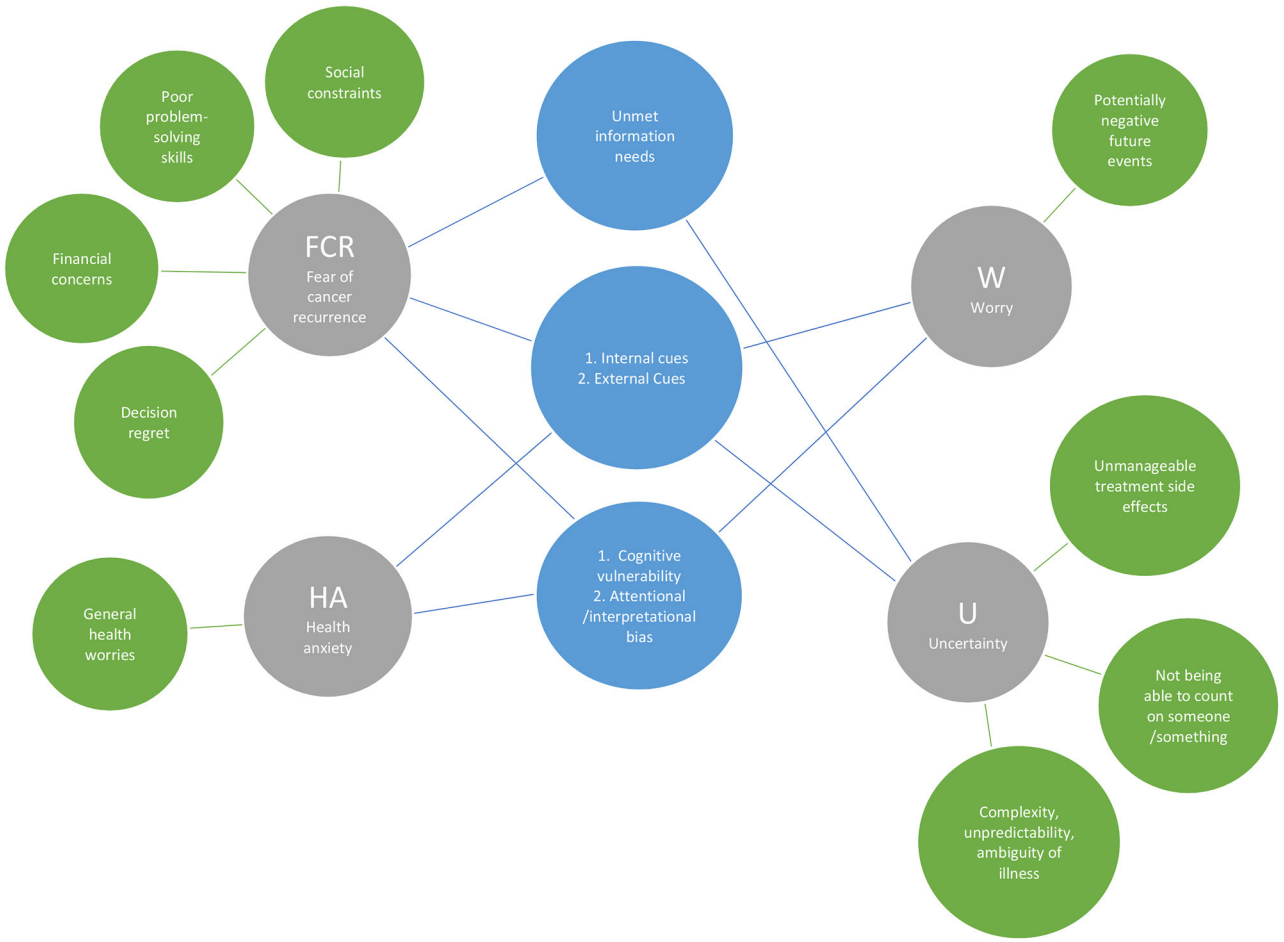

FIGURE 4 | Overlapped and distinguishing triggers of the four constructs.

uncertainty would not necessarily discuss "*cognitive vulnerability to uncertainty*" as a trigger. An alternative explanation could be that this trigger is a better fit to intolerance of uncertainty, a trait like characteristic associated with the tendency to react negatively, emotionally, cognitively, and behaviorally, to uncertain situations (Buhr and Dugas, 2006). The trigger *attentional/interpretational bias* was found to overlap between HA and worry but not FCR. These results are consistent with previous findings linking attentional bias with HA and worry (Butow et al., 2015; Custers et al., 2015; Ng et al., 2020) (not FCR) whereby anxious people are found to pay increased attention to threatening stimuli (attentional bias) (Lees et al., 2005; Kaur et al., 2013; Thewes et al., 2013; Aue and Okon-Singer, 2015). Finally, one trigger, *unmet information needs*, was identified in both FCR and uncertainty and is consistent with the literature. Insufficient and inaccurate information about cancer prognosis and recurrence risks are known to contribute to fear and uncertainty among breast cancer survivors (Lebel et al., 2014, 2018, 2020).

Within the correlates tabulated in **Table 3**, *younger age* was associated with FCR, HA, and worry, but not uncertainty. The finding that younger cancer patients are more likely to experience FCR, HA, and worry is supported in the literature (Janz et al., 2011; Jones et al., 2014; Mirosevic et al., 2019; Chumdaeng et al., 2020), and the reasons may be related to their responsibilities at this time in their life. For instance, younger cancer survivors are more likely to have dependent children and thus their FCR might relate to the future care of their children if their cancer should recur (Maheu, 2009). Similarly, younger cancer survivors are more likely to be engaged in employment (Stone et al., 2017) and therefore may be concerned with work-related problems. However, the lack of association between younger age and uncertainty does not necessarily mean that an association does not exist; on the contrary, younger persons with cancer do experience cancer-related uncertainty which can lead to negative effects (Wonghongkul et al., 2000; Corbeil et al., 2009; Kim et al., 2012). Therefore, the lack of association between younger age and uncertainty found in this review may be due to the lack of literature examining this association, rather than the true absence of it.

Excessive emotional distress and amount of social support were associated with FCR, HA and uncertainty, but not with

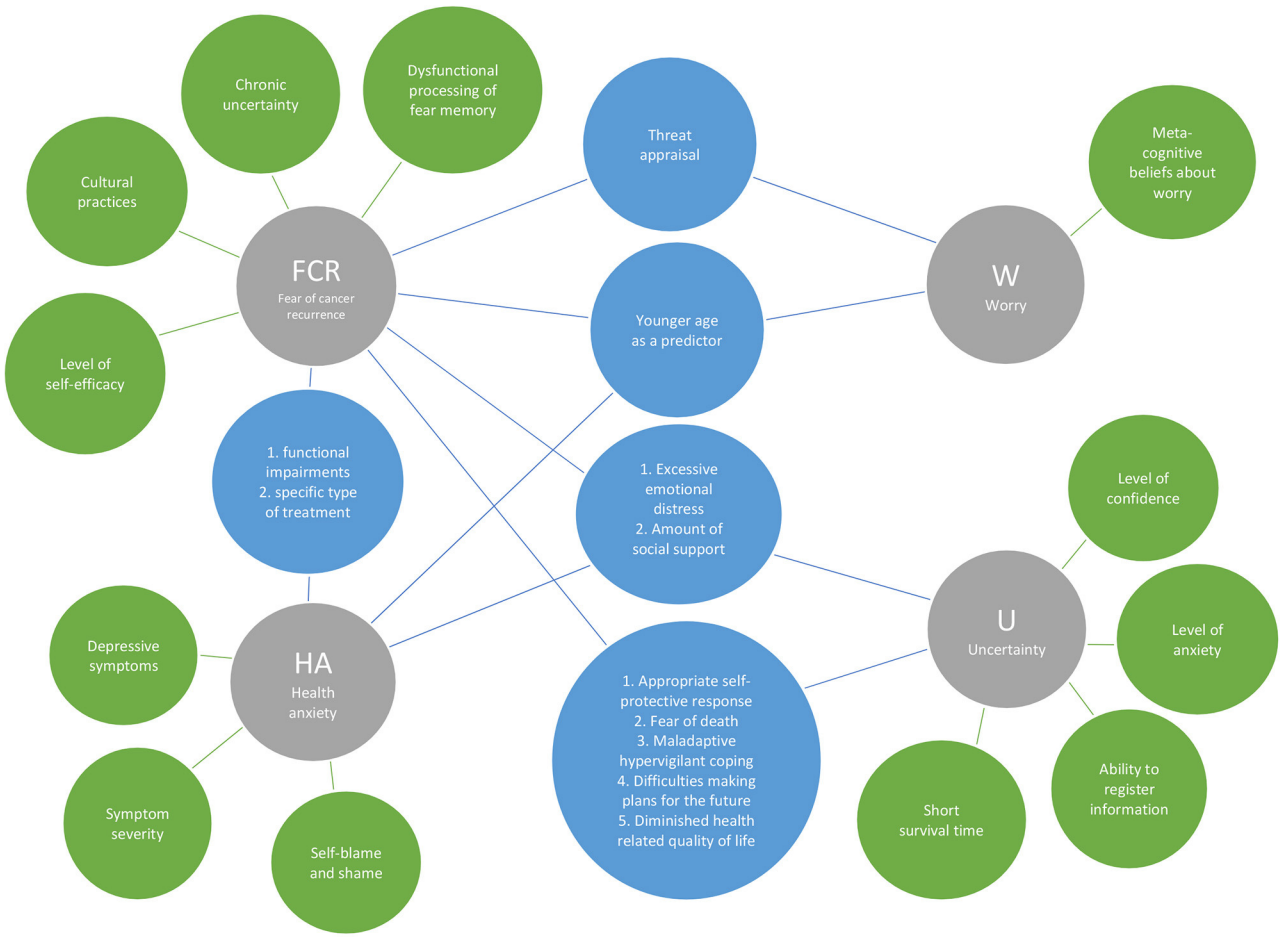

FIGURE 5 | Overlapped and distinguishing correlates of the four constructs.

TABLE 6 | Number and frequency of use of FCR, U, HA, and W Measurements.

Constructs and number of measurements[a]	Measurement tools and number of times used/study # in decreasing number[b]
73 articles examining **FCR**, 15 measurement approaches were used	**CARS** #18; **FCRI** #17; **Semi-structured interviews;** #9; **CWS** #7; **FRQ** #4; **1 item Worry about cancer coming back** #4; **FoP-Q-SF** #3; **3 group items** #3; **CARQ-4** #2; **Worry about Cancer Scale** #2; **Visual Analog Scale** #2; **FCR7/FCR4** #1; **ASC** #1; **FCR-1** #1; **CARES-SF** #1
38 articles examining **HA**, 15 measurement approaches were used	**HADS** #13; **STAI** # 9; **BCAS** #2; **SADS** #2; **Semi-structured interviews** #2; **POMS** #1; **POMS-SF** #1; **PGWB** #1; **DASS-21** #1; **GAD-7** #1; **NVAAS** #1; **BAI** #1; **HAQ** #1; **SHAI** #1; **WI-7** #1
11 articles examining **Worry**, 7 measurement approaches were used	**ASC** #2; **Metacognitions Questionnaire** 30 #2; **CWS** #1; **IES-cancer** #1; **WWQ** #1; **PSWQ** #2; **IWS** #1
15 articles examining **Uncertainty**, 3 measurement approaches were used	**MUIIS** #8; **Semi-structured interviews** #5; **CSQ** #1; **Telephone survey** #1

[a] *It is possible that more than one construct is examined in a single study.*
[b] *Refer to **Table 4**, for abbreviations of the measurement tools.*

worry. Notably, both FCR and HA were also associated with *functional impairments* (i.e., *physical, emotional, and social impairments*), which add contextual considerations for how women with breast cancer may make sense of their diagnosis. Indeed, context is theorized to play an important role in such processes: Leventhal's Common Sense Model (Leventhal et al., 2016) posits that the socio-cultural context (e.g., *amount of social support*) as important to interpret illness (e.g., *functional impairments*) and emotional (e.g., *excessive emotional distress*) outcomes. The Common Sense Model (Leventhal et al., 2016) would refer to an illness representation as well as increased vigilance in somatic sensations (Freeman-Gibb et al., 2017;

Richardson et al., 2017; Tsai et al., 2018; Petricone-Westwood et al., 2019). Implications for researchers or clinicians could be the need for interventions tailored to specific treatment types; in other words, breast cancer patients receiving these specific treatments might experience higher levels of impairment that warrant particular interventions to also target their fear and anxiety. It should include techniques to reduce excessive somatic vigilance in both cases.

FCR and worry share the threat appraisal feeling. This emotion is not only related to the perceived vulnerability of recurrence, but also its grade or severity. Clinically, it is important to consider both aspects, the concept and its intensity as related to worry. Both constructs were identified in this review as ongoing, persistent, and stable over time. Given this potential for FCR and worry to persist as long-lasting conditions if left unaddressed, their interventions must be incorporated into follow-up cancer survivorship plans.

Related to FCR, HA and uncertainty, they are assessed as multi-dimensional concepts (McCormick, 2002; Simard et al., 2010) and as a strength, they are all related to an *appropriate self-protective response*. However, conversely, they represent a hypervigilant, maladaptive way of coping that may interfere with the ability to make future plans, highly related in both cases and identified in this review with attributes such as "*fear of death*"; and "*diminished health related quality of life.*"

Attributes That Could Help Distinguish Between Two or More Constructs

Third, our review identified several attributes that could potentially be used to draw boundaries between the four constructs, but which warrant further investigation. In particular, the level and duration or severity of each construct is instrumental in its diagnosis and treatment. Here we draw on cognitive-behavioral and common-sense theoretical models to expand upon our findings.

The cognitive-behavioral model of HA (Salkovskis and Warwick, 2001) is the most prominent theoretical framework. In the cognitive-behavioral model, dysfunctional beliefs about bodily sensations (e.g., "being healthy means being free from bodily sensations"; "if there are unpleasant bodily symptoms, it must be a sign of serious illness") and negative images (e.g., imagining oneself as having a fatal disease) lead to physiological arousal and emotional distress. In turn, to cope with this distress, maladaptive safety behaviors lead to a vicious, on-going cycle, for example, of reassurance, help-seeking, and body checking (Salkovskis and Warwick, 2001). Accordingly, in their meta-analysis Marcus et al. (2007) related HA to beliefs that physical sensations are harmful, and illnesses are uncontrollable and inevitable. These beliefs are maintained by selective attention to health threats (Owens et al., 2004) and further exacerbated by safety behaviors (Olatunji et al., 2011).

From the cognitive-behavioral perspective, several overlapping theoretical features found in this review are "*worry, rumination or intrusive thoughts,*" "*misinterpretation of bodily symptoms,*" "*adoption of avoidance-oriented coping,*" and "*excessive personal checking*" behaviors. In addition, the result that both FCR and worry were described as constructs that are *ongoing, persisting, and stable over time* might be considered as common indicators of a higher level of FCR, worry, and HA. Yet symptoms of high levels of FCR can meet the former diagnosis of hypochondriasis in DSM IV (Thewes et al., 2013). More specifically, symptoms of excessive and recurrent intrusive thoughts and somatic sensations were the sign of serious illness of higher level FCR and consistent with the diagnosis criteria of somatic symptom disorders of DSM-5. Indeed, higher levels of persistent FCR are defined by maladaptive/emotion-focused coping strategies (Lebel et al., 2016b). All in all, although FCR is not recognized as a mental illness or a psychiatric condition, high levels of FCR or HA may result in pathological psychological disorders that necessitate professional intervention and/or treatment within the CBT framework.

Other overlapping correlates of "*functional impairments*" and "*a specific type of treatment (i.e., chemotherapy and mastectomy)*" of both HA and FCR might be addressed within the context of the common-sense model. Thus, in the early FCR model of Lee-Jones et al. (1997) in which the common-sense model was utilized, the hypothesis that perceptions regarding the consequences of illness and treatment control were the factors that correlated with FCR was supported by the evidence (Llewellyn et al., 2008; Corter et al., 2013).

Critical Attributes: Measurement

Upon analyzing the approaches used to measure all of the four studied constructs, we found that the majority were on par with their intended constructs. Eighteen approaches were used to measure FCR, 15 for HA, eight for worry, and four for uncertainty. Examples of scales used to measure only one construct include for FCR, the Concerns About Recurrence Scale (CARS) (Vickberg, 2003) and the Fear of Cancer Recurrence Inventory (Simard and Savard, 2009), whereas, for worry, the Penn State Worry Questionnaire (Meyer et al., 1990) was mostly used. Uncertainty was mainly measured using the Uncertainty in Illness Scale (Mishel, 1981). Nevertheless, as opposed to using instruments specifically developed to measure HA, this construct was found to be measured mostly using non-specific anxiety scales such as the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) and the State-Trait Anxiety Inventory (Spielberger et al., 1983). Among the 38 HA studies, the only HA-specific instrument used to measure this construct was the Health Anxiety Questionnaire (HAQ) (Lucock and Morley, 1996). This observation is unusual; some of the most widely used and psychometrically validated instruments of HA (Hedman et al., 2015), such as the Health Anxiety Inventory (HAI) (Salkovskis et al., 2002) and the Whiteley Index (WI) (Pilowsky, 1967) have not been found in our sample.

The literature shows that there is still ongoing reflection as to whether these psycho-oncology constructs are best conceptualized and measured as multidimensional or as independent constructs with unique features (Costa et al., 2016; Costa, 2017; Galica et al., 2018; Maheu and Galica, 2018). Some proponents will argue that our understanding of the construct

such as FCR would be best served as a unique construct, rather than aggregating its associated dimensions into a total FCR score (Costa, 2017; Maheu and Galica, 2018). The results of this scoping review provide guidance to assist in identifying main and distinctive features and underlying dimensions to each of the four studied constructs.

RECOMMENDATION FOR PRACTICE

The unique features and differences revealed by this review among the four constructs can provide useful guidance for the design of targeted intervention programs. While the anxiety reduction approach would be important for the four constructs, other factors may yield important impacts. For instance, in FCR, perhaps a broader approach that includes objectives of the cancer survivor would be more effective (i.e., advice or help for work, coping with children communication, and financial concerns) due to the presence of these triggers in FCR. A program should also include general information specially focused on FCR and levels of uncertainty. Moreover, in the development of FCR interventions, both existing CBT methods developed for HA, worry, and uncertainty (due to the common antecedents/triggers, maintaining factors, and consequences) and components of the common-sense model should be taken into account in order to provide a comprehensive illness-specific intervention.

The review results illustrate a consistent behavioral component in the excessive search for relief from a professional (more frequent consultations than required caused by fear or suspicion of physical discomfort or pain that could indicate a relapse). This aspect should be taken into account when designing a treatment program since response prevention is an effective tool. This approach also may work to reduce excessive somatic vigilance, more frequent in FCR and HA. However, behavior-focused psychotherapeutic approaches are not required for uncertainty, a cognitive and emotional construct, for which behavioral patterns such as checking bodily symptoms, seeking reassurance, and the avoidance of stimuli are absent. Younger age was identified as a similar feature for FCR, HA and worry. Hence, when screening for individuals at risk of psychological strain due to cancer, we can assume that three of our four constructs could be at play with younger individuals (Petricone-Westwood et al., 2019). Based on the distinctive and unique features of each of the constructs under review, the general recommendations for practice are as follows. When the focus of a study becomes the concern that cancer will come back or progress, one is looking at FCR. When the focus is on assessing the emotional reaction to cancer, then likely the best construct to study would be worry. In lieu of the association between intolerance of uncertainty and worry, when worry leads to negative behavioral reactions, an intolerant prone trait should be considered (Gu et al., 2020). However, when pre-existing psychological states and their impacts on FCR are in the forefront, then health anxiety should be the primary focus. Finally, when the focus sits more on that state of liminality associated with living with an illness that may return such as cancer (Pilowsky, 1967), then the construct at hand is uncertainty related to the illness.

RECOMMENDATION FOR RESEARCH

This review identified the similarities and differences in the four constructs experienced by women living with breast cancer. Our review of the key attributes of each construct studied will guide researchers in future reviews and theory development. The observed overlap implies an incomplete understanding of the etiology of these psychological constructs, which hinders the thoughtful selection of interventions based on a specific understanding of the target construct and underlying mechanisms. In our review, three out of four of the constructs (i.e., FCR, worry, uncertainty) were measured using specifically focused construct measures. This finding suggests that future research into the unique attributes of each construct can be carried out by deconstructing these measures into their unit scales and conducting correlations studies using path analyses. Such research findings would support the delineation of unique and specific attributes for each construct. For HA, which was found to be measured with non-specific anxiety scales, the recommendation would be to use a HA-specific instrument to measure this construct, such as the Health Anxiety Inventory (Salkovskis et al., 2002), a valid diagnostic instrument that will allow researchers to differentiate HA level between patients with medical problem (e.g., cancer survivors) than those without any illness.

LIMITATION AND CONCLUSION

We acknowledge several limitations of this review. First, there is a potential omission of relevant evidence due to our exclusive focus on breast cancer survivors' research. Potential interpretation bias might also be present in the classification of the critical attributes, despite the use of duplicate independent review of articles during data extraction and analysis. As with all reviews, this scoping review is limited by the quality of evidence being analyzed. Particularly with regard to findings related to the correlates of the four constructs, the majority of primary studies lacked the longitudinal design required to infer temporal relationships between variables. Our review relies on the conceptual and operational definitions of the authors of the primary studies. Moreover, this review followed a scoping review method, which unlike systematic reviews, do not go through the process of quality assessment. As a result, this review might have left the congruence of measures used unchecked. Further, we reviewed the theoretical features but not the original theoretical frameworks related to each of the constructs. Future studies could analyze how researchers apply different theories and models to guide their research into the four constructs.

Despite these limitations, this scoping review established key distinguishing critical attributes of the four psychological constructs, which is necessary for improving consistency in identification criteria/conceptualization and measurement. Our findings have the potential to inform more rigorous approaches

to investigating the psychological impact of breast cancer diagnosis and treatment on survivors.

More work is needed to conceptually differentiate these constructs, as our findings indicate that attributes across constructs overlap. For instance, to move forward with the conceptualization of FCR, it is essential for researchers to choose differentiating languages to describe each of the studied constructs and perhaps contrast them against FCR to identify differences. We recommend using the unique critical attributes that were found in this review, highlighted in **Table 3** to assist in this differentiation. For HA, our findings indicate that its attributes (e.g., its triggers) were very similar to that of anxiety in general, which is not necessarily triggered by cancer diagnosis. Worry was the least mentioned construct according to our search, and it appeared to be more cognitively associated, and was described as a consequence of anxiety triggered by somatic or other external cues. Although not conclusive, our findings offer valuable insights into the unique features that assist researchers and clinicians to differentiate the four psychological constructs, which will eventually contribute to more tailored and targeted care for breast cancer survivors.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

CM and MS: study design and conceptualization. CM and WLT: project coordination. FF: literature search. CM, MS, WLT, AE, and MH: literature screening. CM, WLT, JG, and TE: data extraction. CM, WLT, MS, AE, JG, TE, and MH: manuscript writing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.644932/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Depression and Anxiety in Patients With Cancer: A Cross-Sectional Study

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Objectives: Depression and anxiety persist in cancer patients, creating an additional burden during treatment and making it more challenging in terms of management and control. Studies on the prevalence of depression and anxiety among cancer patients in the Middle East are limited and include many limitations such as their small sample sizes and restriction to a specific type of cancer in specific clinical settings. This study aimed to describe the prevalence and risk factors of depression and anxiety among cancer patients in the inpatient and outpatient settings.

Materials and Methods: A total of 1,011 patients (399 inpatients and 612 outpatients) formed the study sample. Patients' psychological status was assessed using the Hospital Anxiety and Depression Scale (HADS), the Patient Health Questionnaire (PHQ-9), and the Generalized Anxiety Disorder 7-item (GAD-7) scale. The prevalence rate of depressive and anxious symptomatology was estimated by dividing the number of patients who exceeded the borderline score: 10 or more for each subscale of the HADS scale, 15 or more for the GAD-7 scale, and 15 or more in the PHQ-9 by the total number of the patients. Risk factors were identified using logistic regression.

Results: The prevalence of depressive and anxious symptomatology among all patients was 23.4% and 19.1–19.9%, respectively. Depressive symptomatology was more prevalent across patients who were hospitalized (37.1%) compared with patients in the outpatient setting (14.5%) ($p < 0.001$). Similarly, anxious symptomatology was more prevalent in the inpatient setting ($p < 0.001$). In the inpatient setting, depressive symptomatology was more prevalent among patients with bladder cancer, while severe anxious symptomatology was more prevalent across patients with lung cancer. In the outpatient setting, depressive and anxious symptomatology was more prevalent among breast and prostate cancer patients, respectively. Despite that, around 42.7% and 24.8% of the patients, respectively, reported that they feel anxious and depressed, and only 15.5% of them were using medications to manage their conditions.

Conclusion: Our study findings demonstrated a higher prevalence of depressive and anxious symptomatology in the inpatient setting and advanced disease stages. In addition, the underutilization of antidepressant therapy was observed. There is a need

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to consider mental disorders as part of the treatment protocol for cancer patients. Enhanced clinical monitoring and treatment of depression and anxiety of cancer patients are required.

Keywords: outpatient, inpatient, Jordan, depression, cancer, anxiety

INTRODUCTION

In cancer patients, psychological problems such as depression and anxiety persist and can cause an additional burden during their treatment, making it more challenging in terms of its management and control (Walker et al., 2013; Ahmed, 2019), compliance during the treatment course (Ahmed, 2019), duration of hospital stay (Koenig et al., 1992; McDermott et al., 2018), and, ultimately, survival rate (Spiegel et al., 1989; Spiegel and Li, 2007). Previous studies have reported that the prevalence of depressive disorders among cancer patients is two to three times higher than those of the general population (Massie, 2004; Pirl, 2004). Previous studies that evaluated psychological distress among cancer patients have reported various heterogeneous prevalence rates that differed according to clinical settings (outpatient clinics, hospital settings, and palliative care), stage of the disease (newly diagnosed, recurrence, survivorship, or advanced stages), and phase of treatment (Mitchell et al., 2011; Krebber et al., 2014; Caruso et al., 2017), which ranged between 5.0 and 49.0% (Walker et al., 2013). A previous meta-analysis that explored the prevalence of depression among cancer patients and included 211 studies (representing more than 82,000) reported a different prevalence rate of depression—one that differed by the type of instrument, type of cancer, and treatment phase (Krebber et al., 2014). In addition, the prevalence rate of depressive disorders among cancer patients differed by cancer site and ranged from 5.6% for patients with genitourinary cancer to 13.1% for patients with lung cancer (Walker et al., 2014). Furthermore, depression is more common among patients with severe illness and advanced stages of malignancy (Kaasa et al., 1993; Delgado-Guay et al., 2009). A previous critical review that included 11 previous systematic reviews and meta-analyses, which aimed to identify risk factors of depression among cancer patients, has reported a wide range of factors that play a key role in developing depression besides the biological factors (the type of cancer, stage of the disease, and treatment-related factors) (Caruso et al., 2017). This includes individual factors (family history, personal psychiatric history, and personality traits) and interpersonal and social factors (a history of stressful life events, loneliness, social isolation, low-socioeconomic status, and lack of social support) (Caruso et al., 2017). Assessment of psychological distress among cancer patients is important in order to recognize patients who need help and further assessment and, therefore, subsequent healthcare intervention. This increasingly highlights the fact that depression is a substantial problem in cancer patients.

In 2018, a total of 10,898 new cancer cases were diagnosed in Jordan within a population of 9,903,798. An age-standardized incident rate was 157.8 per 100,000, while the age-standardized mortality rate was 89.7 per 100,000. The top five most prevalent cancers were breast cancer, lung cancer, colorectal cancer, bladder cancer, and leukemia (World Health Organization, 2018). Even though depression is a significant complication of cancer and its occurrence is higher than in the general population (Centre for Disease Control and Prevention, 2019), it is often neglected. Studies on the prevalence of depression and anxiety among cancer patients in the Middle East are limited, with many limitations such as small sample size and being restricted to a specific type of cancer in specific clinical settings (Al Ahwal et al., 2014; Abou Kassm et al., 2018; Ahmadi Gharaei et al., 2019). The primary aim of this study is to describe the prevalence and risk factors of depressive and anxious symptomatology in cancer patients in the inpatient and outpatient settings. Additionally, we aimed to explore the pattern of use of antidepressants among the study participants. This will enable us to identify cancer patients who are at higher risk of depression and anxiety. Mental and medical support can be directed to cancer patients who are at higher risk in order to control their psychological problems and improve their clinical outcome. Early identification is critical in the management of depressive symptoms and plays an important role in improving their adherence to the therapy and the overall control of the disease.

MATERIALS AND METHODS

Study Design

This was a cross-sectional study conducted at the King Hussein Cancer Center (KHCC) in Amman, Jordan, between October 2019 and February 2020. According to the last available statistics in 2015, KHCC provides medical care to around 60.0% of all cancer patients in Jordan (Abdel-Razeq et al., 2015). KHCC is the main hospital and the single specialized tertiary hospital in Jordan and provides comprehensive clinical management and cancer care to adults and pediatric patients from Jordan and the surrounding region.

Sampling Strategy

Data were collected from the inpatient and outpatient settings using a convenience sampling technique. Cancer patients who have any type of cancer from any stage and who are willing to participate in the study formed the study population. The inclusion criteria were (a) patients aged 18 years and above with a confirmed cancer diagnosis and (b) patients who had no apparent cognitive deficit. Patients were excluded if they were (a) below 18 years of age and (b) unable to participate in this study due to physical or emotional distress. This is due to the difficulties in detecting depression in cancer patients with emotional distress because of patients' reluctance to discuss their emotional well-being (Krebber et al., 2014). Eligible patients

were identified and assessed by a clinical pharmacist (NM). Recruitment of patients was conducted by two pharmacists (AH and NM). For patients who agreed to participate, the study's aim and objectives were explained thoroughly. Information sheets were provided to the patients for further clarification about the study. In addition, patients were informed that their agreement to participate in the study is considered as written consent. Patients' clinical data were obtained from their medical charts in collaboration with a clinical pharmacist at the cancer center.

Sample Size

The target sample size was estimated based on the WHO recommendations for the minimal sample size needed for a prevalence study (Lwanga and Lemeshow, 1991). Using a confidence interval of 95%, a standard deviation of the prevalence rate of 0.5, a margin of error of 5%, we determined that the required sample size was 385 patients.

Depression and Anxiety Assessment Scales

Previously validated assessment scales, the Patient Health Questionnaire (PHQ)-9, Generalized Anxiety Disorder 7-item (GAD-7) scale, and Hospital Anxiety and Depression Scale (HADS) were used to assess depressive and anxious symptomatology among the study participants. These screening instruments were frequently used and validated as brief screening tools among cancer patients for depressive and anxious symptomatology (Härter et al., 2006; Sawaya et al., 2016; Terkawi et al., 2017). These assessment scales provide a symptomatological assessment based on predefined cut-off points.

Different assessment scales were used to fit the inpatient and outpatient settings, as recommended by previous literature. The HADS and GAD-7 instruments were previously validated to be used for hospitalized patients (secondary care settings) in multiple previous studies, including studies on patients with cancer (Zigmond and Snaith, 1983; Bjelland et al., 2002; Hartung et al., 2017; Esser et al., 2018). In contrast, the PHQ-9 and GAD-7 instruments were recommended for patients in primary care settings (Hinz et al., 2016; Esser et al., 2018; Levis et al., 2019). The PHQ-9 scale is a nine-question instrument given to patients in a primary-care setting to screen for the presence and severity of depressive symptomatology (Hartung et al., 2017). This instrument was used to assess depressive symptomatology among cancer patients in the outpatient setting, and the GAD-7 instrument was used to screen for anxiety among them (Esser et al., 2018). In the inpatient setting, the HADS instrument was used, which is a 14-question instrument given to patients in a secondary-care setting to screen for the presence and severity of depressive and anxious symptomatology (Hartung et al., 2017).

The use of a pre-existing scale has the advantage of using a validated and tested instrument, which increases the reliability of its measure. The PHQ-9 and the GAD-7 instruments ask the patients about the degree of applicability of each item (question), using a 4-point Likert scale. Patients' responses ranged from 0 to 3, where 0 means "Not at all" and 3 means "Nearly every day." The HADS instrument is a 14-question questionnaire that asks the patients about the degree of applicability of each item (question), using a 4-point Likert scale. Patients' response ranges from 0 to 3, where 0 means "Often" and 3 means "Very seldom" or from "Not at all" to "Most of the time."

Methods of Analysis

An Estimate of Prevalence and Classification of Depression and Anxiety

Prevalence rates of depressive and anxious symptomatology were determined using a cut-off point as recommended by the authors of the PHQ-9, GAD-7, and HADS scale. At the inpatient setting using the HADS instrument, depressive and anxious symptomatology were defined as a total score of (10 or more) at "depression subscale" or "anxiety subscale," respectively (Zigmond and Snaith, 1983). At the outpatient setting, depressive symptomatology was defined as a total score of 15 and above in the PHQ-9 instrument, indicating a case with moderately severe or severe depression (Kroenke et al., 2001). Anxious symptomatology was defined using the GAD-7 instrument with a total score of 15 and above, indicating a case with severe anxious symptomatology (Spitzer et al., 2006). The higher the score, the more severe the case identified by any scale.

The prevalence rate of depressive symptomatology was estimated by dividing the number of patients who exceeded the borderline score by the total number of patients. The same procedure was followed to calculate the prevalence rate of anxious symptomatology in the inpatient and the outpatient settings.

At The Inpatient Setting

The HADS instrument was used in the inpatient setting, which includes two subscales (anxiety and depression) with seven items for each. Items are scored from 0 to 3, generating a total score ranging from 0 to 21 on each subscale. A total score of 0–7 indicates a normal case, 8–10 a borderline case, and 11–21 an abnormal case of depressive or anxious symptomatology according to the subscale score (Zigmond and Snaith, 1983). In addition, anxious symptomatology was assessed using the GAD-7 scale as a second measure and results were compared with HADS.

At The Outpatient Setting

The PHQ-9 instrument was used in the outpatient setting, which includes nine items. Items are scored from 0 to 3, generating a total score ranging from 0 to 27. A total score of 0–4 indicates minimal depression, 5–9 mild depression, 10–14 moderate depression, 15–19 moderately severe depression, and 20–27 severe depression (Schwenk et al., 2011). The GAD-7 instrument includes seven items. Items are scored from 0 to 3, generating a total score ranging from 0 to 21. A total score of 5–9 indicates mild anxiety, 10–14 moderate anxiety, and 15–21 severe anxiety (Spitzer et al., 2006).

Statistical Analysis

Descriptive statistics were used to describe patients' demographic characteristics, medication use, and comorbidities. Continuous data were reported as mean ± SD. Categorical data were reported as percentages (frequencies). Logistic regression was used to estimate odds ratios (ORs), with 95% confidence intervals (CIs) for anxious or depressive symptomatology. Logistic regression models were carried out using anxious or depressive symptomatology scores above the cut-off points as highlighted in the section "Materials and Methods." The cut-off point for the PHQ-9 and GAD-7 scale that was used to identify severe depressive symptomatology and severe anxious symptomatology in the outpatient setting was 15 and above. The cut-off for the HADS scales that was used to identify depressive symptomatology and anxious symptomatology in the inpatient setting was 10 and above (whether for the depression or anxiety subscale). A two-sided $p < 0.05$ was considered statistically significant. The statistical analyses were carried out using SPSS for Windows (version 25).

RESULTS

Patient Characteristics

Out of 1,041 patients who were approached during the study period, a total of 1,011 patients (response rate of 97.1%) participated in the study: inpatient setting = 399, outpatient setting = 612. **Table 1** details the baseline characteristics of the patients in the inpatient and outpatient settings. The mean age of the patients was 54.9 years (±15.2). The majority of patients ($n = 560$, 55.4%) were males, married ($n = 833$, 82.4%), and unemployed ($n = 471$, 46.6%), with an income of 500 JD or below ($n = 737$, 72.9%). Around 18.4% ($n = 186$) of the patients reported that their cancer was metastatic. More than half ($n = 566$, 56.0%) of the patients reported being treated with chemotherapy.

The most common cancer type in the study was blood cancer ($n = 196$, 19.3%), followed by colorectal cancer ($n = 178$, 17.6%) and lung cancer ($n = 120$, 11.9%). Please refer to **Supplementary Table 1**, which shows the distribution of cancer types among study participants.

Use of Antidepressants

Around 42.7% ($n = 432$) and 24.8% ($n = 251$) of the patients reported that they feel anxious and depressed, respectively, and only 15.5% ($n = 39$) of them were using antidepressants. The two most commonly used antidepressant medications were sertraline (29.0%, $n = 9$) and citalopram (16.1%, $n = 5$).

The mean age of the patients when they started using antidepressants was 52.2 years (±17.4). Around 51.6% ($n = 16$) of these patients were using antidepressants last year, and 67.7% ($n = 21$) are using it currently. The majority of the patients (80.6%, $n = 25$) were using antidepressant medications under medical supervision. The main indication for the use of antidepressants was to alleviate depression for 83.9% ($n = 26$), and 35.5% ($n = 11$) were using them to alleviate anxiety. Around 92.3% ($n = 36$) of the patients reported that they had received instructions on how to use antidepressants. The main source of these instructions was a physician (94.4%, $n = 34$). The majority of the patients (75.0%, $n = 27$) believe that these instructions are important (**Table 1**).

The main reasons patients consider the healthcare professionals' instructions important include the notion that they increase the safety (27.3%, $n = 6$) and effectiveness (27.3%, $n = 6$) of the medication; they decrease side effects and drug interactions (27.3%, $n = 6$) and increase confidence in therapy (18.2%, $n = 4$). Nine patients reported that they have questions about antidepressants, and they were mainly considering treatment side effects, mechanisms of action, and treatment time (**Supplementary Table 2**).

Supplementary Table 3 highlights characteristics of antidepressant use and patient knowledge. More than half of the patients (56.8%, $n = 21$) reported that they have increased the dose of antidepressant medication without consulting the doctor. Around 40.5% ($n = 15$) of the patients reported that they were experiencing side effects from the use of antidepressants. The main three side effects were nausea, dizziness, and insomnia, suffered by 73.3%, 60.0%, and 40.0% of patients, respectively. About 29.7% ($n = 11$) and 21.6% ($n = 8$) of the patients reported that they think that antidepressant use can cause addiction and tolerance, respectively. More than half of the patients (59.5%, $n = 22$) reported that antidepressant therapy should gradually be withdrawn at the end of the treatment. When the patients were asked about whether they had stopped using antidepressant without consulting the doctor, 32.4% ($n = 12$) reported they had. The two most common reasons for this practice were improved depressive symptoms (50.0%, $n = 6$) and low tolerance of side effects of the medication (41.7%, $n = 5$).

Prevalence of Depression and Anxiety

The prevalence of depressive symptomatology among all patients was 23.4% ($n = 237$; 89 from the outpatient setting and 148 from the inpatient setting). Depressive symptomatology was more prevalent in the inpatient setting (37.1%; $n = 148$) compared to the outpatient setting (14.5%; $n = 89$). The prevalence of anxious symptomatology among all patients was 19.1% ($n = 193$) using the HADS for the inpatients or 19.9% ($n = 201$), using the GAD-7 for the inpatients. Similarly, anxious symptomatology was more prevalent in the inpatient setting, at 35.6% ($n = 142$), using the HADS, or 37.6% ($n = 150$) (using the GAD-7). **Table 2** below details the prevalence of depressive and anxious symptomatology among the patients stratified by severity.

Table 3 below details the prevalence of depressive and anxious symptomatology stratified by severity and type of cancer in the inpatient and the outpatient setting. In the inpatient setting, depressive symptomatology was more common across patients with bladder cancer, and severe anxious symptomatology was more prevalent among patients with lung cancer. In the outpatient setting, depressive symptomatology was more common among patients with breast cancer, and the highest prevalence of anxious symptomatology was among patients with prostate cancer.

TABLE 1 | The baseline characteristics of the patients in the inpatient and the outpatient settings.

Demographics	Overall (*n* = 1,011)	Inpatient (*n* = 399)	Outpatient (*n* = 612)	*P*-value
Gender No. (%)				
Male	560 (55.4%)	225 (56.4%)	335 (54.7%)	0.861
Age (years, mean, and SD)	54.9 (15.2)	55.6 (± 15.6)	54.4 (± 15.0)	0.245
Marital status No. (%)				
Single	99 (9.8%)	37 (9.3%)	62 (10.1%)	0.935
Married	833 (82.4%)	331 (83.2%)	502 (82.0%)	0.672
Divorced	23 (2.3%)	8 (2.0%)	15 (2.5%)	0.830
Widowed	55 (5.4%)	22 (5.5%)	33 (5.4%)	1.000
Employment status No. (%)				
Employed	276 (27.3%)	103 (25.8%)	173 (28.3%)	**0.014**
Unemployed	471 (46.6%)	172 (43.1%)	299 (48.9%)	0.082
Retired	264 (26.1%)	124 (31.1%)	140 (22.9%)	**0.004**
Income No. (%)				
Lower than 500 JD**	737 (72.9%)	327 (82.0%)	410 (67.0%)	**0.000**
500 to 1000 JD**	197 (19.5%)	54 (13.5%)	143 (23.4%)	**0.000**
1000 to 1500 JD**	35 (3.5%)	7 (1.8%)	28 (4.6%)	**0.021**
1500 JD** or above	42 (4.2%)	11 (2.8%)	31 (5.1%)	0.078
Cancer metastasis No. (%)				
Yes	186 (18.4%)	80 (20.1%)	106 (17.3%)	0.116
No	445 (44.0%)	146 (36.6%)	299 (48.9%)	
Don't know	380 (37.6%)	173 (43.4%)	207 (33.8%)	
Stage of metastasis (*n* = 80 in the inpatient, *n* = 106 in the outpatient) No. (%)				
Stage 1	10 (5.4%)	2 (2.5%)	8 (7.5%)	0.331
Stage 2	18 (9.7%)	5 (6.3%)	13 (12.3%)	0.343
Stage 3	25 (13.4%)	8 (10.0%)	17 (16.0%)	0.537
Stage 4	133 (71.5%)	65 (81.3%)	68 (64.2%)	**0.005**
Cancer therapy* No. (%)				
Surgery	40 (4.0%)	40 (10.0%)	0	**0.000**
Chemotherapy	566 (56.0%)	190 (47.6%)	376 (61.4%)	**0.000**
Combination of surgery and chemotherapy	352 (34.8%)	119 (29.8%)	233 (38.1%)	**0.007**
Radiotherapy	298 (29.5%)	116 (29.1%)	182 (29.8%)	0.832
Don't receive treatment (on palliative therapy)	36 (3.6%)	36 (9.0%)	0	**0.000**
Do you think or feel that you feel anxious? No. (%)				
Yes	432 (42.7)	220 (55.1)	212 (34.6)	**0.000**
Do you think or feel that you feel depressed? No. (%)				
Yes	251 (24.8)	148 (37.1)	103 (16.8)	**0.000**
Are you currently using or have you ever used antidepressant? (*n* = 148 in the inpatient; *n* = 103 in the outpatient) No. (%)				
Yes	39 (15.5)	21 (14.1)	18 (17.5)	0.126
Category of use for the antidepressant medications: (*n* = 20 in the inpatient; *n* = 11 in the outpatient)				
Sertraline	9 (29.0)	2 (10.0)	7 (63.6)	
Citalopram	5 (16.1)	5 (25.0)	0	
Mirtazapine	2 (6.5)	2 (10.0)	0	
Fluoxetine	2 (3.2)	1 (5.0)	1 (9.1)	
Amitriptyline	1 (3.2)	1 (5.0)	0	
Escitalopram	1 (3.2)	0	1 (9.1)	
Fluvoxamine	1 (3.2)	0	1 (9.1)	
Paroxetine	1 (3.2)	0	1 (9.1)	
Age first consumed antidepressant (years): (*n* = 20 in the inpatient; *n* = 11 in the outpatient)	52.2 (± 17.4)	50.4 (± 18.7)	54.6 (± 15.9)	0.550
Used in the last year? (*n* = 20 in the inpatient; *n* = 11 in the outpatient)				
Yes	16 (51.6)	10 (50.0)	6 (54.5)	0.689
Currently using antidepressants? (*n* = 20 in the inpatient; *n* = 11 in the outpatient)				
Yes	21 (67.7)	12 (60.0)	9 (81.8)	1.000

(Continued)

TABLE 1 | Continued

Demographics	Overall (*n* = 1,011)	Inpatient (*n* = 399)	Outpatient (*n* = 612)	*P*-value
Medical monitored? (*n* = 20 in the inpatient; *n* = 11 in the outpatient)				
Yes	25 (80.6)	14 (70.0)	11 (100.0)	1.000
Consumption reason (more than one choice could be chosen): (*n* = 20 in the inpatient; *n* = 11 in the outpatient)				
Anxiety	11 (35.5)	5 (25.0)	6 (54.5)	
Depression	26 (83.9)	15 (75.0)	11 (100.0)	
Have you received instruction on how to use the antidepressant therapy? (*n* = 21 in the inpatient; *n* = 18 in the outpatient)				
Yes	36 (92.3)	19 (90.5)	17 (94.4)	0.366
If yes, who gave you these instructions? (*n* = 19 in the inpatient; *n* = 17 in the outpatient)				
Physicians	34 (94.4)	18 (94.7)	16 (94.1)	
Nurse	1 (2.8)	1 (5.3)	0	
Pharmacist	1 (2.8)	0	1 (5.9)	
Do you consider these instructions important? (*n* = 19 in the inpatient; *n* = 17 in the outpatient)				
Yes	27 (75.0)	15 (78.9)	12 (70.6)	0.546

**Patient could select more than one type of therapy; SD, standard deviation.*
***JD, Jordanian Dinar (equal 1.41$). Bold values indicates that the p-value is statistically significant and that there was statistically significant difference between the inpatient and outpatient settings.*

Risk Factors of Depression and Anxiety

In the inpatient setting, logistic regression analysis identified the following groups as being at a higher risk of depressive symptomatology: a) patients with metastatic cancer, OR: 2.62 (95% CI 1.61–4.28) and b) patients at an advanced stage of the disease, stage 3, OR: 5.26 (95% CI 1.05–26.41) and stage 4, OR: 2.73 (95% CI 1.61–4.62). In the outpatient setting, patients with metastatic cancer were the only group that showed a statistically significant increased risk of depressive symptomatology, OR: 3.36 (95% CI 1.33–8.50), compared with others.

Regarding anxious symptomatology, in the inpatient setting the following groups were identified to be at a higher risk using the HADS: a) patients with metastatic cancer, OR: 2.10 (1.29–3.42) and b) patients at stage four of the disease, OR: 2.39 (95% CI 1.42–4.04). On the other hand, patients who are treated with a combination of chemotherapy and surgery showed a lower risk of anxious symptomatology, OR: 0.54 (95% CI 0.33–0.86). On the basis of the GAD-7 scale, the only patient group that showed a higher risk of anxious symptomatology was the group with metastatic cancer, OR: 2.23 (95% CI 1.32–3.74). In the outpatient setting, unemployed patients—OR: 1.89 (95% CI 1.03–3.35)—and patients with metastatic cancer—OR: 2.47 (95% CI 1.15–5.33)—were at higher risk of anxious symptomatology (**Table 4**).

DISCUSSION

This study aimed to identify the prevalence of depressive and anxious symptomatology among cancer patients and to identify key risk factors using validated assessment tools. Additionally, we explored the pattern of use of antidepressants among the study participants. Several dimensions were investigated in this study, including patients' characteristics, the prevalence of anxious and depressive symptomatology according to the type of cancer and treatment settings (inpatient versus outpatient). Our findings showed that the prevalence of depressive and anxious symptomatology among cancer patients was 23.4% and 19.1–19.9%, respectively. Increased likelihood of depressive and anxious symptomatology was detected among

TABLE 2 | Prevalence of depression and anxiety among the patients' stratified by severity.

	Settings
Outpatient settings (*n* = 612)	
	The severity of depression (using PHQ-9)
Minimal depression	282 (46.1%)
Mild depression	165 (27.0%)
Moderate depression	76 (12.4%)
Moderately severe depression	56 (9.2%)
Severe depression	33 (5.4%)
	The severity of anxiety (using GAD-7)
Normal	339 (55.4%)
Mild anxiety	142 (23.2%)
Moderate anxiety	80 (13.1%)
Severe anxiety	51 (8.3%)
Inpatient settings (*n* = 399)	
	The severity of depression (using HADS – depression subscale)
Normal	195 (48.9%)
Abnormal borderline case	56 (14.0%)
Abnormal case	148 (37.1%)
	The severity of anxiety
Using HADS- anxiety subscale	
Normal	208 (52.1%)
Abnormal borderline case	49 (12.3%)
Abnormal case	142 (35.6%)
Using GAD-7	
Mild anxiety	168 (42.1%)
Moderate anxiety	81 (20.3%)
Severe anxiety	150 (37.6%)

HADS, Hospital Anxiety and Depression Scale; GAD, Generalized Anxiety Disorder.

TABLE 3 | Prevalence of depression and anxiety stratified by type of cancer and severity.

		Type of cancer													
		The severity of depression (using PHQ-9)													
		Colorectal cancer	**Head and neck cancer**	**Blood cancer**	**Lung cancer**	**Breast cancer**	**Cervical cancer**	**Bladder cancer**	**Ovarian cancer**	**Stomach cancer**	**Bone marrow cancer**	**Pancreas cancer**	**Prostate cancer**	**Liver cancer**	**Brain cancer**
Outpatient settings (n = 612)	Minimal depression	74 (57.8)	10 (50.0)	59 (45.7)	30 (39.5)	15 (42.9)	12 (34.3)	11 (47.8)	9 (39.1)	9 (37.5)	8 (47.1)	7 (36.8)	7 (46.7)	9 (60.0)	4 (33.3)
	Mild depression	32 (25.0)	4 (20.0)	42 (32.6)	19 (25.0)	5 (14.3)	6 (17.1)	6 (26.1)	7 (30.4)	10 (41.7)	3 (17.6)	7 (36.8)	3 (20.0)	4 (26.7)	4 (33.3)
	Moderate depression	11 (8.6)	4 (20.0)	10 (7.8)	10 (13.2)	5 (14.3)	10 (28.6)	5 (21.7)	5 (21.7)	2 (8.3)	3 (17.6)	3 (15.8)	2 (13.3)	0	3 (25.0)
	Moderately severe depression	7 (5.5)	1 (5.0)	10 (7.8)	13 (17.1)	5 (14.3)	6 (17.1)	1 (4.3)	3 (13.0)	0	2 (11.8)	2 (10.5)	0	1 (6.7)	1 (8.3)
	Severe depression	4 (3.1)	1 (5.0)	8 (6.2)	4 (5.3)	5 (14.3)	1 (2.9)	0	0	3 (12.5)	0	0	3 (20.0)	1 (6.7)	1 (8.3)
	The severity of anxiety (using GAD-7)														
	Mild anxiety	22 (17.2)	7 (35.0)	34 (26.4)	20 (26.3)	10 (28.6)	9 (25.7)	4 (17.4)	7 (30.4)	3 (12.5)	6 (35.3)	5 (26.3)	2 (13.3)	3 (20.0)	3 (25.0)
	Moderate anxiety	10 (7.8)	3 (15.0)	14 (10.9)	14 (18.4)	5 (14.3)	8 (22.9)	2 (8.7)	4 (17.4)	3 (12.5)	2 (11.8)	2 (10.5)	2 (13.3)	3 (20.0)	3 (25.0)
	Severe anxiety	6 (4.7)	1 (5.0)	13 (10.1)	5 (6.6)	6 (17.1)	5 (14.3)	2 (8.7)	1 (4.3)	3 (12.5)	1 (5.9)	0	3 (20.0)	1 (6.7)	1 (8.3)
Inpatient settings (*n* = 399)	**The severity of depression (using HADS- depression subscale)**														
	Normal	25 (50.0)	11 (52.4)	36 (53.7)	16 (36.4)	23 (48.9)	6 (60.0)	8 (44.4)	7 (41.2)	7 (50.0)	5 (27.8)	8 (53.3)	8 (61.5)	6 (46.2)	7 (50.0)
	Abnormal borderline case	6 (12.0)	0	9 (13.4)	7 (15.9)	8 (17.0)	3 (30.0)	1 (5.6)	3 (17.6)	4 (28.6)	1 (5.6)	1 (6.7)	1 (7.7)	3 (23.1)	3 (21.4)
	Abnormal case	19 (38.0)	10 (47.6)	22 (32.8)	21 (47.7)	16 (34.0)	1 (10.0)	9 (50.0)	7 (41.2)	3 (21.4)	5 (27.8)	6 (40.0)	4 (30.8)	5 (38.5)	4 (28.6)
	The severity of anxiety														
	Using HADS – anxiety subscale														
	Normal	28 (56.0)	11 (52.4)	43 (64.2)	17 (38.6)	25 (53.2)	4 (40.0)	9 (50.0)	8 (47.1)	7 (50.0)	4 (22.2)	8 (53.3)	10 (76.9)	8 (61.5)	6 (42.9)
	Abnormal borderline case	5 (10.0)	1 (4.8)	8 (11.9)	4 (9.1)	7 (14.9)	4 (40.0)	2 (11.1)	2 (11.8)	4 (28.6)	2 (11.1)	1 (6.7)	0	2 (15.4)	4 (28.6)
	Abnormal case	17 (34.0)	9 (42.9)	16 (23.9)	23 (52.3)	15 (31.9)	2 (20.0)	7 (38.9)	7 (41.2)	3 (21.4)	5 (27.8)	6 (40.0)	3 (23.1)	4 (30.8)	4 (28.6)
	Using GAD-7														
	Mild anxiety	25 (50.0)	11 (52.4)	35 (52.2)	10 (22.7)	22 (46.8)	4 (40.0)	7 (38.9)	7 (41.2)	8 (57.1)	2 (11.1)	5 (33.3)	7 (53.8)	5 (38.5)	5 (35.7)
	Moderate anxiety	8 (16.0)	1 (4.8)	13 (19.4)	9 (20.5)	7 (14.9)	1 (10.0)	5 (27.8)	5 (29.4)	3 (21.4)	5 (27.8)	6 (40.0)	3 (23.1)	3 (23.1)	2 (14.3)
	Severe anxiety	17 (34.0)	9 (42.9)	19 (28.4)	25 (56.8)	18 (38.3)	5 (50.0)	6 (33.3)	5 (29.4)	3 (21.4)	4 (22.2)	4 (26.7)	3 (23.1)	6 (46.2)	7 (50.0)

HADS, Hospital Anxiety and Depression Scale; GAD, Generalized Anxiety Disorder.

TABLE 4 | Logistic regression analysis.

Variable	Inpatient settings			Outpatient settings	
	Odds ratio (95% CI) for depression according to HADS	Odds ratio (95% CI) for anxiety according to HADS	Odds ratio (95% CI) for severe anxiety according to GAD-7	Odds ratio (95% CI) for severe depression according to PHQ-9	Odds ratio (95% CI) for severe anxiety according to GAD-7
Gender					
Male (Reference)	1.00	1.00	1.00	1.00	1.00
Female	1.12 (0.75–1.68)	1.21 (0.80–1.82)	1.43 (0.91–2.26)	1.29 (0.64–2.59)	1.64 (0.92–2.90)
Age					
Less than 50 years	1.00	1.00	1.00	1.00	1.00
50 years and above	0.76 (0.50–1.18)	1.03 (0.66–1.60)	0.87 (0.54–1.42)	0.81 (0.39–1.65)	0.68 (0.38–1.21)
Marital status					
Single (Reference)	1.00	1.00	1.00	1.00	1.00
Married	1.15 (0.66–1.99)	1.15 (0.66–2.00)	0.83 (0.45–1.50)	0.80 (0.34–1.90)	1.03 (0.48–2.17)
Divorced	1.73 (0.43–7.01)	1.85 (0.46–7.50)	3.29 (0.81–13.40)	–	0.78 (0.10–6.07)
Widowed	0.63 (0.24–1.63)	0.52 (0.19–1.44)	1.21 (0.46–3.18)	1.14 (0.26–4.99)	0.33 (0.04–2.47)
Occupational status					
Employed (Reference)	1.00	1.00	1.00	1.00	1.00
Unemployed	1.15 (0.76–1.73)	1.35 (0.90–2.04)	1.37 (0.86–2.17)	1.45 (0.71–2.95)	1.89 (1.03–3.35)*
Retired	1.16 (0.75–1.80)	1.05 (0.67–1.63)	0.89 (0.54–1.47)	0.74 (0.30–1.83)	0.81 (0.39–1.66)
Income					
Below 500 JD (Reference)	1.00	1.00	1.00	1.00	1.00
500 to 1000 JD	0.68 (0.36–1.27)	0.81 (0.44–1.50)	0.68 (0.33–1.42)	1.05 (0.46–2.39)	0.68 (0.32–1.44)
1000 to 1500 JD	1.28 (0.28–5.79)	1.37 (0.30–6.19)	0.52 (0.06–4.38)	1.37 (0.31–6.05)	1.90 (0.63–5.72)
More than 1500 JD	0.97 (0.28–3.37)	0.67 (0.18–2.57)	0.70 (0.15–3.27)	0.57 (0.08–4.33)	0.35 (0.05–2.65)
Duration of disease					
Less than 12 years (Reference)	1.00	1.00	1.00	1.00	1.00
12 years and above	1.10 (0.72–1.67)	0.71 (0.47–1.08)	0.85 (0.53–1.37)	1.42 (0.68–2.95)	1.35 (0.74–2.46)
Metastasis					
No (Reference)	1.00	1.00	1.00	1.00	1.00
Yes	2.62 (1.61–4.28)***	2.10 (1.29–3.42)**	2.23 (1.32–3.74)**	3.36 (1.33–8.50)*	2.47 (1.15–5.33)*
Stage of cancer					
1 (Reference)	1:00	1.00	1.00	1:00	1.00
2	0.42 (0.05–3.79)	1.21 (0.20–7.33)	0.79 (0.09–7.13)	3.33 (0.71–15.69)	3.44 (0.92–12.94)
3	5.26 (1.05–26.41)*	0.60 (0.12–3.00)	1.92 (0.45–8.20)	1.10 (0.14–8.55)	2.44 (0.68–8.80)
4	2.73 (1.61–4.62)***	2.39 (1.42–4.04)**	–	2.29 (0.95–5.49)	1.30 (0.56–3.02)
Cancer therapy					
Don't receive treatment (Reference)	1.00	1.00	1.00	1.00	1.00
Chemotherapy	1.12 (0.74–1.67)	1.11 (0.74–1.67)	1.13 (0.72–1.80)	0.79 (0.39–1.62)	0.85 (0.47–1.53)
Combination of surgery and chemotherapy	0.77 (0.49–1.20)	0.54 (0.33–0.86)*	0.84 (0.50–1.40)	1.28 (0.62–2.62)	1.19 (0.66–2.14)
Radiotherapy	1.51 (0.97–2.34)	1.10 (0.70–1.72)	1.48 (0.91–2.41)	1.90 (0.92–3.90)	1.01 (0.54–1.90)
Surgery	1.02 (0.52–2.00)	1.55 (0.80–3.00)	1.06 (0.50–2.25)	–	–

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
HADS, Hospital Anxiety and Depression Scale; GAD, Generalized Anxiety Disorder; PHQ, Patient Health Questionnaire.

patients in the inpatient setting (37.1% and 35.6–37.6%, respectively). Screening of frequently prescribed anxiolytics and antidepressants was investigated, revealing that for the most part, SSRIs were prescribed, but as low as 15.5% of depressed and anxious patients received the required treatment (Waraich et al., 2004; Brothers et al., 2011; Findley et al., 2012; Li et al., 2012; Baltenberger et al., 2014; Nakash et al., 2014; Jassim et al., 2015; van den Berg et al., 2015; Kanera et al., 2016; Lengacher et al., 2016; Reich et al., 2017; Ahmed, 2019).

Our research employed two validated tools (GAD-7 and HADS) to assess the prevalence of anxiety among cancer patients in the inpatient setting, and both of them were reliable and showed a significant correlation (correlation

coefficient: 0.812) in terms of the prevalence of anxiety (37.6% versus 35.6% in the inpatient setting). The increased cancer-specific depressive symptomatology was noted across settings (inpatient and outpatient) and was significantly higher in the inpatient settings.

Several factors may impact the development of depression and anxiety among cancer patients, including the cancer type, stage, grade, and treatment option (Smith, 2015). Interestingly, our results are aligned with the findings of several studies, where specific tumor types can lead to depression and anxiety, particularly head and neck, lung, breast, and prostate cancer (Pitman et al., 2018), which, in our research, showed that depression and anxiety are more prevalent in the inpatient setting in patients with head and neck cancer, lung cancer, and bladder cancer, while in the outpatient setting, they were more prevalent among patients diagnosed with prostate and breast cancer.

In addition to the type of cancer, the treatment option impacted the prevalence of anxiety and depression among cancer patients. Cancer treatments that entail chemotherapy may induce depression through specific biological mechanisms. Furthermore, the literature reported that antiemetic medications, steroids, and androgen suppression therapy (for prostate cancer) were reported to induce depression (Smith, 2015; Ismail et al., 2017; Nead et al., 2017; Niedzwiedz et al., 2019). The findings of our study revealed that most cancer patients receive chemotherapy alone (56.0%) or chemotherapy and surgery (34.8%), thus increasing their risk of depression and/or anxiety. The use of chemotherapy-induced nausea and vomiting (CINV) medications, as well as steroids, are a mainstay for the prevention and treatment of CINV (Rao and Faso, 2012) and, consequently, contribute to the high prevalence of anxiety and depression among cancer patients.

Antidepressant Use Patterns

This study also explored the pattern of use of antidepressants among cancer patients stratified by type, where the rate of using antidepressants among patients diagnosed with depression was as low as 15.5%. Low use of antidepressant therapy is an alarming sign, especially for cancer patients who are receiving specialized cancer services (Waraich et al., 2004; Findley et al., 2012; Nakash et al., 2014). Antidepressants should be introduced as soon as the patient is diagnosed with depression. Use of antidepressants should be individualized according to the patient's health profile to address his or her symptoms. The choice of antidepressants should be based on the patient's concurrent medications, history, and symptoms (Ahmed, 2019). Pharmacological therapy is recommended for patients with severe depression, while patients with mild to moderately severe depression are recommended to receive psychotherapy. Several behavioral approaches can be implemented to improve the psychological status of cancer patients, such as cognitive behavioral therapy, mindfulness-based approaches, and self-management strategies. Management of depression and treatment initiation should be under medical supervision, due to the nature of antidepressants and the high probability of drug-drug interaction, adverse effects, and the need for dose adjustment (Ahmed, 2019).

The majority of patients were prescribed selective serotonin reuptake inhibitor (SSRI) antidepressants (sertraline, citalopram, fluoxetine, fluvoxamine, and paroxetine), while tetracyclic antidepressants (mirtazapine) and tricyclic antidepressants (amitriptyline) were prescribed to a lesser extent. The selection of an anxiolytic or antidepressant medication needs to be made under clear guidelines that consider interactions with chemotherapeutic and other concurrently administered medication, as well as side effects, to enable identification of specific contraindications. Sertraline and citalopram are usually recommended for depression and anxiety treatment, as they have the least tendency for interactions and are usually well tolerated (Chochinov, 2001; Smith, 2015). Although the use of medications for depression and anxiety among cancer patients in this study was low, the selection of pharmacological agents is in line with the above recommendations. However, a patient-centered approach and a customized treatment plan need to be considered, as studies reported that the SSRIs need to be avoided in elderly patients due to the risk of hyponatremia. Fluoxetine and paroxetine are contraindicated in patients being treated with tamoxifen. Furthermore, mirtazapine should be avoided where white blood cells are compromised and SSRIs are to be avoided where platelets are compromised (Pitman et al., 2018). Finally, since almost 70.0% of the patients reported that they experienced nausea, SSRIs need to be avoided as this will augment chemotherapy-induced nausea and vomiting.

Risk Factors of Depression and Anxiety

Our findings suggest that severe depressive and anxious symptomatology are substantially more common in patients with cancer in the inpatient than in the outpatient setting. This significant difference could be attributed to the severity of the disease, where hospitalized treatment of cancer patients is mainly employed for the management of acute phases, initial onsets, severe cases, or late stages. A previous study involving more than 5,000 patients has reported that more symptoms of anxiety are associated with cancer within the inpatient setting and in patients in the advanced stages, whereas patients at early stages demonstrated lower anxiety symptoms. Furthermore, disease stage was associated with depression, particularly in men (Vodermaier et al., 2011).

Further analysis using logistic regression was conducted to identify patients at risk of developing depressive and anxious symptomatology. Similar to reported data, the prevalence of anxiety and depression among women is higher than in men (Smith, 2015). As discussed earlier, the advancement of the stage of the disease has an impact on depression and anxiety. Patient vulnerability exacerbates the ability to become depressed and anxious, which is reported to be caused by some socioeconomic factors and disease stages (Chochinov, 2001; Smith, 2015). Such results align with our findings about patients with metastasis, advanced disease stages, and lower-income were more vulnerable to developing anxiety and/or depression. Such findings support the need to consider mental disorders as part of the treatment protocol for cancer patients and calls for enhanced clinical monitoring and treatment of depression and anxiety symptoms among cancer patients.

Strengths and Limitations

To the best of our knowledge, this is the first and largest study in the Middle East region to investigate the prevalence of depressive and anxious symptomatology and use of antidepressants among cancer patients without restriction on the type of cancer or clinical settings. Previous studies have focused on a specific type of cancer (breast cancer and colorectal cancer) (Al Ahwal et al., 2014; Abou Kassm et al., 2018; Ahmadi Gharaei et al., 2019) and had a small sample size (not more than 100 patients) (Al Ahwal et al., 2014; Abou Kassm et al., 2018).

We have explored the prevalence of depressive and anxious symptomatology among cancer patients without any restriction on the age, gender, duration of the disease, or treatment phase. Our broad inclusion criteria have enabled us to explore the difference in severity of depressive and anxious symptomatology among different demographic groups and across different stages of the treatment and the course of illness. This study has many strengths that increase its value and reliability: (a) using validated assessment tools for depressive and anxious symptomatology, (b) anxious symptomatology was assessed using two assessment tools (HADS and GAD-7), and both of them showed consistent findings, (c) employing a large sample size, (d) not restricting the inclusion criteria for the specific type of cancer or specific settings (inpatients or outpatients), which increased the generalizability of our findings, and (e) our exclusion criteria minimized the risk of deriving imprecise information (related to the patients' psychological status) from any suspected physical or emotional distress. On the other hand, this study has limitations: (a) the study design itself, a cross-sectional study design, limited our ability to identify causality between study variables, as it is only capable of showing an association between variables, and (b) the sample size of a few cancer subgroups was small due to a small population in this category nationwide. This might affect our ability to determine the prevalence of depressive and anxious symptomatology among patients with specific types of cancer, especially types for which we have a very low number of patients, such as head and neck cancer; (c) the use of convenience sampling techniques might affect the generalizability of our findings as a prevalent study and may introduce sampling bias (which might not precisely represent the targeted population); (d) the use of different assessment tools to describe the prevalence of depressive symptomatology between the inpatient and the outpatient settings might not provide a fair comparison; (e) there is a lack of non-responder data; and (f) the antidepressant medication information is based on small subsamples making conclusions difficult to sustain. Therefore, our findings should be interpreted carefully.

CONCLUSION

Our study demonstrated a higher prevalence of both depressive and anxious symptomatology within the inpatient setting and advanced stages of the disease. There is a need for cancer management clinical guidelines to consider early assessment and management of depression and anxiety and to continue to monitor it throughout treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Approval for this study was obtained from the Institutional Review Board Committee at King Hussein Cancer Centre in Jordan (No. 19 KHCC 94). For patients who agreed to participate, the study's aim and objectives were explained thoroughly. Information sheets were provided to the patients for further clarification about the study. In addition, patients were informed that their agreement to participate in the study is considered as a written consent.

AUTHOR CONTRIBUTIONS

AN contributed to the study design and did the data analysis. AN, AH, NM, and HK conducted the study and collected the data. AN, ED, NM, and HA wrote the first draft of the article. AN, HA, ED, HA, and NM were involved in interpretation of the data. All authors reviewed the manuscript for important intellectual content, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.585534/full#supplementary-material

Supplementary Table 1 | Type of cancer among the patient stratified by settings.

Supplementary Table 2 | Questions about antidepressants treatment.

Supplementary Table 3 | Characteristics of antidepressants utilization and patients' knowledge about them.

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Cancer Patient Experience of Uncertainty While Waiting for Genome Sequencing Results

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There is limited knowledge about cancer patients' experiences of uncertainty while waiting for genome sequencing results, and whether prolonged uncertainty contributes to psychological factors in this context. To investigate uncertainty in patients with a cancer of likely hereditary origin while waiting for genome sequencing results, we collected questionnaire and interview data at baseline, and at three and 12 months follow up (prior to receiving results). Participants ($N = 353$) had negative attitudes towards uncertainty ($M = 4.03$, SD 0.68) at baseline, and low levels of uncertainty at three ($M = 8.23$, SD 7.37) and 12 months ($M = 7.95$, SD 7.64). Uncertainty about genome sequencing did not change significantly over time [$t(210) = 0.660$, $p = 0.510$]. Greater perceived susceptibility for cancer [$r(348) = 0.14$, $p < 0.01$], fear of cancer recurrence [$r(348) = 0.19$, $p < 0.01$], perceived importance of genome sequencing [$r(350) = 0.24$, $p < 0.01$], intention to change behavior if a gene variant indicating risk is found [$r(349) = 0.29$, $p < 0.01$], perceived ability to cope with results [$r(349) = 0.36$, $p < 0.01$], and satisfaction with decision to have genome sequencing [$r(350) = 0.52$, $p < 0.01$] were significantly correlated with negative attitudes towards uncertainty at baseline. Multiple primary cancer diagnoses [B = −2.364 [−4.238, −0.491], $p = 0.014$], lower perceived ability to cope with results [B = −0.1.881 [−3.403, −0.359], $p = 0.016$] at baseline, greater anxiety about genome sequencing (avoidance) [B = 0.347 [0.148, 0.546], $p = 0.0012$] at 3 months, and greater perceived uncertainty about genome sequencing [B = 0.494 [0.267, 0.721] $p = 0.000$] at 3 months significantly predicted greater perceived uncertainty about genome sequencing at 12 months. Greater perceived uncertainty about genome sequencing at 3 months significantly predicted greater anxiety (avoidance) about genome sequencing at 12 months [B = 0.291 [0.072, 0.509], $p = 0.009$]. Semi-structured interviews revealed that while participants were motivated to pursue genome sequencing as a strategy to reduce their illness and risk uncertainty, genome sequencing generated additional practical, scientific and personal uncertainties. Some uncertainties were consistently discussed over the 12 months, while others emerged over time. Similarly, some uncertainty coping strategies were consistent over time, while others emerged while patients waited for their genome sequencing results. This

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study demonstrates the complexity of uncertainty generated by genome sequencing for cancer patients and provides further support for the inter-relationship between uncertainty and anxiety. Helping patients manage their uncertainty may ameliorate psychological morbidity.

Keywords: uncertainty, genome sequecing, cancer, psychosocial, genomic, genetic testing, anxiety

INTRODUCTION

Cancer is a distressing experience (Foster et al., 2009; Montgomery and McCrone, 2010). Uncertainties about diagnosis and prognosis are major factors that influence patients' cancer experience (Mishel et al., 1984). Uncertainty can change over time but is typically highest at diagnosis when the patient lacks an understanding of their illness. Yet it can also increase when patients undergo scans or tests related to their cancer. Receiving a cancer diagnosis at a younger age (Kornblith et al., 2007) or receiving multiple cancer diagnoses (Thong et al., 2013), can intensify uncertainty. This cascade of uncertainty may include additional uncertainties about the origins of the cancer(s), including whether the cancer risk may have been inherited, and have implications for relatives (Bartley et al., 2021). Intolerance of uncertainty has been associated with poorer psychological outcomes in cancer patients (Kurita et al., 2013).

Patients who are experiencing illness-related uncertainty may seek out information to reduce their uncertainty (Mishel, 1988). For patients with a cancer that is likely due to inherited risk, information seeking may include undergoing genomic testing, including, genome sequencing to determine if they have a gene variant that would indicate a heritable origin for their cancer and/or provide information about their future risk of cancer or another illness.

The complexity of genomics is likely to introduce multiple uncertainties (Han et al., 2017) for patients, such as the scientific uncertainty (i.e., whether genome sequencing will provide disease information), practical uncertainty (i.e., lack of knowledge about processes), and personal uncertainty (i.e., psychosocial effects and implications of results for patients and relatives). A systematic review of studies investigating the patient experience of uncertainty in cancer genomics (Bartley et al., 2020b) concluded that while patients approach genomic testing as a strategy to reduce illness-related uncertainties, genomics may not reduce them. Previous research found that penetrance of a pathogenic variant (moderate vs. high) rather than type of genomic result (positive or negative) influenced patient perception of uncertainty in the cancer hereditary risk context (Lumish et al., 2017; Esteban et al., 2018). However, aambiguity surrounding the meaning of a variant of uncertain significance (VUS) result can create uncertainties about future risk for participants (Solomon et al., 2017). In the treatment context, regardless of the genomic result (positive or negative), participant treatment decision uncertainty was reduced (Holt et al., 2013; Levine et al., 2016). How patients appraise uncertainties, both negatively and positively, is important in how the patient experiences uncertainty, as well as specifying the coping strategies they utilize to manage the uncertainties (Biesecker et al., 2014; Bartley et al., 2020b).

The published literature on uncertainty in cancer genomics has been largely cross-sectional (Braithwaite et al., 2002; Pellegrini et al., 2012; Leventhal et al., 2013; Hitch et al., 2014; Lumish et al., 2017; Solomon et al., 2017), or when longitudinal (Holt et al., 2013; Bradbury et al., 2015; Levine et al., 2016; Esteban et al., 2018) focused on uncertainties at the time of choosing to undergo genomic testing and immediately following receipt of results. Where patients can afford genome sequencing in a clinical context, they will wait ∼16 weeks for their results (Victorian Clinical Genetic Services, 2019). Patients who meet eligibility criteria can access testing within research studies without meeting the specific requirements needed in an Australian clinical context. In this context, genome sequencing is conducted at reduced or no cost (Bartley et al., 2020a). However, the wait of genome sequencing results can be much longer for patients due to the research nature of the study which does not have the same timeline imperatives as a clinical service. There is little known about the experience of managing uncertainty while awaiting results, and the potential psychological impact of prolonged uncertainty about testing for cancer patients. Exploring the uncertainties that patients experience while waiting for genome sequencing results will provide clinicians with a greater understanding of the sources and types of uncertainties that their patients face. Previous research (Bartley et al., 2021) has provided insights into the cancer patients' experience of uncertainty when agreeing to undertake genome sequencing. The aim of this study was to understand the cancer patients' experience of uncertainties while waiting for genome sequencing results, including the influence of attitudes toward uncertainty on the degree of perceived uncertainty about genome sequencing, changes in uncertainty over time, and the psychological outcomes of the uncertainty.

These patients were undertaking genome sequencing to contribute to research and potentially obtain more information about their cancer risk, a circumstance wrought with uncertainty. Further, engaging in genomics research where results are returned has the potential to generate additional practical, personal and scientific uncertainties (Han et al., 2017). As such, we hypothesized that perceptions of uncertainty about genome sequencing would increase with time while participants awaited novel genomic information which they hoped would reduce their illness uncertainty.

Patient appraisal of uncertainty, as well as the coping strategies utilized to manage uncertainties are important in how patients experience uncertainties (Biesecker et al., 2014; Bartley et al., 2020b). Previous qualitative research with this

cohort (Bartley et al., 2021) found that participants who had negative attitudes towards uncertainty experienced ongoing uncertainties throughout the 2–4 weeks following agreeing to pursue genome sequencing. The decision to undertake genome sequencing did not reduce their illness or genome sequencing related uncertainty, as they were still waiting for genome sequencing results. We therefore anticipated that negative attitudes towards uncertainty at baseline would predict greater perceived uncertainty about genome sequencing at 12-month follow-up. As intolerance of uncertainty has also been linked to poorer psychological outcomes in cancer patients, we anticipated that negative attitudes towards uncertainty at baseline would also predict worse psychological outcomes (greater fear of cancer recurrence, higher anxiety, more depressive symptoms, and greater distress) at 12 months.

MATERIALS AND METHODS

The research presented is part of a longitudinal mixed methods psychosocial study: Psychosocial issues in Genomic Oncology (PiGeOn) study (Best et al., 2018). The PiGeOn study is a sub-study of an Australia-wide genomic study being conducted at the Garvan Institute of Medical Research, the Genetic Cancer Risk in the Young (RisC) study. The RisC study aims to identify clinically actionable, pathogenic gene variants that likely contribute to the development of cancer at an early age, and/or to multiple cancers at any age. Adults who have had a cancer diagnosis (other than non-melanoma skin cancer) under the age of 40, or two primary cancer diagnoses at an age younger than 50 years, or three primary cancer diagnoses at any age, are eligible to participate in the RisC study. RisC participants provide a blood sample on which genome sequencing is performed. Participants did not undergo pre-test genetic counseling prior to providing a blood sample for genome sequencing. A researcher provided participants with written information about genome sequencing, and potential results (**Supplementary Material**—PICF), and participants were given the opportunity to ask questions as part of the consent process. Participants choose whether they would like to be informed if they have a pathogenic variant that increases the likelihood of cancer and/or are found to have a secondary finding that may be important to their health, in accordance with the recommendations of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology for reporting secondary findings in clinical exome and genome sequencing (Kalia et al., 2017). Variants of uncertain significance are not returned to participants in this study. If participants are found to carry a pathogenic gene variant, they are referred to a genetic counsellor. If the variant is cancer-related, participants are offered a tailored risk management plan through the Surveillance in Multi-Organ Cancer-prone syndromes study.

Participants consent to the PiGeOn study at the same time they consent to the RisC study. The PiGeOn study is investigating the psychosocial implications of genome sequencing by administering questionnaires and semi-structured interviews (with a subset of participants) completed at baseline (T0, within 1 month of consenting to genome sequencing) and 3 (T1) and 12-month (T2) follow-up. All PiGeOn study data is collected prior to patients receiving results. This manuscript reports on cancer patients' experiences of uncertainties over a 1-year period, while awaiting genome sequencing results.

