DISPARITIES IN CANCER PREVENTION AND EPIDEMIOLOGY

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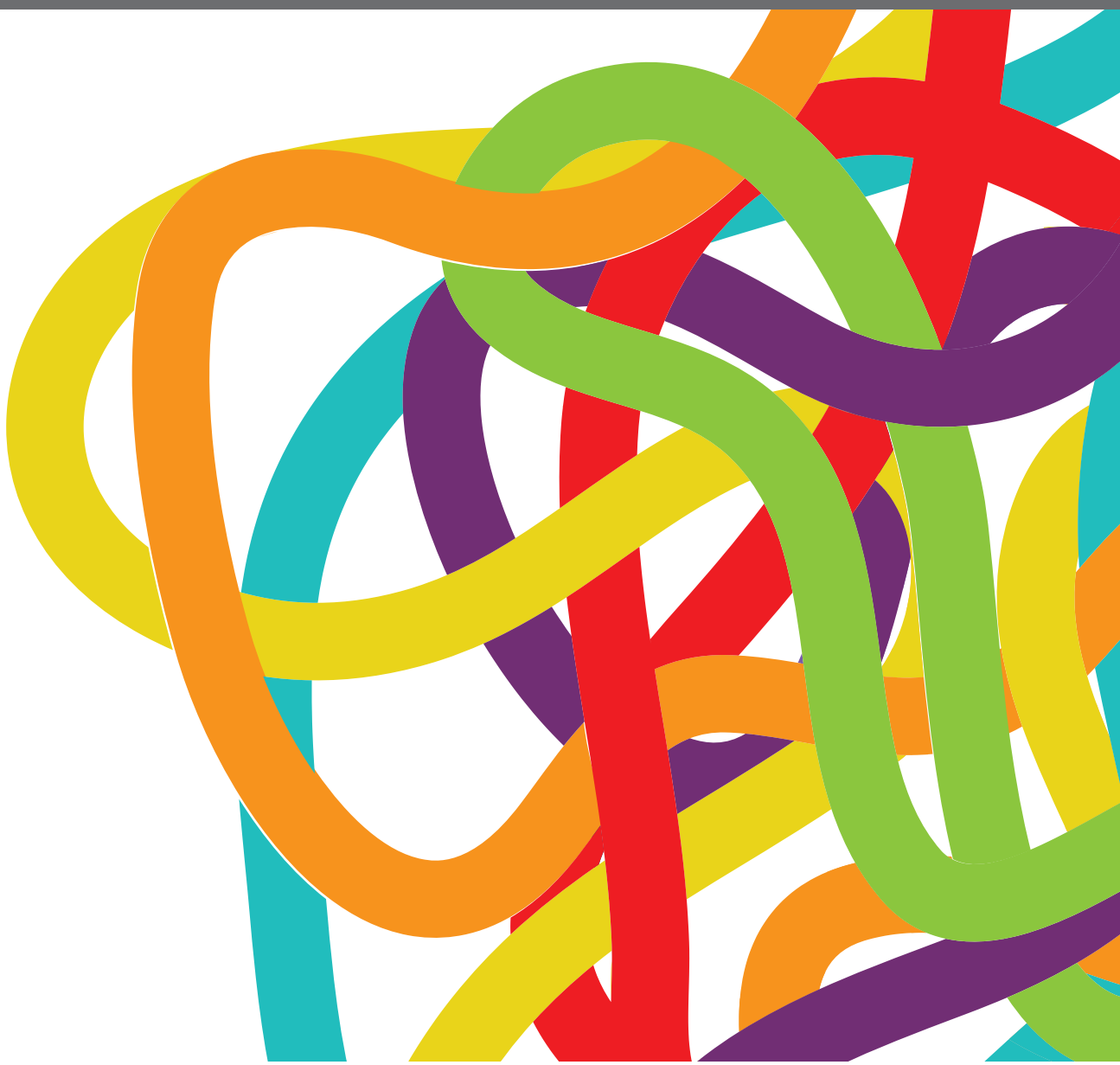

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DISPARITIES IN CANCER PREVENTION AND EPIDEMIOLOGY

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EDITORIAL
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Editorial: Disparities in Cancer Prevention and Epidemiology

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Editorial on the Research Topic

Disparities in Cancer Prevention and Epidemiology

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There were 23.6 million new cancer cases in 2019 in the world, causing 10 million deaths and 250 million disability-adjusted life years (1). The burden of the cancer has dramatically increased since 2010 such that cancer new cases, deaths, and disability-adjusted life years increased by 26.3%, 20.9%, and 16.0%, respectively, in 2019 (1). The largest percentage increases have occurred in the low and low-middle socio-demographic index quintiles, suggesting inequal distributions of cancer cases and burden in different populations. Therefore, not only we generally need to improve cancer prevention and control, but we should also aim to make efforts to address inequal burden of cancer among different groups of patients (1). To do so, Disparities in Cancer Prevention and Epidemiology research topic in Frontiers in Oncology journal attempted to understand the coordinates and causes of the existing disparities in cancer prevention and distribution in groups of patients with the goal of tackling the by means of of evidence-informed and population-specific policy making. **Table 1** provides a summary of the articles in this research topic.

This research topic was established because although there are considerable number of effective and efficient preventive strategies for many types of cancers, still some populations are severely and unequally suffering from cancer. These preventive strategies and practices consist of, but are not limited to, preventing exposure to identified carcinogens, risk factor management, vaccination against cancer, screening for subclinical incidence, and early detection of the clinically present cancers. But these programs are not equally and equitably helping patients in different populations. A part of the unequal benefit of these interventions for different groups of patients is due to patients' biophysical attributes and their differences in the likelihood of developing cancer and the prognosis (2). Nevertheless, the existing disparities among patient populations are mainly caused by inequalities in cancer prevention and care and other related aspects of healthcare rather than biological differences in patients. The followings depict the steps of care in which different factors cause the discussed disparities.

The first stage of cancer prevention is individuals becoming aware that if they belong to high-risk groups for a cancer, they need to be screened for it. Therefore, a potential point of intervention to address inequalities in cancer prevention and care is to increase public awareness of screening

TABLE 1 | Summary of studies included in Disparities in Cancer Prevention and Epidemiology.

Authors	Title	Country of Origin	Aim/Purpose	Number of Participants	Summary of Result	Interpretation
Permuth et al.	Comparison of Radiomic Features in a Diverse Cohort of Patients with Pancreatic Ductal Adenocarcinomas	USA	Investigation of disparities between African American, Non-Hispanic Whites, and Hispanic/Latinx patients with pancreatic cancer based on radiomic tumor profile retrieved from pretreatment CT images	71	Multiple textural radiomics features were identified as being independently associated with poor prognosis among African American patients with PDAC.	There are biological differences in populations with different race and ethnicity that influence their outcome of cancer.
Dasgupta et al.	Access to Aboriginal Community-Controlled Primary Health Organizations Can Explain Some of the Higher Pap Test Participation Among Aboriginal and Torres Strait Islander Women in North Queensland, Australia Paramita	Australia	Investigation of regional differences in the utilization of ACCHO services for cervical screening, as well as variations in screening participation among Aboriginal and Torres Strait Islander women	1,107,233	Aboriginal and Torres Strait Islander women in North Queensland had a higher likelihood of being screened at ACCHOs than women in the rest of Queensland, adjusted for age and area.	Facilitating access to health services reduce regional disparities for cancer screening programs.
Petrick et al.	Racial Disparities and Sex Differences in Early- and Late-Onset Colorectal Cancer Incidence, 2001–2018	USA	Assessing early- and late-onset Colorectal Cancer incidence rates in the US	2,585,621	Blacks and American Indians/ Alaska Natives had the greatest incidence of both early and late-onset Colorectal Cancer. Early-onset Colorectal Cancers were stable in terms of incidence, though neuroendocrine tumors were on the rise. Due to rising rates among Whites, the early-onset Colorectal Cancer difference between Blacks and Whites had narrowed.	Racial disparity in cancer may be rooted in inequality of health care administration policies, social determinants of health, and structural racism.
Jung et al.	Synergistic Effects of Genetic Variants of Glucose Homeostasis and Lifelong Exposures to Cigarette Smoking, Female Hormones, and Dietary Fat Intake on Primary Colorectal Cancer Development in African and Hispanic/Latino American Women	USA	Genomic assessment of insulin resistance as a key biologic mechanism underlying Colorectal Cancer carcinogenesis due to obesity	6,678	Intake of dietary polyunsaturated fatty acids and long-term exposure to female hormones may be important factors in mediating the racial gap in Colorectal Cancer incidence between African American and Hispanic American women.	Differences in modifiable and non-modifiable risk factors of cancers, such as diet, biological, and genetic characteristics of patients, might cause and increase disparities in burden of cancer if they are not addressed in educational and screening programs.
Hamdi et al.	Cancer in Africa: The Untold Story	USA	Identifying the most promising African preventative and treatment approaches	GLOBOCAN report	Based on the Human Development Index and the availability of medical equipment, different regions of Africa had different patterns of cancer incidence and mortality rates.	Paucity of facilities or screening programs cause cancer disparities in different African regions.
Wallace et al.	Preinvasive Colorectal Lesions of African Americans Display an Immunosuppressive Signature Compared to Caucasian Americans	USA	Investigation of possible racially different immunological markers in the early phases of Colorectal Cancer	95	African Americans compared to Caucasian Americans had a lower effector response capacity and an immunosuppressive ('cold') tumor environment.	Inherited carcinogenesis risk factors must be considered in screening program designing.
Mongiovi et al.	Genetic Variants in COX2 and ALOX Genes and Breast Cancer Risk in White	USA	Examining the links between COX2 and three ALOX gene variations and the risk of Breast Cancer in White and Black women	2,574	Variations in the COX2 and ALOX genes were associated with Breast Cancer and varied across White and Black women in subgroups based on their	Genetic differences must be considered in cancer preventive program.

(Continued)

TABLE 1 | Continued

Authors	Title	Country of Origin	Aim/Purpose	Number of Participants	Summary of Result	Interpretation
	and Black Women Jennifer				menopausal and Estrogen Receptor status.	
Chan et al.	Cancer Screening Knowledge and Behavior in a Multi-Ethnic Asian Population: The Singapore Community Health Study Tyson	Singapore	Investigation of cancer screening enrollment rates and screening behavior in a multi-ethnic community	7,125	In Singapore, screening for cervical, breast, and colorectal cancers was correlated with higher educational level, higher household income, and being Chinese as compared to Malay ethnicity.	Socioeconomic status and ethnicity have a significant impact on cancer screening rate and can be tackled by cultural and educational strategies and facilitating screening programs.
Bellaiche et al.	Disparity in Access to Oncology Precision Care: A Geospatial Analysis of Driving Distances to Genetic Counselors in the U.S.	USA	Investigation of equity of access to genetic counselors on a nationwide level	4,813	Access to genetic counselors for patients with cancer varied by area, socioeconomic status, and cancer type in the US.	Inequality in access to healthcare services varied by regions and socioeconomic status leading to disparities in cancer prevention.
Simon et al.	A Review of Research on Disparities in the Care of Black and White Patients with Cancer in Detroit	USA	Summation of nearly 30 years of study on Black-White disparities in cancer incidence, care, and outcomes by investigators at the KCI's PSDR program	Review	Black cancer patients had a poorer prognosis due to racial inequalities in primary cancer site, comorbid medical conditions, treatment, and physician-patient communication.	Disparities in cancer outcome between black and white population might be caused by different factors ranging from almost non-modifiable biological traits to completely modifiable physician-patient. Socio-demographic and clinical differences could account for some of the observed disparities, but the influence of systemic effects of racism against Black people needs to be investigated as well.
Biddell et al.	Racial and Ethnic Differences in the Financial Consequences of Cancer- Related Employment Disruption	USA	Examining the disparities in the financial effects of employment disruption according to race/ethnicity	619	In comparison to Non-Hispanic White participants, Non-Hispanic Black and Hispanic/Latinx patients were more likely to report job-related income loss and changes in health insurance when suffering from cancer.	Disparities in cancer outcomes are not limited to precancerous stages; even after being diagnosed with cancer, there are other aspects such as financial disruption that exacerbates the existing disparities and need to be addressed.
Blackman et al.	Colorectal Cancer Screening Prevalence and Adherence for the Cancer Prevention Project of Philadelphia (CAP3) Participants Who Self-Identify as Black	USA	Investigation of Colorectal Cancer screening prevalence and adherence to national screening recommendations, as well as the link between birth region and Colorectal Cancer screening adherence, among a diverse Black population	357	Caribbean and African immigrants adhered to Colorectal Cancer screening at a higher rate than US-born Blacks.	Disparity in subgroups of black populations might reveal more fundamental aspects of inequality based on historical racism or immigration effects.
Nam et al.	Interactions Between Adiponectin- Pathway Polymorphisms and Obesity on Postmenopausal Breast Cancer Risk Among African American Women: The WHI SHARe Study	USA	Investigation of the interaction of genetic variants linked to adiponectin phenotype, obesity, and the risk of breast cancer in African American women	7,991	Obesity was a significant effect modifier for the association between SNPs and Breast Cancer risk in postmenopausal African American women.	A potential intervention to reduce disparities in cancer outcomes is to design cancer screening programs specific to populations with the goal of addressing their unique needs.
Pinheiro et al.	Endometrial Cancer Type 2 Incidence and Survival Disparities Within Subsets of the US Black Population	USA	Comparing incidence and survival patterns of Endometrial Cancer Type 2 among US Black ethnic groups: US-born Blacks, Caribbean-born Blacks, and Black Hispanics	24,387	The incidence and mortality of Endometrial Cancer Type 2 was higher in people of African descent. And the US-born Blacks, Caribbean-born Blacks, and Black Hispanics groups had substantial intra-racial differences.	Cancer disparities exist even within the race and ethnicity social categories. To tackle the barriers to access to cancer prevention programs, policies should be designed for each specific group of populations.

AA: African American, ACCHO: Aboriginal and Torres Strait Islander Community-Controlled Health organizations, CT: Computed Tomography, KCI: Karmanos Cancer Institute, PDAC: Pancreatic Ductal Adeno Carcinoma, PSDR: Population Studies and Disparities Research.

programs or vaccination and emphasize their importance in groups of patients who are not appropriately utilizing preventive and screening services. The strategies and interventions should be designed to create a comprehensive understanding of screening in populations according to their differential background, education, gender, race, ethnicity, culture, and socioeconomic status. And these interventions should be tailored to specific needs of each patient group. As an example, and in this research topic, Chan et al. showed that the ever-screened rates for cervical and breast cancer improved in parallel with increasing the screening knowledge in Singapore (cervical, 70.1 vs. 77.1%; breast, 54.2 vs. 75.2%), indicating the role of awareness in preventive service utilization. However, the outcome of increasing people's knowledge varied depending on their socioeconomic status and ethnicity which directly supports the argument that each population should have their own intervention uniquely designed.

Having perceived the need, the second stage in cancer prevention is utilizing the preventive healthcare service. Regarding preventive care utilization, we first need to understand where the disparities are coming from and what the barriers to care equity are. Differences in perceived benefits and costs of preventive care is one of the factors that cause unequal access to care. Individuals make the decision to utilize a cancer prevention service by comparing the perceived costs and benefits of a service. And these perceptions are influenced by different factors including their socioeconomic status and financial support (3). Therefore, the costs and benefits of services are not just a matter of objective assessments. Services with exactly similar estimated costs could extremely differ in the cost that patients in different bio-socio-economic groups perceive them. Chan et al. supported this concern and reported that poor understanding of the screening procedure, fear of pain and diagnosis, and scheduling difficulty limit preventive service utilization because these factors increase the patients' perceived cost of screening. To elaborate, a group of patients perceived the preventive service to be more costly and less beneficial than others not because the costs of the service were higher for them or they objectively would benefit less from the care. But because that group of patients did not have appropriate familiarity with the preventive care and the fear of pain, for example, increased their perceived cost.

By studying and identifying what contributes to the perceived costs and benefits of screening in different populations, policies could be particularly designed for each population and effectively address their unique needs. As an illustration, the population in Chan et al. study would benefit most from interventions that address their fear and knowledge of screening while Dasgupta et al. study population need physically closer healthcare provision centers to decrease their perceived cost of care. No matter how much we decrease the fear of pain in the population studied by Dasgupta et al., they still cannot afford to travel the distance and utilize the care. Taken together, the goals of each promising intervention such as social network-based policies, could only be realized if the policy incorporates unique features of the patients' social lives and understand their special needs and barriers (4).

As we previously and slightly discussed, the percevied benefits and costs of care also depend on the accessibility and quality of the preventive care. Human resources, such as professional health care workers, healthcare facilities, and access to necessary technologies are important for cancer patients' preventive care and they must be equitably distributed. Namely, in this research topic, Hamdi et al. showed that there is a huge gap in access to relatively simplest types of preventive care in different populations. They reported that in Western, Eastern, and Central African regions, the higher mortality rate of the most preventable cancers like breast, cervical, and prostate cancer is in tandem with the paucity of facilities or screening programs compared to Northern and Southern settings. And it is worth noting that the preventable services of these cancers are among the most easily accessible and affordable types of care in their setting. Bellaiche et al. also supported this notion by showing that access to a high-quality genetic consult for precision medicine depends on where a patient lives in the United States, indicating that even in a developed country not all patients face similar costs of care. And finally, Dasgupta et al. showed that a great proportion of the existing disparities in preventive care in indigenous women could be addressed/resolved by improving their access to primary health care, supporting the importance of understanding the unique needs of each group of patients.

Population-specific policy design is also important for patients. As an instance populations differ in how much burden their diagnosed cancer could cause them. For example, in some instances, the higher burden of cancer in a group of patients is due to lower acceptability of cancer-related programs and, thus, increasing the acceptability of the provided healthcare services could help to narrow the gap in burden of cancer for different patients. In agreement with this, Chan et al. showed that patients' and physicians' linguistic and ethnic concordance significantly improved healthcare service efficiency. Additionally, some populations are hit harder by cancer and require more protecting interventions. As an illustration, Biddell et al. showed that cancer's cost is different for patients of the non-Hispanic black race, compared to patients of the non-Hispanic white race. Black patients in their study were more likely to lose their income and insurance after being diagnosed with cancer. And while non-Hispanic black patients were diagnosed with more aggressive cancers that required more expensive treatment, their employment flexibility and income were significantly limited compared to non-Hispanic white patients.

As of now, we realized how different factors in each step of healthcare utilization could have contributed to the existing disparities. Nevertheless, some might argue that a great proportion of disparities are caused by factors such as age, gender, race, and ethnicity of patients that are non-modifiable. We argue that healthcare systems can still ameliorate the disparities in cancer prevention and care through the modifiable factors or providing more and specifically designed care to those who are more likely to experience higher cancer burdens due to non-modifiable risk factors (Nam et al., Jung et al.). The changes that target the modifiable contributors to

disparities in cancer burden include the inequalities that are rooted in factors such as, but not limited to, racioethnic discriminations. For example, Pinheiro et al. and Blackman et al. showed that there are disparities in cancer incidence and screening even among the Black population of the US that might be due to some historical racism or immigration effects. This study, per se, enlightens that racism, an example of a modifiable factor, could be used as a point of intervention to address disparities in cancer burden. The modifiable factors could also consist of biophysical conditions of patients. For example, Simon et al. showed that chronic kidney diseases, as preventable comorbidities, were more prevalent at the time of diagnosis and had a more significant adverse impact on renal cell carcinoma incidence in black patients than in white patients. Therefore, by designing prevention strategies that target chronic kidney diseases in black patients, we could decrease the black patients' burden of renal cell carinoma which is higher than white patients. And as previously discussed, even for non-modifiable factors, decision makers could design policies to more intensively help patients with a higher bio-physical probability of being diagnosed with cancer or suffering from more aggressive cancers with the hope of closing the gaps of cancer's burden between different populations. Accordingly, Simon et al., Wallace et al., and Mongiovi et al. showed that Black women in the United States are more likely to be diagnosed with more aggressive breast tumors or different immune responses in colorectal cancer, resulting in a higher incidence and mortality rate. Permuth et al. also demonstrated that some specific radiologic biomarkers for pancreatic cancer have only been reported in African Americans, not non-Hispanic white Americans or Hispanic/Latinx, indicating racial biological variations. To provide an example of what the goal of this research topic is and how it could be realized, we argue that these two studies suggest a potential point of intervention to address inequalities in cancer burden: more aggressively screening Black women for breast cancer and taking extra care of Black women with diagnosed breast cancer and all African Americans with pancreatic cancer. Therefore, a part of the gap in cancer burden could be closed by deliberately providing more care to more vulnerable populations. Taken together, care for cancer prevention and burden has multiple stages and each could be a point of intervention to control modifiable factors in more suffering patients or provide extra attention and support to patients with non-modifiable factors that make them more vulnerable to cancer and cause them to experience higher burdens.

All in all, this research topic presented a non-comprehensive but enlightening collection of research studies on the disparities in cancer prevention and epidemiology and it shed light on the aspects of cancer care that are potential fields for further exploration. Therefore, the reported results could be directly used for popultion-specific and effective intervention designs. Or the studies could serve as a guide for future investigations. This is particularly important because this research topic revealed that there is an absolute need for more research that provides thorough understanding of the life course of cancer patients in different biological, social, and economic groups. This information could help policy makers and researchers to understand what the contributing factors to the existing inequalties in cancer prevention, epidemiology, and burden are and how they could tackle these inequalities through population-specific studies and policy designs.

AUTHOR CONTRIBUTIONS

FMon and HK drafted the manuscript and incorporated the ideas of all authors. BM provided comments and approved of the final version. FMoh devised the idea, supervised the drafting, and finalized the manuscript. All authors contributed to the article and approved the submitted version.

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Cancer in Africa: The Untold Story

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Background: Despite rising incidence and mortality rates in Africa, cancer has been given low priority in the research field and in healthcare services. Indeed, 57% of all new cancer cases around the world occur in low income countries exacerbated by lack of awareness, lack of preventive strategies, and increased life expectancies. Despite recent efforts devoted to cancer epidemiology, statistics on cancer rates in Africa are often dispersed across different registries. In this study our goal included identifying the most promising prevention and treatment approaches available in Africa. To do this, we collated and analyzed the incidence and fatality rates for the 10 most common and fatal cancers in 56 African countries grouped into 5 different regions (North, West, East, Central and South) over 16-years (2002–2018). We examined temporal and regional trends by investigating the most important risk factors associated to each cancer type. Data were analyzed by cancer type, African region, gender, measures of socioeconomic status and the availability of medical devices.

Results: We observed that Northern and Southern Africa were most similar in their cancer incidences and fatality rates compared to other African regions. The most prevalent cancers are breast, bladder and liver cancers in Northern Africa; prostate, lung and colorectal cancers in Southern Africa; and esophageal and cervical cancer in East Africa. In Southern Africa, fatality rates from prostate cancer and cervical cancer have increased. In addition, these three cancers are less fatal in Northern and Southern Africa compared to other regions, which correlates with the Human Development Index and the availability of medical devices. With the exception of thyroid cancer, all other cancers have higher incidences in males than females.