Questionnaire

Psychometrically validated scales were used where available, supplemented by adapted scales or study-developed items when validated scales were unavailable (Best et al., 2018). In addition to demographic and patient disease characteristics, the study questionnaire included measures of knowledge of and attitudes towards and levels of genome sequencing, and psychosocial outcomes (**Table 1**, **Supplementary Material**—PiGeOn RisC T0 questionnaire; **Supplementary Material**—PiGeOn RisC T1 questionnaire; **Supplementary Material**—PiGeOn RisC T2 questionnaire). The Attitude towards Uncertainty Scale (Braithwaite et al., 2002) was administered at baseline (T0). Level of uncertainty about genome sequencing was measured at 3 months (T1) and 1 year (T2) follow up with the adapted Multidimensional Impact of Cancer Risk Assessment (MICRA) Uncertainty sub-scale (Cella et al., 2002). The MICRA was developed to measure the specific impact of results disclosure after genetic testing. As PiGeOn participants were required to wait ∼12 months for their genome sequencing results, our focus was on assessing the impact of waiting for results in this cohort. At the time of designing this study, there were no previously developed scales which specifically measured distress in this context, we adapted the MICRA for this purpose. For example, were the original MICRA item was "Having problems enjoying my life because of my test result" this was adapted to "Having problems enjoying my life while waiting for my test result."

Questionnaire data collection occurred from August 2016 to September 2020.

Semi-Structured Interviews

Qualitative semi-structured telephone interviews were conducted by a trained qualitative researcher (NB). The interview guide (**Supplementary Material**—PiGeOn RisC T0 interview guide; **Supplementary Material**—PiGeOn RisC T1 interview guide; **Supplementary Material**—PiGeOn RisC T2 interview guide) development was informed by existing literature and input from a multidisciplinary advisory group, including consumers (i.e., cancer survivor trained in research processes). An initial draft was piloted with consumers. The interview questions relevant to this article addressed the types of uncertainty being experienced and strategies used to cope with uncertainty. Interview questions were iteratively modified over the course of the study. Interview participants were purposively sampled to ensure diversity in cancer type, age, and gender. Recruitment to the qualitative study continued until data saturation (no new themes emerging after three consecutive interviews) was reached at baseline (T0). All baseline (T0) interviewees were approached to participate in the 3 month (T1) follow up interviews, with additional participants approached to reach data saturation at this time point. All participants interviewed at baseline (T0) and 3 month (T1) follow up

TABLE 1 | Description of quantitative study measures and assessment time points.

Measure	Baseline (T0)	3-month follow-up (T1)	12-month follow-up (T2)
Demographic characteristics included age, sex, marital status, socio-economic status (SES) and accessibility/remoteness (ARIA) determined by postcode, educational level, country of birth, language spoken at home, number of biological children, smoking status, alcohol consumption, occupation.	X		
Clinical characteristics included personal cancer history (diagnosis and date of diagnosis), family history of cancer, prior attendance at a family cancer clinic, prior experience with genetic testing, and treatment history.	X		
Perceived importance of genome sequencing was measured using five items adapted from Hay et al. (2012), e.g., How important is it to you to learn about gene variants that may increase your chances of getting (another) cancer? Responses were scored on a Likert-scale from "not at all important" (1) to "very important" (5). Scores were averaged. Cronbach's alpha = 0.59	X		
Knowledge of genomics was measured using seven multiple choice study-developed questions assessing knowledge of the purpose of genome sequencing, likely frequency of informative results, cancers in which informative results are likely to be found, and utility of genome sequencing results. The number of correct responses was summed, with "Don't know" responses scored as incorrect, and an overall score (0–100%) calculated from the seven items.	X		
Perceived ability to cope with results was measured with four Likert-scale items adapted from Rosenberg et al. (2013), assessing perceived ability to cope with: a germline cancer gene variant result; a variant of uncertain significance; no cancer gene variants being found, and communicating germline results. E.g., I am confident I would be able to cope if a gene variant indicating that I and my family are at risk of some cancer, was found. Response options ranged from "strongly disagree" (1) to "strongly agree" (5). Scores were averaged across the four items, with higher scores indicating greater perceived ability to cope with results. Cronbach's alpha = 0.87	X		
Intention to change behavior if a gene variant indicating cancer risk found was measured with study developed Likert-scale items, e.g., If I knew I had inherited genes which increase my risk of cancer, I would be more careful with my diet. Response options ranged from "strongly disagree" (1) to "strongly agree" (5). Scores were averaged across the items, with higher scores indicating stronger intention to change behavior. Cronbach's alpha = 0.89	X		
Fear of cancer recurrence. The Concerns About Recurrence Questionnaire (CAR-Q) (Thewes et al., 2015) measured fear of cancer recurrence. Responses ranged from "none of the time/not at all" (0) to "all of the time/a great deal" (10). Scores were summed and averaged across the three questions, with higher scores indicating greater fear of cancer recurrence. Cronbach's alpha = 0.93	X	X	X
Perceived susceptibility of (another) cancer was measured with three items adapted from Kasparian et al. (2009). Participants self-rated their chances of developing another cancer from "much lower" (0) to "much higher" (4), and on a visual analogue scale from "no chance" (0%) to "will definitely" (100%). Participants also self-rated their chances of having a gene variant that increased their risk of cancer from "much lower" (0) to "much higher" (4). Likert-scale scores were multiplied by 25, then scores for all three items were averaged. Higher scores indicated greater perceived susceptibility of cancer. Cronbach's alpha = 0.66	X	X	X
Attitude towards uncertainty: The seven-item Attitude towards Uncertainty Scale (Braithwaite et al., 2002) measured attitude towards uncertainty in genome sequencing. Participants rated items on a Likert-scale from "strongly disagree" (1) to "strongly agree" (5). Scores were averaged across the items, with higher score indicating a negative attitude towards uncertainty. Cronbach's alpha = 0.87	X		
Satisfaction with decision to have genome sequencing. The six-item Satisfaction with Decision (SWD) scale (Holmes-Rovner et al., 1996) measured satisfaction with decision to have genome sequencing. Response options range from "strongly disagree" (1) to "strongly agree" (5). Scores were summed, with higher scores indicating greater satisfaction with decision. Cronbach's alpha = 0.92	X	X	X
Genome sequencing related distress, positive experience and uncertainty. The adapted Multidimensional Impact of Cancer Risk Assessment (MICRA) scale (Cella et al., 2002) measured distress, uncertainty and positive experiences specifically in the context of genome sequencing. Response options ranged from "never" (0) to "often" (5). The positive experience items were reverse coded, and item scores summed; thus, higher scores indicate greater distress, uncertainty, or positive experiences.			

(Continued)

TABLE 1 | Continued

Measure	Baseline (T0)	3-month follow-up (T1)	12-month follow-up (T2)
Cronbach's alpha (distress) = 0.92 Cronbach's alpha (positive experience) = 0.88 Cronbach's alpha (family support) = 0.92 Cronbach's alpha (uncertainty) = 0.87		X	X
Genome sequencing specific anxiety. Impact of Events Scale (IES) (Horowitz et al., 1979; Thewes et al., 2001) measured genome sequencing specific anxiety. The scale measures the frequency of intrusions (unbidden thoughts, images, feelings) and avoidance (blunted sensation, behavioral inhibition, emotional numbness) Responses ranged from "not at all" (0) to "often" (5). A total score was obtained by summing the 15 Likert-scale items, with a higher score indicating greater anxiety about genome sequencing. Cronbach's alpha = 0.91		X	X
Anxiety and depression. The 14 item Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) measured general anxiety and depression. A total scale score was obtained by summing each item (range 0–42), with a higher score indicating greater anxiety and depression. Cronbach's alpha = 0.91		X	X
Hope. The 12 item Herth Hope Index (HHI) (Herth, 1992) measures hope and sense of meaning across three subscales: temporality and future, positive readiness and expectancy, and inter-connectedness. Responses range from "strongly disagree" (1) to "strongly agree" (4). Item scores are summed, with higher scores indicating greater hope. Cronbach's alpha = 0.88		X	X

interviews were approached to participate in the 1 year (T2) follow up interviews. Interviewee demographic and disease characteristics were extracted from PiGeOn study baseline (T0) questionnaires. Interviews were conducted between August 2017 and October 2019.

Analysis

Qualitative and quantitative data were collected concurrently and analysed separately. Data was then integrated using a matrix framed by the hypotheses to synthesise the quantitative and qualitative data (Bazeley, 2009).

Quantitative

Descriptive statistical analysis, correlations and regressions were conducted using IBM SPSS Statistics Version 26. Analysis of baseline (T0) data using Pearson's correlations was conducted to examine associations between perceived importance of genome sequencing, knowledge, perceived ability to cope with results, intention to change behavior if gene variant found, fear of cancer recurrence, perceived susceptibility of (another) cancer, satisfaction with decision to have genome sequencing, and attitude towards uncertainty. Cronbach alphas were conducted to determine reliability of scales used in this sample. Repeated measures ANOVA were conducted to investigate changes in means scores for measures administered at all three time points [fear of cancer recurrence, perceived susceptibility of (another) cancer, satisfaction with decision to have genome sequencing]. Paired sample *t*-tests were conducted to determine whether the mean difference for measures (perceived uncertainty about genome sequencing, genome sequencing related distress, genome sequencing related anxiety, general anxiety and depression, hope) administered at 3 (T1) and 12-months (T2) significantly differed. Analysis of longitudinal data using regressions was conducted to examine predictors of perceived uncertainty about genome sequencing and psychological outcomes—distress, fear of cancer recurrence, genome sequencing specific anxiety, general anxiety and depression, and hope. For each of these outcome variables (genome sequencing uncertainty, distress, fear of cancer recurrence, genome sequencing anxiety, general anxiety and depression, and hope), simple regressions with all potential predictor variables were conducted. All predictor variables that met the $\leq$0.20 significance threshold were then included in multiple linear regressions with each of the outcome variables.

Qualitative

Interviews were audio-recorded, transcribed verbatim, anonymized, uploaded to NVIVO 12 and subjected to recurrent cross-sectional (Grossoehme and Lipstein, 2016) thematic analysis (Braun and Clarke, 2006). A hybrid approach of thematic analysis was used, incorporating inductive (Boyatzis, 1998) and deductive (Crabtree and Miller, 1992) methods. The uncertainty coding framework developed from the baseline (T0) interview thematic analysis (Bartley et al., 2021) was applied to the 3 (T1) and 12-month (T2) interviews. Individual coding of an initial three transcripts was completed by two researchers (ZB, NB) to determine if the over-arching themes and sub-themes from the baseline (T0) coding framework was applicable. The framework was then applied to additional transcripts and further developed through an iterative process of review of subsequent transcripts. Once coded the data was organized into a time ordered matrix (Miles and Huberman, 1994; Grossoehme and Lipstein, 2016) to determine if themes and sub-themes differed across the time points. Relevant quotes to illustrate the identified themes were extracted. Differences in researcher interpretation of the data were resolved through discussion, with the multidisciplinary nature of the research team (psychology,

bioethics, medicine) minimizing researcher bias regarding the meaning of the results (Berger, 2015).

RESULTS

Quantitative Findings

Three hundred and fifty-three participants completed the baseline (T0) questionnaire (77% response rate), 346 participants completed the 3-month follow-up (T1) questionnaire (78% response rate), and 285 participants completed the 12-month follow-up (T2) questionnaire (70% response rate), with data for at least two time-points available for 359 participants. The majority (96%) of participants were interested in learning both cancer specific variants and secondary findings. **Table 2** presents the demographic data of the majority female, English-speaking PiGeOn study participants. Most PiGeOn participants had a single primary diagnosis (70.2%), most commonly of a rare cancer (66.6%), and on average 8 years had passed since their diagnosis.

Participants had on average negative attitudes towards uncertainty ($M = 4.03$, SD 0.68) at baseline (T0, **Table 3**). Perceptions of uncertainty about genome sequencing was low at both 3 months (T1, $M = 8.23$, SD 7.37) and 12 months (T2, $M = 7.95$, SD 7.64) follow up, and did not change significantly over time [$t(210) = 0.660$, $p = 0.510$]. At baseline (T0), participants had high perceived importance of genome sequencing, moderate knowledge of genomics, high perceived ability to cope with genome sequencing results, and high intention to change behavior if a gene variant indicating cancer risk was found. Mean fear of cancer recurrence scores were above the clinical cut-off of ≥10 for this scale (Thewes et al., 2015) at all time-points. Participants had low levels of anxiety and depressive symptoms at over the 12 months, with mean scores on genome sequencing anxiety (Horowitz et al., 1979; Thewes et al., 2001), and general anxiety and depression (Zigmond and Snaith, 1983) below the clinical cut-offs for these scales, at all time-points. Participants had high levels of hope across the 12 months, and low to moderate levels of genome sequencing related distress.

We found weak correlations between negative attitudes toward uncertainty and greater perceived importance of genome sequencing [$r(350) = 0.24$, $p < 0.01$], intention to change behavior if a gene variant indicating cancer risk was found [$r(349) = 0.29$, $p < 0.01$], fear of cancer recurrence [$r(348) = 0.19$, $p < 0.01$], and perceived susceptibility for (another) cancer [$r(348) = 0.14$, $p < 0.01$] at baseline (T0). Greater perceived ability to cope with results [$r(349) = 0.36$, $p < 0.01$] was moderately correlated with negative attitudes towards uncertainty. Greater satisfaction with decision to have genome sequencing [$r(350) = 0.52$, $p < 0.01$] was strongly correlated with negative attitudes towards uncertainty (**Figure 1**).

As there was no significant change in perceived uncertainty about genome sequencing or the psychological outcomes (with the exception of fear of cancer recurrence) over time, we report only on 12-month psychological outcomes in this article.

Multiple primary cancer diagnoses [B = −2.364 [−4.238, −0.491], $p = 0.014$], baseline (T0) lower perceived ability to cope with results [B = −0.1.881 [−3.403, −0.359], $p =$

TABLE 2 | Demographic and disease characteristics of the PiGeOn study participants.

Variable	*N* = 359 (%)
Sex	
Female	239 (66.6)
Male	120 (33.4)
Education	
Don't know	1 (0.3)
Secondary school	75 (20.9)
Vocational training	54 (15.0)
University	229 (63.8)
Occupation	
Medical/science	30 (8.4)
Other	329 (91.6)
Language spoken at home	
English	293 (81.6)
Other	66 (18.4)
Accessibility/Remoteness Index of Australia[a]	
Major city	294 (81.9)
Inner regional	42 (11.7)
Outer regional	16 (4.5)
Remote	3 (0.8)
Unknown/overseas	4 (1.1)
Visited a Family Cancer Clinic[a]	
Don't know	15 (4.2)
Yes	103 (28.9)
No	239 (66.9)
Marital status	
Single	93 (25.9)
Married/living with a partner	243 (67.7)
Separated/divorced	16 (4.5)
Widowed	7 (1.9)
Parental status[a]	
Children	195 (54.8)
No children	161 (45.2)
Multiple primary diagnosis	
Yes	107 (29.8)
No	252 (70.2)
Cancer incidence	
Rare	239 (66.6)
Less common	23 (6.4)
Common	97 (27.0)
Age at consent (years)	
Mean (SD)	43.31 (13.98)
Range	16–83
Median (IQR)	39.0 (17)
Socio-Economic Indexes for Australia	
Mean (SD)	7.41 (2.61)
Range	1–10
Time since first diagnosis (years)	
Mean (SD)	8.06 (9.71)
Range	0–52.17
Median (IQR)	4.17 (8.75)

[a]*participant numbers do not add up to 359 due to missing data; percentages reported are valid percent's.*

TABLE 3 | PiGeOn participants' knowledge, attitude, and psychological outcomes over 12 months.

Variable	Baseline (T0) (n = 353)	3- month (T1) (n = 346)	12-month (T2) (n = 285)	Significance test, p-value
Perceived importance of genome sequencing				
Mean (SD)	3.76 (0.55)			
Range	1.4–5.0			
Knowledge of genomics				
Mean (SD)	0.47 (0.24)			
Range	0–1			
Perceived ability to cope with genome sequencing results				
Mean (SD)	4.17 (0.67)			
Range	1–5			
Intention to change behavior if gene variant indicating cancer risk was found				
Mean (SD)	4.25 (0.66)			
Range	1–5			
Attitude towards uncertainty				
Mean (SD)	4.03 (0.68)			
Range	1.57–5			
Fear of cancer recurrence				
Mean (SD)	13.76 (815)	12.36 (7.94)	11.89 (8.15)	$F_{(1.90,494.21)}$ =10.26, p = 0.000
Range	0–30	0–30	0–30	
Perceived susceptibility of (another) cancer				
Mean (SD)	64.78 (16.44)	65.09 (16.33)	65.87 (17.82)	$F_{(1.94,503.19)}$ = 0.69, p = 0.500
Satisfaction with decision to have genome sequencing				
Mean (SD)	26.17 (3.17)	26.74 (3.89)	26.33 (4.13)	$F_{(1.93,494.50)}$ =2.33, p = 0.100
Genome sequencing anxiety				
Mean (SD)		5.78 (9.94)	6.38 (11.82)	$t(265) = -1.160$, p = 0.247
General anxiety and depressive symptoms				
Mean (SD)		7.98 (6.66)	8.53 (7.30)	$t(265)$=-1.610, p = 0.109
Anxiety subscale				
Mean (SD)		5.15 (4.09)	5.48 (4.44)	$t(265)= -1.617$, p = 0.107
Depression subscale				
Mean (SD)		2.83 (3.25)	3.04 (3.45)	$t(265) = -1.205$, p = 0.229
Hope				
Mean (SD)		39.30 (5.52)	39.23 (6.07)	$t(211) = 0.203$, p = 0.839
Distress				
Mean (SD)		22.34 (9.49)	23.20 (10.29)	$t(210) = -1.354$, p = 0.177
Perceived uncertainty about genome sequencing				
Mean (SD)		8.23 (7.37)	7.95 (7.64)	$t(210) = 0.660$, p=0.510

0.016], greater anxiety (avoidance subscale) about genome sequencing [B = 0.347 [0.148, 0.546], p = 0.0012] at 3 months (T1), and greater perceived uncertainty about genome sequencing [B = 0.494 [0.267, 0.721] p = 0.000] at 3 months (T1) significantly predicted greater perceived uncertainty about genome sequencing at 12 months (T2, **Figure 2A**). Greater perceived uncertainty about genome sequencing at 3 months (T1) significantly predicted greater anxiety (avoidance subscale) about genome sequencing at 12 months (T2, B = 0.291 [0.072, 0.509], p = 0.009) (**Figure 2B**). Attitude towards uncertainty at baseline (T0) did not significantly predict psychological outcomes (**Figures 2A–G**).

Qualitative Findings

Semi-structured interviews [N = 20 at baseline (T0), N = 23 at 3 months (T1), and N = 24 at 12 months (T2)] revealed that, while participants were motivated to pursue genome sequencing as a strategy to reduce illness uncertainty, genome sequencing generated additional practical, scientific and personal uncertainties (Han et al., 2017). At baseline (T0), four themes emerged from the qualitative data: 1. Genome sequencing to reduce illness uncertainty; 2. Genome sequencing to reduce uncertainties about relatives' risk; 3: Uncertainty generated by genome sequencing; and 4. Resilience and coping with uncertainty (Bartley et al., 2021). Some uncertainties were consistently present over the 12 months, while others dropped off or emerged over time (**Table 4**).

Genome Sequencing to Reduce Illness Uncertainty

Participants viewed genome sequencing as a way to reduce their illness-related uncertainty throughout the 12 months. They felt

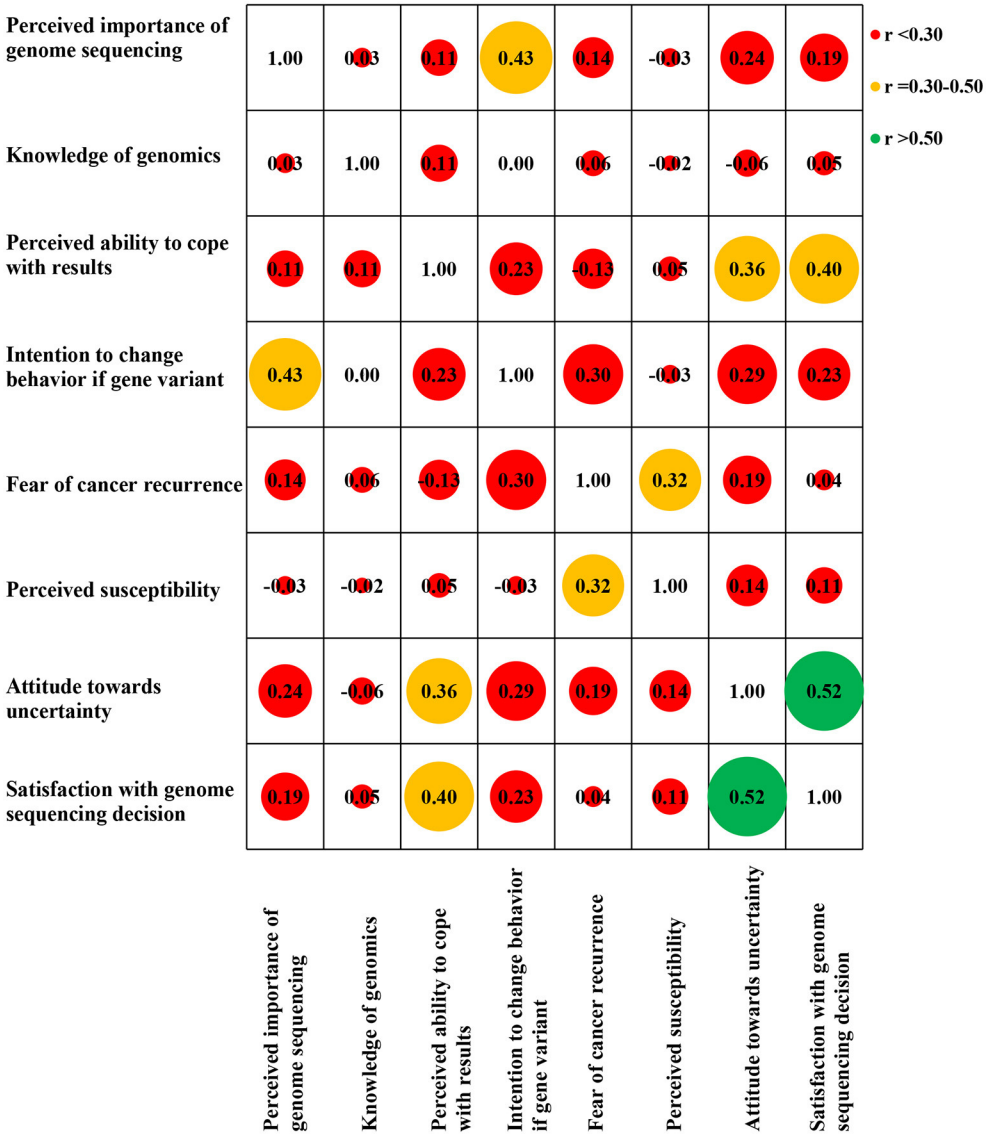

FIGURE 1 | Baseline (T0) variables correlation matrix heat map (Pearson correlation coefficient).

that genome sequencing would increase their understanding of the origin of their cancer and provide clearer estimates of their risk of developing another cancer. At 3 months (T1), four participants discussed disease trajectory uncertainty and that genome sequencing results have the potential to reduce this in that it may give them access to new and more targeted treatments.

> *What I'm hoping is that at some stage there will be some more targeted immunotherapy or more personalized therapy which is developed. I'm just hopeful that the research gets spurred on really quickly and that if I ever really do need to call upon more treatment that the genome sequencing might have made me suitable for some new up-and -coming treatments (Female, 37 years, gastrointestinal tract cancer).*

For some participants, adding to this motivation was previous experience with uninformative genetic testing and the hope that genome sequencing would provide answers.

Concerns about genome sequencing were secondary to disease-related uncertainties. At the 3 (T1) and 12 months' (T2) follow-up interviews, most participants placed even more importance on reducing illness-related uncertainty, noting that even bad news was preferable to not knowing.

> *At the end of the day, I get more concerned with my scans than the gene sequencing and, I guess, that's in the back of my mind (Female, 37 years, central nervous system cancer).*
> *I mean, nobody wants bad news but if you know something, you might be able to do something… if you find something now, well it's better than not knowing (Male, 52 years, parathyroid cancer).*

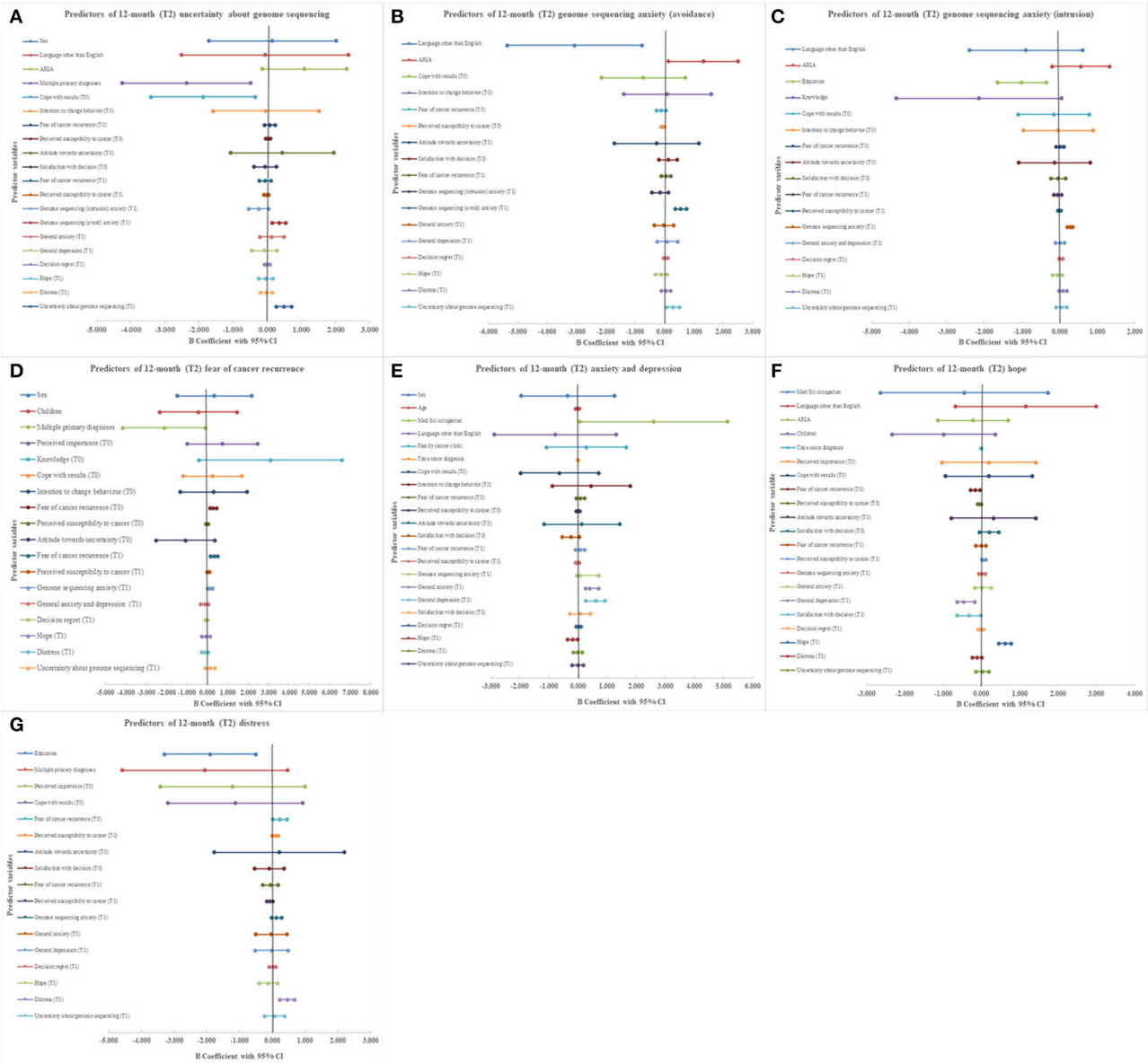

FIGURE 2 | Forest plots presenting results of multiple regression analysis for predictors of psychological outcomes in cancer patients undergoing genome sequencing. **(A)** 12 month (T2) uncertainty about genome sequencing. **(B)** 12 month (T2) genome sequencing anxiety (avoidance). **(C)** 12 month (T2) genome sequencing anxiety (intrusion). **(D)** 12 month (T2) fear of cancer recurrence. **(E)** 12 month (T2) anxiety and depression. **(F)** 12 month (T2) hope. **(G)** 12 month (T2) distress.

However, during the follow-up interviews, a few participants did express a desire to remain uncertain over receiving bad news.

> *I'd rather just be completely oblivious for now… I think it would be finding something that they know nothing about, or something that I can't do anything about. Like, if I was going to get dementia at this point in time, if you get it you get it. I'd probably rather be blissfully unaware (Female, 27 years, ovarian cancer).*

Genome Sequencing to Reduce Uncertainties About Relatives' Risk

Similarly, over the 12 months participants continued to view genome sequencing as a tool to reduce their uncertainty about their relatives' risk of cancer and were still uncertain about how relatives would react to results, or which results they would communicate to relatives and/or how they would approach that communication. At 3-month (T1) follow-up interviews, participants discussed how a family history of illness added to their motivation to have genome sequencing to reduce uncertainty about relatives' risk.

> *My mum died of cancer three years ago, my brother has had a cancer six years ago… another brother had a benign cancer. So, it is something that is in our family and I would be glad if there is something in my genetic code that can help the rest of the family,*

TABLE 4 | Uncertainty themes and sub-themes discussed by PiGeOn interviewees over 12 months.

Themes and sub-themes	Baseline (T0)	3-month (T1)	12-month (T2)
Genome sequencing to reduce illness uncertainty			
Etiology	X	X	X
Own illness risk	X	X	X
Disease trajectory uncertainty		X	
Previous genetic testing		X	X
Illness uncertainty most salient	X	X	X
Continued uncertainty over bad news		X	X
Genome sequencing to reduce uncertainty about relatives' risk			
Relatives illness risk	X	X	X
Children	X	X	X
Family planning	X	X	
Family history of illness		X	
Potential impact on relatives	X	X	X
Family communication	X	X	X
Family history influence on communication			X
Uncertainty generated by genome sequencing			
No uncertainty	X	X	X
Practical—uncertain knowledge	X	X	X
Practical—uncertain of study processes		X	X
Practical—insurance/discrimination	X	X	X
Scientific—limitations of science	X	X	X
Scientific—result ambiguity	X	X	
Scientific—likelihood of results			X
Personal—emotional reaction to results	X	X	X
Personal—life choices	X	X	X
Personal—ethical uncertainty		X	
Decisional uncertainty (to have/not have; which results if any)	X	X	X
Uncertainty reduces/become episodic over time		X	X
Resilience and coping with uncertainty			
Resilience	X	X	X
Mobilizing coping—information seeking	X	X	X
Mobilizing coping—lifestyle	X		X
Mobilizing coping—plan of action	X		
Affect coping—seeking professional support	X		X
Affect coping—seeking informal support	X	X	
Affect coping—positive attitude	X	X	X
Affect coping—trust in experts/research		X	X
Affect coping—reduce expectation			X
Affect coping—don't worry about things outside your control		X	X
Buffering coping—acceptance	X	X	X
Buffering coping—avoidance	X	X	X
Buffering coping—live in the now	X	X	
Unhealthy behaviors	X		
Worry/anxiety	X	X	X

particularly the kids… I have three brothers… The fourth one is the youngest and he's 35, so far, he hasn't had any problem but he's the one that obviously is most interested in understanding if there is a genetic explanation. I would be, not happy—but I'd say curious to know if there is something genetic. Because it is kind of strange that in same family, out of six people, four had a cancer. If it's not genetic, that means that either we are very unlucky or there was something in our family history that was not correct (Male, 44 years, central nervous system cancer).

At 12-month (T2) follow-up, interviewees discussed how a family history of cancer had facilitated communication with their family members about undergoing genome sequencing.

However, this family history also contributed to their feelings of uncertainty around how family members would react to genome sequencing results.

> *Mum's a little bit apprehensive, she's like, "Well, do you really think you need to know?" And it's like, "Well, yeah. I think it's good." I think she's just, she's got my sister and myself are the only children they've got, and both of their kids had cancer. So, from a parent's perspective you don't want to think your kids ever are going to get sick again. So, I suppose for her, she would find it hard to be given that information there and then (Female, 42 years, blood cancer).*

Uncertainty Generated by Genome Sequencing

Participants continued to experience genome sequencing specific uncertainties throughout the 12 months. This included scientific uncertainties, such as recognizing the limitations of science; personal uncertainties, such as potential emotional and behavioral reactions to results; and practical uncertainties, such as lack of genomic knowledge. At follow-up interviews a new practical uncertainty emerged involved being unsure about study processes, for example, where their sequencing was up to and when they would be receiving results. Additionally, a new scientific uncertainty about the likelihood of a gene variant indicating risk being found through the genome sequencing emerged, while scientific uncertainty related to result ambiguity was no longer discussed by interviewees at 12-months (T2). Two participants discussed ethical uncertainty in their 3-month (T1) interview, being unsure if genomics is *playing god a little bit*, and whether patients should access genome sequencing when there is still a level of scientific uncertainty, especially when cancer patients are emotionally vulnerable.

> *I wonder how it's all going, cause I hadn't heard anything, so yeah, sort of apprehensive wondering, how it's all going, if they found anything or things like that (Male, 56 years, genitourinary cancer).*
> *I think before I was very certain, probably something would… oh, I don't know, I'm not so sure. [Doctor] said as well, a lot of it is probably autoimmune-related so I don't know if anything can really be shown through the study… I think I was more positive before but now I'm, like, nothing's ever found (Female, 31 years, head and neck cancer & sarcoma).*
> *A lot of people put a lot of emphasis needing to send samples off overseas and paying out-of-pocket expenses for it and trying to get samples moved between facilities because they're hunting for that magic bullet. We're still in a stage where there's a lot of hype and a lot of promise and not actually a lot of effect, so that worries me and I think that leads itself to being exploited by a whole bunch of practitioners and organizations that will trade on the hope that DNA therapeutics will give people and predictive testing will give people, but the science just isn't there (Male, 35 years, gastrointestinal tract cancer).*

At three (T1) and 12 months (T2), many interviewees discussed their genome sequencing related uncertainty having reduced over time or having become episodic. Interviewees were not thinking about these uncertainties constantly over the 12 months but were prompted by study processes such as questionnaires or the realization that they would be receiving results soon.

> *I suppose I thought I would get the results, so I was trying to brace myself with what would happen. Which is the first time in the whole year that I've done that. So that was interesting for me to be a little bit uptight at times… and hubby would say, "What's wrong?" and I'd go, "Oh, it's just, I suppose I'm going to get these results and it's just going to be interesting, what my life is going to be like once I get that information" (Female, 42 years, blood cancer).*

Resilience and Coping With Uncertainty

Resilience to uncertainty was present across the 12 months. Over the 12 months, interviewees continued to engage in buffering coping strategies, such as acceptance and avoidance, but no longer discussed living in the now as a coping strategy for uncertainty at 12 months (T2). Interviewees continued to engage in mobilizing coping strategies such as information-seeking and maintaining a healthy lifestyle over the 12 months, while having a plan of action as a coping strategy for managing uncertainty was only raised by interviewees at baseline (T0). Interviewees continued to use affect focused coping strategies, such as seeking professional and informal support and maintaining a positive attitude across the 12 months. Interviewees mentioned additional affect coping strategies such as trusting in the experts and research, reducing their expectations of genome sequencing, and not worrying about things outside of their control in their follow-up interviews.

> *Just sort of left it in the hands of the scientists (Female, 41 years, breast cancer).*
> *If you have no expectations then you can't be disappointed, you know. So, bottom line is I really don't have any expectation… the more expectation you put on things, the more chance you are going to worry or be disappointed if the outcome's not what you want (Male, 47 years, gastrointestinal tract cancer & granular cell tumor).*
> *I don't really worry about things I can't control, so I haven't thought about it, because I'll either get results or I won't. It's one thing I learnt during cancer, it's really unhelpful to worry about things you can't influence, and it's very important to know the difference (Female, 43 years, blood cancer).*

DISCUSSION

The results of this study provide further support for the published literature on the topic of cancer patient perceptions of uncertainties related to genomics. The findings indicate that patients are motivated to undergo genome sequencing as a strategy to reduce their illness-related uncertainty, and that genome sequencing generates practical, scientific, and personal uncertainties for patients reinforce those of previous studies (Bartley et al., 2020b). Additionally, the findings build on the existing knowledge by providing important information about patients' experience of uncertainties while waiting for results, as well as the factors contributing to ongoing uncertainties and the psychological impact of the uncertainties.

Previous research has found that individuals without a history of cancer who have negative attitudes towards uncertainty are more likely to undergo predictive genetic testing for colon and breast cancer (Braithwaite et al., 2002), and cancer patients

are motivated to pursue genomic testing by a desire to reduce illness uncertainty (Claes et al., 2004; Sanderson and Wardle, 2008; Bartley et al., 2020a). Mishel's (1990) reconceptualization of the Uncertainty in Illness Theory, proposes that patients experiencing ongoing uncertainty may use coping strategies to adapt to their uncertainty. Our participants who had agreed to genome sequencing, generally had more negative attitudes towards uncertainty related to genome sequencing at baseline (T0), and continually discussed a desire to reduce illness related uncertainty by gaining genomic information, across the 12 months. Our participants however reported low levels of perceived uncertainty associated with genome sequencing results and future plans at 3 (T1) and 12-month (T2) follow-up, suggesting that cancer patients undergoing genome sequencing adapt to their perceived uncertainties over time. Our qualitative data provide further support for this quantitative finding, in that while patients discussed a variety of scientific, personal and practical uncertainties while waiting for their results, they also discussed their uncertainty either reducing or becoming more episodic over the 12-month period. Our participants considered themselves quite resilient to uncertainty and engaged in a variety of coping strategies to help them deal with their uncertainty. This resilience and coping strategies could explain why even though our participants held more negative attitudes towards uncertainty at baseline, their perceived uncertainty about genome sequencing was low at follow up, as they were effectively coping with their uncertainty.

Uncertainty is inherent in cancer. Uncertainty about prognosis, treatment options and effectiveness can produce feelings of uncontrollability, and has been associated with anxiety in cancer patients (Tan et al., 2016; Curran et al., 2017). While we did not find a relationship between attitude towards uncertainty at baseline and perceived uncertainty about genome sequencing or psychological outcomes at 12 months, our results did show an inter-relationship between perceived uncertainty about genome sequencing and anxiety specifically related to genome sequencing. Greater anxiety (avoidance subscale) about genome sequencing significantly predicted greater perceived uncertainty at 12 months (T2) and greater perceived uncertainty about genome sequencing at 3 months (T1) significantly predicted greater anxiety (avoidance subscale) about genome sequencing at 12 months (T2). This relationship is not surprising as uncertainty reduces how efficiently and effectively individuals can prepare for the future and is a basic cognitive process that contributes to anxiety (Grupe and Nitschke, 2013; Carleton, 2016). Participants experiencing ongoing uncertainty about their genome sequencing may not be able to adequately prepare themselves for receiving their results and therefore experience anxiety about the genome sequencing. This is supported by the finding that lower perceived ability to cope with results at baseline (T0) was also a predictor of greater perceived uncertainty about genome sequencing at 12 months (T2). Further supporting this was the acknowledgment by participants across the 12 months that they were uncertain about how they would emotionally and/or behaviorally cope with their genome sequencing results.

Tercyak et al. (2001) found that women participating in genetic counseling and testing for breast and ovarian cancer risk experienced anxiety while waiting for their results. Specifically, women who were high monitors (closely attending to threat-relevant cues) were more likely to experience anxiety when confronted with the uncertainty involved with waiting for cancer risk information. Lazarus and Folkman's (1984) Transactional Model of Stress and Coping proposes that coping strategies are implemented based on how individuals appraise the threat to their well-being. This appraisal is based on the threats personal significance and the individuals perceived ability to cope with outcome. Coping strategies are then engaged based on the appraisal. For example, affect coping strategies such as seeking professional and informal support and maintaining a positive attitude are likely to be engaged when the uncertainty is appraised as out of the patients control. The literature suggests that coping strategies are most effective when the strategy matches the controllability of the threat (Gooding et al., 2006), and that accepting uncertainty is likely to be associated with more helpful coping (Mishel, 1990; Carleton, 2016; Curran et al., 2017). This study also found that coping styles of participants may be an important predictor of psychological outcomes. Our study found that uncertainty about genome sequencing while awaiting results is episodic and that some coping strategies may be engaged over time, while others may be more specific to certain time points. For example, having a plan of action based on the worst-case scenario may be a coping strategy that helps patients deal with the uncertainty associated with how they will respond to results, which facilitates the patient's decision making to have genome sequencing. Whereas, coping strategies to manage affect, such as seeking professional support, maintaining a positive attitude and trusting in the experts or research may be useful while waiting for results, as the decision to have genome sequencing is made and no longer in their control. Understanding which coping strategies are most useful throughout the genome sequencing process could help patients manage their uncertainty, and potentially ameliorate psychological outcomes such as anxiety.

Increasing our understanding of uncertainties that patients experience while waiting for genome sequencing results provides patients and healthcare professionals with useful information about the sources and types of uncertainties which may emerge throughout the process. Healthcare professionals could utilize this information to discuss potential uncertainties with patients during their decision making to pursue genome sequencing, promoting informed consent and realistic expectations of this clinical tool (Biesecker et al., 2014; Han et al., 2017). Healthcare professionals can support patients by coaching them to understand that not all uncertainty needs to be resolved (Newson et al., 2016) and helping them to reappraise some uncertainties as opportunities rather than threats (Mishel, 1990). Knowing about the patient experience can help healthcare professionals provide anticipatory guidance to participants and help them to manage the uncertainties that may be construed as a further threat to their cancer prognosis. Specifically, healthcare professionals can help patients to identify and engage in effective coping strategies to manage their uncertainties while waiting for results, which in turn could reduce their likelihood of developing further anxiety about outcomes from genome sequencing.

Given the diverse range of uncertainty related to genome sequencing revealed in this study and others, we believe that

measures of uncertainty need careful consideration. Developed to measure attitude towards uncertainty related to medical tests, we believe that the Attitude towards Uncertainty scale does not capture the complexity of uncertainty experienced by patients undergoing genome sequencing. Since designing this study, a more relevant tool for capturing patient-perceived uncertainties associated with genome sequencing has been developed, the Perceptions of Uncertainties in Genome Sequencing (Biesecker et al., 2017), which we believe will be of use to researchers investigating uncertainties in genome sequencing.

Limitations and Strengths

The results of the current study are limited by sampling bias, including overrepresentation of female participants, Caucasian participants, highly educated participants, and participants with rare cancers, which limits the generalizability of our findings.

While reporting on the ongoing uncertainty experienced by patients waiting for genome sequencing results is an important addition to the literature in this area, all data were collected prior to participants receiving their genome sequencing results. We believe that further studies would be strengthened by collecting uncertainty data post-results as well, to investigate the impact which different results have on participant uncertainty. Nevertheless, methodological strengths of this study were its longitudinal mixed-methods design. Following our participants over the 12-month period while waiting for genome sequencing results allowed us to investigate changes in uncertainty over time, as well as the impact of uncertainty on psychological outcomes. Utilizing qualitative and quantitative methods allowed us to both investigate relationships between variables, and also describe experiences of participants.

Implications and Future Research

This study demonstrated the complexity of uncertainty generated by genome sequencing for cancer patients and provides further support that while patients are motivated to pursue genome sequencing to reduce illness uncertainty (for self and relatives) it also generates uncertainties (Bartley et al., 2020b). Additionally, the results suggest that uncertainty while waiting for genome sequencing is low, but that patients with uncertainty related to genome sequencing may also be vulnerable to genome sequencing related anxiety. Understanding how uncertainty coping strategies may help patients adapt to their uncertainty over time could assist health care professionals manage patient uncertainty, which in turn may ameliorate psychological outcomes such as anxiety.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The St Vincent's Hospital Human Research Ethics Committee (HREC/16/SVH/24). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PB, MBe, MBa, TS, BB, and NB contributed substantially to the conception and design of the study. NB and CN contributed substantially to data acquisition. NB, ZB, CN, TS, and PB contributed substantially to the analysis and interpretation of data. NB drafted the manuscript. BB, MBe, MBa, ZB, CN, TS, and PB revised the manuscript. All authors had full access to all the data in the study, gave final approval of the current draft, and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.647502/full#supplementary-material

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A Systematic Review of Fear of Cancer Recurrence Among Indigenous and Minority Peoples

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While cancer survivors commonly experience fear and anxiety, a substantial minority experience an enduring and debilitating fear that their cancer will return; a condition commonly referred to as fear of cancer recurrence (FCR). Despite recent advances in this area, little is known about FCR among people from Indigenous or other ethnic and racial minority populations. Given the high prevalence and poor outcomes of cancer among people from these populations, a robust understanding of FCR among people from these groups is critical. The current review identified and aggregated existing literature on FCR amongst adult cancer survivors from Indigenous and minority populations. The protocol of this review was registered with PROSPERO in July 2020 (Registration number: CRD42020161655). A systematic search of bibliographic databases was conducted for relevant articles published from 1997 to November 2019. Data from eligible articles were extracted and appraised for quality by two independent reviewers. Nineteen articles from four countries (United States of America, Canada, Australia and the United Kingdom) met the inclusion criteria, including 14 quantitative, 4 qualitative and 1 mixed-methods study. Only one article reported on an Indigenous population. Few studies reported on FCR prevalence ($n = 3$) or severity ($n = 9$). While the variation in tools used to measure FCR hindered a robust estimate of severity, results suggested some differences in FCR severity between minority and dominant populations, although these may have been due to study metholodological differences. Few factors were reported as being associated with FCR in minorities across multiple studies. The qualitative synthesis found five themes associated with the lived experience of FCR: (i) variations in the lived experience of FCR; (ii) spirituality and worldview impacting on FCR; (iii) the importance of staying positive; (iv) complexities around support; and (v) increasing cancer knowledge. The findings of this review highlight differences in FCR across cultures and contexts, which reinforces the need for culturally-specific approaches to this condition. The dearth of research

in this area is of concern given the significant burden of cancer in these populations. A deeper understanding of this condition among Indigenous and minority populations is critical to developing and delivering appropriate and effective psychosocial care for cancer survivors from these groups. Systematic Review Registration: identifier [CRD42020161655].

Keywords: fear of cancer recurrence, cancer, oncology, review—systematic, minority, Indigenous people

INTRODUCTION

Increasing clinical and research attention over the past two decades has produced a growing evidence base around *fear of cancer recurrence* (FCR) in people with different cancer types and from diverse populations including some vulnerable groups (Thewes et al., 2012a; Crist and Grunfeld, 2013; Koch et al., 2013; Simard et al., 2013; Almeida et al., 2019). FCR is defined as "*the fear, worry or concern relating to the possibility that cancer will come back or progress*" (Lebel et al., 2016). While some degree of FCR is considered a normal response to the experience of having cancer, estimates suggest that 40–70% of cancer survivors experience a level of FCR that is enduring and debilitating (Thewes et al., 2012a). FCR is associated with varied adverse outcomes in cancer survivors, including: psychological distress; impaired social functioning, and coping with work; reduced quality of life and level of enjoyment; and increased healthcare usage and costs (Avis et al., 2005; Hodges and Humphris, 2009; Lebel et al., 2013; Otto et al., 2018). Moreover, cancer survivors identify FCR as one of their major concerns (Simard et al., 2013).

Several factors are associated with a higher prevalence of FCR, including: younger age; female gender; greater burden of physical symptoms; and psychological factors (Härtl et al., 2003; Simard et al., 2013). Progress has also been made in screening for and assessing FCR (Simard and Savard, 2009), as well as in the development of psychological interventions to reduce FCR, which have been demonstrated to be effective predominantly in patients with early stage cancers treated with curative intent (Sharpe et al., 2017; Hall et al., 2018; Butow et al., 2019; Tauber et al., 2019). Despite these advances, little is known about FCR among cancer survivors from Indigenous, ethnic and racial minority populations and it is unclear whether existing programs and interventions aimed at reducing FCR are appropriate or effective for cancer survivors from these groups. This is surprising, given that cancer is a leading cause of illness and death among many Indigenous populations (United Nations Permanent Forum on Indigenous Issues, 2009; de Souza et al., 2016), and minority populations experience significantly poorer cancer outcomes than other groups with respect to risk factor prevalence, cancer incidence, stage at diagnosis and disease outcomes (United Nations Permanent Forum on Indigenous Issues, 2009; de Souza et al., 2016; Wild et al., 2020), including psychosocial outcomes (Garvey et al., 2020).

Indigenous peoples are recognized as the original inhabitants of a country or geographical region and are known as First Peoples or in some countries by more specific terms such as "*Native American*" in the US, "*First Nations*" in Canada, and "*Aboriginal*" and "*Torres Strait Islander*" in Australia. While there are no globally agreed definitions, the United Nations describes Indigenous peoples as "*inheritors and practitioners of unique cultures and ways of relating to people and the environment. They have retained social, cultural, economic, and political characteristics that are distinct from those of the dominant societies in which they live*" (United Nations, 2020). Similarly, definitions of ethnic and racial minorities are manifold, however, the terms generally refer to ethnic or racial groups in a given country in which they are in a non-dominant position in relation to the dominant population (United Nations, 1992). While there are clear and important distinctions between Indigenous peoples and ethnic and other racial minority populations (hereon respectfully referred to as a collective as IM populations), these groups similarly experience significant disparities in cancer outcomes and share many barriers to accessing and engaging with cancer care (United Nations Permanent Forum on Indigenous Issues, 2009; de Souza et al., 2016).

The current review aimed to explore the following questions:

1. What is the prevalence and severity of FCR among IM populations? Are there differences between IM and dominant populations?
2. What demographic, clinical, social and psychological factors are associated with FCR in IM populations?
3. What are the lived experiences of FCR among IM populations?

The establishment of an evidence base in this specific area will facilitate the evaluation and tailoring of programs and interventions to reduce FCR for cancer survivors from IM populations.

METHODS

Protocol Registration

A protocol for this systematic review was published on the PROSPERO: International prospective register of systematic reviews website in July 2020 [Registration number: CRD42020161655].

Search Strategy

The search aimed to identify peer-reviewed literature reporting new empirical data from qualitative, quantitative and mixed-methods studies with a focus on FCR in one or more IM population. The search strategy adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The literature

search included studies published between 1997 and November 2019. Articles published in scientific journals were identified by searching the bibliographic databases CINAHL, EMBASE, PsycINFO, and PubMed. The search aimed to identify any paper about FCR in adults (18 years or older) from IM populations who have been diagnosed with cancer. There was no restriction on cancer type, cancer stage, time since diagnosis, treatment type, or country/region of residence (see **Appendix A** for a detailed description of the search strategy).

The search string for Indigenous populations was adapted from a previously published systematic review of Indigenous populations (Angell et al., 2016). The search string for minority populations was adapted from a previously published systematic reviews of minority populations (Dawson et al., 2018).

Inclusion and Exclusion Criteria

Studies were included if they were: peer-reviewed; published in English; published from 1997 (this start date was chosen as FCR research began to emerge in the literature from this date) to November 2019; report original data from quantitative, qualitative or mixed method studies; involve cancer survivors; and report on the experiences of FCR and/or measures of FCR (e.g., mean FCR score; proportion of participants reporting any/high levels of FCR) separately for at least one IM population, as identified below. All eligible articles were included in the review regardless of quality assessment rating.

Studies were excluded if they were: systematic reviews, meta- and pooled- analyses, reported relative measures only, case studies, case series, commentary, editorial and other opinion papers, even if peer-reviewed; books or book chapters, narrative reviews, conference abstracts, dissertations, and other gray literature; published in languages other than English; or published prior to 1997.

Data Extraction (Selection and Coding)

All citations identified in the search were downloaded into Rayyan Online Software (Ouzzani et al., 2016). After removal of duplicates, the titles and abstracts were screened separately by two independent reviewers (KA and HH). Reference lists of systematic reviews found in the search were screened to identify other relevant articles for the review. Reviewers resolved disagreements through discussion and evaluation against inclusion/exclusion criteria. Full-text records were retrieved for studies that could not be excluded based on title and abstract alone.

Data extraction was completed by three authors (KA, ABS, and AD), which included: publication information (authors, year of publication, country, region); participant characteristics [IM population(s), cancer type, total number of participants, number of participants per IM group, age, sex]; study characteristics (study design; data collection method, study setting). Study outcomes for the quantitative studies and relevant findings of mixed methods papers were extracted by one author (AD) [FCR measure/s used, statistical tests used, proportion, mean, standard deviation (SD), range, effect size, clinically significant cut offs]. Qualitative and mixed methods papers were imported into NVivo 12 (NVivo qualitative data analysis software; QSR International Pty Ltd. Version 12, 2018) for coding and aggregation by one author (KA).

Study Quality Assessment

Three authors (KA, ABS, and BT) conducted a critical appraisal of the included articles using the Mixed Methods Appraisal Tool (MMAT) VERSION 2018 (Hong et al., 2018). An overall score out of five was calculated for each article, by tallying how many quality criteria each study was determined to have met.

Data Synthesis and Aggregation

The quantitative and qualitative syntheses were conducted and presented separately, with the relevant components of any identified mixed methods studies presented in both. Two authors (ABS and AD) synthesized the quantitative data regarding the prevalence, severity, and associated factors of FCR among cancer survivors from IM populations compared to dominant populations (review questions 1 and 2). A meta-synthesis of the qualitative data relating to the *lived experiences* of FCR among cancer survivors from IM populations was conducted by one author (KA).

RESULTS

Of the 304 records retrieved, 302 were identified in the search and two were identified through a handsearch. From these, 108 duplicates were removed, and 197 records were screened by title and abstract. Of those screened by title and abstract, 136 full-text articles were assessed for eligibility, and 19 records were subsequently considered eligible for inclusion (see **Figure 1**).

Characteristics of the Included Articles

A total of 19 studies met inclusion criteria (Braun et al., 2002; Ashing-Giwa et al., 2004; Gill et al., 2004; Krupski et al., 2005; Deimling et al., 2006; Janz et al., 2011, 2016; Liu et al., 2011; Pandya et al., 2011; Bache et al., 2012; Taylor et al., 2012; Butow et al., 2013; Singh-Carlson et al., 2013; Best et al., 2015; Sam, 2016; Ashing et al., 2017; Nápoles et al., 2017; Cho et al., 2018; McMullen et al., 2019). Sixteen studies were conducted in the United States (Braun et al., 2002; Ashing-Giwa et al., 2004; Gill et al., 2004; Krupski et al., 2005; Deimling et al., 2006; Janz et al., 2011, 2016; Liu et al., 2011; Pandya et al., 2011; Taylor et al., 2012; Best et al., 2015; Sam, 2016; Ashing et al., 2017; Nápoles et al., 2017; Cho et al., 2018; McMullen et al., 2019), one in Australia (Butow et al., 2013), Canada (Singh-Carlson et al., 2013) and the United Kingdom (Bache et al., 2012). Fourteen studies were quantitative (Gill et al., 2004; Krupski et al., 2005; Deimling et al., 2006; Janz et al., 2011, 2016; Liu et al., 2011; Pandya et al., 2011; Taylor et al., 2012; Butow et al., 2013; Best et al., 2015; Sam, 2016; Ashing et al., 2017; Cho et al., 2018; McMullen et al., 2019), four were qualitative (Braun et al., 2002; Ashing-Giwa et al., 2004; Bache et al., 2012; Singh-Carlson et al., 2013) and one was mixed-methods (Nápoles et al., 2017). One study included participants from an Indigenous population (Native Hawaiian) (Braun et al., 2002) and all other studies included participants who identified as belonging to one or more minority populations [Latino = 7 (Janz et al., 2011, 2016; Pandya et al., 2011; Sam,

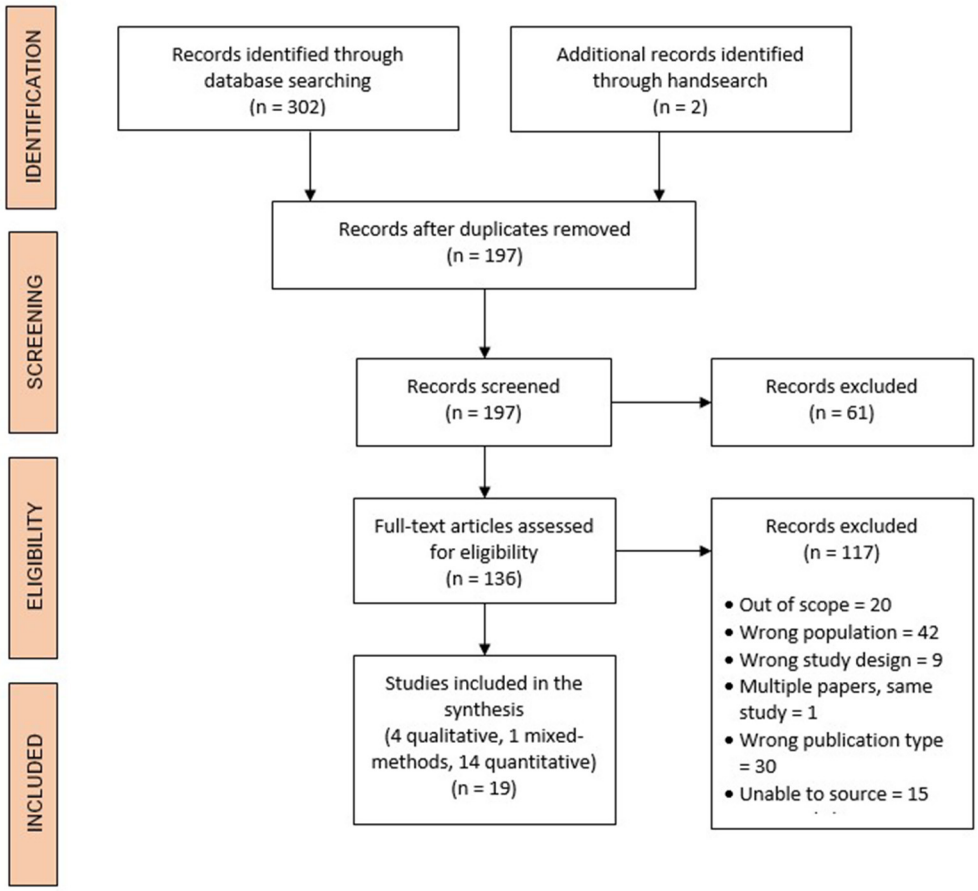

FIGURE 1 | Study selection and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

2016; Ashing et al., 2017; Nápoles et al., 2017; McMullen et al., 2019), African American = 11, (Gill et al., 2004; Krupski et al., 2005; Deimling et al., 2006; Janz et al., 2011, 2016; Pandya et al., 2011; Taylor et al., 2012; Best et al., 2015; Sam, 2016; McMullen et al., 2019). Asian American = 4 (Ashing-Giwa et al., 2004; Ashing et al., 2017; Cho et al., 2018; McMullen et al., 2019) and unspecified "non-White" = 1 (Liu et al., 2011) in the United States; first-generation immigrants from various ethnic groups = 1 (Butow et al., 2013) in Australia; South Asian = 1 (Singh-Carlson et al., 2013) in Canada; and African and Black Caribbean = 1 (Bache et al., 2012) in the United Kingdom]. Eleven studies included only breast cancer survivors (Ashing-Giwa et al., 2004; Gill et al., 2004; Janz et al., 2011, 2016; Liu et al., 2011; Taylor et al., 2012; Singh-Carlson et al., 2013; Ashing et al., 2017; Nápoles et al., 2017; Cho et al., 2018); one study each included gynecological (Sam, 2016); colorectal (McMullen et al., 2019); and prostate cancer survivors (Krupski et al., 2005); and five studies included cancer survivors with multiple cancer types (Braun et al., 2002; Deimling et al., 2006; Bache et al., 2012; Butow et al., 2013; Best et al., 2015). The detailed characteristics of the included studies are presented in **Table 1** (quantitative studies), **Table 2** (qualitative and mixed methods studies). Most quantitative studies used a relevant sampling strategy (12/15) and appropriate statistical analysis (13/15). It was unclear whether the sample was representative of the target population in 10/15 studies, risk of non-response bias was high in 7/15 studies, and only 7/15 studies used a validated FCR measure (see **Appendix B** for results of the quality appraisal).

Quantitative Synthesis

Prevalence of FCR

Seven studies reported FCR prevalence for IM populations (see **Table 3**) (Pandya et al., 2011; Taylor et al., 2012; Janz et al., 2016; Ashing et al., 2017; Nápoles et al., 2017; McMullen et al., 2019). The prevalence of FCR ranged widely, from 14% (8/57) of Non-Hispanic Black breast cancer survivors who were 4 years post-diagnosis (Janz et al., 2016) to 67% (34/51) of African American breast cancer survivors at on average 7 years post cancer diagnosis (Taylor et al., 2012) and 67% (20/30) of Hispanic leukemia survivors (Pandya et al., 2011).

Three studies compared FCR prevalence in minority cancer populations to their Non-Hispanic White/Caucasian counterparts (Pandya et al., 2011; Janz et al., 2016; McMullen et al., 2019), although only two reported FCR prevalence by

TABLE 1 | Characteristics of included quantitative studies.

References	Country (region)	Study design (data collection)	Study setting	Participants: n (response rate)	IM groups: n (% of total sample)	Cancer type: n (%)	Time since diagnosis/ treatment: M (SD)	Age in years: M (SD) [range]	Sex (%)
Janz et al. (2011)	USA (Los Angeles, California)	Cross sectional (postal survey)	Cancer registry	2,290 (73%)	Black (n = 478; 14.3%) Latina (high acculturation; n = 233; 8.1%) Latina (low acculturation; n = 256; 8.9%)	Breast (100%)	9 months	56.8 (11.4)	Female (100%)
Cho et al. (2018)	USA (Los Angeles, New York, and Houston)	Cross sectional (postal survey)	Community cultural events, educational conferences and support groups	77 (77.4%)	Chinese American (n = 77, 100%)	Breast (100%)	18.8 (11.0) months.	54.4 (8.2) [37–77]	Female (100%)
Gill et al. (2004)	USA (North Carolina)	Cross sectional (telephone survey)	Hospital tumor registries	244 (55% of those contacted, 11.3% attrition)	African American (n = 73, 29.9%)	Breast (100%)	Caucasian 6.7 (1.1) years African American 7.0 (1.3) years	64.3 (8.3) [49–87]	Female (100%)
Nápoles et al. (2017)	USA (California)	Cross sectional (telephone survey)	Hospital and community-based cancer support services	118 (51%)	Latinas (n = 118, 100%)	Breast (100%)	68% 0–2 years post-diagnosis	54.9 (12.3)	Female (100%)
Liu et al. (2011)	USA (St Louis, Missouri)	Cross-sectional (computer-assisted telephone interview)	Hospital-based cancer treatment service	506 (65.5%)	Non-white (n = 98, 19.4%)	Breast (100%)	2 years post definitive breast surgery	58 (10)	Female (100%)
Ashing et al. (2017)	USA (West Coast)	Longitudinal (postal survey at 2 time points)	Community-based health organizations	137 (NR, 34% attrition from T1-T2)	Chinese (51%) Other Asian (49%) - Korean (18.2%) - Filipinas (13.1%) - Vietnamese (6.6%) - Japanese (5.8%) - Mixed (0.7%).	Breast (100%)	T1: mean 2.8 (2.6) years T2: +1 year	54.8 (9.6) [31–83]	Female (100%)
Janz et al. (2016)	USA (Los Angeles, California)	Cross-sectional (postal survey)	Cancer registry	510 survivor-partner pairs (73.1%, 5.4% attrition)	Non-Hispanic Black (n = 66; 12.9%) Latina (high acculturation; n = 71, 13.9%) Latina (low acculturation; n = 62, 12.1%)	Breast (100%)	4 years post-diagnosis	No mean age reported. Under 50 years: n = 89, 17.5% 50–65 years: n = 263, 51.6% 65 years and over; n = 158, 31.0%	Female (100%)
Taylor et al. (2012)	USA (Washington DC)	Cross sectional (postal or in person self-report survey)	University Cancer Centre registry	51 (8.5%)	African American (n = 51, 100%)	Breast (100%)	7.2 (4.3) years	64.2 (12.3)	Female (100%)
Krupski et al. (2005)	USA (Los Angeles, California)	Cross-sectional (telephone survey and self-administered questionnaire)	Cancer treatment service	228 (59.2%)	Hispanic (n = 115; 50.4%) African American (n = 42; 18.4%)	Prostate (100%)	Mean months from biopsy: Caucasian = 18.0 Hispanic = 14.6 African American = 10.8 Other = 16.8.	Caucasian: 58.98 Hispanic: 63.27 African American: 58.76 Other: 65.12	Male (100%)

(Continued)

TABLE 1 | Continued

References	Country (region)	Study design (data collection)	Study setting	Participants: n (response rate)	IM groups: n (% of total sample)	Cancer type: n (%)	Time since diagnosis/ treatment: M (SD)	Age in years: M (SD) [range]	Sex (%)
McMullen et al. (2019)	USA (6 sites across Colorado, Southern/Northern California, Oregon/Southwest Washington)	Cross sectional (paper, online, and interactive voice response telephone survey)	Patient Outcomes Research to Advance Learning (PORTAL) Network - registries of 6 health systems and 9 research centres affiliated with those systems	1,947 (50.2%)	Hispanic (n = 267, 13.7%) Non-Hispanic Asian (n = 170, 8.7%) Non-Hispanic Black (n = 149, 7.7%) Multiple/other/unknown (n = 16, 0.8%)	Colon n = 1,418 (72.8%) Rectosigmoid n = 101 (5.2%) Rectal n = 428 (22.0%)	3.3 (1.1) years	68.6 [17.0–99.2]	Male (51.1%)
Pandya et al. (2011)	USA (Texas)	Cross sectional (face-to-face survey)	National Cancer Institute designated cancer centre	55 (NR)	Hispanic (n = 30, 54.5%) African American s (n = 5, 9.1%)	Leukemia (100%)	Survival phase: Acute (on treatment): 38.2% Extended (finished treatment/in remission): 40.0% Permanent (cured): 21.8%	54.3 (17.1)	Male (58.2%)
Sam (2016)	USA (Texas)	Cross sectional (web-based survey)	Local clinical facilities, online cancer support groups, Facebook	352 (94%)	Asian 3.7% Hispanic 2.3% African American/Black 1.4%	Ovarian (60%) uterine/endometrial (31%) Cervical (9%)	Disease-free survival M = 5.7 (4.7) years	57.1 (10.1) [29–80]	Female (100%)
Deimling et al. (2006)	USA (Cleveland, Ohio)	Cross sectional (telephone survey)	Cancer registry	321 (48%, 11% attrition)	African American (n = 121, 37.7%)	Breast (144, 41.4%) Colorectal (96, 29.9%) Prostate (92, 28.7%).	Med survival 10.4 (5.5) years	72.3 (7.5)	Female (59%)
Butow et al. (2013)	Australia (NSW, QLD, VIC)	Cross sectional (postal survey)	Cancer registries	596 (13.6% of those eligible, 26% of those contacted)	Chinese (n = 151, 25.3%) Greek (n = 79, 13.3%) Arabic (n = 57, 9.6%)	Breast = 204 (34%) Prostate = 154 (26%) Colorectal = 105 (18%) Bladder/kidney = 42 (7%) Leukemia, lymphomas = 45 (8%) Head and neck = 25 (4%) Other = 21 (4%)	Minority 45.8 (24.6) months Anglo 42.9 (20.3) months	Minority: 62.5 (11.0) Anglo: 64.1 (10.7)	Male (51%)
Best et al. (2015)	USA (National)	Cross sectional (secondary analysis of data from survey - modality not specified)	14 state cancer registries	9,006 (35%)	African American (n = 933, 10.4%)	Breast (31.5%) Prostate (24.2%) Colorectal (20.8%) Uterine (8.0%) Bladder (6.4%) Melanoma (8.4%) Non-hodgkin lymphoma (0.7%)	2, 5, or 10 years since diagnosis (~one third in each)	67.3 (11.9) [23–100]	Female (55%)

TABLE 2 | Characteristics of included qualitative studies.

References	Country (region)	Data collection method	Study setting	IM population/s	Cancer type	Total participants	Participants per ethnic group	Age	Sex
Ashing-Giwa et al. (2004)	USA (California)	Focus groups and interviews	Cancer support groups, hospitals, community health clinics	African American, Asian American, Latino American	Breast	102	African Americans (n = 24), Asians (n = 34), Latinas (n = 26) and Caucasians (n = 18)	Mean AA = 56 (42–79); Mean Korean = 56 (31–78); Mean Chinese = 56 (42–81); Mean Asian = 53 (40–65); Mean Caucasian = 55 (43–72); Mean American monolingual = 54 (37–67); Mean Latina = 56 (40–73)	Female
Singh-Carlson et al. (2013)	Canada (BC)	Focus groups and individual interviews	Regional cancer centres	South Asian	Breast	24	South Asian = 24	Mean all partic = 55.5; Range = 28–75	Female
Nápoles et al. (2017)	USA (California)	1) a telephone survey of SSBCS; 2) semi-structured interviews with SSBCS; 3) semi-structured interviews with cancer support providers serving SSBCS	Hospital and Community base cancer support services	Latino American	Breast	143	American Latinos (n = 118 in Quant; n = 25 in Qual)		Female
Bache et al. (2012)	UK (London)	Semi-structured, in-depth interviews	Charitable support group	African or Black Caribbean	Multiple	8	African (n = 1), Black Caribbean (n = 5), NR (n = 2)	Range = 35–81	Both
Braun et al. (2002)	USA (Hawaii)	PAR; focus groups	Community health centre	Native Hawaiian	Multiple	45	Native Hawaiian (n = 45)	Mean all partic = 58 years; Range 36–83 years	Both

TABLE 3 | Results from quantitative studies.

References	FCR measure; no. of items [score range].	FCR Prevalence	FCR Severity* M (SD or 95% CI)	Factors associated with higher FCR in IM cancer patients and survivors
Janz et al. (2011)	Study-specific worry about recurrence measure: 3 items [1−5]	NR	White:2.74 Black: 2.47 Latina (high acculturation): 3.08 Latina (low acculturation): 3.78	Sig: compared to whites: higher FCR in latinas lower FCR in blacks
Cho et al. (2018)	Single study-specific item "I worry that my cancer will come back" 0 (not at all) to 4 (very much)	NR	1.75 (1.33)	Sig: worse pain interference, fatigue and emotional well-being Non-sig: pain severity
Gill et al. (2004)	Study-specific checklist of 10 triggers of uncertainty about recurrence and long-term treatment side effects derived from focus groups [0–10]	NR	Average number of triggers per month AA: 1.6 (0.9) White: 1.9 (1.0)	NR
Nápoles et al. (2017)	2 study-specific items "In the past month, how much have you been bothered by: Thoughts that breast cancer will come back Thoughts that will get cancer in other parts of body." % answering "somewhat/quite a bit/a lot" reported	42%	NR	NR
Liu et al. (2011)	Concern about recurrence scale (CARS) 4 items [1–6]	NR	White: 2.05 (0.99) Non-white: 2.00 (1.35) *t*-test, $p = 0.71$	NR
Ashing et al. (2017)	FACT-B V4 additional item on FCR "I worry about my cancer coming back or spreading" 0 (not at all) to 4 (very much)	T1: 0: "Not at all" = 11.8% 1: "A little bit" = 27.7% 2: "somewhat" = 22.1% 3: "quite a bit" = 17.4% 4: "Very much" = 21.0% T2: 0: "Not at all" = 16.1% 1: "A little bit" = 29.2% 2: "somewhat" = 16.8% 3: "quite a bit" = 13.9% 4: "Very much" = 24.1%	T1: 2.01 (1.36) T2: 1.99 (1.43) *t*-test, $p = 0.89$	Sig: other Asian vs. Chinese ethnicity, Lower health care satisfaction, poorer physical well-being, Poorer emotional well-being, poorer functional well-being, poorer breast cancer-specific HRQOL. Non-sig: age, income, education, language, years living in the US, years since diagnosis, chemotherapy, radiotherapy, cancer stage
Janz et al. (2016)	Study-specific worry about recurrence measure: 3 items [1–5]	Non-hispanic white = 27.1% Non-hispanic black = 14.0% Latina (higher acculturation) = 36.5% Latina (lower acculturation) = 50.0%	NR	Sig: compared to whites: higher FCR in Latinas lower FCR in Blacks
Taylor et al. (2012)	Concern About Recurrence Scale (CARS) 4 items [1–6]	67%	2.65 (1.44)	Sig: Overall FCR related to less time since diagnosis, poorer QOL
Krupski et al. (2005)	Previously used fear of recurrence scale 5 items [0–20]	NR	*High scores = low FCR* Caucasian: 16.31 (4.10) Hispanic: 16.16 (4.80) African American: 18.30 (4.70) Other: 17.06 (4.00)	Sig: compared to caucasians: lower FCR in African Americans Non-sig: caucasian vs. hispanic
McMullen et al. (2019)	Single study-specific item "What are your biggest health or lifestyle concerns (other than having cancer) since being diagnosed?" 7 identified concerns including 'possibility of cancer recurrence' yes/no response	Concern regarding the possibility of recurrence Non-Hispanic White = 60% Other = 55%	NR	Sig: IM race/ethnicity associated with lower likelihood of FCR
Pandya et al. (2011)	Study-specific item(s) assessing FCR - Specifics not reported	Caucasian = 30% Hispanic = 67% African American = 40% Chi-squared, $p = 0.031$	NR	NR

(Continued)

TABLE 3 | Continued

References	FCR measure; no. of items [score range]	FCR Prevalence	FCR Severity* M (SD or 95% CI)	Factors associated with higher FCR in IM cancer patients and survivors
Sam (2016)	Kornblith's FOR Scale 5 items [5–25]	NR	White = 13.79 (4.73; 20.0) Non-White = 11.96 (4.56; 16.0) Mann-Whitney *U*-test, $p = 0.065$	Sig: younger age, negative illness perceptions, greater psychological distress Non-sig: survivorship duration†
Deimling et al. (2006)	Cancer Related Health Worry (CRHW) scale 4 items [0–20], higher scores = less worry	NR	11.2 (3.4)	Sig: higher FCR in White/Caucasian vs. Black/African American
Butow et al. (2013)	Cancer Survivors Unmet Needs measure (CASUN) 4 items regarding the future	FCR-related unmet needs: immigrant minorities = 29.6% Anglo-Australians = 17.4%	NR	Sig: need for an interpreter, poorer understanding of the health system, worse anxiety, depression and QOL Non-sig: Immigrant vs. Anglo-Australian background
Best et al. (2015)	Cancer Problems in Living Scale (CPILS) FCR subscale 4 items [0–12]	NR	African American = 1.35 (1.45) Non-African American = 1.30 (1.39) *t*-test, $p > 0.05$	Sig: Less meaning ^, Less peace Non-sig: Time since diagnosis†, Cancer stage†

*Higher score more severe FCR; †Significantly associated with FCR in dominant sample; ^Not significantly associated with FCR in dominant sample.
Sig, statistically significance between-group differences.

specific minority group (Pandya et al., 2011; Janz et al., 2016). In these studies, FCR was reported by a greater proportion of Hispanic/Latina people with cancer [Leukemia: (Pandya et al., 2011) 67%; Breast cancer: (Janz et al., 2016) 37% in high acculturated Latina and 50% in low acculturated Latina] than their Non-Hispanic White counterparts [Leukemia 30%; (Pandya et al., 2011). Breast Cancer: (Janz et al., 2016) 27%] (**Table 3**). Conversely, Janz et al. reported less FCR in Non-Hispanic Black breast cancer survivors compared to Non-Hispanic White breast cancer survivors (14.0 vs. 27.1%) (Janz et al., 2016). While Pandya et al. reported a higher prevalence of FCR in African American than Caucasian Leukemia patients (40 vs. 30%); it is important to note that this study only recruited five African American people (Pandya et al., 2011).

FCR was the most prevalent health/lifestyle concern, emotional concern or symptom among colorectal cancer survivors (McMullen et al., 2019), among Latina breast cancer survivors (Nápoles et al., 2017), and was the highest unmet supportive care need among a mixed sample of immigrant IM cancer survivors (Butow et al., 2013).

Severity of FCR

Nine studies reported on the severity of FCR for IM populations (Krupski et al., 2005; Deimling et al., 2006; Janz et al., 2011; Liu et al., 2011; Taylor et al., 2012; Best et al., 2015; Sam, 2016; Ashing et al., 2017; Cho et al., 2018), while one reported on the mean number of triggers of FCR experienced (Gill et al., 2004). FCR was often measured using purpose-designed items, often a single item, making judgements regarding severity difficult, although most mean scores were in the low/moderate range (**Table 3**). Several studies used the Concerns About Recurrence Scale (CARS) with mean scores ranging from 2.00 (SD = 1.35) in "Non-white" early stage breast cancer survivors (Liu et al., 2011) to 2.65 out of 6.00 (SD = 1.44) in African American breast cancer survivors (Taylor et al., 2012).

Assessment of FCR in distinct IM groups indicate that Hispanic people may experience more severe FCR compared to non-Hispanic Whites. This was observed in older long-term cancer survivors from several cancer groups (Deimling et al., 2006) and survivors of breast cancer (Janz et al., 2011), however no difference was observed between Hispanic and non-Hispanic White non-metastatic prostate cancer survivors (Krupski et al., 2005). In contrast, non-Hispanic Black cancer survivors experienced similar (Best et al., 2015) or less severe (Krupski et al., 2005; Deimling et al., 2006; Janz et al., 2011). FCR compared to non-Hispanic White cancer survivors. One study found Chinese American women reported significantly lower FCR than "other Asian" American women (M = 2.76 years post-diagnosis) (Ashing et al., 2017).

Two studies assessed longitudinal changes in FCR (Janz et al., 2016; Ashing et al., 2017). Higher FCR levels in Hispanic vs. non-Hispanic women 9 months after a breast cancer diagnosis were still evident 4 years post-diagnosis (Janz et al., 2016). Similarly, higher levels of FCR among non-Chinese vs. Chinese Asian-American breast cancer survivors were still evident 1 year post-baseline (Ashing et al., 2017).

Factors Associated With FCR

Factors associated with FCR in cancer patients and survivors from minority populations were explored in six studies (Taylor et al., 2012; Butow et al., 2013; Best et al., 2015; Sam, 2016; Ashing et al., 2017; Cho et al., 2018).

Demographic and Clinical Correlates

Few consistent relationships emerged between minority peoples' FCR and their demographic or clinical characteristics.

TABLE 4 | Summary of main themes identified via meta-aggregation of qualitative studies.

Themes	Key findings	Illustrative quotes
Lived experience of FCR	• FCR is a major concern for some survivors for IM populations • Many negative emotions associated with FCR • FCR is worse than physical effects of cancer • Major concerns around the welfare of their families if they die • Screening tests and symptoms trigger FCR • Some survivors felt abandoned by the health care system after active treatment finishes, which increases anxiety and FCR	*"As a cancer survivor, one of my biggest fear is the 5-year waiting period, to find out if we are going to survive or not. That creates suspense, fear, and negative emotions. Five years is a lot and I never know if I'll be the one winning the battle. I feel like I'm standing on a balance just waiting to see which way it is going to go." (Latina) (Ashing-Giwa et al., 2004)* *"It is not the pain, but it is the anxiety, the fear of it becoming positive. The anxiety is worse than the pain. Pain, I can deal with it. When you're given pain medication, it's relieved. But anxiety, it sticks in your mind." (Asian American) (Ashing-Giwa et al., 2004)* *"As caregivers, we worry about those who depend on us because if something happens to us, who would care and provide for our family, children, parents, etc. who totally depend on us? (Latina) (Ashing-Giwa et al., 2004)* *Every time I'm due for my mammogram, I can't sleep, worrying. I lose sleep until I get the letter with my results. Then I feel at peace again." (FocGrp1#9) (Nápoles et al., 2017)* *"I always worry about mets going to other parts of the body. I do worry, especially when I hear people dying from breast cancer. That hits me; I get really sad." (Age 41) (Singh-Carlson et al., 2013)* *"They give surgery, they give you treatments, they say, 'we got it all.' But you feel a pain, you wonder what is going on, or you feel dizzy. I try not to obsess about it. But I feel it's a legitimate fear. The fact that it might come back and I might have to physically suffer." (African American) (Ashing-Giwa et al., 2004)* *"Once they tell you to stop the pills, 'You're cured, there's nothing wrong with you,' the truth is that one feels, 'Now what do I do? I have no one to help me.' I felt very abandoned." (FocGrp1#5) (Nápoles et al., 2017)*
Cultural beliefs and practices impacting on FCR	• Faith and religion were commonly reported as ameliorating FCR • Participants drew strength from involvement in religious, cultural and community groups • Quiet acceptance and prayer were two cultural norms for dealing with difficulty and uncertainty in some IM cultures • Strength among people from IM populations due to shared histories of surviving adversity was seen as an important coping mechanism and ameliorated FCR	*"We all know cancer is a non-curable disease, if we follow up treatment we can get better, but not cured. So who else can decide if we are making it or not, if it's not God? It is only Him who has the last word, and if He decides time has come, no matter what I do, my time is over." (Latina) (Ashing-Giwa et al., 2004)* *"I just trust God. Everything trust to God and He will give us miracle. You cannot do anything if you already have cancer. God is the one to give us life, he is the one to get our life." (Asian American) (Ashing-Giwa et al., 2004)* *"I draw strength from it because I sing in the choir and you know I pray a lot and feel calm and feel positive from it. It keeps me sane otherwise I don't know." (South East Asian) (Bache et al., 2012)* *"I did all the treatment.... They did the operation; they did the surgery.... What is there to be scared of? You can't do anything about it; just accept it." (Sikh) (Singh-Carlson et al., 2013)* *"Every time I have come across a sister with it, I am very proud to say that whatever things that we have went through, we handle it. I think that honestly, it is in our genes. It is in our ancestry. We do this. We get diagnosed with cancer; we have our moments, because I have fallen apart, but we pull ourselves together like a puzzle... I believe that we just have that stamina. We get back up, and dust yourself of and do this kind of thing." (African American) (Ashing-Giwa et al., 2004)*
Importance of staying positive and not dwelling on illness	• Keeping focused on the positive and not getting caught up in the negative was commonly seen as important to ward of FCR and in surviving cancer more broadly	*"It's too easy to have a negative mind and get depressed and woe is me, I've got cancer, woe woe woe woe woe. I like when people see me, who know my situation, I like when I get the reaction: but you look well though.... Whatever life throws at you I believe it's best to just deal with it. You're gonna have your rough days where you're gonna feel like 'what's the point' but I just feel it's best to just deal with it." (either African or Black Caribbean – not specified) (Bache et al., 2012)*
Complexities around support from family and community	• Relationships with family were very important for survivors to cope, however, they were sometimes fraught with guilt and misunderstanding • Survivors can feel pressure to hide their FCR to avoid upsetting family members • Survivors sometimes felt that family and community members could not understand their experiences	*"If people who have cancer are in each other's company, they come to know and understand each other, because they get* hounsla *[hope or encouragement] from each other. I will feel better if I talk with similar people who give me* hounsla*." (South East Asian) (Singh-Carlson et al., 2013)* *"It is most important to be with people with same disease. Because we understand each other in physical and psychological states. Families don't understand these. They (family members) say they understand, but they expect us to be the same people as before the disease." (Korean) (Ashing-Giwa et al., 2004)*

(Continued)

TABLE 4 | Continued

Themes	Key findings	Illustrative quotes
Increasing cancer knowledge	• Being informed about cancer and maintaining their treatment regimen were seen by some survivors as beneficial to their recovery from cancer • Some survivors preferred to rely on alternative medicine rather than Western medicine and word of mouth rather than doctors' recommendations	*"Ask for a second opinion. Keep track of everything yourself. The doctor might be more alert knowing that you're keeping track of your own body too. (African American)" (African American) (Ashing-Giwa et al., 2004)*

Associations with age were assessed in four studies (Taylor et al., 2012; Best et al., 2015; Sam, 2016; Ashing et al., 2017). Age was not associated with FCR in Asian-American breast cancer survivors (Ashing et al., 2017) or overall FCR in African American breast cancer survivors (Taylor et al., 2012), but was negatively correlated with FCR health worries, role worries and death worries domains (Taylor et al., 2012). Age was also negatively correlated with FCR in a heterogenous group of non-White cancer survivors, more so than in Whites (Sam, 2016). Longer time since diagnosis was associated with lower FCR in African American breast cancer survivors (Taylor et al., 2012), but not African Americans with a mix of cancer types (Best et al., 2015) or Non-white gynecological cancer survivors (Sam, 2016). More advanced cancer stage was associated with higher FCR in minority peoples with breast cancer (Ashing et al., 2017), but not in a mixed sample of cancer survivors (Best et al., 2015).

Psychological Correlates

Various aspects of minority peoples' perceptions of their illness and its treatment were found to be associated with FCR, although no factors were identified in more than one study. There were a few notable differences in relationships between FCR and psychological variables in White vs. non-White people. Best et al. found a significant negative association between *meaning* and FCR in African American survivors but not in non-African American survivors (Best et al., 2015). Gill et al. found that African American breast cancer survivors were less likely than other survivors to have FCR *triggered by external factors*, namely hearing about somebody else's cancer, environmental triggers or cancer-related media coverage or controversy (Gill et al., 2004). In Australian immigrant minority cancer survivors, more severe unmet FCR-related needs were significantly associated with the need for an interpreter and poorer understanding of the healthcare system (Butow et al., 2013). Among Asian Americans, greater healthcare satisfaction predicted lower subsequent FCR (Ashing et al., 2017). FCR was also found to mediate the impact of pain interference and fatigue on emotional wellbeing (i.e., greater pain interference and fatigue were associated with higher FCR, which was further related to poorer emotional wellbeing) in Chinese American breast cancer survivors (Cho et al., 2018).

Outcomes of FCR

Several studies found that minority peoples' FCR was associated with worse psychological distress (Butow et al., 2013; Sam, 2016), physical, emotional, functional quality of life and breast cancer specific quality of life (Taylor et al., 2012; Butow et al., 2013; Ashing et al., 2017). Two studies compared outcomes of FCR across minority and dominant populations (Butow et al., 2013; Sam, 2016). FCR and psychological distress demonstrated positive correlations that were moderate in "non-white" and strong in "white" gynecological cancer survivors (Sam, 2016). FCR-related unmet needs and worse anxiety, depression and quality of life were strongly correlated in immigrant Arabic cancer survivors, and moderately correlated in Anglo-Australian and immigrant Chinse and Greek cancer survivors (Butow et al., 2013).

Qualitative Synthesis

Lived Experience of FCR

Of the four qualitative studies (Braun et al., 2002; Ashing-Giwa et al., 2004; Bache et al., 2012; Singh-Carlson et al., 2013) and one mixed-method study (Nápoles et al., 2017) in this review, two were from the USA [California (Ashing-Giwa et al., 2004) and Hawaii] (Braun et al., 2002), one from Canada (British Columbia) (Singh-Carlson et al., 2013) and one from the UK (London) (Bache et al., 2012). The Hawaiian study was the only study in the review that reported on Indigenous participants (Braun et al., 2002). The meta-synthesis undertaken on the qualitative findings reported in these papers revealed five synthesized findings around the lived experience of FCR: (i) variations in the lived experience of FCR; (ii) spirituality and worldview impacting on FCR; (iii) the importance of staying positive and not dwelling on illness; (iv) complexities around family and community support; and (v) increasing cancer knowledge. These synthesized findings are described below, and the meta-synthesis is presented with illustrative quotes in **Table 4**.

Variations in the Lived Experience of FCR

There were some accounts from cancer survivors from IM populations in these studies about their experiences of FCR, which were contrasted against the experiences of relevant dominant populations and/or other IM groups. Many survivors detailed their experiences of fear, suspense, anxiety and sadness about the thought of their cancer returning (Ashing-Giwa et al., 2004; Singh-Carlson et al., 2013).

Ashing-Giwa et al. found that while cancer survivors from dominant populations in the USA expressed concerns about recurrence associated with incapacitation and loss of autonomy, survivors from African American, Asian American and Latina populations were more concerned about their ability to care for their family if their cancer returned (Ashing-Giwa et al., 2004).

Moreover, Ashing-Giwa et al. and Napoles et al. both found that cancer survivors from IM populations in the USA were more likely than dominant populations to experience FCR when obtaining follow up care, including check-ups and mammograms (Ashing-Giwa et al., 2004; Nápoles et al., 2017).

Singh-Carlson et al. found that among female cancer survivors from South Asian populations in Canada, younger women commonly experienced FCR relating to uncertainty around their future, whereas for middle-aged women the FCR centered around what would happen to their children, and older women were not troubled by FCR (Singh-Carlson et al., 2013).

Singh-Carlson et al. reported that IM survivors in Canada were prone to experiencing FCR when hearing stories about other people who are dying from cancer (Singh-Carlson et al., 2013). Ashing-Giwa et al. also found that physical sensations of pain and dizziness were also triggering for FCR among survivors from IM populations in the USA (Ashing-Giwa et al., 2004).

Spirituality and Worldview Impacting on FCR

Cancer survivors from IM populations reported spiritual and/or fatalistic beliefs regarding the outcomes of their cancer and their future, which were identified as pivotal in moderating survivors' FCR and fostering psychological adjustment to uncertainties of life after cancer (Braun et al., 2002; Ashing-Giwa et al., 2004; Bache et al., 2012; Singh-Carlson et al., 2013). Across the studies, *God* was commonly described by cancer survivors from IM populations as a source of comfort and as the ultimate decider of one's fate (Bache et al., 2012). Additionally, participation in religious practices, such as attending church services and religious support groups, provided emotional support and distraction, which strengthened cancer survivors' ability to cope with their illness (Bache et al., 2012). Ashing-Giwa et al. found that Asian American survivors relied on their personal sense of faith in managing their fear, African American survivors relied heavily on their prayers and support from their faith community, and Latino-American survivors relied on a combination of faith, prayers and support from their faith community (Ashing-Giwa et al., 2004).

Singh-Carlson et al. found that South Asian cancer survivors in Canada demonstrated a *quiet acceptance* of their cancer experience (Singh-Carlson et al., 2013). This was regarded as reflective of Eastern spiritual beliefs that discourage fighting against suffering and discomfort and instead encourage acceptance and endurance of one's negative experiences (Singh-Carlson et al., 2013). The authors found that among South Asian cancer survivors, belief in *faith* and *karma* were commonly reported to moderate apprehension and reduce fear about their cancer returning (Singh-Carlson et al., 2013).

Similarly, Braun et al. found that Native Hawaiian cancer survivors expressed fatalistic views regarding the outcomes of their cancers, which was thought to foster acceptance and likely reduce FCR (Braun et al., 2002). Ashing-Giwa et al. found that many of the African American survivors drew emotional strength from the long legacy of resilience and survivorship in the history of African Americans (Ashing-Giwa et al., 2004).

Staying Positive and Not Dwelling on Illness

Several of the studies in this review found that cancer survivors from IM populations expressed beliefs that maintaining a positive attitude and not dwelling on one's illness are important factors, not just in coping with FCR, but also in overcoming their cancer.

Ashing-Giwa et al. found that a common belief shared across cultural groups was that accepting their illness, but not dwelling on it, was important for coping with cancer (Ashing-Giwa et al., 2004). In order to avoid ruminating on their cancer, older and/or newly emigrated cancer survivors from IM populations, who were often reluctant to seek psychosocial support, distracted themselves from emotional overwhelm with household duties (Ashing-Giwa et al., 2004). Bache et al. also found this to be the case among cancer survivors from IM populations in the United Kingdom (Bache et al., 2012). Survivors attributed emotional and physical resilience to maintaining a positive outlook; and that over-contemplation of illness was thought to accelerate the progression of the cancer (Bache et al., 2012). The researchers postulate that the common avoidance of contemplating cancer, which can lead to missing check-ups and screening and increasing late-detection of cancers, might also be an important component in psychological resilience and a defense against FCR (Bache et al., 2012).

Braun et al. found that many Native Hawaiian cancer survivors had relatives who had died of cancer, which occasioned increased FCR for those people (Braun et al., 2002). This made it difficult to stay positive and some participants took issue with the word *recovery*, as they said: "*You never know... once you get cancer, you might get a recurrence or you might get cancer somewhere else*" (Braun et al., 2002).

Asian and Latina cancer survivors in Ashing-Giwa et al.'s study reported a reliance on inner strength and an emotional response of displacement (e.g., focusing their energy on their families and their household responsibilities) to cope with fear and anxiety around their cancer (Ashing-Giwa et al., 2004). This contrasted with the Caucasian survivors who predominantly drew on a sense of personal empowerment, individual responsibility and knowledge as their source of resiliency (Ashing-Giwa et al., 2004).

Complexities Around Family and Community Support

While family and community were identified across the studies as providing critical support for cancer survivors from IM backgrounds to cope with their cancer experiences, there were also commonly identified stressors associated with these relationships.

Two of the included studies reported African American cancer survivors often found strength and emotional support in family and church communities to cope emotionally with their cancer (Ashing-Giwa et al., 2004; Bache et al., 2012). However, Singh-Carlson et al. found that South Asian cancer survivors were ambivalent about receiving emotional support from family and community (Singh-Carlson et al., 2013). The common stigma around cancer in their communities and the prevalent view of cancer as a death-sentence meant that survivors from IM populations were often unwilling to disclose their cancer diagnosis to family and community (Singh-Carlson et al.,

2013). This occasioned feelings of isolation and depression among survivors, which heightened rumination and FCR. People who sought support from other cancer survivors had improved *hounsla* (morale) and increased hope for the future (Singh-Carlson et al., 2013).

While support from family was important for many cancer survivors, some studies reported cancer survivors felt great pressure from their families to be positive and well, as they were relied upon to be the traditional caregiver in the family (Braun et al., 2002; Ashing-Giwa et al., 2004; Singh-Carlson et al., 2013). Two studies reported that family and community members did not want to discuss the illness or the survivor's experience with them, and the survivor felt isolated and unsupported (Ashing-Giwa et al., 2004; Singh-Carlson et al., 2013). Braun et al. also found that Native Hawaiian cancer survivors reported stigma and shame around a cancer diagnosis, which caused some people to hide their diagnosis (Braun et al., 2002). These pressures on cancer survivors to not express their negative thoughts and emotions about their cancer to family members sometimes intensified cancer survivors' rumination and FCR.

While the involvement of family and community members occasioned complex and often competing emotional issues, support groups were described by some cancer survivors from IM populations as important to emotionally cope with their illness. Ashing-Giwa et al. reported that these groups offered survivors support via a shared understanding of the experience with other survivors, a lack of pressure to suppress fears and negative feelings, and the stories of survival from cancer providing hope (Ashing-Giwa et al., 2004). These opportunities to share gave survivors some relief from their anxieties and accounts of good cancer outcomes on which they could reflect.

Increasing Cancer Knowledge

For some survivors from IM populations, increasing their knowledge about cancer was seen as important in coping and managing FCR—for some people this was via biomedical knowledge and for others it was via traditional medicines and knowledge. Ashing-Giwa et al. found that some cancer survivors relied on alternative medicine and word of mouth rather than rather than Western doctors' recommendations (Ashing-Giwa et al., 2004). Asian American survivors reported that being informed about their illness and maintaining their treatment regimen was beneficial to their recovery from cancer (Ashing-Giwa et al., 2004). Similarly, Bache et al. found that some cancer survivors from IM populations reduced their anxiety by increasing their knowledge about cancer—although it was not known whether such knowledge was philosophically, socially or biomedically based (Bache et al., 2012).

DISCUSSION

The findings of this review highlight diversity in FCR across different IM populations, which might reflect measurement differences, as well as underlying group differences. While this review found some evidence that FCR might be less prevalence in IM populations that other populations, the lack of culturally-specific FCR measures could account for this apparent difference. The current findings also reveal variability in the factors associated with FCR across IM populations, as well as differences in the lived experience of FCR between different IM populations. Most notably, the findings of our review underscore the paucity of research investigating FCR in IM populations, particularly around the reasons for the varying experiences and outcomes of FCR in minority populations and the near absence of such research for Indigenous populations.

The quantitative synthesis found few consistencies across studies in terms of methods for assessing FCR. The most commonly used validated tool was the *Concerns About Recurrence Scale* (*CARS*) (Vickberg, 2003), whilst others used purpose-designed items. There have been no attempts to develop culturally appropriate measures or to validate existing measures of FCR for any IM populations in these studies. It is notable that the FCRI (Simard and Savard, 2009), which is considered one of the most psychometrically sound FCR measures and has been validated in several different languages (Thewes et al., 2012b), was not used in any of these studies.

The prevalence of FCR in IM populations across the studies ranged from 14 to 67%, which is lower than that reported more broadly (39–97%), but still suggests a substantial proportion of IM cancer survivors suffer from FCR (Simard et al., 2013). Direct comparisons of FCR levels between IM groups and dominant groups were limited, but there was some evidence suggesting higher FCR in Hispanic and lower FCR in African American people compaired with non-Hispanic whites. However, differences between IM and dominant groups were not consistent across studies, which could be due to the different tools used to measure FCR (and lack of validation in IM populations), different ways of grouping ethnicities and races for comparison, different countries and contexts, and different cancer types.

Few consistent relationships were evident between IM populations' FCR and their demographic or clinical characteristics, which is consistent with the FCR literature generally (Smith et al., 2018). There were, however, several psychological factors associated with FCR that were notably different for IM compared with dominant cancer survivors, including meaning and trigger factors. The sense of life meaning and purpose associated with the religious/spiritual beliefs held by many IM survivors may help them engage in more goal-directed action consistent with their values, enabling them to disengage from worries about recurrence (Fardell et al., 2016). Additionally, unmet needs and healthcare satisfaction were associated with FCR differently for some IM populations, as was the mediating effect of FCR on pain interference and fatigue on emotional well-being. It appears that the difficulties navigating the healthcare system and lower levels of healthcare satisfaction experienced more commonly by IM cancer survivors may be exacerbating their FCR, perhaps through the greater sense of general uncertainty that this creates (Fardell et al., 2016; Lebel et al., 2018). The identification of factors associated with FCR in these studies was limited by the fact that the majority of quantitative studies in this review were cross-sectional studies. While some of these were large, they often included only a small IM sub-sample.

The findings of the qualitative meta-synthesis suggest some notable differences in the experience of FCR between cancer survivors across IM groups. This finding is broadly consistent with current thinking that FCR might not be a unique/simple fear but rather a set of different fears, which are often experienced differently between people (Almeida et al., 2019). Despite the many differences, there were some noteworthy parallels in the experience of FCR among cancer survivors across IM populations.

Our qualitative findings suggest that FCR in cancer survivors from IM populations might be commonly moderated via spiritual and/or fatalistic worldviews regarding the outcomes of their cancer and their future. While the particular characteristics of such views differed across cultural groups and individuals, some commonality in the psychological strength and solace that they afforded IM cancer survivors was apparent. While this issue has received little research attention in other populations (Almeida et al., 2019), there is some evidence that a sense of connectedness, which has been characterized as spirituality, helps some breast cancer survivors to adjust and cope post-treatment (Shachar Siman-Tov, 2008). Additionally, our review findings suggest that there is a commonly held belief among IM cancer survivors that maintaining a positive attitude is an important factor in coping with FCR and in overcoming their cancer more generally. This type of thinking is sometimes called the *tyranny of positivity* as it is widely accepted that promoting unsupported beliefs regarding maintaining a positive outlook and avoiding stress will prevent or lessen a person's chances of serious illness are dangerous and likely lead to victim-blaming of those who are ill for not being positive enough (Aspinwall and Tedeschi, 2010). While staying positive may assist coping and reduce FCR for some IM cancer survivors, the promotion of positivity to IM survivors should be balanced with consideration of the potential negative effects of overemphasizing its import.

Our qualitative findings around the complexities associated with family and community support for cancer survivors from IM populations were notable. Strong family and community networks are commonly identified as important supports for cancer patients in many IM populations, the pressure and stigma that these networks can occasion for cancer survivors might sometimes serve to heighten FCR, as it prevents cancer survivors from expressing their fears in order to protect those around them (Soriano et al., 2018). Sharing concerns with social supports may help normalize concerns, while internalization of fears may lead to greater rumination and worsening of FCR.

Taken together, the results of our review revealed that FCR is experienced differently across IM populations, which is perhaps unsurprising, considering the diversity of cultural groups, geographic and social contexts and study methods, as well as the documented variability in FCR levels across other populations generally (Almeida et al., 2019). Spirituality, family and community support, and need for cancer information have such marked but variable roles in the experience of FCR for cancer survivors from different IM populations that approaches to reducing FCR must be flexible and adaptable enough to meet each survivor's individual circumstances and needs.

Our review highlights important considerations for future FCR research and practice addressing key priorities [e.g., better FCR detection/screening and more accessible FCR treatment models (Shaw et al., 2021)], to ensure that IM experiences and needs regarding FCR are accommodated. To enable FCR screening in IM populations, further work is needed to validate brief FCR measures in IM populations and adapt them where needed. To date, no interventions specifically targeting FCR in an IM population have been trialed (Tauber et al., 2019). To make FCR interventions accessible and engaging for IM populations it is essential that their diverse cultural beliefs and norms be considered. For instance, interventions incorporating elements of acceptance and commitment therapy may appeal more to IM populations where spiritual beliefs around acceptance are common. Given the importance of community support for many IM populations, but occasionally negative impact of community expectations, delivery of interventions focused on normalizing and coping with FCR, not just for survivors, but also their caregivers and communities, may be beneficial. Our findings make clear that effective measurement and treatment of FCR must take into account the individual and cultural circumstances of cancer survivors. While patient-reported outcome measures are commonly translated for culturally and linguistically diverse respondents, this approach fails to capture critical issues relevant to specific populations. Measures of FCR that include items developed by and with people from IM populations will offer the most effective means of identifying IM patients' concerns associated with this condition. Considering the variable experience of FCR across different IM populations, it is essential that researchers and clinicians partner with representatives of the specific IM communities they are serving, to ensure research and clinical practice is culturally responsive.

Limitations and Future Directions

There are methodological limitations of our review that must be noted. The heterogeneity in the study designs, samples, cancers and methods for assessing FCR across the studies included in this review only enable the aggregation of descriptive statistics. Further, limited evidence was available regarding factors associated with FCR and how these differed between IM and majority populations. This limits the strength of the evidence that can be presented and elicits more questions than answers. As this review aims to establish an evidence base within an under-researched area, this limitation is to be expected.

Most studies included in this review were conducted in the US, which highlights the need for greater research attention to this issue in other countries. The single study reporting on FCR for Indigenous people (also from the US), while offering a valuable insight into the condition for this particular group, cannot reflect the experience of survivors across different Indigenous populations. Given this limitation, it is tenuous to make any generalizations about FCR for other Indigenous populations.

This review is a first attempt to draw attention to the dearth of literature around FCR for cancer survivors from IM populations. The findings of this review are intended to identify the areas in greatest need of research attention. Most notable is the lack of research into FCR among Indigenous cancer survivors. The fact that all papers identified in our review were in Anglophile countries highlights the paucity of FCR research internationally. Fortunately, the number of articles published on FCR in IM

populations appears to be increasing, with an updated search in March 2021 finding seven further relavent papers. We hope this review will stimulate further research in the area and that an update of this review would incorporate many more papers. The development of culturally-appropriate measures of FCR, or the validation of existing measures of FCR for IM populations, would also aid further research. Ensuring that research in this space is conducted by and/or with researchers from IM populations is imperative.

Conclusions

This review highlights the potential impact of culture and context on FCR and reinforces the need for a culturally-specific lens to be used in consideration and measurement of this condition. The paucity of research investigating FCR among cancer survivors from Indigenous groups requires urgent attention.

DATA AVAILABILITY STATEMENT

This paper presents findings from our synthesis of previously reported findings. Each study included in our review is included in our reference list. For original data enquiries, please contact the corresponding authors of these papers.

AUTHOR CONTRIBUTIONS

KA, ABS, and AD participated in research design, writing of the paper, performance of the research, and data analysis. JS, LS, AG, SL, HD, LB, and PB participated in research design and writing of the paper. BT participated in writing of the paper and data analysis. GG participated in research design, writing of the paper, performance of the research, and data analysis. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.621850/full#supplementary-material

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Oncologists' Communication About Uncertain Information in Second Opinion Consultations: A Focused Qualitative Analysis

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Introduction: Uncertainty is omnipresent in cancer care, including the ambiguity of diagnostic tests, efficacy and side effects of treatments, and/or patients' long-term prognosis. During second opinion consultations, uncertainty may be particularly tangible: doubts and uncertainty may drive patients to seek more information and request a second opinion, whereas the second opinion in turn may also affect patients' level of uncertainty. Providers are tasked to clearly discuss all of these uncertainties with patients who may feel overwhelmed by it. The aim of this study was to explore how oncologists communicate about uncertainty during second opinion consultations in medical oncology.

Methods: We performed a secondary qualitative analysis of audio-recorded consultations collected in a prospective study among cancer patients ($N = 69$) who sought a second opinion in medical oncology. We purposively selected 12 audio-recorded second opinion consultations. Any communication about uncertainty by the oncologist was double coded by two researchers and an inductive analytic approach was chosen to allow for novel insights to arise.

Results: Seven approaches in which oncologists conveyed or addressed uncertainty were identified: (1) specifying the degree of uncertainty, (2) explaining reasons of uncertainty, (3) providing personalized estimates of uncertainty to patients, (4) downplaying or magnifying uncertainty, (5) reducing or counterbalancing uncertainty, and (6) providing support to facilitate patients in coping with uncertainty. Moreover, oncologists varied in their (7) choice of words/language to convey uncertainty (i.e., "I" vs. "we"; level of explicitness).

Discussion: This study identified various approaches of how oncologists communicated uncertain issues during second opinion consultations. These different approaches could affect patients' perception of uncertainty, emotions provoked by it, and possibly even patients' behavior. For example, by minimizing uncertainty, oncologists may (un)consciously steer patients toward specific medical decisions). Future research is needed to examine how these different ways of communicating about uncertainty

affect patients. This could also facilitate a discussion about the desirability of certain communication strategies. Eventually, practical and evidence-based guidance needs to be developed for clinicians to optimally inform patients about uncertain issues and support patients in dealing with these.

Keywords: communication, second opinion, oncology, uncertainty, physician-patient relations, patient-centered communication

INTRODUCTION

Cancer treatment has become increasingly complex, involving various treatment modalities that affect tumor growth and side effects in a multitude of ways, making it difficult to predict outcomes/prognosis for individual patients. The meaning and implication of diagnostic tests may also be ambiguous, further adding to high levels of uncertainty in oncology (Parascandola et al., 2002; Politi et al., 2007; Han et al., 2011, 2019; Politi and Street, 2011; Simpkin and Armstrong, 2019). For oncologists it can be complex and demanding to discuss these various uncertainties. Yet, fully informing patients and involving them in medical decision-making is becoming the norm in healthcare and is considered to be a physician's ethical duty (Han et al., 2011, 2019; Balogh et al., 2015; Bhise et al., 2018; Blanch-Hartigan et al., 2019; Simpkin and Armstrong, 2019). Moreover, managing uncertainty is considered one of the key components of patient-centered communication (Epstein and Street, 2007). When consulting with cancer patients who seek a second opinion (SO), providers need to deal with additional uncertainties, given potential discrepancies with the first opinion and/or potential new treatment options. Thus, discussing uncertainty in the setting of oncological SO consultations can be particularly challenging.

Cancer patients themselves have indicated wanting to be fully informed about diagnosis, prognosis, treatment, and side effects, even if the information contains uncertainties (Blanchard et al., 1988; Quill, 2000; Jenkins et al., 2001; Cox et al., 2006; Murtagh and Thorns, 2006; Hancock et al., 2007; Parker et al., 2007; Evans et al., 2009; Ahalt et al., 2012). At the same time, some patients may feel burdened and emotionally overwhelmed by uncertainty (Arora, 2003; Politi et al., 2007; Han, 2013). For example, patients have been found to interpret uncertain information (e.g., risk estimates) too pessimistically (Han, 2013). Awareness of uncertainty may also increase their cancer-related worries and fears, and may rush them into rapid treatment initiation (Denberg et al., 2006; Mishel et al., 2009; Han et al., 2011). Moreover, uncertainty may be an important motivator for cancer patients to seek a second opinion (SO), in an effort to reduce uncertainty (Kurian et al., 2017; Shmueli et al., 2017; Blanch-Hartigan et al., 2019). An oncological SO may indeed reduce uncertainty, for example if it confirms the first opinion. In contrast, a SO may increase uncertainty if it yields additional or even contradicting new information/options (Hillen et al., 2017a,c).

How oncologists discuss uncertain information may be crucial for patients' ability to cope with uncertainty, as indicated in previous research. For example, both in and outside the oncology setting, patients were less trusting of physicians and less satisfied if they expressed uncertainty, as it reduced patients' perceived competence of the physician (Parascandola et al., 2002; Blanch et al., 2009; Cousin et al., 2013). In contrast, other studies reported improved patient satisfaction if physicians expressed uncertainty (Gordon et al., 2000). These contradictory effects may partially be explained by the finding that physicians who expressed more uncertainty also used more positive talk, relationship building, and provided more information to patients (Gordon et al., 2000; Blanch-Hartigan et al., 2019). In other words, *how* uncertain information is communicated may affect patients' perceptions, decisions, and ultimately their well-being.

Practical advice for clinicians on how to communicate uncertainty has been put forth, but empirical evidence to substantiate it is lacking (Han et al., 2019; Simpkin and Armstrong, 2019). Moreover, there is currently limited observational evidence on how healthcare providers communicate about uncertain issues with patients, particularly in highly uncertain settings. Therefore, this study aimed to provide an overview of approaches that oncologists use to discuss uncertain information during SO consultations in medical oncology, which are characterized by high levels of uncertainty. This overview will enable future research to assess the effects of different communication approaches on patients, and develop evidence-based recommendations for communicating uncertain information with patients.

MATERIALS AND METHODS

We present a secondary analysis of data collected in a prospective longitudinal study on communication during SO consultations, the SO-COM study (Lehmann et al., 2020). Data were collected between 2018 and 2019 and the larger study included self-report and observed behavioral data coding of audio-recorded SO consultations. Medical oncologists at two Dutch tertiary referral centers were invited to participate and signed informed consent forms. Patients (treated anywhere in the Netherlands) who were scheduled for a SO with participating oncologists were contacted by the hospitals to introduce the SO-COM study. Interested patients were subsequently called by the research team, and after verbally consenting they were sent informed consent forms and information to complete surveys. SO consultations were audio-recorded by dedicated research staff (not present during the SO). Confidentiality was guaranteed at all times and all procedures were approved by our local ethical committee (NL63087.018.17).

Sample Selection

Eligible participants for the SO-COM study were adult cancer patients with any type of solid tumor, and who were proficient in the Dutch language (Lehmann et al., 2020). A total of $N = 69$ SOs were audio-recorded and for the current qualitative analysis, a purposive selection of audio-recorded consultations was used.

To create maximum variation in communication about uncertainty, we deliberately selected SO consultations based on two characteristics expected to be strongly associated with such communication: (1) the degree of patient-centered communication (PCC) by the oncologists and (2) oncologists' gender. First, PCC can be defined as physician behaviors which enable patients to express their perspectives on illness, treatment and health-related behavior, including symptoms, concerns and expectations (page 662; Zandbelt et al., 2005). Because "uncertainty management" is a key component of PCC (Epstein and Street, 2007), we hypothesized that oncologists' use of PCC would be associated with their communication about uncertainty. Therefore, we purposively selected the $n = 6$ highest and $n = 6$ lowest PCC-scoring consultations for qualitative analysis ($N = 12$). As part of the larger SO-COM study, PCC scores had been rated by trained coders, based on three items of the Euro-communication scale (Mead and Bower, 2000), focusing on whether the oncologists encouraged patients to express themselves, listened, and involved them in any decisions. Second, previous findings suggest that physician's sex may determine how they communicate uncertainty. For example, females may convey uncertainty more apologetically than males (Schumann and Ross, 2010) and female physicians used more non-verbal indicators of uncertainty than male physicians (Blanch et al., 2009). Therefore, we expected that purposive selection for physician sex would enhance variability in our data. We ensured equal representation of both sexes ($n = 6$ each), and selected the $n = 3$ lowest scoring (on PCC) SOs by male and $n = 3$ lowest scoring by female oncologists, and did the same for the highest scoring consultations (i.e., $n = 3$ male, $n = 3$ female). We further increased variability by selecting only one consultation per oncologist (i.e., 12 out of 24 different oncologists were included; see Results section). We closely monitored whether data saturation was achieved after analysis of our initial selection of 12 consultations. We concluded this was the case, as indicated by the two final consultations not yielding any significant new information (Francis et al., 2010).

Qualitative Data Analysis

The 12 purposively selected audio-recorded SOs were transcribed verbatim. Any consultation segments involving talk about the patient's medical history, personal life, or scheduled follow-up appointments, as well as small talk about non-medical issues (e.g., the weather) were first checked. If they did not contain any talk about uncertainty by the consulting oncologist (e.g., treatment options, side-effects, risks, recurrence), these segments were not transcribed and excluded from the analysis. All coding was performed using MAXQDA 2020 (VERBI Software, 2019). An inductive constant comparative approach was chosen to ensure that analysis was data-driven rather than informed by existing literature or a theoretical framework (Strauss, 1987; Boeije, 2002). We coded both verbal expressions of uncertainty that were made by the oncologist spontaneously, as well as those in response to the patient's expression of uncertainty. Communication about uncertainty was defined according to Han et al.'s (2011) definition of uncertainty as any talk by the oncologist indicating his/her subjective awareness of ignorance (p.830). Hence, this included any uncertainty about the likelihood of a future event (e.g., risks of side-effects), uncertainty due to limited available information (e.g., inconsistent test results) or due to complexity (e.g., the interplay between a multitude of causal factors) (Han et al., 2011). All 12 SOs were double-coded by two coders independently (JLS and MH) and subsequently discussed together with VL to resolve issues and constantly adjust the coding scheme. This procedure of researcher triangulation was employed to ensure that multiple perspectives and possible interpretations of the data were incorporated. All codes were clustered into overarching themes using thematic analysis through continuous discussions within the research team. After initial themes were identified, potentially disconfirming evidence was sought in our data and not identified, thus further enhancing the validity of our results (Creswell and Miller, 2000).

RESULTS

Patient Sample

Cancer patients in the 12 SO consultations were on average 53 years old (range 28-85), $n = 7$ were female (58.3%) and $n = 5$ male (43.7%). They had varying educational backgrounds, including high-level education (i.e., college/university, $n = 5$; 41.7%), middle (i.e., secondary vocational training, $n = 4$; 33.3%), and lower education (i.e., high school or low vocational training, $n = 3$; 25%). The majority of patients were in an advanced stage of their disease ($n = 10$; 83.3%) and the most prevalent diagnoses were breast cancer ($n = 4$; 33.3%) and gastrointestinal tumors ($n = 4$; 33.3%). Duration of the selected SO consultations ranged between 27 and 61 min ($M = 41$ min).

Communication About Uncertainty

From the qualitative data analysis, seven different approaches to communicating with patients about uncertainty emerged (see **Supplementary Table 1**): (1) specifying the degree of uncertainty, (2) explaining reasons of uncertainty, and (3) providing personalized estimates of uncertainty to patients. Moreover, it appeared that oncologists pursued certain goals by (4) downplaying or magnifying uncertainty, (5) reducing or counterbalancing uncertainty, or (6) providing support to facilitate patients in coping with uncertainty. Finally, we found variation in oncologists' (7) choice of words/language to convey uncertainty. Although these approaches are presented separately, some may directly follow each other, while specific overlap between them was present in the consultations. For example, specific use of language to express uncertainty (strategy 7) co-occurred with all other strategies.

Discussions of uncertainty were either initiated by the oncologist or in response to patients' expressions of uncertainty, such as questions about life expectancy. Discussions of uncertainty were not limited to specific parts of the consultations,

but were present throughout all phases of the consultations. Moreover, we did not identify a consistent "style" of discussing uncertainty by individual oncologists: oncologists varied widely in their use of the identified approaches, both between and within consultations. For example, within one consultation an oncologist could very explicitly express uncertainty about one topic, yet implicitly discuss another uncertain topic.

Specifying the Degree of Uncertainty

Oncologists varied in the degree of specifying uncertain information, particularly when talking about prognostic matters, such as the risk of side effects or potential success rates of certain treatments. On one end of the spectrum, they would remain rather vague, by using generic words (e.g., *rather, much, many patients*) to describe how uncertain a situation or risk was. In contrast, oncologists would occasionally provide additional quantification, for example by providing qualitative utterances along with specific estimates. For example, "*The [chemotherapy] works for approximately 20%, that is one in five patients, and we still can't predict precisely for whom it will work.*" (male oncologist, male patient)

We did not identify certain patterns among oncologists' use of either strategy. However, overall it appeared that oncologists refrained from specifying the degree of uncertainty and remained rather vague in case of highly unpredictable outcomes, such as in the following example.

> *Everything changed after the tumor responded well [to therapy]. Thus, the chance of recurrence at the start [of treatment] is very different from the chance after having had surgery. That is something to keep in mind: the chance [of recurrence] became a lot smaller.* (male oncologist, female patient).

Explaining Reasons of Uncertainty

Oncologists would sometimes explain underlying causes that made a situation uncertain or explain why they could not provide more precise estimates. Thereby, oncologists would explain the boundaries of medical testing, therapies, or science in general to emphasize that some uncertainty was unavoidable and omnipresent in cancer care.

> *We never know in advance whether a cancer cell is left behind somewhere outside the surgical area. You can't see that, you only know once the disease recurs and realize that you weren't able to remove everything, because something started growing again. We have no method, no test to measure that beforehand.* (female oncologist, female patient)

In other situations, oncologists openly admitted and attributed their uncertainty to the limits of their own personal expertise.

> ***Patient:*** *What do you think of their [other hospital's] advice to radiate 15 times?*
> ***Oncologist:*** *Well, I'm not a radiologist, so I should stay within my own field of expertise. [. . .] But I will discuss it with the radiologist in this hospital, because I don't think they would give that much radiation, but I'm not sure.* (female oncologist, female patient).

Providing Personalized Estimates of Uncertainty to Patients

Oncologists would sometimes provide a personalized estimate of uncertain information based on patients' individual characteristics, even when the evidence was scarce (first example below). Communicating tailored information may increase patients' understanding about their own disease and treatment trajectory. Oncologists appeared to use such strategies in an effort to reduce patients' feelings of uncertainty (second example below).

> *In your case, where the disease returned in your abdomen after surgery, we don't know how much added value [another] surgery would have over this [other treatment]. Based on data from the past, we still think it would improve your chances somewhat. (2018)*

> *We could give you only the first line of chemotherapy. [. . .] Or we could consider to give you the second line of treatment simultaneously [. . .]. Reasons to consider that option are as follows: the [metastases] are growing pretty fast, secondly: you're young, you're fit, and yes I think you could handle it. [. . .] So that could be an option which you have to think about yourself, because it does mean that you will have more side effects from the treatment. But it also means that you will get a more powerful treatment all at once.* (female oncologist, male patient).

Downplaying or Magnifying Uncertainty

In some instances, oncologists appeared to purposively downplay or magnify uncertain information. In doing so, they seemingly attempted to persuade patients, steer their perceptions, or possibly even influence their behavior in a certain direction. For example, if oncologists clearly had a certain treatment preference, they would magnify uncertainty regarding options they did not prefer and/or downplay uncertainty related to their preferred option. The following example illustrates a case where the oncologist is transparent about her treatment preference and only highlights the positive side of this option, while ignoring possible drawbacks and thereby downplaying the risk of side effects.

> *I would encourage you to choose this treatment. It's very different from what you had before. In general, it's well-tolerated. People work with it, do their daily activities. You won't experience hair loss. So that's great. You won't feel nauseous, people travel around the world with it really.* (female oncologist, female patient)

In other cases, oncologists would magnify uncertainty about what it would mean to participate in a clinical trial, and did not mention any potential advantages. They appeared to do so in an effort to steer the patient away from this option (first example below), and/or to temper patients' (unrealistic) hope (second example below).

> *[The trial is] basically a lottery, so half [of the patients] get a pill with nothing in it and the other half gets [medication name]. But because it's a lottery, there's a 50% chance that you get nothing. So I think that's a disadvantage in itself. And the second [disadvantage] is that we don't really know if [the medication] is as good as the other treatment. Whereas, we do know about that [other] treatment*

that it cuts your risk for a relapse in half. (female oncologist, female patient)

I think it's complex. I certainly want to brainstorm with you, but I don't want to create false expectations. When I consider this trial, you may actually be too fragile to participate. In such a trial we give medication to patients, that have not been given to people before. (male oncologist, male patient)

Due to our study setting in SO consultations, uncertainty about whether or not it was possible for patients to switch hospitals was present occasionally. Oncologists would sometimes magnify uncertain factors associated with a treatment transfer (e.g., waiting times) in an apparent effort to discourage patients from pursuing this option.

If you say "I don't care, I still want that treatment here," then of course I will consult with my surgeons about when I could get it done here. However, an important factor is also the waiting time, to be honest. In the end, if I were you, I would choose to have surgery in the place with the first availability. You said they could do it July 19th already? I'm afraid it would be August here. (female oncologist, female patient).

Reducing or Counterbalancing Uncertainty

In response to patients' spontaneous questions or expressions of uncertainty, oncologists would sometimes react by trying to reduce the emotional burden of uncertainty. For example, they would directly provide information in an effort to reassure patients of certain aspects.

Patient: *Doesn't the risk [of recurrence] increase if I stop this [hormone] therapy, or can it lead to a reversed effect?*
Oncologist: *That the 3 years [of hormonal therapy] will [backfire]? No. Actually, the 3 years [of therapy that you had] are in your pocket, and no one can take that from you.* (female oncologist, female patient)

Alternatively, oncologists would offer specific ideas and explain actions that could be taken to actively reduce patients' uncertainty. For example, the oncologist below proposes a plan to reduce uncertainty that the patient expressed about the origin of his fatigue as a side effect of his current treatment.

[…] My advice would be to stop [current treatment]. See what happens to your energy levels. Make a new scan after 2 months, and if something turns out to be active, you have two options: either try out this treatment, or in the most extreme case you could start that other treatment. (male oncologist, male patient)

In other instances, oncologists would introduce uncertainty themselves, but counterbalance it right away by emphasizing aspects that *were* certain. Such counterbalancing appeared to be done in an effort to minimize the psychological burden of uncertainty on patients.

It may still be possible that no cells traveled from the left [breast] to other parts of the body, that is possible. It is also possible that they did, but that those cells cannot grow. We don't know, and we don't have good tests to find that out. What we do know is that in large groups of women, who had this follow-up treatment, the chance of recurrence is two times smaller than for those without this follow-up treatment. (female oncologist, female patient).

Providing Support to Facilitate Patients in Coping With Uncertainty

Oncologists occasionally explicitly tried to support patients emotionally in coping with uncertainty that patients either brought up during the consultation or had beforehand. One way of offering support was through directly asking about or addressing patients' and/or their relatives' worries and emotional reactions to uncertainty.

I've only known you for a bit, but I'm trying to discover why you're anxious, and at the same time to help you. What are you worried about? I can imagine about a lot, but I wanted to ask it as an open question. (male oncologist, wife of male patient)

In other instances, oncologists normalized worries and uncertainty by comparing an individual patient's situation with other patients and/or by placing it into a broader picture.

Patient: *Are there other women who, like me, have stopped or want to stop [adjuvant hormonal treatment]? And how are they doing after a couple of years?*
Oncologist: *Yes, many. That is always good to remember: you're definitely not the only one. I think that 40% of women don't complete the 5 years [of treatment]. Simply because it can cause some pretty bad side effects. And it's certainly true that the moment you use it less [frequently than intended], you have less effect, and then the cancer can recur. But there are also lots of these women for whom the cancer does not recur.* (male oncologist, female patient)

Moreover, oncologists provided support by discussing different scenarios that could be useful to the patient in the future. In the following example, the oncologist tries to offer a roadmap to help the patient cope with uncertainty and/or decisions in the future.

When I look at [your] file, and my colleague did as well, we would have started the treatment in the same way. […] But we can speculate together about "what if." What if at some point, for example, this treatment no longer works, what would be your options by then? There is not just one option, there are multiple, which I am going to discuss with you now. (female oncologist, female patient).

Variations in the Choice of Words/Language to Convey Uncertainty

Finally, throughout all consultations we identified variation in language use or choice of words by oncologists when communicating about uncertainty. These variations particularly included oncologists' level of explicitness and use of personal pronouns. Oncologists would alternate between different degrees of explicitness and pronouns between and even within consultations.

Level of Explicitness

We identified strong variation in how explicitly oncologists expressed uncertainty. On one end of the continuum, oncologists could be very explicit in their expression of uncertainty, by directly stating something was unknown. On the other end, very implicit expressions of uncertainty were used, entailing subtle vocabulary, such as *maybe, might* or *hope,* to express uncertainty. Yet, even within the same consultation, an oncologist would sometimes express uncertainty explicitly and sometimes implicitly. Overall, it appeared that oncologists used more explicit expressions when they wanted to emphasize unavoidable uncertainty.

> *That [side effects at end of life] varies widely. I mean, anything can happen. It is impossible to predict how things will turn out. You can't really make a meaningful statement. That is of no use to you. I just don't know. We cannot predict how it will go for you. I just don't have that, I just don't know.* (male oncologist, female patient)

In contrast, oncologists appeared to use more implicit language particularly when discussing uncertain aspects of which they wanted patients not to become overly conscious or unnecessarily worried about. For example, the following quote includes several implicit expressions of uncertainty (i.e., *hope, less*):

> *You hope that because of that [treatment], the swelling decreases a bit and that you suffer less as a result. And eventually, you hope that the chemotherapy will do its job and that [the tumor] will shrink and that you will experience less pain as a result.* (female oncologist, male patient).

Use of Personal Pronouns

Oncologists also varied in using the first person pronoun "I" to express uncertainty and the plural pronoun "we." Again, this tended to differ both across and within consultations, as oncologists constantly switched between these personal pronouns. It appeared that sometimes more complex and unpredictable information was conveyed using "we" (as in "the medical community") instead of "I," possibly acknowledging that the uncertainty is inevitable and not due to personal incompetence.

> *As doctors we are unable to predict life expectancies. Especially if a patient is sitting in front of you in a stable condition. If people are in hospital and are very sick, you could say: this will take a few days. That we can do. But everything in between, we cannot say.* (male oncologist, female patient).

DISCUSSION

This study explored how uncertainty is communicated by medical oncologists during second opinion (SO) consultations. By virtue, SOs entail a high level of uncertainty and we found a wide variety of approaches that oncologists used to communicate uncertain information. These communication approaches entailed the extent to which oncologists specified, downplayed or magnified uncertain information, and the amount of support they offered to patients while discussing uncertainty, as well as the language they used. Such ways of communicating about uncertainty may influence patients' perception of uncertainty, emotional response to it, and/or subsequent behaviors, which warrants further research.

Previous research indicated that communication about uncertainty may have contradictory effects on patients. Some results suggested that physicians' expressions of uncertainty led to enhanced patient satisfaction, whereas other studies found reduced trust and satisfaction (Parascandola et al., 2002; Denberg et al., 2006; Blanch et al., 2009; Mishel et al., 2009; Han et al., 2011; Cousin et al., 2013). Importantly, these studies focused on the presence vs. absence of communicating about uncertainty, and their opposing findings were proposed to result from varying manners of communication (Gordon et al., 2000), but which manners remained unknown. Thus, insight into approaches that clinicians use to discuss uncertainty was still lacking. This study identified seven approaches to discussing uncertain information with patients, which could have profound effects on patients. For example, by explicitly expressing uncertainty and clarifying the reasons for being uncertain, oncologists may facilitate a shared understanding of why uncertainty exists (Blanch et al., 2009). This experience of "shared uncertainty"—where uncertainty resides in the minds of both the physician and the patient—may reassure patients and enhance their trust (Hillen et al., 2017a). In contrast, oncologists may remain implicit and/or omit specific uncertain information in an attempt to protect patients from experiencing strong emotions by not overly emphasizing uncertainty and potentially worrying them (Stortenbeker et al., 2019). However, this could cause patients to be oblivious to the severity of their situation and unable to take well-informed decisions (Politi et al., 2011). In fact, previous research indicated that oncologists often remained vague about patients' prognosis, which may hinder not only patients' understanding of it, but also a proper discussion of treatment goals (Chou et al., 2017). Our analysis showed various approaches, in which oncologists would express uncertainty explicitly, but still provide patients with some guidance in dealing with it. For example, oncologists would sketch different scenarios for future treatment options, sometimes tailored to the patient specifically. This may be particularly helpful in the setting of providing a SO, because many patients are motivated to seek a SO due to a perceived lack of personalized information from their treating oncologist [i.e., the "first opinion" (Goldman et al., 2009)]. By utilizing some of the communication approaches identified in the present analysis, oncologists could ensure that patients are aware of existing and unavoidable uncertainties, while reducing the emotional impact on patients (Brookes-Howell, 2006; Goldman et al., 2009; Santhosh et al., 2019).

Oncologists are tasked with providing a delicate balance between openly informing patients about uncertainty while protecting them against harmful effects caused by uncertainty. This trade-off is different for each patient, and may be strongly affected by their individual coping styles and overall ability to deal with uncertainty (Hillen et al., 2017b). For example, patients with a more active problem-solving style were found to appreciate oncologists who explicitly express uncertainty, whereas patients with an avoidant coping style preferred expressions of non-disclosure (Mori et al., 2019). Thus,

providers may try to gauge patients' individual preferences, beliefs, and coping styles regarding uncertainty. They could do so by checking patients' existing knowledge, beliefs and feelings about uncertainty, and by exploring how much (more) patients want to hear (Seely, 2013; Pino and Parry, 2019). This would enable providers to tailor their level of explicitness and detail when conveying uncertain information to individual patients. Importantly, oncologists in our study personalized risk estimated to individual patients, but we did not observe that they checked and adjusted to whether and which amount of (uncertain) information the respective patient may have wanted to receive.

This study identified several ways in which oncologists may have (un)consciously steered patients' perception of uncertainty, and possibly their subsequent emotions and behavior. For example, we found that oncologists sometimes downplayed or magnified uncertain information in an apparent attempt to influence patients' treatment choice, particularly regarding participation in clinical trials. The option of participating in a trial is often a motivator for cancer patients to seek a SO, which may be why we observed this approach regularly in this setting. However, previous research also found oncologists in regular breast cancer care to use similar implicit persuasive behaviors to convince patients of the treatment option they believed was in the patient's best interest (Engelhardt et al., 2016). While oncologists may indeed have patients' best interest in mind when trying to persuade a patient, it could also have harmful effects. For example, downplaying certain treatment side-effects in an effort to steer patients toward a treatment option could bias patients' perceptions, undermine their autonomy, and/or leave them unable to make a well-informed decision between treatment options. Oncologists' opinions can carry a lot of weight and may impede patients in forming their own opinion (Engelhardt et al., 2018). More subtly, even smaller word choices, like using the pronoun "we" instead of "I" may affect patients' perception of uncertainty. The phrase "we don't know," referring to the whole medical or research community, carries much weight and may lead patients to believe that uncertainty is inevitable, compared to when the oncologist admits his/her own lack of knowledge by using "I" (Juanchich et al., 2017). Oncologists may not deliberately choose these pronouns each time, but patients can take such linguistic markers into consideration when interpreting uncertain information (Juanchich et al., 2017). Oncologists may need to be extra aware of the different effects their words can have on patients, and of the benefits, drawbacks, and ethical dilemmas in relation to steering patients' perception of uncertainty.

This study further identified that oncologists sometimes actively provided emotional support to patients or counterbalanced uncertainty, seemingly in an effort to help patients deal with uncertainty. Considering the extensive length of these SO consultations (i.e., $M = 41$ min), oncologists have ample opportunities and time to use such "supportive" strategies compared to regular consultations, which are often characterized by time constraints. Nevertheless, such strategies were only observed occasionally in the analyzed consultations. It is recommended that physicians provide emotional support during the complete care process (Armstrong, 2018; Simpkin and Armstrong, 2019), and patients reported to desire this commitment and engagement from their providers (Srivastava, 2011). Although SOs usually involve only one or two consultations, oncologists providing SO consultations could still provide support by actively asking patients how the discussed uncertainty affects them, or by explaining the optimal next steps for patients (Santhosh et al., 2019). For example, oncologists in this study directly asked about patients' emotional reaction to uncertainty, normalized such reactions, or discussed different scenarios that might benefit the patient in the future. Two previously conducted observational studies found that both patients and caregivers highly valued it when the physician emphasized which elements of an uncertain situation they *could* control (Cagle et al., 2016; Olson et al., 2018). Thus, discussing different potential scenarios may benefit cancer patients' emotional responses to uncertainty as well. Moreover, we found that oncologists counterbalanced uncertain with certain information, which they appeared to do in an effort to reduce the psychological burden of uncertainty on patients. A similar strategy was also identified in regular oncological consultations, where oncologists were observed to sometimes alternate uncertain news with more reassuring news (Alby et al., 2017). Overall, such strategies to support patients in dealing with uncertainty are encouraged to be used, and may benefit patients and their families directly.

Although this study offers valuable, in-depth insights into how oncologists communicate uncertain information in SO consultations, some limitations need to be considered. First, our analysis explicitly focused on identifying communicative approaches by oncologists, and did not incorporate patients' responses. Future studies may assess the differential effects of different approaches to convey uncertainty on patients. Ideally, such research would use video instead of audio recordings, to also allow capturing patients' non-verbal responses. Thereby, analyses of patients' direct responses should be complemented with self-report data to provide comprehensive insight into patients' emotions and perceptions. A second limitation is that our analysis focused on SOs in medical oncology, which are particularly long consultations that can entail a high degree of uncertainty. Therefore, the variety of approaches to communicating uncertainty may have been particularly rich due to these specific characteristics, but it remains unclear to what extent our findings can be extrapolated to "regular" oncological or medical consultations. Nevertheless, several "supportive" approaches to communicating uncertainty illustrated here could be useful to providers in various setting. Third, our sample size is limited, but included a purposively selected sample of female and male oncologists with high and low PCC scores to increase variability and ecological validity. We also invested extensive time to double-code and discuss all consultations to minimize potential coder bias and maximize the reliability of our identified communication approaches. Fourth, our audio-recordings did not allow for coding non-verbal behavior, whereas this may also play a relevant role in patient-provider communication (Ogden et al., 2002). Finally, we want to highlight that certain intentions of oncologists (e.g., persuasion/steering) were inferred on our behalf as we judged them as apparent in the consultations. These may not always have been the conscious intentions of

oncologists and we were unable to verify oncologists' intention. Yet, and irrespective of whether intended or not, patients and families may also pick up on such communication behaviors, which could be experienced positively by some (e.g., appreciating a clear preference) and negatively by others (e.g., feeling one's autonomy compromised). It remains to be tested how such communicative behaviors affect patients' perceptions of the oncologist and consultation.

To conclude, this study contributes to the limited empirical evidence by identifying different approaches to how oncologists communicate uncertain information during SOs. We found variation in the degree of specifying/magnifying uncertainty, offering support in dealing with uncertainty, and language use between and within consultations. These different approaches to communication may affect patients' perception of uncertainty, the emotions provoked by it, and possibly even their behavior. In clinical practice, oncologists need to be conscious of the potential effects of their communication on patients, and use communication approaches purposively and carefully. More research is needed to examine how various ways of communicating about uncertainty affect patients. Such evidence could also facilitate a discussion about the desirability of certain communication strategies. Eventually, practical guidance should be developed for clinicians to optimally inform patients about uncertain issues and support them in dealing with it.

DATA AVAILABILITY STATEMENT

The data analyzed in this study are subject to the following licenses/restrictions: Anonymized parts of the dataset may be viewed upon request. Requests to access these datasets should be directed to Marij A. Hillen, m.a.hillen@amsterdamumc.nl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee Academic Medical Center Amsterdam, The Netherlands (NL63087.018.17). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JLS was involved in conceptualization, methodology, data preparation, conducting the analysis, project administration, and writing (original draft, review, and editing). VL was involved in conceptualization, methodology, conducting and supervising the analysis, project administration, and writing (original draft, review, and editing). JMS was involved in conceptualization, providing resources, and writing (review and editing). AS was involved in conceptualization and writing (review and editing). ES was involved in conceptualization, methodology, supervising the analysis, and writing (review and editing). MH was involved in funding acquisition, conceptualization, methodology, conducting and supervising the analysis, data curation, project administration, supervision, and writing (original draft, review, and editing). All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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"Will It Affect Our Chances of Having Children?" and Feeling "Like a Ticking Bomb" —The Fertility Concerns and Fears of Cancer Progression and Recurrence in Cancer Treatment Decision-Making Among Young Women Diagnosed With Gynaecological or Breast Cancer

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Objective: Cancer treatment decision making process is particularly fraught with challenges for young women because the treatment can affect their reproductive potential. Among many factors affecting the process, fears of cancer progression and recurrence can also be important psychological factors. Our aim is to apply Common-Sense Model and shared decision-making model to explore experiences of treatment decision-making women of reproductive age who were diagnosed with gynaecological or breast cancer and the influence of fertility issues and fears of cancer progression and recurrence.

Method: We conducted telephone interviews with 24 women who were diagnosed with gynaecological or breast cancer aged 18–45, who finished active treatment within 5 years prior to study enrolment and had no known evidence of cancer recurrence at the time of participation. They were recruited from three NHS oncology clinics in Scotland and online outlets of cancer charities and support organisations. We analysed the data using Braun and Clarke's thematic analysis method as it allows for both inductive and deductive analyses.

Results: We identified five main themes pertaining to treatment-related decision-making experiences and fertility issues and fear of progression and recurrence: *Becoming aware of infertility as a potential consequence of cancer treatment; Balancing-prioritising cancer and fertility; Decisions about treatments; Evaluation of treatment decisions;* and *The consequences of treatments*. Sub-themes have also been reported. Different factors such as whether the cancer is breast or gynaecological, physicians' willingness of

discussing fertility, influence of others in decision-making, childbearing and relationship status as well as fear of cancer recurrence emerged as important.

Conclusion: The importance of physicians directly addressing fertility preservation in the process of treatment decision-making and not treating it as an "add-on" was evident. Satisfaction with treatment decisions depended on both the quality of the process of decision making and its outcome. Fear of recurrence was present in different parts of the adaptation process from illness perceptions to post-treatment evaluation of decisions. Both Common-Sense Model and shared decision-making model were helpful in understanding and explaining young women's experience of treatment decision-making and fertility concerns.

Keywords: fear of cancer recurrence, fear of cancer progression, fertility, treatment decision-making, common-sense model, breast cancer, gynaecological cancer, shared decision-making model

INTRODUCTION

The incidence of cancer in the United Kingdom has been increasing since the early 1990s (Cancer Research UK, 2020a). Notably among adults aged 25–49, cancer rates between 1993 and 2017 have increased by 21% (Cancer Research UK, 2020a). In this cohort, women were significantly more likely than men to be diagnosed with cancer, and between 2015 and 2017, four out of 10 were diagnosed with breast cancer (Cancer Research UK, 2020a). Cervical, ovarian, and endometrial cancer accounted for 8, 5.2, and 2.6% of all cancers in this group, respectively (Cancer Research UK, 2020a,b,c). Overall, 60% of women aged 25–49 diagnosed with cancer in the UK between 2015 and 2017 faced a disease that could have a considerable impact on their reproductive potential, either because of the disease itself or because of potential consequences of treatment.

The impact of cancer treatments on fertility contributes to poorer psychological well-being including higher levels of distress (Sobota and Ozakinci, 2018; Logan et al., 2019) and decreased quality of life (Sobota and Ozakinci, 2014) among young women with cancer. Oncofertility has emerged as a novel field to address fertility needs of young people with cancer. Research has shown the beneficial effect of discussing fertility preservation as part of oncology consultation (Ussher et al., 2018) and providing young women with decision aids to facilitate decision making around fertility preservation (Wang et al., 2019). While fertility preservation is increasingly available to cancer patients, with national guidelines acknowledging its importance and encouraging to provide the service (National Institute for Health Care Excellence, 2017; Ethics Committee of the American Society for Reproductive Medicine, 2018; Oktay et al., 2018), multiple barriers to accessing fertility preservation including age, relationship status, timing of decisions, and institutional factors still exist (Crawshaw et al., 2009; Lee et al., 2011; Niemasik et al., 2012; Yee et al., 2012; Hershberger et al., 2013a,b; Kirkman et al., 2013; Ruddy et al., 2013; Snyder and Tate, 2013; Corney and Swinglehurst, 2014; Corney et al., 2014; Garvelink et al., 2015).

Another important factor contributing to decisions about fertility preservation is fear of cancer progression and recurrence (Gorman et al., 2011; Lee et al., 2011; Hershberger et al., 2013b; Kirkman et al., 2013; Snyder and Tate, 2013; Garvelink et al., 2015). Fear of cancer progression and recurrence is the "fear, worry or concern relating to the possibility that cancer will come back or progress" (Lebel et al., 2016; p. 3,265). It can affect patients' treatment choices and in a study among breast cancer patients, Stafford et al. (1998) have demonstrated that fear of cancer recurrence was one of the main reasons women tended to choose more radical treatment.

Considering the complexity of cancer treatment-related decision making, we conducted a qualitative study exploring the experiences of treatment decision-making of young women diagnosed with breast or gynaecological cancer and the influence of fertility issues and fears of cancer recurrence and progression on these decisions.

We chose to apply two theoretical models—the Common-Sense Model (CSM) (Leventhal et al., 2004) and shared decision-making model (Elwyn et al., 2012) to study the decision-making processes. In this article, we are reporting on our findings relating to the importance of fertility, fear that cancer may recur or progress, and illness perceptions as defined by CSM on treatment-related decision making, however the broader project has findings that relate to other aspects of the CSM and decision-making process.

The CSM is a model of self-regulation widely used to study illness perceptions and management. The model asserts that in response to a health threat, the individual forms both cognitive representations (illness perceptions) and emotional representations (e.g., fear and worry) of the threat. There are five dimensions to illness perceptions: identity (the label for the threat and the symptoms), perceived cause, perceived timeline, perceived consequences, and perceived curability/controllability of the threat. Both of the representations mean that the individual goes through a process of developing coping procedures which are then evaluated in an appraisal process of whether they worked or not. It has been shown that patients' treatment decision-making processes are frequently driven by their own lay perceptions of illness and treatment (Charles et al., 1998).

Shared decision-making model has also relevance in the context of young women's experience of treatment decision-making and consideration to be given to fertility preservation. The involvement in the process of treatment decision-making can be an empowering experience for the patient (Whitney et al., 2004) and another strategy to cope with cancer. What is crucial in the shared decision-making model is the bidirectional exchange of information whereby the physician shares his or her medical knowledge as well as the opinions about different treatment modalities with the patient and the patient in turn provides the information about his or her values and preferences regarding treatments as well as sharing the pre-existing knowledge he or she has about his or her condition. Once the information exchange process has taken place, both the patient and the physician enter the deliberation stage where information is discussed in an interactional manner. In this process of negotiation, a decision regarding treatment is reached and implemented (Charles et al., 1999).

MATERIALS AND METHODS

Design

Eligible women were invited to participate in an interview and were approached at the time of their outpatient clinic appointment in three UK-based hospitals (Edinburgh, Dundee, Kirkcaldy) or via online outlets of UK-based cancer charities (between October 2014 and May 2015). Based on Cancer Research UK and Office of National Statistics data (Local Government Association, 2015; Cancer Research UK, 2020a,b,c), the cumulative incidence of breast, ovarian, cervical, and womb cancer was ∼97 in 100,000 women aged 25–49 in 2015. With numbers of potentially eligible women being small we anticipated we may encounter difficulties recruiting for the study, therefore we used this mixed approach strategy (NHS and cancer support organisations) to (1) reach a wider patient population and maximise recruitment potential, and (2) attempt to recruit as diverse and representative a sample of women as possible.

Women who consented to take part were interviewed over the phone. Braun and Clarke thematic analysis 2006 was used to explore women's experiences of cancer treatment-related decision-making.

This study has been reported in accordance with the COREQ criteria (Tong et al., 2007) (see **Appendix 1**). See the interview guide in **Appendix 2**.

Participants

Women meeting the following inclusion criteria were invited to participate:

- received a diagnosis of breast or gynaecological cancer between the ages of 18–45 years old;
- were menstruating at the time of diagnosis;
- had chemotherapy (neo-adjuvant or adjuvant) as part of their treatment if they were diagnosed with breast cancer;
- finished active treatment (with the exception of endocrine therapy for breast cancer) within 5 years prior to study enrolment;
- had no known evidence of cancer recurrence at the time of participation;
- spoke English or Polish.

We chose to focus on breast and gynaecological cancers for several reasons. First, these are some of the most common cancer diagnoses among women aged 25 to 49 (Cancer Research UK, 2020a,b,c). Second, their treatments can either impair fertility, or make one's fertility status post-treatment uncertain. As the literature seems to suggest that it is women's subjective perception of, rather than the objective fertility status that affect's women's well-being (Sobota and Ozakinci, 2014), we decided to include women who had any treatment with the potential to affect fertility. This included women who had chemotherapy for breast cancer as it is associated with uncertainty regarding individual fertility which may be difficult to predict (Wallace et al., 2005; Knobf, 2006; Duffy and Allen, 2009); women with early stage cervical cancer who underwent a cone biopsy or trachelectomy because while both treatments preserve fertility, they can be associated with adverse obstetric outcomes such as second trimester miscarriage (with a rate nearly twice as high as for the general population), and pre-term birth (Tirlapur et al., 2017). Also, according to the recent review, up to 61% of women who had a trachelectomy need artificial reproductive technologies to conceive (Tirlapur et al., 2017) which can be associated with uncertainty about one's fertility. Both atypical hyperplasia and early stage endometrial cancer (often grouped together), can be treated with progestogens, however, fertility outcomes are poorer than in the general population (Wei et al., 2017). The gold standard treatment for endometrial cancer—hysterectomy and bilateral salpingo-oophorectomy (Amant et al., 2018), will have the same impact on women's fertility as cytoreductive surgery for ovarian cancer, which is by far the most common surgical treatment for ovarian cancer due to the delay in its diagnosis (Cancer Research UK, 2017).

Although childbearing status affects the degree of importance women attach to fertility when diagnosed with cancer (Gorman et al., 2010; Canada and Schover, 2012; Ruddy et al., 2014) we did not include it in our inclusion and exclusion criteria and decided to recruit both women who did and those who did not have children prior to diagnosis. This was to achieve a wide variety of experiences and data saturation.

Participants were provided with a standard research pack including a cover letter, a participant information sheet, an opt-in form (not for participants recruited online), two copies of the consent form, an interview schedule, a debriefing form and two stamped-addressed envelopes. Women who opted in to take part were then contacted via phone to fill out the consent form and agree the interview date.

To recruit for the study, we relied on convenience sampling. This was to decrease the pressure to participate in the project investigating sensitive topics. Nonetheless, our sampling strategy yielded participants with a wide range of characteristics in terms of cancer diagnoses and treatments, age, relationship and childbearing status, and the use of fertility preservation. While the inclusion criteria indicate that Polish-speaking women would be included in the study, these participants were not actively

sought. Although two were approached for participation, they decided not to participate.

Overall, 56 women expressed interest in taking part in the study and 24 were recruited (10 via clinics and 14 via online outlets; participation rate = 43%). Thirty-two women who initially expressed interest in participating, but did not make further contact with the research team were not re-approached, hence the reasons for non-participation remain unknown.

Data Collection

All women were interviewed by the same researcher (AS) by phone. Interview by phone was selected primarily to facilitate data collection from participants who were recruited via online outlets and thus could potentially live in any part of the UK but they also possess other merits important for this study. This mode of interviewing allows the participant to remain anonymous, permits privacy, diminishes social pressure, and thus enables participants to disclose sensitive or intimate information more freely (Novick, 2008).

The interviews were guided by an interview schedule (see **Appendix 2**). Each interview started with an opening question asking the participant to describe the circumstances of her cancer diagnosis and the treatment process. Each interview ended with an open-ended question and this is where participants had a chance to speak about other issues they faced because of cancer diagnosis at a young age. Answers yielded additional themes that were not directly related to the research questions yet enriched the understanding of the participants' cancer experiences. Participants were asked to provide basic socio-demographic details (current age, country of origin, relationship status, childbearing status, monthly income before tax, and the highest education level) and disease characteristics (type of cancer, stage of cancer at diagnosis, types of cancer treatment received and date of diagnosis) if these were not mentioned during the interview. The interviews lasted on average 55 min (range = 22–121 min).

All interviews were digitally recorded and transcribed verbatim. Identifying details were removed from the transcripts and each transcript was assigned a numeric code. Notes taken during the interviews and reflections written after the interviews were assigned the same numeric code to link all the relevant participant data.

Analysis

The data were analysed using the principles of thematic analysis outlined by Braun and Clarke (2006) which was conceived as a standalone data analysis method for "identifying, analysing, and reporting patterns (themes) within data" (p. 79). The analysis followed six steps of: (1) Familiarisation with data, (2) Generation of initial codes, (3) Searching for themes, (4) Reviewing themes, (5) Defining and naming themes, and (6) Producing the report.

One of the important advantages of thematic analysis is its flexibility. As opposed to other methods of qualitative analysis it is not tied to any particular epistemological or theoretical approach (Braun and Clarke, 2006). It can, therefore, be adapted to the researcher's needs in terms of epistemological or theoretical framework. Another benefit of thematic analysis lies in the fact that, while many qualitative methods are purely inductive, thematic analysis can be used in both an inductive and deductive manner. A method that would allow for a deductive approach and application of specific theoretical frameworks to the data was essential for this study and thematic analysis fulfilled these criteria. The CSM was chosen from the outset and guided both the design and the analysis of the data while shared decision-making model was selected to guide the data analysis.

Notably, Braun and Clarke's thematic analysis can be used as a realist method focusing on peoples' personal experiences and the meanings they attach to their lived realities, a constructionist approach where these meanings and experiences are considered an effect of discourses operating in society, or finally a contextualist approach which sits between realism and constructionism, and acknowledges that meanings and experiences, while grounded in one's reality are also a factor of broader societal and cultural constructs (Braun and Clarke, 2006).

In the inductive stage of our data analysis, we assumed a realist approach. As a paradigm it is often used to "discover knowledge" and purports that peoples' accounts reflect reality (Madill et al., 2000). By adopting it we aimed to tap into our participants' realities and "discover [categories/codes] within the data" (Madill et al., 2000). Therefore, the derived codes reflected our participants' understanding of their experiences and decision-making processes during cancer treatment in the wider context of preserving fertility and fear of cancer recurrence. At the end of this step, these initial codes were categorised into patterns, and patterns were then used as a foundation to which we applied our theoretical lens.

In the deductive stage of the analysis, we applied theoretical frameworks rooted in cognitive psychology of health and illness (the CSM) and health-related decision making (the shared decision-making model) to the patterned codes whereby moving our analysis into the contextualist territory. Contextualism postulates that all human experience is context specific and subjective, and that phenomena can be interpreted in multiple ways (King and Brooks, 2016). These interpretations depend on the specific context of research and the stance of the researcher. As such, based on the aforementioned theories, we derived the final themes from the codes. This approach positions our analysis within contextual thematic analysis spectrum. This type of analysis has been successfully used within (Fielden et al., 2011; Faric et al., 2019) as well as outside of health research (Goldingay et al., 2018).

From the practical perspective, the interview transcripts were first read and reread for a thorough familiarisation with the data. Next, all the transcripts were uploaded to QSR International's NVivo 10 Software (NVivo qualitative data analysis Software, 2012) and the first cycle coding method—the descriptive coding—was applied to the data. Descriptive coding uses short phrases to summarise topics reoccurring in the data (Saldaña, 2015). Once all the data were coded, the second cycle coding method—the pattern coding—was applied. The pattern coding allows for grouping of the descriptive codes and making sense of the relationships among them (Saldaña, 2015). Through further reading and rereading of the interviews, secondary codes were

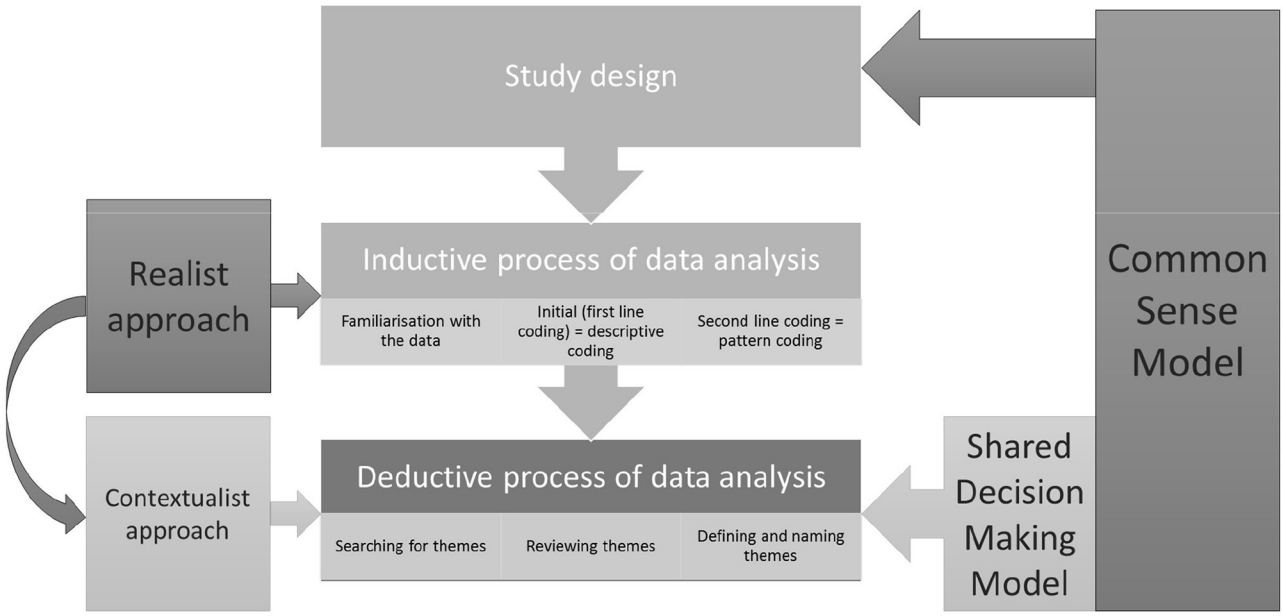

FIGURE 1 | Data analysis process.

refined to better reflect the data. Up to this point the data analysis was conducted by one researcher (AS). In the next step, the map of secondary codes was applied to three out of 24 interviews by the second researcher (GO). Where discrepancies in coding between the researchers occurred, these were discussed until a consensus was reached and codes were clarified and reorganised to better fit the data.

The analysis up to this point was carried out in an inductive manner. However, since this study focused particularly on the experiences of treatment-related decision-making and was driven by two theoretical models, once the secondary codes were obtained, the rest of the analysis was conducted in deductive manner.

This type of analysis, as suggested by Braun and Clarke (2006), focuses on answering a particular research question and exploring the theory, rather than on providing the description of the whole dataset (understood as all the data collected for the particular project). This approach results in a more detailed analysis of certain aspect of the dataset—in this case the data related to treatment decision-making in the context of fears of cancer progression and recurrence, and fertility. Therefore, at this point in analysis, all the codes were reviewed again and those that did not contribute directly to answering any of the research questions were moved to a separate folder. The remaining codes were iteratively reread and arranged according to the main concepts involved in the CSM and shared decision-making model. Codes categorised as belonging to the same concepts within the theoretical models were then conceptualised into internally homogenous and externally heterogeneous themes. These themes were subsequently discussed within the research team to assure the credibility and the rigour of the analysis.

In summary, we initially approached data analysis from a realist perspective—looking for participants literal experience of cancer-treatment decision making, and moved into the contextualist territory—applying the theoretical lens of CSM and shared decision making model to contextualise the data. At the same time, our analysis progressed from an inductive to a deductive one. The CSM informed the study design (interview schedule), and both inductive and to a greater extent deductive data analysis, while the shared decision-making model was applied to the deductive part of the data analysis process. These processes are represented in **Figure 1**.

Reflexivity Statement

Qualitative inquiry involves a degree of subjectivity and a neutral observer as such does not exist (Malterud, 2001), it is therefore important to outline the researcher's own effect on the process of data collection and analysis.

The data for this study was collected and primarily analysed by AS. This constituted part of her PhD project and all participants were made aware of this. AS approached this study bringing in both a personal and a professional perspective, the latter including that of a junior doctor, psychologist, and researcher. They have all contributed to how this project was conducted and are discussed below.

Personally, AS acknowledges that her attitude toward motherhood is rather ambivalent and she is unsure whether she wishes to ever have children. However, she believes that motherhood may be an important experience and one that, if missed, may cause the feeling of regret. With this in mind, AS found herself emotionally affected by participants' storeys. With some women being very close in age to AS, it proved difficult for her to completely distance herself from the extremely

complex decisions these women had to make. Perhaps some of these emotions were projected on the way the interviews were conducted and the data subsequently analysed.

Professionally, AS' perspective of a junior doctor often prevailed over her identity as a psychologist and she approached this research project with a practical focus in mind trying to pinpoint issues that could be changed and improved rather than to purely look for psychological constructs in the data. Theoretical frameworks were used while working with the data and this was to facilitate future practical application of the findings.

Finally, this was AS' first qualitative project. The little experience she had before possibly influenced the way interviews were conducted, particularly in the early stages of the study. Someone with more experience in qualitative research, and specifically in research into sensitive topics might have handled the interviews differently. AS felt she needed some time to gain confidence in her own skills and feel comfortable probing participants about more personal issues.

Ethics Approval

The ethical approval for the project was sought and received from the East of Scotland Research Ethics Service (REC1) (13/ES/0129) as well as from the School Ethics Committee at the School of Medicine, University of St Andrews (MD10852).