Conclusion: Our results show that the African continent suffers from a shortage of medical equipment, research resources and epidemiological expertise. While recognizing that risk factors are interconnected, we focused on risk factors more or less specific to each cancer type. This helps identify specific preventive and therapeutic options in Africa. We see a need for implementing more accurate preventive strategies to tackle this disease as many cases are likely preventable. Opportunities exist for vaccination programs for cervical and liver cancer, genetic testing and use of new targeted therapies for breast and

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prostate cancer, and positive changes in lifestyle for lung, colorectal and bladder cancers. Such recommendations should be tailored for the different African regions depending on their disease profiles and specific needs.

Keywords: cancer, Africa, epidemiology, incidence rates, mortality rates, risk factors, medical devices, human development index

INTRODUCTION

Cancer is an emerging health problem in Africa that needs to be addressed appropriately in order to control for increased incidence and mortality rates (1, 2). It has been suggested that by 2030 there will be a 70% increase in new cancer cases due to population growth and aging (3). In Africa, this ever present disease has coexisted with more recently discovered communicable diseases such as Malaria, Ebola, AIDS and COVID19 (4, 5). Even though cancer death rates have surpassed those of AIDS, tuberculosis, and malaria combined, there remains a lack of commitment to fighting cancer in Africa. Indeed, most attention goes to investigating communicable diseases while disregarding the challenges posed by several non-communicable diseases such as cancer (6). Additionally, due to the cost of care and the absence of facilities, cancer mortality rates are expanding in Africa (7). Cancer death rates in Africa are projected to exceed the global average by 30% in the next 20 years (8). Cancer is a genetically driven disease that interacts with other risk factors to determine an individual's risk.

Three of these associated risk factors speak to the need for making cancer detection and therapy a priority for African nations. The first concerns health care improvements. Based on data from the world bank, life expectancy of Africans has been growing faster than the global average, and is now thought to be about 60 years continent wide. For example, advancements in AIDS therapy and other factors have raised life expectancy for rural Kwa-Zulu Natal from 49 years in 2003 to 60.5 in 2011 (9). As cancer incidences and cancer mortality increase with age, such progress in life expectancy directly leads to more cancer cases. The second follows from the growth in wealth and prosperity in Africa. Changes in lifestyles are associated with increased cancer risks and exposures to carcinogens and mutagens. Such changes include increased urbanization, emergence of different sources of pollution exposure, increase and changes in tobacco and alcohol usage, and changes in diets towards more meat, sugar and processed foods. Environment and lifestyle associated cancer risks can both increase incidences in younger age classes and exacerbate cancer incidence in the elderly. Third, Africa includes diverse ethnicities and sub-populations manifesting a number of genetically associated cancers that disproportionately affect different groups over others. As other health risks decline, these group-dependent cancer rates will become more apparent and take a relatively larger toll on life.

The Global Initiative for Cancer Registry Development (gicr.iarc.fr), led by International Agency for Research in Cancer (IARC), is a partnership of leading cancer prevention organizations that seeks to address data availability, ensuring the robustness of cancer incidence data by improving their quality, comparability and use. Data collected in this framework is available through IARC's GLOBOCAN database. The estimated number of cancer cases and deaths from the year 2002 through the year 2018 are available at the Global Cancer Observatory (http://gco.iarc.fr). In assembling regional and global profiles, the GLOBOCAN methods for incidence and mortality estimation rely upon the best available data from a given country (10, 11).

Records from 56 different African countries are available on GLOBOCAN. Cancer incidences in population-based cancer registries are mainly determined by the cancer cases reported from hospitals (population-based cancer registries: PBCR). Mortality statistics are collected and made available by the WHO. Here, our objective is to study the trends in cancer incidence and fatality rates in Africa. We collated data on 10 different cancer types from 56 African countries grouped into 5 different regions. From these data, we estimated cancer incidence (number of afflicted individuals per 100,000 at a given time point), and fatality rates (number of deaths from the cancer per year per number of afflicted individuals) over a span of 16 years (2002-2018). For many cancers, we can track incidence by gender. We use our statistical analyses of incidences, fatality rates, temporal trends and regional trends to prioritize regional and cancer-specific needs for treatment and prevention strategies. Additionally, we analyze the availability of medical devices used in cancer care across Africa's regions; and we assess the association between the Human Development Index (HDI) and cancer incidence and fatality rates in Africa.

MATERIAL AND METHODS

Data Sources and Population

We extracted data from the 4 latest GLOBOCAN reports Global Cancer Statistics https://gco.iarc.fr) for 56 African countries covering cancer incidence and fatality rates for the last 16 years (2002-2018). The cancer incidence refers to the number of diagnosed cases per 100,000 inhabitants at that time point. The fatality rate is calculated from the ratio of deaths per year from the cancer divided by the number of persons afflicted with the cancer that year (deaths per year divided by the number of currently diagnosed cases). Given that one has the cancer, the fatality rate represents the probability of dying from that cancer per year. When multiplied by 100, the fatality rate represents a percentage of those with a particular cancer who die per year. We

also examined temporal trends (2002-2018) for 10 cancer types by selecting registries with long standing and high quality data over the period.

Statistical Analyses

From collected GLOBOCAN data, we created a database of incidence and mortality for each of the 10 cancers. We calculated cancer incidences (IR) and fatality rates (FR) by using the estimated population size by country, by African regions, and by year (12). For example, cancer incidence was measured by dividing the total number of people affected by a specific cancer by the total population and multiplying by 100,000. For the fatality rate we divided the total number of deaths from that cancer (by year) by the total number of individuals afflicted by the cancer during that year.

Table S1 lists the countries by region. Data were structured according to the Northern, Western, Eastern, Central and Southern African regions. Cancer mortality data were available for just three cancer types: breast, prostate, and cervical cancers. The estimated incidence and fatality rates for 2002, 2008, 2012 and 2018 are presented using maps of Africa. Patterns in the recorded incidences by cancer type and sex are presented as bar charts. All analyses were performed using Python programming language (13) and R statistical language (14). For generating maps, we used the GeoPandas package in Python (15, 16).

We favored regional analyses over individual countries for three reasons: 1) aggregating data across a number of countries increases sample sizes and the calculation of regional averages reduces the fluctuations due to the quality of country by country reports, 2) countries within a region do share ethnic, socio-economic, and cultural affinities, and 3) any region by region differences likely represent strong signals of region-specific cancers and their temporal trends. That said countries within a region can show striking differences in socio-economic measures.

Graphics and Basic Statistics

For each region, we summed cancer incidence for the countries in the area using Readerscan to assess the number of cases during the last 16 years. The increase or decrease of incidence rates is represented on the maps by the shade and contrast of the color. Similarly, average region-specific fatality rates for breast, prostate and cervical cancers were computed from the average of fatality rates among the countries of a specific region. The figures show where in Africa specific cancer types are most or least frequent suggesting where increased attention to treatment and prevention would be most effective.

Available Medical Devices Data

The initial objective with gathering data on the availability of cancer medical device was to show that the higher mortality rates in some areas is due to a lack of equipment. Data on medical devices including equipment for Computed Tomography, Magnetic Resonance Imaging, Positron Emission Tomography, Gamma Camera or Nuclear Medicine, Linear accelerator, Telecobalt unit, Radiotherapy, Mammographs[1] were extracted from the WHO (https://apps.who.int/gho/data/node.country). Data are available in **Table S14** (Central African region), **Table S15** (Eastern African region), **Table S16** (Northern African region), **S17** (Southern African region) and **Table S18** (Western African region). Statistics on this equipment are spotty. Such equipment is often required for the detection of certain cancers or necessary for care. At best there is some availability, and at worst the equipment is completely absent from the medical infrastructure in Africa.

Human Development Index

The Human Development Index (HDI) is a summary measure of achievement in key dimensions of human development: a long and healthy life, standard of living, and education levels. The HDI is the geometric mean of normalized indices for each of these three dimensions. It also offers other composite indices as broader proxies for some of the key issues of human development such as wealth or income inequality, gender disparity, and poverty rates. Country specific HDI data were downloaded from UNESCO (http://uis.unesco.org/), see **Table S12**. In order to harmonize with our data, we calculated a regional HDI average for 2018 only (there was no HDI data for 2002, 2008 and 2012). We tested for associations between the HDI and the incidence rate, IR (**Figure 12A**). Using the least squares approach, **Figure 12B** shows the best fit relationship between fatality rates, FR, and HDI.

RESULTS

Cancers listed in this report are ordered first by those for which we have mortality data and then roughly in descending order of overall incidence. Data on cancer classification and ranking worldwide as well as the number of new cases and deaths have been cited based on the last GLOBOCAN report (https://gco.iarc.fr/today/home).

Breast Cancer

During the last decades, breast cancer has become the most common type of cancer among women worldwide (18). It is a multifaceted disease involving environmental, genetic, and lifestyle risk factors. Breast cancer also represents a collection of clinically heterogeneous diseases ranging from indolent to aggressive. Several differences have been observed in breast cancer epidemiology between populations (19). It has been shown that American women of African origins are three

[1] Density per 1,000,000 females aged from 50-69 old. Several countries have adopted breast cancer screening programs as an effective way for early detection of the disease, using tools such as mammography machines (17). This indicator shows the number of dedicated mammography machines (those designed exclusively for taking mammograms) available in Africa. From the age pyramids of the various African countries (https://www.populationpyramid.net/), the data of Mammographs per 1,000,000 inhabitants was adjusted. This adjustment involved multiplying the number of mammographs (data available are the density per 1,000,000 females aged from 50-69 old) by the population percentage of women between 50 and 69 years old, see **Table S13** and **Figure S3**.

times more likely than Caucasian Americans to develop highly aggressive triple-negative and inflammatory forms of breast cancer (20). Moreover, several studies have shown that high rates and long histories of consanguinity, observed in some upper income countries in Asia and elsewhere, decrease incidences of breast cancer by decreasing the frequency of mutations on the two major susceptibility genes *BRCA1* and *BRCA2* (21, 22).

Breast Cancer Incidence Rates (IR)

The incidence of breast cancer has increased dramatically in Northern and Southern Africa (**Figures 1A, B**). Incidence in North Africa has doubled from 2002 to 2018 with 23.3 cases per 100,000 inhabitants in 2002 to 48.9 cases per 100,000 inhabitants in 2018 (**Table S2**). This is mainly explained by the adoption of a western lifestyle in both Northern and Southern Africa such as nulliparity, breastfeeding, use of oral contraceptives, hormone replacement therapy (HRT) after menopause, nutrition, stressful lifestyle and pollution (23, 24). In Eastern, Central and Western Africa, the incidence has remained stable since 2002. Perhaps this can be explained by fewer changes in lifestyle and habits that increase incidences of breast cancer. These regions of Africa may have yet to see increases in obesity or decreases in physical activity (23). These regions may have a smaller proportion of urban dwellers and hence less exposure to urban pollution, mutagens and carcinogens.

Breast Cancer Fatality Rates (FR)

In all African regions, breast cancer fatality rates have decreased from 2002-2008, and then have remained relatively constant from 2012-2018 (**Figure 1C**). This observation demonstrates the importance of dedicating more efforts, such as early detection, to reducing mortality from this cancer. Northern and Southern Africa exhibit lower fatality rates than other African regions because of available facilities in terms of screening, diagnosis and treatment (including imaging, disease-specific pathologists, surgery, chemotherapy, hormonal therapy and radiotherapy) as compared to Eastern, Central and Western Africa. Finally,

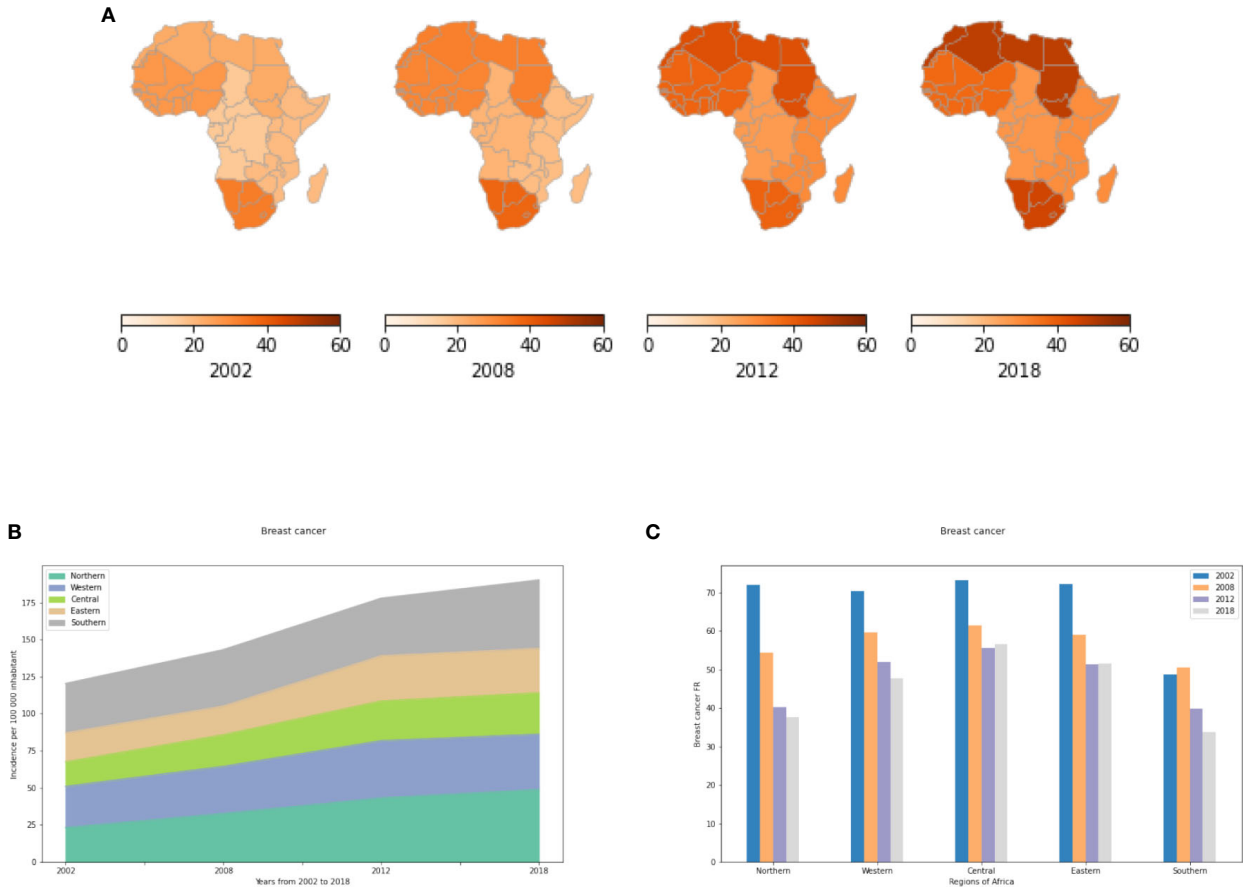

FIGURE 1 | Incidence and fatality rates of breast cancer per 100,000 inhabitants from 2002 to 2018. IR refers to active cancer cases per year and per region per 100 000 inhabitants. The FR of a region per year is obtained by dividing the number of cancer deaths by the total number of active cancer cases per year in a specific region and multiplying by a hundred to give a percent. **(A)** Breast cancer incidence rates in the different African regions per 100,000. **(B)** Changes in incidence rate from 2002 to 2018. **(C)** Breast cancer fatality rates (percent mortality per year of those afflicted) in the different African regions given as a percent.

fatality rates may remain high across all of Africa due to the paucity of facilities related to precision oncology such as genetic testing, targeted therapies, and immunotherapy.

Prostate Cancer

Prostate cancer is a common malignancy among men and perhaps the third most aggressive neoplasm worldwide, causing approximately 90,000 deaths per year in Europe. International guidelines became more conservative over the past decades in the management of prostate cancer cases. Prostatectomy and/or external beam radiotherapy are the most common intervention, followed by maintenance on androgen deprivation therapy (ADT) known as chemical castration. Standard of care in prostate cancer includes a combination of next generation endocrine therapies like enzalutamide, with cytotoxic agent docetaxel. Medical and biological advances have led to new promising treatments for this cancer that include Radium-223 for bone metastases, pembrolizumab as immunotherapy (PDL1 blocker) for microsatellite instability (MSI) disease, and poly ADP ribose polymerase (PARP) inhibitors for those with mutations in homologous recombination genes, most commonly *BRCA2*.

Other than age, few risk factors have been characterized. The best known include smoking (25, 26), diet (27), obesity (28) and genetic predispositions. The most common mutations involved in prostate cancer include *BRCA1/2*; *ATM* (odds ratio (OR) = 2.18), *HoxB13* (OR = 3.23), genes involved in repairing mismatched genes and genes associated with Lynch Syndrome (OR = 4.87), and *CHEK2* (OR = 1.98) (29). Prostate cancer seems to have a strong ethnic association. Men of African ancestry are at an increased risk of the disease. In the US, African Americans are more likely to be diagnosed with prostate cancer and 2.5 times more likely to die from the disease. A recent literature review showed that African American men were less likely than European American men to seek treatment as a direct or indirect consequence of health disparities such as financial barriers, lack of health insurance, and/or poor health-seeking behavior (30). Furthermore, some men may be reluctant to seek treatment because of concerns regarding the side-effects of therapy such as incontinence and sexual dysfunction.

Prostate Cancer IR

Figures 2A, B show a low overall IR for prostate cancer in Northern Africa that has slowly increased from 5 to 13 cases per 100,000 inhabitants from 2002 to 2018 (**Table S3**). In Eastern, Central and Western Africa, prostate cancer is 2 to 6 fold more prevalent with an IR that reaches 35 cases per 100,000 population in 2018 in Central Africa. In Southern Africa, prostate cancer IR is alarming with a prevalence that is 5 times more than that of Northern Africa in 2018. The increased prostate cancer risk in Sub Saharan Africa may be explained by genetics, though the potential carcinogenic impact of environmental and lifestyle factors cannot be ignored. Indeed, it is well documented that the population with the highest reported incidence and mortality rates globally are African Americans. In 2009, Odedina and collaborators, suggested that the roots of the high burden of prostate cancer among African American can be explained (at least in part) by increased genetic susceptibility dating back to the approximately 360,000 transatlantic slaves, mainly from West/Central West Africa (31). In addition, the VhaVenda Vhembe District of the Limpopo Province in South Africa has practiced residential dichlorodiphenyltrichloroethane (DDT) spraying for malaria control since 1945 (32). The identification of a link between maternal DDT exposure and urogenital birth defects in newborn VhaVenda boys provides one of several links between pesticide use in Sub Saharan Africa and prostate cancer (33). In addition, a case-control study from Southern Africa showed that prostate cancer is associated with high intake of fat, meat, and eggs; eating out of the house; and low consumption of vegetables (34).

Prostate Cancer FR

In the literature, prostate cancer is the most deadly cancer for men in Southern Africa (12). It is also the most commonly diagnosed cancer and the leading cause of cancer death in men in Central Africa. It ranks before lung cancer in terms of fatality rates for men in Northern Africa. Our study shows that prostate cancer IR has been increasing steadily since 2002. Most cases are recorded from Southern Africa where the number of new cases has increased by more than 60% from 2002 to 2018. Unlike IR, the FR in Southern Africa is significantly less than in Northern, Western, Central and Eastern Africa (**Figure 2C**). In 2002, this cancer had over 80% FR in the five regions. While the FR is lower by 2018, more than 6 out of 10 cases died within 12 months after diagnosis in Central, Western and Eastern Africa and more than 4 out of 10 in the North and South.

Cervical Cancer

Cervical cancer is the fourth most common cancer in women worldwide. Around 85% of the global burden occurs in low and middle income regions, where it accounts for almost 12% of all female cancers. In comparison, in upper income regions, cervical cancer accounts for less than 1% of all cancers in women (35). Cervical cancer, the only cancer that is almost entirely preventable and curable if detected early, affects mainly middle-aged women (30 to 50 years) (36). It is caused by sexually acquired infections from certain types of Human papillomaviruses (HPV) (37). Two HPV types, 16 and 18, are responsible for approximately 70% of cervical cancer cases and pre-cancerous cervical lesions, globally. There is also evidence linking HPV to other cancer types such as anus, vulva, vagina, penis and oropharynx cancers. Three HPV vaccines are now available in many countries throughout the world - a bivalent, a quadrivalent, and a nonvalent vaccine. All three vaccines are highly effective in preventing infection with HPV types 16 and 18. The vaccines are also highly efficient in preventing precancerous cervical lesions caused by these virus types. The WHO national immunization program against HPV includes most Eastern and Southern African countries. Libya is the only North African country using this vaccine to prevent cervical cancer (**Figure S1**). Ivory Coast, Gambia and Senegal are the only three Western African countries that have been included in this program. However, no vaccination against HPV has been recorded in Central Africa.

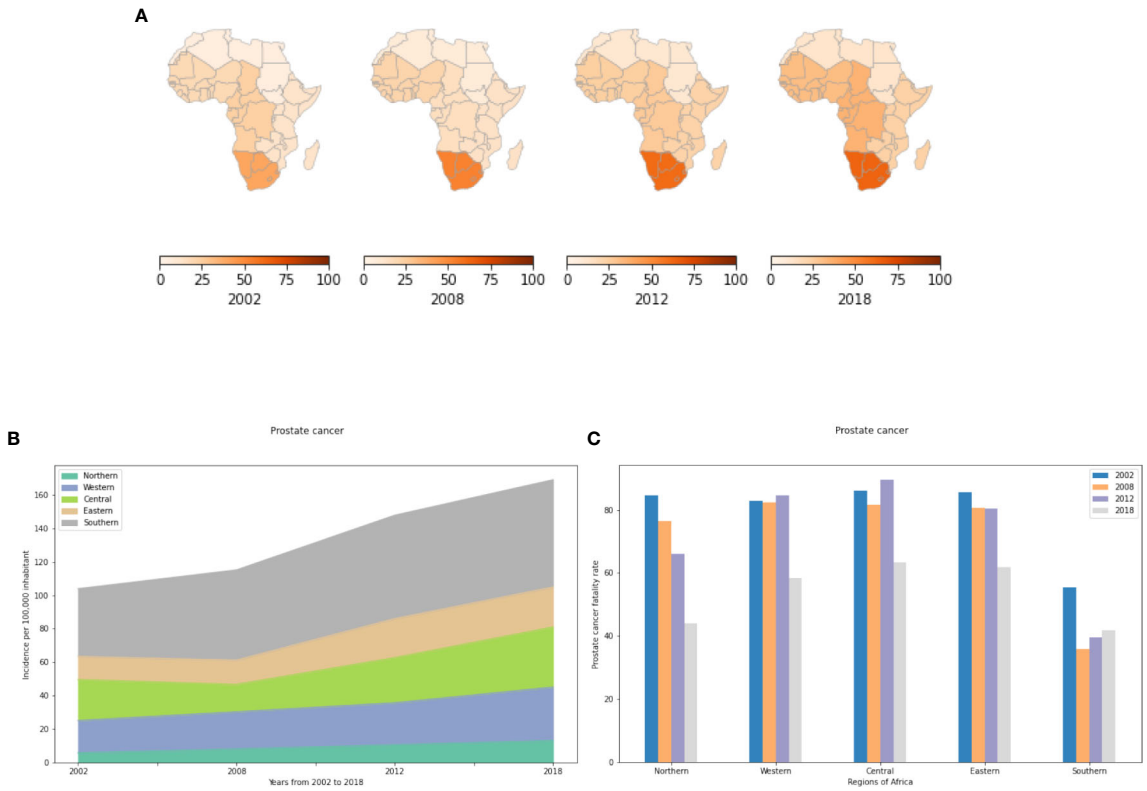

FIGURE 2 | Incidence and fatality rate for prostate cancer per 100,000 inhabitant from 2002 to 2018 in Africa. **(A)** Prostate cancer incidence rates in the different African regions per 100,000 inhabitant. **(B)** Incidence rates from 2002 to 2018. **(C)** Prostate cancer fatality rates (percent mortality per year of those afflicted) in the different African regions.