RESULTS

Participants

Participant characteristics are presented in **Table 1**.

TABLE 1 | Participants' characteristics.

Characteristic	Number (%)
Current Age (Years)	
≤30	1 (4%)
31–35	11 (46%)
36–40	6 (25%)
41–45	6 (25%)
Cancer Diagnosis	
Breast	11 (46%)
Cervical	6 (21%)
Ovarian	4 (17%)
Uterine	4 (17%)
Time Since Diagnosis (Years)	
0–2	16 (67%)
3–5	8 (33%)
Partnership Status At Diagnosis	
Partnered	18 (75%)
Unpartnered	6 (25%)
Partnership status at interview	
Partnered	19 (79%)
Unpartnered	5 (21%)
Education	
Less than university education	5 (21%)
At least some university education	19 (79%)
First Language	
English	23 (96%)
Other	1 (4%)
Fertility Preservation	
Yes	8 (33%)
Artificial reproductive technologies	4 (17%)
Gonadotropin-releasing hormone agonist injections	2 (8%)
Trachelectomy	2 (8%)
No	16 (67%)
Childbearing Status	
No children	15 (63%)
Child(ren) before diagnosis but not after diagnosis	7 (29%)
No child(ren) before but child(ren) after diagnosis	1 (4%)
Child(ren) before and after diagnosis	1 (4%)

Themes

We identified five main themes pertaining to treatment-related decision-making experiences and fear of progression and recurrence among young women diagnosed with breast or gynaecological cancer: *Becoming aware of infertility as a potential consequence of cancer treatment; Balancing-prioritising cancer and fertility; Decisions about treatments; Evaluation of treatment decisions;* and *The consequences of treatments*. Subthemes within the themes are described in detail. See **Figure S1** for the visual representation of the main themes.

The themes were first organised around the four components of the CSM: "appraisal of health threat," "illness perceptions," "strategies to cope with illness," and "appraisal of coping strategies."

The appraisal of health threat and illness perceptions are represented throughout the following themes: *Becoming aware of infertility as a potential consequence of cancer treatment;* and *Balancing-prioritising cancer and fertility*. Treatment decision-making processes were conceptualised as a strategy to cope with the illness and are represented in the theme *Decisions about treatments*. The subthemes that were identified within this theme reflect the concepts of the shared decision-making model as it pertains to the clinical settings. Finally, the themes *Evaluation of treatment decisions* and *The consequences of treatments* represent the last component of the CSM—the appraisal of coping strategies.

There were elements of "illness perceptions" in *The consequences of treatments* theme as well. Traditionally, in the CSM, the information gained through the appraisal process feeds back into the coping strategies and allows for their modification as appropriate to a specific situation. In the case of treatment decisions, however, that would be impossible since once treatments had been administered one cannot take back one's decision (e.g., to pursue fertility preservation or not) and opt for a different regimen. One can only cope with the consequences of these decisions made at the time under difficult circumstances. The last theme describes these consequences as well as women's attempts to cope with them in a situation where the change of treatment decisions is impossible.

Becoming Aware of Infertility as a Potential Consequence of Cancer Treatment

Often women described experiencing a shock upon receiving a cancer diagnosis at a young age. There was a disconnect between the diagnosis and what they perceived themselves to be: a healthy young woman. In addition to transitioning from being healthy to a cancer patient, women also became aware of what this meant for their fertility as a consequence of this disease.

Whether they were diagnosed with gynaecological or breast cancer, most of the women perceived treatments having a potential to be detrimental for their fertility. While for some that was not an issue, others wanted to know what could possibly be done to spare or preserve their fertility. Two scenarios became apparent: fertility discussions were either part of the consultation and initiated by the physicians or they needed to be broached by the women themselves.

For some women, a member of their clinical team brought up the topic of fertility in a consultation. Most women appreciated this, irrespective of whether they were interested in preserving their fertility. They welcomed the opportunity to receive the relevant information and be able to consider what it meant for them. The consequences of those decisions for cancer growth were highlighted by their clinicians.

> *I mean the gynaecologist I had was fantastic. Honestly, absolutely fantastic. And he talked through everything. He also said that if I didn't want to go through a hysterectomy just now he could monitor it over a period of time, they could try and give me … oestrogen I think it was and to see if I would … if I could conceive over a period of time and they would help me … But he then told me the consequences of doing that, which is the cancer could grow quicker, you know it might be that I could conceive but I couldn't carry a child, loads of different things. He explained everything fully, gave me the pros and cons and then you know, sent me away to think about it.*

P06, womb cancer diagnosed at 35, no children

When fertility discussions constituted a standard part of a consultation, women had a chance to express their preferences without having to broach the topic themselves. However, that was not always the case. When fertility was not a standard part of the consultation, the onus of initiating the discussion was on women or their relatives.

> *So, when I was* first *diagnosed my husband just happened to … say … "Will it affect our chances of having children?" and I'm so glad he thought of asking that 'cause I … I just wouldn't have asked it. 'Cause … 'cause obviously I had lots of other things going on in my head.*

P15, breast cancer diagnosed at 32, no children

On occasion, women had to assume the responsibility for getting informed regarding fertility preservation. They had to be the ones to start the conversation and at times even force their consultants to engage in the discussion about the fertility aspect of their treatment.

> *Yeah, it was Dr. [name] who was my* first *oncologist [inaudible], but that was only like I said after I … stood up and said "Is there anything we could do to preserve the fertility?" […] He wasn't willing to discuss it. It was only when I approached it … and then he said he would go away and think about it and look at my case. And it was only when he looked at my case notes and realised I was young and not like 50—40 and was only … like a … grade I and grade Ia that he decided to send me for the clinical trial.*

P02, womb cancer diagnosed at 32, no children

In those cases, women often felt that fertility was not important to their physicians and was treated as an "*add-on*" or something extra and not part of standard care. Some even questioned whether fertility would have been discussed at all had they not broached the subject themselves.

Balancing—Prioritising Cancer and Fertility

Faced with a life-threatening illness, women weighed the importance of fertility against the desire to survive the disease. Through this process they formulated their priorities which were used to guide their treatment decisions.

Women underwent a process of "balancing-prioritising cancer and fertility" in their decisions. Regardless of how important fertility was at the time of diagnosis, most women reported that they wanted to give themselves the best chance at surviving the cancer and prevent any future recurrence.

> *Because I was worried maybe if it was gonna be growing to something … more serious. And I was worried it was gonna turn into cancer, so I just wanted everything cleared out.*

P22, borderline ovarian tumour diagnosed at 39, no children

Some of the participants were prepared to undergo the most aggressive treatments to ensure that no stray cancer cells were left behind even if that meant having to deal with the treatment side-effects and increasing the risk of losing fertility to cancer.

Women who already had children, whether they considered their family complete or not, felt their existing children and getting better for them were their primary concern. Even if fertility preservation was presented as an option, they felt they could not afford an attempt at the potential cost of worsening their prognosis.

> *We were very much of the mind, that we have to try our best to … for me to stay alive for my son, for my child and, you know, then not … so that kind of meant that … we said that preserving fertility just wasn't an opt … you know, getting … doing an IVF effectively wasn't an option.*

P10, breast cancer diagnosed at 32, 1 child before and 1 child after diagnosis

Women who did not have children were the ones for whom finding this balance between preserving their fertility and the desire to survive cancer was the most difficult since the two were often valued as equally important. However, even this group of participants admitted that it would only make sense to preserve

fertility if they were at some point well-enough to actually become pregnant and have a child.

> *And he's [the oncologist]… he's always said, which I agree, it's a balance of … it's alright having a baby but you've got to be there, to be around to bring it up (laughter). … It's quite a stark way of saying it.*

P01, breast cancer diagnosed at 32, no children

The balancing-prioritising process certainly differed between women who considered fertility important at the time of their cancer diagnosis and those who did not. However, within the group of women for whom fertility was important, this process also differed between women diagnosed with breast vs. gynaecological cancers. The difference appeared to be related to the distinct consequences that treatment decisions had for the two groups.

For women with breast cancer, receiving chemotherapy did not automatically mean infertility but meant that their post-cancer fertility status would be uncertain. Although chemotherapy could hasten the menopause, if their menstrual cycles returned after chemotherapy, they could still conceive naturally. Therefore, even without fertility preservation, there was hope that their fertility would remain unaffected by cancer treatments. Additionally, in the case of breast cancer, fertility preservation was a process separate from cancer treatments. Women could choose to undergo fertility preservation as an additional procedure which involved a separate decision-making process to the one about cancer treatments. Although potentially not neutral to their cancer prognosis, for women with breast cancer, fertility preservation was not directly related to their cancer treatments.

For women with gynaecological cancers, on the other hand, the two were intrinsically intertwined and therefore the desire to preserve fertility and potentially forgo some of the cancer treatments could have a much bigger impact on their prognosis and survival. There was also no element of uncertainty—once they had radical treatment, their chance of carrying a pregnancy was taken away permanently.

These differences could potentially explain why women diagnosed with gynaecological cancers were much more hesitant while progressing through the balancing-prioritising process. Despite these difficulties however, most of them did choose to go forward with treatments, even at the cost of fertility.

Only one woman positioned herself in opposition to other participants and clearly stated that her priority was her fertility and save it if at all possible, even at the cost of her longer-term prognosis. After weighing the pros and cons she eventually decided to opt in for a radical trachelectomy instead of a hysterectomy.

> *The long-term survival wasn't … my longer-term prognosis didn't really ever enter my mind. I would say it did for my family, it did for my partner. I think it may have been there vaguely in the background for me but all I wanted to do was that my fertility wasn't taken away and that my desire to carry a child wasn't taken away. And I didn't want it taken away by cancer if I could at all help it.*

P13, cervical cancer diagnosed at 31, no children.

Decisions About Treatments

Although women might have prioritised their fertility and survival in different ways, there were similarities in terms of the processes that all of them went through. Also, even though some of the decisions needed to be made at the time of diagnosis and others later, the processes involved in both were very much alike. Henceforth, these main processes are presented for all the participants and all the decisions together under the following subthemes: *Informing vs. involving others;* and *Alignment of treatment preferences between women and their physicians, and its consequences.* Where differences occurred between treatment decisions and decisions relating specifically to fertility preservation or between decisions made at the time of diagnosis and those made later, these are presented within the subthemes. Factors specific to fertility preservation and interrupting the tamoxifen treatment are summarised separately under the subtheme *Specific considerations related to immediate fertility preservation and tamoxifen.*

Informing vs. Involving Others

Physicians were automatically involved in the decision-making process. Irrespective of the type of treatment women were referring to, the vast majority considered their consultants' opinion to be the most important factor that swayed or even dictated their treatment-related decisions entirely. Yet, there were also other people such as partners and parents whose opinions women took into consideration while making decisions.

There was a clear difference between the degree of involvement of the significant others in the decisions that concerned only cancer treatments and the ones that could also potentially impact on fertility. Treatment decisions, in general, were made between the patient and her clinical team. Women informed their parents and partners about what was going to happen rather than sought their advice. Although family members lent their support to patients' decisions, they rarely played an active role.

> *I come from a medical family so of course I spoke to family members and discussed what my consultants were talking to me about […] but I was solely guided by my consultants.*

P14, breast cancer diagnosed at 27, no children

On the other hand, decisions that involved fertility were more often discussed with the significant others. Partnered women often described these decisions as joint decisions. Since fertility was something that couples negotiated between themselves, women considered it important for their partners to partake in decision-making which could potentially affect that aspect of their relationship. Negotiating when to stop the tamoxifen in order to conceive was also described as a joint decision. Partnered women wanted to establish their priorities as a couple

and make a decision in line with those priorities, regardless of its final outcome.

> *We sort of decided between us that, yes, we did want a family, we wanted that chance. So rather than it being sort of completely taken away from us … at least we'd have the opportunity.*

P15, breast cancer diagnosed at 33, no children

With respect to interrupting the tamoxifen, women specifically emphasised the importance of partner's involvement because of the consequences (e.g., increased risk of cancer recurrence) that such a decision could carry.

> *I think he [partner] would have been happy for me to just go and make a decision but I so much felt like I needed that to be a joint decision. If … the shit hits the fan basically … I couldn't ever have him saying "You kind of … you wanted this, you went off and did it" kind of … to me that wasn't … I wasn't comfortable with that … it had to be what we kind of all wanted.*

P10, breast cancer diagnosed at 32, 1 child before and 1 child after diagnosis

Women who were in the early stages of their relationships felt that cancer brought forward the discussions and decisions about having children together with their new partners and they did not necessarily feel comfortable with that. Yet, they still did prefer to make decisions about treatments potentially affecting fertility jointly with their partners.

> *Not only was it kind of absorbing the fact that I had cancer, it was also putting my partner and I in a position of, well we haven't really spoken about this because we haven't been together a great deal of time … to suddenly, "do we want to have children?" I know I did and we had spoken about it briefly but not to the point of "well am I gonna lose my fertility or keep my fertility?." So, we did have some time to think about it. And it just … to me it was always everything that I wanted to do, to keep fertility. Yeah and we agreed that that would be what we would do.*

P13, cervical cancer diagnosed at 31, no children

Single women often consulted with their parents and sought their advice regarding the treatment options.

> *I spoke to my dad and he obviously then … said to me … he said "I'd rather you still be with me that having kids. I want you to be healthy." And he kind of reassured me … and said to me, you know "Have the full operation and you can always adopt, you can always do fostering and stuff like that."*

P22, borderline ovarian tumour diagnosed at 39, no children.

Alignment of Treatment Preferences Between Women and Their Physicians, and Its Consequences

With respect to fertility, women engaged in the prioritising-balancing process described in the *Balancing-prioritising cancer and fertility* theme. This process enabled women to clarify the value fertility had for them at the time of diagnosis and incorporate it into the decision-making processes about treatments involving the fertility aspect accordingly. Women's preferences, however, were not sufficient to guide treatment decisions. The priority their doctors gave to fertility and patients' childbearing desires equally played a role in the treatment decision-making process. The extent to which the priorities of these two parties involved in the process were in line with each other affected the decision-making.

For women for whom fertility was not an issue, the situation was fairly straightforward since neither they nor their physicians had to factor it into the treatment plan. For women who wished to consider fertility while making treatment decisions and who were under the care of physicians who acknowledged their priorities, the situation was similar and boiled down to discussing the available options and drawing the treatment plan around them.

The situation became more complicated for women who considered fertility while making decisions and who were under the care of the physicians whose priorities differed from theirs. Some women clearly considered preserving their fertility equally important to treating cancer whereas physicians treated it as an "*add-on*." This created a confusing situation for women who, on the one hand, wanted to follow their consultants' lead and accept the treatments that were suggested to them and on the other, prioritised their fertility differently from their physicians. While many women in this situation ended up accepting treatments suggested by their physicians, some went against the advice they received or consulted another physician.

> *So within the* first *week of me being diagnosed I was referred by my oncologist to a gynaecologist at the hospital. And I went to see him and it was, it was quite an awful meeting really because he basically said he wasn't happy doing anything with me because I had oestrogen-positive breast cancer … which, it was just a really awkward meeting, my partner was there with me and we thought it felt like a bit, like we're being interviewed about our relationship and he was very down on it all and said that he would not do anything at all until after I had chemo and I was sort of trying to explain "Well, I've been told that actually … the chemo is going to affect my eggs and my ovaries possibly and my fertility so shouldn't we try and do it before and …" And anyway he just wasn't, he wasn't interested and wasn't going to help me at all. […] A friend of the family went to a consultant [fertility specialist] so my partner and me went to see him, I think this was like the day before my surgery. So it was all like a real mad rush to get it done. And he said "Yeah don't worry at all." He was brilliant actually. He'd said that he'd treated other women with tumours and there was a pill I could take during the IVF process that would keep my oestrogen levels down and he was just really good and really sympathetic and just sort of gelled with him very quickly.*

P01, breast cancer diagnosed at 32, no children

On the other side of the spectrum were women who opted in for the most aggressive treatments. Some of them saw this as the only way to restore their quality of life which deteriorated because of the symptoms they had prior to diagnosis. However, the most frequent reason for wanting radical treatments was the fear that

by doing less, some of the cancer cells would be left behind and the cancer could eventually recur.

> *If I hadn't had chemotherapy … there would be a higher risk of recurrence so, I think everything that was thrown at me and everything that was on offer … it can only be positive because you want to throw everything at it.*

P07, breast cancer diagnosed at 39, no children

The physicians acquiesced to patients' preferences regarding treatments as long as they thought these were reasonable. Women's preferences and their consideration were therefore tempered by their physicians' perception of need for treatment.

Specific Considerations Related to Immediate Fertility Preservation and Tamoxifen

In addition to above influences, there were certain factors women spoke about that related specifically to fertility-related decisions. These included institutional issues, the timing of the initial treatment decisions, and the length of time participants needed to be on the tamoxifen before they could try for a pregnancy.

The availability or services and efficiency of the referral pathways acted as facilitators to receiving fertility sparing or preserving treatment. However, not all women who wanted to take advantage of these services were easily able to do that. Even though assisted conception services for cancer patients are available under the health care scheme, some patients could not get an appointment on time or were disqualified from their use based on age or type of diagnosis. Some of these patients decided to organise a consultation privately. The lack of experience in navigating through the private healthcare system while trying to set up a fertility appointment added to their burden at the time of diagnosis. Cost of the procedures was another issue they had to resolve before pursuing fertility preservation privately.

> *So I did feel like in those 3–4 weeks of … from being diagnosed I was going pretty much every day to see an oncologist, or for a blood test or for a different scan or … that every day was taken up with … preparing for my operation and lots of medical appointments … and then on top of that I'm having, I was having to research and try and find somebody to help me [with fertility]. And that was very, very difficult and exhausting I suppose. […] sat trying to get funding, or sat trying to get an appointment for this and that. So, the whole process could have been very much made a lot easier for me and if there was … someone to go to.*

P01, breast cancer diagnosed at 32, no children

Timing of the decisions and haste with which they needed to be made constituted further challenges. Women's impression was that cancer treatment was needed urgently. They explained how their physicians stressed the importance of them getting their treatments as soon as possible and without undue delays. Although time pressure did not necessarily affect the decisions for women with gynaecological cancers who could opt for fertility sparing surgery (e. g., trachelectomy), it was a barrier for women who wanted to take advantage of the assisted conception services.

> *When we saw doctor [name], on that* first *time she said, "Look, we can … I can put you forward for egg collection and IVF but that's gonna be another month to 6–8 weeks that I don't particularly want to wait based on your diagnosis. So unless you are absolutely dead set on that, my advice is that we start treatment straight away."*

P16, breast cancer diagnosed at 32, 1 child before cancer

Although in a different way, time also played a role in decisions regarding the tamoxifen. Women's biggest issue when considering whether to stop the tamoxifen was the length of time they should take it for before they could safely interrupt it to conceive. Neither the research, nor the opinions of the doctors were clear with respect to that which made women uncertain as to what the best course of action would be.

> *There hasn't been that much that I can find on the Internet, and articles, medical articles about the risks of re-occurrence with coming off tamoxifen before you are advised to and trying for a baby and the effects of hormones on you etc. So, trying to find that information, reading it through and then sort of making that informed decision is important to both of us.*

P01, breast cancer diagnosed at 32, no children.

Evaluation of Treatment Decisions

The over-riding feeling among women irrespective of the type of decisions they made was that these decisions were right for their particular circumstances. Most women who preserved fertility were grateful they were able to do this. Women found comfort in that their reproductive choices were still theirs as opposed to being entirely out of their hand because of cancer treatments. They also expressed relief at avoiding the regret that they could have potentially felt, had they not acted to preserve fertility. All these women, however, felt well and as far as they were concerned their actions to preserve fertility were not in any way detrimental to their health. Only one woman who had recurrence scares subsequently to her treatment questioned her decision about trying to preserve her fertility at all cost.

> *And it was … almost now made me feel like it was the right decision back then in July and August to have the trachelectomy but with complications that have come up and scares that have come up from them, I now feel a bit like a ticking time bomb in that it was right then but I have elements of doubt as to whether perhaps a hysterectomy may have been … a better option?*

P13, cervical cancer diagnosed at 31, no children

Similar to women who preserved fertility, those who did not also felt they made the right decisions regarding their course of treatment. Some found making those decisions easy. Others, despite finding them less straightforward felt that at least they were in control of what was happening to them. One woman, however, felt that she made a mistake by deciding to undergo the treatment whereby her fertility was permanently lost.

I wish I hadn't done it [had hysterectomy]. It was the biggest mistake in my life.

P05, womb cancer diagnosed at 31, 1 child before cancer.

The Consequences of Treatments

Irrespective of whether women decided to preserve their fertility throughout cancer treatments, their treatment decisions inevitably had consequences for their post-cancer lives. Fertility-related consequences of cancer treatments are discussed in the subtheme *Cancer-related factors controlling reproductive choices.*

Cancer-Related Factors Controlling Reproductive Choices

Cancer diagnosis and treatments, irrespective of whether the participant decided to preserve fertility, changed the context of women's reproductive decisions. It took away this spontaneity and brought about additional cancer-related external and internal factors that constrained the realisation of women's fertility-related plans. The external factors included dependence on healthcare professionals and other people to help women either conceive or become a parent through alternative means. Fear of recurrence was an internal factor that acted as a barrier to having children.

Women who pursued artificial reproductive technologies observed that their embryos could only be released to them after a certain amount of time had passed since their treatment.

I don't think you're allowed to have those embryos released prior to 2 years after treatment.

P07, breast cancer diagnosed at 39, no children

Although they were in a position to make a decision whether to use them, they were not in control of when that would happen. Not only were the healthcare professionals involved in deciding when to release the embryos to the patients but also in carrying out the procedure of the embryo transfer which meant that their assistance was crucial for women.

I think fertility is the big one *because it's just taken away the … the sort of … I suppose being able to spontaneously think about having a family. That has to be now more of a … more steps in place before being able to do that.*

P15, breast cancer diagnosed at 33, no children

Since women's decisions regarding the length of time they should be on the tamoxifen were also highly influenced by the advice they were given by their physicians, the time of their eventual pregnancy was again only partially within their control.

Once we'd started the IVF cycle and I went back to see my surgeon, at the time he said that I'd need chemo, he then said "Well the evidence shows that tamoxifen is more effective for 10 years" so in my mind then I was thinking "Well we're [inaudible] eggs collected we have, you know, we're gonna have embryos but I'm not gonna be able to do anything with them because in 10 years" time I'll be, you know, 44." Originally when we started thinking about doing IVF cycle … and it would have been 5 years on tamoxifen, that kind of would have been fine cause I'd be sort of 39ish so …

P15, breast cancer diagnosed at 33, no children

Women who underwent trachelectomy for cervical cancer noted multiple possible pregnancy complications that awaited them should they decide to conceive. They were aware that they would require help from the obstetric services to carry the pregnancy and deliver safely. Although these women preserved the ultimate choice of whether to have children, at the same time cancer diagnosis deprived them of the full control over their reproductive decisions. The help of the healthcare professionals became an inherent part of their reproductive choices.

Additionally, women who received the trachelectomy felt as if by the fact that they were offered this procedure, they were also somehow expected to eventually conceive. They were either given a specific timeframe within which they should try for a child or reminded by their physicians that the procedure was done in view of them getting pregnant at some point.

On more than one *occasion by more than* one *person it's been suggested that this operation was given to me almost, and in fact* one *professional used that expression … it was given to me … because of the situation I was in, you know, 31 and childless kind of thing. And … they almost, I kind of … I get the impression I'm meant to be grateful for that. I mean, don't get me wrong, I'm grateful for the fact that and the end of the day it saved my life and it was the best option. But it's almost like by not having a child yet I am … I don't know what the best way to put it is. It's almost like I am insulting them by not seeing it through.*

P08, cervical cancer diagnosed at 31, no children

Even women who could not or decided not to preserve fertility noted that their reproductive choices were to a certain extent medicalised. Pursuing surrogacy or adoption depended not only on their wish to do so, but also on their health status and being free of cancer for a specific length of time.

Like I know I've still got options of like adoption and like a hope that I can still go down this route. I know you've got to be cancer-free for 5 years. And I just hope that I can …

P02, womb cancer diagnosed at 32, no children

Women who wished to pursue alternative parenting routes also feared the process of their parenting competencies being assessed by other people—a situation that would not have occurred had they not had cancer. For them the ability to extend their families was limited by other people's judgement—potential surrogate mothers in the case of surrogacy, or social services in the case of adoption.

As opposed to these external factors, fear of recurrence was an internal factor which also affected women's plans to have children. Whether they were thinking about biological or alternative parenting, women questioned if it was responsible to have a child knowing that cancer could come back at any time. Some of them thought it would be selfish to pursue pregnancy.

The threat of cancer recurrence was of particular importance to women who were diagnosed with breast cancer. They often linked their disease to hormonal issues and therefore perceived interrupting tamoxifen in order to conceive as potentially increasing their risk of recurrence. They stressed the importance of not "*cutting corners*" with their endocrine treatment to avoid a situation whereby driven by a desire to have a child they would provoke a recurrence and eventually leave a child without a mother. Women who already had children before cancer questioned whether they had the right to take the risk extending their families at the potential cost of their existing children's well-being.

> *Yeah … well I do worry about … like … is there a risk of it coming back and … and … and … leaving a child without a mother is an awful thought … and whether that's not a responsible thing to do.*

P04, breast cancer diagnosed at 29, no children.

DISCUSSION

The aim of this qualitative study was to gain an in-depth understanding of young women's cancer treatment decision-making and the extent to which, as well as the reason why, their decisions were influenced by fertility issues and fear of cancer recurrence and progression. The study was guided by the CSM and shared decision-making model therefore the findings are discussed within these theoretical frameworks.

Our data showed that women's responses to the cancer diagnosis often involved a shock and a sense of disbelief of having cancer at their age. The formation of illness perceptions as a result of the cancer diagnosis soon revolved around its consequences, particularly in relation to fertility. Discussion with their physicians on the impact of treatment on fertility and how fertility could be preserved was expressed as important part of their experience.

Women often appreciated having their physicians initiate a conversation around fertility preservation. Although for some women these discussions occurred in the course of their first consultation and were initiated by a member of their clinical team, for others this was not the case and these women were often disappointed by their physicians trying to avoid the topic and treating it like an *"add-on."* This is in line with the findings from the literature which suggest that providing women with fertility-related information gives them the sense of agency and control over their lives (Snyder and Tate, 2013) while withholding the information from them engenders the feelings of lack of control and powerlessness (Niemasik et al., 2012; Kirkman et al., 2014). In our study, all of the participants received the relevant information. Nonetheless, some of them reported that they had to take the responsibility for initiating the discussions and felt that had they not done that, the topic might have been ignored.

The literature suggests that upon learning about fertility-related consequences of cancer treatments women engage in the process of finding a balance between survival and fertility (Pellegrini et al., 2010; Gorman et al., 2011; Lee et al., 2011; Hershberger et al., 2013b). The findings of this study align with this concept. Regardless of whether fertility was important to the women, engaging in a balancing and prioritising process enabled them to consolidate their perception of illness and clarify their values with respect to the outcome they wanted to achieve through treatment (to preserve fertility or not). This, in accordance with the CSM, allowed them then to devise appropriate coping procedures and action plans to undertake.

Shared decision-making model (Charles et al., 1997) assumes that for the shared decision-making to occur four conditions need to be fulfilled. First, there needs to be at least two participants in the decision-making—the patient and the physician. However, Charles et al. (1999) specify that this is the minimum number and emphasise that other people such as family members can also be involved. Second, both (or all) parties need to be willing to participate in the process in the sense that both (or all) agree to share the decision-making. If one side does not wish to participate, the decision-making cannot be shared. Third, the information needs to be exchanged between the physician and the patient. The information here encompasses not only the medical knowledge and opinions about different treatments on the part of the physician but also patient's opinions and values that he or she wishes to take into account while making treatment decisions. The information exchange usually happens through the deliberation process where all opinions are weighed and reviewed. Finally, through negotiations, the treatment decision needs to be reached and agreed upon by all parties involved in the process. The assumptions of the shared decision-making model do not preclude the patient from simply agreeing to the treatment suggested by one's physician. However, if one feels coerced to do so, then the process of the decision-making cannot be considered shared.

Women in our study sought healthcare professionals' advice and wished to be guided by experts with regard to their treatment choices which is in line with the first two assumptions of the shared decision-making model. While there is evidence suggesting that young women are more likely to want to participate in cancer treatment decision making (Kane et al., 2014), as well as be active players in the decision-making process compared to their older counterparts (Hamelinck et al., 2018), research also underlines the importance of eliciting patient's preference as to their role in the decision-making process (Weber et al., 2013; Hamelinck et al., 2018). The concordance between patient's desired and actual level of involvement in the decision-making process, as opposed to the level of involvement alone, is likely to be associated with the satisfaction with treatment choice (Keating et al., 2002).

This is also echoed in our study. While both the patients' and physicians' preferences played an important role in the decision-making process in this study, it was the concordance between them that proved to be critical. When women's and their physicians' preferences with respect to fertility were congruous, the decision-making took an unproblematic course. However, when women's preferences with respect to fertility preservation differed from their physicians' priorities, accommodating them in the decision-making process seemed to become more problematic. In the latter situation, two scenarios were most common. One involved women following the expert's advice at

the cost of their own fertility-related preferences. In the other, women acted in accordance with their priorities, even if that meant searching for second opinions or going against the will of their physicians.

For the majority of women who may have had particular preferences with respect to fertility, the desire to follow the expert's advice overrode their priorities and dictated their treatment decisions. However, these women also exhibited an understanding why physicians were suggesting treatments which, while lifesaving, could affect fertility. They accepted that fertility was a price they needed to pay to survive their diagnosis. Their physicians took the time to explain that to them. While there might not have been the concordance between the patients' and the physicians' preferences with respect to fertility in those instances, there was congruence between the patients' expectations regarding treatment-decisions and the physicians' practise styles. In their review Kiesler and Auerbach (2006) suggest that it is the latter that matters in terms of satisfaction with the decision-making processes and subsequent psychological outcomes.

In our study, having a trustworthy relationship with the physician facilitated women's decision-making processes. This type of a relationship was usually achieved through open communication, particularly with respect to fertility issues. While physicians were willing to discuss various treatment options, the initiation of fertility-related discussions was often up to the patient. This mirrors the findings of several other studies that looked at fertility preservation among patients with cancer where women had to bring the topic up themselves suspecting that it would not have been addressed at all otherwise (Yee et al., 2012; Corney and Swinglehurst, 2014; Kirkman et al., 2014).

Some women in our study perceived fertility-related communication as far from ideal. Research has shown that physicians frequently have negative preconceptions about initiating fertility discussions and suggesting fertility preservation in the cancer setting (Goossens et al., 2014). As fertility preservation is a time-sensitive issue among women with breast cancer, and strictly related to cancer treatment among women with gynaecological cancers, clinicians may feel that for some patients pursuing any type of fertility preservation is not a viable option and therefore is omitted in discussions and shared-decision making. There is evidence that clinicians are more likely to involve patients in sheared decision-making where equal treatment options providing an actual choice exist (Kane et al., 2014).

However, omitting fertility-related discussions completely for the fear of disagreement between the physician's and the patient's values and excluding it from the shared decision making may have opposite to the desired effect. Occasionally in our study, when the physician was reluctant to discuss fertility, women for whom it was an important topic changed their healthcare providers, even if that meant eventually having to pay for the services.

Finally, evidence shows that women who are unsure of their fertility preferences at the time of diagnosis are more inclined to follow their physician's advice with respect to fertility preservation (Snyder and Tate, 2013). If this advice is not in favour of fertility preservation, it could potentially lead to situations where some women opt against it even if their particular circumstances allow for it. This emphasises the need for the physicians to create an open-minded and non-judgmental environment for the patients to at the very least be able to discuss their fertility concerns and clarify their desires with respect to post-cancer childbearing. The failure to do so in this study may not have resulted in missed opportunities at preserving fertility, however, led some of the women to change their physician or go against their physician's advice to ensure that their priorities were accounted for.

Healthcare professionals were not the only people women wanted to include in the decision-making. Many of the partnered women wished for their partners to be involved in the decisions which could have impact on fertility. They often described these decisions as "*joint*." While this makes for a complex triadic relationship, a recent review by Gonçalves et al. (2020) highlights the importance of facilitating partners' involvement in fertility-related decisions in the context of cancer. Improved communication of information between the couple and healthcare providers is suggested to contribute to better decision making and ultimately, mental health outcomes (Gonçalves et al., 2020). In the absence of a partner, some of the single women wished to include their parents in the decision-making processes. Although not specific to fertility, a study by Hubbard et al. (2010) points to other benefits of involving family members in cancer-treatment related decision-making. The findings of this study suggest that family members can act as an additional channel of communication with the physicians as well as aid patients in choosing appropriate treatments.

In this study, we also observed elements of fear of cancer recurrence impacting on treatment decisions. Radical treatments were seen as a way of minimising risk of recurrence. The findings of our study are in line with our review on fear of cancer recurrence among breast cancer survivors showing how these fears can impact decisions about pursuing aggressive treatments as well as post-cancer pregnancy decisions (Ozakinci et al., 2014).

The last phase of the shared decision-making process involves reaching a treatment decision between the physician and the patient. An issue specific to fertility preservation reported by women in this study was the timing of the decisions. Often women only had a very short window to make their decision to avoid delaying their cancer treatment. While this evidence corroborates the findings of the literature that the timing of fertility-related decisions is limited and can act as a barrier (Crawshaw et al., 2009; Kirkman et al., 2013; Snyder and Tate, 2013; Garvelink et al., 2015), it also reveals the preferences that physicians had with respect to their patients' treatments, namely that delaying cancer treatments to preserve fertility was not advisable.

According to the CSM, outcome appraisal is an integral part of the process of adaptation to a health threat. The information gained throughout this process feeds back into the organisation of a health threat perception. The altered representation acts as new baseline to modulate subsequent coping strategies which promote adjustment to the illness. Since this study concentrated specifically on treatment-related decision-making as a strategy

to cope with cancer diagnosis, the outcome appraisal pertained to the evaluation of the treatment decisions made by the participants and their physicians.

The majority of women in this study felt that decisions they made with respect to treatments were right for their particular circumstances. Two factors possibly contributed to that—the satisfaction with the process of the treatment decision-making, already described earlier and the satisfaction with the outcome of their decisions.

There were two possible outcomes women could have achieved through making their treatment decisions—fertility preservation or lack of thereof. Women who preserved their fertility were generally happy with this outcome although one participant (P13) later questioned whether that was the right thing to do due to cancer recurrence scares she had. Although most women were satisfied with the decisions they made at the time of diagnosis, going back to life as they knew it before cancer proved to be more difficult than some of them might have expected.

In terms of the CSM, the appraisal of coping procedures serves to refine them and improve the adjustment to illness. In many instances it is possible that when one coping strategy fails or is found unacceptable, one can choose from an array of other strategies. This process however, does not fully apply to the case of cancer treatment decisions that can affect fertility. Women only have one chance at making the "right" decision because its consequences are irreversible. Any adjustments to treatment decision-making as a coping strategy can only be made before any actions are carried out. Once the treatments have been administered, the feedback loop is interrupted and any adjustments to treatment decision-making as a coping strategy become impossible. In the post-treatment phase women were left to deal with the consequences of their treatments, pertaining to both fertility and fears of cancer recurrence.

One of the reasons why women decided to preserve fertility was to preserve their choice, however, this proved to be only partially effective. Whilst after cancer women were still in charge of the ultimate decision of whether to have children at all, they were at the same time constrained in how and when to realise their fertility-related plans. Studies reviewing the outcomes of fertility preservation among cancer patients have demonstrated 13–23% utilisation rates of cryopreserved embryos (Barcroft et al., 2013; Dolmans et al., 2015). It would appear that even following treatment, cancer continue to have an impact on reproductive decisions—an irreversible consequence that can prove challenging to women who preserved fertility.

Limitations and Strengths

Because of the methodology of the study, it has the drawbacks inherent to qualitative research in that its results cannot be easily generalizable. The study sample consisted mainly of well-educated, White, British women and this is the population that the findings could potentially be extended to. Any extrapolations, particularly to different cultural setting warrant caution.

It is possible that due to the recruitment strategy, especially the online method, participants who were interviewed for this study were a self-selected sample of women particularly interested in the issue of fertility after cancer. This would mean that the findings may apply to other women similarly preoccupied by fertility in the context of cancer.

In this study, we used face to face and online methods to approach and invite women to take part. Tackling the differences between these two groups was not the focus of this study, however, reflecting back on the results the following could be observed:

1. Among participants recruited using the face to face method in the NHS clinics were both women who were and those who were not interested in preserving their fertility at the time of cancer diagnosis. Hence, this group was potentially more representative of the population of young women diagnosed with cancer. Qualitative inquiry does not strive to be generalizable in statistical terms but rather to provide an insight into a particular phenomenon (e.g., in the case of this study it was treatment-related decision-making in the context of fertility), therefore representativeness of the sample can be considered less of an issue in qualitative studies compared to the ones using quantitative approach. However, a sample of participants with diverse points of view can provide a more in-depth account of a particular phenomenon and strengthens the analysis in terms of its credibility through the analysis of negative cases. It was additionally observed that, in this study, women who were recruited via the NHS had a rather positive experience of how their fertility issues at the time of diagnosis were addressed. Although clinicians were not informed which of their patients eventually participated in the study and all data were anonymised, it is possible that women who had negative experience with treatment provision were less inclined to take part fearing that their accounts could be made known to their healthcare providers and this in turn could affect the care they were receiving.
2. As opposed to the participants recruited via the NHS, the majority of those who were recruited online reported some issues with how their fertility concerns were addressed at the time of their diagnosis. This could be related to the fact that being informed about the study outside the context of direct healthcare provision (which is in contrast to the women approached for participation via the NHS) potentially made women more confident about and comfortable sharing negative experiences. It is also possible that women recruited online were generally more interested in the topic of the study and therefore less representative of the population of young women with cancer. As they were not directly approached for participation, it can be purported that they either actively searched for information about this particular type of project (e.g., by accessing the research sections of cancer charities websites where advertisement of the project was frequently placed) or their attention was drawn by the project topic as the advertisement appeared on social media accounts of cancer charities.

In conclusion, women diagnosed with breast or gynaecological cancer at a young age undergo a complex process of balancing the wish to survive cancer diagnosis against their desire to preserve fertility to enable them to pursue their reproductive

plans. This is best done when decisions regarding treatments that are life-saving but could potentially impact on fertility are shared between women and their physicians. Involvement of partners is also crucial at the stage where fertility is considered. Open communication and expression of one's preferences and values facilitates the decision-making process. Alignment of desired and actual level of involvement in the decision-making as well as the congruence between the patients' expectations regarding treatment-decisions and the physicians' practise styles contribute to the satisfaction with both the process of the decision-making and its outcome. It is important to remember that once treatments are completed, regardless of whether fertility was preserved or not young women struggle with the limitations to their reproductive choices.

These findings need to be interpreted accounting for the limitations of our study. The differences in participants' experiences of and perspectives on treatment-related decision-making in the context of fertility based on the recruitment method (NHS clinics vs. online) could guide recruitment to future oncofertility studies. For projects aiming to obtain a more diverse participant sample and investigate treatment-related decision-making among young women with cancer from a broader perspective it would be advisable to use the clinic-based strategy. For projects that wish to focus on particular issues related to fertility concerns at the time of diagnosis, and the existing issues in addressing them within the clinical setting, an online recruitment strategy would be preferable.

DATA AVAILABILITY STATEMENT

The dataset generated and analysed during the current study is not publicly available due to the conditions accepted by the participants upon consenting to taking part in the study. This was also approved by the ethics committees involved in reviewing the study [NHS, East of Scotland Research Ethics Service REC1/ University of St Andrews Teaching and Research Ethics Committee (UTREC)].

ETHICS STATEMENT

The ethical approval for the project was sought and received from the East of Scotland Research Ethics Service (REC1) (13/ES/0129) as well as from the School Ethics Committee at the School of Medicine, University of St Andrews (MD10852). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

This study was conducted as part of AS' Ph.D. project. AS and GO designed the study and AS did the interviews, analysed the data, and wrote up the findings. GO assisted with interpretation of the data and co-wrote this manuscript with AS. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.632162/full#supplementary-material

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Identifying the 'Active Ingredients' of an Effective Psychological Intervention to Reduce Fear of Cancer Recurrence: A Process Evaluation

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Purpose: Psychological interventions targeting fear of cancer recurrence (FCR) are effective in reducing fear and distress. Process evaluations are an important, yet scarce adjunct to published intervention trials, despite their utility in guiding the interpretation of study outcomes and optimizing intervention design for broader implementation. Accordingly, this paper reports the findings of a process evaluation conducted alongside a randomized controlled trial of a psychological intervention for melanoma patients.

Methods: Men and women with a history of Stage 0–II melanoma at high-risk of developing new primary disease were recruited *via* High Risk Melanoma Clinics across Sydney, Australia and randomly allocated to receive the psychological intervention (n = 80) or usual care (n = 84). Intervention participants received a tailored psycho-educational resource and three individual psychotherapeutic sessions delivered *via* telehealth. Qualitative and quantitative data on intervention context, processes, and delivery (reach, dose, and fidelity), and mechanisms of impact (participant responses, moderators of outcome) were collected from a range of sources, including participant surveys, psychotherapeutic session audio-recordings, and clinical records.

Results: Almost all participants reported using the psycho-educational resource (97%), received all intended psychotherapy sessions (96%), and reported high satisfaction with both intervention components. Over 80% of participants would recommend the intervention to others, and a small proportion (4%) found discussion of

melanoma-related experiences confronting. Perceived benefits included enhanced doctor-patient communication, talking more openly with family members about melanoma, and improved coping. Of potential moderators, only higher FCR severity at baseline (pre-intervention) was associated with greater reductions in FCR severity (primary outcome) at 6-month follow-up (primary endpoint).

Conclusions: Findings support the acceptability and feasibility of a psychological intervention to reduce FCR amongst individuals at high risk of developing another melanoma. Implementation into routine melanoma care is an imperative next step, with FCR screening recommended to identify those most likely to derive the greatest psychological benefit.

Keywords: fear cancer recurrence, intervention, melanoma, survivorship, psychological stress, process evaluation

INTRODUCTION

Fear of cancer recurrence (FCR) is one of the most common psychological difficulties experienced by people with cancer, and over 70% of people with a history of melanoma report clinically concerning levels (Costa et al., 2016). FCR is described as persistent worry and uncertainty about the possibility of developing new or recurrent disease, and is associated with poorer psychological well-being (Koch et al., 2013; Mutsaers et al., 2016), self-care, and health-related quality of life (Crist and Grunfeld, 2013; Simard et al., 2013; Lebel et al., 2020), as well as increased health service use and costs (Lebel et al., 2013; Simard et al., 2013). While a substantial proportion of individuals with melanoma report FCR and unmet emotional needs (Kasparian, 2013; Beesley et al., 2015; Stamataki et al., 2015; Costa et al., 2016; Fu et al., 2020), few receive professional psychological support (McLoone et al., 2012).

To address this gap in clinical care, our group developed a novel intervention comprising two components designed for people at high risk of developing new primary melanoma: (a) a tailored psycho-educational resource in booklet format, and (b) three individual psychotherapeutic sessions delivered *via* telehealth (Dieng et al., 2015, 2017; Kasparian et al., 2016). We tested the efficacy of this intervention in a longitudinal randomized controlled trial (RCT). Compared to those who received usual care, participants who received the intervention reported significantly lower FCR severity and psychological distress, fewer triggers to FCR, and improved melanoma-related knowledge at 6 months post-intervention (Dieng et al., 2016b). Moreover, reductions in FCR severity were sustained at 12-month follow-up (Dieng et al., 2020), and the study was found to be cost-effective and reasonable value for money in reducing FCR (Dieng et al., 2019).

While these results are positive, the multiple components of our intervention raises questions about the "active ingredients" contributing to successful outcomes. During study design, planning, and implementation, several factors were hypothesized to contribute to the potential effects of the intervention, such as greater time spent engaging with the psychologist (i.e., longer telehealth sessions), reading the psycho-educational resource more thoroughly, and increased knowledge about melanoma. To examine these hypotheses, we carried out a process evaluation alongside our longitudinal RCT.

Process evaluations are an important, yet scarce adjunct to published intervention trials and aim to identify potential barriers and facilitators to translation. Briefly, process evaluations examine the quantity and quality of what was implemented during an intervention trial, how and by whom, and provide data to support or augment the interpretation of outcomes (Moore et al., 2014). Across psycho-oncology, there is a dearth of published process evaluations of psychological interventions, limiting our ability to effectively translate research findings into clinical practice and address unmet mental health needs. Key functions and components of process evaluations have been described (Moore et al., 2015), with the UK Medical Research Council framework providing a comprehensive guide (**Figure 1**). Process data can assist with interpreting intervention outcomes as well as inform the refinement of existing interventions and guide implementation by providing information on reach (who received the intervention), dose (what was delivered to, and received by, participants), fidelity (the extent to which the intervention was implemented in line with the protocol), and how participants perceived the intervention (satisfaction and helpfulness). Process data can also highlight barriers and contextual factors related to the environment in which the intervention was delivered that could influence outcomes. Therefore, the aims of this process evaluation were to:

a. Examine implementation (reach, fidelity, dose, and context) of an effective psychological intervention targeting fear of cancer recurrence amongst people at high-risk of developing new primary melanoma, as well as potential mechanisms of impact;
b. Assess participants' perceptions of the intervention, including acceptability and satisfaction; and
c. Provide data to assist in interpreting trial outcomes, as well as how best to implement the intervention in the future to maximize benefits and minimize risks in settings where ongoing dermatologic care is provided for people with melanoma.

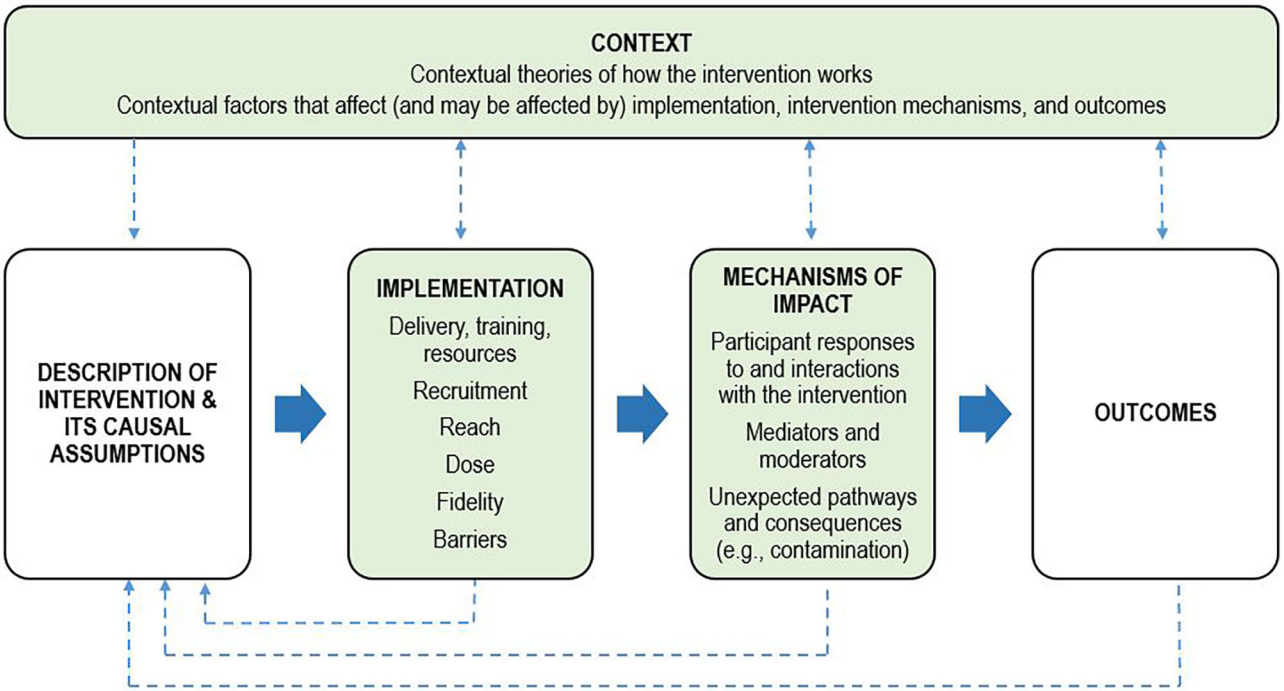

FIGURE 1 | Process evaluation framework. Adapted from the UK Medical Research Council framework for conducting and reporting process evaluation studies (Moore et al., 2015). Key components of the process evaluation are in green boxes. Investigation of these components is shaped by clear descriptions of the intervention and its causal assumptions. Implementation refers to how the intervention was delivered, and mechanisms of impact refers to how the intervention produced change. The dotted lines indicate the relations between context, the intervention, implementation, mechanisms, and outcomes.

MATERIALS AND METHODS

Design and Measurement Approach

This process evaluation was conducted alongside a longitudinal randomized controlled trial. Intervention development (Kasparian et al., 2016), the trial protocol (Dieng et al., 2015, 2016a), pilot test results (Dieng et al., 2017), main results (Dieng et al., 2016b, 2020), and economic evaluation (Dieng et al., 2019) have been published elsewhere.

Existing frameworks were used to plan, organize, and operationalize process evaluation components, including the UK Medical Research Council framework (Baranowski and Stables, 2000; Moore et al., 2015). Quantitative and qualitative process data were collected using survey instruments, psychologist session notes and audio-recordings, fidelity checklists, the study protocol, and research notes (see **Supplementary Materials** for a summary of the operationalization of each process evaluation concept and measurement techniques). Data were collected from participants with a history of Stage 0–II melanoma who were current patients of one of three High Risk Melanoma Clinics (HRCs) in Sydney, Australia. Most of the quantitative and qualitative data for the process evaluation (e.g., barriers, satisfaction, dose, contamination) were derived from participant surveys completed at 6-month follow-up. Fear of new or recurrent melanoma was assessed at baseline (pre-randomization), and at 1-, 6- and 12-month follow-up using the 9-item Severity subscale of the validated 42-item Fear of Cancer Recurrence Inventory (FCRI; Simard and Savard, 2009).

Intervention Description

The intervention comprised two main components: a newly-developed, 68-page psycho-educational resource provided in color booklet format (called, "*Melanoma: Questions and Answers*") and three individual psychotherapeutic sessions with a psychologist, delivered *via* telehealth (by telephone) and scheduled in conjunction with patients' dermatology appointment (see **Figure 2** for session timing). *Melanoma: Questions and Answers* was developed in response to patient education needs and preferences (McLoone et al., 2012), and includes seven standalone modules covering medical, psychological, behavioral, social, and practical aspects of melanoma, with an emphasis on fear of cancer recurrence. It also includes tools tailored to the needs of people with melanoma, such as graphics to communicate information about melanoma risk, photographs to illustrate complex health behaviors (e.g., skin self-examination), a question prompt list to facilitate doctor-patient communication, verbatim quotes from Australian melanoma patients, care planning tools to record various aspects of melanoma care (such as diagnoses, treatments, moles being monitored for change, and

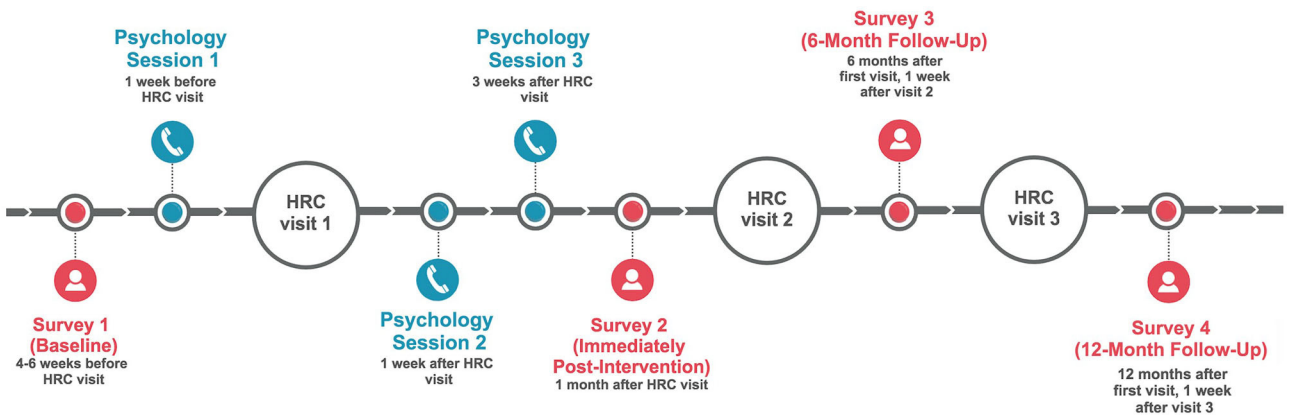

FIGURE 2 | Schedule and timing of individual psychology telephone sessions and study survey assessments. HRC, High Risk Clinic.

clinical test results), and lists of relevant, reputable services and websites.

In accordance with established evidence (Kasparian, 2013; McLoone et al., 2013a; Kasparian et al., 2016) and brief psychodynamically-oriented psychotherapy principles (Abbass et al., 2009; Shedler, 2010), the overall goals of the psychological intervention sessions were to provide empathic, active listening and to assist participants in fostering strategies to manage health-related distress. Goals of Session 1 (up to 90 min) included discussion and assessment of each participant's background (e.g., family, work, friendships), experience of melanoma and clinical care, information and support needs, and their hopes and goals for the intervention. Sessions 2 and 3 (up to 50 mins each) involved discussing the previous session and each participant's recent dermatology appointment, as well as exploring and addressing individual needs and concerns, and utilizing psychological techniques and components of *Melanoma: Questions and Answers,* as needed. With permission, all sessions were audio-recorded and a detailed summary was prepared by the psychologist immediately after each session.

All participants (intervention and control) also received a copy of the Australian Cancer Council booklet, *Understanding Melanoma*, which includes easy-to-read information about melanoma diagnosis, treatment, and general tips for living well after treatment.

Participants in the control group received usual care, comprising their usual dermatological appointments within the same HRCs and a copy of the Cancer Council booklet, *Understanding Melanoma*.

Context of Intervention Delivery

Recruitment occurred at all three high-risk melanoma clinics (HRCs) across the state of New South Wales (Sydney Melanoma Diagnostic Center at the Royal Prince Alfred Hospital, Melanoma Institute Australia in North Sydney, Newcastle Skin Check Clinic); two in metropolitan Sydney and one in regional Newcastle. The clinics provide specialized dermatological care using numerous medical imaging diagnostic interventions for people at high risk of melanoma and patients attend clinics at least 6-monthly (Maloney et al., 2014). To attend, patients need to meet one or more of the following criteria:

1. Previous diagnosis of ≥1 invasive melanoma and dysplastic nevus syndrome;
2. Previous diagnosis of ≥2 invasive melanomas, with at least one diagnosed within the past 10 years;
3. Previous diagnosis of ≥1 invasive melanoma and a family history of ≥3 first-degree or second-degree family members with melanoma; or
4. Carrier of a *CDKN2A* or *CDK4* gene mutation.

Intervention sessions were distance-delivered *via* telephone to overcome geographical barriers to accessing care and to meet previously-identified patient preferences for less travel (McLoone et al., 2013a,b). The first psychotherapeutic session occurred in the week prior to patients' dermatological appointment, when anxiety amongst melanoma patients is known to be highest (Baughan et al., 1993; Morton et al., 2013).

Process Evaluation Components: Delivery, Training, and Resources

The psycho-educational resource was developed in partnership with patients and an interdisciplinary team of health professionals and researchers (Kasparian et al., 2016). After comprehensive training that included education on melanoma and clinical management, skills-based training in telehealth for people with cancer, observation of HRC appointments, training in use of the treatment manual and intervention resources, and simulation sessions with a professional actor, three licensed psychologists, each with ≥5 years of clinical experience, delivered the intervention, receiving weekly, distance-delivered (telephone-based) clinical supervision with an experienced psychologist throughout the trial.

Intervention Reach, Dose, and Fidelity

As outlined in Baranowski and Stables (2000), reach was defined as the extent to which the intervention contacted or was

received by the targeted group. Intervention reach was assessed using enrolment, response, and completion rates, including the proportion of eligible patients who enrolled in the trial, the proportion of enrolled patients who were contacted and received the intervention, and the number of participants who received all intervention components. Sociodemographic characteristics of those who received the intervention were also examined. Dose was defined as the amount of intervention received by participants (i.e., number of sessions and number of minutes spent with the psychologist), and how thoroughly participants reported reading the resources provided on a scale from 0 ("I did not read the booklet") to 4 ("Read from cover to cover"). Fidelity to the intervention manual (to determine whether the intervention was delivered as intended), was assessed independently by two assessors using a purposively-designed, 24-item checklist (available from authors on request). Initially, the two assessors and a senior supervising psychologist listened to and rated one intervention session individually. Ratings were discussed as a group until consensus was reached and a scoring protocol was devised. For 10% of participants, selected at random and stratified by psychologist, all three intervention session recordings were assessed for fidelity. A sample of these participants (20%) was also used to determine inter-rater reliability, calculated as the percentage of item ratings agreed upon by both assessors.

Barriers

Participants were asked to rate the perceived level of difficulty experienced in engaging with intervention components, from 0 ("not at all difficult") to 10 ("extremely difficult") in the 6-month follow-up questionnaire. Barriers to intervention implementation were measured from the patient perspective only.

Mechanisms of Impact

Participant Satisfaction

At 6-month follow-up, participants rated their satisfaction with each intervention component on a scale from 0 ("not at all satisfied") to 10 ("extremely satisfied"). Participants rated overall ***perceived quality of information and support*** provided during the study on a scale from 1 ("poor") to 5 ("excellent"). ***Perceived benefit*** of each component was assessed from 0 ("not at all beneficial") to 10 ("extremely beneficial"). Participants also rated the degree to which the intervention was felt to have changed various aspects of their life (e.g., improved communication with their clinician, greater understanding of melanoma risk), from 0 ("strongly disagree") to 4 ("strongly agree"), as well as how helpful they found the different modules and tools provided in *Melanoma: Questions and Answers*. Participants in the control arm responded to the same questions for satisfaction, perceived benefit, and quality of information and support for the Cancer Council *Understanding Melanoma* booklet only.

Contamination

To determine whether study outcomes may have been contaminated by access to information outside of the study protocol, participants were asked at 6-month follow-up if they had accessed additional information, and if so, to indicate the sources accessed.

Potential Moderators of Intervention Effect

Factors that may have influenced changes in the primary outcome (i.e., change in FCRI Severity scores from baseline to 6-month follow-up) were examined. These factors were: participant sex, time since most recent melanoma diagnosis, baseline FCRI Severity scores, amount of intervention received (i.e., how thoroughly participants reported reading the psychoeducational resource and total duration of psychotherapy sessions), satisfaction with the psychoeducational resource and with psychotherapy sessions, and change in melanoma-related knowledge, as determined by the difference in correctly answered questions (from baseline to 6-month follow-up) on a 9-item melanoma knowledge scale.

Statistical Analyses

Descriptive statistics were used to examine quantitative aspects of recruitment, reach, fidelity, dose, participant satisfaction, barriers, and contamination. Independent *t*-tests were used to examine potential differences in dose (i.e., how thoroughly participants read the resources provided), satisfaction, and barriers between intervention and control group participants. For the intervention group, paired *t*-tests were used to determine if there were differences in session duration between the psychologists; how thoroughly the resources, *Understanding Melanoma* and *Melanoma: Questions and Answers*, were read; and reported satisfaction and barriers encountered between the two booklet resources and the psychotherapy sessions. Pearson Chi-Squared tests were used to determine potential differences between the intervention and control groups in terms of whether participants would recommend the program to others, as well as whether external information or support was accessed. Multiple linear regression was used for moderator analyses, with sex, time since last melanoma diagnosis, baseline FCRI Severity score, satisfaction with *Melanoma: Questions and Answers*, thoroughness of engagement with the psychoeducational resource, change in melanoma-related knowledge, total duration of psychology sessions, and satisfaction with sessions examined as potential predictors of the primary outcome (i.e., change in FCRI Severity score). Confidence intervals were set to 95%. Quantitative data were analyzed using IBM SPSS Statistics 25 (Armonk, NY: IBM Corp). Qualitative data from participant surveys on satisfaction, perceived benefits, and barriers were analyzed thematically using *NVivo 11*.

RESULTS

Intervention Implementation

Reach

Of the 346 patients identified as eligible, 183 individuals (53%) consented into the trial. In the period between consent and randomization, 19 participants (10%) withdrew or did not return their baseline questionnaire, leaving 164 participants randomized to the intervention ($n = 80$) or usual care ($n = 84$). Reasons for withdrawal included not needing support ($n = 5$), or lack of time

to participate ($n = 5$). Most participants completed the 1-month (87%, $n = 143$) and 6-month (92%, $n = 151$) questionnaires. More men (55%) than women (45%) were recruited into the study, and most participants were from metropolitan areas. The mean participant age was 58.5 ± 11.9 years (Range: 31–83 years). Mean time between last melanoma diagnosis and randomization was 7.6 ± 6.7 years [Range: −0.5 (new diagnosis during study) to 42.6]. Two-thirds (68%) of participants reported FCRI Severity scores of 13 or above at baseline, suggestive of clinically concerning FCR warranting psychological intervention (Simard et al., 2013).

Examining intervention sessions, the first psychologist was assigned to facilitate sessions with 39 participants (49%), second psychologist with 12 participants (15%), and third psychologist with 29 participants (36%). Four of 80 intervention participants (5%) did not take part in the sessions due to not being contactable ($n = 2$), becoming ineligible ($n = 1$), or because they stated that they did not require support ($n = 1$). Three participants in the control arm reported not receiving the Cancer Council *Understanding Melanoma* booklet. All intervention participants reported receiving both *Melanoma: Questions and Answers* and *Understanding Melanoma* booklets.

Dose Delivered

Of those who participated in the psychotherapy sessions ($n = 76$), most ($n = 70$) engaged in all three sessions. Four participated in one session and two participated in five sessions due to requiring additional support. Reasons for engagement in only one session included participants feeling they did not require support ($n = 2$), finding talking upsetting ($n = 1$), and becoming unavailable ($n = 1$). Mean session duration ($n = 76$) was 100.7 ± 61.2 min (Range: 2–150 min). When examined by session, the average session length was 53.2 ± 24 min for Session 1, 28 ± 20.7 min for Session 2, and 22 ± 17.8 min for Session 3. Overall, Psychologist 2 facilitated significantly longer sessions (158.9 ± 51.7 min) than Psychologist 1 (96.8 ± 65.5 min, $t_{47} = -2.99$, $p = 0.004$) and Psychologist 3 (79.2 ± 40 min, $t_{36} = 5.2$, $p < 0.001$). No difference in session duration was found between Psychologists 1 and 3 ($t_{60} = 1.31$, $p = 0.19$).

Dose Received

Psychologists recorded the content covered in each session (**Table 1**). Most Session 1 discussions (95%) included an assessment and exploration of the participant's melanoma history. Nearly half the intervention group discussed

TABLE 1 | Content of telehealth-based psychotherapeutic sessions and the proportion of participants who received this content.

Content		Session 1 $n = 76$	Session 2 $n = 72$	Session 3 $n = 72$
Assessment and melanoma history and experiences		95%	–	–
Discussion of HRC appointment				
	Concerns around next appointment	48%	25%	14%
	Update of most recent appointment	–	99%	100%
Review of last phone session		–	81%	88%
Resource content (MQA booklet)	Types of melanoma	30%	3%	3%
	Diagram of melanoma diagnosis statistics	13%	1%	3%
	Melanoma and genetic factors	12%	3%	–
	Skin self-examination	30%	4%	4%
	The role of vitamin D	9%	1%	–
	Sun exposure	13%	1%	–
Unmet information needs	Prognosis	21%	3%	–
	Type of melanoma	11%	4%	–
	Genetic risk	12%	–	4%
	Sun exposure/sun screen	17%	1%	–
	Skin self-examination	18%	3%	3%
	Risk to children due to genetic or other factors	24%	1%	1%
Psycho-therapeutic techniques	Worry postponement	5%	8%	6%
	Detached mindfulness	3%	8%	11%
Referral for further psychological care		5%	7%	15%
Sleep		9%	10%	7%
Anxiety		11%	3%	6%
Depression		4%	3%	6%
Stress		8%	10%	4%
Experience of intervention participation and feedback		–	–	85%

Dash (–) indicates content not covered.
MQA, Melanoma: Questions and Answers.

concerns about their upcoming HRC appointment (48%), and about one-third (30%) discussed types of melanoma and skin self-examination. Much of Session 2 and Session 3 (80–100%) involved reviewing previous sessions as well as participants' experiences of their recent HRC appointment. For one-quarter of participants, Session 2 included discussion of concerns about their next HRC appointment. Resource-related content and unmet information needs were covered more in Session 1 than in Sessions 2 and 3. Tools, such as the skin self-examination guide, mole tracking sheets, and education on coping were more frequently covered in Sessions 2 and 3 than Session 1.

Overall, intervention participants reported reading *Understanding Melanoma* more thoroughly ($M = 2.7 \pm 1.1$ out of 4) than control participants ($M = 2.27 \pm 1.3$, $t_{143} = -2.15$, $p = 0.03$). Reasons cited by control participants for not thoroughly reading *Understanding Melanoma* included having enough information about melanoma ($n = 3$) and not feeling worried ($n = 1$). Reasons for intervention participants not reading *Melanoma: Questions and Answers* thoroughly included already having enough information ($n = 2$) and not enjoying reading in general ($n = 1$). Mean ratings for how thoroughly intervention participants read *Understanding Melanoma* ($M = 2.70 \pm 1.13$ out of 4) and *Melanoma: Questions and Answers* ($M = 2.75 \pm 1.11$ out of 4) did not differ ($t_{66} = -0.83$, $p = 0.41$). Three participants in the intervention group explicitly reported not remembering how thoroughly they read the resources.

Fidelity

Overall fidelity to the intervention manual across all three psychotherapeutic sessions was high (88%), with high inter-rater reliability between the two assessors (87%). Fidelity was 83% for Session 1, 88% for Session 2, and 90% for Session 3. Fidelity was 87% for Psychologist, 96% for Psychologist 2, and 86% for Psychologist 3.

Barriers

Both groups reported little difficulty engaging with the educational resources. Mean perceived difficulty engaging with *Understanding Melanoma* was very low and did not differ between intervention ($M = 1.00 \pm 1.88$ out of 10) and control groups ($M = 1.45 \pm 2.25$ out of 10, $t_{141} = 1.28$, $p = 0.20$; **Table 2**). In the intervention group, mean difficulty engaging with *Understanding Melanoma* ($M = 1.0 \pm 1.88$ out of 10) and *Melanoma: Questions and Answers* ($M = 0.99 \pm 1.85$ out of 10, $t_{66} = 0.57$, $p = 0.57$) was also low and did not differ. While intervention participants reported little difficulty engaging with the psychotherapy sessions ($M = 1.8 \pm 2.55$ out of 10), the mean difficulty rating for the sessions was higher than that for the *Understanding Melanoma* booklet ($t_{64} = 3.43$, $p = 0.001$) and *Melanoma: Questions and Answers* ($t_{64} = 3.55$, $p = 0.001$); however, all difficulty ratings were low. Three participants (4%) found discussing their melanoma experiences with the psychologist confronting, and two participants (3%) reported difficulty finding a suitable time and location to take part in the telehealth sessions.

Mechanisms of Impact

Participant Satisfaction

Satisfaction scores for the Cancer Council *Understanding Melanoma* booklet were significantly higher in the intervention ($M = 7.87 \pm 2.34$ out of 10) than control group ($M = 6.75 \pm 2.61$ out of 10, $p = 0.008$; **Table 2**). In the intervention group, no differences were found between mean satisfaction ratings for *Understanding Melanoma* and *Melanoma: Questions and Answers* ($t_{66} = 0.78$, $p = 0.44$). Moreover, mean satisfaction ratings for the telehealth-based psychotherapy sessions ($M = 7.70 \pm 2.81$ out of 10) and *Melanoma: Questions and Answers* resource ($M = 7.93 \pm 2.29$) were high did not differ significantly ($t_{65} = -0.58$, $p = 0.57$). Perceived quality of information provided in the study was significantly higher in the intervention ($M = 4.41 \pm 0.74$ out of 5) than control group ($M = 3.95 \pm 1.07$ out of 5; $t_{138} = -2.94$, $p = 0.004$), as was the perceived quality of support

TABLE 2 | Mean perceived satisfaction, benefit, and difficulty of study components. Each component was rated from 0 ("not at all") to 10 ("extremely").

Intervention Component		Satisfaction *Mean (SD)*	Perceived Benefit *Mean (SD)*	Perceived Difficulty *Mean (SD)*
Understanding Melanoma information booklet	Control group	6.75 (2.61)	6.13 (2.73)	1.45 (2.25)
	Intervention group	7.87 (2.34)	7.52 (2.44)	1.00 (1.88)
Melanoma: Questions and Answers psycho-educational resource		7.93 (2.29)	7.48 (2.42)	0.99 (1.85)
Psychotherapeutic sessions *via* telehealth		7.70 (2.81)	7.08 (3.06)	1.80 (2.55)
Overall study participation		7.79 (2.33)	7.28 (2.65)	1.51 (2.44)

"Melanoma: Questions and Answers psycho-educational resource," "Psychotherapeutic sessions via telehealth," and "Overall study participation" refer to those in the intervention group only. Intervention group n = 67, Control group n = 77.

(intervention group, $M = 4.30 \pm 0.84$ out of 5, control group, $M = 3.61 \pm 1.19$ out of 5; $t_{131.3} = -4.02$, $p < 0.001$).

Perceived Benefits

Perceived benefit ratings for the *Understanding Melanoma* booklet were significantly higher in the intervention ($M = 7.52 \pm 2.44$ out of 10) than control group ($M = 6.13 \pm 2.73$ out of 10, $t_{141} = -3.18$, $p = 0.002$; **Table 2**). Participants who received the intervention rated the benefits of both educational resources, *Understanding Melanoma* ($M = 7.52 \pm 2.44$ out of 10) and *Melanoma: Questions and Answers* ($M = 7.48 \pm 2.42$ out of 10), highly ($t_{65} = 0.55$, $p = 0.58$). In addition, intervention participants' ratings of the benefits of *Melanoma: Questions and Answers* and the psychology sessions ($M = 7.08 \pm 3.06$) did not differ ($t_{65} = 1.03$, $p = 0.31$). Qualitatively, participants spontaneously reported many benefits of the psychological intervention, including improved or reinforced melanoma-related knowledge ($n = 5$), increased risk awareness ($n = 4$) and health behaviors ($n = 2$), and better communication with their clinician and family members ($n = 2$). Ten participants referred to the intervention as "informative", while others ($n = 3$) believed the knowledge gained empowered better coping and decision-making, and one participant reported increased optimism regarding survival. Eight participants spontaneously reported deriving benefit from the psychotherapy sessions and three participants mentioned sharing the resources with others. Some participants ($n = 4$) believed the intervention would have been more beneficial if provided at the time of melanoma diagnosis, and others ($n = 7$) believed it would be more beneficial for individuals with higher levels of melanoma-related worry.

In survey responses, participants identified improved communication with their melanoma care team as the greatest benefit of the intervention (**Table 3**). Other perceived benefits included learning how often to check their skin, greater understanding of their risk of recurrence, and feeling less worried about HRC appointments.

Information presented in *Melanoma: Questions and Answers* rated most helpful included information about the different types of melanoma ($M = 2.35 \pm 0.81$ out of 3) and about how to monitor moles for changes ($M = 2.35 \pm 0.76$ out of 3; **Table 4**). The most used and most helpful tool in *Melanoma: Questions and Answers* was the Skin Self-Examination Guide, used by 73% of intervention participants and perceived as helpful by 71% of those who used it (**Table 5**). The least used tool was the SunSmart App (19% usage); this and the Appointment Calendars were perceived as the least helpful tools.

Over 80% of intervention participants reported they would recommend the intervention to other people with melanoma, and 82% of control group participants would recommend *Understanding Melanoma*. The two groups did not differ in terms of whether they would recommend the program to others [$\chi^2_{(2,141)} = 1.12$, $p = 0.57$].

Moderators

Multiple linear regression was used to examine a range of potential moderators of intervention effect; however, only one of the hypothesized moderators (baseline FCRI Severity score) was found to predict the primary outcome (i.e., change in FCRI Severity scores from baseline to 6-month follow-up). Higher FCRI Severity scores at baseline were associated with a greater decrease in FCR severity at 6-month follow-up (**Table 6**). Overall, the model accounted for only 7% of the variance in the primary outcome.

TABLE 3 | Perceived effects of participation in the intervention ($n = 67$), with ratings from 0 ("strongly disagree") to 4 ("strongly agree").

Participating in this psychological study has helped me to:	*Mean (SD)*
Talk more openly with my High Risk Melanoma Clinic doctor and ask questions when I need to	2.90 (0.89)
Know how often it is recommended that I check my skin	2.88 (0.75)
Better understand my risk of developing another melanoma	2.87 (0.78)
Know more about the recommended ways to check my skin and what to look	2.85 (0.74)
Feel less worried about my High Risk Melanoma Clinic appointments	2.63 (0.81)
Find the information I need to cope as best as I can with melanoma	2.63 (0.76)
Talk more openly with my family about melanoma	2.60 (0.78)
Feel more confident in my ability to cope with worries or concerns I have about melanoma	2.58 (0.74)
Understand why I feel the way I do about my melanoma risk	2.57 (0.74)
Feel more confident in my ability to cope with worries or concerns in general	2.46 (0.75)
Find the emotional support I need to cope as best as I can with melanoma	2.40 (0.84)
Find other services that may be helpful for me or my family	2.39 (0.72)
Feel more confident to use coping strategies such as Detached Mindfulness	2.31 (0.82)
Get emotional help and support about issues unrelated to my melanoma risk	2.21 (0.75)

Contamination

External sources of information accessed by participants during the study included internet sites, their general practitioner, and family and friends. Access to additional information sources did not differ between groups, with 19 (28%) intervention participants and 18 control participants (24%) reporting use of additional information sources [$\chi^2_{(1,143)} = 0.41$, $p = 0.52$]. Key findings from the process evaluation are summarized in **Table 7**.

DISCUSSION

To our knowledge, this is the first process evaluation of a psychological intervention targeting fear of cancer recurrence, and one of very few in cancer. Results complement and strengthen the published outcomes of the original clinical trial by demonstrating that the intervention was delivered as

intended and was acceptable, feasible, and very well received by participants. Attrition throughout the trial was considerably lower than other published trials of FCR interventions involving in-person sessions (e.g., ConquerFear; Butow et al., 2017), which could be due in part to our intervention being more accessible and suggests that telehealth-based interventions are a feasible and potentially preferred alternative to interventions delivered in-person. Nearly all participants used the psycho-educational resource, engaged in all psychotherapy sessions, and reported high satisfaction with both of these intervention components. Difficulty ratings were very low, indicating limited barriers to engaging with the intervention. Over

TABLE 4 | Mean perceived helpfulness ratings for each component of *Melanoma: Questions and Answers* ($n = 66$), with ratings from 0 ("not at all helpful") to 3 ("very helpful").

Psychoeducational resource component	Perceived helpfulness *Mean (SD)*
Different types of melanoma	2.35 (0.81)
Monitoring moles for change	2.35 (0.76)
Risk of developing melanoma presented in 100-person risk diagrams	2.21 (0.83)
Skin self-examination	2.33 (0.74)
Genetics and family history	2.17 (0.80)
Sun protection after a melanoma diagnosis	2.18 (0.88)
Vitamin D	2.09 (0.86)
How melanoma can affect the way I feel	1.91 (0.87)
Coping with melanoma	1.92 (0.94)
Living with the fear that melanoma may come back	1.74 (0.87)
Quotes and messages from people who have had melanoma	1.62 (0.96)

TABLE 5 | Reported use and perceived helpfulness of the tools included in *Melanoma: Questions and Answers* ($n = 69$).

Tool	Percentage of participants who reported use	Percentage of participants who perceived tool as helpful
Skin self-examination guide	73%	71%
Moles and spots record	62%	62%
UV index explainer	44%	54%
Question prompt list	46%	44%
Menu of coping strategies	38%	44%
Checklist for recognizing signs of stress	32%	38%
Future melanoma appointments	29%	38%
List of useful websites and services	26%	38%
Diagnosis and treatment record	26%	35%
Appointment calendars	25%	30%
SunSmart app	19%	30%

TABLE 6 | Multiple linear regression examining potential moderators of intervention effect ($n = 61$).

Factor	Unstandardized coefficient	95% CI	Standardized coefficient	*p*-value	Unique variance accounted for (%)
Participant sex	−0.65	−3.24, 1.95	−0.07	0.620	0.41
Time since last melanoma diagnosis	0.00	−0.02, 0.01	−0.03	0.853	0.06
Baseline FCRI Severity score	−0.17	−0.33, −0.01	−0.28	**0.044**	7.02
Satisfaction with the psycho-educational resource, *Melanoma: Questions and Answers*	0.00	−0.58, 0.58	0.00	0.991	0.00
Thoroughness of engagement with the psycho-educational resource	0.05	−1.13, 1.23	0.01	0.930	0.01
Change in melanoma-related knowledge	0.03	−0.21, 0.26	0.03	0.816	0.09
Total duration of psychotherapy sessions	0.00	−0.02, 0.02	0.00	0.984	0.00
Satisfaction with psychotherapy sessions	0.17	−0.29, 0.63	0.11	0.462	0.90

Significant results in bold typeface. CI, confidence interval.

TABLE 7 | Summary of the main findings of the process evaluation.

Intervention implementation	Main findings
Reach	• Of the 346 eligible patients, 183 (53%) consented into the trial. In the time between consent and randomization, 19 participants (10%) withdrew or did not return their baseline questionnaire. • 164 participants randomized to the intervention ($n = 80$) or usual care ($n = 84$). • Most participants completed the 1-month (87%, $n = 143$) and 6-month (92%, $n = 151$) assessments. • More men (55%) than women (45%) were recruited, and most participants were from metropolitan areas. Mean participant age was 58.5 ± 11.9 years (Range: 31–83 years). • Mean time between last melanoma diagnosis and randomization was 7.6 ± 6.7 years. • Two-thirds (68%) of participants reported FCRI Severity scores of 13 or above at baseline, suggestive of clinically concerning FCR warranting psychological intervention. • Four of 80 intervention participants (5%) did not participate in the psychotherapy sessions.
Dose delivered	• Of those who participated in the sessions ($n = 76$), most ($n = 70$) engaged in all three sessions. • Mean session length was 53.2 ± 24 min for Session 1, 28 ± 20.7 min for Session 2, and 22 ± 17.8 min for Session 3. • Overall, Psychologist 2 facilitated significantly longer sessions than Psychologist 1 and Psychologist 3.
Dose received	• Most Session 1 discussions (95%) included assessment and exploration of the participant's melanoma history, as well as concerns about one's upcoming HRC appointment. • Much of Session 2 and Session 3 (80–100%) involved reviewing previous sessions and participants' experiences of their recent HRC appointment • Intervention participants reported reading *Understanding Melanoma* more thoroughly than control participants. • Mean ratings for how thoroughly intervention participants read *Understanding Melanoma* and *Melanoma: Questions and Answers* did not differ.
Fidelity	• Fidelity of the psychotherapeutic sessions to the intervention manual was high (88%), with high inter-rater reliability between the two assessors (87%). • Fidelity was 83% for Session 1, 88% for Session 2, and 90% for Session 3.
Barriers	• Both groups reported little difficulty engaging with the educational resources. • Engaging in the psychotherapy sessions was perceived as more difficult than engaging with the informational and psycho-educational resources; however, all difficulty ratings were low.
Mechanisms of impact	**Main findings**
Participant satisfaction	• Satisfaction scores for the Cancer Council *Understanding Melanoma* booklet were significantly higher in the intervention than control group. • Perceived quality of information provided throughout the study was significantly higher in the intervention than control group, as was perceived quality of support.
Perceived benefits	• Perceived benefit ratings for the *Understanding Melanoma* booklet were significantly higher in the intervention than control group. • Reported benefits of the psychological intervention included improved or reinforced melanoma-related knowledge, increased risk awareness and health behaviors, and better communication with participants' clinician and family members. • Participants identified improved communication with their melanoma care team as the greatest benefit.
Moderators	• Only one of the hypothesized factors—baseline FCRI Severity score—was found to moderate intervention effect (i.e., change in FCRI Severity scores from baseline to 6-month follow-up), with higher FCRI Severity scores at baseline associated with a greater decrease in FCR severity at 6-month follow-up.
Contamination	• External sources of information accessed by participants during the study included internet sites, participants' general practitioner, and family and friends. Reported access to additional information sources did not differ between groups.

80% of participants would recommend the intervention to others and identified numerous benefits that may have direct positive impact on their experience of melanoma and clinical care, with the most highly rated benefits being enhanced doctor-patient communication, talking more openly with family members about melanoma, and improved coping. Trial outcomes appear to be due to direct effects of the intervention and were unlikely due to external factors. While external sources of information were accessed by some participants, this did not differ between intervention and control groups, indicating low contamination and providing increased confidence that improved FCR outcomes were a result of intervention participation.

The results of this process evaluation augment the outcomes of the RCT and provide indications as to why the intervention was effective. One possible "active ingredient" is increased engagement with melanoma-related information. Intervention participants reported reading the Cancer Council booklet, *Understanding Melanoma,* more thoroughly than participants in usual care, which may partially explain why intervention participants reported higher satisfaction and greater benefit from the booklet than control participants. While change in melanoma-related knowledge was not a moderator of intervention effect, the brief measure we used to assess knowledge may not have captured other informational benefits gained from the resources. Another "active ingredient" could be increased

confidence in one's ability to manage melanoma. This is supported by findings in the intervention group that information about melanoma, moles, and skin self-examination in *Melanoma: Questions and Answers* was rated most helpful and used most often. Additionally, the most commonly reported benefits of the intervention included being able to talk more openly with one's doctor, knowing more about how and when to perform skin checks, and better understanding one's of risk of melanoma recurrence. Finally, receiving tailored support from a trained and experienced psychologist could be an "active ingredient." Intervention participants reported receiving significantly better quality of information and support compared with the control group, indicating that the intervention provided benefit over and above resources available as part of usual care. The finding that intervention participants reported reading the Cancer Council booklet, *Understanding Melanoma,* more thoroughly than the control group may reflect an effect of the psychologists referring to resource content during sessions, prompting and supporting participants to utilize and meaningfully engage with the resources more. Future studies comparing provision of the psycho-educational resource (*Melanoma: Questions and Answers*) alone vs. coupled with psychotherapy sessions could provide further clarity on the role of the therapist in psychological interventions for people with melanoma.

The process evaluation also offers rich information about how participants engaged with the intervention. Satisfaction with and reported benefits of the two resources were similar amongst intervention participants, indicating the newly-developed resource, *Melanoma: Questions and Answers,* was as acceptable as the pre-existing resource, *Understanding Melanoma*, despite being 16-pages longer. While the briefer information provided by the Cancer Council booklet was well accepted by both groups, our findings suggest it alone was insufficient in addressing patients' needs. Overall, these results support a combination of psychologist-assisted and self-directed activities (e.g., reading informational and psycho-educational resources) was more favorably perceived than the informational booklet alone and led to greater psychological benefits for patients.

Intervention participants were provided with a large amount of medical and psychological information, as well as psycho-educational tools, and covered a range of topics within psychotherapy sessions. Information about melanoma, moles, and skin self-examination were rated the most helpful and most used components of the resource, aligning with research showing that health-related information is one of the greatest unmet needs reported by people with melanoma and other cancers (Beesley et al., 2015; Sarkar et al., 2015; Stamataki et al., 2015; Fu et al., 2020; Mutsaers et al., 2020). The SunSmart App was the least used and least helpful tool, which may reflect the preferences of the older demographic of our study (Lim, 2010). Calendars were also not perceived as very useful and participants may already employ other strategies to keep track of appointments. Although the psychology sessions followed a clear framework, session scope and content were tailored to participants' specific goals, preferences, needs, and difficulties. Areas most frequently covered in sessions, and therefore more likely to be important to participants, included reflection on one's experiences with melanoma, information about the different types of melanoma, discussion of skin self-examination, and working through worries and concerns about upcoming dermatology appointments. Less commonly discussed topics included anxiety, depression, and specific psychotherapeutic techniques, such as mindfulness. This may reflect a relatively lower need for specific psychological strategies, especially as some participants may have entered the study with relatively low FCR, and a greater need for accurate information about melanoma and an empathic health professional with which to discuss one's experiences.

We examined a range of potential moderators of intervention effects (e.g., participant sex, amount of intervention received, time since last melanoma diagnosis, baseline FCRI Severity scores, and satisfaction with the intervention) and found that baseline (pre-intervention) FCR severity was the only significant moderator. Higher FCR severity at baseline was associated with a greater decrease in FCR severity at 6-months post-intervention. This suggests that people with higher FCR were more likely to derive benefit from the intervention, and that the intervention was successful in targeting the primary outcome of interest (i.e., FCR; Dieng et al., 2016b). The data did not support our hypothesis that participants who received a greater dose of the intervention (i.e., longer duration with the psychologist, more thorough engagement with *Melanoma: Questions and Answers*) would report a greater decrease in FCR than those who were less engaged with the intervention. In addition, while information was perceived by many as a helpful component of the intervention, change in melanoma-related knowledge was not related to change in FCR severity. Previous research has shown that psycho-educational interventions can lower distress amongst people with melanoma (McLoone et al., 2013a) and that supportive psychotherapy, where participants have opportunities to discuss the issues most important to them, can reduce distress in other cancer populations (Classen et al., 2001; Breitbart et al., 2018). Overall, our findings suggest that regardless of factors such as participant sex, intervention dose, and time since last melanoma diagnosis, the intervention had the greatest impact on those who reported the greatest need.

Study Limitations

Several limitations warrant discussion. Three participants (4%) reported not remembering how thoroughly they read their resources, as the survey was administered 6 months after receiving the booklets, suggesting recall bias may have affected the accuracy of process evaluation results (Bowling, 2005). The moderator analysis showed that baseline FCRI Severity scores, a participant characteristic and not a process component, was the only factor that predicted change in FCRI Severity scores. Although our results suggest potential benefits of pre-intervention screening, baseline FCRI Severity scores were analyzed as a continuous variable in the regression and it was beyond the scope of this study to determine what constitutes a "high" baseline score. Data on the proportion of psychotherapy sessions that covered various topics or themes provided insight into the nature and scope of the sessions; however, further information could be gathered on potential patterns in session

content and themes, the total time spent discussing different themes, and whether this affected intervention outcomes. While this analysis would be time-consuming and resource heavy, it could provide highly valuable insights into specific mechanisms of, or pathways to, psychotherapeutic outcomes and effects.

Barriers that may have impeded intervention implementation were measured only from the patient perspective, limiting our understanding of other factors that may have influenced treatment engagement. Future research is needed to explore barriers experienced by psychologists when facilitating and delivering psychological interventions, as well as systemic and environmental factors, to better understand the feasibility of implementing this and other psychological interventions in routine clinical practice. Finally, most of the researchers involved in the design, implementation, and outcome evaluation of the intervention were also involved in the process evaluation and were not blinded to treatment condition. This may have introduced potential biases in how data were presented and interpreted. Separating process evaluation and outcome evaluation teams could be considered in future research. Pros and cons of separating or integrating process and outcome evaluation teams have been discussed elsewhere (Moore et al., 2015).

Recommendations for Translation into Clinical Practice and Future Research

Process evaluations are an important adjunct to outcome studies as they enhance researchers' ability to interpret intervention outcomes and provide valuable evidence to inform translation into clinical practice. The results of this process evaluation support a number of recommendations (**Table 8**) for effective delivery of a psychological intervention targeting fear of cancer recurrence amongst melanoma patients.

Our findings demonstrate the ways in which future trials would benefit from inclusion of a structured process evaluation. In addition, we offer the following recommendations for future research:

- This study showed that people with higher levels of FCR at baseline reported the greatest decrease in FCR post-intervention; however, there is currently no consensus regarding what cut-off score constitutes "high" FCR, nor what score is indicative of referral for intervention. Brief measurement tools have shown promise and may reduce the cognitive burden on patients while quickly identifying those with greatest clinical need (Fardell et al., 2018; Rudy et al., 2020; Smith et al., 2020). Further research to identify a clinically-meaningful FCR cut-off score for people affected by melanoma will allow for pre-intervention screening and more precise targeting of treatments and interventions (Lebel et al., 2017). In terms of our intervention, having a clearly defined clinical cut-off score would also facilitate future research examining whether offering the intervention to those with clinical levels of FCR only would lead to different results and "active ingredients."
- Psycho-educational resources should include information and tools relating to different types of melanoma, moles,

TABLE 8 | Clinical recommendations based on outcomes of the process evaluation.

Outcome	Clinical recommendations
The psychological intervention was delivered as intended (high fidelity) and was well-received by participants.	• Implementation of the psychological intervention, into routine clinical care for Stage 0–II melanoma patients at high risk of new primary disease. • Assess fear of cancer recurrence and unmet information and support needs, and offer the intervention based on patient need and preference.
Satisfaction and perceived benefits of the educational resources (*Melanoma: Questions and Answers* and *Understanding Melanoma*) were high.	• In resource-limited environments, offering two resources to patients—one that provides brief information about melanoma (i.e., *Understanding Melanoma*) and one that contains detailed and tailored psychoeducation (i.e., *Melanoma: Questions and Answers*)—is a low-cost initial step to addressing unmet information and support needs.
Participants who received the intervention reported greater satisfaction with the Cancer Council booklet, compared with participants who received usual care. Intervention participants also perceived the quality of information and support throughout the study as greater than participants in the control group.	• Psychologist support is recommended in conjunction with informational and psycho-educational resources. • Psychologists can assist patients in utilizing and engaging with resource content, which may lead to higher levels of satisfaction with care. • A patient-centered psychological intervention including written information and opportunities to discuss and reflect on experiences with a trained mental health professional offers best practice care to patients.
Number and duration of telehealth sessions with a psychologist varied between participants in the intervention group.	• Up to three psychology sessions is likely to be sufficient for most Stage 0-III melanoma patients. • At least 3 sessions can be offered, though the number and duration of sessions should be tailored to each individual patient and should be timed around upcoming dermatological appointments (see **Figure 2**).
Nearly all intervention participants engaged in the psychology sessions. Distance-delivered sessions provided *via* telehealth were acceptable and rated low in terms of difficulty.	• Trained mental health professionals such as psychologists should be included as part of the clinical care team. • Tailored, patient-centered psychotherapy sessions should be implemented as part of routine care, and should provide opportunities to discuss patients' experiences of melanoma as well as their worries about upcoming clinic visits. • Distance-delivered interventions, provided *via* telehealth, minimize common barriers to accessing mental health care and are highly acceptable to melanoma patients.
Baseline fear of cancer recurrence was the only significant moderator of intervention effect.	• Routine FCR screening for all Stage 0–II melanoma patients prior to dermatological appointments may assist in identifying those people likely to derive the greatest benefit from interventions targeting FCR. • Wide dissemination of the intervention is strongly recommended, as factors such as participant sex, age, and time since melanoma diagnosis did not influence efficacy.

and skin self-examination, while appointment calendars and Smartphone apps may be optional or omitted, depending on patient age, smartphone use, and type of app.
- Intervention delivery by experienced psychologists who received tailored training and ongoing supervision proved highly successful in this study. Other implementation models, such as in-person or videoconference sessions with a psychologist, cancer nurse, or social worker, could also be considered in future research.
- The effectiveness of a stepped-care model, where resources are allocated based on patient preference and level of need, could also be explored. All patients could be offered screening using an FCR measure and then provided with the psycho-educational resource as a first step, followed by telehealth-based psychotherapy sessions for those with greater need. At a minimum, our findings suggest telehealth-based sessions should include discussions about the patient's melanoma experience, unmet information needs, and concerns regarding upcoming dermatology appointments.

Conclusions

Overall, the findings of this process evaluation confirm that the published psychological intervention aimed at reducing FCR amongst individuals at high-risk of developing another melanoma was feasible and highly effective, implemented as intended, very well-received by participants, and led to numerous benefits for participants. Results suggest the "active ingredients" of our intervention included increased engagement with melanoma-related information, and highly accessible support from a trained and experienced mental health professional. The clearest recommendation for implementation into routine care is FCR screening to identify those most likely to derive the greatest benefit from intervention referral; however, given the lack of consensus regarding a clinical cut-off score in this population and our observation that participants may derive other health and educational benefits, we cannot conclude that this intervention should be provided only to patients who report "high" FCR without further investigation. Guidelines and suggestions for how FCR can be managed in clinical practice have been outlined elsewhere (Butow et al., 2018; Mutsaers et al., 2020). General recommendations follow a stepped care approach, including routine use of an FCR measure (especially at the end of cancer treatment and during follow-up appointments), and provision of psychoeducational resources and sessions with a trained mental health professional, when indicated. Implementation in clinical settings is a vital next step if we are to provide all melanoma patients with the opportunity to access care that is person-centered and meets their medical, informational and psychological needs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Sydney Local Health District Ethics Review Committee, Department of Health and Ageing Human Research Ethics Committee, the University of Sydney Human Research Ethics Committee, and the Australian Institute of Health and Welfare Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NK, AC, MD, PB, DC, RM, SWM, SM, and GM: conception and design. AC, NK, and GM: financial support. NK and SWM: provision of study materials or patients. MD, AC, NK, and ST: collection and assembly of data. JK, DC, NK, SM, and ST: data analysis and interpretation. JK, NK, ST, MD, DC, PB, SWM, RM, GM, and AC: manuscript writing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.661190/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Can Physical Activity and Healthy Diet Help Long-Term Cancer Survivors Manage Their Fear of Recurrence?

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Objective: Fear of cancer recurrence (FCR) adversely affects quality of life, but health behaviors such as physical activity (PA) and fruit and vegetable intake (FVI) may help alleviate FCR for some survivors. This cross-sectional study tested the common-sense model (CSM) of FCR by investigating associations between constructs from the CSM (perceived illness consequences, control over health, and timeline), and survivors' health behaviors, health self-efficacy, and FCR.

Methods: Using wave 3 data from the American Cancer Society Longitudinal Study of Cancer Survivorship-I, path analyses were conducted among mixed-cancer participants (N = 2,337) who were on average 8.8 mean years post-diagnosis.

Results: A final good fitting model [χ^2 (5, N = 2,337) = 38.12, $p < 0.001$; SRMR = 0.02; CFI = 0.99; RMSEA = 0.05] indicated that perceiving fewer illness consequences, and greater control over one's health, were directly associated with higher PA (β = 0.15 and −0.24, $p < 0.01$, respectively) and higher health self-efficacy (β = 0.24, −0.38, $p < 0.01$, respectively). Timeline (i.e., perceiving cancer as chronic) was directly associated with lower health self-efficacy (β = −0.15, $p < 0.01$) and higher FCR (β = 0.51, $p < 0.01$). Both greater PA and FVI were directly associated with higher health self-efficacy (β = 0.10 and 0.11, $p < 0.01$, respectively) which in turn showed a direct association with lower FCR (β = −0.15, $p < 0.01$).

Conclusion: Increasing survivors' sense of control over health, decreasing perceived chronicity of the illness, and mitigating its consequences may increase their health behaviors and health self-efficacy, which in turn could decrease their FCR. Longitudinal and experimental studies are needed to confirm these findings.

Keywords: cancer survivors, common-sense model, diet, fear of cancer recurrence, self-efficacy, physical activity

INTRODUCTION

The population of cancer survivors is growing in North America (American Cancer Society, 2016). After cancer treatment, cancer survivors are left facing several psychosocial challenges, including fear of cancer recurrence (FCR; Simard et al., 2013; Simonelli et al., 2017). FCR is defined as the fear, worry, or concern relating to the possibility that cancer will come back or progress (Lebel et al., 2016). Thus far, FCR research has mainly focused on identifying detrimental coping responses to FCR (i.e., reassurance seeking, body checking, and avoidance), which contribute to the maintenance of cancer survivors' distress. Helpful coping responses to manage FCR, however, remain understudied (Simard et al., 2013).

With the growing body of evidence demonstrating that lifestyle changes have a countering effect on cancer progression/recurrence and promote healthy survivorship (Pekmezi and Demark-Wahnefried, 2011), cancer survivors are encouraged by health care practitioners to engage in health behaviors (i.e., physical activity and healthy diet). Specifically, the American Cancer Society recommends that cancer survivors engage in 150 min of moderate physical activity or 75 min of vigorous physical activity weekly and the intake of at least five portions (5-a-day) of fruits and vegetables each day (Kushi et al., 2012).

While the role of health behaviors in reducing the risk of cancer recurrence in survivors is well-established, little is known of their impact on FCR. Specifically, can engaging in health behaviors help survivors manage their FCR? Investigating relationships between FCR and health behaviors is a first, necessary step before further testing the hypothesized role of health behaviors as a positive coping strategy in longitudinal or experimental studies. Leventhal's common-sense model (CSM) of self-regulation and Bandura's self-efficacy theory were used as theoretical frameworks to examine these relationships.

Conceptualizing FCR Using the Common-Sense Model

The CSM is the most comprehensive and evidenced-based theoretical approach applied to FCR (Fardell et al., 2016). Originally developed to encompass the cognitive, behavioral, and emotional responses to various illnesses (Leventhal et al., 1992), Lee-Jones et al. (1997) applied the CSM components to the context of cancer in their FCR theoretical formulation. The CSM components have since been empirically validated in cancer survivors (Fardell et al., 2016; Simonelli et al., 2017). According to this theoretical formulation, when an *illness threat* (triggers, i.e., aches and pains) is perceived, it activates the cancer survivor's *illness representation* informing the selection of *coping* response, which will ultimately influence the illness and emotional *outcomes*, including FCR (Leventhal et al., 1992; Lee-Jones et al., 1997).

The illness representation is comprised of five illness attributes: *illness identity* – refers to the illness label (cancer) and related symptoms (e.g., fatigue); *consequences* – refers to the perceived impact of cancer on an individual's life, including social, psychological, and physical consequences (e.g., impact on family); *control* – refers to the perceived level of control over cancer or curability by oneself or others (e.g., incurable, recurrence preventable); *timeline* – refers to the perceived time frame of cancer growth, illness course, and recovery (e.g., acute, chronic, or cyclical); and *causes* – refers to the perceived cause of cancer (e.g., stress, unhealthy lifestyle, or family history; Leventhal et al., 1992).

These attributes will inform the coping response chosen by the patient to manage emotional (typically with emotion focused coping) and/or illness outcomes (typically with problem-focused coping; Hagger et al., 2017). In samples of chronically ill patients, illness identity, consequences, and timeline are often correlated with emotion-focused coping, while control is more related to problem-focused coping (Richardson et al., 2016; Hagger et al., 2017). Health behaviors are generally conceptualized as problem-focused coping to manage illness outcomes (Richardson et al., 2016; Hagger et al., 2017); however, they have been shown to help manage emotional outcomes such as depression and quality of life (Aguiñaga et al., 2018). Therefore, from a theoretical standpoint, it is possible that health behaviors can help manage FCR, an emotional outcome.

Conceptualizing Health Behaviors as a Coping Strategy

Based on the CSM, if health behaviors are a coping response to FCR, cancer survivors with an illness representation that is indicative of a more severe illness (e.g., those who perceive cancer to be chronic or its consequences to be more significant) are expected to engage in more physical activity (PA) and fruit and vegetable intake (FVI). Subsequently, if these coping strategies are appraised as effective, FCR should be reduced. The few studies using the CSM framework to test the relationship between illness representation, PA and FVI, have yielded mixed results (Mullens et al., 2004; Costanzo et al., 2011; Burris et al., 2012; McGinty et al., 2012; Green et al., 2014), suggesting the need for further investigation.

Additionally, previous studies of FCR and health behaviors using the CSM were restricted to one or two disease sites and confined to early survivorship (i.e., 2 years post active treatment; Stanton et al., 2015) limiting their generalizability. Additional studies are required to clarify the contradictory findings using a large sample of survivors with a range of cancer diagnoses.

Adding Self-Efficacy

In the context of cancer survivorship, self-efficacy is defined as the perceived confidence in handling problems related to one's health (Bandura, 1997). In one study, the inclusion of self-efficacy improved the fit of the CSM in predicting personal control over illness in older adults with 10 different chronic diseases (Schüz et al., 2012). Additionally, several studies have found that self-efficacy played a mediating role in predicting FCR. For example, improvements in self-efficacy were found to mediate the effects of a brief communication intervention on FCR (Shields et al., 2010), between FCR vulnerability factors such as trait anxiety and cancer reminders and FCR in women with breast cancer (Ziner et al., 2012), and between physical

symptoms and FCR in men with prostate cancer (Torbit et al., 2015). In the present study, health self-efficacy was conceptualized as the appraisal of the coping response (i.e., the health behaviors) and was expected to mediate the relationship between the coping and the emotional outcome, FCR.

Study Objectives

This cross-sectional study aimed to explore the relationships between constructs from the CSM and self-efficacy theory, and health behaviors (PA and FVI) and FCR in a population-based sample of survivors of 10 cancers [tobacco use was not included in the current analyses as its relationship with FCR was the focus of a separate study by Westmaas et al. (2019)]. We used data from wave 3 of the American Cancer Society's Study of Cancer Survivors-I (SCS-I) because only the wave 3 survey included assessment of three constructs from the CSM (described below) in addition to health behaviors, self-efficacy, and FCR. The following relationships were expected (see **Figure 1**):

1. Illness representation → health behaviors: cancer survivors who reported (a) more illness consequences, (b) more control, and (c) viewed cancer as chronic were expected to report more health behaviors. (2) Health behaviors → self-efficacy: survivors who endorsed more health behaviors were expected to report greater self-efficacy. (3) Self-efficacy → FCR: survivors who reported greater self-efficacy were expected to display lower FCR. Similar trends were hypothesized for both health behaviors, PA and FVI (Mullens et al., 2004; Costanzo et al., 2011; Burris et al., 2012; Green et al., 2014).

MATERIALS AND METHODS

Procedure

The current cross-sectional study is part of a larger longitudinal study examining FCR and health behaviors (Séguin Leclair et al., 2019) using data from the American Cancer Society's SCS-I, a national prospective longitudinal study of American cancer survivors with data collected in three waves beginning in 2000, T1, M = 1.3 years (SD = 0.32), T2, M = 2.2 years (SD = 0.34), and T3, M = 8.8 years (SD = 0.63) post cancer diagnosis. Participant eligibility criteria were the following: diagnosed with one of the 10 most highly incident cancers [prostate, breast, lung, colorectal, bladder, non-Hodgkin lymphoma (NHL), skin melanoma, kidney, ovarian, and uterine], over 18 years old at diagnosis, residing in one of the target states at the time of diagnosis, and diagnosed with a local, regional, or distant SEER Summary Stage cancer. Survivors were ineligible for the study if they were unable to complete the survey due to mental incompetence, unable to communicate in

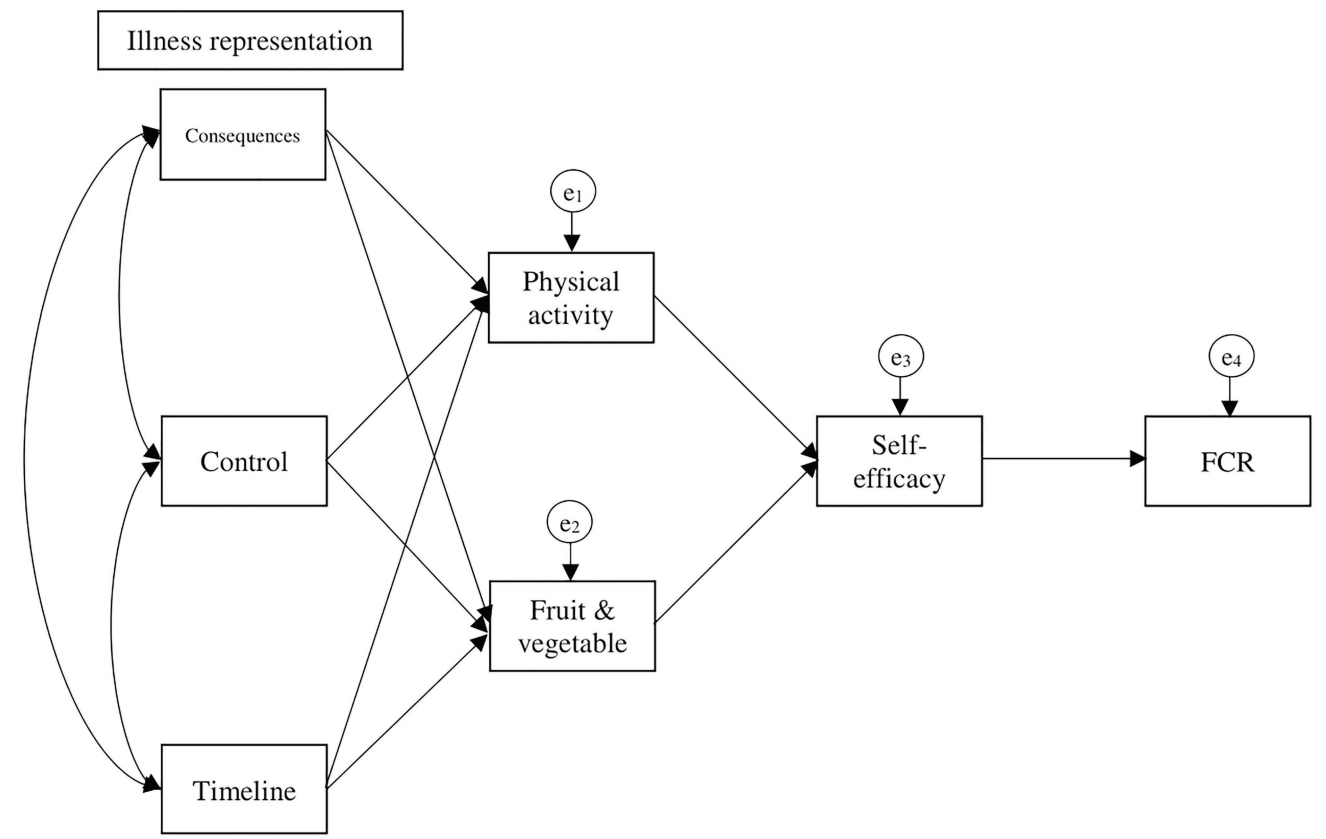

FIGURE 1 | Hypothesized model based on the theoretical FCR common-sense model (Lee-Jones et al., 1997) and self-efficacy theory (Bandura, 1997).

English or Spanish, or had terminal illness (Smith et al., 2007). The studies were approved by the Institutional Review Board of Emory University (Atlanta, GA, United States), for each state, including the Connecticut Department of Public Health Human Investigation Committee, and the University of Ottawa Research and Ethics Board (Ottawa, Ontario). Additional details on recruitment and methodology are available elsewhere (Smith et al., 2007).

Measures

Socio-Demographic and Medical Characteristics

The following socio-demographic and medical variables were examined and controlled for: age at diagnosis, sex, ethnicity, education, cancer site, and cancer stage based on their known relationship with FCR (Séguin Leclair et al., 2019). Relationship status, family income, and occupation were included for sample description purposes only.

Illness Representation Attributes

Illness Consequences

Illness consequences were measured using the Medical Outcomes Study Short Form – Physical Health subscale (Ware et al., 1996). Using a 5-point Likert scale, respondents indicated their perception of physical functioning, impact of health on various roles, bodily pain, and general health. For example, "*During the past 4 weeks, how much of the time did you accomplish less than you would like as a result of your physical health?*" This measure has good test–retest reliability after 2 weeks (r = 0.86) and construct validity (r = 0.91) with the original Medical Outcomes Study Form. Final scores ranging from 0 to 100 were obtained by computing items scores and comparing them to age-specific reference groups. Higher scores indicated less illness consequences.

Control

The 9-item Perceived Health Competence Scale (Smith et al., 1995; Arora et al., 2002) was used to determine respondents' impression of their ability to control their health. Items were rated on 5-point Likert scales ranging from strongly disagree to strongly agree (Cronbach's α = 0.87). For example, "*No matter how hard I try, my health just does not turn out the way I would like*." Total scores were computed, with higher scores indicating less control over health.

Timeline

The perceived time frame of the cancer (i.e., acute vs. chronic) was assessed using the susceptibility subscale of the Revised Health Belief Model Scale (Champion, 1999). These three items used a 5-point Likert scale ranging from *strongly agree* to *strongly disagree*; respondents indicated their perceived susceptibility of getting a cancer recurrence. For example, "*It is likely that I will get cancer again*." It showed good internal consistency (α = 0.87), good test–retest reliability after 6 weeks (r = 0.62), and good construct validity (r = 0.87–0.91) with the original Susceptibility subscale of the Health Belief Model Scale (Champion, 1999). Total scores were computed, with higher scores indicating higher perceived chronicity of cancer.

Health Behaviors

Physical Activity

The Leisure-Time Exercise Questionnaire (LTEQ) was used in this study to assess PA. Respondents indicated the number of minutes they spent doing mild, moderate, and vigorous physical activity in a typical week (Godin and Shepard, 1985). The scale has shown good test–retest reliability after 2 weeks (r = 0.74) and good convergent validity with maximum oxygen intake (r = 0.83) and values of body fat (r = 0.85; Godin and Shepard, 1985). For the analysis, the total number of minutes spent doing moderate and vigorous PA weekly were computed (Kushi et al., 2012).

5-A-Day: Fruit and Vegetable Intake

The 5-A-Day measure is a one item questionnaire developed by the ACS to measure adherence to the recommended five servings of fruits and vegetables a day (Smith et al., 2007). Respondents indicated in a typical week in the past month, how many days per week they consumed the daily five servings of fruits and vegetables.

Self-Efficacy

The 8-item Perceived Health Competence Scale (Smith et al., 1995) has shown good internal consistency (α = 0.82–0.90) and construct validity in healthy and chronically ill samples (Smith et al., 1995). An example of an item is "*I'm generally able to accomplish my goals with respect to my health*." Higher total scores indicate a greater self-efficacy to manage health.

Fear of Cancer Recurrence

Fear of cancer recurrence was assessed using the 9-item Fear of Cancer Recurrence Inventory-Short Form (FCRI-SF; Simard and Savard, 2009). An example of an item is "*I am worried or anxious about the possibility of cancer recurrence*." The FCRI-SF ranges from 0 to 32, has good internal consistency (α = 0.89) and good test–retest reliability after 1 month (r = 0.80; Simard and Savard, 2009). The initial cut-off score for clinical FCR was 13 (Simard and Savard, 2009) but additional studies have suggested cut-off scores of 16 and 22 (Fardell et al., 2018).

Data Analysis Strategy

Data were screened and cleaned using IBM SPSS 25. See Séguin Leclair et al. (2019) for detailed description of sample selection. Means, SD, and bivariate correlations were computed for all model variables. Statistical assumptions for regression analysis were verified.

Path analysis was conducted to test the hypothesized model (see **Figure 1**) using IBM AMOS at a level of significance $p < 0.05$. Path coefficients were standardized to facilitate comparison and interpretation of data. Bootstrapping with 2,000 samples and 95% CIs was used to calculate indirect effects. Model fit was established using the following goodness-of-fit indices with corresponding criteria: a small and non-significant chi-square likelihood ratio statistic (χ^2), standardized root mean square residual (SRMR) $\leq$ 0.08, comparative fit index (CFI) $\geq$ 0.95, and root mean square error of approximation

(RMSEA) ≤ 0.06 (Hayduk et al., 2007). Using the modification indices proposed by AMOS, additional regression weights were sequentially added to the model until the goodness-of-fit indices reached previously mentioned criteria. Concurrently, theoretical meaning was considered before the addition of parameters in the model. Adequate sample size was reached for the total sample (with 19 model parameters the minimum sample size required is n = 190), based on the suggested 10 participants/parameter (Kline, 2015). Given that variables met the normality assumption, the maximum likelihood estimation method was used.

RESULTS

Study Sample

The 2,337 participants in this sample were mostly Caucasian (89.9%) women (60.4%) with college education or more (68%) and with a mean age of 56 at diagnosis. The most common cancer sites were breast (28.6%), prostate (21%), and colorectal (13.6%). See **Table 1** for all participants' socio-demographic and medical characteristics.

TABLE 1 | Participant characteristics, N = 2,337.

Variable	*M*	*SD*
Age at diagnosis (years)	**56.22**	**11.19**
Time since diagnosis (years)	**8.8**	**0.63**
	n	***%***
Sex		
Male	936	39.6
Female	1,411	60.4
Ethnicity		
Caucasian	2,100	89.9
African American	116	5
Hispanic	66	2.8
Other	45	1.9
Not indicated/missing	10	0.4
Education		
High school or less	727	31.1
College or more	1,588	68
Not indicated/missing	22	0.9
Cancer type		
Breast	668	28.6
Prostate	490	21
Colorectal	317	13.6
Uterine	152	6.5
NHL	152	6.5
Melanoma	139	5.9
Kidney	127	5.4
Lung	103	4.4
Ovarian	100	4.3
Bladder	89	3.8
Cancer stage		
Stage 0–1	1,649	70.6
Stage 2–3	688	29.4
Civil status		
Married/cohabitating	1,813	77.6
Divorced/separated	226	9.7
Widowed	145	6.2
Single	145	6.2
Not indicated/missing	8	0.3
Household income		
0–9,999	57	2.4
10,000–19,999	144	6.2
20,000–39,999	456	19.5
40,000–74,999	749	32
75,000 or more	641	27.4
Not indicated/missing	290	12.4
Occupation		
Employed full-time	1,127	48.2
Employed part-time	196	8.4
Retired	577	24.7
Homemaker	148	6.3
Leave or unemployed due to illness	119	5,1
Unemployed	73	3.1
Student	9	0.4
Not indicated/missing	88	3.8

Descriptive Statistics and Correlations for Model Variables

Table 2 displays the means, SDs, and bivariate correlations for the seven variables (illness consequences, control, timeline, physical activity, FVI, self-efficacy, and FCR) in the hypothesized model. Overall, survivors reported an average score of M = 11.4 (SD = 7.1) on the FCRI-SF, with 32.9% scoring above the clinical cut-off >13. The average number of days participants consumed five servings of fruits and vegetables per week was 3.31 days (SD = 2.17). Participants reported engaging in 97.59 (SD = 151.28) min of moderate to vigorous physical activity per week.

Path Analysis

The hypothesized model was tested but yielded poor goodness-of-fit indices, χ^2 (9, N = 2,337) = 1718.72, p < 0.001; SRMR = 0.16; CFI = 0.49; RMSEA = 0.29. By adding four additional paths as suggested by the modification indices, the model fit improved [χ^2 (5, N = 2,337) = 38.12, p < 0.001; SRMR = 0.02; CFI = 0.99; RMSEA = 0.05; see **Figure 2**]. The chi-square likelihood ratio statistic remained significant, but the model was deemed acceptable given its large sample size.

The final model indicated that both perceiving fewer illness consequences, and greater control over one's health, were directly associated with higher PA (β = 0.15 and −0.24, p < 0.01, respectively) but also higher health self-efficacy (β = 0.24, −0.38, p < 0.01, respectively). Timeline was not directly associated with PA or FVI but was associated with lower health self-efficacy (β = −0.15, p < 0.01) and higher FCR (β = 0.51, p < 0.01). Both greater PA and FVI were directly associated with higher health self-efficacy (β = 0.10 and 0.11, p < 0.01, respectively), which in turn was directly associated with lower levels of FCR (β = −0.15, p < 0.01).

Small indirect effects were also observed between illness perception variables and health self-efficacy and FCR: timeline had an indirect effect on FCR (β = 0.06, p < 0.01), control had indirect effects on health self-efficacy (β = −0.01, p < 0.01) and FCR (β = 0.10, p < 0.01), and illness consequences also had indirect effects on health self-efficacy (β = 0.001, p < 0.01) and FCR (β = −0.02, p < −0.01). Last, PA and FVI had small indirect effects on FCR (β = −0.001 and −0.05, p < 0.01, respectively).

TABLE 2 | Means, SDs, and bivariate correlations for the seven variables in the hypothesized model (n = 2,337).

Variable	*M*	*SD*	1	2	3	4	5	6	7
1. Consequences	48.47	11.06	-						
2. Control	13.53	4.48	−0.46**	-					
3. Timeline	8.26	2.68	−0.20**	0.17**	-				
4. Physical activity	97.59	151.28	0.27**	−0.32**	−0.10**	-			
5. Fruit and vegetable	3.31	2.17	0.12**	−0.23**	−0.06**	0.16*	-		
6. Self-efficacy	3.57	0.63	0.48**	−0.57**	−0.28**	0.32**	0.26**	-	
7. FCR	11.40	7.08	−0.23**	0.16	0.55**	−0.09**	−0.05*	−0.29**	-

*FCR, fear of cancer recurrence measured with the Fear of Cancer Recurrence Inventory-Short Form. *p < 0.05; **p < 0.01.*

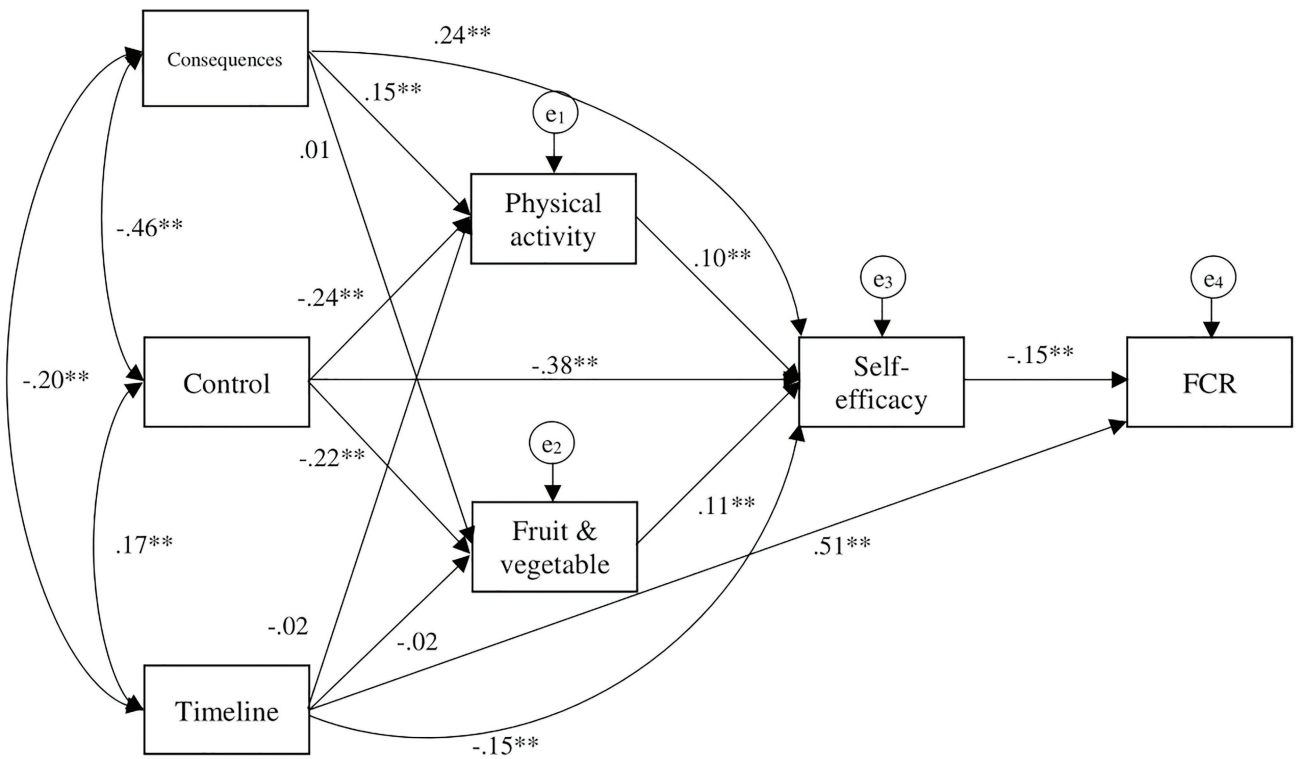

FIGURE 2 | Final model path analysis diagram with standardized coefficients **p < 0.01.

DISCUSSION

The goal of this study was to explore the relationship between health behaviors (PA and FVI) and FCR in a population-based sample of mixed long-term cancer survivors using the CSM and self-efficacy theory.

As hypothesized, survivors who perceived more control over health reported more PA and FVI. These results are congruent with the body of CSM literature, where perceived control is an important predictor of health behaviors in chronically ill samples (Richardson et al., 2016; Hagger et al., 2017). Contrary to our hypothesis, illness consequences and timeline were, for the most part, uncorrelated with health behaviors. Also as hypothesized, cancer survivors reporting more health behaviors endorsed greater health self-efficacy, which in turn correlated with lower levels of FCR.

The relationships between health behaviors and the CSM illness attributes lends tentative support for their conceptualization as problem-focused coping behaviors used to manage illness outcomes. While emotion-focused coping tends to be associated with consequences and timeline, problem-focused coping is strongly related to perceived control (Richardson et al., 2016; Hagger et al., 2017), which the present study also found.

Additional paths revealed another important factor predicting FCR. Specifically, timeline was the variable that showed the strongest association with FCR, congruent with previous studies (Phillips et al., 2013; Moon et al., 2017). In addition, survivors who perceived more illness consequences, their cancer to be chronic, and less health-related control reported lower self-efficacy, which in turn was related to higher FCR. Of course, no causality can be assumed in the present preliminary cross-sectional study and it is possible that survivors with lower

FCR report greater health self-efficacy, which could contribute to their adherence to recommended health behaviors. Longitudinal and experimental studies are needed to confirm the present findings.

Study Limitations

Although the American Cancer Society had developed a protocol to obtain an optimal sample of American cancer survivors, individuals who completed the questionnaire packages have specific characteristics, such as being female, White, and higher education (Smith et al., 2007). This limits the generalizability of findings. In addition to its cross-sectional design, this study captured FCR, CSM, self-efficacy, and health behaviors later in the cancer survivorship trajectory. While FCR severity was found to be stable across the three waves of data of the SCS-I (Séguin Leclair et al., 2019), factors in the CSM model have been shown to fluctuate over time (Leventhal et al., 2016). Furthermore, information of disease recurrence/progression was not available. Future studies should monitor health behaviors, including changes in these behaviors from pre-diagnosis, and CSM factors periodically throughout the survivorship trajectory, controlling for possible recurrence/progression (Leventhal et al., 2016). While the questionnaires used to assess illness representation components in this study were adequate measures of the constructs, the Revised Illness Perceptions Questionnaire was not used in this study (Moss-Morris et al., 2002). Given that this measure is commonly used in other CSM studies, this limits generalizability across studies. Moreover, the perceived cause of cancer recurrence, another component of illness representation in the CSM model, was not included in the original SCS-I survey questionnaire. As previous studies have consistently shown, causal attribution of cancer to poor diet or lack of exercise predicts adherence to health behaviors (Mullens et al., 2004; Costanzo et al., 2011; Burris et al., 2012); the absence of this measure might limit the understanding of factors predicting health behaviors. This study only focused on one possible emotional outcome outlined in CSM, FCR. Future studies could include additional outcomes that are associated with illness representation such as psychological distress (Llewellyn et al., 2007).

Future Directions

It would be important to replicate the present study using a longitudinal design that would allow taking into account FCR trajectories, given the emerging empirical evidence that cancer survivors can be classified into three FCR severity sub-groups: low, moderate, and high, which have distinct survivorship profiles and patient characteristics (Simard and Savard, 2009; Simonelli et al., 2017; Séguin Leclair et al., 2019). As part of the larger study (Séguin Leclair et al., 2019), we found three stable FCR trajectories (low, moderate, and high); furthermore, cancer survivors in the high FCR trajectory group engaged in less health behaviors than other survivors. Therefore, it is possible that health behaviors may play less of a role in modulating FCR for those with persistently high FCR. It would also be interesting to see if these relations we observed in the present sample differ by sex, ethnicity, or cancer stage.

Clinical Implications

The results of this study offer preliminary evidence that engaging in PA or consuming fruits and vegetables may increase health self-efficacy, which in turn may be beneficial to manage FCR in long-term survivors. In a previously published paper using the three waves of data from the SCS-I, we also found that survivors who quit smoking at T1 reported significant reductions in FCR at T3 compared to those who continued smoking (Westmaas et al., 2019). Together, these results support stepped care models that propose that all survivors would receive educational programs on health behaviors to help manage FCR (Stanton, 2012). The CSM showed a good fit across participants, further supporting its use in current FCR conceptualizations (Fardell et al., 2016; Simonelli et al., 2017) and interventions (Maheu et al., 2016; Butow et al., 2017). Timeline (i.e., perceiving cancer to be chronic) stood out as the strongest correlate of FCR in the model; hence interventions targeting the perceived chronicity of cancer may help cancer patients manage their FCR. Furthermore, improving cancer survivors' self-efficacy to manage their health could be an FCR intervention target.

CONCLUSION

Overall, the CSM, with the addition of self-efficacy, showed a good fit in the present sample of mixed long-term cancer survivors, in line with recent recommendations to combine both theoretical frameworks to improve the management of chronic illness (Breland et al., 2020). This study found that engaging in recommended health behaviors was correlated with increased health self-efficacy. Timeline and health self-efficacy were related to FCR and could be incorporated in future FCR interventions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Emory University (Atlanta, GA, United States), for each state, including the Connecticut Department of Public Health Human Investigation Committee, and the University of Ottawa Research and Ethics Board (Ottawa, Ontario). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Psychosocial Impact of Cancer Care Disruptions in Women With Breast Cancer During the COVID-19 Pandemic

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Background: The COVID-19 pandemic caused significant disruptions in cancer care, and preliminary research suggests that these disruptions are associated with increased levels of psychosocial distress among cancer survivors. The purpose of this study was to offer a descriptive report of the psychosocial functioning, perceived risk and fear of cancer progression, and COVID-19 pandemic impact and experiences in a unique, high-risk patient cohort: breast cancer survivors whose cancer treatment was delayed and/or changed due to the COVID-19 pandemic.

Methods: This cross-sectional study included 50 women with dual carcinoma *in situ*, lobular carcinoma *in situ*, or invasive breast cancer whose cancer surgery was postponed due to the pandemic. As they awaited delayed surgery or shortly after they received delayed surgery, participants completed questionnaires on psychosocial functioning (depression, anxiety, sleep, and quality of life), their perceived risk and fear of cancer progression, patient-provider communication about disruptions in their care, personal impact of the pandemic, worry/threat about COVID-19, and COVID-19 symptoms/diagnoses. Descriptive statistics and bivariate correlations were computed among continuous study variables. Independent samples *t*-tests explored group differences in psychosocial functioning between survivors who were still awaiting delayed surgery and those who had recently received it.

Results: Overall, the sample denied that the pandemic seriously negatively impacted their finances or resource access and reported low-to-moderate levels of psychosocial distress and fear about COVID-19. Twenty-six percent had clinically significant levels of fear of cancer progression, with levels comparable to other recent work. About a third were still awaiting delayed cancer surgery and this group reported lower satisfaction with communication from oncology providers but overall did not seem to report more psychosocial difficulties than those who already had surgery.

Conclusion: Shortly before or after primary breast cancer surgery that was delayed due to the COVID-19 pandemic, this sample of survivors appears to be generally managing well psychosocially. However, many psychosocial difficulties (e.g., fear of cancer recurrence/progression) typically have an onset after the completion of treatment, therefore, research should continue to follow this cohort of cancer survivors as the pandemic's direct impact on their care likely increases their risk for these difficulties later in survivorship.

Keywords: fear of cancer recurrence, fear of cancer progression, breast cancer, COVID-19, cancer survivorship

INTRODUCTION

As of April 2021, there have been over 135 million COVID-19 cases and nearly 3 million deaths due to COVID-19 globally (WHO Coronavirus Disease (COVID-19) Dashboard, 2021). Individuals with cancer are at particularly elevated risk of a severe course of COVID-19 because they tend to be of older age (American Cancer Society, 2019) and are at a greater risk for needing intensive care and for mortality (Saini et al., 2020; Tian et al., 2020).

In the United States, the COVID-19 pandemic caused significant disruptions in non-COVID-related health care including cancer care. On March 13, 2020, the American College of Surgeons recommended that elective surgical procedures – including most cancer surgeries (John Hopkins Medicine, 2020) – be postponed to prevent COVID-19 transmission among health care providers and patients and mitigate the resource burden on the health care system (American College of Surgeons, 2020). In a survey on the impact of the COVID-19 pandemic on cancer survivors, 50% reported delays and/or changes in their health care (American Cancer Society Cancer Action Network, 2020). Among survivors with active cancer, 55% reported delays and/or changes in their health care, 13% reported not knowing when their care would be rescheduled, and 8% reported delays and/or changes in their anti-cancer therapy (American Cancer Society Cancer Action Network, 2020). Among breast cancer survivors specifically, 44% reported disruptions in their cancer care (Papautsky and Hamlish, 2020). Note that here, the definition of survivor is a person from the time of diagnosis to end-of-life, including those awaiting or actively receiving cancer treatment (we adopt this definition and use the terms survivor and patient interchangeably throughout this article; National Cancer Institute, 2011). Disruptions in breast cancer care included not only breast cancer surgery delays, but also delays and/or changes across the cancer care trajectory (e.g., diagnostic imaging and lab testing, anti-cancer therapies, and follow-up appointments; Papautsky and Hamlish, 2020). Given the great deal of uncertainty in pandemic cancer care and the potential impact of disruptions in care on cancer outcomes, cancer survivors diagnosed and treated during the COVID-19 pandemic may be at a particularly elevated risk for long-term psychosocial distress and poor mental health (Young et al., 2020).

Decisions to disrupt cancer care must carefully weigh the relative risks of COVID-19 exposure (and community spread) and poorer cancer prognosis due to care disruptions. Indeed, the impact of delays in breast cancer care on mortality has been well-documented (Hanna et al., 2020; Ho et al., 2020). The results from a review and meta-analysis indicated that just a 4-week delay in breast cancer surgery is associated with an 8% increase in the risk of death, after adjusting for important prognostic indicators including cancer stage (Hanna et al., 2020). The review concluded that if all individuals diagnosed with breast cancer in 1 year's time were to experience a 12-week delay in surgery (e.g., due to a global pandemic), there would be an excess of 66,100 deaths in the United States alone (Hanna et al., 2020). A similar United Kingdom-based study predicted that these pandemic-related treatment delays will cause an 8–10% increase in breast cancer deaths in the first 5 years post-diagnosis (Maringe et al., 2020). Moreover, a study on excess mortality in individuals with cancer during the COVID-19 pandemic projected that there will be an excess of 33,890 deaths among this population in the United States as a result (Lai et al., 2020).

There have been numerous published guidelines to inform these complex decisions about cancer care during the COVID-19 pandemic (for reviews, see Garg et al., 2020; Zaniboni et al., 2020). For example, Smith et al. (2020) published recommendations for the prioritization of breast cancer surgeries delayed as a result of the pandemic. This system was developed using published data and the clinical judgment of a multidisciplinary breast oncology team. Per this system, each breast cancer survivor awaiting surgery is assigned a risk score based on patient and tumor factors, length of delay in cancer surgery, and for those who received neoadjuvant treatment, tumor response to this treatment. These scores form three classifications: (1) *Very urgent*, recommended the surgery in 2–4 weeks following the completion of chemotherapy; (2) *Limited delay acceptable*, recommended the surgery in 2–4 months (or longer if responding to neoadjuvant endocrine therapy); and (3) *Lowest priority*, recommended to wait until elective surgeries resume as usual. However, a recent review of the published guidelines for cancer care during the COVID-19 pandemic concluded that they are often discordant and based on limited evidence (Garg et al., 2020).

In addition to changes in health care systems and their decisions on prioritization, changes in functioning at the individual (person) level may also contribute to disruptions in cancer care during the COVID-19 pandemic. Breast cancer survivors who were diagnosed during the COVID-19 pandemic were found to refuse surgery at a higher rate than those diagnosed pre-pandemic, primarily due to fear of COVID-19 infection (Vanni et al., 2020). It seems those cancer survivors' psychological and behavioral reactions to the pandemic (e.g., COVID-19-related

fear) may be contributing to disruptions in care above and beyond those caused by system-level changes. Furthermore, COVID-19-related fear may be particularly high in this population. In a survey conducted with cancer survivors, caregivers, and healthcare workers early in the pandemic (i.e., April 2020), 66% of cancer survivors reported feeling "very much" or "extremely" fearful of COVID-19 – a rate significantly higher than that observed in healthcare workers (Ng et al., 2020). Compared to caregivers and health care workers, cancer survivors perceived themselves to be at greater risk for severe complications due to and non-recovery from COVID-19 (Ng et al., 2020). Evidence suggests that COVID-19-related fear may be highest among individuals with breast cancer as compared to individuals diagnosed with other cancers (the authors speculated that this may be due to gender differences; Sigorski et al., 2020).

In addition to uncontrollable system changes in their cancer care and their own psychological and behavioral responses to the pandemic, social distancing – strongly recommended for cancer survivors due to their high risk of COVID-19 infection – further increases this group's risk of psychosocial difficulties. This includes loneliness and isolation (Garutti et al., 2020), which are among the most potent psychosocial influences on mental and physical health (Hawkley and Cacioppo, 2010). Indeed, loneliness was a top concern among cancer survivors seeking psycho-oncology treatment during the COVID-19 pandemic (Schellekens and Lee, 2020). Among individuals being treated for breast cancer during the pandemic, one in two reported moderate or severe levels of loneliness (Bargon et al., 2021).

In addition to the high rates of psychological distress in the general population during the COVID-19 pandemic (Xiong et al., 2020), an emerging body of work has examined the psychosocial impact of the COVID-19 pandemic on cancer survivors. This emerging evidence suggests that during the COVID-19 pandemic, individuals with cancer experience higher levels of depression and anxiety than the general population as well as cancer survivors pre-pandemic (Chen et al., 2020; Han et al., 2020; Ng et al., 2020; Wang et al., 2020). Research conducted in the epicenter of the pandemic in China suggests that levels of depression and anxiety may be comparable among breast cancer survivors and frontline female nurses and that breast cancer survivors had even higher levels of insomnia (Cui et al., 2020).

Moreover, emerging evidence also suggests that disruptions in cancer care are related to these mental health symptoms (Chen et al., 2020; Swainston et al., 2020); breast cancer survivors who reported the discontinuation of their cancer treatment due to the pandemic were more likely to report moderate or severe symptoms of depression, anxiety, and insomnia (Juanjuan et al., 2020). In addition, cancer survivors whose cancer care has been impacted by the pandemic may be at risk for experiencing more fear of cancer progression (FCP), which is the "fear, worry, or concern relating to the possibility that cancer will come back or progress," (Lebel et al., 2016, p. 3266). Given the impact of cancer care disruptions on cancer outcomes, including mortality, FCP is a particularly relevant outcome for individuals diagnosed with cancer during the COVID-19 pandemic and whose cancer care was delayed or changed. Indeed, among breast cancer survivors, approximately 54% reported concerns regarding the efficacy of anti-cancer therapies that were delayed and/or changed due to the pandemic (Juanjuan et al., 2020). We are aware of two published studies examining FCP among cancer survivors during the COVID-19 pandemic (Chen et al., 2020; Massicotte et al., 2021). Among cancer survivors in the pandemic epicenter in China, 86.5% reported some degree of FCP, and importantly, the study found that having had disruptions in cancer care was significantly predictive of FCP (Chen et al., 2020). Another study conducted in Canada similarly found that among women with non-metastatic breast cancer receiving chemotherapy, 52.8% had clinically significant levels of FCP, but whether or not participants experienced treatment delays and/or changes due to the COVID-19 pandemic was not reported (Massicotte et al., 2021).

The primary aim of the present paper was to provide a comprehensive baseline characterization of the psychosocial functioning of a cohort of breast cancer survivors whose cancer care had been delayed and/or changed due to the COVID-19 pandemic in the United States. While prior studies examined psychosocial functioning among breast cancer survivors across the continuum of cancer care, little is known about the cohort whose surgery was delayed and/or changed due to the pandemic. Therefore, we conducted a cross-sectional study of survivors who were awaiting delayed surgery or who recently underwent delayed surgery. Our goal was to provide a broad description of a sample from this unique cohort who may be at high risk of experiencing long-term psychosocial sequalae as a result of the COVID-19 pandemic.

MATERIALS AND METHODS

Participants

Data were from a cross-sectional study titled *Impact of COVID-19 on Women Recently Diagnosed with Breast Cancer* (Christiana Care Health System IRB approval: FWA00006557; CCC# 40079). The purpose of this study was to examine the psychosocial impact of the COVID-19 pandemic on women diagnosed with dual carcinoma *in situ* (DCIS), lobular carcinoma *in situ* (LCIS), or invasive breast cancer whose cancer surgery was postponed as a result of the pandemic. Following from their surgery status, all potential participants had non-metastatic (operable) breast cancer (Stage 0 to III). Eligibility for the study included women who (1) were diagnosed with DCIS, LCIS, or invasive breast cancer, (2) whose cancer surgery was postponed as a result of the COVID-19 pandemic, and (3) spoke English. Note that although LCIS is neither technically considered cancer nor "pre-cancer," participants with DCIS/LCIS whose treatment plans included surgical intervention (i.e., excisional biopsy) to reduce the likelihood of disease progression and rule out any other disease process were included in this study. This decision was made based on the study's focus on concerns about disease progression, the levels of which have been found in prior research to be comparable across patients DCIS/LCIS and those with stage I cancer (Liu et al., 2011).

Christiana Care Health System postponed all elective surgical procedures on March 17, 2020. As a result, 172 breast surgeries

were postponed at Christiana Care's Helen F. Graham Cancer Center and Research Institute. Breast surgeries resumed at the Cancer Center on May 15, 2020. To prioritize the scheduling of the large backlog of breast surgeries, the Helen F. Graham Cancer Center and Research Institute used a combination of the recommendations made by the COVID-19 pandemic breast cancer consortium and the system created by Smith et al. (Dietz et al., 2020; Smith et al., 2020). Each pending breast surgery case was assigned a risk score based on patient and tumor factors (e.g., age, tumor grade, and size), the length of delay in cancer surgery (e.g., time since biopsy), and for those who received neoadjuvant treatment, tumor response to this treatment (e.g., imaging response score and physical exam response score). Higher scores reflected greater potential risk and, therefore, greater urgency for surgery. There were some changes to the specific protocol and scoring procedure as new data emerged during the pandemic, and as a result, about half of potential participants did not have documented risk scores using the system created by Smith et al. (2020).

Participant flow is detailed in **Figure 1**. Of the 172 cases pending for breast surgery, 41 had a diagnosis other than DCIS, LCIS, or invasive breast cancer (e.g., atypical ductal hyperplasia) and one was deceased by the start of the study. Of those contacted to participate (n = 130), 18 denied postponements in their cancer surgery, four did not speak English, 23 actively declined, and 10 passively declined. Seventy-five agreed by phone to participate and 50 completed the informed consent and cross-sectional survey.

As previously mentioned, breast surgeries at the Helen F. Graham Cancer Center and Research Institute resumed on May 15, 2020. Data collection for the present study occurred between June 27 and August 13, 2020. Therefore, by the time of data collection, most of the sample had received delayed breast cancer surgery (more detail described in section Results).

Procedure

A list of the pending breast surgery cases was maintained by the Helen F. Graham Cancer Center and Research Institute and was used to screen for potential eligibility. All cases with a diagnosis of DCIS, LCIS, or invasive breast cancer (n = 130) were mailed a letter containing an invitation to participate, a brief description of the study, and study contact information. Approximately 1 week after mailing this letter, all potential participants were contacted by phone by a clinical psychology doctoral student. During these phone calls, a script was used to invite potential participants to take part in the study, describe the study procedures, describe the potential risks and benefits of participation, and answer potential participants' questions about the study. Five potential participants indicated that they did not have access to the internet and were therefore offered

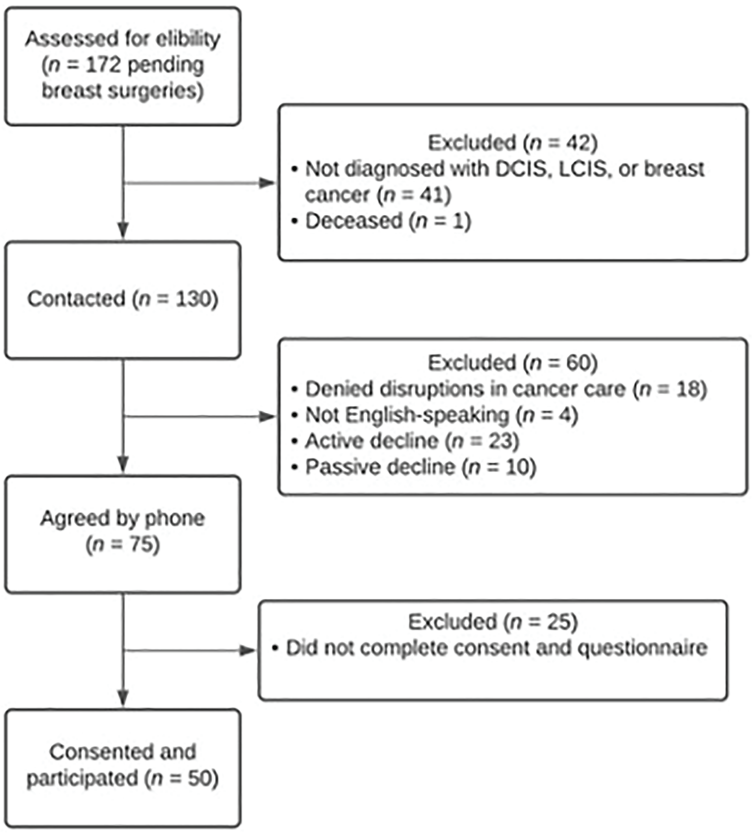

FIGURE 1 | Participant flow.

to complete the informed consent form and study questionnaire *via* mail. Those who could not be reached were contacted by phone up to two additional times (for a maximum of three phone calls) before being considered as passive decliners.

Those who agreed by phone to participate (n = 75) were sent additional information about the study, the informed consent form, and study questionnaire. Those who expressed interest in completing the informed consent and study questionnaire online were sent these materials *via* email (n = 70) and those who expressed interest in completing the informed consent and study questionnaire *via* mail (n = 5) were sent these materials *via* mail. Those who were sent study materials *via* email received up to three reminder emails and one reminder call (spaced approximately 4 days apart) if they had not yet completed the informed consent and study questionnaire online. Those who were sent the study materials *via* email were not provided with reminder emails or calls. Forty-nine participants completed the informed consent (signed and dated electronic form) and study questionnaire online and one participant completed the informed consent and study questionnaire *via* mail on paper, resulting in a total sample of 50 participants. Participants were not compensated for taking part in the study.

The informed consent form included an authorization for the request of medical information. This authorization was optional and if authorized, allowed the research staff to access participants' electronic medical records – specifically, medical oncology notes for more detailed clinical data such as breast cancer stage.

Materials

See the summary of measures administered in **Table 1**.

TABLE 1 | Measures administered.

Variable/measure	Description
Sociodemographic characteristics	Race, ethnicity, gender, education, and income
Cancer history and treatment	Prior cancer diagnoses and current cancer treatment
Patient-provider communication	Two items; content and perceived quality of communication re: COVID-19
COVID-19 impact	Five items; financial and resource access changes (Conway et al., 2020)
COVID-19-specific threat sensitivity	Three items; worry and perceived COVID-19 threat (Conway et al., 2020)
Cancer progression risk perception	Three items; perceived risk given COVID-19-related treatment changes
Fear of cancer progression (FCP)	Eight items; adapted from FCRI-SF (Fardell et al., 2017)
Generalized anxiety and depression	PROMIS Short Form Anxiety 4a and Depression 4a (Cella et al., 2010)
Sleep quality	One item from PSQI (Buysse et al., 1989)
Quality of life	One item from FACT-G (Cella et al., 1993)

Measures without a citation listed were developed by the authors for the purposes of this study. FCRI-SF = Fear of Cancer Recurrence Inventory-Short Form (Simard and Savard, 2009; Fardell et al., 2017); PSQI = Pittsburgh Sleep Quality Index (Buysse et al., 1989); FACT-G = Functional Assessment of Cancer Therapy-General (Cella et al., 1993).

Sociodemographic Characteristics

Participants reported on their race, ethnicity, gender identity, education, family income, pre-pandemic employment status, and COVID-19-related changes in employment status.

Cancer History and Treatment

Participants reported on the previous history of breast and other cancers. They were also were asked whether they had received surgery for their current breast cancer diagnosis, as of the day of questionnaire completion. If they responded *no*, they were asked whether their surgery had been scheduled. Finally, participants were asked whether they received neoadjuvant hormone therapy and/or chemotherapy.

Patient-Provider Communication About Pandemic-Related Treatment Changes

Two questions assessed survivors' perceptions of communication with their health care team about delays and/or changes in cancer treatment due to the pandemic. The first question asked what, if anything, the oncologist told the survivor about how the delay/change in treatment might affect the risk of cancer progression; response options were, "*They told me my risk would be lower because of the delay/changes in my treatment*," "*They told me my risk would be about the same*," "*They told me my risk would be higher because of the delay/changes in my treatment*," and "*They did not talk to me about how the delay/changes might affect my risk*." The second question assessed survivor satisfaction with the communication from their medical team about COVID-19-related delays/changes in their cancer treatment. Response options ranged from one ("*not at all satisfied*") to five ("*completely satisfied*").

COVID-19 Impact

COVID-19 impact was assessed using a modified version of the Coronavirus Impacts Questionnaire-Short Version (Conway et al., 2020). The Coronavirus Impacts Questionnaire-Short Version was modified by replacing one resource impact item ["*It has been difficult for me to get the things I need due to the coronavirus (COVID-19)*"] with an item assessing impact to health insurance coverage specifically ["*My health insurance coverage has been negatively affected by the coronavirus (COVID-19)*"]. Because psychosocial functioning had already been assessed in this study, two psychosocial impact items ["*I have become depressed because of the coronavirus (COVID-19)*" and "*The coronavirus outbreak has impacted my psychological health negatively*"] were replaced with one item assessing impact to household responsibilities ["*My household responsibilities (child care, chores) have increased and/or are more difficult to manage due to the coronavirus (COVID-19)*"]. Each item was rated from one ("*not true of me at all*") to seven ("*very true of me*"). Items were averaged to assess the overall COVID-19 impact, and the modified scale in this sample had acceptable reliability (α = 0.81).

COVID-19 Experiences

Participants responded to the Personal Diagnoses/Symptoms Scale of the Coronavirus Experiences Questionnaire-Short

Version (Conway et al., 2020), which includes three items assessing whether participants had ever been diagnosed with COVID-19, had COVID-19-like symptoms at any point in the prior 2 months, or had been sick with something other than COVID-19 and breast cancer in the prior 2 months.

COVID-19-Specific Threat Sensitivity

COVID-19-specific threat sensitivity was assessed using a modified version of the Perceived Coronavirus Threat Questionnaire-Short Version (Conway et al., 2020), which consists of three items assessing how worried or threatened respondents feel about COVID-19. Given that individuals with cancer are at increased risk for severe complications from COVID-19, we added a fourth item that read, "*I am anxious or worried about surviving the coronavirus (COVID-19) if I caught it*." All four items were rated from one ("*not true of me at all*") to seven ("*very true of me*"). Responses were averaged to create a composite score, with greater scores reflecting greater COVID-19-specific threat sensitivity. The alpha coefficient (α = 0.91) reflected acceptable reliability.

Cancer Progression Risk Perception

Three items measured the perceived risk of cancer progression. One item assessed overall concern about cancer progression ["*How concerned are you about your cancer progressing (growing or spreading in the same or another part of the body)?*"] with responses ranging from one ("*not at all concerned*") to seven ("*extremely concerned*"). The second item assessed the perceived risk of progression ("*Considering any delays or changes in your cancer treatment due to coronavirus (COVID-19), what do you think of your chance is of your cancer progressing?*"), with a continuous slider scale ranging from 0% ("*no chance of cancer progression*") to 100% ("*cancer will definitely progress*"). The final item assessed the perceived change ("*much lower*," "*about the same*," or "*much higher*") in progression risk due to COVID-19-related delays/changes in treatment ["*Considering information from your medical team, overall, how do you think your chance of cancer progression compares to breast cancer patients whose treatment was not delayed or changed due to coronavirus (COVID-19)?*"].

Fear of Cancer Progression

FCP was assessed using a modified version of the Fear of Cancer Recurrence Inventory Severity subscale (Simard and Savard, 2009), also termed as FCRI-Short Form (FCRI-SF; Fardell et al., 2017). The FCRI is a well-validated measure of FCP but was specifically designed to assess recurrence rather than progression, the former being more relevant for survivors who have completed cancer treatment and the latter for survivors with active cancer (i.e., the current sample). The FCRI-SF consists of nine items assessing intrusive thoughts about and the perceived risk of recurrence over the past month. Eight items were modified to refer to *progression* instead of *recurrence* (e.g., "*I was worried or anxious about the possibility of cancer recurrence*" became "*I was worried or anxious about the possibility of cancer progression*") and one item was dropped ("*How long have you been thinking about the possibility of cancer recurrence?*") because some of the response options (e.g., "*A few years*" and "*Several years*") were not applicable, as only recently diagnosed survivors participated. All eight items were rated from zero to four. Responses were averaged to create a composite score, with higher scores reflecting greater FCP. The alpha coefficient (α = 0.88) reflected acceptable reliability of this modified scale. The current recommended cutoff score to establish clinical levels on the FCRI-SF is a sum score > 22 (Fardell et al., 2017), equivalent to a mean score > 2.44, which we used here as an approximate indicator of FCP severity on our adapted measure. To facilitate comparison to other recently published findings on FCP during the COVID-19 pandemic (Massicotte et al., 2021), we also reported the percentage of scores exceeding the lower cutoff of > 13 (equivalent to a mean score > 1.44), which is often still used as recommended by original measure developers (Simard and Savard, 2009).

Generalized Anxiety and Depressive Symptoms

The PROMIS Short Form Anxiety 4a and Depression 4a were administered as brief measures of generalized anxiety and depressive symptoms (Cella et al., 2010). Each scale includes four items assessing the severity of symptoms experienced in the past 7 days, with responses ranging from one ("*never*") to five ("*always*"). A composite score for each scale is converted to a *T*-score (population M = 50, SD = 10). For these PROMIS scales, *T*-scores between 55 and 60 are considered mild, 60–70 moderate, and > 70 severe. Reliability was acceptable for the Anxiety (α = 0.93) and Depression scales (α = 0.89).

Sleep Quality

A single item from the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) asked participants, "*During the past month, how would you rate your sleep quality overall?*" Responses ranged from one ("*very good*") to four ("*very bad*").

Quality of Life

A single item from the Functional Assessment of Cancer Therapy Functional Well Being subscale (FACT-G; Cella et al., 1993) was used to assess subjective quality of life-based on "*how you have been feeling the past 7 days*." The item was "*I am content with the quality of my life right now*," with responses ranging from one ("*not at all*") to five ("*very much*").

Statistical Analysis

Analyses were conducted using SPSS v.26 (IBM Corp., 2019). Most variables had no missing values, with the exception of a few skipped questions [e.g., two participants skipped the question about the perceived risk of cancer progression (%)]. Descriptive analyses were based on all available data from the full sample of 50 participants. Descriptive sample statistics, including means, frequencies, standard deviations, and ranges were computed for all variables, and their distributions examined. Bivariate correlations were also computed among all key study variables. Independent samples *t*-tests were conducted to explore group differences in psychosocial functioning between survivors who were still awaiting

delayed surgery (n = 17) and those who had recently received it (n = 33). Values of p (α = 0.05) for these tests were reported but interpreted cautiously with a greater focus on effect sizes given the relatively small sample size (N = 50).

RESULTS

Medical Record Data

A list of the pending breast surgery cases was maintained by the Helen F. Graham Cancer Center and Research Institute. This list included data on diagnosis (e.g., DCIS, LCIS, or invasive breast cancer) but not breast cancer stage for those with invasive breast cancer. Per this list, most women in the final sample of 50 survivors were diagnosed with invasive breast cancer (78%), with 18% having been diagnosed with DCIS and 4% with LCIS. Forty-one women (82%) authorized access to their medical records. Of these 41 women, most (n = 18, 36%) had been diagnosed with clinical stage I breast cancer. Ten women (20%) had been diagnosed with clinical stage 0, 7 women (14%) with clinical stage II, and 4 women (8%) with stage III. Breast cancer stage could not be obtained for two women who authorized access to their medical records (e.g., participant decided to seek treatment out of state). As mentioned in the Participants section above, less than half of the current sample (44%) had documented risk scores calculated using the system created by Smith et al. (Smith et al., 2020; the remaining were missing because of changes in the site's internal risk scoring protocol early in the COVID-19 pandemic). The mean risk score for these participants was 17.5, which falls in the (2) *Limited delay acceptable* group (score between 10 and 29; n = 15 had scores in this range), and Smith et al.'s recommendation was that this group can generally wait 2–4 months or longer if they continued to respond to neoadjuvant treatment. Only three participants had scores that fell in the (3) *Lowest priority* group (score < 10), where the recommendation was that this group can likely wait until elective surgeries resume. Only four participants would be in the (1) *Very urgent* group (score ≥ 30), where surgery is recommended in 2–4 weeks.

Psychosocial Characteristics

Descriptive statistics for self-report variables are shown in **Table 2**.

Sociodemographic Characteristics

All participants identified as women. The average age of participants was 60.1 years (SD = 13.2). The majority of the sample identified as White (74%), 20% Black or African-American, and 4% Asian (one participant skipped the question). Most participants identified as not Hispanic/Latino (92%), with one participant who skipped this item. Fifty-eight percent of participants reported having a college or post-graduate degree. The modal annual family income exceeded $100,000. Prior to the pandemic, 52% of participants indicated that they were employed full-time for wages, 28% retired, 8% self-employed, 4% employed part-time for wages, 4% out of work for a year or more, 4% unable to work (disabled), and 2% were homemakers. Over a third (36%) of participants reported that there had been no changes in their work because of COVID-19, 26% reported that they transitioned to working from home, 6% reported an *increase* in work responsibilities, 6% reported a *decrease* in work responsibilities, 6% reported being essential workers with regular physical presence required, 4% reported decreased pay, and 1% reported being laid off, fired, or forced to close business (multiple response options were allowed for this item).

TABLE 2 | Descriptive statistics.

Variable	Mean	SD	Range
COVID-19 impact	2.23	1.48	1–7
COVID-19 threat sensitivity	4.14	1.82	1–7
Perceived risk of progression (concern)	3.94	2.00	1–7
Perceived risk of progression (0–100%)	30%	28%	0–100%
Fear of progression	1.85	0.89	0.38–3.71
PROMIS anxiety	54.71	9.67	40.30–81.60
PROMIS depression	48.99	7.90	41.00–73.30
Sleep quality	2.24	0.77	1–4
Quality of life	3.42	1.18	1–5

N = 50 for all variables except for the perceived risk of progression (0–100%), an item that two participants skipped (n = 48). Only continuous variables included in table.

Cancer History and Treatment

The majority indicated that this was their first breast cancer diagnosis (88%) and denied having any other cancer diagnoses in the past (84%). At the time of data collection (between June 27 and August 13, 2020), most of the sample (66%) self-reported that they had already received surgery for their current breast cancer. Of those who indicated they did not yet have surgery (34%), 41% reported that they had a scheduled surgery date in the future while the remaining 59% did not. Regarding neoadjuvant treatment, a portion (74%) of this sample reported that they received hormone or chemotherapy treatment prior to surgery.

Patient-Provider Communication About Pandemic-Related Treatment Changes

Regarding communication from their oncology team, 48% reported that the impact of treatment delays on their cancer progression risk was not discussed at all, whereas 44% reported being told that their risk would be *about the same*. Only 4% reported being told that their risk was *higher* because of the treatment delay/changes, and 4% reported being told that their risk was *lower* because of the treatment delay/changes. Regarding satisfaction with this communication from their health care providers, the modal response was "*very satisfied*," with less than 15% of the sample reporting poor to low ("*not at all*" or "*a little*") satisfaction (M = 3.92, SD = 1.11).

COVID-19 Impact

The overall COVID-19 impact scores were relatively low on average (M = 2.23, see **Table 2**). Responses to the five items

assessing COVID-19 impact on personal finances and access to essential resources, including health care, indicated that at least half the sample denied experiencing any of the impact areas assessed, with a modal score of 1 (the lowest possible impact) on each item. Less than 20% of participants had scores greater than the scale midpoint on any of the impact items. The mean response to the item assessing whether COVID-19 had negative financial impacts was 2.83 (SD = 2.17), with a small subgroup endorsing moderate to extreme negative impacts (20%). Even fewer participants endorsed great negative impact in the form of household responsibilities (M = 2.59, SD = 2.24), job income loss (M = 2.00, SD = 1.99), access to essential resources (M = 2.32, SD = 2.00), and health insurance changes (M = 1.45, SD = 1.50).

COVID-19 Experiences

None of the participants reported having received a COVID-19 diagnosis. Only five participants (10%) said that they had COVID-19-like symptoms at some point over the past 2 months, and only two (4%) said they had been sick with something other than COVID-19 and breast cancer over that same period.

COVID-19-Specific Threat Sensitivity

There was substantial spread in participant scores on the COVID-19 threat sensitivity items (M = 4.14, SD = 1.82, range = 1–7). The composite scores were approximately normally distributed, although most scores were in the moderate range, many were also observed at both the extreme low and high ends of the scale.