Cervical Cancer (IR)

Cervical cancer is most prevalent in sub-Saharan Africa (**Figures 3A, B**). North Africa had the fewest number of cases reported in 2018 with approximately 7 cases per 100,000 women compared to 27 to 30 cases per 100,000 women in the Central and Western regions and 40 to 43 cases/100,000 women in Eastern and Southern Africa (**Table S4**). The low incidence rate in North Africa is mainly explained by advances in cervical cancer screening such as regular Papanicolaou (Pap) and human papillomavirus (HPV) DNA testing. In addition, socio-cultural and religious norms might influence sexual and reproductive health behavior in a manner reducing cervical cancer incidence rates in Northern Africa. In Eastern, Central and Western Africa, IR has decreased slightly during the last 4 years basically due to HPV vaccination programs in parts of these regions (**Supplementary Figure S1**). However, despite the HPV vaccine being used in South Africa (free HPV vaccine for schoolgirls started in March 2014) cervical cancer incidence rates in South Africa are still increasing dramatically. Therefore, other risk factors seem to contribute to cervical cancer incidence rates.

Cervical Cancer (FR)

Cervical Cancer, apparently the only cancer that can actually be prevented, exhibits high fatality rates in Africa. Even in 2018, more than 75% of affected women died of this cancer per year in East, Central, and West Africa. Fatality rates are decreasing only in Southern Africa. In all other African regions, fatality rates have increased during the last 4 years including Northern Africa where the incidence rate is very low but fatality rates are high (**Figure 3C**).

Lung Cancer

Lung cancer, the most common cancer in the world for several decades, saw around 2.1 million new cases in 2018 (12). It is a highly aggressive cancer responsible for more than 1.6 million deaths per year worldwide (38). Significant decreases in lung cancer mortality rates have been observed in upper income countries due to increased awareness of the harmful effects of smoking and other risk factors (39). In contrast, lung cancer incidence and mortality rates have increased in some low and middle income countries (40). This difference is mainly due to increases in smoking (increase of tobacco, water pipes, cannabis smoking and passive smoking), as well as limited access to screening, diagnosis facilities and to appropriate targeted therapies. Several other risk factors such as asbestos exposure, dust, fumes, nickel, silica and insecticides have been reported. In Africa, there are countries that have yet to ban or restrict asbestos (39). In addition, increased life expectancies throughout Africa increase the likelihood of contracting and dying from lung cancer. Moreover, many studies have described the genetic

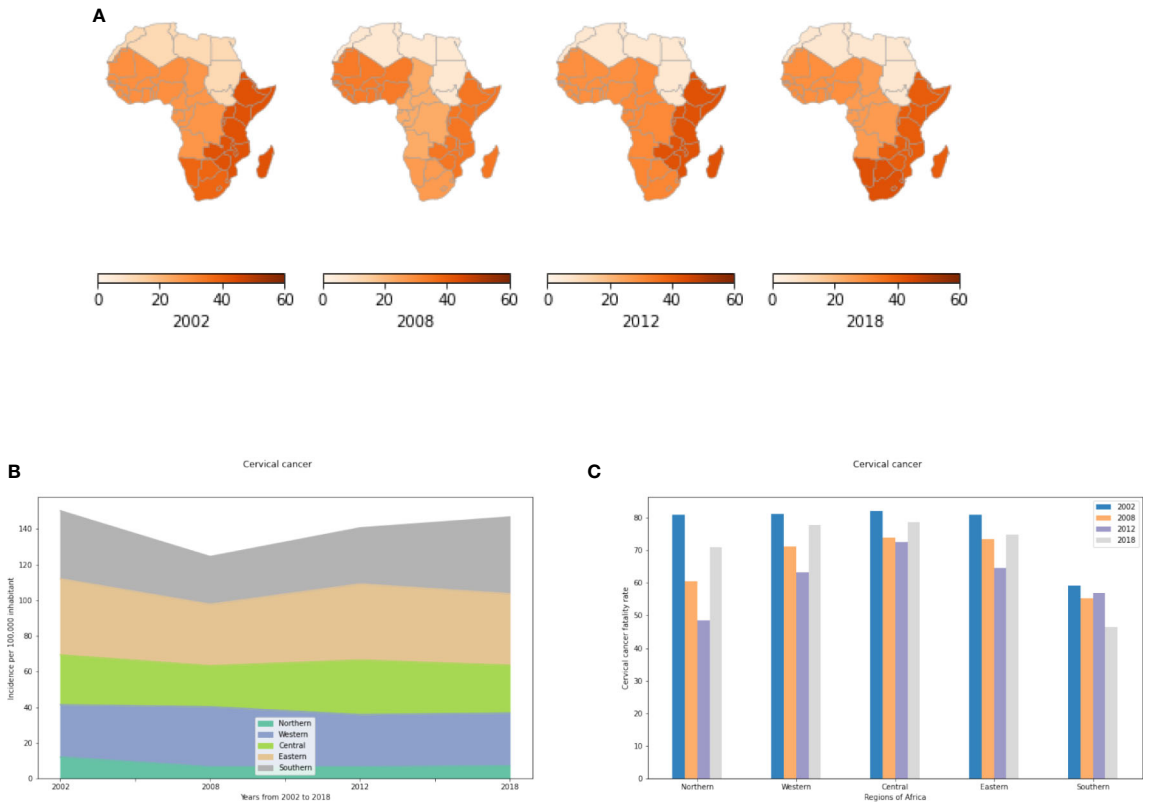

FIGURE 3 | Cervical cancer incidence and fatality rates in the different African regions. **(A)** Incidence of cervical cancer per 100,000 inhabitant by African regions. **(B)** Evolution of Incidence rates from 2002 to 2018. **(C)** Fatality rates (percent mortality per year of those afflicted) of cervical cancer.

susceptibility to develop lung cancer especially in North Africa by identifying genetic biomarkers in *EGFR*, *KRAS* and *ALK* genes (41).

Our results show that Lung cancer is highest and on the rise in Northern and Southern Africa in both men and women (**Figures 4A, B**) mainly because of the increasing number of smokers with a prevalence of 3 to 5 fold higher among males compared to females (**Figure 4C**). The IR in Southern Africa is twice that of Northern Africa. This is likely explained by high tobacco, cannabis and alcohol use in Southern Africa. In the Eastern, Central and Western areas, the number of cases was less than 3 cases per 100,000 inhabitants in men and women combined in 2018 (**Table S5**). While currently not available in the data, for the future, a priority should be placed on distinguishing small cell lung cancer and squamous cell lung cancer (common to smokers) from non-small cell lung cancer (common to non-smokers). Such information would aid health officials with cancer sources, prevention, early detection, and public health mitigation programs.

Stomach Cancer

Stomach cancer is the sixth most common cancer worldwide with 1,033,701 new cases reported in 2018. About half of these cases occurred in Eastern Asia. It also remains the third leading cause of cancer related deaths worldwide with a median overall survival of 9-16 months once metastatic (42). Several risk factors are involved in the development of stomach cancer including a diet high in salty and smoked foods, a diet low in fruits and vegetables, family history of stomach cancer and stomach polyps, long-term stomach inflammation, pernicious anemia, smoking, and infection with *Helicobacter pylori (H. pylori)*. *H. pylori* is a gastric pathogen that infects approximately 50% of the world's population. Infection with *H. pylori* causes chronic inflammation and significantly increases the risk of developing duodenal and gastric ulcer disease, and gastric cancer. Africa had the highest rate of *H. pylori* infection with a prevalence of 70.1%, followed by South America and Western Asia with prevalences of 69.4% and 66.6%, respectively (43). Moreover, a family history of gastric cancer, of Lynch syndrome and of familial adenomatous polyposis, and genetic mutations mainly on the *CDH1* gene are strong risk factors known to be associated with hereditary stomach cancer.

In this study, we showed that incidence rates of stomach cancer are relatively constant across African regions with a consistent gender bias as more men than women exhibit the cancer. In 2002, Central Africa far exceeded other regions with Southern and Eastern Africa showing the next highest incidence. Central Africa in 2002 had 13 cases per 100,000 population (**Figure 5A**, **Table S6**). This is mainly explained by high *H. pylori* infection rates in this region at that time. The majority of

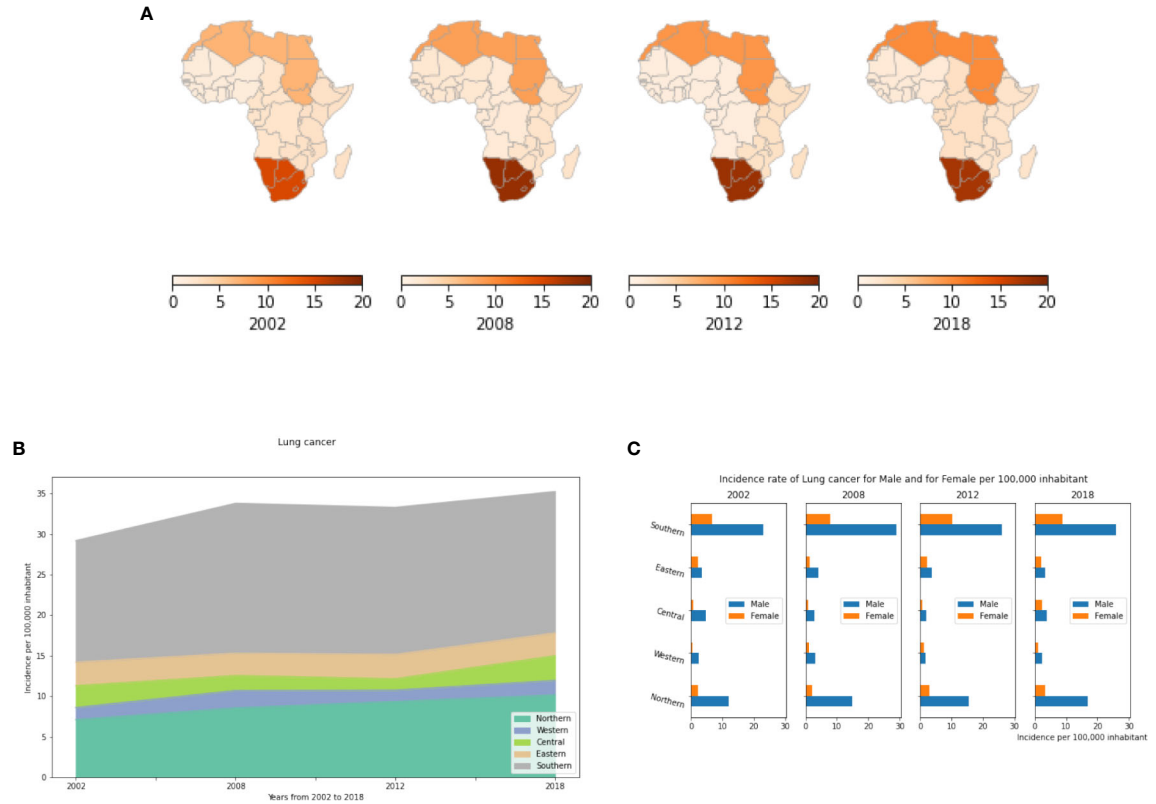

FIGURE 4 | Lung cancer incidence rates by African region, per year and by gender. **(A)** Incidence rate per 100,000 inhabitant by African regions. **(B)** Dynamics of Changes of incidence rates from 2002 to 2018. **(C)** Lung cancer Incidence rates by gender in different African regions. This represents the number of active cancer cases per year per 100,000 men and per 100,000 women in each African region.

literature on *H. pylori* in Central Africa was reported from Cameroon, and similarly to other African studies, a strong association between gastritis and *H. pylori* was found (44). Ankouane and colleagues observed that 71.2% of patients with atrophic gastritis were *H. pylori* positive. The authors also found a statistically significant association between the severity of atrophic gastritis and *H. pylori* infection. Since 2008, stomach cancer incidence rates have decreased dramatically in most African regions (**Figure 5B**) with slight increases in Northern Africa. By 2018, all African regions were seeing just 3 to 5 cases per 100,000 inhabitants (**Table S6**). Our estimates still show that more cases are reported in Sub-Saharan Africa compared to Northern Africa (**Supplementary Figure S2**). **Figure 5C** shows that stomach cancer is more prevalent in males compared to females in all African regions notably in Northern and Southern Africa where its prevalence is 2 fold higher in males compared to females.

Colorectal Cancer

Colorectal cancer is the sixth most common cancer in Africa (3, 45). At diagnosis, most cases are metastatic and in an advanced state. Consequently, fatality rates are high (46). Potential risk factors such as diet, lifestyle, socio-economic status, urbanization, Crohn's disease, and diabetes mellitus predispose one to colorectal cancer. While arguable, prior *Schistosomiasis* infection may also be a risk factor (47). In addition, 5% of colorectal cancer cases may include underlying genetic predispositions from germline disorders such as Lynch syndrome, familial adenomatous polyposis, and mutations on genes involved in the mismatch repair pathway (48). Hereditary factors may be pronounced in Africa, since 25% of affected individuals are under the age of 40 years (45, 49).

Results presented in **Figure 6** show that incidences of colorectal cancer have been increasing since 2002 in all African regions. Southern Africa has the highest incidence followed by Northern Africa (**Figures 6A, B**). Southern Africa began with a high incidence in 2002, and since, there has been a 1.3 fold increase up to 2018. (**Table S7**). In Northern and Central Africa the incidence rates have doubled between 2002 to 2018 with 4.55 and 2.89 cases per 100,000 population in 2002 to 8.85 and 6.35 cases per 100,000 population in 2018, respectively. Except for Southern Africa where colorectal cancer is 1.2 to 2 fold more prevalent in males than in females, no significant gender differences were observed in other African regions (**Figure 6C**).

Esophageal Cancer

Esophageal cancer (EC) is the tenth most common and the sixth most common cause of mortality among cancers worldwide. There

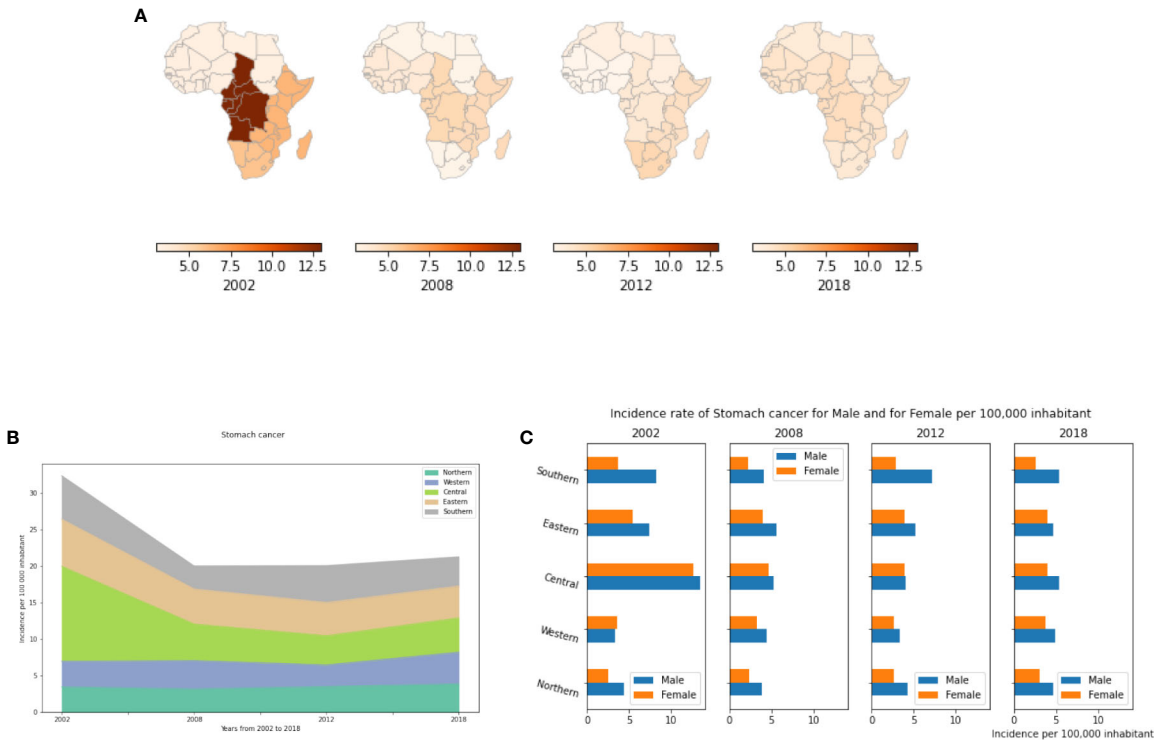

FIGURE 5 | Stomach cancer incidence rates by year, by African region and by gender. **(A)** Stomach cancer incidence per 100,000 inhabitant in African regions. **(B)** Dynamics of incidence rates from 2002 to 2018. **(C)** Stomach cancer incidence by gender.

were records of 572,034 new cases worldwide in 2018 representing 3.2% of all cancers, among them 28,494 (5.0%) were recorded from African (12). Risk factors for developing EC include smoking and chewing tobacco (50, 51), heavy consumption of alcohol (52), drinking hot beverages (53), exposure to polycyclic aromatic hydrocarbons (PAH) (54), consuming red meat (55), poor oral health (54), low intake of fresh fruits and vegetables (56), and acid reflux. Moreover, certain viruses, e.g., human papillomavirus, herpes simplex virus, cytomegalovirus, and Epstein-Barr virus, have been implicated in EC development by infecting the esophageal epithelium. Often EC manifests first as Barrett's esophagus, which then may or may not progress to cancer. In Europe and North America, Barrett's Esophagus is diagnosed early, monitored, and sometimes treated. Such early detection is unavailable to most Africans.

Our results showed an exceptionally high prevalence of the disease in both Eastern and Southern Africa compared to other African regions (**Figure 7A**), though both of these regions have seen declines over the period from 2002 to 2018 (**Figure 7B**). In 2018, there were less than 2 cases per 100,000 inhabitants in the Northern, Central and Western regions, compared to over 8 cases per 100,000 people in Eastern and Southern Africa (**Table S8**). Like previous cancer types, analysis of all subgroups suggests that Age-standardized incidence rates of EC in Africa are generally higher in men than in women, and almost double in males compared to females in Southern and Eastern Africa (**Figure 7C**). This is mainly explained by the prevalence of tobacco and alcohol consumption that are much higher in males than females in Africa (57). However, disparities in smoking prevalence estimates have been observed between different countries and/or regions in Africa. Indeed, a recent study provided estimates of smoking prevalence and smokeless tobacco (SLT) use at the country-level and assessed their social determinants in 30 African countries. The authors showed that smoking prevalence differs significantly across African regions, which may explain the disparities in incidence rates of smoking related diseases such as cancer (58).

Liver Cancer

Liver cancer is the seventh most common cancer worldwide, fifth in males, and ninth in females. In Africa, it is the fourth most common cancer, where its prevalence and etiology show some differences between North and sub-Saharan Africa. Despite its well-known and preventable risk factors, mortality due to this cancer remains very high. In addition, its IR are known to be significantly associated with high levels of viral infection and synergistic environmental risk factors. Viral hepatitis and the human immunodeficiency virus (HIV) are known to increase a person's lifetime risk of liver cancer. Moreover, the rapid increase of urbanization has promoted a sharp increase in additional risk factors like coinfection, aflatoxin exposure, iron overload, type 2 diabetes mellitus and obesity.

Our analysis showed that while incidence of liver cancer across all of Africa has been declining since 2002, regional

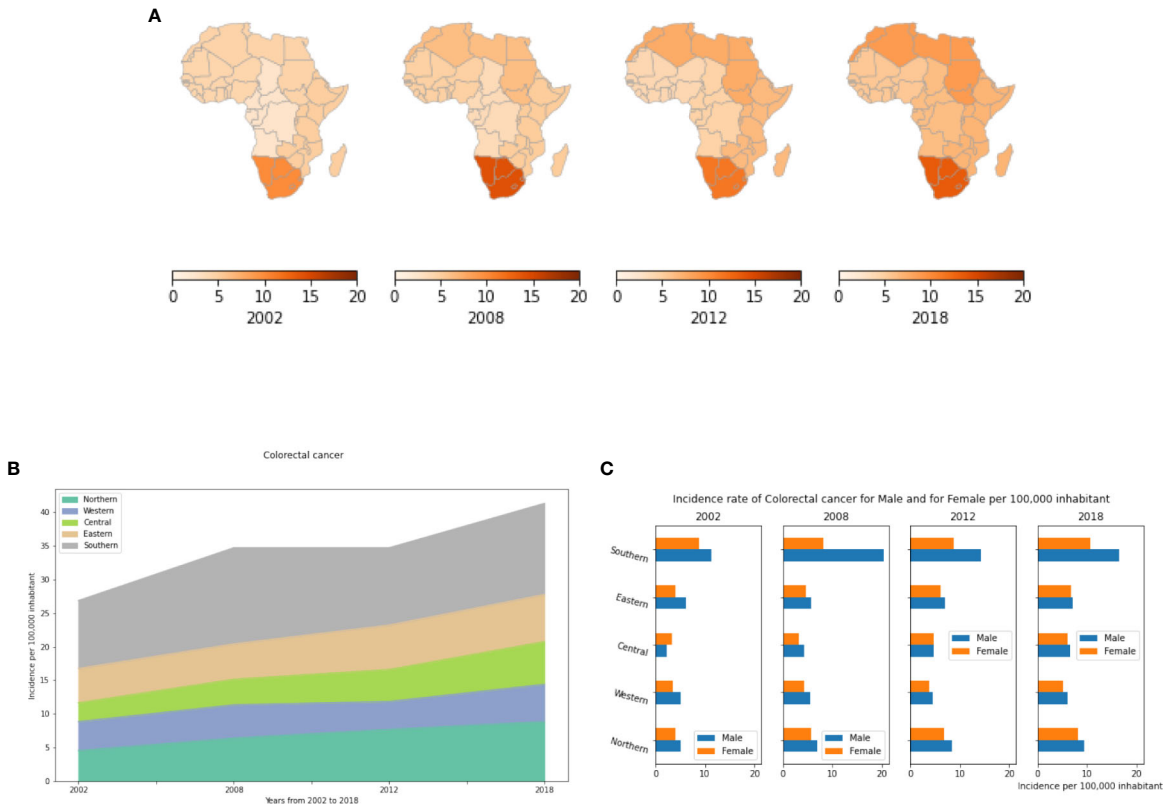

FIGURE 6 | Colorectal cancer incidence rates per year, by African region and by gender. **(A)** Colorectal cancer incidence rates per 100,000 inhabitant in different African regions. **(B)** Dynamics of incidence rates from 2002 to 2018. **(C)** Colorectal cancer Incidence rate by gender in Africa.

trends differ in striking ways (**Figure 8A**). In 2002, Central and Eastern Africa had the highest and second highest incidences, respectively. Since then, both regions have seen substantial declines. While among the lowest of regions in 2002, Northern Africa has seen an alarming increase to now being the highest among all regions. The number of diagnosed cases has risen from 3.2 in 2002 to 14.3 cases per 100,000 in 2018 (**Table S9**). The high incidence of liver cancer in North Africa is mainly due to the unusually high prevalence of hepatitis C virus (HCV) infection in Egypt. In the other African regions, liver cancer incidence rates have decreased to less than 8 cases per 100,000 population in 2018 (**Figure 8B**, **Table S9**). Males have higher incidences than females, with male-to-female ratios as high as 3:1 in some African regions such as Central and Southern Africa (**Figure 8C**). This gender difference may be linked to higher exposure to carcinogens such as tobacco and alcohol, as well as the natural protective influences of estrogen against liver inflammation (59).