Cancer Progression Risk Perception

There was also marked variability in participants' self-reported concern about cancer progression, M = 3.94, SD = 2.00, range = 1–7. The modal response was two on a scale of one ("*not at all concerned*") to seven ("*extremely concerned*"). Forty percent of participants reported concern in the low-moderate range (score < 4) and 20% reported concern at the high end of the scale (score > 6). In light of any COVID-19-related delays or changes in care, participants' own estimate of their risk of cancer progression on average was 30% (SD = 28%). A third (33%) of the sample reported that their chance of cancer progression was 12% or less and 33% reported estimates between 15 and 30%. Eight percent of participants indicated a 50% risk of progression, with the remaining responses scattered between 30 and 100%. The majority of participants (80%) endorsed the belief that their risk of progression was "*about the same*" compared to patients whose treatment was unaffected by COVID-19, with only 12% stating they felt their risk was much higher and 8% felt their risk was much lower.

Fear of Cancer Progression

FCP composite scores were approximately normally distributed in this sample, M = 1.85, SD = 0.89, range = 0.38–3.71. Using the recommended clinical cutoff of 2.44 on the original FCRI-SF as a rough point of comparison (Fardell et al., 2017), FCP appeared moderate on average. About a quarer (26%) of the sample had scores exceeding this cutoff, suggesting elevated FCP of potential clinical concern. Using the lower clinical cutoff of 1.44 (recommended by Simard and Savard, 2009 but later found to be too low for optimal sensitivity and specificity; Fardell et al., 2017), 60% of participants had scores in the clinically significant range.

Generalized Anxiety and Depressive Symptoms

The mean PROMIS Anxiety T-score was 54.71, SD = 9.67, with 64% of participants having scores greater than 50 (population mean). Twenty-six percent of participants had anxiety scores in the mild range, 26% in the moderate range, and 4% in the severe range. The mean PROMIS Depression T-score was 48.99, SD = 7.90, with 44% of participants having scores over 50. Rates of clinical depressive symptoms were relatively low in this sample, with 14% reporting mild symptoms, 6% reporting moderate, and 2% severe.

Sleep quality

The modal response to the question concerning subjective sleep quality over the past month was "*fairly good*" (score = 2), M = 2.24, SD = 0.77, range = 1–4. Only three participants reported "very bad" sleep quality.

Quality of life

Survey responses indicated that on average, participants were generally content with their quality of life, M = 3.42, SD = 1.18, range = 1–5, with the modal response being "*somewhat content*" (score = 3). About 15% of participants indicated a low quality of life (score < 3).

Bivariate Correlations

Bivariate correlations among continuous variables are shown in **Table 3**. We found that greater patient-provider communication around pandemic-related surgery delays was significantly correlated with lower COVID-19 impact ($r = -0.50$, $p < 0.01$), lower perceived risk of cancer progression ($r = -0.32$, $p < 0.05$), lower FCP ($r = -0.36$, $p < 0.05$), and fewer depression symptoms ($r = -0.29$, $p < 0.05$). We also found that higher COVID-19 impact scores significantly correlated with greater perceived risk of cancer progression ($r = 0.29$, $p < 0.05$), more generalized anxiety symptoms ($r = 0.35$, $p < 0.05$), and lower quality of life ($r = -0.39$, $p < 0.01$). Higher sensitivity to the threat of COVID-19 was significantly correlated with generalized anxiety levels ($r = 0.44$, $p < 0.01$), depression symptoms ($r = 0.34$, $p < 0.05$), and poorer sleep ($r = 0.29$, $p < 0.05$), but not with concern about or the perceived risk of cancer progression. Perceived risk (concern), the perceived risk estimate (0–100%), and FCP were all highly inter-related (rs.64–0.69, ps < 0.01). Of these three variables, FCP showed the highest number of significant bivariate relationships with other psychosocial variables – including communication satisfaction, perceived risk (concern), perceived risk (0–100%), generalized anxiety, depression, sleep quality, and quality of life – all suggesting evidence of poorer psychosocial functioning (see **Table 3** for full results).

Mean Differences by Surgery Status

Independent samples *t*-tests examined mean differences in continuous variables between participants who already received surgery and those still awaiting their surgery date. *T*-statistics were used to compute effect sizes (Hedges' *g*). Results are shown in **Table 4**. A moderate-to-large-sized effect ($g = 0.721$) was observed for mean differences in communication satisfaction [$t(48) = -2.42$, $p = 0.019$], such that survivors who had already received their postponed breast cancer surgery were more satisfied with the communication from their oncology providers ($M = 3.88$) than those still awaiting their postponed surgery ($M = 3.12$). A moderate-sized effect ($g = 0.56$) was also observed for a mean difference in PROMIS Depression scores [$t(48) = 1.87$, $p = 0.067$], indicating that survivors still awaiting surgery had somewhat higher levels of depressive symptoms ($M = 52$) than those post-surgery ($M = 48$). A moderate-sized effect ($g = 0.53$) was also found for the perceived risk of cancer progression (0–100%, $t(46) = 1.73$, $p = 0.091$), such that survivors awaiting surgery also estimated that they had higher risks of cancer progression ($M = 40\%$) than those post-surgery ($M = 25\%$). The remaining *t*-tests revealed smaller mean differences ($g < 0.4$) between the groups (i.e., weak evidence found for meaningful group differences in levels of COVID-19 impact, COVID-19 threat sensitivity, concern about the perceived risk of progression, FCP, PROMIS Anxiety, sleep quality, and quality of life).

DISCUSSION

This study aimed to provide a comprehensive description of the psychosocial functioning of a unique cohort, high-risk of breast cancer survivors in the United States whose cancer care had been delayed and/or changed due to the COVID-19 pandemic. These are survivors who had been recently diagnosed with non-metastatic, operable breast cancer and thus likely have a favorable prognosis, with a 5-year relative survival rate of 99% for localized breast cancer and 86% for regional breast cancer (American Cancer Society, Inc., 2021). Prior to the pandemic, a large body of literature documents lingering psychosocial concerns among cancer survivors, such as fear of cancer recurrence, that can be problematic well into the years after cancer has been successfully treated (Stanton, 2006).

TABLE 3 | Bivariate correlations.

	1	2	3	4	5	6	7	8	9
1. Communication satisfaction	-								
2. COVID-19 impact	−0.501**	-							
3. COVID-19 threat sensitivity	−0.138	0.144	-						
4. Perceived risk (concern)	−0.186	0.165	0.109	-					
5. Perceived risk (0–100%)	−0.319*	0.288*	−0.079	0.641**	-				
6. Fear of cancer progression	−0.359*	0.274†	0.260†	0.689**	0.659**	-			
7. PROMIS anxiety	−0.217	0.350*	0.441**	0.514**	0.319*	0.681**	-		
8. PROMIS depression	−0.293*	0.199	0.343*	0.463**	0.222	0.614**	0.679**	-	
9. Sleep quality[a]	−0.082	0.199	0.289*	0.287*	0.254†	0.374**	0.382**	0.330*	-
10. Quality of life	0.219	−0.391**	−0.211	−0.412**	−0.399**	−0.413**	−0.550**	−0.407**	−0.562**

*N = 50. **p < 0.01; *p < 0.05.*
†p < 0.10.
[a]Higher score indicate worse sleep quality.

TABLE 4 | Means of continuous variables by cancer surgery status.

	Mean (SD)		*t*(48)	*p*	Effect size (Hedges' *g*)[a]
	Awaiting surgery (*n* = 17)	Received surgery (*n* = 33)			
Communication satisfaction	3.12 (1.17)	3.88 (0.99)	−2.42*	0.019	0.721
COVID-19 impact	2.62 (1.79)	2.03 (1.28)	1.36	0.181	0.401
COVID-19 threat sensitivity	4.25 (2.00)	4.08 (1.75)	0.30	0.762	0.093
Perceived risk (concern)	4.41 (2.27)	3.70 (1.85)	1.20	0.236	0.355
Perceived risk (0–100%)[‡]	39.56 (32.01)	24.94 (25.33)	1.73†	0.091	0.528
Fear of cancer progression	2.05 (0.99)	1.75 (0.84)	1.12	0.267	0.336
PROMIS anxiety	55.00 (8.51)	54.55 (10.34)	0.15	0.879	0.046
PROMIS depression	51.83 (6.89)	47.52 (8.08)	1.87†	0.067	0.559
Sleep quality	2.47 (0.72)	2.12 (0.78)	1.54	0.130	0.460
Quality of life	3.18 (1.42)	3.55 (1.03)	−1.05	0.299	0.315

*N = 50. *p < 0.05.*
†p < 0.10.
‡df = 46 (two participants skipped this question).
[a]Hedges' g is in pooled standard deviation units (similar to Cohen's d) and accounts for unequal sample sizes.

However, the current sample represents a group who may be at an even greater risk of experiencing these and other difficulties given that their cancer treatment was directly impacted (i.e., delayed and/or changed) due to the COVID-19 pandemic. In this paper, we described how this group fared psychosocially shortly before or after their postponed breast cancer surgery.

About two-thirds of the sample had recently received their breast cancer surgery, which had been delayed due to the COVID-19 pandemic, whereas the remaining third comprised survivors still awaiting their delayed surgery date. The majority of these survivors had received neoadjuvant treatment (either endocrine therapy or chemotherapy), which may have been recommended to mitigate increased risks associated with delays in primary surgery. In terms of race and ethnicity, the sample is roughly comparable to the typical cancer survivor in this Mid-Atlantic region of the United States (US Census Bureau, 2019). However, the current sample was less representative in terms of socioeconomic status (higher income and education level). This higher socioeconomic status is also consistent with the finding that the majority of participants denied that the COVID-19 pandemic seriously impacted their finances or limited their access to essential resources, including health care. In addition, few reported job losses or pay cuts during the pandemic. There was a small subgroup of participants who reported job loss or pay decreases (5%) or reported being frontline essential workers (6%). On the other hand, 20% of the current sample was African-American, a group disproportionately impacted by COVID-19 (Tai et al., 2020). These sample characteristics are important to consider when interpreting the results discussed below.

Despite the fact that this sample was selected on the basis of their breast cancer treatment being delayed and/or changed due to the pandemic, 48% reported that their oncology providers never discussed with them how this disruption would affect their cancer prognosis (i.e., risk of cancer progression). Most of the remaining participants (44%) reported that they were told the delay and/or change in their treatment would not change their prognosis or cancer progression risk. Because we do not have detailed medical records available for these participants, the accuracy of these statements cannot be estimated. Consistent with the relatively high proportion of participants who denied having a discussion with their providers about this, 18 survivors identified by the hospital records as having delayed and/or changed breast cancer surgery declined to participate because they did not believe that their cancer treatment was altered due to the pandemic. Unfortunately, we did not collect corroborating data from participants' oncology providers to determine the extent to which these results reflect actual (objective) patient-provider interactions, participants' comprehension of information communicated by providers, and/or other individual-level factors that may color their perception, memory, or judgment about prior discussions with their providers. Future research may be able to explore these questions by incorporating more detailed clinical data, data from patients' oncology providers, and/or direct observation of patient-provider discussions about risk and prognosis. Nonetheless, it may have been challenging for oncology providers to navigate these discussions with survivors due to the unprecedented nature of the pandemic and limited empirical data on change in risk due to these delays. Importantly, despite this, most participants reported satisfaction with their communication by their oncology team. Although, interestingly and perhaps understandably, satisfaction was higher on average among those who already had surgery and lower among those still awaiting their delayed surgery.

There also was a moderate-sized correlation between satisfaction with oncology provider communication and low COVID-19 impact. Sociodemographic factors may partially explain this effect; for example, individuals who are Black or living in poverty are both more likely to be affected by COVID-19 (CDC, 2020) and less likely to be satisfied with provider communication and their medical care in general (compared to Whites or higher-income individuals, e.g., Haviland et al., 2005; McFarland et al., 2017). In addition, results of the current study showed that those who were more satisfied with communication tended to report lower estimates of their perceived risk of cancer progression and, correspondingly, lower FCP. It is possible that receiving or perceiving "better news" from a provider (i.e., being told that they have a lower risk of cancer progression) causes the patient to feel more satisfied with the provider's communication and also serves to lower the patient's own risk estimate and, consequently, FCP.

We also examined several indicators of psychosocial distress, including the perceived threat of COVID-19, FCP, generalized anxiety and depressive symptoms, sleep quality, and perceived quality of life. The pattern of findings for these variables suggested that overall, this sample on average reported low-to-moderate levels of psychosocial concerns and fear related to COVID-19. Given that extant data are suggestive of potentially poorer cancer prognosis when surgery is delayed (as was the case for these participants), we speculated that this sample is likely at higher risk for experiencing high FCP, which is already a relatively normative experience among cancer survivors even in the absence of a global pandemic. Results indicated that about a quarter of this sample experienced clinically elevated FCP, as defined by the most recent psychometric evidence (Fardell et al., 2017). A recent study of non-metastatic breast cancer survivors during the COVID-19 pandemic found that 53% had FCP scores in the clinical range (Massicotte et al., 2021), but used a lower cutoff score recommended in earlier work (Simard and Savard, 2009). Using this same lower cutoff, 60% of the current sample had clinical levels of FCP, yielding findings consistent with those reported by Massicotte et al. (2021).

Perhaps surprisingly, mean levels of FCP did not significantly differ between survivors pre- vs. post-surgery, yet prior work found delays in cancer care to be significantly related to survivors' FCP (Chen et al., 2020). Critically, however, FCP is known to become prevalent and potentially problematic among cancer survivors after treatment ends and their cancer has been successfully treated (King et al., 2000; McKinley, 2000). Therefore, it will be of key importance that future work continues to follow this cohort of cancer survivors as they progress through

this survivorship trajectory – re-assessing them after they have completed surgery and adjuvant treatment, when told by their providers that their cancer is in remission. Anecdotally, during this time in the survivorship trajectory individuals begin to have questions, doubts, and fears about their cancer coming back. Indeed, it seems reasonable to speculate that this cohort is still at greater risk for experiencing clinically significant FCP (or fear of recurrence) than their pre-pandemic counterparts. Moreover, it is possible that future research will reveal additional areas of difficulty for survivors whose treatment was delayed and/or changed as a result of the pandemic.

This study had a number of strengths. Most notably, this was the first study, to our knowledge, to specifically target the assessment of breast cancer survivors whose primary cancer surgery was postponed due to the COVID-19 pandemic. Prior research on cancer survivors during the pandemic has not selected participants on the basis of their care being directly affected (i.e., delayed). At the same time, our sample was heterogeneous with regard to being pre- vs. post-surgery, receipt of neoadjuvant treatment, and sociodemographic variables. Nevertheless, there were also important limitations to this study. First, the sample size was relatively small and thus these results should be considered as tentative pending a well-powered replication. Second, while this sample was racially and ethnically representative of the patient population, participants were generally financially secure, highly educated, and did not report being severely impacted by the COVID-19 pandemic. Thus, more research is needed to better understand the needs of even higher risk groups of cancer survivors during and after the COVID-19 pandemic. Future research could benefit from identifying and describing other patient populations whose cancer care was affected by COVID-19, particularly patients who may be at higher risk, including those of lower socioeconomic status, as well as patients with other cancer diagnoses; this work may help to identify key sociodemographic or clinical characteristics that impact psychosocial response to COVID-19. Third and finally, the use of short forms or single items to assess psychological symptoms and multidimensional constructs may not fully capture these concepts, thus limiting the interpretation of the results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Christiana Care Health System IRB approval: FWA00006557; CCC# 40079. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ES: conceptualization, data curation, formal analysis, methodology, and writing – original draft. CP: conceptualization, data curation, formal analysis, investigation, methodology, project administration, and writing – original draft. AO: conceptualization, methodology, and writing – review and editing. AF: writing – review and editing. SS: conceptualization, methodology, resources, and supervision, writing – review and editing. DD-W: conceptualization, resources, supervision, and writing – review and editing. LC: conceptualization, resources, supervision, writing – review and editing. J-PL: conceptualization, data curation, resources, supervision, and writing – review and editing. All authors contributed to the article and approved the submitted version.

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Prognostic Awareness in Advanced Disease: A Review Update and Concept Analysis

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Purpose: Although subjective knowledge about the prognosis of an advanced disease is extremely important for coping and treatment planning, the concept of prognostic awareness (PA) remains inconsistently defined. The aims of the scoping review were to synthesize a definition of PA from the most recent literature, describe preconditions, correlates and consequences, and suggest a conceptual model.

Methods: By using scoping review methodology, we searched the *Web of Science* and *PubMed* databases, and included publications, reviews, meta-analyses or guidelines on all physical diagnoses, as well as publications offering a conceptual or an operational definition of PA. The data were analyzed by means of content analysis techniques.

Results: Of the 24 included publications, 21 referred exclusively to cancer, one to patients with hip fractures and two to palliative care in general. The deduced definition of PA comprised the following facets: adequate estimation of chances for recovery, knowledge of limited time to live, adequate estimation of life expectancy, knowledge of therapy goals, and knowledge of the course of the disease. Further content analysis results were mapped graphically and in a detailed table.

Conclusion: There appears to be a lack of theoretical embedding of PA that in turn influences the methods used for empirical investigation. Drawing on a clear conceptual definition, longitudinal or experimental studies would be desirable.

Keywords: prognosis, advanced disease, cancer, oncology, palliative care, patient-centered care, systematic review

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INTRODUCTION

The concept of PA has received increased attention within health care research in recent years. In 2000, the term was used by Chochinov et al. (2000) as the acknowledgment of an advanced medical diagnosis in order to prepare for an imminent death. Jackson et al. (2013) understand PA "as a patient's capacity to understand his or her prognosis and the likely illness trajectory"

Abbreviations: PA, prognostic awareness.

(p. 894). From a theoretical perspective, in their common sense model of self-regulation of health and illness, Leventhal et al. (1998) outline the role of so-called representations (i.e., individual definitions of illness) for coping behaviors. They assume various different dimensions of such representations: the disease *label* (e.g., cancer) and its symptoms (e.g., breast lump), the *timeline* (regarding the development of the disease, its duration and recovery), perceptions of *causes,* and *consequences*, as well as *control* beliefs (e.g., disease assessed as preventable, curable or possible to prevent its progress). The common sense model also highlights the importance of emotions, either as part of illness representations themselves, or as a response to them (Diefenbach and Leventhal, 1996). Referring to this model, PA could be regarded as a specific component of the timeline dimension. Nonetheless, PA is mostly viewed as an independent construct, with a rather weak theoretical embedding.

PA is assumed to be associated with better quality care, i.e., earlier hospice and palliative care, and fewer resuscitations (Jackson et al., 2013). As PA may support patients in adapting medical care and personal decisions to their needs, values and goals, it is highly relevant (Jackson et al., 2013). One strategy to promote PA is through patient-practitioner-communication, specifically the empathic exploration of patients' knowledge, and the subsequent transfer of information in a way that helps patients to manage and integrate the given prognostic information (Jackson et al., 2013).

Recently, Applebaum et al. (2014) defined PA as the "awareness of a terminal prognosis or shortened life expectancy" of palliative patients (p. 1103). From a systematic review, they deduced the following facets of PA: (a) awareness of a metastatic, advanced or terminal disease, (b) awareness of shortened life expectancy or the specific likelihood of survival and (c) awareness of the purpose of treatment (Applebaum et al., 2014). The primary studies included in the review involved between one and all of these aspects, which hampers comparisons and resulted in the large range (0–75%) of patients described to show adequate PA (Applebaum et al., 2014). Despite its influence on the research field, the review focused on cancer and on the measurement of PA, and the authors presented their results only narratively. The search was completed in 2012, which is why the review does not cover recent studies, whereas publications on PA increased especially during the last 5 years.

Therefore, the aims of our current update were to (i) derive a definition of PA from the most recent literature, (ii) describe preconditions, correlates and consequences, and based on the results, (iii) suggest a conceptual model of PA in advanced disease in general.

MATERIALS AND METHODS

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher et al., 2009; PRISMA flow diagram available upon request from the corresponding author). As we aimed to update and complement the narrative review of Applebaum et al. (2014), we decided on a scoping review methodology. Such a review is a systematic, but economic evidence synthesis, focusing on central concepts and an overview of the current state of research (Levac et al., 2010; Armstrong et al., 2011; Colquhoun et al., 2014).

Search and Inclusion Criteria

The electronic search was conducted in two key psychosocial and medical databases, i.e., *Web of Science* and *PubMed*. To refer to the current evidence, we built on the previous search (Applebaum et al., 2014) by starting our search on 01 January 2013, and defining the search date itself (15 February 2019) as its end point. We further decided to extend the previous search terms, and thus combined the term prognose* with each of the following concepts: aware*, know*, attitude*, and understand*. We included peer-reviewed original publications, reviews, meta-analyses and guidelines written in English. In order to take a broad perspective, we did not restrict the search to a specific physical diagnosis, to cancer or to adults. Publications with a conceptual definition, description or explanation of PA, but also those using an operational definition of PA were eligible for inclusion.

Screening and Selection

A reviewer (MH) screened the search results for titles and abstracts, so as to exclude records that were clearly irrelevant (e.g., biological or technical papers). Then, the reviewer retrieved the full-texts of the remaining records and screened them for inclusion. Disagreements were resolved by discussion with a second team member during regular meetings (FK or UG). Since we expected a broad spectrum of definitions, we refrained from connecting definitions with quality ratings, and thus decided against the assessment of study quality.

Concept Analysis

For the concept analysis, we referred to the approach proposed by Scholl et al. (2014), and used MAXQDA (2020) software. Referring to content analysis techniques (Mayring, 2014; Kuckartz, 2018), MH inductively derived sub-categories for the main categories *definition*, *preconditions*, *correlates,* and *consequences*. Preconditions and consequences were extracted from longitudinal studies or experimental and intervention designs only. If one aspect was relevant to two or more categories, it was assigned to all relevant categories. In order to concentrate on relevant topics, we established a new sub-category (see subheadings under 3.1.-3.4.) if an issue was mentioned in at least two publications. Since only a limited number of publications mentioned preconditions and consequences, i.e., concerned causal relations, we changed our procedure, and included any entry that referred to a precondition or a consequence. To enhance the analysis, a coding guideline with a description of each category and illustrative examples was developed. Again, disagreements were resolved by discussion with a second team member (FK or UG).

In a second step, another team member (LPW) familiarized herself with the data, and then independently classified all units of meaning into the category system by using the coding guide. Inter-rater agreement was $\kappa = 0.85$; values > 0.70 are

assumed to be appropriate (Wirtz, 2017). Finally, a definition was proposed and the categories were mapped conceptually, including the preconditions, correlates and consequences of PA (see **Supplementary Material 1**).

RESULTS

N = 24 publications were included; two of them were systematic reviews, and one was a theoretical paper (**Supplementary Material 2**). 16 of the original publications used cross-sectional designs, four were longitudinal or intervention studies, and one study used qualitative methods. Whereas, 21 publications dealt with cancer patients, one referred to patients with hip fractures and two included a palliative population with various diagnoses. In 20 publications, the stage of the disease was described as terminal, advanced or metastasized.

Definition of PA

According to our content analysis, *PA primarily comprises the appropriate estimation of chances for recovery (i.e., incurable disease), knowledge of limited time to live and the appropriate estimation of shortened life expectancy, and secondarily, the appropriate estimation of therapy goals as well as knowledge of the course of a disease.* Below, each component of PA is outlined further. Relations between concepts are mapped in **Supplementary Material 2**.

Appropriate Estimation of Chances for Recovery

With n = 16 (66.7%) of entries (Diamond et al., 2014, 2017; El-Jawahri et al., 2014, 2015; Tang et al., 2014, 2016a,b, 2018; Shin et al., 2016; Chen et al., 2017a,b, 2019; Kurita et al., 2018; Mack et al., 2018; Sato et al., 2018; Janssens et al., 2019), this was one of the most important components of PA. Often (n = 11), patients with advanced disease were only considered to have accurate PA if they viewed their disease as incurable (Diamond et al., 2014, 2017; Tang et al., 2014, 2016a,b, 2018; Chen et al., 2017a,b, 2019; Sato et al., 2018; Janssens et al., 2019); other authors (n = 4) asked patients to rate their chances of recovery in percent (0–100%; El-Jawahri et al., 2014, 2015; Shin et al., 2016; Mack et al., 2018). All patients who stated 0–10% chances of recovery and/or whose view was concordant with their physician's assessment were then classified as having adequate PA. Furthermore, in two publications, knowing the exact stage of the disease was also rated as having adequate PA (Chen et al., 2017a; Kurita et al., 2018).

Knowledge of Limited Time to Live

This category (n = 15, 62.5%) refers to patients' knowledge of the proximity of death, i.e., knowledge about a life-limiting disease, death approaching in near future, or considering a disease as terminal (Diamond et al., 2014, 2017; El-Jawahri et al., 2014; Tang et al., 2014, 2016a,b, 2018; Enzinger et al., 2015; Fisher et al., 2015; Chen et al., 2017a,b, 2019; Nipp et al., 2017; Kurita et al., 2018; Shen et al., 2018).

Appropriate Estimation of Life Expectancy

Ten publications (41.7%) considered this aspect as important to PA (Diamond et al., 2014, 2017; Liu et al., 2014; Enzinger et al., 2015; Fisher et al., 2015; McLawhorn et al., 2016; Chen et al., 2017a; Eikelboom et al., 2018; Kurita et al., 2018; Shen et al., 2018). For reconciliation, physician's assessments or statistical values were used.

Appropriate Knowledge of Therapy Goals

Six publications (25%) included this component of PA (Jackson et al., 2013; El-Jawahri et al., 2014; Fisher et al., 2015; Chen et al., 2017a; Nipp et al., 2017; Sato et al., 2018), and the subjective goal of therapy was often dichotomized (i.e., curative vs. non-curative; El-Jawahri et al., 2014; Fisher et al., 2015; Chen et al., 2017a; Nipp et al., 2017; Sato et al., 2018), and the latter was associated with adequate PA.

Knowledge of Course of Disease

In three publications (12.5%), this aspect of PA referred to both a more general view and to specifics such as the expected physical level of functioning (Jackson et al., 2013; McLawhorn et al., 2016; Eikelboom et al., 2018).

Precondition: Readiness/Preference for and Obtained Information

Only one publication (4.2%) was considered relevant for this category (Chen et al., 2019). It explained that the patients' readiness for prognostic information and the information they actually received (via conversations with physicians or family) were associated with more adequate PA.

Correlates of PA

Time Between Diagnosis and Death

Eight publications (33.3%) dealt with the role of time, i.e., more time passed since diagnosis, and proximity to death were correlated with higher PA (Liu et al., 2014; Tang et al., 2014, 2016a,b; Enzinger et al., 2015; Chen et al., 2017b, 2019; Janssens et al., 2019). To the contrary, another publication considered a more advantageous prognosis with an expected positive course as associated with higher PA (Mack et al., 2018).

Mental Health

Higher PA was associated in four studies (16.7%) with more depressiveness (El-Jawahri et al., 2015; Shin et al., 2016; Nipp et al., 2017; Sato et al., 2018), and in three studies (12.5%), with increased anxiety (El-Jawahri et al., 2014; Nipp et al., 2017; Sato et al., 2018).

Quality of Life

In all eight publications (33.3%) that contributed entries to this category, more adequate PA was associated with lower emotional, physical and social quality of life (El-Jawahri et al., 2014, 2015; Fisher et al., 2015; Tang et al., 2016a; Nipp et al., 2017; Kurita et al., 2018; Sato et al., 2018; Janssens et al., 2019). One of those publications indicated that high PA was associated with higher existential quality of life (Fisher et al., 2015).

Quality of Treatment

Four studies (16.7%) described a correlation between high PA and more care conversations (e.g., advanced care planning) as well

as receiving less aggressive treatments (Tang et al., 2014, 2016b; Enzinger et al., 2015; Shen et al., 2018).

Readiness/Preference for and Obtained Information

Four studies (16.7%) characterized a more pronounced readiness/preference of patients for information and open communication of prognostic information by health care practitioners and caregivers as associated with higher PA (Diamond et al., 2014; Liu et al., 2014; Tang et al., 2014; Enzinger et al., 2015).

Context Characteristics

The authors of three publications (12.5%) described differences in PA dependent on country (Chen et al., 2017a), region (Tang et al., 2014), or site (Tang et al., 2014; Fisher et al., 2015). The frequency of adequate PA was rated highest in Australia and lowest in southern Europe and the United Kingdom (Chen et al., 2017a).

Patient Characteristics

According to three studies (12.5%), accurate PA was correlated with younger age (Tang et al., 2014) higher educational level (Tang et al., 2014), higher cognitive capacity (Fisher et al., 2015), and also with unemployment (Sato et al., 2018). One study each described female (Sato et al., 2018) or male (Tang et al., 2014) gender as correlated with higher PA. In one study, lung cancer patients were described as more likely to adequately understand their prognosis (Tang et al., 2014).

Consequences of PA

Quality of Treatment

In two publications (8.3%), the more adequate the PA, the more conversations about care were conducted and the less aggressive treatments patients received (Tang et al., 2018; Chen et al., 2019).

Depressiveness

The authors of one publication described depressive symptoms as a consequence of more accurate PA (El-Jawahri et al., 2015).

DISCUSSION

The purpose of this scoping review was to update and refine the definition of PA, derive its preconditions, correlates and consequences from the current literature, and then to suggest an empirically based conceptual model. Given our results, and in line with Applebaum et al. (2014), PA represents a multi-faceted construct. Awareness of a metastatic, advanced or terminal disease (facet a) turns up in the present categories of the appropriate estimation of chances for recovery and the knowledge of limited time to live. The shortened life expectancy or the likelihood of survival (facet b) is reflected in the adequate estimation of life expectancy. Knowledge of the purpose of treatment (facet c) resembles the current appropriate estimation of therapy goals. Furthermore, understanding the future course of the illness is viewed as a component of PA. Thus, our scoping review confirms and refines previous results. Thus, by drawing on recent primary studies, the review supports the consistency of the definition.

Contrary to the previous review (Applebaum et al., 2014), our study highlights the role of mental health (symptoms of depression and anxiety) and of quality of life, which were both negatively correlated to PA. In line, active coping strategies are important for mental health in advanced disease (Nipp et al., 2017). On the other hand, our results confirm that proximity to death plays a crucial role in the development of PA, and that adapted conversations about prognosis and treatment options are particularly important for high-quality care. Furthermore, the needs and wishes of palliative patients concerning their extent of participation in decision-making may vary considerably, depending for example on the type or stage of the disease, cultural background or emotional distress (Enzinger et al., 2015). If patients and their caregivers prefer a shared involvement in decision-making, both seem to benefit in terms of improved knowledge about care goals, advanced care planning and treatment options (Fisher et al., 2015). The information preferences of patients and caregivers may vary considerably too; with caregivers tending to vaccinate between open conversations and the desire to maintain hope for their patients (Applebaum et al., 2018).

Some of the included studies suggested demographic and regional effects, that is, PA was correlated with younger age, higher educational level and cognitive capacity of patients. Nonetheless, the broader evidence on shared decision-making points to the significance of patient beliefs and expectations about their role and expertise in determining involvement of patients in decision-making (Janssens et al., 2019). These authors conclude from their comprehensive review that the power imbalance between physicians and patients, and also the perceived acceptability of patient involvement are more important than individual variables (e.g., age, culture) *per se*, and even than patients' information preferences. They call for a change in attitudes so as to foster shared decision-making (Janssens et al., 2019). Above, PA may be considered within the concept of health literacy, which basically refers to "people's knowledge, motivation and competences to access, understand, appraise, and apply health information [. . .]" (Sørensen et al., 2012, p. 3).

As a limitation to our review, most included studies used correlational designs. The results on the preconditions and consequences stem from four studies only, so that they must be interpreted with caution. The majority of studies stemmed from cancer populations, thus it is too early to generalize our results to other diseases. One of the few longitudinal investigations of PA reveals little change in patient and caregiver PA during the progression of illness, but clearly, more such research is necessary (Liu et al., 2014). Experimental studies manipulating PA in analogue samples may complement our understanding of underlying mechanisms. In addition to qualitative interviews, quantitative studies using brief measures of illness perceptions (Broadbent et al., 2006) or on treatment preferences (Mack et al., 2018) may add to the PA literature.

Although we used a structured and systematic approach, we focused our resources, and concentrated on two common literature databases. Since one reviewer screened for inclusion, regular team meetings were scheduled in order to discuss

decisions. Unlike previous reviews on the topic, we referred to structured, qualitative methods to analyze the data, indicated inter-rater agreement, mapped the results in a detailed table, and depicted them graphically. PA seems to comprise knowledge about incurability and shortened life-expectancy, but also an adequate understanding of the course of the disease and the therapy goals. By clarifying the construct, the review contributes to a broader understanding of PA. Obtaining stakeholder views on the definition proposed would be useful, to guide future research.

AUTHOR CONTRIBUTIONS

FK, MH, UG, MP, and AL had the idea for the article. MH performed the literature search. FK, MH and UG analyzed the data. All authors drafted the manuscript and critically revised the work.

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SUPPLEMENTARY MATERIAL

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SYSTEMATIC REVIEW
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Does Cancer Type Influence the Impact of Recurrence? A Review of the Experience of Patients With Breast or Prostate Cancer Recurrence

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Objective: Patients will experience a plethora of issues when faced with a recurrence of their cancer. It is unclear if cancer type is a significant factor in how recurrence is experienced by an individual. The aim of the current review is to explore the evidence base and summarise the experiences of patients specifically with a recurrence of breast or prostate cancer (the most common for women and men, respectively) and then provide a comparison of these experiences. These experiences include the physical, psychological and psychosocial issues that arise at this time.

Methods: A systematic search was conducted of studies published between January 1994 and April 2019. Due to the mix of research designs used previously in the literature, this review was conducted in an integrative manner; allowing for inclusion of diverse research designs. Results were synthesised narratively, with data categorised according to physical, psychological, and psychosocial indices of quality of life. The review protocol was registered in the international database of prospective systematic reviews in health and social care- (CRD42019137381).

Results: Fifteen breast cancer and six prostate cancer articles were identified, each reporting one relevant study. Patients reported several negative issues at the time of a breast or prostate cancer recurrence. Similarities were found between cancer types, with physical problems such as fatigue, psychological issues including anxiety and depressive symptoms, and psychosocial concerns such as issues with healthcare professionals common in both cancers. Certain findings were inconsistent across studies, with some experiences differing between studies rather than due to cancer type.

Conclusions: Differences in the experience of recurrent cancer appear to be more heavily influenced by individual factors, rather than cancer type. Findings are confounded by gender; and should be considered preliminary. Effects of recurrence should be studied in samples where cancer type and gender are not confounded. Concerns are raised

about available study quality and differing outcome measures in this interpretation. Care and support of the individual at the time of a cancer recurrence is a key focus. Future research suggestions with implications for clinical practise are included.

Systematic Review Registration: PROSPERO 2019 CRD42019137381.

Keywords: breast cancer, oncology, prostate cancer, integrative review, quality of life, cancer recurrence

INTRODUCTION

Individuals will experience a range of negative consequences when faced with a cancer diagnosis, and the significance of an initial diagnosis is well-established in the literature (Schouten et al., 2019). However, it has been suggested that cancer recurrence may have a more significant impact on the individual than the initial disease as it often represents a more serious diagnosis (Step and Ray, 2011), particularly if the recurrence is not local. Consequently, the fear that cancer will recur is a common issue (Lebel et al., 2016); and has been addressed through psychological interventions (Chen et al., 2018).

In accordance with the negative consequences of a recurrence of cancer, some previous research has sought to capture the experience of patients at this time. A meta-ethnography (Wanat et al., 2016) reviewed qualitative studies involving recurrent cancer patients. This added to an earlier narrative review (Vivar et al., 2009) that summarised findings from varying study designs describing the impact on family members as well as the patient. Both reviews highlighted a complex range of issues patients face when dealing with a recurrence in relation to their physical well-being, emotional state, relationships- both personal and with healthcare professionals, as well as adjusting to new uncertainty and coming to terms with their own mortality.

In the UK, breast cancer is the most common malignancy in females, and prostate cancer the most common in males (Cancer Research, U. K., 2017b,c), and naturally the manner in which recurrence manifests will differ. In prostate cancer a patient may be diagnosed with biochemical recurrence. This refers to rising levels of prostate specific antigen (PSA) in the blood, but patients may not experience local or distant recurrence for some years after this (Artibani et al., 2018). In comparison, breast cancer recurrence may be identified in a manner similar to initial diagnosis, that is physical symptoms (Cancer Research, U. K., 2017a). With cancer in general it is known that several factors (including cancer characteristics) are important in understanding the well-being of patients (Schouten et al., 2019), but it is suggested that recurrence is a unique experience (Wanat et al., 2016) and yet there is little understanding of the effect of cancer type on how a recurrence affects the well-being of patients. Whilst being very common, these cancers manifest very differently, and as such may be a more useful point of comparison when establishing differences in reactions to recurrence than cancers with a more similar physical manifestation and treatment profile.

The aim of this review is to explore the existing literature in order to clarify if cancer type will influence the perceived impact of recurrence. By specifically examining prostate and breast cancer this review will explore highly prevalent, physically contrasting, and predominately gender based cancers; leading to a pertinent and multifaceted comparison. This will be conducted by summarising studies that evaluated the experiences of patients specifically with a recurrence of breast or prostate cancer; and then comparing these. For the purposes of this review, the patient experience refers to physical, psychological, and psychosocial issues that arise after a recurrence of cancer that may impact quality of life. For clarity, these experiences will relate to outcomes from studies assessing patient-reported levels of physical, psychological, and psychosocial indices of quality of life (QoL).

By addressing the question of cancer type potentially influencing the impact of recurrence it is suggested that findings from this review will help to develop a wider understanding of recurrence, highlighting differences (or the lack thereof) in personal reactions to a recurrence of these cancers. It is hoped that this will contribute knowledge to clinical care settings with implications for healthcare professionals treating patients with these cancer types. This includes professionals involved in regular personal care with these patients, such as cancer nurses. This is particularly important as, for some time, the NHS has outlined the need for a comprehensive approach to healthcare, in particular "person-centred" care- identifying the individual's wider well-being as crucial to their overall recovery, thereby providing a more personalised experience than in the past (Howe, 2020).

METHODS

In the literature, studies relevant to cancer recurrence feature a variety of research designs. Therefore, the current review was conducted in an integrative manner. This was considered a suitable method as it allows for inclusion, and deep understanding of diverse research designs (Hopia et al., 2016). The review was implemented in a systematic manner conforming to the methodological approach by Whittemore and Knafl (2005) that reduces the likelihood of biases and errors (Souza et al., 2010). The review protocol was registered in the international database of prospective systematic reviews in health and social care- PROSPERO 2019 CRD42019137381.

Search Strategy

Following the rationale of previous reviewers (Wanat et al., 2016) who highlight that there have been significant changes in treatments for cancer and within healthcare services, it was decided to restrict the search from January 1994 to April 2019. Four electronic databases were searched: PsycInfo, CINAHL

complete, Medline, and Pubmed. The following search terms were used:

- cancer* or carcinoma* or malignan* or tumour or tumour or neoplasm*
- patient experience or recur* or relapse or time or metastatic* or progress*
- psycholog* or psychosocial or experience* or supportive care or social
- breast cancer or prostate cancer
- fear or anxiety or worry or shock.

Inclusion Criteria

Articles were included if they: reported a study which explored the experience of any patients with a prostate or breast cancer recurrence (both local or distant recurrence were applicable, and data could have been collected at any time from directly after recurrence to end of life); used either quantitative or qualitative methodology to gather and analyse results; were published between January 1994 and April 2019; and were published in English.

Exclusion Criteria

Articles were excluded if they: did not explicitly state that in their studies, participants had recurrent cancer and were subsequently included in data analysis. That is, studies may include participants with metastatic cancer which is not necessarily recurrent, hence these would be excluded. In addition, if no distinction is made between cancer types in analysis (i.e., breast or prostate cancer patients may be included in a study but analysed together with other cancers with no distinction) they were excluded.

Screening Procedure

Two researchers (RJS, SC) independently screened articles that were identified through the database searches. First, titles and abstracts were screened, and non-relevant articles were excluded. Second, full articles of remaining studies were obtained and screened against this inclusion and exclusion criteria. Lastly, as a supplemental approach, reference lists of articles deemed to match the inclusion criteria were scanned. The procedure for database searching and study screening is outlined in **Figure 1**.

Data Extraction

Extracted data included: sample characteristics; study aim and design; and cancer type and stage. Data were extracted by one researcher (RJS) and checked by a second (SC) for accuracy. Study quality and risk of bias were both independently assessed by two researchers (RJS, SC) using the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). The MMAT allows for the quality assessment of all study designs and is therefore suitable for this review. Any discrepancies in data extraction and quality appraisal were resolved through discussion.

Data Abstraction and Synthesis

With consideration to the aim of the review as well as the heterogeneous character of eligible studies, there was limited scope for meta-analysis; instead, formal narrative synthesis was conducted with no minimum number of articles required. Using a convergent synthesis design (Hong et al., 2017), data from quantitative studies were combined with data from qualitative studies and were coded, and findings were categorised into themes based on the breakdown of different experiences. The outcomes synthesised in this review were measured either qualitatively or quantitatively by reliable and valid assessment tools and related to patient-reported levels of physical, psychological, and psychosocial indices of quality of life (QoL) that have impacted on the patients' experience of cancer recurrence. Themes related to the experience of prostate cancer patients with a cancer recurrence were compared to those of breast cancer patients with a cancer recurrence.

The precise timing of a recurrence will have a specific impact on the individual's health-related quality of life. This impact will differ between studies. If there is a comparison group alongside a recurrence group the difference between these will be used to judge the impact of recurrence. If there is no comparison group the impact of recurrence will be based upon scores from quantitative measures (if used by the authors). These measures will have scoring guidelines to judge what would be considered a normative or "standard" score. If there are qualitative findings with no comparison group these will be used to supplement results to build a wider comprehensive "picture" of the experience of patients at the time of recurrence. A within-subjects comparison can also be made where reference is made to previous assessments from patients at their primary diagnosis.

After the results have been presented from both cancer types, a comparison will take place. Any main similarities and differences will be outlined at this point and evaluating these will allow for judgement of if the subjective experience of recurrent breast cancer is broadly similar or different to that of prostate cancer, i.e., if several findings emerge in breast as well as prostate studies this would perhaps suggest a similar experience, whereas differing results would possibly suggest a different experience. Due to the outlined physical manifestations of breast and prostate cancer more credence will be given to the psychological and psychosocial concerns at this time when considering this comparison.

RESULTS

Overall, 392 articles were identified by the search strategy, of which 21 met inclusion criteria (**Figure 1**). Each article reported one relevant unique study.

Description of Studies

Included articles were published between 1996 and 2017. Ten were conducted in the USA; three in Sweden; two in Japan; and one each in Australia, Finland, Israel, Italy, the Republic of Ireland, and the UK. **Table 1** summarises details of the breast cancer studies and **Table 2** the prostate cancer studies. Fifteen articles that met inclusion criteria examined the patient experience of breast cancer recurrence, whereas six articles examined the patient experience of prostate cancer recurrence. Reporting of age differed throughout studies. For the studies examining the experience of breast cancer recurrence 11 reported mean ages, and these had an aggregate mean of 56.7 years

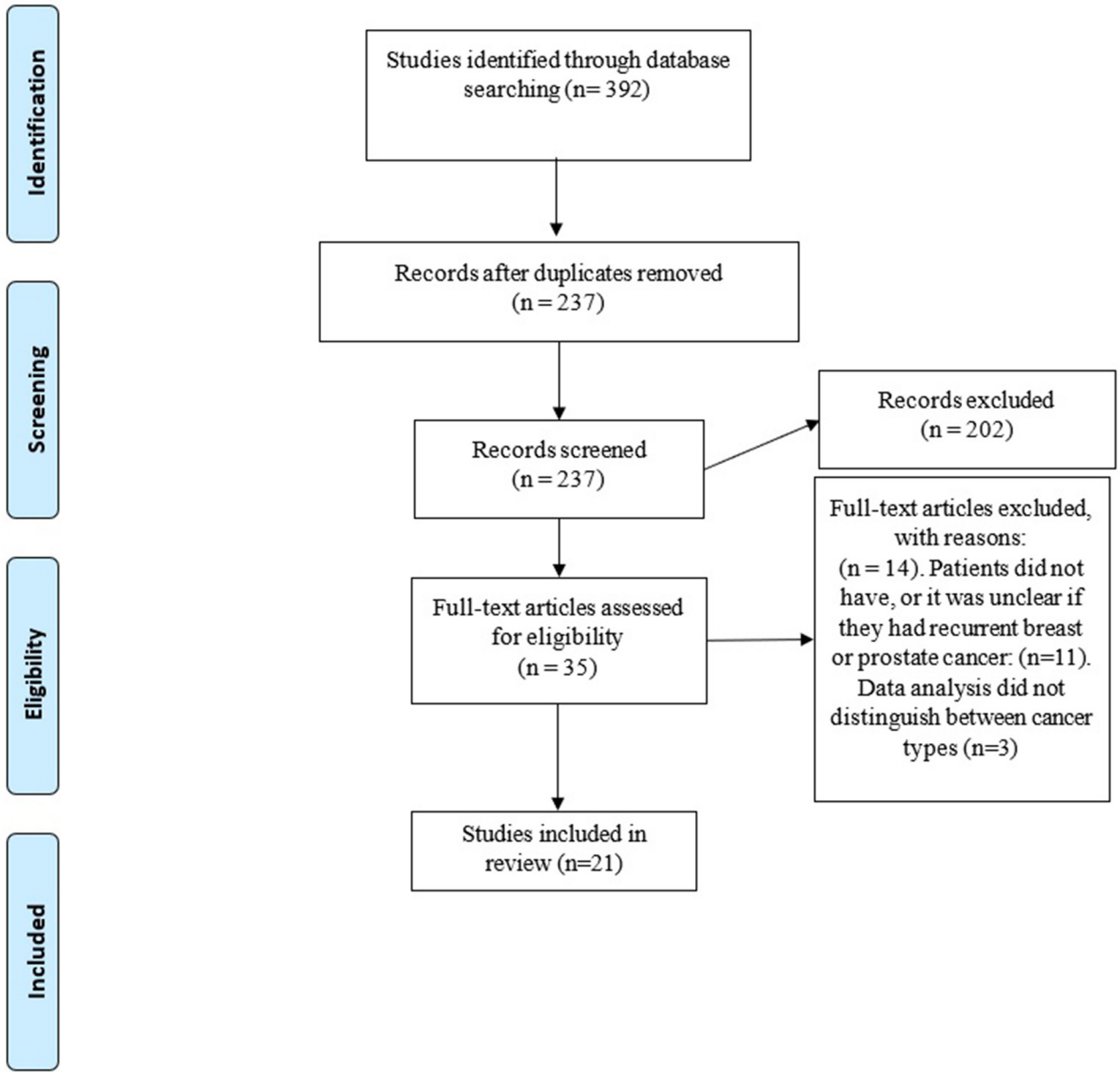

FIGURE 1 | Flow diagram of database searching and study screening.

old. Two studies reported a median age- one of 50 (Brady and Helgeson, 2000) and the other of 57 (Cleeland et al., 2014). The last two studies reported age ranges: one simply 75 years and younger (Hall et al., 1996) and the other an age range of 55–81 years old (Sarenmalm et al., 2009). It is important to note that three of these articles used the same sample of participants, but for slightly different research aims- as such any findings highlighted in this review will be referenced to which particular article they came from (Sarenmalm et al., 2007, 2008, 2009). Of those studies examining the experience of prostate cancer recurrence, four (Pietrow et al., 2001; Ullrich et al., 2003; Lehto et al., 2015; Maguire et al., 2017) reported mean ages, with an aggregate mean of 66.2; and the other two (Ames et al., 2008, 2011) each reported a median age of 76, respectively.

Study Methods

Of those studies examining the experience of breast cancer all but three were conducted with quantitative methods; with two using qualitative methods (Hall et al., 1996; Sarenmalm et al., 2009) and the other utilising mixed methods (Turner et al., 2005). One study (Ames et al., 2008) utilised mixed methods to examine the experience of prostate cancer, the remainder were conducted quantitatively. The research aims of included studies are described in **Tables 1**, **2**.

TABLE 1 | Breast cancer studies included in review.

References	Aim	Sample characteristics	Design	Outcome measures	Quality score
1. Andersen et al. (2005)	To analyse patients' reactions to a recurrence of cancer	30 females, mean age = 52 (SD = 11.6)	Controlled Prospective Study	IES; POMS; CES-D-SF; SF-36; SNI; PSS-Fa; PSS-Fr; DAS; KPS; SWOG rating scale.	****
2. Brady and Helgeson (2000)	To explore the relationship between social support and adjustment after a recurrence of breast cancer.	41 females, median age = 50	Quantitative	Adapted social support questions; BSI; COPE inventory	****
3. Bull et al. (1999)	Clarify relationship between recurrent breast cancer and quality of life	69 females, mean age = 53.3 (SD = 8.89)	Longitudinal study	Specifically designed scales.	****
4. Cleeland et al. (2014)	To characterise symptom burden, activities of daily living, health-related quality of life and work-related ability in order to inform clinical trials and treatments.	152 females, median age = 57	Observational cohort study	MDASI; WPAI; RSCL	***
5. Cohen (2002)	To explore emotional distress and coping strategies in patients with primary breast cancer vs. patients with recurrent breast cancer	41 females, mean age = 62.3 (SD = 7.7)	Observational cohort study	SCL-90; WCQ	*****
6. Hall et al. (1996)	To explore psychological morbidity in recurrent breast cancer patients.	61 females, age = 75 and younger.	Qualitative	Semi-structured interview	*****
7. Northouse et al. (2002)	To assess the quality of life of patients and their family members after recurrence	189 females, mean age = 54 (SD = 11.2)	Cross-sectional study	SF-36; FACT	*****
8. Oh et al. (2004)	To explore the quality of life of breast cancer survivors after a recurrence	54 females, mean age = 59.5	Observational cohort study	SF-36; CES-D; PANAS; IES-R; RDAS; MOS-SSS; PTGI; SBI-15R; Specifically developed Meaning and Vulnerability Scale	*****
9. Okamura et al. (2000)	To study the prevalence of psychological distress and risk factors of these following recurrence of breast cancer.	55 females, mean age = 52 (SD = 9)	Cross-sectional study	Structured clinical interview; POMS	*****
10. Okamura et al. (2005)	To examine the prevalence of, and factors linked with psychiatric disorders, and the impact on quality of life after recurrence.	50 females, mean age = 53 (SD = 10)	Cross-sectional study	Structured clinical interview; MAC scale; EPQ-R; EORTC QLQ-C30; EORTC QLQ-BR23	****
11. Sarenmalm et al. (2007)	To examine predictors of health-related quality of life in postmenopausal women with recurrent breast cancer.	56 females, mean age = 65	Cross-sectional study	MSAS; HADS; SOC-13; EORTC QLQ-C30; IBCSG QoL	****
12. Sarenmalm et al. (2008)	To explore the symptom experience and predictors of distress and quality of life in women with recurrent breast cancer [the same sample as Sarenmalm et al., 2007 was assessed].	56 females, mean age = 65	Longitudinal study	MSAS; HADS; EORTC QLQ-C30	****

(Continued)

TABLE 1 | Continued

References	Aim	Sample characteristics	Design	Outcome measures	Quality score
13. Sarenmalm et al. (2009)	To assess the main concerns of women with recurrent breast cancer, and how they were dealing with their situations (this sample was derived from the earlier Sarenmalm et al. studies).	20 females, age range 55–81	Qualitative	Semi-structured interview	*****
14. Thornton et al. (2005)	To clarify the effects of being diagnosed with cancer for a second time on health-related quality of life.	140 females, mean age = 53 (SD = 9.7)	Prospective data extracted from larger Randomised Control Trial	SF-36	***
15. Turner et al. (2005)	To define the key emotional concerns of women newly diagnosed with recurrent or metastatic breast cancer.	68 females, mean age = 54.7 (SD = 13.5)	Mixed Methods	Semi-structured interview; HADS; IES; CARES-SF	****

*BSI, Brief Symptom Inventory; CARES-SF, Cancer Rehabilitation Evaluation System-short form; CES-D, Center for Epidemiological Studies-Depression; COPE, Coping Orientation to Problems Experienced; DAS, Dyadic Adjustment Scale; EORTC QLQ-C30 (BR23), European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (breast cancer specific); FACT, Functional Assessment of Cancer Therapy; HADS, Hospital Anxiety and Depression Scale; IBCSG- QoL, International Breast Cancer Study Group- Quality of Life; IES, Impact of Events Scale (R)(Revised); KPS, Karnofsky Performance Scale; MAC, Mental Adjustment to Cancer; MOS-SSS, Medical Outcomes Study-Social Support Scale; MSAS, Memorial Symptom Assessment Scale, PANAS, Positive and Negative Affect Schedule; POMS, Profile of Mood States; PSS-(fa; fr), Perceived Social Support (family; friends); PTGI, Posttraumatic Growth Inventory; RDAS, Revised Dyadic Adjustment Scale; RSCL, Rotterdam Symptom Checklist; SBI-15R, System of Belief Inventory; SCL-90, Symptom Checklist; SF-36, Short Form Health Survey; SOC-13, Sense of Coherence Scale; SNI, Social Network Index; SWOG, Southwest Oncology Group; WCQ, Ways of Coping Questionnaire; WPAI, Work Productivity and Activity Impairment. *** refers to meeting 3 out of 5 quality criteria, **** is 4 out of 5, and ***** is 5 out of 5.*

Themes

Themes that emerged during data analysis were assigned to three broad categories: physical, psychological, and psychosocial issues. For ease of comparison between cancer types the main findings that emerged in included studies are outlined in **Table 3**, but more detail is described below.

Breast Cancer

Physical Issues

Physical symptoms experienced by breast cancer patients with a recurrence included: fatigue; sweats; coughing; a lack of appetite; dry mouth; pain; nausea and vomiting; drowsiness; swelling of limbs; numbness, feeling bloated; dizziness; taste change; problems with sex; constipation; diarrhoea; issues with urination; mouth sores; weight loss; shortness of breath; and difficulty concentrating (Turner et al., 2005; Sarenmalm et al., 2007, 2008; Cleeland et al., 2014). Furthermore, one study (Northouse et al., 2002) found that, in comparison to cancer patients in general, those with a recurrence rated their overall physical health lower. Further, patients' perceptions of their physical health at recurrence were found to be lower compared to: pre-recurrence (Bull et al., 1999); primary diagnosis (Andersen et al., 2005; Thornton et al., 2005); cancer patients in general (Northouse et al., 2002); and both population norms and disease-free breast cancer survivors (Oh et al., 2004). One study (Thornton et al., 2005) found that perceptions of physical health of women with distant recurrence were rated significantly lower than women with local recurrence.

Psychological Issues

Psychological problems were common among those with a breast cancer recurrence (Northouse et al., 2002; Turner et al., 2005). In a qualitative study (Hall et al., 1996), half of the sample (of a total of 38) were found to be clinically depressed or anxious (or both). Okamura and colleagues (Okamura et al., 2000) reported that 42% of their participants met criteria for major depressive disorder or adjustment disorders; with the prevalence rate of major depressive disorder akin to that found in patients after a primary diagnosis of cancer. However, a later study (Okamura et al., 2005) found the prevalence rate of psychiatric disorders to be lower, at 22% of their sample of recurrent breast cancer patients. Further, one study (Oh et al., 2004) found that in their sample, women with recurrent breast cancer did not suffer from clinical depression, prior to or following recurrence. There were different negative emotions experienced by those with a recurrence: high cancer-related stress (Andersen et al., 2005); emotional distress (Bull et al., 1999); general stress; worry; sadness; and irritability (Sarenmalm et al., 2007, 2008, 2009). Though another study (Oh et al., 2004) found that patients generally had good overall mood, as well as low levels of cancer-specific stress. A qualitative study (Sarenmalm et al., 2009) reported that participants often viewed recurrence as more distressing that their initial cancer diagnosis; but one study (Andersen et al., 2005) reported that patients' stress was equivalent at initial diagnosis as it was at recurrence, and another (Oh et al., 2004) reported some patients felt it was more stressful but others did not. Findings from one study (Cohen, 2002) suggested that, in comparison to women with primary breast cancer, women with local or metastatic recurrence displayed higher levels of depression, anxiety, and somatisation.

Psychosocial Issues

Self-reported overall QoL was negatively impacted by the diagnosis of a recurrence: in comparison to pre-recurrence (Bull

TABLE 2 | Prostate cancer studies included in review.

References	Aim	Sample	Design	Outcome measures	Quality rating
1. Ames et al. (2008)	To appraise the psychological needs of men with a biochemical recurrence of prostate cancer	28 males, median age=76	Mixed Methods	Semi-structured focus group; FACT-P; SF-36; MAX-PC; POMS-B; LES; PSS	***
2. Ames et al. (2011)	To evaluate the acceptability effect size of a quality of life intervention for men with a biochemical recurrence of prostate cancer	57 males, median age = 76	Pilot study of randomised controlled trial	FACT-P; SF-36; MAX-PC; PSS-10; POMS-B	***
3. Lehto et al. (2015)	To investigate experiences and psychological well-being in prostate cancer patients who received various types of treatment.	74 males, mean age = 67	Cross-sectional study	Specifically designed survey; RSCL; SWLS; IIEF	*****
4. Maguire et al. (2017)	To examine the associations between prostate cancer survivors' treatment appraisals and fear of recurrence.	1,229 males (222 had recurrence), mean age = 68.48 (SD = 7.87)	Cross-sectional study	EORTC QLQ-C30; Fear of recurrence scale; DRS	*****
5. Pietrow et al. (2001)	To define the impact of PSA recurrence on health-related quality of life radical retropubic prostatectomy.	88 males, mean age = 63.4	Observational cohort study	SF-36; UCLA-PCI	****
6. Ullrich et al. (2003)	To compare cancer fear and mood disturbance after biochemical recurrence of prostate cancer with those without recurrence.	45 males, mean age = 66.1 (SD = 6.4)	Observational cohort study	AUA Symptom Index; Previously used Cancer Fear questions; POMS	****

*AUA, American Urological Association; DRC, Decisional Regret Scale; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; FACT-P, Functional Assessment of Cancer Therapy- Prostate; IIEF, International Index of Erectile Function; MAX-PC, Memorial Anxiety Scale-Prostate Cancer; LES, Life Experiences Survey; POMS (B) Profile of Mood States (Brief); PSS-10 Perceived Stress Scale; RSCL, Rotterdam Symptom Checklist; SF-36, Short Form Health Survey; SWLS, Satisfaction With Life Scale; UCLA-PCI, University of California Los Angeles-Prostate Cancer Index. *** refers to meeting 3 out of 5 quality criteria, **** is 4 out of 5, and ***** is 5 out of 5.*

et al., 1999; Andersen et al., 2005; Thornton et al., 2005); and compared to those with an early-stage primary diagnosis of cancer (Northouse et al., 2002). Issues with medical staff were reported; satisfaction with medical professionals was found to be fairly low (Bull et al., 1999; Turner et al., 2005). Furthermore, several patients in the study by Turner et al. (2005) expressed frustration at the method in which the diagnosis was given, and over 40% of their sample felt that there had been too long a delay between their reporting of concerning symptoms and the subsequent action by medical professionals leading to diagnosis of recurrence. Thirty out of 38 patients in one study (Hall et al., 1996) claimed to have received no support whatsoever from their hospital following recurrence.

Patients were concerned about their loss of independence and the impact on family members (Turner et al., 2005), and limitations to their social roles (Northouse et al., 2002; Thornton et al., 2005). Cleeland et al. (2014) reported several patients faced impairment with daily activities as well as issues with missing work and impairment when they were able to work. Social functioning (the ability to fulfil social roles) was found to be negatively impacted by recurrence (Bull et al., 1999; Northouse et al., 2002; Andersen et al., 2005; Thornton et al., 2005). Some patients described the good quality of their interpersonal relationships (Oh et al., 2004; Andersen et al., 2005). Brady and Helgeson (2000) examined the correlations between social support and adjusting to breast cancer recurrence. They found that emotional support from a partner and communicative support from an oncologist were correlated with fewer physical issues, but not to psychological distress. Further, psychological distress was related to decreased emotional support from a partner. Findings from the qualitative study by Sarenmalm et al. (2009) suggest that re-examining and altering social relationships was found to be a method of adjusting to cancer recurrence, and distress was lessened by receiving reassurance in regards to fears and uncertainty. Patients from this study found importance in changing their expectations from being cured, focussing on the quality of life rather than quantity and concentrating on the present rather than the past or future. An interesting finding from one study (Cohen, 2002) suggested that women with recurrent breast cancer were significantly less likely to use the adoption of a positive attitude as a coping mechanism than women with a primary diagnosis.

TABLE 3 | Common patient-reported issues after cancer recurrence.

Breast cancer			Prostate cancer		
Physical	**Psychological**	**Psychosocial**	**Physical**	**Psychological**	**Psychosocial**
Fatigue	Anxiety	Low QoL	Fatigue	Anxiety	Low QoL
Urination problems	Depression	Issues with medical staff	Urination problems	Depression	Issues with medical staff
Sexual problems	Stress	Importance of social support	Sexual problems	Frustration	Importance of social support
Shortness of breath	Emotional distress	Poor social functioning	Loss of muscle strength	Fluctuating mood	–
Poor appetite	Worrying	Unable to fulfil daily activities	Hot flushes	Anger	–
Taste change	Sadness	–	Incontinence		–
Weight loss	Irritability	–	–	–	–
Mouth sores	–	–	–	–	–
Dry mouth	–	–	–	–	–
Pain	–	–	–	–	–
Nausea and vomiting	–	–	–	–	–
Drowsiness	–	–	–	–	–
Limb Swelling	–	–	–	–	–
Numbness	–	–	–	–	–
Dizziness	–	–	–	–	–
Difficulty concentrating	–	–	–	–	–
Feeling bloated	–	–	–	–	–
Constipation	–	–	–	–	–
Diarrhoea	–	–	–	–	–
Coughing	–	–	–	–	–
Sweating	–	–	–	–	–

Prostate Cancer

Physical Issues

For recurrent prostate cancer patients, problems with sexual activity were reported (Pietrow et al., 2001; Ames et al., 2008; Lehto et al., 2015), such as sexual dysfunction and low libido. Patients also had issues with experiencing hot flushes from their treatment, frequent urination and incontinence, fatigue, as well as loss of muscle strength (Ames et al., 2008; Maguire et al., 2017). Patients suffered pain, as well as reporting low levels of physical well-being (Ames et al., 2008, 2011).

Psychological Issues

Patients commonly reported high levels of anxiety (Ames et al., 2008; Lehto et al., 2015) due not only to the recurrence itself, but to PSA testing and subsequent results and related to their physical issues. Some patients reported anger and bitterness (Ames et al., 2008; Lehto et al., 2015) regarding their situation, as well as a frustration at the lack of a cure. One study (Lehto et al., 2015) described patients with depressive thoughts and fluctuating mood that were more pronounced than general prostate cancer patients. Though, Ames et al. (2011) found generally, participants had relatively low levels of anxiety, stress, and mental health issues, as well as reasonably raised mood. Moreover, an inconsistent picture emerged in the study by Ames et al. (2008) wherein participants rated their mood as high when measured qualitatively, which contrasted when measured quantitatively. Ullrich et al. (2003) found that recurrence in itself was not associated with greater mood disturbance or cancer-related fear. However, when patients with recurrence also had urinary symptoms they displayed high psychological distress; suggesting that these symptoms may be a more important factor.

Psychosocial Issues

Issues that arose in the study by Lehto et al. (2015) related broadly to the relationship between patients and their healthcare professionals. Several patients felt unhappy with the information given to them at diagnosis of recurrence. Some reported dissatisfaction at the way in which they learned of their condition in that some felt it too impersonal. Others deemed the behaviour and communication of healthcare professionals to be unsatisfactory, and half of their participants reported unhappiness with the care received (Lehto et al., 2015); however, experiences varied between the treatments undertaken. Maguire et al. (2017) noted that most of their sample were satisfied with the information they received about their condition and largely felt low regret over their choices regarding treatment. The participants in one (Ames et al., 2008) study reported generally good relationships with their doctors. In terms of social relationships, participants in the same study reported the maintenance of good social relationships as an important marker

of their QoL, and social support from friends and family was commonly reported as a useful method of coping with the cancer (Ames et al., 2008; Lehto et al., 2015). In the study by Lehto et al. (2015) most participants regarded their condition as having no effect on the relationship with their partner. One study (Ames et al., 2008) found that men with a recurrence of prostate cancer had worse health-related and prostate cancer-specific QoL than patients without recurrence, though the general QoL of recurrent patients in this study was higher than patients with other chronic illnesses. Pietrow et al. (2001) found small negative differences in health-related QoL in patients with recurrence vs. those without, but deemed overall QoL to be very similar in these two groups.

Comparison Between Breast and Prostate Cancer

Despite differences in the physical manifestation of breast and prostate cancer, some physical symptoms were highly prevalent in both types of cancer: pain; fatigue; problems with sexual activity; and bowel and bladder issues. Psychological morbidity was common for both cancer types. Some negative emotions, common with either type of cancer recurrence, were: sadness, worry, irritability, anxiety, uncertainty, and stress. Several, though not the majority of patients of both cancer types expressed dissatisfaction with medical professionals. The importance of social relationships as a means of emotional support was commonly reported across both cancer types. Noting differences is complex due to the disparity in the number of breast and prostate cancer studies. For example, as opposed to breast cancer (Okamura et al., 2000, 2005), no studies assessed prostate cancer patients for formal criteria of psychological disorders. More physical problems were associated with breast cancer recurrence, though the above issue may in part account for this.

Quality Appraisal

The MMAT includes five criteria of quality to judge studies (Hong et al., 2018). Included studies' quality scores ranged from meeting three out of the five criteria to meeting all five criteria. These criteria differ based upon the design of each study. Most studies were found to be of moderate quality. Of the 15 studies with a quantitative design it was observed that quality differed, with only five judged to meet all five criteria (Okamura et al., 2000; Northouse et al., 2002; Oh et al., 2004; Lehto et al., 2015; Maguire et al., 2017). The two studies with a qualitative design (Hall et al., 1996; Sarenmalm et al., 2009) were judged to meet all five criteria. The two studies with mixed-methods methodology were judged to only meet three criteria (Turner et al., 2005; Ames et al., 2008). An issue with both of these studies was that the authors did not outline explicitly how each research component integrated with the other. Many studies had small sample sizes as well as being at risk of non-response bias, which lowered the generalisability of the results. **Table 4** contains full details of the quality assessment of the included studies; and for ease of comparison, quality scores are displayed in **Tables 1**, **2** alongside study details.

DISCUSSION

From the available evidence, there appears to be several similarities in the experience of recurrent breast and prostate cancer. Moreover, most disparities appear within cancer types, with mixed results for certain outcomes across studies. The reported psychological factors indicate the biggest differences between studies (and not between cancer types). It is worth consideration that this could be in part related to the different outcome measures used to capture the experience of recurrent cancer. This is perhaps best demonstrated by the disparity already identified within Ames et al. (2011), wherein participants rated their mood highly when measured qualitatively but low when measured quantitatively.

The prostate cancer study (Ames et al., 2011) that reported generally positive mood of patients with recurrence was rated moderately, meeting 3 out of 5 quality criteria. The same rating was given to the study (Ames et al., 2008) where participants' mood rated high when measured qualitatively, but not quantitatively. Little difference in QoL between patients with recurrence and those with primary diagnosis was found by Pietrow et al. (2001), and this study was judged to meet 4 out of 5 quality criteria; a rating also given to the study (Ullrich et al., 2003) which found that recurrence in itself was not a significant factor on cancer fear and mood disturbance. However, fear was considered higher in patients with recurrence than without in the study by Maguire et al. (2017). This set of results initially suggests that the quality of studies may be important in interpreting results. However, the findings from the breast cancer studies may counter this opinion with one study (Oh et al., 2004) finding generally good mood and low levels of cancer specific-stress. This particular study was judged to meet all 5 quality criteria.

As this review was not examining the efficacy of a treatment or intervention, but rather examining the experiences of included patients, the process of distinguishing between RCTs and other study designs, in terms of levels of evidence, would not be as pertinent as it may otherwise be. Hence, the study featuring an RCT was a prostate cancer study (Ames et al., 2011) and diverged most from the other prostate cancer studies. It is interesting that this was a pilot study and therefore had a relatively small sample size. Inconsistent results were found within other study designs which suggests therefore that these design features do not necessarily explain differences found between studies.

The articles reviewed infer that gender may not explain differences in the recurrence experience. Interestingly, a recent meta-analysis suggests that fear of cancer recurrence is stronger in women than men, but whether this applies to emotional distress after actually experiencing a recurrence is unclear from this review. There is some suggestion that gender plays a role in how primary cancer is experienced (Pud, 2011; Linden et al., 2012); however, the literature is mixed in that some research has found little difference or inconsistent results in relation to various aspects of the cancer experience between genders (Miaskowski, 2004; Garrett et al., 2011; Ahmed et al., 2017).

It has been suggested that the fear of cancer recurring decreases with age (Lim and Humphris, 2020), so that younger cancer survivors will be more concerned about this possibility.

TABLE 4 | Quality appraisal.

Qualitative	**Is the qualitative approach appropriate to answer the research question?**	**Are the qualitative data collection methods adequate to address the research question?**	**Are the findings adequately derived from the data?**	**Is the interpretation of results sufficiently substantiated by data?**	**Is there coherence between qualitative data sources, collection, analysis and interpretation?**
Hall et al. (1996)	Yes	Yes	Yes	Yes	Yes
Sarenmalm et al. (2009)	Yes	Yes	Yes	Yes	Yes
Quantitative randomised controlled trials	**Is randomisation appropriately performed?**	**Are the groups comparable at baseline?**	**Are there complete outcome data?**	**Are outcome assessors blinded to the intervention provided?**	**Did the participants adhere to the assigned intervention?**
Ames et al. (2011)	Can't tell	Yes	Yes	No	Yes
Quantitative non-randomised	**Are the participants representative of the target population?**	**Are measurements appropriate regarding both the outcome and intervention (or exposure)?**	**Are there complete outcome data?**	**Are the confounders accounted for in the design and analysis?**	**During the study period, is the intervention administered (or exposure occurred) as intended?**
Andersen et al. (2005)	Can't tell	Yes	Yes	Yes	Yes
Cleeland et al. (2014)	Yes	Yes	No	Yes	No
Cohen (2002)	Yes	Yes	Yes	Yes	Yes
Northouse et al. (2002)	Yes	Yes	Yes	Yes	Yes
Oh et al. (2004)	Yes	Yes	Yes	Yes	Yes
Pietrow et al. (2001)	Yes	No	Yes	Yes	Yes
Ullrich et al. (2003)	Yes	No	Yes	Yes	Yes
Quantitative descriptive	**Is the sampling strategy relevant to address the research question?**	**Is the sample representative of the target population?**	**Are the measurements appropriate?**	**Is the risk of non-response bias low?**	**Is the statistical analysis appropriate to answer the research question?**
Brady and Helgeson (2000)	Yes	Yes	No	Yes	Yes
Bull et al. (1999)	Yes	Yes	Yes	No	Yes
Lehto et al. (2015)	Yes	Yes	Yes	Yes	Yes
Maguire et al. (2017)	Yes	Yes	Yes	Yes	Yes
Okamura et al. (2000)	Yes	Yes	Yes	Yes	Yes
Okamura et al. (2005)	Yes	Yes	Yes	No	Yes
Sarenmalm et al. (2007)	Yes	Yes	Yes	No	Yes
Sarenmalm et al. (2008)	Yes	Yes	Yes	No	Yes
Thornton et al. (2005)	Yes	Yes	Yes	No	No
Mixed methods	**Is there an adequate rationale for using a mixed methods design to address the research question?**	**Are the different components of the study effectively integrated to answer the research question?**	**Are the outputs of the integration of qualitative and quantitative components adequately interpreted?**	**Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?**	**Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?**
Ames et al. (2008)	No	No	Yes	Yes	Yes
Turner et al. (2005)	Yes	No	Yes	No	Yes

This is plausibly explained by younger people having a longer life expectancy. In the current review breast cancer patients with recurrence were generally younger than those with prostate cancer, and so this could apply to the lived experience of recurrence rather than just the fear. However, with minimal difference found between the cancer types this suggestion is not supported.

In summary, findings from this review point to differences in the recurrent cancer experience being based upon individual factors, rather than having either recurrent breast or recurrent prostate cancer. There is evidence in this review to support this interpretation. As indicated previously, social support was important to patients at the time of recurrence. Previous research (Yoo et al., 2017) has found a link between higher perceived social support and higher quality of life and lower depressive symptoms among patients with a primary diagnosis of cancer, thus logically this may apply at the time of recurrence. Further, there was indication that treatment received may be an important factor in quality of life. It has been suggested that differing treatment in primary prostate cancer patients led to different physical problems (Bacon et al., 2001), and this could therefore subsequently impact on psychological well-being. Thus, it is possible that the experiences of patients may differ based on factors such as these, and would be would be worthy of further investigation.

Comparison to Previous Research

Within the literature, it is firmly established that fear of cancer recurrence, as well as an actual recurrence of cancer, are sources of emotional distress (Simard et al., 2013; Schouten et al., 2019); as such, this review is consistent with findings from the meta-ethnography carried out by Wanat et al. (2016) and the earlier narrative review by Vivar et al. (2009), which both described a wide range of negative issues that accompany cancer recurrence. This review adds to this research by conducting a comparison of cancer types, based upon the available literature. As noted, breast and prostate cancer were chosen as they differ in a number of ways, not least as they effect males and females (almost) exclusively, but future research could be designed to capture a wider range of cancer types than just breast and prostate cancers. Such research would help to clarify these findings.

Limitations

Though the review was exploratory in nature, the cancer type comparison conducted should be read with the caveat that there were far fewer studies included examining the experience of patients with recurrent prostate cancer as opposed to breast cancer. All prostate cancer studies were quantitative, and whilst the integrative nature of this review means the study design is less important, it is perhaps indicative of the relative lack of research into the experience of recurrent prostate cancer patients. As such, there were some aspects of the patient experience that were measured solely in breast cancer patients and therefore cannot be compared. Whilst a gender difference is an interesting comparison point, with the two cancer types selected it is not possible to delineate between cancer type and gender as factors in how cancer recurrence is experienced, this is a major limitation of the review. This is partially offset by being only one of a number of factors discussed, but to further distinguish between gender and cancer type it would be beneficial in any future comparison to include another cancer type that affects men and women on a fairly equal proportion. In addition, several of the studies were not primarily exploring the experience of patients with recurrent cancer but had some patients who had recurred included in their analysis. Another limitation is the variety of timing when patients were investigated. For example, there were different time points when data were collected, as well as the time between initial diagnosis and recurrence varying across studies.

Recommendations

An exploratory, longitudinal study directly comparing cancer types at the time of a recurrence would greatly add to the findings of this review. Ensuring high methodological quality of such research would address concerns raised in this review. This review has touched on factors that may result in lower quality of life in recurrent cancer patients (such as age, disease stage, and treatment received) that were not easily compared here. As such these could be explored as moderating variables in this new suggested research.

Clinical Implications

Healthcare professionals may find this review of assistance to clarify what patients may experience at the time of a cancer recurrence with two prevalent cancer types. It was demonstrated that between these cancers, the experience of cancer recurrence might have many similarities, and as such due consideration is needed toward the care and support of the individual at the time of a cancer recurrence.

CONCLUSIONS

This review primarily sought to identify if, based on evidence from the published literature, the type of cancer a patient had at the time of a recurrence had an impact on how cancer recurrence is experienced- based upon physical, psychological, and psychosocial indices of QoL in recurrent breast and prostate cancer patients. It highlights the multifarious issues created for cancer patients at the time of a cancer recurrence, thereby building upon findings from such previous research (Vivar et al., 2009; Wanat et al., 2016). Based upon the comparison conducted, findings suggest that it is likely that any differences in the experience of recurrent cancer are more heavily influenced by individual factors, rather than cancer type, though concerns have been raised about available study quality and differing outcome measures in this interpretation. Adding to the literature, this review is the first to specifically explore and compare the experience of patients with recurrent prostate or breast cancer; the most common cancers in males and females, respectively. As such, it has been possible to explore potential reasons for differences in experience.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

RS, SC, JD, and GH conceived of the review. RS and SC were responsible for study screening and quality assessment. RS conducted data analysis and drafting of the manuscript. SC, JD, and GH made important revisions to the paper. All authors contributed to the article and approved the submitted version.

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Which Head and Neck Cancer Patients Are Most at Risk of High Levels of Fear of Cancer Recurrence

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Background: Fear of cancer recurrence (FCR) is recognized as a common concern for patients with head and neck cancer (HNC). The aim of this study is to describe in greater detail the demographic and clinical characteristics of HCN patients who indicate a high level of FCR in their review consultation.

Methods: A pragmatic cluster-controlled trial was conducted between January 2017 and December 2018 at two UK HNC centers (Leeds and Liverpool) to test the efficacy of a prompt tool called the Patient Concerns Inventory (PCI). Patients completed the PCI and the UW-QOLv4 which included a single 5 category rating of FCR. Secondary statistical analyses focused on variables associated with high FCR.

Results: Two hundred and eighty-eight trial patients were recruited in this trial. At a median of 194 days after diagnosis and 103 days after the end of treatment 8% stated ($n = 24$) "I get a lot of fears of recurrence and these can really preoccupy my thoughts" and 3% ($n = 8$) "I am fearful all the time that my cancer might return, and I struggle with this." Thus, 11% ($n = 32$) responded in the worst two categories, 95% Confidence interval 7.7–15.3% for high FCR. Stepwise logistic regression resulted in female gender ($p < 0.001$), age ($p = 0.007$), and receiving financial benefits ($p = 0.01$) as independent predictors.

Conclusions: Around one in ten HNC patients attending routine outpatient follow-up consultations report high FCR, however for female patients under the age of 55 the rate was one in three. This group requires specialist attention and could be the focus of a multicenter intervention trial.

Keywords: fear of cancer recurrence, quality of life, patient concerns inventory, head and neck cancer, randomized trial

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INTRODUCTION

Head and neck cancer (HNC) is the eighth most commonly diagnosed cancer in the UK (Cancer Research UK, 2017) with approximately 12,200 new cases each year. Risk factors include smoking and alcohol and recently the Human Papilloma virus (HPV) (Cooper et al., 2009; Dhull et al., 2018). The 5-year disease specific survival is around 60% for both men and women (Cadoni et al., 2017). Most HNC recurrences occur within the first 2 years following diagnosis (Kissun et al., 2006) and

have a poor prognosis with survival in terms of months (Fullarton et al., 2016). With this backdrop it is hardly surprising that Fear of Cancer Recurrence (FCR) is (Humphris and Ozakinci, 2008) one of the most frequent issues patients wish to talk about in their out-patient review consultations (Kanatas et al., 2012). Given the likelihood of early recurrence, clinicians often stress the importance of vigilance and adherence to follow-up visits. One of the greatest challenges is carefully balancing the degree of emphasis on recurrence without alarming the patient. Fear of Cancer Recurrence is of particular interest as this fear holds considerable psychological stress which in turn negatively affects the patient's quality of life (QoL) (Smith et al., 2006; Dunne et al., 2017), daily functioning (Lee-Jones et al., 1997), relationship with carers (Hodges and Humphris, 2009), and mental well-being (Humphris et al., 2003). HNC survivors with inadequate health literacy have increased FCR compared to those with adequate health literacy (Clarke et al., 2021).