Bladder Cancer

Bladder cancer is a significant health problem. Evidence is emerging regarding gene-environment interactions associated with acquiring bladder cancer. Tobacco and occupational exposures remain the highest risk factors (60). Cigarette smokers compared to non-smokers are more likely to be diagnosed with invasive bladder cancer (61). In addition, cancer rates may be elevated in workers exposed to chemical products such as printing companies, hairdressers and truck drivers (62). Other risk factors include bladder birth defects, not drinking enough fluids, consumption of certain medicines or herbal supplements, and chronic bladder irritation and infections. Genetic risk factors associated with bladder cancer include mutations of the retinoblastoma, *RB1*, gene as well as mutations in *PTEN* that are also associated with breast and thyroid cancers and Cowden disease. People with Lynch syndrome might also have an increased risk of bladder cancer as well as other cancers of the urinary tract.

In the present study, we demonstrate that in Africa, bladder cancer represents a comparatively uncommon cancer that has been declining since 2002 in all regions. Incidence rates vary significantly between regions. Northern Africa has the highest incidence (**Figures 9A, B**). This might be explained by some genetic predispositions between the different African regions, and it may be related to the very high consumption of tobacco in Northern Africa. In 2018, 8.75 cases were recorded in Northern Africa compared to less than 3.9 cases per 100,000 inhabitants in the other regions (**Table S10**). Moreover, this cancer is much more common in men than in women. In North Africa, its incidence in men is 5 fold higher than in women (**Figure 9C**). In Tunisia, bladder cancer represents the second most common cancer in males after lung cancer.

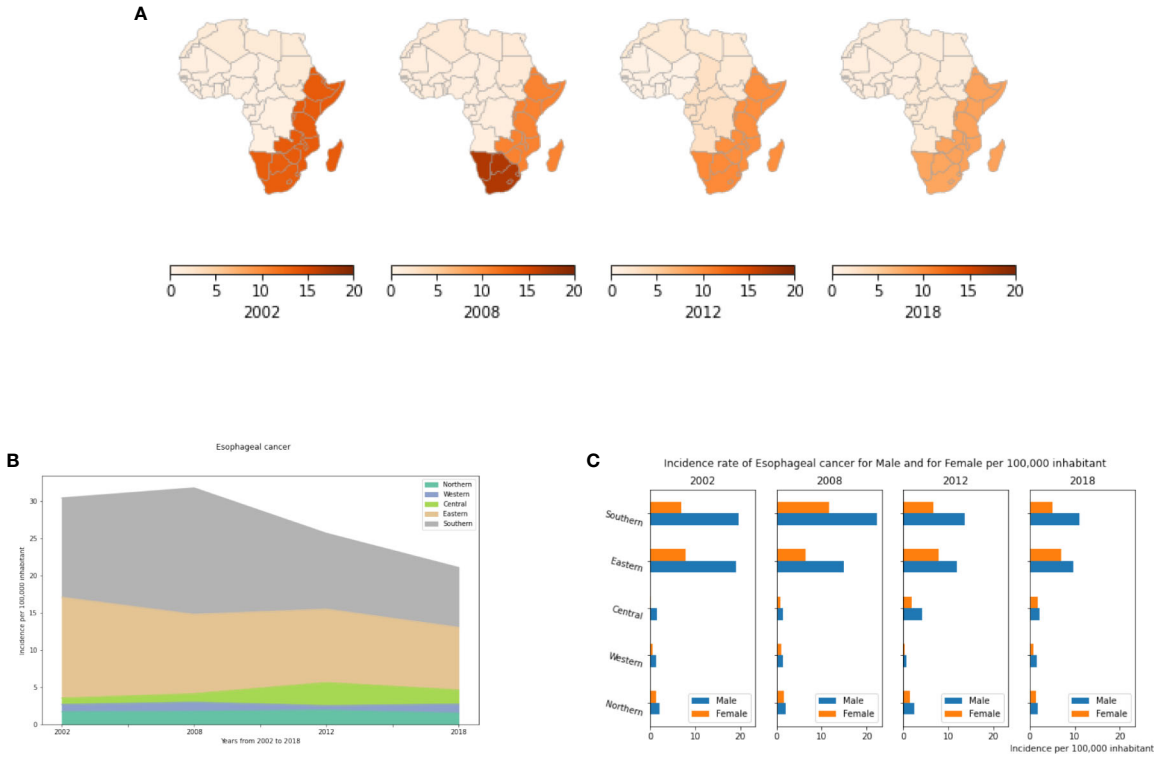

FIGURE 7 | Esophageal cancer incidence rates per year, by African region and by gender. **(A)** Esophageal cancer incidence per 100,000 inhabitant in African regions. **(B)** Dynamics of incidence rates from 2002 to 2018. **(C)** Esophageal cancer incidence by gender.

Thyroid Cancer

Thyroid cancer develops from the tissues of the thyroid gland (63). In 2012, 298,000 new cases occurred globally. Incidence rates have increased in the last few decades, which is believed to be due to improvements in diagnostics. Globally, there were 567,233 recorded new cases and 41,071 reported deaths in 2018. Thyroid cancer most commonly manifests between the ages of 35 and 65 (64).

Several risk factors have been proven to be associated with thyroid cancer. The most studied and proven risk factors being radiation exposure. Sources of such radiation include certain medical treatments as well as radiation fallout from power plant accidents or nuclear weapons. Other risk factors include being overweight and having a diet low in iodine. Although the genetic component of thyroid cancer is still not well defined, several hereditary forms have been identified including:

- Familial medullary thyroid carcinoma (FMTC). FMTC can occur alone, or it can be seen along with other tumors caused by mutations in the *RET* gene.
- People with Familial adenomatous polyposis (FAP) known to develop many colon polyps and or colon cancer also have a very high risk of developing papillary thyroid cancer.
- People with Cowden disease have an increased risk of thyroid problems and certain benign growths (including some called hamartomas). The thyroid cancers tend to be either the papillary or follicular type. This syndrome is most often caused by mutations in the *PTEN* gene.
- People with Carney complex, type I may develop a number of benign tumors and hormone problems. They also have an increased risk of papillary and follicular thyroid cancers. This syndrome is caused by mutations in the *PRKAR1A* gene.
- Familial non medullary thyroid carcinoma: genes on chromosome 19 and chromosome 1 are suspected of causing these familial cancers.

Moreover, like other cancer types, the number of cancer cases and mortality rates differ between populations. Those of Asian ancestry exhibit higher incidences (65, 66).

In Africa, thyroid cancer is a rare. In 2002, Northern and Eastern Africa had the highest incidences (**Figures 10A, B**). While most regions remained relatively stable in their incidence rates, from 2002 to 2018, Northern and Southern Africa had increases in the number of thyroid cancer cases. The number of cases has increased 3.5 fold between 2012 and 2018 in Southern Africa, and 1.25 fold in Northern Africa (**Table S11**). Unlike other cancer types, thyroid cancer is much more common in women than in men (**Figure 10C**). In 2018, the number of affected women was 2-3 fold higher than men in almost all African regions.

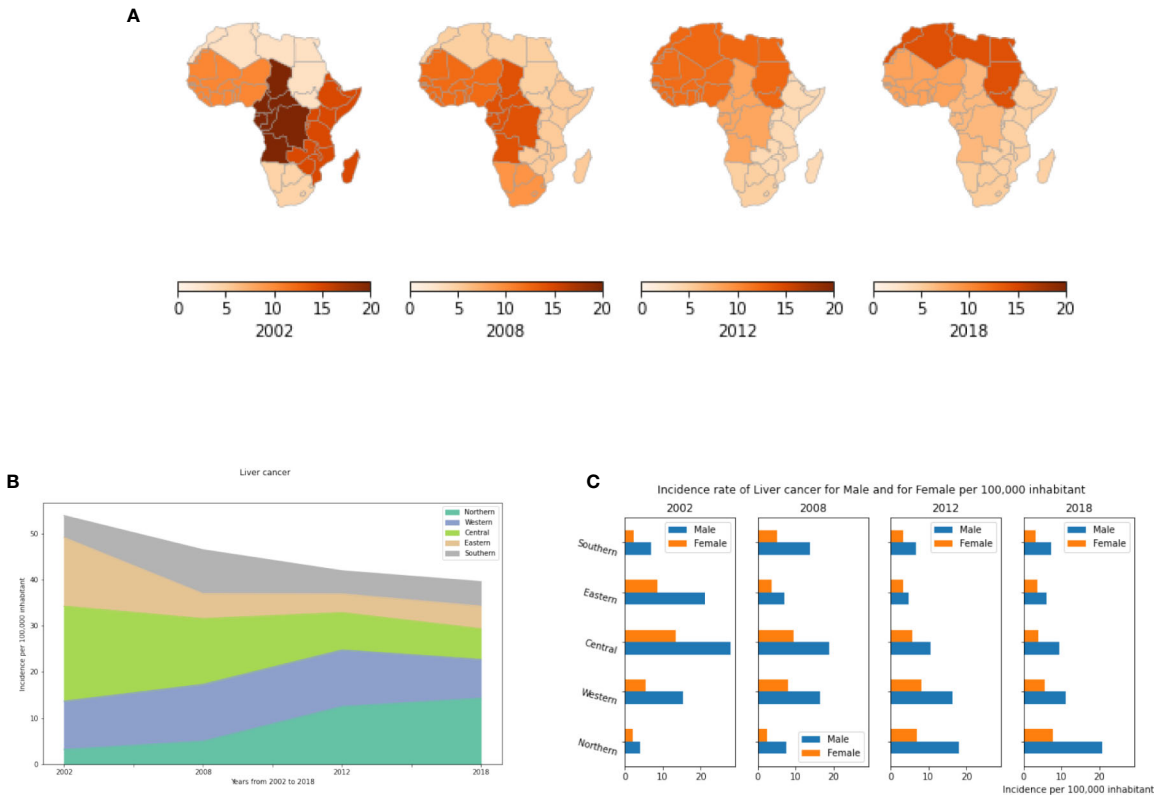

FIGURE 8 | Liver cancer incidence rates by year, by African region and by gender. **(A)** Liver cancer incidence rate per 100,000 inhabitant in different African regions. **(B)** Dynamics of the incidence from 2002 to 2018. **(C)** Liver cancer incidence by gender.

Available Medical Devices

We extracted data on the list and availability of medical devices in each African country from the Global atlas of medical devices provided by the World Health Organization (2017). This data includes statistics on national policy on health technology, medical device incorporation, inventory and maintenance, lists of medical devices, healthcare facilities per 100,000 population, and medical equipment per 1,000,000 population. **Figure 11** shows the distribution of the following cancer medical devices in Africa: mammographs, computed Tomography (CT, a three-dimensional imaging method using x-rays to scan body areas slice-by-slice), gamma camera (also called Anger camera or scintillation camera used in nuclear medicine for the visualization of physiological or biochemical functions in the body), Magnetic Resonance Imaging (MRI, a 3-D imaging method well suited for soft tissue diagnostics), Positron Emission Tomography (PET, an imaging method for diagnostics in nuclear medicine using positron-emitting radionuclides), and radiotherapy equipment (using ionizing radiation to control or destroy malignant cells). Data on these medical devices are not available for all African countries. The best equipped countries, according to the available data per 1,000,000 inhabitant, are in descending order: Seychelles (33.3), Mauritius (24.5), Tunisia (17.4), Libya (17.3), Cape Verde (14.9), Namibia (9.5) and Gabon (9.1). Countries with either little equipment or missing data include: Liberia, Mozambique, Lesotho, Guinea-Bissau, Guinea, Rwanda, Equatorial Guinea, Djibouti, Democratic Republic of the Congo, Sao Tome and Principe, South Sudan and Somalia (**Figure 11**). If we assume that the lack of data from a country correlates with a lack of equipment, then we believe that the country by country map in **Figure 11** provides an ordinal but not absolute scale of availability. And, if so, we see regional trends where northern and southern Africa have the highest concentration of equipment while central Africa has the lowest where Gabon provides a notable exception.

Human Development Index (HDI) and Cancer (Breast, Prostate, and Cervical)

We used least-squares linear regression analyses to test for correlation between the HDI and the incidence (IR) and fatality rates (FR) of the three most common cancer types (breast, prostate and cervical) in the five African regions (**Figure 12**). This generated 15 data points for each analysis: 3 cancers by five regions. There was no detectable relationship between HDI and incidence, though the scatter among cancer types is much higher for the two regions (Northern and Southern Africa) with the highest HDIs. Fatality rates decline significantly with HDI. If we classify Northern and Southern Africa as medium HDI, and the remaining three regions as low HDI,

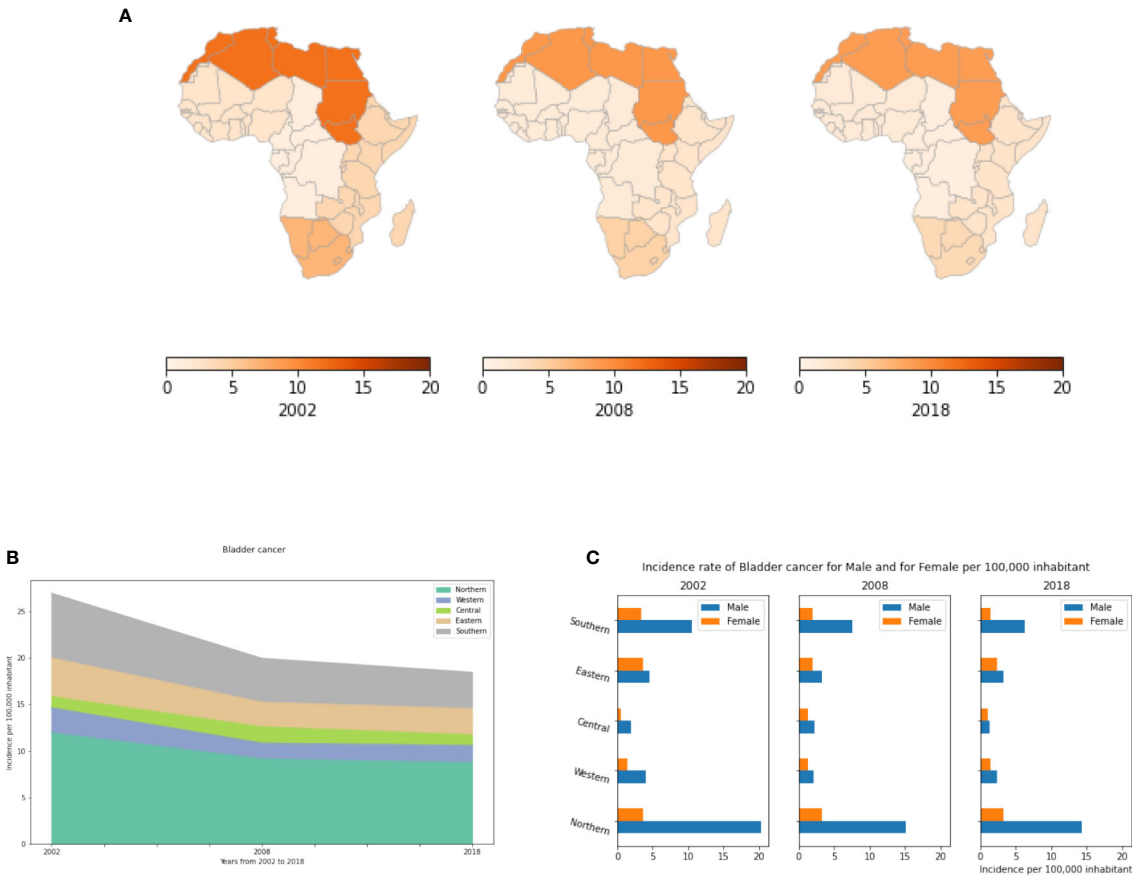

FIGURE 9 | Bladder cancer incidence rates per year, by African region and by gender. **(A)** Bladder cancer incidence per 100,000 inhabitant in all Africa regions. **(B)** Dynamics of incidence rates from 2002 to 2018. **(C)** Bladder cancer incidence by gender.

then the striking difference concerns the significantly higher fatality rates for the low HDI regions compared to the medium HDI ones. HDI likely correlates with early detection and a broader range of therapy options for those burdened with cancer. We add two caveats to these results. First, countries can vary strikingly in HDI within regions, though overall, high HDI countries are clustered in northern and southern Africa. Second, country by country reporting of variables comprising the HDI may have discrepancies. Placed in these contexts the results are intriguing, tentative and deserving of follow-up.

DISCUSSION

Population origin and diversity are known to influence cancer incidence, survival, drug response, molecular pathways, and ultimately the treatment outcome (67). Although these factors differ widely among human populations, most genetic and epidemiological cancer studies and discoveries have been reported on non-African populations, particularly those of European descent (68). Appropriately, much effort in Africa has been invested towards managing and curing communicable diseases such as Malaria, Tuberculosis and HIV. However, cancer has received much less attention even as incidences and mortality from the various cancer types are generally increasing continent-wide. For cancer in Africa, little is known regarding its epidemiology, specific risk factors, and genetic components, particularly in terms of how Africa may differ from Western countries. Africa seems noteworthy for the large proportion of young patients and aggressive forms of the disease (69). Additionally, Africans continue to face a burden of biotic (e.g., infectious) and abiotic factors as well as lifestyle changes that impact cancer susceptibility and outcome. In terms of pan-African trends in prevalence, thyroid, colorectal, lung, prostate and breast cancer rates have been trending upwards from 2002 to 2018. Cervical and Stomach cancers have remained relatively stable. Incidences of bladder, liver and esophageal cancers have declined. Pan-African fatality rates for cervical, breast and prostate cancer have mostly been trending downwards from 2002 to 2018. In 2018, fatality rates from cervical, breast and prostate cancer hovered around or above 50%, 40% and 30%, respectively, across the five regions. As expected, there is considerable region to region variability in incidences and fatality rates.

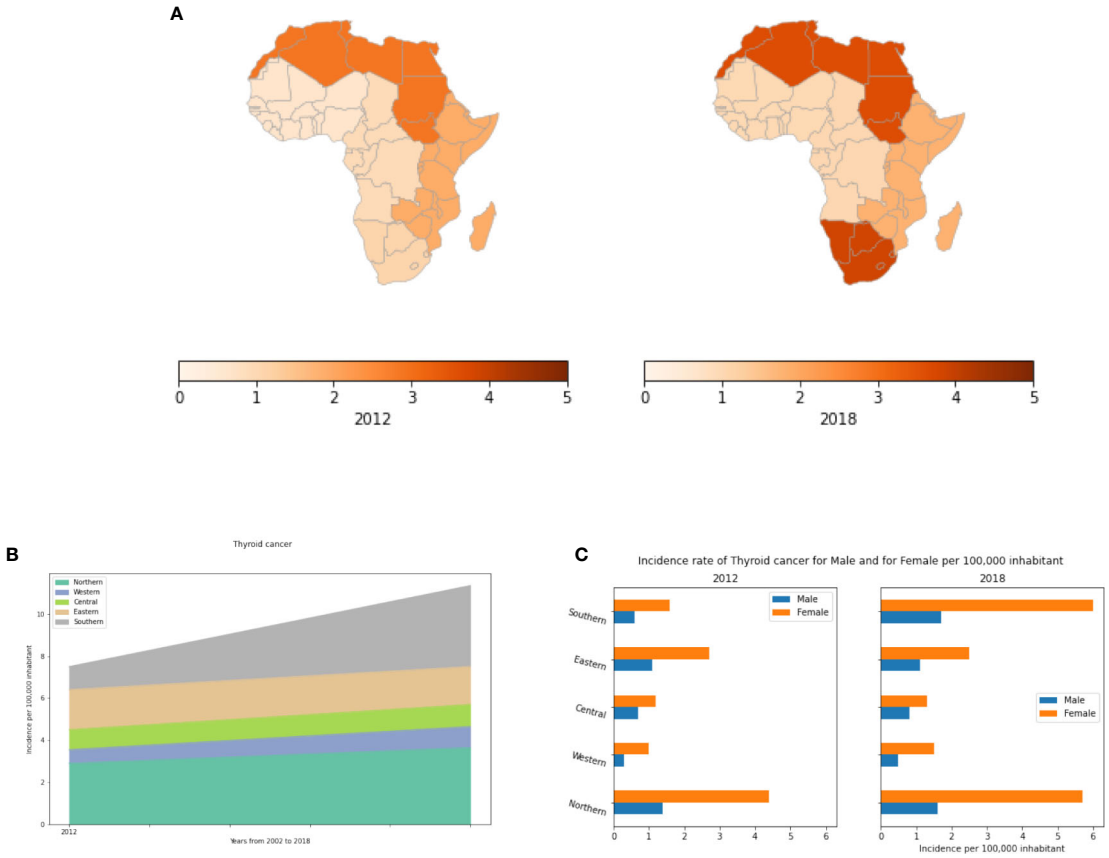

FIGURE 10 | Thyroid cancer incidence rates per year, by African region and by gender. **(A)** Incidence rates per 100,000 inhabitant in different African regions. **(B)** Dynamics of the incidence from 2012 to 2018. **(C)** Thyroid cancer incidence rates by gender in Africa.

In this study we show some of the disparities in cancer incidence and fatality rates that exist between the different African regions. In general, Southern Africa is a high-incidence area with a pattern of risk factors similar to those identified in Northern Africa. Recent decades have seen many lifestyle changes for Southern and Northern Africans, including urbanization, adopting of Western lifestyle habits, and increasing tobacco and alcohol consumption. Availability of diagnostic equipment and screening methods in Southern and Northern Africa can also identify cases and raise incidence rates. Hence, lower incidences in Central, Eastern and Western Africa may be more apparent than real as a result of failures to diagnose. Not all African countries have the same facilities in terms of screening and disease detection. This will influence the degree to which a country unintentionally under-reports actual incidence rates. In this context, our results also showed a significant association between Human Development Index and cancer fatality rates. For most cancer types, fatality rates were lower in Northern and Southern Africa compared to other African regions. These differences can stem from under-diagnosis of actual incidence rates, the severity of the disease at diagnosis, and access to therapy. Three major risk factors seem to influence cancer incidence rates in Africa: environmental factors, genetics and infectious agents. Consequently, changing lifestyle habits, having access to genetic testing, and vaccination would help decrease incidence rates. In Northern and Southern Africa, the most frequent cancers are those observed in Western countries (breast, colon, and prostate). This pattern differs from that of other African regions and countries, where infection-related cancers predominate (**Figure 13**). Early detection and better access to more diverse treatment options would likely bring down fatality rates.

In Southern and Northern Africa with very high incidences of prostate, colon and breast cancer, early detection and some lifestyle shifts could allow for early cure and lower incidences, respectively. To reduce IR and FR of these three cancer types, health systems could apply accurate genetic testing, and use newer targeted and immunotherapies, as these two regions have some access to the most up-to-date technologies and therapies. In Western, Central and Eastern regions, cervical cancer, a highly preventable cancer, creates a large public health burden. Therefore, we support widely available vaccinations and campaigns to increase awareness of the links between sexual behavior and cervical cancer. The high incidence of some specific cancers in certain regions remains largely unexplained. For instance, esophageal cancer is much more prevalent in Eastern

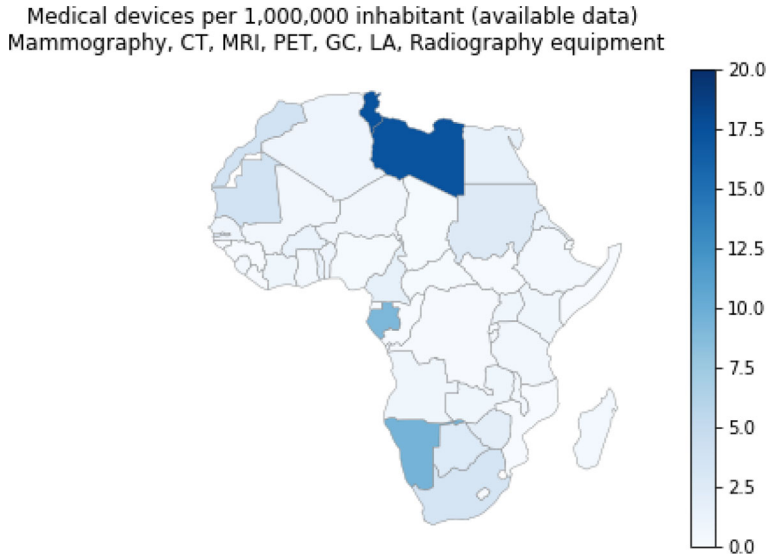

FIGURE 11 | Cancer Medical devices per 1,000,000 inhabitants. These include the following medical devices: Mammographs, Computed Tomography, Magnetic Resonance Imaging, Positron Emission Tomography, Gamma Camera or Nuclear Medicine, Linear accelerator, Telecobalt unit, Radiotherapy. Source Global atlas of medical devices, World Health Organization, 2017.

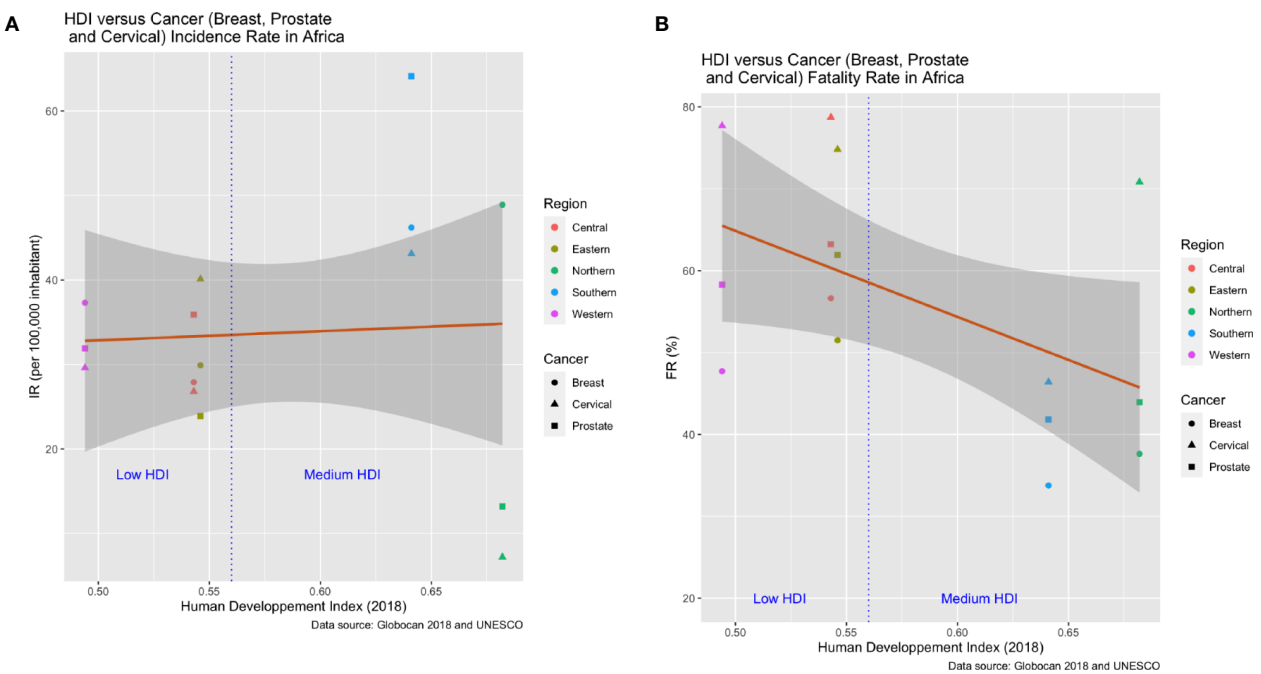

FIGURE 12 | Association between human development index (HDI) and cancer incidence and fatality rates for the five African regions in 2018. The data include fifteen points per graph resulting from three cancer types (breast, prostate and cervical) per region. **(A)** The relationship between HDI and cancer incidence rates is not significant and shows no trends other than higher variance among the cancer types for the two regions (Northern and Southern Africa) with the highest HDI. **(B)** Cancer fatality rates decline significantly with HDI for the three most frequent cancer types.

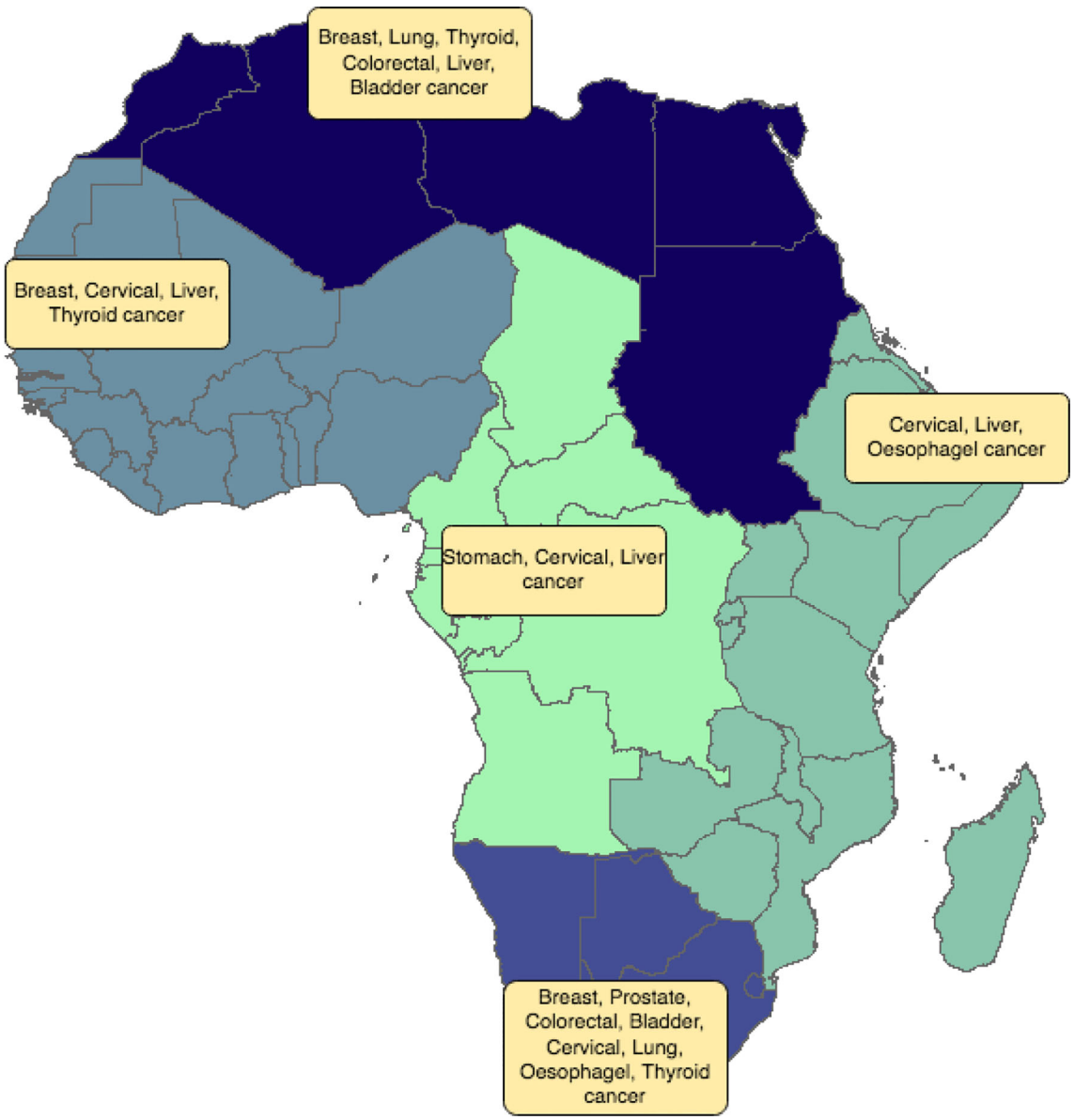

FIGURE 13 | Distribution of the most frequent cancer types by African region. Different colors refer to the different African regions (North, East, West, Central and Southern Africa).

Africa than in any other region. The prevalence of bladder and thyroid cancer in Northern Africa seems anomalous. We advocate epidemiological studies on cancer risk factors tailored specifically for each African region (or country), and relevant cancer types. Such studies are necessary to understand the conditions that have created the perfect storm that drives disparities in cancer outcomes inside Africa. The goal should be country- and region-specific plans to reduce cancer incidences and mortality among Africans.

Except for thyroid cancer, our results reveal higher incidences of the remaining cancer types in males compared to females (not withstanding breast and cervical cancer). Sometimes the difference is 2-5 fold! Some of this difference may be attributable to smoking, alcohol consumption and exposure to environmental carcinogens at work or outside of the home. Higher male incidence than females has also been observed in non-African populations. A portion of the difference may be the absence of a second X chromosome in males (70). showed that a subset of X-chromosome tumor suppressor genes can escape from X-inactivation that might occur from a gene mutation on one of the X-chromosomes. The authors conclude that biallelic expression of these genes in females explains a portion of the reduced cancer incidence compared to males across a variety of cancer types. How large this effect is should be studies and remains unknown.

Our work reveals unanswered questions regarding cancer epidemiology and genetics in Africa. Therefore, we highly recommend African governments, policy makers, and international organizations such as the World Health Organization direct efforts towards cancer research that will improve decision making, and improve the health of African populations. For Africa, cancer research is a necessity, not a luxury. Indeed, very few or no resources are allocated for cancer research in Africa, and very few data are available on medical devices used in cancer care. Much can be gained by better and more comprehensive record keeping. When collated, curated, and stored electronically such data can identify patterns, and opportunities for interventions. Indeed, a limitation of our analyses rests on making estimates of incidence and fatality rates, HDI, and medical devices from the Global Cancer Observatory database, UNESCO, and WHO. While the best sources currently available, their representation of the data relies on the representativeness and quality of the source information as gleaned from or provided by individual countries and their Health Ministries. Therefore, country or continent-wide data repositories can direct research towards cancers and regions where most needed. Healthcare, clinical and epidemiological research allow for evidence based formulations of health policies and allocations of scarce resources towards facilities, diagnostics and therapeutics. The lack of evidence based decision making in Africa squanders opportunities related to cancer research and cancer care (71).

Untapped opportunities exist to reduce the burden and disparities due to cancer by enhancing cancer communication and public health messages about affordable care and prevention strategies and by expanding the targets of engagement to include private sector stakeholders, researchers, epidemiologists, learned societies and advocacy groups.

As in the case of cervical cancer, the fatality rates of all cancers in Africa will be influenced by sociocultural, religious and gender norms. Such norms will vary across regions and between countries. Particular norms will influence cancer screening, a person's ability or willingness to seek treatment, and health disparities, This points to the need to include social scientists, social workers and diverse public health officials in taking broad-based approaches to improving cancer prevention and outcomes. Future work could include evaluating the role of norms in facilitating or hindering cancer care in Africa.

CONCLUSION

Cancer has received low priority for health care services in Sub-Saharan Africa. This study shows that there are several disparities in cancer diagnosis and screening between the different African regions that can be one of the reasons for differences in cancer incidence and mortality rates across regions. There are pending concerns regarding cancer care in the continent. Therefore, Africa has to invest in cancer prevention, management and in evidence-based care. Investing in cancer research will help to understand risk factors specific to Africa or to specific regions of Africa. The improvement of cancer clinical care in Africa can be achieved by making evidence based decisions using key indicators including metrics on urbanization, HDI, co-morbidity, availability of medical devices, vaccination and life expectancy. Cancer incidence data need to be evaluated at the national and regional level by implementing accurate cancer control programs. The relative advances in cancer screening and diagnosis in Southern and Northern Africa can be taken as a model for other African countries and regions.

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.

AUTHOR CONTRIBUTIONS

YH, IA-T, and AB designed the workflow and wrote this paper. AZ and IA-T collected the data and analyzed it. SA, SB, and JB revised the manuscript. 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/fonc.2021.650117/full#supplementary-material

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Preinvasive Colorectal Lesions of African Americans Display an Immunosuppressive Signature Compared to Caucasian Americans

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Background: African Americans (AAs) have higher colorectal cancer (CRC) incidence and mortality rate than Caucasian Americans (CAs). Recent studies suggest that immune responses within CRCs contribute to the disparities. If racially distinct immune signatures are present in the early phases of carcinogenesis, they could be used to develop interventions to prevent or slow disease.

Methods: We selected a convenience sample of 95 patients (48 CAs, 47 AAs) with preinvasive colorectal adenomas from the surgical pathology laboratory at the Medical University of South Carolina. Using immunofluorescent-conjugated antibodies on tissue slides from the lesions, we quantified specific immune cell populations: mast cells ($CD117^+$), Th17 cells ($CD4^+RORC^+$), and NK cell ligand (MICA/B) and inflammatory cytokines, including *IL-6, IL-17A*, and *IFN-γ*. We compared the mean density counts (MDCs) and density rate ratios (RR) and 95% CI of immune markers between AAs to CAs using negative binomial regression analysis. We adjusted our models for age, sex, clinicopathologic characteristics (histology, location, dysplasia), and batch.

Results: We observed no racial differences in age or sex at the baseline endoscopic exam. AAs compared to CAs had a higher prevalence of proximal adenomas (66% *vs.* 40%) and a lower prevalence of rectal adenomas (11% *vs.* 23%) (p =0.04) but no other differences in pathologic characteristics. In age, sex, and batch adjusted models, AAs *vs.* CAs had lower RRs for cells labeled with IFNγ (RR 0.50 (95% CI 0.32-0.81); p=0.004) and NK cell ligand (RR 0.67 (0.43-1.04); p=0.07). In models adjusted for age, sex, and clinicopathologic variables, AAs had reduced RRs relative to CAs for CD4 (p=0.02), NK cell ligands (p=0.01), Th17 (p=0.005), mast cells (p=0.04) and IFN-γ (p< 0.0001).

Conclusions: Overall, the lower RRs in AAs *vs.* CAs suggests reduced effector response capacity and an immunosuppressive ('cold') tumor environment. Our results also highlight the importance of colonic location of adenoma in influencing these differences; the reduced immune responses in AAs relative to CAs may indicate impaired immune surveillance in early carcinogenesis. Future studies are needed to understand the role of risk factors (such as obesity) in influencing differences in immune responses by race.

Keywords: race, disparities, colorectal adenomas, immune infiltrate, immune cells

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy among men and women in the US and the second leading cause of cancer death (1). African Americans (AAs) experience higher incidence and mortality from CRC than Caucasian Americans (CAs), especially at younger ages (2–5). Although the disparities are not fully understood, we found that racial differences in the immune landscape of CRC's play an essential role in patient survival (6). However, whether race-related differences in immune responses are present in the early phases of the carcinogenesis process is unknown (7–9).

The immune system's role in controlling the growth of established CRC or limiting metastatic expansion is well documented (7, 10, 11). Higher densities of tumor-infiltrating lymphocytes (TILs) with cytotoxic or effector properties (such as Th1, CD8+Tcells, NK cells) are associated with lower recurrence, and better prognosis (10, 12, 13), whereas a greater infiltration with inflammatory Th17 or IL17a cytokines are associated with poorer outcomes (7, 14, 15). Recent evidence has identified lower cytotoxic responses (e.g., Granzyme B, *IFNG*) in CRCs of AAs compared to CAs (16–19), yet higher expression for inflammatory or markers of exhausted T-cells (19). Understanding whether racial differences in immune signatures are evident in earlier phases of carcinogenesis have important consequences for primary and secondary prevention (20, 21).

Earlier data has pointed to the importance of clinicopathologic features (location, histology, grade) in shaping immune responses in colorectal neoplasms (22–24). These features also differ in prevalence by race (4, 5, 25) suggesting the potential for confounding. In the present study, we compared a diverse group of immune cell markers and cytokines in colorectal adenomas from AAs and CAs. We hypothesized that AAs compared to CAs would present at diagnosis with lower density counts for cytotoxic cells/cytokines (NK ligands, mast cells, IFN-γ) and higher inflammatory responses (Th17, Il17a) based on published data in invasive disease (18, 19). Specifically, we compared mean density counts (MDCs) and density rate ratios (RR and 95% CI) for mast cells (CD117), Th17 cells (CD4/RORC), CD4 helper T-cells, NK cell ligands (MICA/B), and cells labeled with inflammatory cytokines, including IL-6, IL-17A, and IFN-γ while adjusting for potential confounding clinicopathologic characteristics.

MATERIALS AND METHODS

In this cross-sectional study, we used the Medical University of South Carolina (MUSC) pathology laboratory information system CoPath (Cerner Corporation, Kansas City, MO), to identify a convenient sample of colorectal adenomas excised from patients who underwent a sigmoidoscopy or colonoscopy with polypectomy between October 2012 and May 2016. Patient samples were excluded if the lesion was < 5 mm, as estimated by the study pathologist (SS), or if there was a known familial hereditary syndrome (FAP or Lynch syndrome). The MUSC Institutional Review Board has approved the research study (IRB # PRO-00007139).

Select of Patient Cohort

The Co-Path system was queried to identify patients diagnosed with an advanced colorectal adenoma. We included search terms colorectal, colon or rectal, adenoma or polyp, as well as high-grade dysplasia, focally high-grade dysplasia, sessile, or traditional serrated adenoma with high-grade dysplasia, or dysplasia). We identified 126 patients (152 lesions) who met the initial screening criteria (dates, advanced histology, colon or rectal polyp, or adenoma) in our search of the Co-Path system. Cases were excluded if the lesion was of non-colonic origin, < 5 mm, as estimated by the MUSC pathologist, or a known familial hereditary syndrome (FAP or Lynch syndrome). Of these, 102 patients were confirmed as having at least one pre-invasive colorectal adenoma with sufficient tissue to be analyzed; 14 of these patients had more than one lesion present at diagnosis. We selected 95 analytic cases (48 CAs, 47 AAs) with at least one conventional adenoma per patient (i.e., tubular, tubulovillous, or villous histology) for the current analysis. We excluded patients (n=7) with a serrated histology lesions (sessile or traditional) index lesion because of potential differences in the prevalence of serrated histology by race (26) and immune infiltrate (27, 28).

For all cases, we abstracted personal characteristics (age at diagnosis, sex, race) from the electronic medical records and clinicopathologic data (anatomic location, grade, degree of dysplasia) from CoPath. To ensure uniformity of diagnoses, an independent pathologist (CB) reviewed all cases using a newly prepared Hematoxylin and Eosin (H&E) slide. The pathologist was blind to any patient or clinical information associated with the lesions and documented the dominant histologic pattern within the adenoma (tubular adenoma, tubulovillous adenoma, villous adenoma) and graded the villous component (0-100%). The pathologist also identified the lesion's grade according to the most dysplastic area on the slide (i.e., none, low, focally high, high). Each patient contributed one lesion per analysis.

Immunofluorescence (IF) Optimization, Staining, and Scanning Procedures

The University of North Carolina Translational Pathology Laboratory (TPL) performed the immunofluorescence (IF) multiplex staining. Prior to initiating the IF procedures, all antibodies were optimized using positive (e.g., tonsil) and negative control tissues as recommended by the vendors. A small number of colorectal polyps (similar in size, age and histology to the polyps in the study cohort) and invasive colorectal cancers were also stained and analyzed to demonstrate feasibility. All stains were reviewed by the study immunologist (JW), the pathologist (DL), a cancer epidemiologist (KW), and TPL Director (NNF) to ensure agreement and proper staining of cell types (e.g., visual inspection by a pathologist that CD4 was staining lymphocytes). Consecutive duplex (CD117-MICA and CD4-RORC) or triplex (IFN-γ, IL-6, IL-17A) IF stains were performed in the Leica Bond-Rx fully automated staining platform (Leica Biosystems Inc., Norwell, MA). Slides were dewaxed in Bond^{TM} Dewax solution (#AR9222) and hydrated in Bond Wash solution (#AR9590). The application order of the pretreatment and staining steps, including epitope retrieval (ER), peroxidase and protein blocking, primary and secondary antibodies, and the Tyramide Signal Amplification (TSA), are shown in **Supplemental Table 1**. The ER for the 1st targets (MICA/B, IL-6) was maintained for 20 minutes in Bond ER solution 1 at pH 6.0 (#AR9661) and in ER solution 2 at pH 9.0 (#AR9640) for CD4; and all other targets (2nd and 3rd) for 10 min in ER solution 1. The ER was followed with 10 minutes of endogenous peroxidase blocking using freshly made 3% H_20_2 (Fisher BP2633-500) in methanol (Fisher A433P-4). Stains were completed in succession from 1st to 3rd. Slides were counterstained with Hoechst 33258 (# H3569, Life Technologies, Carlsbad, CA) and mounted with ProLong® Gold Antifade Mountant (#P36930, Life Technologies). Positive and negative controls (in which all primary antibodies were omitted) were included in each staining run. Single stain controls (with one primary antibody omitted) were also included to check the cross and detection's cross-reactivity.

Automated Image Analysis

We imaged slides in the Leica Aperio-FL (Leica Biosystems) in the Hoechst (blue), Cy2 (green/cyan), Cy3 (green), Cy5 (red) channels. The pathologist and analyst manually annotated regions containing tumor or non-tumor glandular colon tissue on the entire image, only excluding regions containing tissue artifacts or non-cellular areas. Annotated tissue regions were digitally analyzed using Tissue Studio Composer software version 2.7 (Tissue Studio Library version 4.4.2; Definiens Inc., Carlsbad CA). Tissue Studio software was used to identify all nucleated cells within the area on the image (mm^2). The software determined whether the average staining intensity was above the background threshold determined by negative regions on test slides for each immune protein marker. Tissue Studio software identified cells that expressed or co-expressed the targeted immune markers. We calculated the total number of nucleated cells within the polyp region and the number of these cells positive for each marker. To signify Th17 cells, we used colocalization of CD4 and RORC. Representative stained images and software generated images are shown in **Supplementary Figure 1**.