The issue of FCR can be hard to elicit in the follow-up clinic, whether this be face to face or virtual, as imposed by restrictions due to the COVID-19 pandemic. The Patients Concerns Inventory (PCI) is a condition specific prompt list devised in collaboration with patients as a means by which they can raise issues of concern with the clinician (Rogers et al., 2009) (**Supplementary Material**). A systematic review and content comparison of unmet needs self-report measures favored the PCI over 13 other tools (Shunmugasundaram et al., 2019). In a randomized trial the PCI has been shown to be a low-cost intervention which is feasible in routine clinical practice and is associated with a positive effect on QoL and socio-emotional dysfunction (Rogers et al., 2020).

Although the PCI can help to identify the frequency of FCR (Rogers et al., 2010a; Kanatas et al., 2012; Ghazali et al., 2013), thus far specific details of which kind of patient is most at risk are lacking. The PCI randomized trial (Rogers et al., 2020) has given an opportunity to evaluate in much greater depth the issue of FCR and this is of particular merit as the trial is based in standard practice and involved 15 consultant HNC surgeons. Hence, the aim of this study is to describe the demographic background and clinical characteristics for those HCN patients who indicate a high level of FCR in their review consultation. This may allow prompt identification of those patients in need of further support during their clinical consultations.

MATERIALS AND METHODS

Setting and Participants

The methodology of this trial has been described in detail (Rogers et al., 2018a). Briefly, this is a pragmatic cluster-controlled trial, with consultants (clusters) randomized to "using" or "not using" an intervention incorporating the PCI prompt list at all their trial clinics, i.e., at both baseline and at all follow-up clinics. Two centers participated, Aintree and Leeds, with 15 consultants of whom 8 used the PCI and 7 did not. We report results from the first "baseline" trial clinic and focus on findings regarding fear of recurrence (FCR). We also report FCR results after 12 months of follow-up. Eligible patients were treated curatively for primary HNC, and all sites, stages of disease and treatments were included, and second primary tumors were later accepted. Patients treated palliatively or with a recurrence or with a history of cognitive impairment, psychoses or dementia were excluded.

Measures

The UW-QOL v4 questionnaire comprises 12 single item domains, with between 3 and 5 response options scaled evenly from 0 (worst) to 100 (best) according to response hierarchy (Rogers et al., 2002). UW-QOL domains are presented within two subscales, physical function and social-emotional function (Rogers et al., 2010b) with each subscale score being the mean of six domain scores (http://www.hancsupport.com/professionals/quality-life/qol-questionnaires/university-washington). The physical function score is the mean of the appearance, swallowing, chewing, speech, taste and saliva domain scores, while the social-emotional score is the mean of the pain, activity, recreation, shoulder, mood, and anxiety domain scores. Criteria derived from earlier work was used to highlight domains in which patients have a significant problem or dysfunction (Rogers and Lowe, 2009). There was also a single item overall QOL question on the UWQOL v4 for which patients are asked to consider not only physical and mental health, but also other factors, such as family, friends, spirituality, or personal leisure activities important to their enjoyment of life. The study HRQOL data also included the Distress Thermometer score (Hegel et al., 2008) and EQ-5D-5L (Rogers et al., 2016).

The FCR question has five response options: (A) I have no fear of recurrence, (B) I have a little fear, with occasional thoughts but they don't really bother me, (C) I am sometimes having fearful thoughts, but I can usually manage these, (D) I get a lot of fears of recurrence and these can really preoccupy my thoughts, (E) I am fearful all the time that my cancer might return and I struggle with this. There is also a separate question asking patients whether FCR had been important to them (Yes/No) during the past 7 days. From earlier work (Rogers et al., 2016) it was postulated that those patients responding in the worst two categories should be considered for added assessment and support; we define these patients as having a significant problem or dysfunction with FCR.

The PCI is a condition-specific item prompt list (Rogers et al., 2009) comprising 56 items, which patients select from before seeing their consultant, to help guide the outpatient consultation, and it covers a range of symptoms and potential problems patients may face after treatment. It helps focus the consultation, aids doctor–patient communication, and helps route patients to other professionals for advice and support. It can be integrated into routine clinical practice (Rogers et al., 2018b).

Pre-consultation questionnaires including the PCI prompt list were completed electronically (desktop, tablet, iPAD) apart from one Liverpool hospital (non-PCI consultant) that used paper. PCI patients took into their consultations a summary sheet of paper that listed (a) all PCI items they selected for discussion, (b) any University of Washington (UWQOL) questionnaire domains in which there was a significant problem or dysfunction, (c) their overall QOL response, (d) their Distress Thermometer score, and (e) health professionals they wanted to see. This one page paper summary printout was the visible difference

between trial arms as far as contact between consultant and patient was concerned. Control patients completed exactly the same pre-clinic information apart from the PCI prompt list but neither they nor their consultant saw any summary sheet. Both groups completed the EQ-5D-5L for purposes of health economic assessment.

Baseline clinical and demographic data were collected using a baseline clinic questionnaire based on that of the Head and Neck 5000 project (Ness et al., 2014), or by extraction from baseline clinical records. Information was collected as to whether patients lived alone or with others, whether they were working and whether they lived in a household that received UK state financial benefits. Lifestyle factors about tobacco and alcohol use were also collected, as was patient gender and age. Clinical details about primary tumor site, grade, treatment, WHO, and ACE27 comorbidity were obtained from clinical records. Index of Multiple Deprivation (English Indices of Deprivation–IMD, 2019) scores were derived from patient postcodes using publicly available data and these provide a relative measure of deprivation at a small area level across England.

Statistical Analyses

The statistical analysis focused on variables associated with FCR dysfunction. We considered patient and clinical casemix variables and also a wide range of HRQOL measures. Fishers Exact test was used to compare patient groups regarding FCR dysfunction (Yes/No). Logistic regression was used to form predictive models of FCR dysfunction. Univariate models with each predictor variable were run and the Nagelkerke R square value (R^2) was noted for each model, these values providing an indication of which models better predict FCR dysfunction; the higher the value the better the prediction. Multivariable logistic regression modeling was done using significant univariate casemix variables (**Table 1**) and a stepwise regression approach with $p < 0.01$ for inclusion was adopted for the consideration of the many HRQOL predictor variables (**Table 2**). Given the number of tests performed for this paper, statistical significance was regarded as $p < 0.01$.

RESULTS

Patients for the trial were first discussed at MDT meetings between January 2017 and December 2018, with first trial clinics between April 2017 and October 2019. Characteristics of the 288 trial patients can be determined from **Table 1**. Median (IQR) age at baseline was 62 (55–69) and 69% (198) were male. Baseline clinics were a median (IQR) of 194 (125–249) days after diagnosis and 103 (71–162) days after the end of treatment. Regarding FCR, 15% (43) stated "I have no fear of recurrence," 44% (127) "I have a little fear, with occasional thoughts but they don't really bother me," 30% (86) "I am sometimes having fearful thoughts but I can usually manage these," 8% (24) "I get a lot of fears of recurrence and these can really preoccupy my thoughts," and 3% (8) "I am fearful all the time that my cancer might return and I struggle with this." Thus 11% (32) responded in the worst two categories, 95% Confidence interval 7.7–15.3% for FCR dysfunction, and this rate was notably higher in females and in patients younger than 65 years (**Table 1**). No significant variation was seen regarding tumor site, clinical stage, or treatment. It was also higher in those still smoking and in those with households receiving financial benefits. Stepwise logistic regression with gender, age (<55/55–64/≥65), financial benefits (Yes/No), and smoking habit (Current/Ex/Never) resulted in gender ($p < 0.001$), age ($p = 0.007$), and financial benefits ($p = 0.01$) as independent predictors, $n = 265$. The first two predictors, gender and age, were retained to preserve the full sample size. In female patients under the age of 55 the rate was 36% (10/28), while for those aged 55–64 it was 29% (8/28) and for those ≥65 it was 3% (1/34); for males the rates were 12% (5/43), 7% (6/88), and 3% (2/67), respectively.

Most of the HRQOL measures in this study were associated with FCR (**Table 2**) and with each other (results not shown). Fear of Cancer Recurrence dysfunction was present in 49% (24/49) of those with dysfunction in anxiety (UWQOL), in 47% (21/45) of those with dysfunction in mood (UWQOL), in 44% (21/48) with moderate, severe, or extreme problems with anxiety/depression (EQ5D), in 43% (10/23) with dysfunction in recreation (UWQOL) and 42% (11/26) with poor or very poor overall quality of file (UWQOL). Comparison of the R^2 values indicated that the most predictive variables from **Table 2** were UWQOL anxiety ($R^2 = 41.1$), EQ5D anxiety/depression (37.0), UWQOL Mood (31.2) and UWQOL social-emotional function subscale score (26.9). In comparison the R^2-value for the model with gender and age group was 18.2. When gender and age and all the variables from **Table 2** were considered within a stepwise regression at $p < 0.001$ for entry then UWQOL anxiety ($p < 0.001$, $R^2 = 41.1$) was selected first, followed by UWQOL Mood ($p < 0.001$, $R^2 = 46.4$ combined) and then gender ($p = 0.002$, $R^2 = 52.1$ combined). If patients had both UWQOL anxiety and mood dysfunction then 66% (19/29) also had FCR dysfunction (males: 61%, 11/18; females: 73%, 8/11). If patients had UWQOL anxiety and mood dysfunction but not both then 19% (7/36) had FCR dysfunction (males; 9%, 2/22; females: 36%, 5/14). For other patients only 3% (6/223) had FCR dysfunction (males: 0%, 0/158; females: 9%, 6/65).

One-third (97/288) of patients said that FCR had been important to them in the past week, and this varied from 81% (26/32) of those with FCR dysfunction, 50% (43/86) of those sometimes having fearful thoughts, 19% (24/127) of those having a little fear and 9% (4/43) of those without fear at the time of data entry. In the group who sometimes had fearful thoughts, there were no significant differences in patient characteristics between the 43 patients regarding FCR as important and the 43 patients for whom it was not important (**Tables 1**, **2**) apart from an association with EQ5D anxiety/depression ($p < 0.001$) in **Table 2** which only affected the balance between not being anxious or depressed and being slightly anxious or depressed. Patients in the PCI intervention group could select the FCR item from the PCI prompt list if they wanted to discuss this during their consultation, and 34% (48/140) did select this item. Of the 16 patients with FCR dysfunction then 8 wanted to discuss their fears and 8 did not (**Table 3**). About half (53%, 23/43) of patients who sometimes had fearful thoughts but could usually manage them wanted to discuss their fears, 74% (14/19) if FCR had been

TABLE 1 | Patient and clinical characteristics and fear of recurrence.

			Fear of recurrence response category*					% with FCR dysfunction (A&B)	*P*-value***	R^2-value****
		Patients	A&B)	C+	C–	D	E			
	Total	288	32	43	43	127	43	11		
Trial group	PCI	140	16	19	24	62	19	11	>0.99	<0.1
	Non-PCI	148	16	24	19	65	24	11		
Hospital	Aintree	178	19	30	26	76	27	11	0.85	0.1
	Leeds	110	13	13	17	51	16	12		
Days from diagnosis to first clinic (TERTILES)	≤144	96	12	14	14	39	17	13	0.60	
	125–227	96	8	15	18	41	14	8		0.8
	≥228	96	12	14	11	47	12	13		
Days from end of treatment to first clinic (TERTILES)	≤79	96	13	13	16	37	17	14	0.29	1.8
	80–138	98	7	16	15	47	13	7		
	≥139	94	12	14	12	43	13	13		
Duration of consultation (min) TERTILES	≤8 min	92	7	9	13	38	25	8		1.8
	9–12 min	103	10	17	16	47	13	10	0.32	
	≥13 min	88	13	17	14	39	5	15		
Gender	Female	90	19	18	16	26	11	21	0.001	8.3
	Male	198	13	25	27	101	32	7		
Age	<55	71	15	12	13	27	4	21	0.002	10.3 (<55, 55–64, ≥65)
	55–64	116	14	19	18	50	15	12		
	65–74	67	3	7	10	35	12	4		
	≥75	34	0	5	2	15	12	0		
Tumor site:	Oral cavity	134	18	18	23	57	18	13	0.77	1.0
	Oropharynx	91	8	20	12	37	14	9		
	Larynx	41	4	3	4	21	9	10		
	Other	22	2	2	4	12	2	9		
Overall clinical stage	Advanced 3–4	164	18	29	26	71	20	11	>0.99	<0.1
	Early 1–2	124	14	14	17	56	23	11		
Primary treatment**:	S only	95	12	9	10	44	20	13	0.93	
	S only and FF	21	1	5	4	8	3	5		
	RT or RT/CT only	58	7	11	11	24	5	12		1.0
	S and (RT or RT/CT)	68	7	13	9	31	8	10		
	S and (RT or RT/CT) and FF	46	5	5	9	20	7	11		
WHO comorbidity	0	179	15	31	27	82	24	8	0.10	
	1	67	9	6	11	32	9	13		2.8
	2–4	42	8	6	5	13	10	19		
ACE27 comorbidity	None	137	15	23	20	59	20	11	0.50	1.1
	Mild	95	11	14	13	43	14	12		
	Moderate	48	4	6	8	22	8	8		
	Severe	8	2	0	2	3	1	25		
Living situation	Alone in house/flat	65	4	8	7	29	17	6	0.26	
	With others in house/flat	220	27	35	36	97	25	12		1.5
Working	Yes	88	7	15	9	46	11	8	0.31	0.9
	No	192	24	27	31	79	31	13		

(Continued)

TABLE 1 | Continued

			Fear of recurrence response category*					% with FCR dysfunction (A&B)	*P*-value***	R^2-value****
		Patients	A&B)	C+	C–	D	E			
Financial (household) benefits	Yes	107	17	14	18	44	14	16	0.01	4.8
	No	158	10	26	20	77	25	6		
Smoking habit	Current	37	9	2	11	10	5	24	0.009	
	Former	163	19	27	22	72	23	12		6.1
	Never	80	4	13	9	41	13	5		
Alcohol habit	Current	194	20	26	29	89	30	10	0.65	
	Former	73	9	13	11	31	9	12		0.3
	Never	13	2	3	2	3	3	15		
IMD 2019 quintile	1 = least deprived	34	3	7	5	14	5	9	0.73	
	2	55	4	13	7	20	11	7		
	3	49	5	7	8	23	6	10		1.7
	4	40	4	4	4	24	4	10		
	5 = most deprived	110	16	12	19	46	17	15		

*(A), I have no fear of recurrence; (B), I have a little fear, with occasional thoughts but they don't really bother me; (C+), I am sometimes having fearful thoughts but I can usually manage these, and important during the past 7 days; (C–), I am sometimes having fearful thoughts but I can usually manage these and NOT important during the past 7 days; (D), I get a lot of fears of recurrence and these can really preoccupy my thoughts; (E), I am fearful all the time that my cancer might return and I struggle with this.

**Surgery (S), RadioTherapy (RT), ChemoTherapy (CT), Free Flap transfer (FF).

***Fishers Exact test.

****Nagelkerke R^2-value provides an indication of which models better predict FCR dysfunction; the higher the value the better the prediction.

important to them during the past week and 38% (9/24) if FCR had not been not important. About one quarter (27%, 17/62) with just a little fear wanted to discuss FCR, 56% (5/9) if FCR had been important, and 23% (12/53) if not important. None of the 19 patients without FCR wanted to discuss the issue. Of those wanting to discuss their fears, most (40/48) did not have FCR dysfunction.

During the trial patients attended a median (IQR) of 4 (3–5) clinics, range 1–10. Follow-up results at around 12 months were available for 205 patients, at a median (IQR) of 357 (329–391) days from baseline. The percentages with FCR dysfunction were 8% (17/205) at the first study clinic and 6% (13/205) after about 12 months. Five patients had FCR dysfunction on both occasions, 12 only at first, 8 only later, and 180 on neither occasion. In female patients under the age of 65 the rates for FCR dysfunction were 25% (10/40) and 13% (5/40), while for older females they were 0% (0/22) and 5% (1/22); for males 6% (6/96), 7% (7/96), and 2% (1/47), 0% (0/47), respectively. Of 83 lost to the study between baseline and follow-up, 18% (15) had significant fears at the first clinic. The FCR item from the PCI prompt list was selected by 36% (36/100) at baseline and 17% (17/100) at follow-up.

DISCUSSION

Fear of Cancer Recurrence is an issue that is common in HNC and one that is amenable to intervention (Humphris and Rogers, 2012). Its prevalence rate overall was in the region of one in ten patients and this is similar to previous studies (Llewellyn et al., 2008). A more recent survey in the Netherlands using the Cancer Worry Scale has reported "approximately one in two of all patients newly diagnosed with HNC had FCR levels above the validated cut-off for high FCR shortly after diagnosis (Mirosevic et al., 2019)." There may be differences with the proportion of patients categorized as stating they have high FCR according to the measure employed. For example, the Mirosevic et al. article (Mirosevic et al., 2019) set their cut-off against the validated Fears of Cancer Recurrence Inventory (FCRI). A review of the FCRI has raised concerns about the low cut-off on this measure (Smith et al., 2020). Hence, careful attention needs to be paid to the actual wording and psychometric properties of the measures used. Our single item follows the principles of keeping the assessment of FCR focused and with face valid wording, expressed by Costa (2017). Furthermore, our group subscribe to the view that moderate levels of FCR are probably of value, and not regarded as dysfunctional, as the patient remains reasonably vigilant to changes to symptom experience. The caveat would be for patients to have the support from the H&N team should these fears become heightened, and maintained, and for the staff to monitor and discuss their FCR to reverse back to a moderate level. Among the variables that clinicians can use to identify patients with H&N cancer and high FCR indicated by this data set, include the following:

Age

A significant relationship between the younger age of these patients and dysfunctional FCR was found. This was 21% in those under 55, 14% in those aged 55–64 and only 3% in those over 65. The median age in this study was 62 implying that nearly half of the patient population is at higher risk. This association is in line with previous research indicating

TABLE 2 | HRQOL measures and fear of recurrence.

			Fear of recurrence response category*					% with FCR dysfunction (A&B)	*P*-value***	R^2-value****
		Patients	A&B)	C+	C–	D	E			
	Total	288	32	43	43	127	43	11		
UWQOL Overall Quality of life	Outstanding/Very good	105	4	9	12	58	22	4	<0.001	16.1
	Good	94	9	20	12	41	12	10		
	Fair	63	8	11	15	23	6	13		
	Very Poor/Poor	26	11	3	4	5	3	42		
Distress thermometer (DT)	Zero	79	0	3	4	46	26	0	<0.001	17.5 (0–3, 4–5, 6–10)
	1–3	80	5	14	13	39	9	6		
	4–5	60	9	12	7	27	5	15		
	6–10	69	18	14	19	15	3	26		
UWQOL social-emotional subscale	<60	72	24	14	16	17	1	33	<0.001	26.7
	60–79	98	5	18	18	46	11	5		
	80–100	118	3	11	9	64	31	3		
UWQOL physical function subscale	<60	91	20	18	18	27	8	22	0.001	
	60–79	108	8	14	17	53	16	7		10.4
	80–100	89	4	11	8	47	19	4		
Social-emotional subscale										
• Pain	Best possible response	108	8	12	7	56	25	7	0.20	
	Somewhere in-between	97	11	14	22	37	13	11		2.2
	Dysfunction	83	13	17	14	34	5	16		
• Activity	Best possible response	86	3	7	9	46	21	3	<0.001	
	Somewhere in-between	168	19	31	25	74	19	11		10.2
	Dysfunction	34	10	5	9	7	3	29		
• Recreation	Best possible response	109	8	9	10	58	24	7	<0.001	
	Somewhere in-between	156	14	28	32	64	18	9		12.1
	Dysfunction	23	10	6	1	5	1	43		
• Shoulder	Best possible response	160	6	25	26	73	30	4	<0.001	
	Somewhere in-between	92	18	14	13	38	9	20		13.8
	Dysfunction	36	8	4	4	16	4	22		
• Mood	Best possible response	97	0	4	6	58	29	0	<0.001	
	Somewhere in-between	146	11	34	26	63	12	8		31.2 (dysfunction, other)
	Dysfunction	45	21	5	11	6	2	47		
• Anxiety	Best possible response	103	1	2	4	56	40	1	<0.001	
	Somewhere in-between	136	7	28	31	68	2	5		41.1
	Dysfunction	49	24	13	8	3	1	49		
Physical function subscale										
• Appearance	Best possible response	75	3	10	9	30	23	4	0.003	
	Somewhere in-between	185	21	28	28	91	17	11		7.7

(Continued)

TABLE 2 | Continued

			Fear of recurrence response category*					% with FCR dysfunction (A&B)	*P*-value***	R^2-value****
		Patients	A&B)	C+	C–	D	E			
	Dysfunction	28	8	5	6	6	3	29		
• Swallowing	Best possible response	104	9	12	10	54	19	9	0.03	
	Somewhere in-between	142	13	23	22	64	20	9		4.5
	Dysfunction	42	10	8	11	9	4	24		
• Chewing	Best possible response	117	8	11	13	63	22	7	0.09	
	Somewhere in-between	133	17	28	18	54	16	13		3.1
	Dysfunction	38	7	4	12	10	5	18		
• Speech	Best possible response	123	11	15	13	60	24	9	0.02	
	Somewhere in-between	142	14	25	24	62	17	10		4.9
	Dysfunction	23	7	3	6	5	2	30		
• Taste	Best possible response	90	3	9	11	50	17	3	<0.001	
	Somewhere in-between	141	20	23	21	59	18	14		6.6
	Dysfunction	57	9	11	11	18	8	16		
• Saliva	Best possible response	80	3	6	7	43	21	4	0.03	
	Somewhere in-between	109	14	21	17	42	15	13		5.1
	Dysfunction	99	15	16	19	42	7	15		
Other item:										
• Intimacy	Best possible response	212	13	25	26	108	40	6	<0.001	
	Somewhere in-between	61	15	15	12	16	3	25		11.9
	Dysfunction	15	4	3	5	3	0	27		
EQ-5D										
Mobility (walking about)	No problems	180	12	22	23	93	30	7	0.002	
	Slight problems	43	5	9	6	14	9	12		7.9
	Moderate/severe/unable	65	15	12	14	20	4	23		
Self-care (washing or dressing myself)	No problems	222	15	34	30	103	40	7	<0.001	
	Slight problems	34	5	4	5	17	3	15		13.6
	Moderate/severe/unable	32	12	5	8	7	0	38		
Usual activities	No problems	143	9	16	16	73	29	6	0.001	
	Slight problems	74	6	14	13	33	8	8		9.4
	Moderate/severe/unable	71	17	13	14	21	6	24		
Pain (or discomfort)	No pain or discomfort	104	7	10	8	52	27	7	0.04	
	Slight pain or discomfort	96	9	17	17	43	10	9		4.4
	Moderate/severe/extreme	88	16	16	18	32	6	18		
Anxiety/Depression	Not anxious or depressed	145	1	4	19	83	38	1	<0.001	
	Slightly anxious or depressed	95	10	30	14	39	2	11		37.0
	Moderate/severe/extreme	48	21	9	10	5	3	44		
EQ-5D-5L TTO crosswalk values (TERTILES)	≤0.6950	96	24	19	18	32	3	25	<0.001	

(Continued)

TABLE 2 | Continued

			Fear of recurrence response category*					% with FCR dysfunction (A&B)	*P*-value***	R^2-value****
		Patients	A&B)	C+	C–	D	E			
	0.6951–0.8370	109	3	21	18	48	19	3		18.3
	≥0.8371	83	5	3	7	47	21	6		
EQ5D Visual analog scale (VAS) TERTILES	≤69	96	19	15	20	36	6	20	0.007	
	70–81	96	7	23	11	37	18	7		7.1
	≥82	96	6	5	12	54	19	6		

**(A), I have no fear of recurrence; (B), I have a little fear, with occasional thoughts but they don't really bother me, (C+), I am sometimes having fearful thoughts but I can usually manage these, and important during the past 7 days, (C–), I am sometimes having fearful thoughts but I can usually manage these, and NOT important during the past 7 days, (D), I get a lot of fears of recurrence and these can really preoccupy my thoughts, (E), I am fearful all the time that my cancer might return and I struggle with this.*
**** Fishers Exact test.*
***** Nagelkerke R^2-value provides an indication of which models better predict FCR dysfunction; the higher the value the better the prediction.*

TABLE 3 | Selection of FCR item from the PCI prompt list for 140 PCI patients, by self-reported level of fear of recurrence (FCR) and by whether FCR had been important over the past 7 days.

Single FCR question	FCR item selected from PCI prompt list		FCR important in the past 7 days	FCR item selected from PCI prompt list	
	%	Patients		%	Patients
I am fearful all the time that my cancer might return and I struggle with this	50	8/16	Yes	57	8/14
I get a lot of fears of recurrence and these can really preoccupy my thoughts			No	0	0/2
I am sometimes having fearful thoughts but I can usually manage these	53	23/43	Yes	74	14/19
			No	38	9/24
I have a little fear, with occasional thoughts but they don't really bother me	27	17/62	Yes	56	5/9
			No	23	12/53
I have no fear of recurrence	0	0/19	Yes	0	0/1
			No	0	0/18
Total	34	48/140	Yes	63	27/43
			No	22	21/97

age was a predictor of FCR (Humphris et al., 2003; Lim and Humphris, 2020). There are several potential explanations as to why age plays a significant role in fears of recurrence. Researchers (Hutton and Williams, 2001) have argued that older patients are not always able to differentiate the interference caused by treatment and the natural degeneration of aging, with a cancer diagnosis becoming increasingly more predictable with older age. In comparison, younger patients find the diagnoses of cancer much more unanticipated and abrupt as it threatens their ability to fulfill major life events, such as having grandchildren or marriage of children (Simard et al., 2013).

Gender

The finding that gender is associated with FCR has been highlighted in a recent systematic review (Pang and Humphris, 2021). One explanation as to why females experience higher FCR is because they tend to experience more symptoms of dysfunctional anxiety (Faravelli et al., 2013). A Norwegian and Swedish HNC study found that those who were under 65 and female were the most likely to develop anxiety (Hammerlid et al., 1999). In this analysis' parent study, 17% of patients experienced dysfunctional anxiety symptoms according to the UWQOL social-emotional subscale. As anxiety levels were not included in their secondary analysis, we must leave room to consider whether present FCR are a surface level manifestation of other psychiatric comorbidities that have been previously found to be significant within this sub-population.

Financial Benefits

In this study, it was found that a significant predictor of developing FCR was living in a household in receipt of financial benefits. Head and neck cancer has a serious impact on patient

finances and is associated with poor HRQOL (Rogers et al., 2012). Previous evidence has shown that rates of financial instability are the highest within HNC in comparison to all other cancer types (Avis et al., 2005). This is exemplified within this study with 37% of participants in households receiving financial benefits. A systematic review of FCR found that of the 10 studies investigating financial difficulties and FCR, the association was only found to be significant in three (Simard et al., 2013). However, previous studies regarding FCR and financial position should be applied carefully as this fear could be more prominent in countries whose national health programme relies solely on private hospitals. In a previous study within our group, it was found that FCR had a weak relationship with deprivation which would partially support this finding of patients reporting to receive state benefits (Rylands et al., 2016). This mirrors the findings of a study by Clarke et al. (2021) in which HNC survivors with inadequate health literacy reported lower levels of self-management behaviors, lower functional HRQOL, and increased FCR.

Health Related Quality of Life

Functional/symptom items on H&N cancer HRQOL questionnaires have potential utility in respect to FCR as symptoms that patients experience might trigger anxiety regarding the possibility of recurrence. This is especially so in the field of H&N cancer care where previous reports of patient experience of physical symptoms have focused our group to build on the FCR model proposed by Lee-Jones et al. (1997) and promoted the AFTER intervention (Humphris and Ozakinci, 2008) to reduce high FCR. Most of the HRQOL measures in this study were associated with FCR, for example, 42% in those with poor or very poor overall QOL had dysfunctional FCR. There was anxiety or mood dysfunction in 65 patients (23% of the whole sample) and this group accounted for 81% (26/32) of all those with FCR dysfunction. These relatively broad-brush HRQOL questionnaires, such as the UW-QOL mood and anxiety items and, interestingly a similar amount of variance explained with another well-developed measure, namely: the EQ-5D, together with the EORTCc30, these assessments have shown the ability to identify patients with high FCR. Due to the high degree of overlap between these HRQOL measures, only one or, at most, two would be required to assist with identifying patients with possible high FCR. Within England the NHS England QOL Metric study outcome measures include the EQ-5D and EORTCc30 (NHS England Cancer Data, 2021). Hence, it would enable all cancer patients in England to be given the opportunity to complete the questionnaires at the 18 month post diagnosis window. Those scoring badly, for example, on the EQ-5D will have possibly high FCR which would need to be further assessed. These assessment approaches are part of a possible development to construct stepped-care programmes of support and intervention for moderate to high scorers of FCR which is being explored in patients with melanoma (Lynch et al., 2020).

The regression R^2-values (**Table 2**) indicated that the age and gender associations with FCR were dwarfed relatively by the associations between the HRQOL measures and FCR. Logistic regression on FCR using all variables in **Table 2** as predictors selected anxiety, mood, and gender. For patients with anxiety or mood dysfunction or both—there was dysfunctional FCR for 56% of females (13/25) and 32% (13/40) of males; for patients without anxiety of mood dysfunction—there was dysfunctional FCR for 9% (6/65) of females and 0% (0/158) of males.

Our results have included a split of the FCR patient responses to the middle category of the rating scale. The split was whether, or not, FCR had been "important" to the patient within the previous 7 days. We found on close inspection little difference about this split—in either patient/clinical characteristics or across the HRQOL measures. Hence the important message that this reinforces is that dysfunction in FCR is best measured by the worst two FCR response options only and that the middle option if important should not be added to this. This recommendation was postulated in a previous paper (Rogers et al., 2016). In addition, it is worth emphasizing that a degree of FCR is "normal" and to be expected. In our sample, three quarters reported "I have a little fear, with occasional thoughts but they don't really bother me" (44%) and "I am sometimes having fearful thoughts but I can usually manage these" (30%).

Exploring the longitudinal data, FCR severe rates remain relatively unchanged over the year with evidence of a slight improvement 8–6%. This serves to highlight how imbeded this fear can be for patients. Patients still wish to talk about FCR involving one in three at the start of the trial and one in five at the last consultation. The PCI prompt is potentially a useful adjunct to the conversation with the health professional as even with the passage of time it helps the patients to broach what can be a sensitive and distressing issue and this provides an opportunity to reassure on repeated occasions as prompted by the patient themselves.

There are several potential limitations of this work. Firstly, in the trial of those approached to be recruited, around one in five declined to participate. It might be that patients with an anxiety disorder are less likely to take part and that these are more likely to experience high FCR. Thus, this current analysis might underestimate the rates of FCR. The findings should have a reasonable level of generalisability, as although involving only two centers, 15 different consultants were involved, and the sample comprised 80% of eligible patients. The second limitation relates to the single FCR item question used as part of the HRQOL survey. It is recognized that this question will not be as reliable as other more comprehensive FCR measures (Thewes et al., 2012). However, this together with the PCI item on FCR gives a unique opportunity to analyse characteristics that might be predictive of higher FCR dysfunction. Because of the variety of different criteria and definitions of FCR, direct comparisons to this research with other studies should be treated with caution (Mirosevic et al., 2019). This should also be considered in any future work.

The potential value of using a prompt list (PCI) as part of the consultation is that patients might be more amenable to raise the FCR issue through this prompt, and also to discuss their fear in preference to discussing other psychological issues

such as depression or anxiety. Fear of Cancer Recurrence is perceived as an understandable concern that both the patient and the clinician can relate to. When talking through natural and health concerns the clinician can gauge the extent of the fear and can offer additional support. A specific FCR intervention could be considered for those most distressed. Considerable work is now being conducted to develop interventions for those with high levels of FCR (Tauber et al., 2019). Further research is needed to carefully construct and evaluate the cost effectiveness of a tiered programme of support. However, a straightforward means to highlight the issue of FCR in routine oncology clinics, either by clinical characteristics, questionnaire caseness, or a prompt from the patient themselves, or a combination of these, could be a suitable starting point for both informal and formal Interventions, with the desired outcome being less distress and improved HRQOL.

DATA AVAILABILITY STATEMENT

The raw data can be made available by the authors, without undue reservation, to any qualified researcher through due process.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Liverpool. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SR, DL, GH, and AK: study design and critical revision of the manuscript. SR, DL, and AK: data collection. All authors analysis, interpretation, drafting of the manuscript, and approved the final version for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.671366/full#supplementary-material

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Factors Associated With Fear of Cancer Recurrence in Family Caregivers of Cancer Survivors: A Systematic Review

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Objective: Fear of cancer recurrence (FCR) is a significant concern for family caregivers of cancer survivors and is associated with many adverse outcomes, including increased emotional distress and poorer quality of life. Although several theoretical models have been proposed to account for FCR in cancer survivors, their applicability to caregivers is unknown. The aim of this review was to identify clinical, demographic and psychological factors that are associated with, and predict, FCR in caregivers of cancer survivors.

Method: AMED, CINAHL, Medline, PsycINFO, and Scopus were systematically searched for relevant studies reporting quantitative data on factors associated with FCR or similar constructs (e.g., worry or anxiety about cancer recurrence) in family caregivers of adult cancer survivors. Included studies were assessed for methodological quality using a standardized checklist adapted from the Agency for Healthcare Research and Quality.

Results: Sixteen studies, half of which were cross-sectional, were included and summarized narratively. Non-modifiable factors, including age ($n = 6$) and treatment modality ($n = 4$), were found to be associated with increased FCR. Significant positive associations were also reported between illness perceptions and FCR ($n = 3$). However, there was heterogeneity across included studies with regards to factors examined and most were conducted in the USA. There were also several methodological limitations to the included studies.

Conclusions: Research examining FCR in caregivers of cancer survivors has predominantly focused on demographic and clinical factors. Given the paucity of research exploring the psychological mechanisms underpinning FCR, future research should investigate theoretical underpinnings of FCR in caregivers of cancer survivors to support the development of psychological interventions for this population.

Systematic Review Registration: PROSPERO, identifier [CRD42019119729].

Keywords: cancer survivors, family caregivers, fear, recurrence, systematic review

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INTRODUCTION

Although improvements in cancer care have led to earlier diagnosis and more effective, targeted medical treatment (Arnold et al., 2019), family caregivers of survivors continue to experience adverse effects of the illness, both physically and psychologically (Pitceathly and Maguire, 2003; Kurtz et al., 2004; Girgis and Lambert, 2009). Specifically, cancer caregiving responsibilities can result in issues such as pain, fatigue, financial difficulties and social isolation (Girgis and Lambert, 2009; Stenberg et al., 2010). One of the most distressing concerns for survivors and their families is fear of cancer recurrence (FCR) (Simard et al., 2010), defined as "fear, worry, or concern about cancer returning or progressing" (Lebel et al., 2017). Prevalence of FCR is high in family caregivers (Yeo et al., 2004) and can be higher than for the cancer patients (Longacre et al., 2012; Gold et al., 2016). Managing worries about cancer returning is a commonly-reported unmet need for caregivers (Girgis et al., 2013; Turner et al., 2013; Balfe et al., 2016), which is associated with elevated emotional distress (Longacre et al., 2012) and poorer quality of life (QoL) (Simard et al., 2013).

Although psychological interventions for FCR have been widely researched for cancer survivors (Simard et al., 2013; Maheu and Galica, 2018), there is currently little evidence to support the utility of specific psychological interventions for family caregivers experiencing FCR (Simonelli et al., 2017). To develop more effective interventions for this patient group, we must first understand the psychological processes that underpin and maintain FCR in caregivers of cancer survivors. Much of what we know about these processes is derived from research investigating FCR in patients. Many of the theoretical frameworks proposed to account for FCR in cancer survivors consist of similar components, including internal (e.g., physical symptoms, treatment side effects) and external (e.g., clinical follow-up) cues that trigger a cognitive response associated with FCR (Simonelli et al., 2017). Following an appraisal of such cues, a variety of coping responses, some less helpful than others, are implemented which are influenced by the social environment and other contextual factors (Lee-Jones et al., 1997; Simonelli et al., 2017). Such coping responses may include avoidance, limited future planning, symptom checking and misinterpretation of symptoms, and reassurance seeking from health professionals and family members, which in the longer term can increase FCR (Lee-Jones et al., 1997).

Similar to cancer survivors, caregivers often engage in unhelpful coping behaviors such as avoidance of cancer-related discussions, reluctance to make plans for the future and reassurance seeking (Lambert et al., 2013; LeSeure and Chongkham-ang, 2015). Furthermore, although caregivers do not experience internal cancer-related cues (e.g. cancer symptoms or delayed treatment effects), the cancer journey is experienced by the family as a whole (Kayser et al., 2007). Therefore, caregivers are often aware of survivors' physical experiences of cancer diagnosis and treatment, through helping patients to manage physical symptoms such as treatment side effects (LeSeure and Chongkham-ang, 2015). Caregivers are exposed to many external cues and situations which may trigger FCR, including cancer-related conversations, media references to cancer, appointments with health professionals and survivors' follow-up appointments and feeling unwell themselves (Simard and Savard, 2009).

Although many components of the FCR models will be applicable to understanding FCR experienced by caregivers, some may not be relevant and there may be other factors which are only relevant to caregivers of cancer survivors. To date, only two reviews have examined FCR in caregivers (Simard et al., 2013; Maheu and Galica, 2018). Maheu and Galica briefly summarized literature regarding factors associated with FCR in caregivers, but did not take a systematic approach to identify or analyse data. Simard and colleagues conducted a systematic review of quantitative studies examining FCR in adult cancer survivors, within which they briefly summarized the results of nine studies, published prior to 2011. Collectively, the two previous reviews indicate that non-modifiable factors such as caregiver age and gender, and treatment type, may be associated with caregiver FCR. However, a systematic synthesis of contemporaneous studies examining correlates and predictors of caregivers' FCR does not exist. This systematic review aims to address this gap by critically appraising and synthesize the findings of quantitative studies investigating any demographic, clinical and psychosocial correlate or predictor of FCR in adult family caregivers of adult cancer survivors.

MATERIALS AND METHODS

Review Conduct and Reporting

Review conduct and reporting adhered to recommendations by Centre for Reviews Dissemination (2009) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (Moher et al., 2009). The protocol was registered on the international prospective register of systematic reviews, Prospero, in January 2019 (reg. number CRD42019119729) and can be accessed at https://www.crd.york.ac.uk/PROSPERO.

Search Strategy

AMED, CINAHL, Medline, PsycINFO, and Scopus were systematically searched for published literature using the following search terms: partner (partner*, couple*, spous*, dyad*, carer, caregiver, care-giver, care giver, caregiv*, husban*, wife or wives) and (fear* or worr* or anxiet* or concer* or afraid) and (recur* or relaps* or reoccur* or return* or progress*) and (cancer* or tumor* or tumor*). There were no restrictions placed on publication date. Searches were repeated in March 2020 to identify any new publications relevant to the review question.

Inclusion and Exclusion Criteria

To be included in the review, studies had to report quantitative data on factors associated with FCR or similar constructs (e.g., worry or anxiety about cancer recurrence) in adult family caregivers (partners, family members, and close friends) of adult cancer survivors (both aged $\geq$18 years). Patients were classed as cancer survivors if they had received a diagnosis of cancer and had not been diagnosed with a secondary cancer. Articles had

to be published in English in a peer-reviewed journal. Studies were excluded if cancer patients had not yet received treatment, in order to ensure findings were deemed to be taken from a survivorship phase. Studies which did not report data separately for cancer survivors were also excluded (e.g., studies reporting data from survivors and patients with metastatic disease). All case studies, commentaries, conference abstracts, dissertations, editorials, qualitative studies, and review articles were excluded.

Screening and Selection

Two reviewers (LOR and AW) independently assessed the titles and abstracts of potentially relevant papers. The reviewers then independently reviewed the full-text papers against the inclusion and exclusion criteria. Papers which did not meet the inclusion criteria were removed. Discrepancies ($n = 3$) were discussed with the wider research team (MGC, PF, SC) until a negotiated conclusion was reached.

Data Extraction

For each study, relevant demographic, methodological and summary data were extracted using a standardized data extraction form by LOR and independently checked for accuracy by AW. Uncertainty ($n = 1$) was resolved through discussion with the wider research team. Authors were contacted if data were unclear or had not been reported within the paper. The following information was extracted: (i) author, (ii) year of publication, (iii) study design, (iv) clinical and treatment characteristics of the survivor (diagnosis, stage, time since diagnosis and treatment type), (v) caregiver demographics (age, gender, ethnicity, and relationship length), and (vi) main findings, including correlates and predictors of FCR. Where studies reported multiple analyses, only data from the most complex relevant multivariate analyses were extracted. This is because multivariate analyses that eliminate potential sources of confounding through statistical control of multiple potential covariates are considered stronger tests of association than univariate analyses. Studies that reported data from the same larger database, but focused analyses on different outcomes were interpreted and referred to as separate studies, with their linked status noted. Correlates and predictors were grouped under the following headings: (i) demographic factors (including age, gender and ethnicity); (ii) clinical factors (treatment, cancer stage, co-morbidities and medical follow-up); and (iii) psychosocial factors (emotional distress, interpersonal factors (including FCR in patients), stress and coping, quality of life and psychological beliefs). Data were analyzed narratively; heterogeneity in study findings precluded meta-analysis.

Risk of Bias

Studies were assessed for risk of bias using a quality appraisal tool adapted from the Agency for Healthcare Research and Quality (Williams et al., 2010), which assesses risk of bias in studies across various domains relevant to research with physical health populations. This tool considers risk of bias across key methodological areas, such as sample selection, size, description, handling of missing data and analysis (Taylor et al., 2015), thus allowing for comparison of studies across domains. Two reviewers (LOR and AW) separately assessed risk of bias in the included studies. Uncertainty ($n = 4$) was resolved through discussion with the wider research team (MGC, PF, SC). In line with Centre for Reviews Dissemination (2009) guidance, studies were not excluded based on outcome of the risk of bias assessment.

RESULTS

The search strategy identified 1,729 potentially relevant records. After exclusion of duplicates and screening of titles and abstracts, 40 potentially eligible articles remained. After reviewing their full-text, eight articles, reporting seven studies, were identified for inclusion for review. Nine studies were identified during the updated search, resulting in the inclusion of 19 articles, reporting 16 studies[1]. The process of identification of papers to inclusion for review is summarized in **Figure 1**. Demographic, clinical and psychosocial factors examined by each study are summarized in **Table 1**.

Study Characteristics

The main characteristics of the studies are shown in **Table 2**. Nine studies, reported in 12 articles, were conducted in the USA (Mellon and Northouse, 2001; Mellon et al., 2006, 2007; Kim et al., 2012; Boehmer et al., 2016; Janz et al., 2016; Cohee et al., 2017; Soriano et al., 2018a,b, 2019; Perndorfer et al., 2019; Wu et al., 2019). The remainder were conducted in Taiwan (Chien et al., 2018), UK (Hodges et al., 2009; Dempster et al., 2011; Graham et al., 2016), Ireland (Maguire et al., 2017), The Netherlands (van de Wal et al., 2017) and China (Xu et al., 2019). Studies used a convenience or purposive sampling strategy and were either cross-sectional (Mellon and Northouse, 2001; Mellon et al., 2006, 2007; Dempster et al., 2011; Kim et al., 2012; Boehmer et al., 2016; Janz et al., 2016; Cohee et al., 2017; Maguire et al., 2017; van de Wal et al., 2017; Soriano et al., 2018a) or longitudinal surveys (Hodges et al., 2009; Graham et al., 2016; Chien et al., 2018; Soriano et al., 2018a,b, 2019; Perndorfer et al., 2019; Wu et al., 2019; Xu et al., 2019). Seven studies recruited patients with breast cancer, four with head and neck cancer, three with prostate cancer, and two with mixed cancer diagnoses. The shortest time since diagnosis or treatment was 90 days (Wu et al., 2019), whilst the longest time was 7.3 years (*SD* 3.6) (Boehmer et al., 2016).

Out of the 16 studies, nine focused on partners (Janz et al., 2016; Cohee et al., 2017; van de Wal et al., 2017; Chien et al., 2018; Soriano et al., 2018a,b, 2019; Perndorfer et al., 2019; Wu et al., 2019; Xu et al., 2019), whilst seven studies reported data on caregivers, including other family members and friends. Caregivers were predominantly White, female, and middle-aged. Education level varied across studies, with college or above

[1]The samples of 26, 27, 28, 38, and 39 were drawn from a larger database (SEER). Thirty-eight and 39 used the same sample and therefore will be considered as one study. Twenty-six−28 studied non-overlapping samples and therefore will be interpreted and referred to as separate studies. Similarly, samples of 29 and 30 were drawn from a larger study (OPA, UK) but will be interpreted as separate studies as they used non-overlapping samples. Thirty-one, 35, and 36 were based on data from the MDCSS database and used the same sample, therefore will be considered as one study.

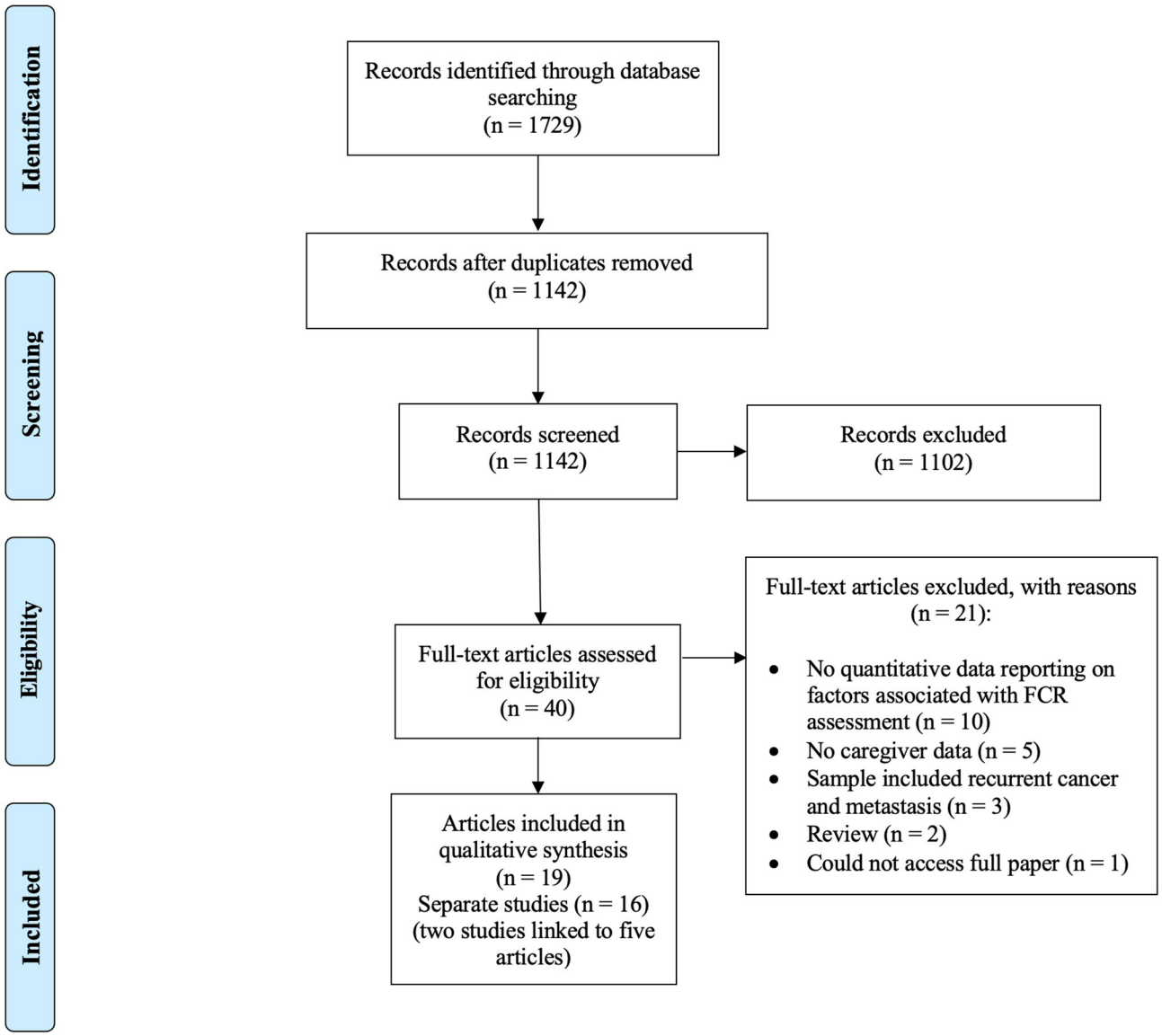

FIGURE 1 | Flowchart of literature search (based on PRISMA guidelines; Moher et al., 2009).

tending to be the most reported education level. Relationship length varied, with the longest mean length of relationship between caregiver and survivor being 43.0 years (range 8–57 years) (van de Wal et al., 2017) and the shortest being 24.40 years (*SD* 13.8) (Soriano et al., 2018a).

Results of Assessment of Risk of Bias

The results of the assessment of risk of bias are outlined in **Table 3**, and indicate that most domains, including unbiased selection of cohort, validated measures of outcome and dependent variables, and appropriate analyses rated highly. Several limitations were identified in relation to study design, assessment of FCR and justification of sample sizes. Only five studies reported a sample size calculation (Mellon et al., 2006; Hodges et al., 2009; Kim et al., 2012; Maguire et al., 2017; van de Wal et al., 2017). Out of the 16 studies, only four studies followed caregivers up for an adequate period (defined as at least 12 weeks). However, half of the studies included for review were cross-sectional therefore could not be assessed against this criterion. Most studies provided adequate descriptions of the study cohort, but three studies provide limited demographic data (Dempster et al., 2011; Graham et al., 2016; Xu et al., 2019). Most used validated methods for assessing predictor variables; however, in one study (Soriano et al., 2018b), it was not clear if the measures used had been validated. Most studies used validated measures of assessing FCR; however, in four studies (Kim et al., 2012; Janz et al., 2016; Wu et al., 2019; Xu et al., 2019), it was unclear if adapted questionnaires had been validated. In one

TABLE 1 | Measures of demographic, clinical, and psychosocial factors.

Correlate or predictor variables		Studies analyzing correlate or predictor variables	Studies with significant results (*n*)
***Demographic* (*n* = 12 studies reported in 13 articles)**			
	Age	sig. (29, 32, 34, 39, 42, 43) n.s. (26, 27, 28, 30, 38, 40, 41)	6
	Gender	sig. (42) n.s. (32, 40, 41)	1
	Ethnicity	sig. (28) n.s. (27, 32)	1
	Education	sig. (27) n.s. (26, 28, 32, 38, 41, 43)	1
***Clinical* (*n* = 14)**			
Treatment	Time since diagnosis	sig. (26, 42) n.s. (27, 29, 32, 39, 40, 43)	2
	Treatment type	sig. (26, 28, 35, 42) n.s. (32, 38, 43)	4
	Medical follow-up	sig. (36, 37)	2
Cancer Stage	Cancer stage	n.s. (26, 28, 26, 32, 38-42)	0
	Cancer severity	sig. (29)	1
Comorbidities	Comorbidities	sig. (26, 28) n.s. (32, 39, 40)	2
	Survivor physical health	sig. (29)	1
***Psychosocial* (*n* = 15 studies reported in 18 articles)**			
Emotional distress	Anxiety	sig. (29, 34, 36)	3
	Emotional distress	sig. (41)	1
Interpersonal factors	Survivor/caregiver FCR	sig. (26, 29, 30, 32, 33, 34, 36, 41, 43) n.s. (35, 38)	8 studies reported in 9 articles
	Relationship quality	sig. (34) n.s. (38)	1
	Social support	sig. (26) n.s. (30, 31, 32, 42)	1
	Loneliness	sig. (42)	1
	Communication	sig. (27, 33, 34, 37, 44)	4 studies reported in 5 articles
	Spousal negative affect	sig. (34)	1
Stress and coping	Stress	sig. (30, 31, 32, 42)	2 studies reported in 4 articles
	Coping strategies	sig. (39, 40)	2
Quality of life		sig. (29, 30, 31, 42, 43)	4 studies reported in 5 articles
Psychological beliefs	Meaning of illness	sig. (30, 31, 32)	1 study reported in 3 articles
	Illness perceptions	sig. (39, 40, 44)	3

sig, significant results; n.s., Non-significant results.

study, it was unclear if confounding demographic variables were controlled for in analyses (Chien et al., 2018).

Demographic Factors

There were significant associations between age and FCR. Twelve studies, reported in 13 articles, examined the relationship between age and FCR. Of these, one study found a weak negative association between age and FCR ($r = -0.17$) (Kim et al., 2012) whilst five studies reported a significant association which remained significant when other clinical and demographic variables were controlled (Mellon et al., 2007; Dempster et al., 2011; Maguire et al., 2017; van de Wal et al., 2017; Soriano et al., 2018a). However, no details regarding cancer stage and treatment type were reported in one study (Dempster et al., 2011). Four studies assessed the relationship between gender and FCR, one of which found a significant weak association between gender and FCR, with female carers reporting higher FCR than male carers (Maguire et al., 2017). Of the three studies that assessed the relationship between ethnicity and FCR, only one found a significant relationship, reporting that Latino partners were significantly more likely to worry than White partners, whilst Black partners were less likely to report worry (Janz et al., 2016). However, as this study used an adapted FCR measure, it is not clear if this has been validated. Seven studies assessed the relationship between education and FCR. Of these, one study found a very weak negative association between education and FCR ($r = -0.16$) (Cohee et al., 2017), however as there is no evidence of a sample size calculation, it is unclear if the study is sufficiently powered.

Clinical Factors

Treatment

There was limited support for significant associations between time since diagnosis and FCR. Two out of the eight studies that assessed the relationship between time since diagnosis and FCR found that those caring for more recently diagnosed survivors

TABLE 2 | Study characteristics.

			Caregiver			Survivor			
Author, (year), country	**Design**	***n***	**Age (years) (SD)**	**Gender, *n* (%)**	**Relationship to survivor, *n* (%)**	**Cancer type**	**Stage, *n* (%)**	**Time since diagnosis (SD)**	**Treatment, *n* (%)**
Boehmer et al. (2016), USA	Cross-sectional	H[a] 43	*M* = 62.4 (8.0)	Female: 7 (16.3) Male: 36 (83.7)	Partner: 36 (83.7) Child: 3 (7.0) Sibling: 2 (4.7) Parent: 1 (2.3) Friend: 1 (2.3)	Breast	I: 18 (42.9) II: 12 (28.6) III: 4 (9.5)	5.8 years (3.9)	L: 41 (95.3) M: 0 (0.0) M + (Re): 2 (4.7) R: 32 (74.4) H: 31 (72.1)
		M[b] 124	*M* = 55.8 (9.3)	Female: 116 (93.5) Male: 8 (6.5)	Partner: 106 (85.5) Child: 0 (0.0) Sibling: 3 (2.4) Parent: 3 (2.4) Friend: 12 (9.7)	Breast	I: 46 (37.1) II: 40 (32.3) III: 12 (9.7)	7.3 years (3.6)	L: 105 (84.7) M: 10 (8.1) M + (Re): 9 (7.3) R: 80 (64.5) H: 88 (71.0)
Chien et al. (2018), Taiwan	Longitudinal (T4 = 24 weeks)	T4 =46	*M* = 62.0 (7.8)	Female: 48 (100.0) Male: 0 (0.0)	Partner: 48 (100.0)	Prostate	II: 30 (62.5) III: 18(37.5)	Recruited when first diagnosed	S: 37 (77.1) R: 11 (22.9)
Cohee et al. (2017), USA	Cross-sectional	222	*M* = 47.98 (7.2)	Not reported	Partner: 222 (100.0)	Breast	Not reported	5.83 years (1.51)	Not reported
Dempster et al. (2011), UK	Cross-sectional	382	*M* = 62 (10.91)	Female: 257 (67) Male: 125 (33)	Partner: 359 (94.0) Other family: 23 (6.0)	Esophageal	Not reported	*Mdn* = 46 months (19–81)	Not reported
Graham et al. (2016), UK	Longitudinal (T2 = 12 months)	171	*M* = 62.56 (10.05)	Female: 124 (72.5) Male: 47 (27.5)	Partner: 165 (96.49) Other: 6 (3.51)	Esophageal	Not reported	*M* = 4 years (2–7)	Not reported
Hodges et al. (2009), UK	Longitudinal (T2 = 6 months)	101	*M* = 56.26 (30 – 76)	Female: 73 (72.3) Male: 28 (27.7)	Partner: 86 (85.1) Non-partner: 15 (14.9)	Head and neck	1-2 = 27 (60) 3-4 = 16 (35.6) 5 = 2 (4.4)	Not reported	Not reported
Janz et al. (2016), USA	Longitudinal[c]	510	<50 N = 70 (13.7%) 50-65 N = 218 (42.75%) >65 N = 222 (43.5%)	Not reported	Partner: 510 (100.0)	Breast	0 :125 (24.5) I-II: 388 (66.3) III: 46 (9.0)	4 years	L: 324 (63.6) (U)M:128 (25.1) (B) M:51 (10.0) R: 363 (71.1) C: 229 (44.9)
Kim et al. (2012), USA	Cross-sectional	455	*M* = 56.19 (13.01)	Female: 288 (63.3) Male: 167 (36.7)	Spouse: 305 (67.1) Offspring: 84 (18.5) Other: 66 (14.4)	Mixed[d]	Localized: 292 (64.2) Regional: 124 (27.3) Distant: 39 (8.6)	2.2 years (0.40)	Not reported
Maguire et al. (2017), Ireland	Cross-sectional	180	*M* = 57.3 (12.48)	Female: 136 (76.0) Male: 44 (24.0)	Spouse: 132 (73.4) Offspring or parent: 34 (18.8) Other:14 (7.8)	Head and neck	I-II: 81 (54.4) III-IV: 68 (45.6)	4.9 years (3.79)	S: 31 (17.2) C: 47 (26.1) R: 122 (67.4)

(Continued)

TABLE 2 | Continued

Author, (year), country	Design	*n*	Caregiver			Survivor			
			Age (years) (SD)	Gender, *n* (%)	Relationship to survivor, *n* (%)	Cancer type	Stage, *n* (%)	Time since diagnosis (SD)	Treatment, *n* (%)
Mellon and Northouse (2001), Mellon et al. (2006, 2007), USA	Cross-sectional	123	*M* = 55 (14.5) (21-80)	Female: 80 (65) Male:43 (35)	Spouse: 65 (52.8) Child: 36 (29.3) Sibling: 10 (8.1) Significant other: 12 (9.8)	Mixed[e]	Not reported	3.39 years (1.0)	S: 108 (87.8) R: 48 (39.0) C: 28 (22.8) H: 4 (3)
Perndorfer et al. (2019), USA	Longitudinal (21-day diary)	69	*M* = 58 (10)	Not reported	Partner: 69 (100.0)	Breast	0: 8 (12) IA: 37 (53) IIA: 17 (25) IIB: 6 (9) IIIA: 1 (1)	5 months (2.09) after treatment	C: 21 (30) R: 50 (72) H: 58 (84)
Soriano et al. (2018a), USA Study (1)	Cross-sectional	46	*M* = 54.57 (13.31)	Not reported	Partner: 46 (100.0)	Breast	0: 11 (24) I: 17 (37) II: 15 (32) IIIa: 3 (7)	7.70 months after treatment	C and/or H: 15 (33)
Soriano et al. (2018a), USA Study (2)	Longitudinal (21-day diary)	72	*M* = 59.49 (10.34)	Male:70 (97) Female: 2 (3)	Partner: 72 (100.0)	Breast	0: 10 (14) I: 34 (47) II: 27 (37) IIIa: 17 (23)	5.77 weeks after treatment	C: 24 (33) H: 58 (81)
Soriano et al. (2019), USA	Longitudinal (21-day diary)	57	*M* = 60 (10)	Male: 55 (96) Female: 2 (4)	Partner: 57 (100.0)	Breast	0: 7 (12) IA: 30 (53) IIA: 14 (25) IIB:5 (9) IIIA: 1 (1)	12.2 months (1.9)	C:17 (30) R: 41 (72) H: 48 (84)
van de Wal et al. (2017), The Netherlands	Cross-sectional	168	*Mdn* = 67.4 (40-86)	Not reported	Partner: 168 (100.0)	Prostate	Not reported	*Mdn* = 7.5 years (0.9-20.0)	S:126 (75) S + R: 41 (25)
Wu et al. (2019), USA	Longitudinal (T1 = 6 months; T2 = 12 months)	62	*M* = 64.3 (8.4)	Not reported	Partner: 62 (100.0)	Prostate	Not reported	89.8 days (95.0)	R: 36 (52.2) S: 18 (26.1) B: 7 (10.1) R + B: 3 (4.3) S + R: 1 (1.4) WW: 1 (1.4) Missing: 3 (4.3)
Xu et al. (2019), China	Longitudinal (10 days)	54	Not reported	Not reported	Partner: 54 (100.0)	Breast	I: 22 (40.7) II:14 (25.9) III:18 (33.3)	22.1 months (19.88)	Not reported

[a] *Cancer survivors who identify as heterosexual women (HSW).*
[b] *Cancer survivors who identify as sexual minority women (SMW).*
[c] *Partners surveyed at Time 2 only.*
[d] *Mixed cohort = breast, prostate, colorectal, lung, ovarian, kidney, uterine, bladder, non-Hodgkin's lymphoma, skin melanoma.*
[e] *Mixed cohort = Breast, prostate, colon-rectal, uterine.*
Treatment modality: S, Surgery; C, Chemotherapy; R, Radiotherapy; L, Lumpectomy; M, Mastectomy; M + Re, Mastectomy and Reconstruction; (U)M, Unilateral Mastectomy; (B)M, Bilateral Mastectomy; H, Hormonal therapy; B, Brachytherapy; WW, Watchful waiting.

TABLE 3 | Assessment of risk of bias.

Author	Unbiased selection of cohort?	Sample size calculation?	Adequate description of cohort?	Validated method for assessing predictor/ outcome variables?	Validated method for assessing fear of cancer recurrence?	Adequate follow-up period?	Missing data minimal?	Confounders controlled for?	Appropriate analyses?
Boehmer et al. (2016)	●	○	●	●	●	N/a	●	●	●
Chien et al. (2018)	●	○	●	●	●	●	●	◐	●
Cohee et al. (2017)	●	○	●	●	●	N/a	●	●	●
Dempster et al. (2011)	◐	○	◐	●	●	N/a	◐	●	●
Graham et al. (2016)	●	○	◐	●	●	●	○	●	●
Hodges et al. (2009)	●	●	●	●	●	●	●	●	●
Janz et al. (2016)	●	○	●	●	◐	N/a	●	●	●
Kim et al. (2012)	●	●	●	●	◐	N/a	●	●	●
Maguire et al. (2017)	●	●	●	●	●	N/a	●	●	●
Mellon and Northouse (2001)	●	○	●	●	●	N/a	●	●	●
Mellon et al. (2006)	●	●	●	●	●	N/a	●	●	●
Mellon et al. (2007)	●	○	●	●	●	N/a	●	●	●
Perndorfer et al. (2019)	●	○	●	●	●	○	●	●	●
Soriano et al. (2018a) Study (1)	●	○	●	●	●	N/a	●	●	●
Soriano et al. (2018a) Study (2)	●	○	●	●	●	●	●	●	●
Soriano et al. (2019)	●	○	●	◐	●	○	●	●	●
Soriano et al. (2019)	●	○	●	●	●	○	●		●
van de Wal et al. (2017)	●	●	●	●	●	N/a	●	●	●
Wu et al. (2019)	●	○	●	●	◐	●	●	●	●
Xu et al. (2019)	●	○	○	●	◐	○	◐	●	●

● = *Yes;* ◐ = *Unclear, Partially;* ○ = *No; N/a = Not applicable.*

reported higher FCR (Boehmer et al., 2016; Maguire et al., 2017) which remained significant when controlling for other demographic and clinical factors (Maguire et al., 2017). Of these studies, one study met all of the quality assessment criteria (Maguire et al., 2017), however sample size calculation was not reported in Boehmer et al. (2016)'s study, which may indicate issues regarding statistical power and potential for Type I errors.

Data demonstrated mixed support for significant associations between type of medical treatment and FCR. Seven studies assessed the relationship between type of treatment and FCR. Of these, one study reported a very weak positive association between chemotherapy and FCR ($r = 0.14$) (Maguire et al., 2017), whilst three studies reported significant results which remained significant after controlling for other demographic and clinical variables (Boehmer et al., 2016; Janz et al., 2016; Maguire et al., 2017; Wu et al., 2019). Those caring for survivors who had received anti-estrogen therapy (Boehmer et al., 2016) or chemotherapy (Janz et al., 2016; Maguire et al., 2017) reported higher FCR. Two studies found that those caring for survivors who had undergone major surgery were more likely to have lower FCR (Maguire et al., 2017; Wu et al., 2019). This finding was significant when controlling for other demographic and clinical variables at 6 months post-treatment, but not at 12-months (Wu et al., 2019).

Cancer Stage

Seven studies explored the relationship between cancer stage and FCR, none of which found a significant association (Mellon et al., 2007; Hodges et al., 2009; Kim et al., 2012; Boehmer et al., 2016; Janz et al., 2016; Maguire et al., 2017; Chien et al., 2018). One study assessed the relationship between cancer severity and FCR, and found a significant positive association when controlling for other demographic and clinical variables (Kim et al., 2012). However, as this study used an adapted FCR measure, its psychometric properties are unknown.

Comorbidities

There was limited support for associations between comorbidities and FCR. Of the five studies that assessed the relationship between comorbidities and FCR, two found that greater number of comorbidities resulted in higher FCR when controlling for other variables, specifically survivor comorbidities (Boehmer et al., 2016) and caregivers' own reported number of comorbidities (Janz et al., 2016). One study examined the relationship between FCR and survivor's physical health and found that increased caregiver FCR was associated with poorer physical health of survivors (Kim et al., 2012).

Medical Follow-Up

One study, reported in two articles, used a three week diary to investigate the impact of a mammogram on FCR, which reported that there was a significant increase in FCR during days leading up to the mammogram, and avoidance of threatening stimuli was predictive of FCR on the day of the mammogram (Soriano et al., 2019). However, it was not stated whether confounding demographic variables were controlled for in this analysis. Following the mammogram, partner responsiveness (response perceived as genuine and enthusiastic) predicted lower caregiver FCR, whilst patient capitalization attempts (disclosure of positive events) predicted greater FCR at week 3 (Soriano et al., 2018b). However, Soriano et al. (2018b) did not report a sample size calculation, therefore findings may be at risk of Type I errors.

Psychosocial Factors

Emotional Distress

There were significant associations found between level of anxiety and FCR. Three studies assessed the relationship between anxiety and FCR, all of which reported a weak positive association between anxiety and higher FCR (r =0.24 to 0.39) (Kim et al., 2012; Soriano et al., 2018a, 2019)[2]. One study used the Hospital Anxiety and Depression Scale to examine the relationship between emotional distress (anxiety and depression combined) and FCR and reported a strong positive association ($r = 0.73$) (Hodges et al., 2009).

Interpersonal Factors

Data indicated mixed support for significant associations between survivors' and family caregivers' FCR (**Table 4**). Nine studies, reported in ten articles, assessed the relationship between survivors' and caregiver FCR. Of these, eight studies found weak to moderate associations between survivor and family caregiver FCR scores ($r = 0.19$ to 0.53) (Mellon and Northouse, 2001; Mellon et al., 2007; Kim et al., 2012; Boehmer et al., 2016; van de Wal et al., 2017; Soriano et al., 2018a, 2019; Perndorfer et al., 2019), which remained significant when controlling for other variables at 6 months post-diagnosis (Hodges et al., 2009). However, the quality of studies that report these findings are mixed, as six of the nine studies do not report a sample size calculation (Mellon and Northouse, 2001; Mellon et al., 2007; Boehmer et al., 2016; Soriano et al., 2018a, 2019; Perndorfer et al., 2019), whereas three studies did state this calculation (Hodges et al., 2009; Kim et al., 2012; van de Wal et al., 2017). Consequently, it is unclear if the aforementioned studies are sufficiently powered and are potentially at risk of Type I errors.

Two studies examined the association between relationship quality and FCR, with one study reporting a significant positive association which was also found in next-day FCR when measured over 21 days (Soriano et al., 2018a). Three studies, reported in five articles, assessed the relationship between social support and FCR. Of these, one study found that social support was significantly negatively associated with FCR when controlling for other variables (Boehmer et al., 2016). One study investigated the relationship between loneliness and FCR, reporting a weak positive association between loneliness and FCR ($r = 0.27$) (Maguire et al., 2017).

One study examined the relationship between negative affect (assessed using the Positive and Negative Affect Schedule) and FCR, which found that as spousal negative affect increased, so did FCR level (Soriano et al., 2018a).

[2]Anxiety was assessed using the Profile of Mood States – Short Form (34), the Hospital Anxiety and Depression Scale (27), and the PROMIS Anxiety Short Form questionnaire (38).

TABLE 4 | Main study findings.

Author, (year)	Dependent variable FCR score (SD)	Analysis	Independent variables: Non-psychosocial (demographic, clinical)	Independent variables: Psychosocial	Significant findings
Boehmer et al. (2016)	FRQ[a] HSW[b]: 75.2 (13.6) SMW[c]: 71.8 (16.5)	Multivariate logistic regression	Sexual orientation; Co-residence; Years since diagnosis; Treatment type; Survivor comorbidities; Chemotherapy; Co-residence	Caregiver use of counseling in relation to cancer diagnosis; Social support (Survivor, Caregiver); Experience of discrimination (Caregiver); FCR score (Survivor)	*Non-psychosocial* Years since diagnosis ($\beta = -0.25^{***}$); Anti-estrogen therapy ($\beta = 0.22^{***}$); Survivor comorbidities ($\beta = 0.25^{***}$) *Psychosocial* Caregiver and Survivor FCR: $r_2 = 0.29^{***}$ Social support (Caregiver) ($\beta = -0.24^{***}$)
Chien et al. (2018)	MAX-PC[d] 5.22 (1.78)	Multivariate logistic regression	Age (Patient); Religion (Patient, Partner); Employment status (Patient, Partner); Education level (Patient, Partner); Self-perceived health status (Patient); Treatment type (radiotherapy); Cancer stage; Living arrangement (Partner)	FCR score (Patient); Relationship satisfaction (Patient, Partner)	*Non-psychosocial* None. *Psychosocial* None.
Cohee et al. (2017)	CARS[e] 11.794 (4–24)	Correlation; Mediation	Age (Survivors, Partners); Ethnicity; Education; Religion; Comorbidities; Time since diagnosis	Social constraints; Cognitive processing	*Non-psychosocial* Education $r = -0.164^{*}$ *Psychosocial* X (social constraints); M (cognitive processing) Indirect effect = 0.184, 95% bootstrap CI = 0.119 to 0.271. Direct effect = 0.038, $p = 0.469$, 95% CI = −0.066 to−0.142. [$F_{(3,215)} = 27.917$, $R^2 = 0.280$, $p < 0.001$]
Dempster et al. (2011)	CARS 13.93 (5.83)	Correlations; Regression	Age; Gender; Relationship to survivor; Months since diagnosis; Comorbidities	Anxiety; Depression; Illness perceptions: Acute/chronic timeline; Cyclical timeline; Treatment control; Emotional cause; Behavioral cause; Externalized cause; Consequences (Patient, Carer); Personal control (Patient, Carer); Illness coherence (Patient, Carer) Coping strategies (Reflection/relaxation, Positive focus, Diversion, Planning, Interpersonal)	*Non-psychosocial* Age ($\beta = -0.171^{***}$) *Psychosocial* Cyclical timeline: $r = 0.275^{***}$; Consequences (Patient): $r = 0.306^{***}$; Consequences (Carer): $r = 0.475^{***}$ Reflection/relaxation: $r = 0.333^{***}$; Diversion: $r = 0.327^{***}$; Interpersonal: $r = 0.354^{***}$ Illness coherence (Carer) ($\beta = -0.093^{*}$); Consequences (Carer) ($\beta = 0.273^{***}$); Externalized cause ($\beta = -0.124^{**}$) Reflection/relaxation ($\beta = 0.165^{**}$); Positive focus ($\beta = -0.107^{*}$); Interpersonal ($\beta = 0.179^{**}$)
Graham et al. (2016)	CARS T1:13.65 (5.58) T2: 13.97 (5.59)	Hierarchical regression	Age; Gender; Relationship to survivor; Living arrangement; Months since diagnosis; Other illness/medical condition	Anxiety; Depression; IPQR-Cluster 2 vs. 1[f]; IPQR-Cluster 3 vs. 1; Coping strategies (Planning, Interpersonal, Relaxation, Positive focus)	*Non-psychosocial* None. *Psychosocial* IPQR-Cluster 3 vs. 1 ($\beta = -0.205^{*}$); Interpersonal ($\beta = 0.218^{*}$)

(Continued)

TABLE 4 | Continued

Author, (year)	Dependent variable FCR score (SD)	Analysis	Independent variables: Non-psychosocial (demographic, clinical)	Independent variables: Psychosocial	Significant findings
Hodges et al. (2009)	WOC[g] T1: 11.77 (4.98) T2: 11.71 (5.21)	Correlations; Path analysis	Age (Patient, Carer); Gender (Patient, Carer); Relation to patient; Co-habiting status; Children; Employment status; Cancer site; Cancer stage	Anxiety; Depression; FCR score (Patient)	*Non-psychosocial* None. *Psychosocial* Carer FCR (3 and 6 months) $r = 0.754^{***}$; Patient and carer FCR (6 months) $r = 0.375^{**}$ Carer distress: $r = 0.734^{**}$; ($\beta = 0.20^{**}$); Patient FCR (3 months) ($\beta = 0.18^{**}$); Carer FCR (3 months) ($\beta = 0.69^{*}$)
Janz et al. (2016)	Worry scale[h] $N = 212$ (47.1%)	Logistic regression	Age; Ethnicity; Education level; Health status; Comorbidities; Cancer stage; Treatment type (Chemotherapy, Radiation, Surgery)	Received enough information on risk of recurrence from health care providers; Emotional support from health care providers;	*Non-psychosocial* Non-Hispanic Black ($\beta = 0.053^{**}$); Latino (higher acculturation) ($\beta = 3.05^{**}$); Latino (lower acculturation) ($\beta = 2.96^{**}$); One or more comorbidities ($\beta = 1.95^{*}$); Chemotherapy ($\beta = 2.77^{**}$) *Psychosocial* None.
Kim et al. (2012)	Adapted item[i] −0.04 (0.99)	Correlations; Modeling analysis	Age (Survivor, Caregiver); Cancer severity	Anxiety; Quality of life (QoL): mental health and physical health (Survivor, Caregiver); FCR score (Survivor)	*Non-psychosocial* Age: $r = -0.174^{***}$; Cancer severity ($\beta = 0.197^{***}$) *Psychosocial* QoL Mental health (Caregiver): $r = -0.296^{***}$; Anxiety: $r = 0.239^{***}$; Survivor and Caregiver FCR: $r = 0.19^{***}$; QoL Physical health (Survivor): ($\beta - 0.127^{**}$); Mental health (Caregiver): ($\beta = -0.147^{***}$)
Maguire et al. (2017)	WOC 9.6 (5.82)	Correlations; Multiple regression	Age (Survivor, Caregiver); Gender (Caregiver); Time since diagnosis; Cancer stage; Treatment type (Surgery, Chemotherapy, Radiotherapy); Relationship to survivor; Employment status	Financial stress of caring; Time caring; Social support; Loneliness; QoL (Survivor)	*Non-psychosocial* Time since diagnosis: $r = -0.18^{*}$; Chemotherapy: $r = 0.14^{*}$; Extent of surgery: $r = -0.25^{***}$ Age (Survivor) ($b = -0.22^{*}$); Age (Caregiver) ($b = 0.22^{*}$); Caregiver gender: ($r = 0.21^{*}$); ($b = 0.25^{***}$); Extent of surgery ($b = -0.23^{***}$) *Psychosocial* Survivor QoL: $r = -0.28^{***}$; Time caring: $r = 0.34^{***}$; Loneliness: $r = 0.27^{***}$ Financial stress of caring: ($b = 0.20^{*}$); Time caring: ($b = 0.37^{***}$); Loneliness: ($b = 0.25^{***}$)

(Continued)

TABLE 4 | Continued

Author, (year)	Dependent variable FCR score (SD)	Analysis	Independent variables: Non-psychosocial (demographic, clinical)	Independent variables: Psychosocial	Significant findings
Mellon et al. (2006)	FRQ 73.1 (14.1)	Correlations	None.	Family stressors; Family hardiness; Social support; Family meaning of illness; Family QoL; Somatic concerns (Patient)	*Non-psychosocial* None. *Psychosocial* Family stressors: $r = 0.29^{*}$; Meaning of illness: $r = -0.28^{**}$; QoL: $r = -0.29^{*}$
Mellon et al. (2007)	FRQ NR	Correlations; Modeling analysis	Age (Survivor, Caregiver); Gender (Survivor, Caregiver); Ethnicity (Survivor, Caregiver); Education level (Survivor, Caregiver); Role of relationship to survivor; Time since diagnosis; Other health problems	Concurrent family stressors (Actor effect, Partner effect); Family hardiness; Social support; Family meaning of cancer illness (Actor effect, Partner effect); Somatic concerns; FCR score (survivor)	*Non-psychosocial* Age (Partner effect): ($\beta = -0.52^{*}$) *Psychosocial* Concurrent family stressors: $r = 0.29^{**}$; Meaning of cancer illness: $r = -0.28^{**}$; Survivor FCR: $r = 0.41^{***}$ Concurrent family stressors (Actor effect): ($\beta = 0.34^{***}$); Family meaning of cancer illness (Actor effect): ($\beta = -1.24^{**}$); Survivor vs. family caregiver: ($\beta = -4.89^{***}$)
Mellon and Northouse (2001)	FRQ NR	Correlations	None.	Family QoL; Family stressors; Family hardiness; Family social support; Family meaning of illness; Somatic concerns; FCR score (Patient)	*Non-psychosocial* None. *Psychosocial* Family QoL: $r = -0.33^{***}$; Family stressors: $r = 0.24^{**}$; Patient FCR: $r = 0.40^{***}$; Family meaning of illness: $r = -0.27^{**}$
Perndorfer et al. (2019)	FCRI[j] Spouse evening FCR:1.43	Correlations	None.	Daily protective buffering (Patient, Spouse); Intimacy; Evening FCR score (Patient, Partner)	*Non-psychosocial* None. *Psychosocial* Protective buffering (Patient): $r = 0.15^{***}$; Protective buffering (Spouse): $r = 0.25^{***}$; Evening intimacy (Patient): $r = -0.12^{***}$; Evening FCR score (Patient): $r = 0.21^{***}$
Soriano et al. (2018a) Study (1)	Global FCR: CARS = 3.18	Correlations; Modeling analysis	Age (Patient); Patient physical symptoms	Social Constraints (Patient, Spouse); Anxiety; Depression; Relationship quality (Patient, Spouse)	*Non-psychosocial* Age (Patient) ($\beta = -0.028^{*}$) *Psychosocial* FCR (Patient and Spouse): $r = 0.53^{***}$; Anxiety $r = 0.31^{*}$; Social constraints (Spouse): ($\beta = 0.561^{*}$); Relationship quality (Spouse): ($\beta = 0.050^{*}$)

(Continued)

TABLE 4 | Continued

Author, (year)	Dependent variable: FCR score (SD)	Analysis	Independent variables: Non-psychosocial (demographic, clinical)	Independent variables: Psychosocial	Significant findings
Soriano et al. (2018a) Study (2)	FCRI = 1.51	Correlations; Modeling analysis	None	Social Constraints (Patient, Spouse); Negative affect (Patient, Spouse); Relationship quality (Patient, Spouse); FCR score (Spouse same day)	*Non-psychosocial* None. *Psychosocial* FCR score (Patient and Spouse): $r = 0.22^{***}$; Social constraints: $r = 0.27^{**}$; Negative affect: $r = 0.32^{**}$ (DV: Same day FCR): Social constraints (Spouse): ($\beta = 0.978^{***}$)[k]; Social constraints (Patient): ($\beta = 1.088^{*}$); Negative affect (Spouse): ($\beta = 0.496^{**}$) (DV: Next day FCR): Negative affect (Spouse): ($\beta = 0.255^{**}$); Relationship quality (Spouse): ($\beta = 0.091^{*}$)
Soriano et al. (2019)	FCRI Baseline[l] = 5 (4). T1 = 1.117 (1.754) T2 = 0.840 (1.296) T3 = 0.570 (1.483)	Modeling analysis	None	Capitalization attempt (Spouse, Patient); Perceived partner responsiveness (Spouse); Event positivity	*Non-psychosocial* None. *Psychosocial* T3: Capitalization attempt (Spouse)[m] ($\beta = 0.488^{**}$); Patient capitalization attempt (Patient)[23] ($\beta = -0.662^{**}$); Perceived partner responsiveness[n] ($\beta = -0.421^{**}$)
Soriano et al. (2019)	FCRI 0.96 (1.78)	Correlations; Modeling analysis	None	Threat sensitivity (Patient, Spouse); Anxiety (Patient, Spouse); FCR score (Patient)	*Non-psychosocial* None. *Psychosocial* Patient FCR: $r = 0.29^{*}$; Anxiety (Spouse): $r = 0.39^{*}$; Threat sensitivity (Spouse): ($\beta = 0.408^{**}$)
van de Wal et al. (2017)	CWS[o] 12.6 (3.5)	Regression; Mean comparison	Age (Partner); Years a couple; Cancer history (Partner); Education level (Partner); Children; Time since diagnosis; Type of treatment	FCR score (Survivor); Health-related QoL (physical, social, physical role and emotional role functioning; mental health; vitality; pain; general health)	*Non-psychosocial* Age: ($\beta = -0.295^{*}$) *Psychosocial* Survivor FCR score: ($r = 0.44^{***}$); ($\beta = 0.304^{***}$) High partner FCR vs low partner FCR: Emotional role functioning ($p = 0.023^{*}$); Mental health ($p < 0.001^{***}$); Vitality ($p = 0.038^{*}$); General health ($p = 0.042^{*}$)

(Continued)

TABLE 4 | Continued

Author, (year)	Dependent variable FCR score (SD)	Analysis	Independent variables: Non-psychosocial (demographic, clinical)	Independent variables: Psychosocial	Significant findings
Wu et al. (2019)	Cancer specific worry measure[p] NR	Modeling analysis	Type of treatment (Radiation, Surgery)	FCR scores at baseline and six-months (Patient, Spouse)	*Non-psychosocial* Six-month time point: Surgery (β = −0.25**) *Psychosocial* Six-month time point: Baseline FCR (Spouse) (β = 0.62***) Twelve-month time point: Six-month FCR (Spouse) (β = 0.73***)
Xu et al. (2019)	Adapted measure[q] 19.82 (17.77)	Modeling analysis; Mediation analysis	None	Illness representation; Daily Couple Communication (perceptions of positive and negative information)	*Non-psychosocial* None. *Psychosocial* Spouses' perception of positive information: (β = −0.168***); Spouses' perceptions of negative information: (β = 1.045***)

[a] *FRQ = Fear of Cancer Recurrence Questionnaire (Northouse, 1981). Higher scores indicate greater level of FCR (score range 22 – 110).*
[b] *Caregivers of cancer survivors who identify as heterosexual women (HSW).*
[c] *Caregivers of cancer survivors who identify as sexual minority women (SMW).*
[d] *MAX-PC = Memorial Anxiety Scale for Prostate Cancer (Roth et al., 2003). Scale consists of 18 items, four-point Likert scale. Higher scores indicative of higher anxiety.*
[e] *CARS = Concerns About Recurrence Scale (Vickberg, 2003). Four items, ranging from 0 to 5. Higher scores indicative of greater FCR.*
[f] *IPQ Clusters: Cluster 1 = Carers have increasingly strong causal beliefs, particularly beliefs in emotional cause; Cluster 2 = Carers increasingly believe that they and the survivor understand condition, and feel over time that there will be less severe consequences for themselves and the survivor; Cluster 3 = Carers report decreasing belief in severe consequences for survivor and carer, increase in perception that condition is acute and increase in all control beliefs.*
[g] *WOC = Worry Of Cancer scale (Easterling and Leventhal, 1989). Total composite score from two items used ranged from 0-20.*
[h] *Adapted worry scale used in previous publications (Janz et al., 2011, 2014). Scores M = ≥ 3 considered "worriers".*
[i] *Adapted from Zhao et al. (2009). measure. Higher score reflects greater FCR, zero score reflects moderate levels of FCR.*
[j] *FCRI = Fear of Cancer Recurrence Inventory (Simard and Savard, 2009). Six items ranging from 0-4. Higher scores indicative of greater FCR.*
[k] *Random effects greater but still significant.*
[l] *One week prior to diary period.*
[m] *N = 56 couples.*
[n] *N = 53 couples.*
[o] *CWS = Cancer Worry Scale, stipulating a cut-off score for high FCR as ≥14.*
[p] *Diefenbach et al. (1999). Mean of two responses calculated, higher scores indicated greater FCR.*
[q] *Five items adapted from prior research (Thewes et al., 2012), rated on a seven-point Likert scale.*
Methods: Multivariate regression models analysis (regression, mixed models and generalized linear); Modeling analysis (path analysis, structure equation modeling and actor-partner interdependence model). NR = Not Reported.
****p < 0.001; **p < 0.01; *p < 0.05.*

Five studies investigated the impact of communication on FCR, all of which found significant results. Specifically, on a day that partners perceived the cancer survivor to be less available or responsive to discussions of cancer-related worries, partners were more likely to have greater FCR on that same day, but not the next day (Soriano et al., 2018a). One study found that patient disclosures of positive events resulted in decreased FCR as did partner responsiveness which was perceived to be genuine and enthusiastic (Soriano et al., 2018b). However, it is unclear if the adapted measure used to assess partner responsiveness is validated. Similar findings were reported whereby partners' perceptions of positive information (e.g., supportive and inclusive) and negative information (e.g., indifferent) resulted in a change in FCR (Xu et al., 2019). One study reported that cognitive processing mediated the relationship between social constraints and FCR (Cohee et al., 2017). Attempting to protect one's partner by hiding cancer-related concerns was weakly positively associated with increased FCR ($r = 0.15$) (Perndorfer et al., 2019).