Statistical Analysis

For cases, the primary endpoint was the count of immune markers within adenomas. We modeled the log count of positive cells using a negative binomial generalized linear model (GLM), with the logarithm of the sample area included as a model offset for each analyte (29). Briefly, in GLMs for count response variables, the offset is an adjustment term (equivalent to a covariate with unit slope) included in the model whenever the expected count is proportional to an index. Here, we expect the labeled cell counts to be proportional to the spatial area of nucleated cells, a feature that must be accounted for to appropriately isolate the effects of model covariates. Race was included in all models as the primary independent variable of interest, and group comparisons of mean immune marker counts were performed using model-based contrasts (AAs vs. CAs).

Univariable and multivariable models estimated the mean density counts (MDC) and density count rate ratios (RR) and their 95% confidence intervals (CI) for AAs and CAs for each marker type. All multivariable models were adjusted for age (continuous), sex, and IF batch (indicator variables for six batches) (base model). Additional multivariable models were constructed by adding each of the following clinicopathologic variables individually to the base model: lesion anatomic location (proximal colon, distal colon, rectum), percent of villous component (0-100%), and degree of dysplasia (not high, high-grade); fully adjusted models controlled for age, sex, batch, location, histology, and dysplasia. P-values for the differences in models were based on Wald tests. We also tested the interactions between race and clinicopathologic variables and immune counts using the likelihood ratio test. All tests were two-sided, with a significance level (alpha) of $p < 0.05$.

RESULTS

We analyzed preinvasive lesions from 95 patients (48 CAs, 47 AAs). Univariate associations of personal and clinicopathologic characteristics with race are shown in **Table 1**. AAs had a higher prevalence of proximal adenomas (66% *vs.* 40%) than CAs and a lower prevalence of rectal adenomas (11% vs. 23%) ($p = 0.04$). AAs compared to CAs presented with a similar prevalence of high-grade dysplasia lesions compared to CAs (53% vs. 40%, $p=0.18$). No difference was detected in the percent of villous histology by race ($p=0.96$).

Table 2 shows the MDCs for each immune marker by race and the RR (95% CI) of the immune markers and race in the multivariable models. In age, sex, and batch adjusted models, AAs had lower RRs for cells labeled with IFNγ ($p=0.01$) and NK cell ligand ($p=0.07$) than CAs. In the multivariable models additionally adjusted for colonic location, AAs compared to CAs had significantly lower RRs for cells labeled with CD4, Th17, NK ligands, mast cells, and IFNγ. Further adjustment for percent villous histology and degree of dysplasia did not materially alter the RRs further (i.e., fully adjusted models, **Table 2**). There were

TABLE 1 | Patient and lesion characteristics at diagnosis in African Americans (AAs) and Caucasian Americans (CAs).

Baseline Variables	AAs	CAs	*p*-value*
	N = 47	N = 48	
Age, mean (SD)	63.2 (9.5)	63.3 (10.1)	0.96
Sex, n (%)			0.58
Female	18 (38)	21 (44)	
Male	29 (62)	27 (56)	
Villousness, n (%)			0.96
0-25%	12 (26)	11 (23)	
26-75%	18 (38)	19 (40)	
76%+	17 (36)	18 (37)	
Location, n (%)			0.04
Proximal	31 (66)	19 (36)	
Distal	11 (23)	17 (40)	
Rectal	5 (11)	11 (23)	
Dysplasia, n (%)			0.18
High	25 (53)	18 (40)	
Not High	24 (47)	34 (60)	

**p-values determined using chi-square tests for categorical variables and t-tests for continuous.*

no statistically significant interactions between race and any clinicopathologic variables (location, degree of dysplasia, percent villous histology) on the immune counts.

DISCUSSION

Overall, we observed few differences in the prevalence of personal or adenoma characteristics by race at the endoscopic exam. The notable exception being that AAs, compared to CAs, had a higher prevalence of proximal neoplasia. For the immunologic markers, AAs had significantly lower CD4, Th17, mast cells, NK ligands, and *IFN-γ* in the fully adjusted models than CAs. IL17a was non-significantly higher in the same race comparison. Our results point to pervasive differences in immune densities in preinvasive lesions by race.

A few studies (30–34) have described the immune cell contextures within preinvasive lesions, but none have considered these differences by race. Our results point to a dampened immune response in AAs compared to CAs across multiple analytes known to have different functions in the tumor bed. For example, NK ligands, mast cells, and IFNγ play essential roles in orchestrating the cytotoxic (killing) response in the tumors, enabling the host to recognize and eliminate neoplastic cells (7, 14, 35). Reduced cytotoxic responses in AAs *vs.* CAs could suggest compromised immune surveillance capability and the promotion of an environment favorable for tumor growth. Our data pointed to a high density of IFNγ markers and NK cell ligands within the tumor bed relative to other cell types suggesting these immune markers may be very active in early carcinogenesis. Other studies have found that the higher densities of Th1 cytokines and NK cells are inversely related to tumor progression and high grade dysplasia (30, 36). The consequences of lower Th17 densities in adenomas of AAs relative to CAs are less clear due to the functional plasticity of Th17 cells. Th17 cells can promote an inflammatory or immunosuppressive tumor environment depending on the cytokine milieu (37–39) but also play a fundamental role in epithelial barrier homeostasis and control of microbial populations in the gut (40–42). The lower Th17 densities in AAs *vs.* CAs could lead to mucosal barrier compromise and increased microbial translocation, while the trend toward higher IL17a responses may reflect an inflammatory reaction to tumor associated microbes (41, 43). Cui and others (32) found IL17a increased from low to high dysplastic lesions, suggesting a positive correlation with tumor progression in early carcinogenesis; no studies have examined Th17 cells in adenomas. More research is needed to understand the benefits/harms of Th17/IL17a in the tumor environment and their role in tumor progression.

Lower cytotoxic or effector T cell responses in CRCs of AAs *vs.* CAs have been observed in a few previous studies in colorectal cancers (16–19). Basa et al. (18) identified lower protein expression of granzyme B in CRCs of AAs compared to CAs. Granzyme B plays a crucial role in the apoptosis of tumor cells and is secreted by many cells, including NK cells (44), CD8+ T-cells (44), and mast cells (45). Other recent data showed that CRCs in CAs vs. AAs had greater expression of cytotoxic genes *GZMB* and *IFNG* (19). In that study, AAs also exhibited a greater immunosuppressive and exhausted T-cell phenotype than CAs and increased expression of antimicrobial inflammatory cytokines (46). There is also evidence of reduced cytotoxic responses (47) or immune suppression (48) in AAs compared to CAs with prostate cancer and non-cancer contexts (49). Whether there are shared

TABLE 2 | Mean density counts (MDC) and density rate ratios (RR) in African American (AA) and Caucasian American (CA) tumor immune markers.

Immune markers	AAs N=47 MCDs[1] (95% CI)	CAs N=48M CDs[1] (95% CI)	AAs *vs.* CAsRR[2] (95% CI)	AAs *vs.* CAsRR[3] (95% CI)
CD4+	81 (59-110)	103 (75-140)	0.78 (0.49-1.26)	**0.53 (0.33-0.87)**
Th17	65 (46-90)	89 (64-125)	0.72 (0.43-1.20)	**0.43 (0.26-0.74)**
NK cell Ligand	1288 (959-1729)	1931 (1443-2583)	0.67 (0.43-1.04)	**0.57 (0.37-0.88)**
IL17a	254 (199-325)	197 (154-251)	1.29 (0.90-1.85)	1.33 (0.93-1.91)
IFNγ	1065 (781-1451)	2112 (1556-2866)	**0.50 (0.32-0.81)**	**0.40 (0.25-0.65)**
IL6	749 (599-938)	898 (720-1121)	0.83 (0.60-1.17)	0.79 (0.58-1.08)
Mast Cells	44 (32-60)	62 (45-83)	0.71 (0.45-1.13)	**0.63 (0.41-0.97)**

[1]Mean density counts (MDC) per mm² adjusted for age, sex, batch. [2] RR AA vs. CA (referent) adjusted for age, sex, batch [3]RR AA vs. CA (referent) adjusted for age, sex, location, degree of dysplasia, percent villous histology, and batch. P-value for difference by race were determined using Wald statistics. P-values < 0.05 are bolded.

risk factors or genetic characteristics influencing these results is not known; however, the racial differences appear to be influenced by tumor location in the colorectum.

The tumors of the proximal colon (compared to distal or rectal) are more apt to be immunologically active (or 'hot') (50, 51). In an earlier study in this population six of the seven markers studied (all except IL-17a) had significantly higher density counts in the proximal colon than distal colon or rectum. The higher immune activity in the proximal colon appears to be shaped by many factors, including the porousness of the mucosal barrier, microbiota, and metabolic activity (52, 53). It's tempting to speculate that differences in the prevalence of risk factors for proximal colon neoplasia (such as diabetes, obesity) (54–56) – which are more common in AAs– contribute to the diminished immune responses we observed in AAs vs. CAs. Metabolic dysregulation, common in obesity and diabetes, is associated with chronic immune activation and overtime, reduced antitumor effector responses, immune cell death, and tumor progression (57–59). AAs compared to CAs have a higher prevalence of proximal neoplasia (24, 60, 61), consistent with our findings in the present study. Previously, we identified a higher prevalence of metabolic risk factors (i.e., obesity, diabetes, hypertension) in AAs vs. CAs in patients undergoing colonoscopy (62, 63). Future studies will be needed to investigate whether the higher prevalence of metabolic risk factors in AAs compared to CAs contributes to the diminished immune responses observed in the present study when adjusting for colonic location.

Our study has several advantages. It is the first study to compare the immune environment in preinvasive colorectal lesions by race. We adjusted our results for important potential confounders such as age, location, grade, histology. We analyzed immune counts in the entire slide (*vs.* cores), which represent the whole tumor. An independent pathologist with no knowledge of the clinical or personal characteristics of the patients provided blinded diagnoses. We are also aware of several limitations of this study. We had a relatively small number of cases. We did not assess immune counts in different regions of the polyp (e.g., stromal, epithelial), which appear important for CRC outcomes (64). Our study lacks information about the ancestral informative markers to characterize the ancestry in our population.

Our results suggest that detailed immunologic profiling of preinvasive lesions will be an essential next step to understand the contributions of different immune cell subsets in CRC risk and prognosis. We lack a comprehensive inventory of immune signatures by race. Although small, our study demonstrates that AAs have an immunosuppressive phenotype at the initial phases of carcinogenesis. If confirmed in a larger cohort of patients, this signature could be used as a prognostic biomarker to guide interventions when therapeutic options may be more effective in preventing progression and recurrence.

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 Medical University of South Carolina Institutional Review Board has approved the research study (IRB # PRO-00007139). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KW: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript; administrative, technical, or material support; study supervision. GN: analysis and interpretation of data; drafting of the manuscript; statistical analysis. CB: study concept and design; acquisition of data; analysis and interpretation of data. DL: study concept and design; acquisition of data; analysis and interpretation of data; study supervision. CP: analysis and interpretation of data; critical revision of the manuscript NN-F: acquisition of data; analysis and interpretation of data; critical revision of the manuscript; administrative, technical, or material support; study supervision. SC: analysis and interpretation of data; critical revision of the manuscript; administrative, technical, or material support; study supervision. SG: critical revision of the manuscript. EC: critical revision of the manuscript. AB: analysis and interpretation of data. EH: study concept and design; analysis and interpretation of data; statistical analysis. JW: study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript; obtained funding. JB: study concept and design; critical revision of the manuscript. AA: study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript. 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/fonc.2021.659036/full#supplementary-material

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Disparity in Access to Oncology Precision Care: A Geospatial Analysis of Driving Distances to Genetic Counselors in the U.S.

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In the US, the growing demand for precision medicine, particularly in oncology, continues to put pressure on the availability of genetic counselors to meet that demand. This is especially true in certain geographic locations due to the uneven distribution of genetic counselors throughout the US. To assess these disparities, access to genetic counselors of all specialties is explored by geography, cancer type, and social determinants of health. Geospatial technology was used to combine and analyze genetic counselor locations and cancer incidence at the county level across the US, with a particular focus on tumors associated with *BRCA* mutations including ovarian, pancreatic, prostate and breast. Access distributions were quantified, and associations with region, cancer type, and socioeconomic variables were investigated using correlational tests. Nationally, in 2020, there were 4,813 genetic counselors, or 1.49 genetic counselors per 100,000 people, varying between 0.17 to 5.7 per 100,000 at the state level. Seventy-one percent of U.S. residents live within a 30-minute drive-time to a genetic counselor. Drive-times, however, are not equally distributed across the country – while 82% of people in metropolitan areas are 30 minutes from a genetic counselor, only 6% of people in nonmetro areas live within 30 minutes' drive time. There are statistically significant differences in access across geographical regions, socioeconomics and cancer types. Access to genetic counselors for cancer patients differs across groups, including regional, socioeconomic, and cancer type. These findings highlight areas of the country that may benefit from increased genetic counseling provider supply, by increasing the number of genetic counselors in a region or by expanding the use of telegenetics a term used to describe virtual genetic counseling consults that occur *via* videoconference. Policy intervention to allow genetic counselors to bill for their services may be an effective route for increasing availability of genetic counselors' services However, genetic counselors in direct patient care settings also face other challenges such as salary, job satisfaction, job recognition, overwork/burnout, and appropriate administrative/clinical support, and addressing these issues should also be considered along with policy support. These results could support targeted policy

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reform and alternative service models to increase access to identified pockets of unmet need, such as telemedicine. Data and analysis are available to the public through an interactive dashboard[1].

Keywords: Genetic counseling, health access, social determinants of health, geographic information system, cancer care, precision medicine, *BRCA*, healthcare equity

INTRODUCTION

Advances in genomic research, new testing technologies, increased use of electronic medical records, and general public interest have led to the expansion of precision medicine, which is an approach to patient care that allows doctors to select treatments that are most likely to help patients based on a genetic understanding of their disease (1). Precision medicine offers the potential to improve health outcomes by allowing providers and patients to select treatments most likely to be effective considering an individual's genetic, environmental, and lifestyle traits (1). The expansion of genetic and genomic testing has increased demand for providers along the oncology patient journey, particularly on genetic counselors, to educate patients and promote informed decision-making (2). Previous research has shown that current and forecast demand for genetic counselors exceeds supply, that the spatial distribution of genetic counselors is variable across the southern United States, and that local access to a genetic counselor is related to social determinants of health (SDoH) such as race or household income (2–4). To measure differences in access and health system equity, it is imperative to describe the spatial patterns of provider access for cancer patients, as well as how access is affected by factors such as socioeconomics, geographical region and cancer type (2, 5).

Genetic counseling is particularly relevant for cancer care, where genetic counselors meet with patients to advise on risk of hereditary cancer syndromes and discuss cancer screening, risk-reduction, and treatment options. National consensus guidelines recommend genetic counseling for patients with a personal and/or family history of cancer that is suggestive of a hereditary cancer syndrome (6), highlighting the pivotal role played by these providers for precision oncological care. The National Comprehensive Cancer Network recommends germline *BRCA* testing for individuals with a personal and/or family history of ovarian or pancreatic cancer, and a personal and/or family history of breast or prostate cancer as long as other criteria are met (age of diagnosis, number of family members with associated cancers, ethnicity, etc.) (6). These recommendations represent numerous patients and a source of stress on the medical system. Although the COVID-19 pandemic has caused a dramatic transition to telework and telehealth, significant barriers exist to the expansion of such alternative service delivery models for virtual genetic counseling, such as Medicare policy that does not recognize genetic counselors as providers eligible for reimbursement of any services, virtual or in-person (7). Furthermore, 26 states require licensure for genetic counselors, but the lack of license reciprocity options can limit the ability of genetic counselors to practice across state lines when offering telegenetics or virtual genetic counseling appointments (8). As such, access to in-person genetic counselors remains critical to understand.

Geographical information systems (GIS) offer a method to understand spatial distributions of cancer patients, including subsets of those with cancers associated with *BRCA* mutational status such as breast, ovarian, prostate and pancreatic (9), and providers in the context of local factors that may affect health outcomes. This technology has been applied to medical contexts, including linking hotspots of kidney disease with water contamination, partitioning the United States into regions based on SDoH and describing distributions of vaccine providers relative to patients (10–12). The objective of the current analysis was to leverage GIS methods to map and quantify the spatial distributions of genetic counselors at the national level, incorporate data on disease burden and population characteristics to measure real demand for genetic counseling, quantify the degree of supply-demand match *via* per-capita access metrics, derive time to travel to genetic counselors across the country, and investigate differences in these distributions according to SDoH.

MATERIALS AND METHODS

Geospatial methods were used to understand the relationship between genetic counselor locations, patient population locations, and SDoH in the US. Data were collected along three categories: location of genetic counselors working in direct patient care, incidences of cancers (for all cancer subtypes and those specifically associated with *BRCA* mutations: breast, ovarian, prostate, and pancreatic cancers) and socioeconomic variables.

Data on genetic counselors in the United States were extracted from three sources: the Centers for Medicare & Medicaid Services (CMS) National Plan and Provider Enumeration System (NPPES) National Provider Identifier (NPI) registry, and the public-facing member directories of both the American Board of Genetic Counseling (ABGC) and the National Society of Genetic Counselors (NSGC) (see **Supplement**). All data were obtained between May and July of 2020. Although NSGC and ABGC datasets included information on provider specialty, the NPPES dataset did not include that information. The present analysis did not stratify by provider specialty, such as cancer genetics.

The office addresses of the genetic counselors (as self-reported in the public-facing membership directories or present in the

[1]Interactive dashboard available at https://gisgeneticcounselor.shinyapps.io/CounselorExplorer/.

business practice location address field of NPPES) were converted into latitude and longitude using Google Maps Geocoding. Individual datasets were cleaned and reconciled into a registry of 4,813 unique genetic counselors across the 50 states and the District of Columbia (See **Supplemental Figure 3** for count of genetic counselors by data source).

Cancer incidence rates for the years 2013-2017, the latest years for which incidence data are available, were downloaded from the Centers for Disease Control and Prevention (CDC) United States Cancer Statistics (USCS) program and filtered to county-level statistics on total (sum of all cancer types), breast, ovarian, pancreatic and prostate cancer. Note that USCS does not contain data on Kansas or Minnesota incidence rates, as those states prohibit release of county-level data (state-level data were available and incorporated into relevant analyses).

County-level demographic data were downloaded from the American Community Survey (ACS) 2018 5-year estimates, including total population, median household income, median age (for all residents and separately for men and women), and estimates of population stratified by sex, race, Hispanic origin, highest educational attainment for those aged at least 25 years, employment status for those aged at least 16 years (either civilian or armed forces), and health insurance coverage (public, private, and either). Counties were classified into metropolitan and nonmetropolitan categories using Rural-Urban Continuum Codes downloaded from the Economic Research Service at the United States Department of Agriculture[2].

Patient access to care, in this study meaning patient's physical proximity to genetic counselors, was calculated at the state level by taking the weighted median of county-level drive-time to the closest provider, weighted by cancer incidence rate, for all cancer types or by each of four *BRCA*-associated tumor sites. County shapefiles for GIS were downloaded from the US Census Bureau and used to categorize counties into two groups, depending on whether any genetic counselor latitude/longitude point fell within a county polygon. The distance between each county and the closest genetic counselor was determined by calculating the Haversine distance (surface distance between two points on a sphere) between population-weighted county centroids (from the US Census Bureau) and all providers. Population weighted-county centroids reflect population distributions within a county, in contrast to geographic centroids. The Mapbox Matrix API was used to calculate drive-times to the nearest 20 genetic counselors for each county to render the calculation computationally feasible on standard machines.

Hypothesis tests were conducted for differences in SDoH between counties in the two access groups and for differences in access to care between Census regions, cancer types, and combinations of regions and cancer types. SDoH variables considered were age, sex, race, ethnicity, household income, employment, health insurance coverage and education. An analogous analysis of virtual state-level access and correlations with SDoH was also performed (see **Supplemental**). The Wilcoxon rank-sum test was used to investigate access differences, the Kruskal-Wallis test was used to investigate overall differences in access, the pairwise Wilcoxon test was used to investigate pairwise differences in access, and p-values were Bonferroni-corrected to account for multiple comparisons. Statistical analyses were performed using the R Statistical Software (13).

[2] Downloaded from https://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx.

RESULTS

A total of 4,813 genetic counselors were identified, or 1.49 genetic counselors per 100,000 people nationally. Mississippi demonstrated the lowest rate of 0.17 genetic counselors per 100,000 people, and Washington, D.C. had the highest rate of 5.7 per 100,000. **Figures 1A, B** show maps of genetic counselor locations and county-level drive-time to the nearest provider, with a median drive-time of 60.3 minutes (range 1.7 – 7102.4, IQR 57.3). These spatial distributions show that genetic counselors tend to cluster together especially in urban areas, resulting in varied access to care. Distributions in **Figures 1C, D** show that metropolitan counties have systematically shorter drive-times to care: weighting by population shows that while 71% of people in the U.S. are within 30 minutes of their nearest genetic counselor, it is 82% for metro residents (median 33 minutes, range 2 – 374, IQR 34), in contrast to 6% for nonmetro residents (median 79 minutes, range 3 – 7102, IQR 56).

Figure 2 shows disparities in access to care as correlations between physical proximity to care and geographical region (A) and cancer type (B), or between genetic counselor access and SDoH (C). Distributions of the outcome variables (SDoH or access) show differences by genetic counselor access consistent with differences between metropolitan and nonmetropolitan counties, and similar differences exist when explicitly testing for differences due to metropolitan county status.

Physical access to care significantly differs between regions ($p = 0.001$), with the largest difference between the West and Northeast regions ($p = 0.006$). There are also significant differences in access between different types of incident cancer patients ($p < 0.001$), with the largest between prostate and ovarian cancer ($p < 0.001$; for complete results see **Supplemental Tables 1**, **2**). These tests were repeated using physical distance instead of drive-time with similar results (see **Supplemental**).

Further analysis investigated correlations between SDoH and genetic counselor access, revealing significant differences between counties with and without genetic counselor access in all demographic variables – age, sex, race, Hispanic origin, employment status, health insurance coverage and educational attainment (see **Supplemental Table 3**). The largest effect was for median household income ($p < 0.001$) — counties with a genetic counselor had a median income of $60,000/year while counties without a genetic counselor had median income under $50,000/year.

Virtual access was also investigated, though these analyses were limited by the fact that only NSGC reported data on which members provide telegenetic services. The average state-level virtual access was 2 genetic counselors per 100,000 people (range

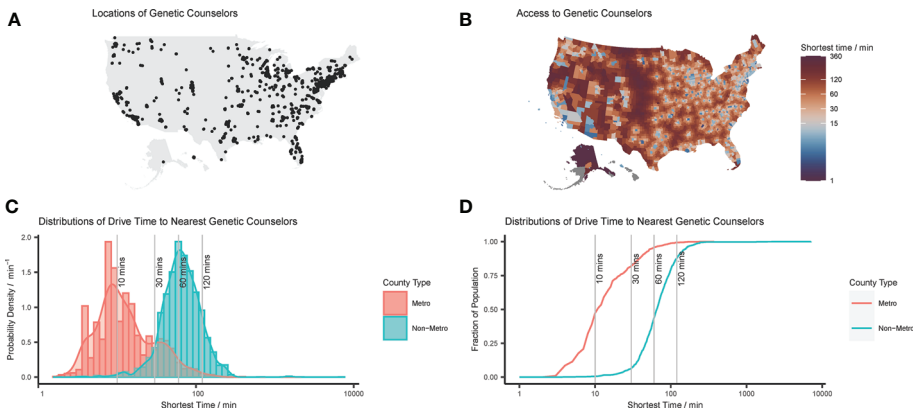

FIGURE 1 | Distributions of genetic counselors in the United States: **(A)** point locations of genetic counselors reconciled from disparate data sources; **(B)** mapped distribution of county-level drive-time to closest genetic counselor; **(C)** histogram and probability density function of county-level drive-time to nearest genetic counselor; and **(D)** cumulative density function of county-level drive-time to nearest genetic counselor. Note that in **(C, D)** the shortest drive-times to a genetic counselor are plotted on log axes, and that these values are population-weighted to take into account relative county populations.

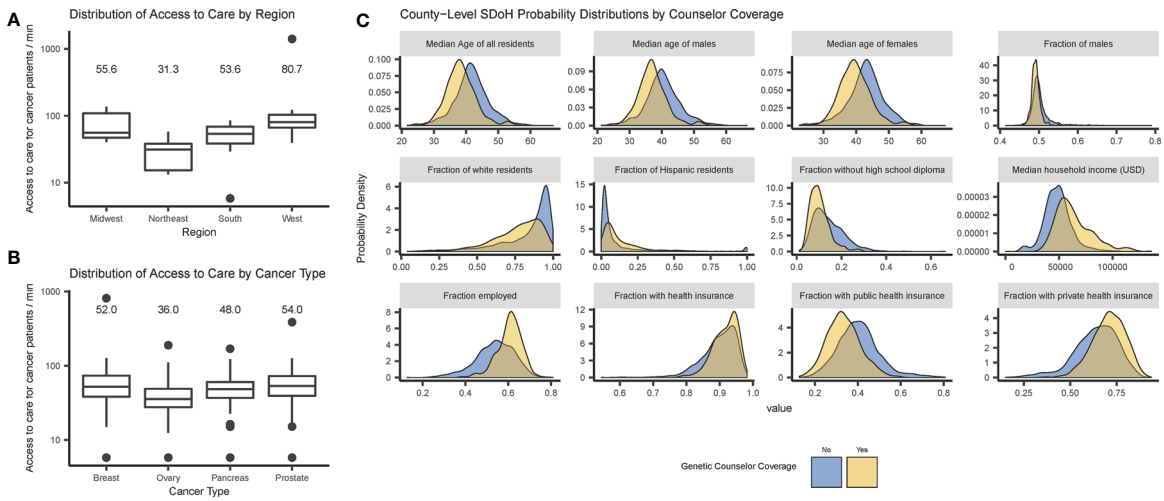

FIGURE 2 | Disparities in access to care by cancer patients and genetic counselor access: **(A)** box plots of access metric by U.S. Census region; **(B)** box plots of access metrics by cancer type; and **(C)** probability densities of county-level SDoH distributions by genetic counselor access. Note that in **(A, B)**, state-level access (defined as the median drive time for a cancer patient to a genetic counselor) is plotted on a log axis, and the medians are provided as labels.

0.3 – 10 per 100,000), with genetic counselors assumed to provide services only to residents of their states as reported in the NSGC registry. Note that this calculation does not consider the effects of multi-state licensure, i.e., cases in which a genetic counselor could technically provide services in additional states beyond those self-reported due to lack of licensure. Genetic counselors may provide both in-person and telegenetics from the same location.

DISCUSSION

The purpose of this study was to evaluate equity of access to genetic counselors at a national level across the United States. The number of genetic counselors per 100,000 people was 1.49, on average, but this belies considerable state-level variability, ranging from 0.17 to 5.7. These findings show systematic differences in access to care between regions, and provide insight for potential policy action, e.g., in the southern United States where overall cancer incidence is relatively high and genetic counselors are relatively few. Furthermore, there are associations between socioeconomic characteristics and access, with counties with genetic counselors being younger, more diverse, with a higher level of education, and with higher incomes, consistent with previous studies and typical for urban locales (4).

The novelty of this study is its national scale and use of GIS to connect disease burden to provider supply, allowing for direct measures of access equity. The method allows for granular identifications of areas with differential access: for example, Williamson County, Tennessee, and Runnels County, Texas, have similar cancer burdens (approximately 435 incident patients per 100,000 annually), but their per-capita access is 0.5 and 38.8 respectively. Underserved patient populations are revealed for further research, e.g., for policy reform to improve access to either in-person or virtual genetic counseling (also known as telegenetics). For example, Gloucester County, New Jersey had among the poorest mismatches between genetic counselor supply and demand, with one genetic counselor for a population of nearly 300,000 people despite having an annual cancer incidence rate of 542.2 per 100,000, the fifth highest rate across all U.S. counties. To communicate these results more directly to the public an interactive dashboard is available that includes maps of genetic counselor locations and visuals of accessibility distributions[3].

Measurements of driving time required to see a genetic counselor are particularly telling, showing that most metropolitan residents live within one hour of a genetic counselor, but most nonmetropolitan residents do not. Previous research has shown that patients that are more than an hour from care are less likely to access the health system and are associated with poorer health outcomes (14, 15). Long drive times to a provider have negative implications for patient adherence to standard-of-care recommendations and are therefore important for continuity of care. Telegenetics has the potential to increase access to genetic counselors for these patients who do not live within a reasonable driving distance to a genetic counselor, or even for individuals who are on a long waitlist to see an in-person genetic counselor.

The Supplemental Information includes analogous analysis of available telegenetic access data, but these are complicated by nuances such as differences in state licensure requirements and provider eligibility in payer reimbursement rules, which are beyond the scope of this study as no robust single data source exists to capture these complications. Virtual genetic counseling care has potential to increase patient access to genetic counselors, both in-state with a far driving distance as outlined above or supporting access across state lines as drive time and distance is no longer a barrier. Currently, only 26 states require licensure (8) to practice and other states only require board certification (so they could be accessible to all 3077 genetic counselors identified in the ABGC data). Furthermore, some states demonstrated a high degree of disparity between the number of in-state genetic counselors versus virtual genetic counselors. For example, Wyoming had only one in-state genetic counselor but up to 58 virtual genetic counselors practicing in the state. Expanding such alternative service delivery models would, however, require policy shifts such as legislative changes to allow genetic counselors to be reimbursed for virtual care through Medicare for their services of both in-person and virtual appointments (7).

[3]Interactive dashboard available at https://gisgeneticcounselor.shinyapps.io/CounselorExplorer/.

Limitations of this study include reconciling non-standardized genetic counselor data from NSGC, ABGC, and NPPES which included manual review and may have introduced error. A sensitivity analysis, however, showed no changes in statistical results when the genetic counselor data were subset by source (see **Supplemental**). As any genetic counselor is able to provide services within any medical specialty without the need for formal accreditation and specialty was only available in one of the data sources (NSGC), data were not stratified by self-reported specialty. As a result, access to genetic counselors who exclusively specialize in cancer care may be lower than what is presented in these results. The numbers of genetic counselors are overestimated as registries include those in private third-party labs, academia or industry that do not see patients. Furthermore, the data represents the genetic counselor population at a single point in time (May 2020 - July 2020) and may include individual genetic counselors that have stopped seeing patients since that time, but does not include genetic counselors who have graduated from genetic counseling training programs. While the data were collected during the beginning of the COVID-19 pandemic, the dataset only included genetic counselors who noted they provided telegenetics in the NSGC directory and did not include any genetic counselors who began utilizing telegenetics during the COVID-19 pandemic, but did not update their NSGC public-facing profile to reflect this change in their practice. In addition, the dataset likely does not capture the full volume of genetic counselors who currently provide telegenetic counseling today as it has become more common as the COVID-19 pandemic continued.

Distance calculations used population-weighted county centroids and these locations could be misleading in edge cases such as multiple islands making up one county. Furthermore, distance is only one aspect of access to care, and other aspects, such as reimbursement policy or licensure requirements, should be considered in future research. In the instances where these points are not accessible *via* driving, the nearest accessible location was used. The drive-time analysis did not consider traffic patterns or time of day.

Lastly, this approach is limited by the lack of causal analysis. Socioeconomic variables, such as household income, may be associated with region and metropolitan/rural status, but these effects have not been controlled for here because reliable data at the county-level were not available.

This study represents a first step in understanding patients' ability to receive genetic counseling at the country-level, by comprehensively mapping access to in-person care using three major national data sources. Future work should build on this by analyzing access to virtual care more closely, especially considering the rising importance of this delivery channel due to the COVID-19 pandemic. Such an analysis would need to address complexities with differences in state-level licensure requirements and incorporate data on clinician time and capacity.

Future work could also refine measures of access to include public transport and could incorporate health outcomes and measures of provider utilization to investigate the effects of access to care. Additional analyses could establish how these determinants combine to enable or block access and utilization.

Finally, forming partnerships between health researchers and professional societies such as NSGC or ABGC may improve data sharing, reduce data integration issues, and allow for deeper analysis that includes patient load, appointment wait times, and workforce trends.

Ultimately these results demonstrate systematic differences in proximity to genetic counseling, illustrating disparity in access to genetic counselors throughout the US. Such findings establish GIS as a powerful tool for investigating the ability of patients to physically interact with the healthcare system and provide implications for policy interventions to expand access, especially in regions with a high unmet need and few genetic counselors.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: NSGC https://www.nsgc.org/page/find-a-gc-search, USCS https://www.cdc.gov/cancer/uscs/dataviz/download_data.htm, ABGC https://www.abgc.net/about-genetic-counseling/find-a-certified-counselor/, and NCI SEER https://seer.cancer.gov/data/access.html.

AUTHOR CONTRIBUTIONS

MB, BG, FS, and CB: conceptualization, methodology, writing—original draft, writing—review and editing, supervision, and project administration. WF, HW, and EM: data curation, formal analysis, investigation, visualization, writing—original draft, and writing—review and editing. RM and WM: conceptualization, methodology, writing—original draft, and writing—review and edition. 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/fonc.2021.689927/full#supplementary-material

Supplementary Figure 1 | Provenance of genetic counselor data: Venn diagram of numbers of unique genetic counselors extracted from each source of provider information.

Supplementary Figure 2 | Access to care by patients with *BRCA*-associated cancers by cancer type and U.S. region: box plots of access metric by combination of U.S. Census region and cancer type. Note that the state-level access to care (defined as the median drive time for a cancer patient to a genetic counselor) is plotted on a log axis.

Supplementary Figure 3 | Virtual genetic counselor access: histogram of state-level per-capita numbers of virtual counselors and measures of central tendency.

Supplementary Figure 4 | State-level SDoH: probability densities of state-level SDoH distributions by mean-split per-capita virtual genetic counselor density.

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Genetic Variants in *COX2* and *ALOX* Genes and Breast Cancer Risk in White and Black Women

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COX and *ALOX* genes are involved in inflammatory processes and that may be related to breast cancer risk differentially between White and Black women. We evaluated distributions of genetic variants involved in *COX2* and *ALOX*-related pathways and examined their associations with breast cancer risk among 1,275 White and 1,299 Black cases and controls who participated in the Women's Circle of Health Study. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariable-adjusted logistic regression models. Our results showed differential associations of certain genetic variants with breast cancer according to menopausal and ER status in either White or Black women. In White women, an increased risk of breast cancer was observed for *COX2*-rs689470 (OR: 2.02, P = 0.01) in the dominant model, and was strongest among postmenopausal women (OR: 2.72, P = 0.02) and for estrogen receptor positive (ER+) breast cancers (OR: 2.60, P = 0.001). A reduced risk was observed for *ALOX5*-rs7099874 (OR: 0.75, P = 0.01) in the dominant model, and was stronger among postmenopausal women (OR: 0.68, P = 0.03) and for ER+ cancer (OR: 0.66, P = 0.001). Four SNPs (rs3840880, rs1126667, rs434473, rs1042357) in the *ALOX12* gene were found in high LD (r^2 >0.98) in White women and were similarly associated with reduced risk of breast cancer, with a stronger association among postmenopausal women and for ER– cancer. Among Black women, increased risk was observed for *ALOX5*-rs1369214 (OR: 1.44, P = 0.003) in the recessive model and was stronger among premenopausal women (OR: 1.57, P = 0.03) and for ER+ cancer (OR: 1.53, P = 0.003). Our study suggests that genetic variants of *COX2* and *ALOX* genes are associated with breast cancer, and that these associations and genotype distributions differ in subgroups defined by menopausal and ER status between White and Black women. Findings may provide insights into the etiology of breast cancer and areas for further research into reasons for breast cancer differences between races.

Keywords: breast cancer, Black women, cyclooxygenase 2, arachidonate 12-lipoxygenase, 5-LOX, polymorphism

HIGHLIGHTS

Genetic variants of *COX2* and *ALOX* are associated with breast cancer. These associations and genotype distributions differ in subgroups defined by menopausal and estrogen receptor status between White and Black women.

INTRODUCTION

Among women in the United States, breast cancer is the most common cancer and the second leading cause of cancer death (1). It is well documented that the risk and burden of this disease varies across women of different age, race, ethnicity, and socioeconomic status (2, 3). Although the incidence of breast cancer has historically been higher among White women compared to Black women, incidence rates have converged for the two populations, while the mortality gap is widening (1). Some of this disparity is partly due to differences in access to screening and optimal cancer treatment (4), but Black women are also more likely to be diagnosed with aggressive tumors, i.e., high stage, high grade and negative for estrogen receptor (ER) status (5). Other key factors contributing to these differences are still largely unknown.

One hypothesis is that there may be variation in the molecular and cellular mechanisms in response to chronic inflammation, a process involving the immune system and various inflammatory regulators (6, 7). The common pathological features of chronic inflammation and carcinogenesis include elevation of proinflammatory mediators, such as cytokines, chemokines, prostaglandins and leukotrienes, which orchestrate crosstalk between various cells to create a tumor-supporting microenvironment, and consequently promote tumor initiation, growth and progression (8). Polymorphisms in genes encoding enzymes in these pathways may affect their expression or activity, and ultimately alter an individual's susceptibility to breast cancer risk. Our studies have identified genetic variants in multiple chemokine- and cytokine-related genes associated with breast cancer risk, with differing associations between White and Black populations (9–11), but prostaglandin- and leukotriene-related pathways remain to be investigated.

Cyclooxygenase 2 (COX-2), also known as prostaglandin-endoperoxide synthase 2 (PTGS2), a key enzyme in prostaglandin synthesis, is known to play a role in carcinogenesis and tumor progression, including breast cancer (12, 13). COX-2 expression is induced by inflammatory stimuli, and aberrant expression is commonly found in epithelial malignancies. Specifically in breast cancer, previous research has shown that overexpression of COX-2 is observed in nearly 60% of invasive breast cancer, while barely detectable in most normal tissues, thus, it may be an early event in mammary tumorigenesis (14–16). Pre-clinical studies have found that COX-2 overexpression can lead to a higher production of prostaglandin E2 (PGE2), an important mediator of inflammation and contributor to immunosuppression, resulting in cell proliferation, apoptosis inhibition, and tumor angiogenesis (16–18). Several variations in *COX2* gene have been associated with susceptibility to breast cancer (19, 20). In addition to the prostaglandin pathway, the key genes in the arachidonate lipoxygenase (ALOX) pathway, including *ALOX5*, *ALOX5AP*, and *ALOX12*, and associated metabolites, such as leukotrienes, play an important role in inflammation and carcinogenesis (21, 22). However, the impact of both *COX2* and *ALOX* genetic variants have been minimally explored among women of minority ancestral backgrounds and current data are inconclusive.

In this large case-control study, we examined associations between genetic variants of *COX2* and three *ALOX* genes and risk of breast cancer among White and Black women. We further considered if associations varied according to menopausal and ER status. We hypothesized that deviations from the standard distribution of "at-risk" alleles for specific single nucleotide polymorphisms (SNPs) could be associated with risk of breast cancer and may vary between races.

MATERIALS AND METHODS

Study Population

The Women's Circle of Health Study (WCHS) was a case–control study designed to assess risk factors associated with early onset and aggressive breast cancer among White and Black women. Further details on the study design, enrollment criteria, biospecimen and questionnaire data collection have been previously described (11, 23, 24). Briefly, women with primary incident breast cancer were initially identified using hospital-based case ascertainment in four boroughs of metropolitan New York City (2002–2008) and later through population-based rapid case ascertainment by the New Jersey State Cancer Registry (2006–2012) for 10 counties in New Jersey. Eligible cases were English speaking women 20–75 years of age who self-identified as White or Black and had been recently diagnosed with primary, histologically confirmed breast cancer. Women who had a previous history of cancer other than non-melanoma skin cancer were excluded. Controls were initially recruited from the target population in the same residential area using random digit dialing and then through various community recruitment efforts for Black women (25). Cases and controls were frequency matched based on self-reported race and 5-year age groups. Data and DNA samples from 1,275 White (637 cases, 638 controls) and 1,299 Black (584 cases, 715 controls) participants were included for this analysis. This study was approved by institutional review boards at the Roswell Park Comprehensive Cancer Center, the Rutgers Cancer Institute of New Jersey, Mount Sinai School of Medicine (now the Icahn School of Medicine at Mount Sinai), and participating hospitals in New York City. Signed informed consent was obtained from each participant prior to interview and biospecimen collection.

Data and Sample Collection

Detailed data on demographic characteristics, medical history, family history of cancer, lifestyle factors, and anthropometric measures were collected in-person by trained interviewers. Blood samples, as a source of DNA, were initially collected from approximately 850 participants until we transitioned to

collection of saliva samples using Oragene™ kits (DNA Genotek Inc., Kanaya, Ontario, Canada) as a source of DNA. Pathology data including ER status, grade, and stage were collected and abstracted from patient records by trained staff.

Genomic DNA was extracted from blood samples using FlexiGene™ DNA isolation kits (Qiagen Inc., Valencia, CA) and from saliva samples using Oragene™ kits. DNA was then evaluated and quantified by Nanodrop UV-spectrometer (Thermo Fisher Scientific Inc., Wilmington, DE) and PicoGreen-based fluorometric assay (Molecular Probes, Invitrogen Inc., Carlsbad, CA). Samples were stored at −80°C until analysis.

SNP Selection and Genotyping

We surveyed the Human Genome Epidemiology (HuGE) Navigator for the four genes involved in *COX-2* and *ALOX* inflammation-related pathways to identify SNPs that were previously associated with risk of any cancer or cancer outcome, with a focus on SNPs that were previously shown to be functional (26). A panel of 31 SNPs were then selected and genotyped at the Genomics Shared Resource at Roswell Park using the Illumina GoldenGate assay (Illumina Inc., San Diego, CA). To account for population admixture in the analysis, all samples were also genotyped for a panel of 100 ancestry informative markers (AIMs) that were previously validated in the Black Women's Health Study (27). Proportions of European Ancestry and African Ancestry of individual White and Black women were computed quantitatively using the Bayesian Markov Chain Monte Carlo clustering algorithm implemented in STRUCTURE, based on data from the 100 genotyped AIMs. Since the sum of two ancestral proportions in each individual is always one, we used only the proportion of European Ancestry in all analyses (28). As a quality control measure in both genotyping efforts, 5% duplicates and two sets of in-house trio samples were included across all plates. One SNP (*COX2*-rs20417) was removed due to the violation of Hardy–Weinberg Equilibrium, all other SNPs were included in the analysis.

Statistical Analysis

Descriptive analysis was done using chi-square tests for categorical variables and t-tests for continuous variables between 1,275 White and 1,299 Black cases and controls. Odds ratios (ORs) and 95% confidence intervals (CIs) for each SNP were derived from multivariable logistic regression models with adjustment for age (continuous), proportion of European ancestry (continuous), and family history of breast cancer (yes, no). Other covariates did not significantly affect the risk estimates and thus were not included in the multivariable-adjusted analysis. Participants with the most common homozygous genotype among White controls were treated as the referent group. Genotypic (co-dominant) models were assumed for SNP effects. Based on the risk estimates, heterozygotes were combined with either homozygous rare or homozygous common genotypes to explore dominant and recessive models, respectively. Additive genotype coding on the number of rare alleles was analyzed as an ordinal variable in tests for linear trend. Analysis was performed separately for White and Black women, and interactions by race were tested by including an interaction term SNP*race in multivariable logistic models and performing the likelihood ratio test. Additional stratified analyses were conducted to examine whether SNP associations with breast cancer risk differed by menopausal or ER status.

All analyses were conducted using SAS V 9.4 (SAS Institute, Cary, NC). Linkage disequilibrium (LD) was determined by calculating r^2 values between SNP pairs using Haploview (29). Statistical tests were two-sided and considered statistically significant for uncorrected $P < 0.05$. All significant p-values were further adjusted for multiple comparisons using Bonferroni correction, with $P < 0.002$ (0.05/30) considered statistically significant.

RESULTS

Participant Characteristics

Characteristics of White and Black cases and controls are shown in **Table 1**. In both races, cases were slightly older and were more likely to have a history of benign breast disease. Compared with White controls, cases had lower proportion of European ancestry, received less college and post-graduate education, and were more likely to have a family history of breast cancer. Among Black women, cases were more likely to be postmenopausal. As expected, Black cases were more likely than White cases to be diagnosed with ER negative breast cancer (32.1% *vs.* 18.8%).

Associations of SNPs With Breast Cancer Risk in White and Black Women

Genotype distributions of each SNP and their associations with overall breast cancer risk in White and Black women are shown in **Supplemental Table S1**. We observed differences in genotype distributions between White and Black populations, and for seven of these SNPs, the minor allele variant was reversed between the two groups. A number of SNPs were statistically significantly associated with overall breast cancer risk in either AA or EA women, with results shown in **Table 2**. In White women, an increased risk of breast cancer was observed for *COX2*-rs689470 (OR: 2.02, 95% CI: 1.16–3.53) in the dominant model and *ALOX5*-rs1487562 (OR: 1.80, 95% CI: 1.02–3.18) in the recessive model, while the association among Black women was essentially null. A reduced risk among White women was also observed for *ALOX5*-rs7099874 (OR: 0.75, 95% CI: 0.60–0.94) in the dominant model. Four SNPs (rs3840880, rs1126667, rs434473, rs1042357) in the *ALOX12* gene were in high LD (r^2 >0.98) and were similarly associated with reduced risk in White women. These SNPs, however, were not in LD (r^2 <0.43) in the Black population and were not associated with overall breast cancer risk. Among Black women, significant associations were observed for *ALOX5*-rs1369214 (OR: 1.44, 95% CI: 1.13–1.84) and rs1051713 (OR: 0.53, 95% CI: 0.28–0.98) in the recessive models. Although these genotype-breast cancer associations differed in strength according to race, significant SNP-race interactions were observed only for *COX2*-rs689470 and *ALOX5*-rs1487562 (*P*-interaction = 0.006 and 0.03, respectively), as shown above, both SNPs were associated with increased risk of breast cancer among White women.