Stress and Coping

Two studies, reported in four articles, assessed the relationship between stressors and FCR, all of which found significant results. Specifically, care-related stressors (financial impact and time-burden associated with caregiving) (Maguire et al., 2017) were positively associated with FCR, whilst a weak positive relationship was reported between stressors related to ill health and FCR ($r = 0.24$ to 0.29) (Mellon and Northouse, 2001; Mellon et al., 2006, 2007).

Two studies assessed the relationship between coping strategies and FCR. Of these, one study reported a weak positive association between interpersonal coping (e.g., seeking support from cancer survivor) and FCR ($r = 0.35$) (Dempster et al., 2011), whilst another study found that this association remained significant when other variables were controlled (Graham et al., 2016). Although the latter study indicated a 40% drop out rate over time, there were no significant differences on depression or FCR between participants who provided complete data and those who provided data at one time point only (Graham et al., 2016). One study found that increased use of reflection and relaxation was a significant predictor of higher FCR at 12 months follow-up, whilst those with a hopeful and in-control outlook exhibited lower FCR (Graham et al., 2016). The authors suggested that the association between increased use of diversionary and relaxation coping skills and greater anxiety may be indicative of such strategies reinforcing avoidance, which may be beneficial in the short term but maintains anxiety in the longer term.

Quality of Life

Four studies, reported in five articles, assessed the relationship between QoL and FCR. All studies found a significant result, indicating a weak positive association between QoL and FCR ($r = -0.28$ to 0.33) (Mellon and Northouse, 2001; Mellon et al., 2006; Kim et al., 2012; Maguire et al., 2017). Specifically, higher FCR was linked to lower QoL scores, including poorer caregiver mental health (Kim et al., 2012), lower survivor QoL (Maguire et al., 2017) and poorer family QoL (Mellon and Northouse, 2001; Mellon et al., 2006). One study found significant differences between health-related QoL in partners with high and low FCR, reporting that partners with high FCR obtained significantly lower scores on social functioning, emotional role functioning, mental health, vitality and general health (van de Wal et al., 2017). Most of the studies that reported on QoL met the key criteria of the quality assessment and reported on relatively large sample sizes ranging from 123 to 455.

Psychological Beliefs

One study, reported in three articles, examined the relationship between the meaning of illness and FCR, reporting a weak negative association between negative meaning of illness and FCR ($r = -0.27$ to -0.28; (Mellon and Northouse, 2001; Mellon et al., 2006, 2007). Three studies assessed the relationship between illness perceptions and FCR, all of which reported significant findings (Dempster et al., 2011; Graham et al., 2016; Xu et al., 2019). Specifically, one study found that an understanding of the disease was negatively associated with FCR, whilst belief of less serious consequences and control over condition were positively associated with FCR (Dempster et al., 2011). One study reported that caregivers with a reduction in beliefs of severe consequences and causes of the condition, and an increase in control beliefs and understanding of the condition was associated with decreased FCR over a 12-month time period (Graham et al., 2016). One study found that over a 10 days period, spouses' negative illness representations were negatively associated with their own disclosures of positive information (Xu et al., 2019). However, this study did not state a sample size calculation therefore statistical analysis may be underpowered and at risk of Type I error rates.

DISCUSSION

This review summarized cross-sectional and prospective quantitative research investigating the demographics, clinical and psychological factors associated with FCR in caregivers of cancer survivors. Sixteen studies, reported in 19 articles, were included and summarized narratively. Significant associations were found between FCR and certain non-modifiable factors, including younger age and treatment modality. Although there was only limited research investigating psychological processes ($n = 3$), significant associations were found between illness perceptions and FCR. Specifically, a good understanding of the cancer diagnosis was negatively associated with FCR, whilst belief of less serious consequences and control over the condition were positively associated with FCR.

There were mixed findings with regards to demographic factors and level of FCR. Younger age was significantly associated with FCR (Mellon et al., 2007; Dempster et al., 2011; Kim et al., 2012; Janz et al., 2016; Maguire et al., 2017; van de Wal et al., 2017; Soriano et al., 2018a), which may be due to the unexpectedness of cancer in younger age and the perceived negative physical, social or economic impact of such a disease (Llewellyn et al., 2008; Lebel et al., 2013). Limited significant outcomes were reported with regards to the remaining demographic factors. Similar findings have been reported in the cancer survivor literature, whereby

no demographic, clinical or social factors reliably predicted subsequent distress in cancer survivors (Cook et al., 2018).

Of the 13 studies that assessed the association between clinical outcomes and FCR, six reported significant associations. Specifically, time since diagnosis (Boehmer et al., 2016; Maguire et al., 2017) was significantly associated with higher FCR, whilst which contrasts with the cancer survivorship literature (Crist and Grunfeld, 2013; Koch et al., 2013; Simard et al., 2013). Four studies found that treatment modality was significantly associated with FCR, which is consistent with the cancer patient and survivorship literature that indicates that different treatment approaches are significantly associated with FCR (Yang et al., 2017a,b; Maguire et al., 2018). Patients who have had chemotherapy or radiotherapy are likely to experience side effects, and an increased number of hospital trips and inpatient episodes, which may contribute to psychological morbidity (Denlinger and Barsevick, 2009). Furthermore, research has indicated that some patients may choose more invasive surgeries even when the risk of recurrence is low, in order to eliminate risk to the greatest possible extent (Williams and Jeanetta, 2016). Consequently, caregivers may perceive surgery as a more conclusive treatment, and therefore may be of the view that the cancer is less likely to return, as opposed to treatment side effects and multiple hospital trips which may act as triggers of FCR. Only one study explored the association between clinical follow-up (mammogram) and FCR, which reported a significant association (Soriano et al., 2019). As caregivers often attend medical appointments with the survivor (LeSeure and Chongkham-ang, 2015), it is likely that such follow-ups may also act as a trigger for FCR in caregivers.

Two studies reported a significant association between comorbidities and caregiver FCR (Boehmer et al., 2016; Janz et al., 2016). Internal physiological cues related to comorbid conditions may be misinterpreted as possible cancer recurrence, thus symptoms may act as a reminder of vulnerability and trigger FCR (Leventhal et al., 1980; Lee-Jones et al., 1997; Crist and Grunfeld, 2013). Caregivers are likely to witness survivors expressing somatic concerns and reporting treatment side effects, therefore, they may be more vigilant regarding changes in the survivors' physical health which may exacerbate worries that the cancer might return. Furthermore, lack of communication between the dyad may lead to worry regarding somatic concerns and side effects (Cohee et al., 2017; Soriano et al., 2018a). However, similarly to demographic factors, clinical indicators are not as critical as psychological factors in the development and maintenance of FCR, and there are intrapersonal factors which need to be considered.

Of the psychosocial factors examined, communication significantly affected FCR. The less someone was able to tell their partner about their cancer-related concerns, the more likely they were to experience FCR (Cohee et al., 2017; Soriano et al., 2018a). Unsupportive partner behaviors (i.e., critical or avoidant responses) are associated with both patient and partner reports of hiding concerns and disengagement (Manne et al., 2014). One study reported that caregivers hiding their own cancer-related worries in an attempt to protect the survivor was associated with increased FCR (Perndorfer et al., 2019). Caregivers can be reluctant to discuss emotions relating to cancer for fear of burdening or upsetting the patient (LeSeure and Chongkham-ang, 2015; Tolbert et al., 2018), but this may be contraindicated as a helpful strategy.

The review findings indicated that caregivers relied on various coping strategies, including reflection, relaxation, diversion and interpersonal approaches (e.g., through requiring frequent reassurance regarding FCR), which were significant predictors of higher FCR (Dempster et al., 2011; Graham et al., 2016). Research also highlights that caregivers engage in a high use of avoidance, distraction and denial (Papastavrou et al., 2012; Lambert et al., 2013), yet acknowledge that such strategies are only temporarily effective (LeSeure and Chongkham-ang, 2015). Consequently, it is likely that FCR is exacerbated and maintained as the psychological distress is not explicitly addressed.

Significant outcomes were reported for psychological processes, specifically illness perceptions (Dempster et al., 2011; Graham et al., 2016; Xu et al., 2019). Similar findings have been reported in the cancer survivorship, as illness perceptions have been associated with higher FCR and worry about cancer more generally (Corter et al., 2013; Park et al., 2013; Simard et al., 2013). Furthermore, individual interpretations or representations are often more influential than clinical characteristics in determining FCR (Llewellyn et al., 2008). However, a review of psychological distress in cancer survivors reported no consistent evidence that illness appraisals predicted longer-term distress (Cook et al., 2018).

This review provides preliminary evidence that theoretical models used to understand FCR in cancer survivors may also be applicable to caregivers. For example, the limited research investigating psychological beliefs indicates that illness perceptions explained additional variance in FCR when controlling for demographic and clinical characteristics. This provides support for the Common Sense Model (Leventhal et al., 1980) which states that individuals create cognitive and emotional interpretations of an illness threat, in order to appraise and determine if the threat is serious and requires attention. However, the limited explanatory power of the three studies that examined illness perceptions suggest that this model does not fully account for variance in FCR in caregivers of cancer survivors and indicate a need to look beyond illness perceptions. The broader blended model of FCR (Lebel et al., 2018) argues that triggers, perceived risk of recurrence and illness uncertainty predict FCR, whilst positive beliefs about worrying and intolerance of uncertainty act indirectly to increase FCR by increasing maladaptive coping. In this review, interpersonal factors such as communication and social support, as well as type of treatment and clinical follow-up were significantly associated with increased FCR, therefore lending support for the utility of this model in understanding FCR experienced by caregivers. Furthermore, the findings of this review suggest that caregivers implement maladaptive coping strategies such as diversion and reassurance seeking, which were significant predictors of FCR. Interventions that aim to reduce FCR in patients which focus on cognitive processing and metacognitions, rather than the content of thoughts, have been found to be more effective than traditional cognitive behavioral approaches (Tauber et al., 2019). Given that

similar factors are reported to exist for caregivers as survivors, it may be that interventions based on the aforementioned theoretical frameworks may also be applicable to caregivers.

Study Limitations and Implications for Research

There are several limitations which must be taken into consideration. As only published data were searched and included in this review, there is a possibility that relevant studies were missed. Furthermore, only citations written in English were considered for inclusion for review, which may have resulted in a language, selection or cultural bias. The aim of the review was to synthesize correlates and predictors of FCR in cancer survivors so as to produce a comprehensive overview of the current state of evidence with regards to factors associated with, and underpinning, FCR. As such, we only included quantitative studies. However, inclusion of qualitative studies may have provided valuable context or additional insights into the findings of this review. Meta-analysis of data was not possible to heterogeneity in included studies, which limited the depth of analysis possible. We focused, instead, on narratively summarizing the results of univariate and multivariate analyses, with preference given to the most complex/controlled analyses. However, this may make comparison with other literature difficult, and should be considered when interpreting findings.

Various methodological limitations of the included studies were identified. There is likely to be a risk of self-selection bias as recruitment methods were reliant on patients responding to the research adverts. Eight out of the 16 studies used a cross-sectional study design, thus precluding the ability to draw causal inferences. Only four of the prospective studies included in the review reported an adequate follow-up period; the remainder used experiential sampling methodology with follow-up periods ranging from 10 days to 3 weeks. Most studies reported data from the USA and participants were predominantly Caucasian females, thus may not reflect a representative sample of the population. It is also important to note that cancer patients were in different stages of diagnosis, therefore associations with FCR could differ as those caring for patients with more advanced cancer may perceive the diagnosis as being more serious and more likely to recur (Simard et al., 2013). Future research should attempt to address the observed limitations by recruiting larger, more representative samples of carers of patients with a range of different cancers.

With regards to the quality of studies, only five studies reported a sample size calculation, thus studies are potentially statistically underpowered and at risk of Type I error rates. Researchers should ensure that this is stipulated in future research papers, in order to ensure confidence in the statistical power of findings. Only three studies considered psychological beliefs associated with FCR in family caregivers (Dempster et al., 2011; Graham et al., 2016; Xu et al., 2019); further prospective research in this area is warranted.

Clinical Implications

Health professionals may want to consider certain demographic and clinical factors, such as younger age and treatment modality, when offering information on treatment approaches and providing the space to discuss concerns about recurrence. Previous research has identified a need for planning for transition from patient to "survivor" (Gilbert et al., 2008; Houlihan, 2009), which involves discussions around treatment, ongoing management, managing FCR and identifying triggers for seeking help and support from healthcare team (Humphris and Ozakinci, 2006). Caregivers should be involved in care planning with the opportunity to discuss their fears about the cancer returning. Involvement in care planning would provide the caregiver with greater guidance on the most appropriate ways of supporting the cancer survivor. In cases where the patient does not want the caregiver to be involved in the care plan, caregivers should be offered their own support as the cancer experience can result in the caregiver adapting to a potentially altered future and sense of self (Tolbert et al., 2018).

CONCLUSIONS

The results of the review indicate that caregiver FCR is a significant concern and highlights the importance of furthering current understanding of this prevalent issue. Weak to moderate associations were found between certain demographic and clinical factors and increased FCR. Further research examining modifiable factors are required, in order to enhance understanding of the psychological processes that are involved in the development and maintenance of FCR in caregivers of cancer survivors. By investigating modifiable factors, this will provide evidence and guide the development of appropriate and effective interventions for this population.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

PF, MC, and LO'R conceived the study. MC and PF supervised the conduct of the review and provided extensive feedback on drafts. LO'R searched for data, screened and selected studies, extracted data, quality assessed included studies, and drafted the initial manuscript. AW screened and selected studies and cross-checked data extraction and quality assessment. SC provided clinical input into the review. All authors commented on a final draft of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association Between Daily Worry, Pathological Worry, and Fear of Progression in Patients With Cancer

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Background: Fear of progression (FoP), or fear of cancer recurrence (FCR), is characterized by worries or concerns about negative illness-related future events. Actually, to worry is a common cognitive process that, in its non-pathological form, belongs to daily life. However, worry can also become pathological appearing as a symptom of mental disorders. This study aimed at investigating the associations among daily worry, pathological worry, and FoP in patients with cancer.

Methods: This is a cross-sectional study that includes 328 hospitalized patients with cancer. Patients filled out the FoP Questionnaire (FoP-Q), the Worry Domains Questionnaire (WDQ) for the assessment of daily worry, and the Penn State Worry Questionnaire (PSWQ) for the assessment of pathological worry. Depressive, anxiety, and somatic symptoms were measured with modules of the Patient Health Questionnaire [Patient Health Questionnaire-Depressive Symptoms (PHQ-2), Generalized Anxiety Disorder-2 (GAD-2), and Patient Health Questionnaire-Somatic Symptoms (PHQ-15)]. Furthermore, a structured clinical interview was conducted for the assessment of anxiety disorders. The hierarchical multiple linear regression analysis was used to identify factors independently associated with FoP.

Results: Mean age of the participants was $M = 58.5$ years (SD = 12.8), and 64.6% were men. FoP and worry were significantly intercorrelated ($r = 0.58$–0.78). The level of FoP was most strongly associated with daily worry ($\beta = 0.514$, $p < 0.001$), followed by pathological worry ($\beta = 0.221$, $p < 0.001$). Further significant determinants were younger age and depressive and anxiety symptoms. Clinical variables were not independently associated with FoP. The final model explained 74% of the variance.

Discussion: Fear of progression is strongly associated with daily worry and pathological worry. These results bring up the question of whether FoP is an expression of a general tendency to worry. Whether a general tendency to worry, in fact, represents an independent vulnerability factor for experiencing FCR/FoP needs to be investigated in a longitudinal research design.

Keywords: anxiety, cancer, distress, fear of progression, fear of recurrence, psycho-oncology, worry

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INTRODUCTION

Many people experience recurrent thoughts about possible risks and threats. To think repetitively about such future uncertainties and dangers is quite common. In a study with community-dwelling elderly people, Golden et al. (2011) found that 78.7% of the respondents worried during the previous month. Furthermore, 37.1% stated that they worried excessively, and 20.0% experienced excessive uncontrollable worry. Such excessive and uncontrollable worry, but not non-severe worry, was associated with depression and reduced quality of life (Golden et al., 2011). Worry has been associated with several negative outcomes, including general anxiety disorder (GAD) as a manifestation of excessive and uncontrollable worry (Golden et al., 2011; Hirsch et al., 2013). Some researchers have also highlighted the positive functions of worry. Worry can act as a motivator and buffer (Sweeny and Dooley, 2017), it can reflect a constructive problem-solving process (Szabo and Lovibond, 2002), and it can facilitate goal pursuit and threat reduction (McNeill and Dunlop, 2016). Several measures for the assessment of worry were developed, focusing on the experience of daily worry (e.g., Worry Domains Questionnaire, WDQ; Tallis et al., 1992) as well as on the phenomenon of excessive pathological worry (e.g., Penn State Worry Questionnaire, PSWQ; Meyer et al., 1990).

Regarding specific worry topics, people tend to worry about interpersonal relationships, self, work, future events, finances, and mostly health (Tallis et al., 1992; Golden et al., 2011). For instance, it is quite common that healthy people worry about developing cancer (Jensen et al., 2010; Murphy et al., 2018).

For people who suffer from cancer, to worry about future uncertainties represents quite an adequate response as there are many real risks and threats in the disease course. Patients with cancer often worry about illness- and treatment-related aspects, e.g., the side effects of treatment or taking time away from the family (Pisu et al., 2017). However, most important is the worry about cancer progression or recurrence (Simard et al., 2013; Dinkel and Herschbach, 2018). Fear of cancer recurrence (FCR) has been defined as "fear, worry, or concern about cancer returning or progressing" (Lebel et al., 2016, p. 3266). Although nearly all patients and survivors with cancer experience FCR to some degree (Simard et al., 2013), an excessive FCR has been linked to several negative outcomes such as reduced quality of life and worse psychosocial wellbeing (Koch et al., 2013; Simard et al., 2013; Simonelli et al., 2017; Dinkel and Herschbach, 2018; Lebel et al., 2020). FCR and the very similar construct fear of progression (FoP) have been conceptualized as multidimensional (Herschbach et al., 2005; Simard and Savard, 2009). However, worry represents one central aspect in current conceptualizations of non-pathological and clinical FCR/FoP (Fardell et al., 2016; Mutsaers et al., 2016, 2020). In fact, some researchers solely focused on worry when assessing FCR (Vickberg, 2003; Custers et al., 2014).

Despite the prominent role of worry in the understanding and conceptualization of FCR/FoP, there have been few empirical attempts to link FCR/FoP to the literature on worry from the fields of clinical psychology and psychopathology. Some studies with patients with cancer used the PSWQ and investigated pathological worry as an outcome or mediator, showing that pathological worry can be reduced by a psycho-oncological intervention (Wells-Di Gregorio et al., 2019) and that worry mediates the effect of mindfulness on psychological distress (Labelle et al., 2015; Brown et al., 2020). Recent studies aiming at validating theoretical models of FCR assessed meta-cognitive beliefs about worry, but not worry itself (Lebel et al., 2018; Smith et al., 2018; Curran et al., 2020). Only one study investigated the association between FCR and pathological worry (PSWQ), showing that the two were moderately correlated ($r = 0.49$). Furthermore, clinical FCR was more frequent at higher levels of pathological worry (Hovdenak Jakobsen et al., 2018).

In a previous study, we investigated the comorbidity pattern between FoP and anxiety disorders in patients with cancer (Dinkel et al., 2014). We found that patients with pure clinical FoP (without comorbid anxiety disorder) did not differ from patients with pure anxiety disorder (without comorbid clinical FoP) regarding pathological worry. However, patients with cancer with pure clinical FoP showed even higher levels of daily worry than patients with pure anxiety disorder. Patients with comorbid clinical FoP and anxiety disorder indicated the highest levels of worry (Dinkel et al., 2014). These results suggest a prominent role of daily and pathological worry in FoP.

Thus, in this study, we investigated whether daily worry and pathological worry would be independently associated with FoP, controlling for well-known covariates as well as potential sociodemographic, clinical, and mental health covariates, i.e., variables with inconsistent or few positive findings with regard to FCR/FoP. Such results would be helpful for the empirical validation of current models of FoP/FCR (Fardell et al., 2016; Mutsaers et al., 2016, 2020).

METHODS

Design and Procedure

This is a secondary analysis of the study by Dinkel et al. (2014). In brief, this was a cross-sectional investigation with patients with cancer undergoing inpatient treatment. Patients from the surgical or the hematological department of a large university hospital were sampled consecutively during 1 year (i.e., from March 2010 to March 2011). Inclusion criteria for study participation were confirmed diagnosis of gastrointestinal cancer or hematological malignancy, >18 years of age, and fluency with the German language. Exclusion criteria were severe psychiatric illness (except an anxiety disorder), severe physical, emotional, or cognitive impairment (rating of clinicians), and current treatment in the intensive care unit. Patients were approached by one of the authors (KK). Those patients who agreed to participate gave written informed consent. All participants underwent a structured clinical interview for the assessment of anxiety disorders and hypochondriasis and then filled out the self-reporting questionnaires. This study was approved by the local Ethics Committee (ethics vote: 2721/10).

Measures

Sociodemographic and Clinical Characteristics

Sociodemographic characteristics were recorded using a documentation sheet. Medical records were assessed to extract the data on clinical characteristics. The functional status of patients was assessed using the Karnofsky Performance Status (KPS; Karnofsky and Burchenal, 1949) during the personal interview with the patient by one of the authors (KK). Furthermore, for the assessment of comorbidity, patients indicated whether they had been diagnosed with selected chronic conditions other than cancer.

Fear of Progression

The FoP Questionnaire (FoP-Q) by Herschbach et al. (2005) was used to measure FoP. This is a multidimensional, reliable, and valid measure (Thewes et al., 2012) that has been used in international research. The "coping with anxiety" subscale was not applied as this subscale does not contribute to the total score of the FoP-Q (see Herschbach et al., 2005). Thus, we presented 34 items that belong to one of the four subscales, namely, "affective reactions," "partnership/family issues," "occupation," and "loss of autonomy." Each item is rated on a 5-point scale ranging from 1 (never) to 5 (often). The total score is computed as the sum of the mean scores of subscales. Higher scores represent higher levels of FoP. Internal consistency in this study was $\alpha = 0.95$. The 80th percentile of the FoP-summary score represented clinical FoP (Dinkel et al., 2014).

Worry

Two measures were applied for the assessment of worry.

The WDQ (Tallis et al., 1992; Stöber, 1995) was designed to measure non-pathological, daily worry. This is a content-oriented measure, asking participants to indicate on a 5-point scale from 0 (not at all) to 4 (extremely) how much they worry with regard to specific topics. The 25 items represent the five subscales, namely, "relationships," "lack of confidence," "aimless future," "work incompetence," and "financial." A summary score ranging from 0 to 100 can be computed. Cronbach's alpha in this study was $\alpha = 0.95$.

In contrast, the PSWQ (Meyer et al., 1990; Stöber, 1995) was developed to assess pathological worry, which is the main characteristic of GAD. The PSWQ represents a trait measure of the general tendency to worry excessively. It consists of 16 statements that do not relate to specific worry content but to the intensity and perceived uncontrollability of worry (e.g., "My worries overwhelm me"). Participants are instructed to indicate how typical the statements are for them. They responded on a 5-point scale ranging from 1 (not at all typical) to 5 (very typical). Five items are reverse scored. A total score, ranging from 16 to 80, is calculated by summing up all items. Cronbach's alpha in this study was $\alpha = 0.91$.

For both measures, higher scores indicate higher levels of worrying.

Depression and Anxiety Symptoms

Symptoms of depression and anxiety were assessed using the ultra-short screening versions of the Patient Health Questionnaire (PHQ), i.e., PHQ-2 and GAD-2. Both modules comprise two items, which are rated on a 4-point scale from 0 (not at all) to 3 (nearly every day) (Löwe et al., 2010). Higher scores represent higher depression and anxiety. Internal consistency in this study was $\alpha = 0.82$ (PHQ-2) and $\alpha = 0.80$ (GAD-2).

Anxiety Disorder

In light of the aim of this study (see Dinkel et al., 2014), only anxiety disorders and hypochondriasis were assessed using the Structured Clinical Interview for DSM-IV Axis I (SCID-I) (Wittchen et al., 1997). The interviews were conducted by one coauthor (KK) who is a clinical psychologist trained in conducting SCID-I interviews.

Somatic Symptom Burden

The PHQ module, PHQ-15 (Kroenke et al., 2002; Kocalevent et al., 2013), was applied for the assessment of common somatic symptoms. Patients were asked to indicate the severity of 15 somatic symptoms during the previous 4 weeks. The symptoms were rated on a 3-point scale ranging from 0 (not bothered at all) to 2 (bothered a lot). Higher scores indicate a higher symptom load. Cronbach's alpha in this study was $\alpha = 0.80$.

Statistical Analysis

Descriptive statistics were computed for the study variables. The research question was investigated using the hierarchical multiple linear regression analysis. In order to control for known and potential covariates, sociodemographic characteristics were entered in the first step, clinical variables in the second step, and mental health variables in the third step. As our main study (Dinkel et al., 2014) showed that there is some overlap between anxiety disorder and FoP, we controlled for the presence of any anxiety disorder. However, as the presence of clinician-defined anxiety disorder and patient-reported anxiety symptoms do not correspond perfectly, we decided to control for both self-reported mental health symptoms and clinician-defined anxiety disorder. In the fourth step, the full model is presented. The full model includes the following variables: age, gender, current partnership, educational level, cancer site, disease status, duration of disease, functional status, comorbidity, depressive symptoms, anxiety symptom, somatic symptoms, anxiety disorder, daily worry, and pathological worry. Within each step, variables were entered simultaneously. We presented the adjusted R^2 as the measure of variance explained as well as ΔR^2 indicating the change in R^2 between each step of the hierarchical regression. The following variables were dichotomized for the regression analysis: educational level (lower/higher), cancer site (gastrointestinal/hematological), comorbidity (none/present), and disease status (first occurrence/all others). For additional analyses, Pearson's correlations were used to assess intercorrelations between worry and FoP, and differences in worry mean scores between groups of clinical versus non-clinical FoP were investigated using the independent sample t-test. Effect sizes (Cohen's d) are reported for these group differences. Alpha level was set as $p < 0.05$. All analyses were conducted using SPSS/PC software package version 24 (SPSS, Chicago, IL, USA).

RESULTS

Study Sample

Of 529 patients who were approached for participation, 49 patients met the exclusion criteria. Thus, 480 patients were available for study participation. A total of 343 patients (71.5%) agreed to take part. Patients who declined participation did not differ from the study participants with regard to sex or cancer site, but patients who declined were older ($M = 63.1$, SD = 11.6) than those patients who agreed ($p < 0.001$). Of those who agreed, 15 patients did not provide the data on FoP, leaving 328 patients available for the analysis. In light of the low number of patients who were excluded from the analysis, we refrained from conducting a drop-out analysis.

The mean age of the patients was $M = 58.5$ years (SD = 12.8; minimum–maximum: 20–87). The majority of them (64.6%) were men. A total of 60.7% of the patients suffered from gastrointestinal cancer (mainly colorectal cancer, $n = 81$) and 39.3% suffered from hematological malignancy (mainly lymphoma, $n = 43$). For most of the patients, this was the first occurrence of the disease (69.0%), and the mean time since the first cancer diagnosis was 27.1 months (SD = 56.8; minimum–maximum: 0–546 months). Further sociodemographic and clinical characteristics are presented in **Table 1**.

Bivariate Associations

Descriptives of the continuous variables are given in **Table 2**. Regarding intercorrelations, the results revealed that FoP correlated $r = 0.78$ with daily worry (WDQ) and $r = 0.64$ with pathological worry (PSWQ). The two worry measures correlated $r = 0.58$ (all correlations $p < 0.001$).

Patients with clinical FoP ($n = 66$) showed significantly higher ($p < .001$) daily worry (**Figure 1**) as well as pathological worry (**Figure 2**) [see also **Supplementary Material 1**].

Multiple Linear Regression

We conducted a hierarchical multiple linear regression analysis to identify the determinants of FoP. The sociodemographic data were entered in the first step. The results showed that younger age and lower educational level were significantly associated with FoP. While age remained a significant determinant until the last step, the educational level lost significance in the third step when variables representing psychological distress were entered. Regarding clinical variables, which were entered in the second step, the results showed that only lower functional status was significantly associated with FoP. However, this association became non-significant in the third step. In the third step, depressive, anxiety, and somatic symptoms showed a significant association with FoP.

Finally, in the last step, daily worry and pathological worry were entered into the regression. Controlling for sociodemographic, clinical, and mental health variables, both daily worry and pathological worry were independently associated with FoP. In fact, the two worry variables showed the highest beta weights of all variables, with daily worry being most strongly associated with FoP ($\beta = 0.514$, $p < 0.001$). The final regression model revealed that younger age, current partnership,

TABLE 1 | Sociodemographic and clinical characteristics ($N = 328$).

	M	SD	n	%
Age, years ($n = 328$)	58.5	12.8		
Sex ($n = 328$)				
Men			212	64.6
Women			116	35.4
Marital status ($n = 328$)				
Single			54	16.5
Married			222	67.7
Divorced			35	10.7
Widowed			17	5.2
Current partnership ($n = 326$)				
Yes, living together			246	75.5
Yes, living apart			28	8.6
None			52	16.0
Children ($n = 326$)				
Yes			237	72.7
None			89	27.3
Educational status ($n = 324$)				
Elementary school			121	37.3
Secondary school/junior high			69	21.3
High school			118	36.4
Other			16	4.9
Employment status ($n = 327$)				
Full-time			94	28.7
Less than full-time			27	8.2
Unemployed			16	4.9
Homemaker			13	4.0
Retired/Disability pension			141	43.1
Other			36	11.0
Net household income ($n = 251$)				
< 1000 Euro			32	12.8
< 2000 Euro			68	27.1
< 3500 Euro			94	37.4
> 3500 Euro			57	22.7
Subjective economic situation ($n = 324$)				
Very good			34	10.5
Good			143	44.1
Satisfactory			123	38.0
Not so good			15	4.6
Poor			9	2.8
Cancer site ($n = 328$)				
Gastrointestinal			199	60.7
Hematological			129	39.3
Disease status ($n = 326$)				
First occurrence			225	69.0
Second/third primary cancer			33	10.1
Recurrence			39	12.0
Complete/partial remission			23	7.0
Unknown			6	1.8
Treatment intent ($n = 282$)				
Curative			214	75.9
Palliative			68	24.1

(Continued)

TABLE 1 | Continued

	M	SD	n	%
Current treatments ($n = 327$)				
Surgery			138	42.2
Chemotherapy			110	33.6
Immunotherapy			1	0.3
Stem cell transplantation			20	6.1
In planning			19	5.8
Aftercare			14	4.3
Other			25	7.6
Duration of the disease[a], months ($n = 315$)	27.1	56.8		
Functional status (KPS[b]) ($n = 328$)				
≤ 60			22	6.7
≤ 70			48	14.6
≤ 80			52	15.9
≤ 90			90	27.4
> 90			116	35.3
Comorbid chronic condition[c] ($n = 315$)				
Yes			93	29.5
None			222	70.5
Anxiety disorder ($n = 328$)				
Yes			60	18.3
None			268	81.7

Data may not be summed to the full sample size due to missing data.
[a]Duration since first cancer diagnosis.
[b]KPS, Karnofsky Performance Status.
[c]This category includes the following diagnoses: asthma, bipolar disorder (former episode), chronic kidney disease, chronic obstructive pulmonary disease, coronary heart disease, Crohn's disease, depression (current and former episode), diabetes mellitus, epilepsy, fibromyalgia, HIV, hyperthyroidism, liver cirrhosis, multiple sclerosis, Parkinson's disease, rheumatoid arthritis, and ulcerative colitis.

TABLE 2 | Mean (M) and standard deviation (SD) of study variables.

Variable	M	SD
Fear of progression (FoP-Q) ($n = 328$)	7.1	2.6
Daily worry (WDQ) ($n = 318$)	13.1	14.8
Pathological worry (PSWQ) ($n = 312$)	37.4	11.3
Depressive symptoms (PHQ-2) ($n = 327$)	1.3	1.6
Anxiety symptoms (GAD-2) ($n = 327$)	1.6	1.6
Somatic symptoms (PHQ-15) ($n = 327$)	8.2	5.5

FoP-Q, Fear of Progression Questionnaire; WDQ, Worry Domains Questionnaire; PSWQ, Penn State Worry Questionnaire; PHQ-2, Patient Health Questionnaire-Depressive Symptoms; GAD-2, Generalized Anxiety Disorder-2; PHQ-15, Patient Health Questionnaire-Somatic Symptoms.

higher anxiety, depressive, and somatic symptoms, absence of an anxiety disorder, and higher worry were significant determinants of FoP (**Table 3**). The final regression model explained 74% of the variance.

DISCUSSION

Patients who suffer from a chronic disease often experience fears that relate to the illness and its biopsychosocial consequences (Berg et al., 2011; Lebel et al., 2020). FoP and FCR represent adequate psychological responses to real threats and risks of the cancer experience that, nonetheless, can become dysfunctional (Simonelli et al., 2017; Dinkel and Herschbach, 2018; Lebel et al., 2020). The main feature of current conceptualizations and definitions of FCR/FoP is worry (Fardell et al., 2016; Mutsaers et al., 2016, 2020). Worry is common in daily life, but it can also occur at degrees that can be characterized as pathological (Golden et al., 2011). Interestingly, these different lines of research—psycho-oncology on the one hand, and clinical psychology and psychopathology on the other hand—have not met with regard to worry and FCR/FoP. In this study, we aimed at connecting these different lines of research, investigating whether daily worry and pathological worry would be independently associated with FoP.

As a main result, our analysis revealed that daily worry and pathological worry were the most relevant determinants of FoP, controlling for sociodemographic variables, clinical characteristics, and symptom burden, i.e., patients with cancer who indicated a high level of worry in a measure designed for the assessment of non-pathological worry and who indicated to experience a high amount of excessive and uncontrollable worry reported higher levels of FoP. These results suggest that patients who are characterized by a general tendency to worry are more prone to experience FoP when diagnosed with cancer. Clearly, the cross-sectional nature of this study precludes strong inferences regarding causal or longitudinal associations. Thus, whether a general tendency to worry, in fact, represents an independent vulnerability factor for experiencing FCR/FoP needs to be investigated in a longitudinal research design. Nonetheless, these results fit very well with the current conceptualizations of FCR, which include meta-cognitive beliefs about worry (Fardell et al., 2016; Lebel et al., 2018) and a cognitive-attentional syndrome, characterized by worry, rumination, and attentional bias to threat-related information (Fardell et al., 2016).

In an attempt to derive not only at a conceptualization of FCR but also on a theoretical model of anxiety in the context of cancer, Curran et al. (2017) reviewed the literature and developed a model quite similar to that by Fardell et al. (2016), which relates to FCR. Curran et al. (2020) tested some of the assumptions of this general model of anxiety in patients with cancer with regard to FoP as an outcome. In this cross-sectional study with 211 patients with cancer, the authors investigated the association of rumination, assessed by a measure of transdiagnostic repetitive thinking, with FoP. These two variables correlated $r = 0.60$, but rumination—or repetitive thinking—did not emerge as an independent determinant of FoP after death anxiety, intrusions, and threat appraisal had been entered into the regression. Worry and rumination—or repetitive thinking—share relevant features, thus both this study as well as the study by Curran et al. (2020) underscore the strong association between repetitive cognitive processes and the experience of FoP. In this study, worry emerged as the most relevant determinant of FoP. However, in contrast to the study by Curran et al. (2020), we did not investigate the role of death anxiety, intrusions, or threat appraisal. Thus, it remains to be shown whether worry will be an independent vulnerability factor for FCR/FoP.

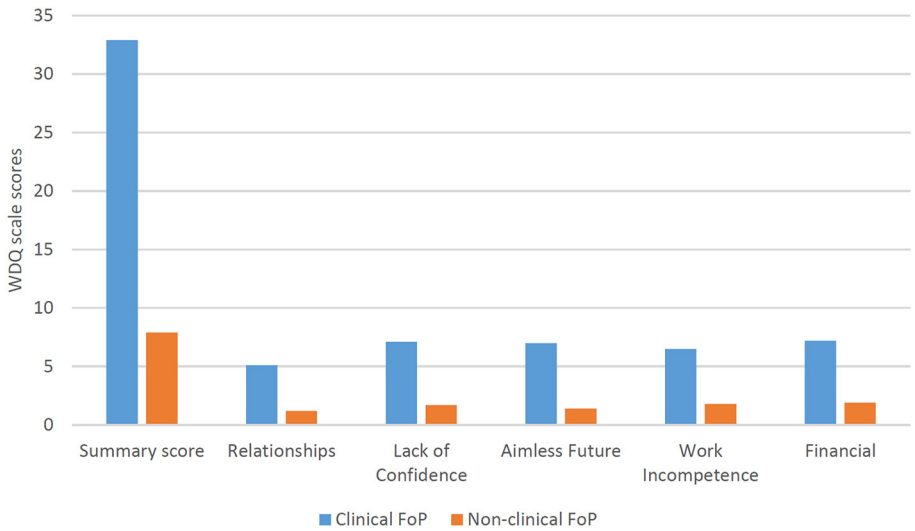

FIGURE 1 | Differences in the scales of the Worry Domains Questionnaire between patients with cancer with clinical versus non-clinical fear of progression (FoP-Q; cut off: 80th percentile).

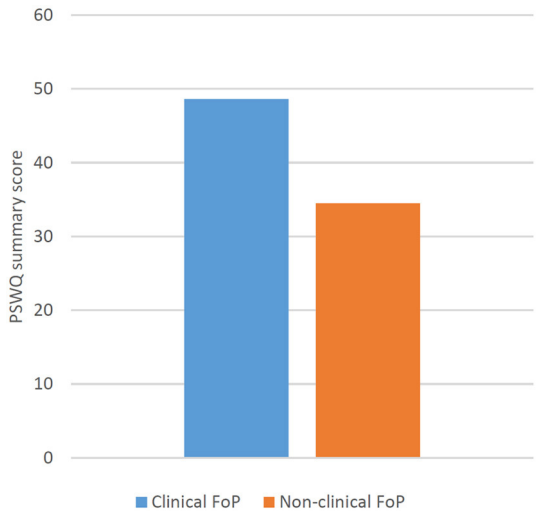

FIGURE 2 | Differences in the summary scale score of the Penn State Worry Questionnaire between patients with cancer with clinical versus non-clinical FoP (FoP-Q; cut off: 80th percentile).

According to several reviews of FCR/FoP (Crist and Grunfeld, 2013; Simard et al., 2013; Dinkel and Herschbach, 2018; Lim and Humphris, 2020), lower age and higher somatic symptom burden represent the most consistent predictors of higher levels of FCR/FoP. While the effect of age was replicated in this study, the association between somatic symptoms and FoP disappeared after the inclusion of worry. In accordance with available evidence (Simard et al., 2013), depressive and anxiety symptoms were also significantly associated with FoP in this study. Likewise, in accordance with other studies (Simard et al., 2013; Smith et al., 2018), clinical characteristics were not independently associated with FoP. Interestingly, we found that the absence of an anxiety disorder represented a determinant of FoP. However, this effect was quite weak ($\beta = -0.08$), and the significance of this finding remains unclear.

Finally, our results also support some current psycho-oncological interventions addressing FCR/FoP. A recent systematic review and meta-analysis showed that psycho-oncological interventions are effective in reducing FCR/FoP (Tauber et al., 2019). This meta-analysis also revealed that contemporary cognitive-behavioral therapies, i.e., approaches that focus on cognitive processes—like worry or rumination—were more effective, at least in the short run, than traditional cognitive-behavioral approaches, defined as those interventions that focus primarily on the content of cognition. This view is supported by the independent association between pathological worry and FoP, as we assessed pathological worry with a content-free measure that focused on the intensity and perceived uncontrollability of worry. However, our results also support approaches focusing on the content of cognition, like our own therapeutic approach, which applies exposure-based techniques. Similar to the cognitive-behavioral approach for GAD, which focuses on the exposure of worry themes, patients with cancer are asked to vividly recount their worries and to work through a worst-case scenario (Dinkel and Herschbach, 2018). This approach has proven feasible and effective in reducing FoP of patients with cancer (Herschbach et al., 2010; Dinkel et al., 2012; Rudolph et al., 2018) and is supported by the independent association between our measures of daily worry, which focuses on the content of worrying thoughts.

This study has some strengths, such as the detailed assessment of worries in patients with cancer, the reasonable sample size, and the inclusion of a set of covariates. But, clearly, it also has some limitations. First, the cross-sectional design precludes inferences about longitudinal associations between worry and FoP. Then,

TABLE 3 | Results of the hierarchical multiple regression analysis predicting fear of progression (FoP-Q) ($n = 281$).

Step	Variable	B	SE B	Beta	*p*	Adj. R^2	ΔR^2	p ΔR^2
1						0.093		
	Age	−0.053	0.011	−0.268	< 0.001			
	Gender	0.429	0.305	0.081	0.161			
	Current partnership	0.700	0.403	0.100	0.084			
	Educational level	−0.723	0.300	−0.137	0.017			
2						0.119	0.026	0.026
	Age	−0.063	0.013	−0.319	<0.001			
	Gender	0.403	0.306	0.076	0.189			
	Current partnership	0.788	0.407	0.112	0.054			
	Educational level	−0.758	0.298	−0.144	0.012			
	Cancer site	0.147	0.310	0.028	0.636			
	Disease status	−0.038	0.352	−0.007	0.915			
	Duration of the disease	0.003	0.003	0.058	0.360			
	Functional status	−0.040	0.012	−0.198	0.001			
	Comorbidity	0.004	0.348	0.001	0.990			
3						0.467	0.348	<0.001
	Age	−0.045	0.010	−0.228	<0.001			
	Gender	−0.119	0.242	−0.023	0.621			
	Current partnership	0.863	0.322	0.123	0.008			
	Educational level	−0.249	0.236	−0.047	0.293			
	Cancer site	0.106	0.242	0.021	0.661			
	Disease status	0.082	0.276	0.015	0.767			
	Duration of the disease	0.004	0.002	0.082	0.101			
	Functional status	0.005	0.010	0.024	0.632			
	Comorbidity	−0.222	0.273	−0.038	0.417			
	Depressive symptoms	0.388	0.101	0.244	<0.001			
	Anxiety symptoms	0.467	0.103	0.294	<0.001			
	Somatic symptoms	0.099	0.026	0.215	<0.001			
	Anxiety disorder	0.176	0.305	0.027	0.564			
4						0.739	0.272	<0.001
	Age	−0.022	0.007	−0.109	0.003			
	Gender	0.029	0.170	0.005	0.865			
	Current partnership	0.782	0.226	0.112	0.001			
	Educational level	−0.184	0.166	−0.035	0.268			
	Cancer site	−0.093	0.170	−0.018	0.584			
	Disease status	0.227	0.193	0.041	0.240			
	Duration of the disease	0.003	0.002	0.062	0.073			
	Functional status	−0.004	0.007	−0.020	0.562			
	Comorbidity	−0.193	0.191	−0.033	0.313			
	Depressive symptoms	0.203	0.072	0.127	0.005			
	Anxiety symptoms	0.208	0.076	0.131	0.007			
	Somatic symptoms	0.203	0.072	0.061	0.129			
	Anxiety disorder	−0.515	0.218	−0.080	0.019			
	Daily worry	0.088	0.007	0.514	<0.001			
	Pathological worry	0.049	0.010	0.221	<0.001			

Coding of dichotomous variables: gender: men = 0; current partnership: none = 0; educational level: lower = 0; cancer site: gastrointestinal = 0; comorbidity: none = 0; disease status: first occurrence = 0; anxiety disorder: none = 0.

there is a sampling bias as patients who declined participation were older than those who agreed to take part. Furthermore, we did not assess other psychological variables that have proven relevant as possible control variables, especially those that are regarded as important in current theoretical conceptualizations of FCR/FoP, e.g., meta-cognitive beliefs. Moreover, we did not

assess the whole spectrum of mental disorders but restricted our assessment on the anxiety disorders. Finally, there might be a bias due to shared method variance. We applied three self-reporting measures focusing on different aspects of worry that were moderately to highly intercorrelated. Thus, the results of this study should be replicated using different assessment approaches.

CONCLUSION

This study has shown that worry represents an independent determinant of FoP. As such, the results support current theoretical conceptualizations of non-clinical and clinical FCR/FoP (Fardell et al., 2016). However, these results also bring up the question of whether FoP is an expression of a general tendency to worry. Thus, associations between repetitive cognitive processes and FCR/FoP should be investigated further in future studies.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because participants did not provide consent for public availability of the data. Requests to access the datasets should be directed to Andreas Dinkel, a.dinkel@tum.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of the Faculty of Medicine, Technical University of Munich. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AD designed the study. KK was responsible for data acquisition. KK and BM-M prepared and analyzed the data. AD wrote the first draft. All authors contributed significantly to the interpretation of the data and the final version of the manuscript and gave final approval of the version to be published.

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SUPPLEMENTARY MATERIAL

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Interpretation Bias in Breast Cancer Survivors Experiencing Fear of Cancer Recurrence

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Introduction: Fear of cancer recurrence (FCR) is a prevalent and persistent challenge that many cancer survivors endure. While the role of interpretation bias, a tendency to perceive ambiguous situations as threatening, has been established in the onset and maintenance of FCR, few studies have examined cancer-related interpretation bias specifically. Grounded in the cognitive formulation of FCR, the current study aimed to fill this gap by investigating the relationship between cancer-related interpretation bias, FCR, and somatic symptoms, and examining whether bias mediates the relationship between somatic symptoms and FCR.

Materials and Methods: This study used baseline data from a randomized controlled trial of a cognitive bias modification intervention. Breast cancer survivors (n = 110) provided demographic and medical background information as well as self-report measures of FCR and severity of somatic symptoms. A computer-based assessment of interpretation bias was used to measure cancer-related interpretation bias on several bias indices: percentage of cancer-related threat endorsement, and percentage of benign endorsement; mean reaction time (RT) for threat, and mean RT for benign endorsement.

Results: Higher threat endorsement was linked to higher Overall Fear and emerged as a mediator of the relationship between overall somatic symptoms and Overall Fear. We also found that older age was related to longer benign endorsement RT.

Conclusion: This study contributes understanding of factors related to cancer-related interpretation bias and provides evidence that bias may influence the relationship between somatic symptoms and FCR in cancer survivors.

Keywords: fear of cancer recurrence, interpretation bias, somatic symptoms, breast cancer survivors, mediation

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INTRODUCTION

Fear of cancer recurrence (FCR) is a prevalent problem in cancer survivors. With estimated rates ranging from 39 to 97%, cancer survivors have identified managing FCR as their top unmet need (Simard et al., 2013). Some degree of FCR is adaptive for managing medical follow-ups and motivating health-promoting behaviors (Simonelli et al., 2017), but excessive FCR can compromise

quality of life through psychological distress, functional impairments (Simard and Savard, 2015), and maladaptive behaviors, including hypervigilance for symptoms of recurrence in the future.

Assessment of FCR has posed challenges. Although there exist over 30 instruments measuring FCR, many provide no psychometric data, and few offer clinical cut-off scores to identify those most in need of intervention (Smith et al., 2018). Assessment is further complicated by the multidimensional nature of FCR, which incorporates several factors including triggers activating FCR, the severity of intrusive thoughts surrounding FCR, psychological distress, coping strategies to manage FCR, functioning impairments, insight regarding the intensity of FCR, and reassurance behaviors (Simard and Savard, 2009). Despite a growing body of research on factors associated with FCR, few correlates have been identified as consistent and "strong" predictors (Humphris and Ozakinci, 2008). Thus, identifying common contributors underlying the etiology and maintenance of FCR, empirically validating their relationship with FCR, and identifying potential intervention targets remain research priorities (Lebel et al., 2017).

One known potent trigger of FCR is interpreting physical symptoms as potential indicators of cancer recurrence (Crist and Grunfeld, 2013; Hall et al., 2019). Cognitive formulations of illness representation suggest that if appraised as potential symptoms of recurrent disease, benign somatic experiences can elicit a fear response (Easterling and Leventhal, 1989; Lee-Jones et al., 1997; Fardell et al., 2016). This is consistent with cognitive theories of anxiety, which propose that biased information processing, such as interpreting ambiguous information as threatening can contribute to elevated anxiety (Ouimet et al., 2009; Chen et al., 2020). Interpretation bias involves a tendency to interpret external or internal information in a negative manner (see Hirsch et al., 2016 for a review) and has been implicated in health anxiety (Antognelli et al., 2020), pain (Heathcote et al., 2016), chronic fatigue syndrome (Hughes et al., 2016), cancer-related fear (Miles et al., 2009), distress (Lam et al., 2018), and FCR (Lichtenthal et al., 2017).

This study was grounded in a similar cognitive formulation specific to FCR and its antecedents (Lee-Jones et al., 1997). The cognitive formulation of FCR suggests that if external (e.g., follow-up oncology appointments) or internal cues (e.g., somatic symptoms) are appraised as potentially threating, corresponding negative cognitions can result in elevated FCR. Increased cancer fears can, in turn, lead to maladaptive behaviors (e.g., excessive body checking) and greater health anxiety, exacerbating the tendency to interpret environmental and internal cues as cancer-related (i.e., cancer-related interpretation bias) and ultimately perpetuating a cycle of maladaptive thoughts and behaviors and emotional distress.

Because interpretation bias has been linked to the development and exacerbation of impairing anxiety symptoms, a broad range of experimental paradigms have been developed to explore (Schoth and Liossi, 2017) and modify (Beard and Peckham, 2020) interpretation bias, including the Word Sentence Association Paradigm (WSAP; Beard and Amir, 2009; Gonsalves et al., 2019), a reliable and valid assessment of interpretation bias across a variety of populations. Our team utilized WSAP to assess changes in interpretation bias in a randomized clinical trial (RCT) of a cognitive bias modification (CBM) intervention to target FCR in breast cancer survivors.

While this intervention resulted in significant reduction in cancer-related interpretation bias and FCR-related health worries measured post-intervention and at a 3-month follow-up (Lichtenthal et al., 2017), the presumption that interpretation bias, FCR, and somatic symptoms were correlated at baseline was not established. Endorsement of a greater number of physical symptoms has been associated with greater FCR (Hall et al., 2019), but the mediating role of implicit cognitive processes in this relationship has not yet been investigated. Finally, although few correlates have emerged as consistent predictors of FCR, there is evidence that certain demographic and medical characteristics including disease stage, time since treatment completion, age, being a parent, and having racially/ethnically minoritized status may be linked to FCR (Crist and Grunfeld, 2013; Simard et al., 2013). However, the relationship between these characteristics and cancer-related interpretation bias has not been thoroughly examined and warrants attention.

Current Study

The first aim of this study was to examine theoretically proposed relationships between interpretation bias, FCR, and somatic symptoms (Lee-Jones et al., 1997). We hypothesized that interpretation bias would be related to more FCR, and overall problematic somatic symptoms. Further, given the link between somatic symptoms and FCR, along with presumptive links between interpretation bias and both these constructs based on the cognitive formulation of FCR, the second goal of this study was to examine interpretation bias as a mediator of the association between somatic symptoms and FCR. We hypothesized that interpretation bias would mediate the relationship between somatic symptoms and FCR. A third exploratory aim was to examine associations between demographic and medical variables linked to FCR in relation to cancer-related interpretation bias to elucidate the role of these factors in cancer-related cognitions and to inform whether these variables fit in the cognitive formulation of FCR.

MATERIALS AND METHODS

Participants

The current investigation utilized baseline data collected from October 2012 through November 2015 as a part of an RCT of a CBM intervention (Lichtenthal et al., 2017). Participants (n = 110) were English-speaking women (self-identified) ages 18 or older who were diagnosed with stages 0–III breast cancer, had no history of recurrence or metastases, and had completed active treatment for their breast cancer. Women were eligible if they scored at least a "3" on the Concerns About Recurrence Scale (CARS) Overall Fear Index (Vickberg, 2003), suggesting at least moderate FCR. Following Institutional Review Board approval, patients from a large urban cancer center were recruited through in-clinic approaches, mailed study

TABLE 1 | Baseline correlations between cancer-related interpretation bias and psychological and somatic factors.

	Rate of threat endorsement	Threat endorsement RT	Rate of benign endorsement	Benign endorsement RT
Fear of recurrence (CARS)				
CARS Overall Fear	$r = 0.30^{**}$	$r = -0.16$	$r = 0.08$	$r = -0.08$
Physical well-being (QOL-CS)				
Overall problematic somatic symptoms	$r = -0.29^{**}$	$r = 0.09$	$r = -0.17$	$r = 0.09$

Unadjusted findings are reported.
$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

invitations and telephone calls. Breast cancer survivors were screened for eligibility, and informed consent was obtained from those interested in participation. Participants received a total of $50 compensation for completion of the study. The current paper is a secondary examination of baseline characteristics reported by the trial participants.

Measures

Interpretation Bias

The WSAP assessment in the current study consisted of cancer-specific stimuli given the goal of reducing cancer-related interpretation bias. The WSAP assessment required participants to determine whether benign or cancer-related words and sentences describing ambiguous situations were related. Each trial began with a fixation cross presented on a computer screen for 500 milliseconds (ms) to alert participants about the start. Subsequently, the fixation cross disappeared and a benign (e.g., "Sleep") or threat (e.g., "Cancer") word was presented on the screen for 500 ms. When the word disappeared, an ambiguous sentence appeared on the screen (e.g., "You have been tired lately"). Participants were then prompted to indicate whether they thought that the word and sentence were related (by pressing number "1" on the computer keyboard) or not related (by pressing number "3"). The next trial (i.e., fixation cross, a cancer-related word or benign word, an ambiguous sentence) appeared immediately after for a total of 118 trials. As done in prior studies using the WSAP, we used four separate interpretation bias metrics to assess the extent of interpretation bias toward cancer-related threat. We calculated (1) the percentage of cancer-related threat endorsement (i.e., "Rate of Threat Endorsement"), (2) the percentage of benign interpretation endorsement (i.e., "Rate of Benign Endorsement"), (3) the mean reaction time (RT) for threat endorsement, and (4) the mean RT for benign endorsement. Consistent with the WSAP literature (Beard and Amir, 2009), higher threat endorsement rates and lower benign endorsement rates were believed to indicate more interpretation bias. Similarly, faster RT for threat endorsement and slower RT for benign endorsement were theorized to indicate more interpretation bias.

Fear of Cancer Recurrence

Fear of cancer recurrence was measured using the CARS (Vickberg, 2003), a widely used, reliable and valid 30-item self-report instrument that that assesses the extent and nature of women's FCR across five domains. Subscales include Overall Fear – assessing frequency/intensity of FCR using four questions (e.g., "How much time do you spend thinking about the possibility that your breast cancer could recur?") with a response scale ranging from 1 (*I don't think about it at all*) to 6 (*I think about it all the time*), Health Worries (11 items; e.g., "I worry that a recurrence of breast cancer would threaten my physical health."), Womanhood Worries (seven items; e.g., "I worry that a recurrence of breast cancer would interfere with my sense of sexuality."), Role Worries (six items; e.g., "I worry that a recurrence of breast cancer would keep me from fulfilling my responsibilities [in my job or at home.]"), and Death Worries (two items; e.g., "I worry that a recurrence of breast cancer would cause me to die"). Final scores were computed by averaging responses. We used the Overall Fear score in main analyses, and the remaining subscale scores in *post hoc* analyses.

Overall Somatic Symptoms

Overall somatic symptoms were assessed using eight questions from the Physical Well-Being subscale of the quality of life-cancer survivors measure (QOL-CS; Ferrell et al., 1995). QOL-CS is a 41-item valid and reliable instrument (Pearce et al., 2008) designed to assess somatic, psychological, social, and spiritual well-being in cancer survivors. The Physical Well-Being subscale assessed the extent to which quality of life was affected by the cancer experience across eight different somatic symptoms: fatigue, appetite changes, aches or pain, sleep changes, weight gain, vaginal dryness/menopausal symptoms, menstrual changes or fertility, and physical health. The response scale ranges from 0 (*no problem*) to 10 (severe problem) and was recoded so that a lower score would represent a stronger severity of the symptom (indicating lower quality of life) in any of the above-named domains. We used the *overall problematic somatic symptoms* score in main analyses, and specific symptoms scores in *post hoc* analyses.

DATA ANALYSIS

To examine associations between cancer-related interpretation bias metrics, Overall Fear, and overall problematic somatic symptoms (aim 1), we calculated a series of Pearson's correlations. Next, we explored cancer-related interpretation bias as a mediator of the link between somatic symptom score and the Overall Fear score (aim 2). The mediation model was identified based on significant associations between a predictor (i.e., overall problematic somatic symptoms score) and a mediator (i.e., an index of cancer-related interpretation bias), and an outcome (i.e., Overall Fear score), and a predictor and an outcome.

To test mediation, we used the PROCESS macro for SPSS (Hayes, 2013), which calculates 95% bias-corrected confidence intervals of indirect effects using 1000 bootstrap samples. To test exploratory relationships between medical and demographic factors and cancer-related interpretation bias (exploratory aim 3), we used independent samples *t*-tests for associations between categorical and continuous variables and Pearson's correlations for associations between continuous variables. To determine the strength of the associations tested for each of these three aims, we calculated effect sizes (i.e., correlation coefficient (r) for Pearson's correlations, Cohen's d for t-tests, and standardized B's for mediation). To account for multiple comparisons, we used the Benjamini–Hochberg (Benjamini and Hochberg, 1995) procedure ($Q = 0.05$) to adjust p-values for all examined associations, including those examined in mediational models. Finally, we conducted *post hoc* analyses to examine relationships between the remaining subscales of the CARS scale, and specific symptoms of the QOL-CS scale, and all indices of cancer-related interpretation bias.

RESULTS

Participant Characteristics

Participants were 55 years old on average (SD = 8.10), highly educated (51% had more than a college degree) and mostly White, non-Latinx (74%). A detailed description of the demographic characteristics of participants is included in the publication of the RCT findings (Lichtenthal et al., 2017).

Associations Between Cancer-Related Interpretation Bias and Fear of Cancer Recurrence

Greater rates of threat endorsement were associated with higher Overall Fear [$r(92) = 0.30$, $p = 0.003$]. Associations between Overall Fear and threat endorsement RT, benign endorsement, and benign endorsement RT were non-significant. See **Table 1** for more details. *Post hoc* analyses revealed that higher scores on Health Worries and Role Worries subscales were each associated with greater rates of threat endorsement ($p < 0.01$). No other indices of interpretation bias were related to FCR.

Associations Between Overall Problematic Somatic Symptoms and Cancer-Related Interpretation Bias

Greater rates of threat endorsement were associated with more overall problematic somatic symptoms [$r(92) = -0.29$, $p = 0.005$]. Associations between the remaining indices of bias and overall problematic symptoms were not significant ($p > 0.05$). See **Table 1** for additional details. Investigating associations between somatic symptoms rated as problematic and cancer-related interpretation bias showed that ratings of fatigue ($p < 0.01$), sleep changes ($p < 0.001$), menstrual changes or fertility problems ($p < 0.05$), and poorer physical health ($p < 0.05$) were all associated with higher rates of threat endorsement. *Post hoc* analyses revealed that ratings of fatigue ($p < 0.01$), sleep changes

TABLE 2 | Baseline associations between cancer-related interpretation bias and medical and demographic characteristics.

	Rate of threat endorsement (%)			Threat endorsement RT (ms)			Rate of benign endorsement (%)			Benign endorsement RT		
Variable (*n*)	***M* (SD)[a]**	***t***	**Effect size[b,c]**	***M* (SD)[d]**	***t***	**Effect size[b,c]**	***M* (SD)[e]**	***t***	**Effect size[b,c]**	***M* (SD)[f]**	***t***	**Effect size[b,c]**
Stage												
0 and 1 (47)	51.21 (16.00)	$t(92) = -1.24$	$d = 0.26$	1529 (602)	$t(92) = -0.17$	$d = 0.03$	72.48 (12.26)	$t(92) = -1.03$	$d = 0.21$	1369 (477)	$t(92) = -0.45$	$d = 0.09$
2 and 3 (47)	56.07 (21.50)			1551 (671)			75.51 (16.01)			1416 (550)		
Minoritized status												
White, not Hispanic (68)	51.43 (19.98)	$t(90) = -1.92$	$d = 0.46$	1532 (627)	$t(90) = 0.16$	$d = 0.04$	72.89 (15.24)	$t(90) = -1.09$	$d = 0.26$	1404 (502)	$t(90) = 0.61$	$d = 0.15$
Other (24)	60.07 (15.38)			1508 (657)			76.62 (11.46)			1329 (555)		
Children												
No (26)	54.32 (23.92)	$t(91) = 0.28$	$d = 0.05$	1527 (676)	$t(91) = -0.20$	$d = 0.05$	69.22 (20.03)	$t(91) = -1.99^{*}$	$d = 0.50$	1372 (535)	$t(91) = -0.29$	$d = 0.07$
Yes (67)	53.08 (16.91)			1557 (619)			75.71 (11.01)			1407 (508)		
Time since treatment	–	–	$r = -0.07$	–	–	$r = 0.10$	–	–	$r = -0.05$	–	$r = 0.21^{*}$	–
Age	–	–	$r = 00$	–	–	$r = 0.17$	–	–	$r = -0.10$		$r = 0.29^{**}$	–

Unadjusted findings are reported. $^{*}p < 0.05$, $^{**}p < 0.01$. [a]Lower mean value represents less bias. [b]d = Cohen's d. [c]r = Pearson's correlation. [d]Higher mean value represents less bias. [e]Higher mean value represents less bias. [f]Lower mean value represents less bias.

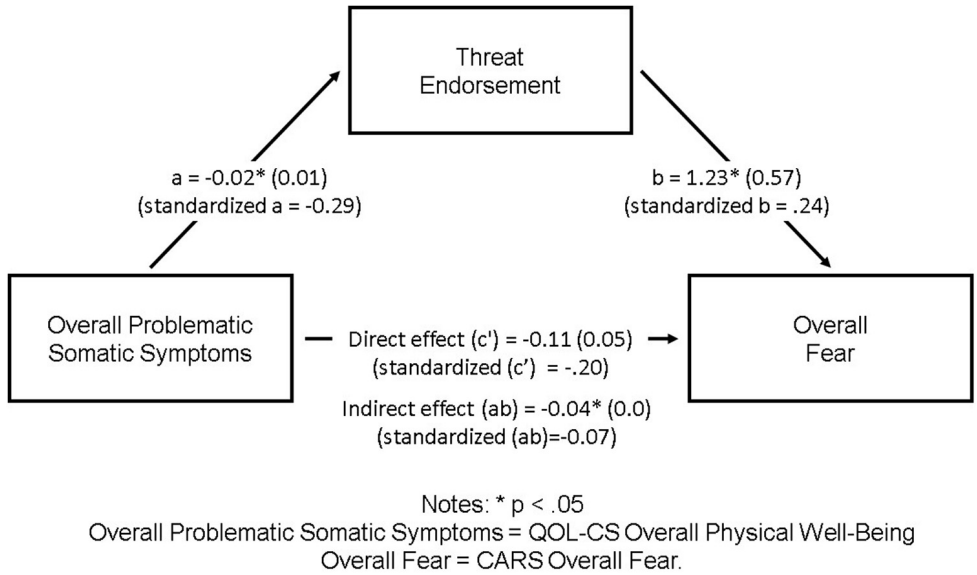

FIGURE 1 | Threat endorsement as a mediator of the association between overall problematic somatic symptoms and Overall Fear. *$p < 0.05$. Overall problematic somatic symptoms, QOL-CS overall physical well-being; Overall Fear, CARS Overall Fear.

($p < 0.001$), menstrual changes or fertility problems ($p < 0.05$), and poorer physical health ($p < 0.05$) were all associated with higher rates of threat endorsement.

Associations Between Medical and Demographic Factors and Cancer-Related Interpretation Bias

Longer benign endorsement RT was associated with greater time since cancer treatment completion [$r(92) = 0.21$, $p = 0.041$] and older age [$r(92) = 0.29$, $p = 0.005$]. We also identified higher rates of benign endorsement of [$t(91) = -1.99$, $p = 0.049$, $d = 0.50$] in participants who had at least one child. Interpretation bias was not related to other demographic or medical variables (ps > 0.05). The Benjamini–Hochberg adjustment resulted in non-significant findings (adjusted ps > 0.05) for the relationships between bias, time since treatment completion, and having at least one child. See **Table 2** for more information.

Interpretation Bias as a Mediator

Based on significant associations ($p < 0.05$) between potential predictor, mediator, and outcome variables, threat endorsement was identified as a potential mediator of the association between Overall Fear and overall problematic somatic symptoms. Specifically, more problematic somatic symptoms were related to higher threat endorsement, and higher threat endorsement was subsequently related to higher Overall Fear. See **Figure 1** for details.

DISCUSSION

The current study examined whether interpretation bias is associated with FCR, as prior research has suggested (Lee-Jones et al., 1997; Lichtenthal et al., 2017; Pradhan et al., 2021). We also examined somatic, demographic and medical correlates of cancer-related interpretation bias. In our sample of post-treatment breast cancer survivors, we found that the tendency to make threatening interpretations in the WSAP bias assessment was associated with Overall Fear, and overall problematic somatic symptoms. Mediation analyses further elucidated these links showing the mediating role of interpretation bias between overall problematic symptoms and increased FCR, which provides empirical validation of cognitive formulation of FCR (Lee-Jones et al., 1997).

Our examination of cancer-related interpretation bias and demographic and medical correlates showed that prior to p-value adjustments, age, time since treatment, and parent status were related to longer RT for benign but not threat interpretations. Breast cancer survivors who were older and those who were further out from their treatment took longer to react to benign interpretations. Although longer benign endorsement RTs are theorized to represent greater cancer-related interpretation bias, slowed processing speed can be partly a function of age-related changes in cognitive motor performance (Eckert et al., 2010) and/or cancer-related cognitive impairment (Pendergrass et al., 2018), rather than a marker of greater interpretation bias. It is also possible that those who were farther out from treatment may have developed strategies to initially avoid thinking about recurrence but that their cognitive biases can still be identified through the more implicit marker, slowed RT. Given that similar patterns did not emerge for slowed responses for threat, implies that the valence of the stimuli (i.e., neutral or threat) differentially impacts RT in people who are older or farther away from completing active treatment.

Having at least one child versus not having any, was associated with higher rates of benign endorsement. While

research on parenthood and FCR is scarce, studies generally report that cancer survivors with children endorse higher FCR (Crist and Grunfeld, 2013). However, qualitative research suggests that parenthood in non-recurrent cancer can serve as a source of meaning and strength for continuing day-to-day activities (Arès et al., 2014). Thus, although having children may overall increase FCR worries, certain social profile characteristics may buffer against select negative consequences of FCR.

Post hoc analyses showed that greater threat endorsement was linked to health and role worries, which implies that health worries and worries about functional impairment in managing important responsibilities at work or home and social realm may drive Overall Fear, and are elicited, at least partly, by threat interpretations of ambiguous cues. These links warrant more attention and further emphasize the potential importance of intervening on interpretation bias. Threat endorsement was also linked to fatigue, sleep changes, menstrual changes or fertility problems, and ratings of poorer physical health. This elucidates which somatic symptoms may be most salient for somatic vigilance, cognitive catastrophizing, and FCR.

Clinical Implications

This study contributes greater understanding of factors underlying cancer fears and is a critical step toward refining theoretical models of FCR. Given the links between interpretation bias and FCR, and that cancer-related bias can be reduced with intervention (Lichtenthal et al., 2017), these results suggest that negative cognitions may be an important intervention target in treating FCR. Mental health clinicians and health care providers should be made aware that those breast cancer survivors who tend to interpret ambiguous medical scenarios or somatic symptoms as a sign of cancer recurrence are also likely to have higher anxiety about cancer recurrence. It may be helpful to provide cancer survivors with psychoeducation about the link between cancer-related interpretation biases and FCR as well as concrete guidance about when symptoms are cause for concern. Cancer survivors walk a difficult line as they feel compelled to remain attuned to their bodies so that they can report concerning symptoms to their medical team while also wishing to interpret benign symptoms as such. Determining when to focus on their symptoms is a significant psychological challenge (Sharpe, 2019). However, given how hard it is to walk this line consciously, intervention approaches that operate on an implicit level of information processing, such as CBM, may hold promise (Lichtenthal et al., 2017).

Study Limitations and Future Research Directions

This study was limited by the relatively small, homogenous sample, which consisted of primarily White, well-educated, ciswomen (i.e., persons whose gender identity matches their sex assigned at birth) pooled *via* convenience sampling from a large urban comprehensive cancer center. Although the eligibility specificity of our study sample (i.e., early-stage breast cancer survivors) allowed for identifying FCR triggers relevant to this group, these parameters limit the study's generalizability to individuals with advanced metastatic disease, recurrent breast cancer, breast cancer survivors who identify as persons of color (Janz et al., 2011), those who do not identify as ciswomen (Kamen et al., 2015), those with less educational attainment (Koch et al., 2013), and those with different cancer types (Hall et al., 2018).

The study is also limited by the assessments of FCR and anxiety utilized. Research on FCR and its intersection with anxiety more broadly continues to evolve. Given individuals experiencing generalized anxiety disorder (GAD) are more likely to interpret ambiguous stimuli as threatening (Mathews et al., 1989), the extent to which generalized anxiety and related interpretation biases are driving our observed findings is unclear. Additional research is needed to tease apart these relationships and to further examine the relationships between medical and demographic characteristics and cancer-related interpretation bias.

Mediation was tested using a cross-sectional, small dataset rather than an adequately powered longitudinal dataset. This limits our ability to draw conclusions about temporal precedence and causality, although the observed results provide some preliminary data suggesting the relevance of interpretation bias in connecting physical symptoms with FCR and thus should be considered hypothesis-generating.

Overall, this study contributes to the literature on the role of cognitive biases, and specifically interpretation bias, on FCR. It also provided evidence that interpretation bias acts as a mediator of the relationship between internal symptoms and interpretation bias. Longitudinal investigations and studies that include external situations theorized to trigger emotional arousal (e.g., medical appointments) would provide for more robust understanding of the role of cues for interpretation bias, FCR and their relationships to profiles of cancer survivors.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of ethical and privacy concerns. Requests to access the datasets should be directed to WL, lichtenw@mskcc.org.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Memorial Sloan Kettering Cancer Center's Institutional Review Board (IRB). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MT and KR: conceptualization, project administration, database organization, methodology, statistical software, and formal analysis. GC: project coordination, database organization, methodology, and formal analysis. CB: conceptualization, investigation, supervision, data curation, methodology, and resources. CF and TC: formal analysis, statistical software, and resources. ESl: project administration, database organization, statistical software,

methodology, and formal analysis. ESc: statistical consultation. WL: conceptualization, investigation, supervision, project administration, methodology, formal analysis, and funding acquisition. All authors contributed to manuscript writing, revision, read, and approved the submitted version.

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