In stratified analyses, associations between each SNP and breast cancer risk were examined separately in pre- and post-menopausal

TABLE 1 | Characteristics of 1,275 White and 1,299 Black cases and controls in the WCHS[a].

Characteristics	White			Black		
	Cases (n = 637)	Controls (n = 638)	*P-value*[c]	Cases (n = 584)	Controls (n = 715)	*P-value*[c]
Age (yr), mean (SD)[b]	52.2 (10.0)	49.7 (8.7)	**<0.0001**	51.7 (10.4)	48.7 (9.5)	**<0.0001**
Body mass index, kg/m^2, mean (SD)[b]	27.3 (6.6)	27.4 (7.1)	0.76	31.2 (6.8)	31.9 (7.9)	0.06
% European ancestry[b]	96.7 (8.1)	98.5 (3.7)	**<0.0001**	14.1 (16.1)	13.9 (13.9)	0.89
Menopausal status, n (%)			0.30			**0.03**
Premenopausal	331 (52.0)	350 (54.9)		286 (49.0)	393 (55.0)	
Postmenopausal	306 (48.0)	288 (45.1)		298 (51.0)	322 (45.0)	
Family history of breast cancer in first degree relative, n (%)			**0.0006**			0.13
No	481 (75.5)	533 (83.5)		498 (85.3)	630 (88.1)	
Yes	156 (24.5)	105 (16.5)		86 (14.7)	85 (11.9)	
Education, n (%)			**<0.0001**			0.42
≤high school	19 (3.0)	6 (0.9)		80 (13.7)	95 (13.3)	
High school graduate or equivalent	112 (17.6)	65 (10.2)		178 (30.5)	187 (26.2)	
Some college	140 (22.0)	113 (17.7)		159 (27.2)	201 (28.1)	
College graduate	198 (31.0)	208 (32.6)		102 (17.5)	139 (19.4)	
Post-graduate degree	168 (26.4)	246 (38.6)		65 (11.1)	93 (13.0)	
History of benign breast disease, n (%)			**0.0006**			**<0.0001**
No	368 (58.4)	431 (67.8)		399 (68.6)	564 (79.0)	
Yes	262 (41.6)	205 (32.2)		183 (31.4)	150 (21.0)	
Estrogen receptor (ER) Status, n (%)[d]			–			–
Positive	450 (81.2)			351 (67.9)		
Negative	104 (18.8)			166 (32.1)		

[a]*Number may not add up to the total number due to missing values.*
[b]*SD, standard deviation.*
[c]*P-value were from t-test for continuous variables and Chi-square test for categorical variables.*
[d]*ER status were available for 554 (87.0%) White cases and 517 (88.5%) Black cases.*
Bold, significant P-values.

women (**Supplemental Table S2**). In these analyses, a number of SNPs were significantly associated with breast cancer risk in pre- or post-menopausal women in either White or Black women, with results shown in **Table 3**. Among pre-menopausal White women, *ALOX5AP*-rs9315048 was associated with increased risk of breast cancer (OR: 2.11, 95% CI: 1.05–4.28) in the recessive model. Among postmenopausal White women, *COX2*-rs689470 and *ALOX12*-rs2292350 were associated with increased risk (OR: 2.72, 95% CI: 1.16–6.40 and OR: 1.50, 95% CI: 1.04–2.16, respectively) in the dominant models, while *ALOX5*-rs7099874 was associated with reduced risk (OR: 0.68, 95% CI: 0.48–0.96) in the dominant model. Further, for the four *ALOX12*-SNPs in LD that showed similar significant associations with overall breast cancer risk among White women, the reduced risk was stronger among post-menopausal women, as shown for rs3840880 (OR: 0.57, 95% CI: 0.40–0.83). Among pre-menopausal Black women, an increased risk was observed for *ALOX5*-rs1369214 (OR: 1.57, 95% CI: 1.05–2.37) and *ALOX5AP*-rs9315045 (OR: 1.39, 95% CI: 1.01–1.93) in the dominant models, whereas a reduced risk was observed for *ALOX5*-rs1051713 (OR: 0.35, 95% CI: 0.13–0.95) in the recessive model. In post-menopausal Black women, a reduced risk was observed for *COX2*-rs2745557 (OR: 0.63, 95% CI: 0.44-0.92) and *ALOX5AP*-rs4293222 (OR: 0.45, 95% CI: 0.23–0.92) in the dominant models.

Associations of each SNP and risk of ER positive (ER+) and ER negative (ER−) breast cancer were examined separately (**Supplemental Table S3**). Several associations were suggested to be specifically stronger and significant for ER+ or ER− breast cancer in either White or Black women (**Table 4**). In White women, an increased risk of ER+ breast cancer was observed for *COX2*-rs689470 (OR: 2.60, 95% CI: 1.46–4.63) in the dominant model, whereas a reduced risk was observed for *ALOX5*-rs7099874 (OR: 0.66, 95% CI: 0.51–0.85) in a dominant model. *ALOX5AP*-rs9315048 was associated with increased risk of ER− breast cancer (OR: 2.56, 95% CI: 1.25–5.25) in the recessive model. Among Black women, an increased risk of ER+ cancer was observed for *ALOX5*-rs1369214 (OR: 1.53, 95% CI: 1.15–2.03) and *ALOX5AP*-rs9579648 (OR: 2.36, 95% CI: 1.15–4.84) in the recessive models. A reduced risk was also observed for *COX2*-rs2745557 (OR: 0.64, 95% CI: 0.43–0.96) with risk of ER− breast cancer in the dominant model. In addition, although there was no significant association observed in either White or Black women, *COX2*-rs5275 was associated with increased risk among post-menopausal Black women and specifically a significant increased risk for ER− breast cancer (OR: 1.54, 95% CI: 1.08–2.19) in a recessive model. In contrast, there was an indication of inverse association for this SNP among post-menopausal White women (OR=0.69, 95% CI: 0.40–1.19) (**Supplemental Table S2**). The four *ALOX12*-SNPs that showed significant associations in White women were found to be associated with stronger reduced risk for ER− breast cancer, as shown for rs3840880 (OR: 0.62, 95% CI: 0.40–0.96).

DISCUSSION

In this large case-control study of White and Black women, we examined candidate genetic variants in four genes involved in *COX-2* and *ALOX* inflammation-related pathways and risk of

TABLE 2 | SNPs of inflammation-related pathways and risk of breast cancer among White and Black women in the WCHS.

Gene	SNP	Chr	Coordinate	Genotype	White			Black			
					# Case/Control	OR (95% CI)[a, b]	$P^{c, d, e}$	# Case/Control	OR (95% CI)[a, b]	$P^{c,d,e}$	P^{f}
COX2	rs689470	1	186641058	CC	589/618	1.00 (ref)	**0.005**	205/262	1.00 (ref)	0.86	**0.006**
				CT	47/17	2.37 (1.32–4.27)		273/325	1.07 (0.83–1.38)		
				TT	1/3	0.05 (0.00–2.19)		102/127	1.06 (0.77–1.48)		
				CT/TT *vs.* CC	48/20	2.02 (1.16–3.53)	**0.01**	375/452	1.07 (0.84–1.35)	0.58	
ALOX5	rs1369214	10	45900729	GG	195/190	1.00 (ref)	0.83	112/156	1.00 (ref)	**0.01**	0.08
				GA	316/310	1.03 (0.79–1.33)		274/367	1.04 (0.78–1.40)		
				AA	123/134	0.94 (0.68–1.30)		196/189	1.48 (1.08–2.04)		
				AA *vs.* GG/GA	511/500	0.92 (0.69–1.12)	0.57	386/523	1.44 (1.13–1.84)	**0.003**	
ALOX5	rs1487562	10	45928822	CC	419/428	1.00 (ref)	0.13	337/400	1.00 (ref)	0.33	**0.03**
				CT	180/190	1.01 (0.78–1.29)		211/258	0.97 (0.77–1.23)		
				TT	37/20	1.80 (1.02–3.20)		34/57	0.71 (0.45–1.12)		
				TT *vs.* CC/CT	599/618	1.80 (1.02–3.18)	**0.04**	548/658	0.72 (0.46–1.12)	0.14	
ALOX5	rs7099874	10	45928911	GG	328/281	1.00 (ref)	**0.02**	429/525	1.00 (ref)	0.99	0.15
				GC	249/304	0.71 (0.56–0.9)		133/165	0.98 (0.75–1.28)		
				CC	55/48	0.98 (0.64–1.51)		17/19	1.00 (0.51–1.98)		
				GC/CC *vs.* GG	304/352	0.75 (0.60–0.94)	**0.01**	150/184	0.98 (0.76–1.27)	0.89	
ALOX5	rs1051713	10	45938746	CC	437/440	1.00 (ref)	0.41	393/486	1.00 (ref)	0.10	0.07
				CT	173/180	0.98 (0.76–1.26)		174/193	1.10 (0.85–1.40)		
				TT	24/16	1.54 (0.80–2.98)		15/34	0.54 (0.29–1.02)		
				TT *vs.* CC/CT	610/620	1.55 (0.81–2.99)	0.19	567/679	0.53 (0.28–0.98)	**0.04**	
ALOX12	rs3840880[g]	17	6897844	TT	221/187	1.00 (ref)	0.08	133/159	1.00 (ref)	0.94	0.19
				TG	313/316	0.88 (0.68–1.13)		279/345	0.96 (0.73–1.28)		
				GG	101/131	0.68 (0.49–0.95)		171/211	1.01 (0.74–1.38)		
				GG *vs.* TT/TG	534/503	0.74 (0.55–0.99)	**0.04**	412/504	1.03 (0.74–1.45)	0.80	

[a]*OR, odds ratio; 95%CI, 95% confidence interval.*

[b]*Adjusted for age, family history of breast cancer in a first-degree relative, and proportion of European ancestry.*

[c]*P-trend for genetic dose response determined by coding genotypes as having 0, 1, or 2 variant allele, which was subsequently analyzed as an ordinal variable.*

[d]*P for heterogeneity from dominant or recessive models.*

[e]*All significant p-values were further adjusted for multiple comparisons using Bonferroni correction, with P <0.002 (0.05/30) considered statistically significant.*

[f]*P for interaction term including genotype and race in the multivariable logistic model.*

[g]*Several SNPs on the ALOX12 gene, rs3840880, rs1126667, rs434473, rs1042357, were found in high LD in White women (r^2 >0.98), but not in LD in Black women (r^2 <0.43).*

Bold, significant P-values.

breast cancer. Allele frequencies of some of the SNPs in these genes varied significantly between White and Black populations. A number of these SNPs in *COX2*, *ALOX5*, *ALOX5AP*, and *ALOX12* genes were found to be associated with overall breast cancer risk, as well as breast cancer risk in subgroups defined by menopausal and ER status, in either White or Black women. To our knowledge, this is among the first study to examine associations of genetic variants of these genes with breast cancer within and across White and Black populations, specifically in a large number of Black women.

The *COX2*–prostaglandin pathway links inflammation and tumorigenesis by providing a tumor-promoting microenvironment (13). Elevated levels of *COX-2* and its metabolites, such as PGE2, an inflammatory mediator, have been associated with aggressive breast cancer phenotypes and poor survival (13, 30, 31), whereas inhibition of *COX-2* activity has shown anti-tumor and therapeutic effects in preclinical models and population studies (12, 32–35). Particular attention has been given to the influence of rs5275, which is located in the 3′ untranslated region (3'UTR) and is among the most common *COX-2* polymorphisms in White women (36). Associations for rs5275 with breast cancer have been inconsistent; studies focusing on Whites in a US population suggested a reduced risk for TT (37) or CC genotypes (36, 38), whereas one study in a Brazilian population reported an increased risk for the heterozygous TC genotype (39) and others reported no significant association (40–42). In our study, rs5275 was not associated with overall breast cancer risk in either White or Black women, but a significant increased risk for ER– cancer was observed for the CC genotype among Black women, while there was a suggestive reduced risk among White postmenopausal women. *COX2*-rs689470 was significantly associated with increased risk for breast cancer in White women, with stronger associations among those who were post-menopausal and for ER+ breast cancer. Compare to our study, an earlier small study involving 180 breast cancer cases in postmenopausal women, however, failed to observe a significant association (43). Both SNPs are located in the 3'UTR and may contribute to breast carcinogenesis through transcriptional or post-transcriptional regulation of *COX2* expression. Among Black women, rs2745557 was associated with decreased risk, specifically among postmenopausal women and for ER– breast cancer. This SNP has been linked to an increased breast cancer risk among primarily White populations in previous studies (36, 44). Our above observations, coupled with existing evidence that *COX-2* levels vary by menopausal and ER status (45–47), suggest a potential menopausal/estrogen-mediated role in the *COX2*–prostaglandin-carcinogenesis pathway. Previous studies have been mostly limited to White populations and have not considered menopausal or ER status, which may explain the

TABLE 3 | SNPs of inflammation related pathways and risk of breast cancer by menopausal status in the WCHS.

Gene	SNP	Genotype	White						Black					
			Pre-menopausal women			Post-menopausal women			Pre-menopausal women			Post-menopausal women		
			# Case/ Control	OR (95% CI)[a, b]	P[c, d, e]	# Case/ Control	OR (95% CI) [a, b]	P[c, d, e]	# Case/ Control	OR (95% CI) [a, b]	P[c, d, e]	# Case/ Control	OR (95% CI) [a, b]	P[c, d, e]
COX2	rs689470	CC	310/338	1.00 (ref)	0.07	279/280	1.00 (ref)	**0.02**	103/158	1.00 (ref)	0.49	102/104	1.00 (ref)	0.99
		CT	20/9	2.01 (0.86-4.69)		27/8	2.72 (1.16–6.40)		124/160	1.23 (0.87–1.74)		149/165	1.00 (0.69–1.44)	
		TT	1/3	0.03 (0.00–2.24)		0/0			56/74	1.19 (0.77–1.84)		46/53	0.96 (0.58–1.60)	
		CT/TT *vs.* CC	21/12	1.46 (0.67–3.19)	0.34	27/8	2.72 (1.16–6.40)	**0.02**	180/234	1.22 (0.88–1.68)	0.23	195/218	0.99 (0.69–1.41)	0.95
COX2	rs2745557	GG	214/223	1.00 (ref)	0.27	190/174	1.00 (ref)	0.84	200/284	1.00 (ref)	0.69	230/219	1.00 (ref)	**0.03**
		GA	97/101	1.07 (0.76–1.52)		100/102	0.94 (0.65–1.35)		76/94	1.14 (0.80–1.63)		61/96	0.60 (0.41–0.88)	
		AA	18/26	0.61 (0.31–1.18)		16/11	1.20 (0.52–2.78)		9/15	0.85 (0.36–1.99)		7/6	1.16 (0.38–3.58)	
		GA/AA *vs.* GG	115/127	0.97 (0.70–1.34)	0.85	116/113	0.97 (0.68–1.37)	0.85	85/109	1.10 (0.79–1.55)	0.58	68/102	0.63 (0.44–0.92)	**0.02**
ALOX5	rs1369214	GG	100/101	1.00 (ref)	0.94	95/89	1.00 (ref)	0.61	42/87	1.00 (ref)	**0.02**	70/69	1.00 (ref)	0.18
		GA	158/172	0.96 (0.67–1.38)		158/138	1.18 (0.80–1.75)		140/197	1.39 (0.90–2.14)		134/170	0.81 (0.53–1.22)	
		AA	72/76	0.92 (0.59–1.43)		51/58	0.99 (0.59–1.63)		102/108	1.90 (1.20–3.01)		94/81	1.15 (0.72–1.82)	
		GA/AA *vs.* GG	230/248	0.95 (0.67–1.33)	0.75	209/196	1.13 (0.78–1.63)	0.53	242/305	1.57 (1.05–2.37)	**0.03**	228/251	0.92 (0.62–1.36)	0.67
ALOX5	rs7099874	GG	167/161	1.00 (ref)	0.52	161/120	1.00 (ref)	**0.006**	219/293	1.00 (ref)	0.76	210/232	1.00 (ref)	0.72
		GC	139/157	0.87 (0.63–1.21)		110/147	0.60 (0.42–0.86)		58/88	0.87 (0.60–1.27)		75/77	1.17 (0.80–1.72)	
		CC	22/30	0.74 (0.40–1.36)		33/18	1.29 (0.67–2.47)		6/9	0.95 (0.32–2.79)		11/10	1.06 (0.43–2.61)	
		GC/CC *vs.* GG	161/187	0.85 (0.62–1.16)	0.31	143/165	0.68 (0.48–0.96)	**0.03**	64/97	0.88 (0.61–1.26)	0.47	86/87	1.16 (0.81–1.67)	0.43
ALOX5	rs1051713	CC	227/251	1.00 (ref)	0.56	210/189	1.00 (ref)	0.32	204/276	1.00 (ref)	0.11	189/210	1.00 (ref)	0.58
		CT	90/89	1.18 (0.83–1.69)		83/91	0.84 (0.58–1.22)		76/97	1.07 (0.75–1.53)		98/96	1.17 (0.82–1.66)	
		TT	11/9	1.36 (0.54–3.41)		13/7	1.75 (0.64–4.75)		5/19	0.36 (0.13–0.97)		10/15	0.81 (0.34–1.90)	
		TT *vs.* CC/CT	317/340	1.30 (0.52–3.23)	0.57	293/280	1.84 (0.68–4.98)	0.23	280/373	0.35 (0.13–0.95)	**0.04**	287/306	0.77 (0.33–1.78)	0.54
ALOX5AP	rs4293222	GG	136/148	1.00 (ref)	0.89	135/129	1.00 (ref)	0.74	13/31	1.00 (ref)	0.27	28/13	1.00 (ref)	0.09
		GC	148/150	1.06 (0.76–1.48)		127/126	0.94 (0.65–1.36)		104/148	1.56 (0.77–3.15)		115/128	0.46 (0.22–0.96)	
		CC	47/52	0.95 (0.59–1.52)		44/33	1.17 (0.68–2.01)		168/214	1.75 (0.87–3.50)		154/181	0.45 (0.22–0.92)	
		GC/CC *vs.* GG	195/202	1.03 (0.75–1.41)	0.87	171/159	0.99 (0.70–1.39)	0.96	272/362	1.66 (0.84–3.28)	0.14	269/309	0.45 (0.23–0.92)	**0.03**
ALOX5AP	rs9315045	TT	181/194	1.00 (ref)	0.94	174/162	1.00 (ref)	0.91	92/159	1.00 (ref)	0.10	92/101	1.00 (ref)	0.71

(Continued)

TABLE 3 | Continued

Gene	SNP	Genotype	White						Black					
			Pre-menopausal women			Post-menopausal women			Pre-menopausal women			Post-menopausal women		
			# Case/ Control	OR (95% CI)[a, b]	$P^{c, d, e}$	# Case/ Control	OR (95% CI) [a, b]	$P^{c, d, e}$	# Case/ Control	OR (95% CI) [a, b]	$P^{c, d, e}$	# Case/ Control	OR (95% CI) [a, b]	$P^{c, d, e}$
		TC	121/130	1.02 (0.73–1.42)		109/108	0.94 (0.66–1.35)		135/167	1.33 (0.94–1.88)		162/169	1.08 (0.75–1.56)	
		CC	28/25	1.11 (0.61–2.03)		23/18	1.07 (0.54–2.13)		59/63	1.57 (1.01–2.45)		43/51	0.89 (0.53–1.49)	
		TC/CC *vs.* TT	149/155	1.04 (0.76–1.42)	0.83	132/126	0.96 (0.68–1.35)	0.82	194/230	1.39 (1.01–1.93)	**0.04**	205/220	1.03 (0.73–1.47)	0.85
ALOX5AP	rs9315048	GG	185/211	1.00 (ref)	0.09	183/177	1.00 (ref)	0.93	124/198	1.00 (ref)	0.11	146/156	1.00 (ref)	0.90
		GT	120/125	1.12 (0.80–1.55)		100/95	1.07 (0.74–1.54)		124/160	1.22 (0.88–1.69)		121/134	0.93 (0.66–1.32)	
		TT	26/13	2.20 (1.08–4.51)		23/16	1.09 (0.54–2.21)		36/33	1.72 (1.02–2.91)		27/30	0.90 (0.50–1.62)	
		TT *vs.* GG/GT	305/336	2.11 (1.05–4.28)	**0.04**	283/272	1.07 (0.53–2.14)	0.85	248/358	1.56 (0.95–2.59)	0.08	267/290	0.93 (0.53–1.63)	0.80
ALOX12	rs2292350	GG	109/100	1.00 (ref)	0.56	89/107	1.00 (ref)	0.06	227/304	1.00 (ref)	0.41	235/238	1.00 (ref)	0.24
		GA	164/187	0.83 (0.58–1.18)		149/131	1.41 (0.95–2.07)		55/80	0.90 (0.61–1.34)		57/79	0.71 (0.47–1.06)	
		AA	57/61	0.84 (0.53–1.34)		67/49	1.76 (1.08–2.86)		3/9	0.42 (0.11–1.59)		5/5	1.02 (0.28–3.71)	
		GA/AA *vs.* GG	221/248	0.83 (0.59–1.16)	0.28	216/180	1.50 (1.04–2.16)	**0.03**	58/89	0.86 (0.58–1.26)	0.44	62/84	0.72 (0.49–1.08)	0.11
ALOX12[e]	rs3840880[f]	TT	103/109	1.00 (ref)	0.67	118/78	1.00 (ref)	**0.006**	62/87	1.00 (ref)	0.56	71/72	1.00 (ref)	0.35
		TG	172/173	1.11 (0.78–1.58)		141/143	0.62 (0.42–0.92)		141/177	1.10 (0.74–1.64)		138/168	0.86 (0.57–1.30)	
		GG	54/64	0.92 (0.58–1.47)		47/67	0.47 (0.28–0.77)		82/129	0.90 (0.59–1.39)		89/82	1.15 (0.72–1.82)	
		TG/GG *vs.* TT	226/237	1.06 (0.76–1.48)	0.74	188/210	0.57 (0.40–0.83)	**0.003**	223/306	1.02 (0.70–1.48)	0.92	227/250	0.95 (0.65–1.40)	0.81

[a]*OR, odds ratio; 95%CI, 95% confidence interval.*

[b]*Adjusted for age, history of breast cancer in a first-degree relative, and proportion of European ancestry.*

[c]*P-trend for genetic dose response determined by coding genotypes as having 0, 1, or 2 variant allele, which was subsequently analyzed as an ordinal variable.*

[d]*P for heterogeneity from dominant or recessive models.*

[e]*All significant p-values were further adjusted for multiple comparisons using Bonferroni correction, with P <0.002 (0.05/30) considered statistically significant.*

[f]*Several SNPs on the ALOX12 gene, rs3840880, rs1126667, rs434473, rs1042357, were found in high LD with rs3840880 (r^2 >0.98) in White women, with a similar association pattern (**Supplemental Table 2**).*

Bold, significant P-values.

TABLE 4 | SNPs inflammation-related pathways and risk of breast cancer by ER status in the WCHS[a].

Gene	SNP	Genotype	White						Black					
			Estrogen Receptor Positive			Estrogen Receptor Negative			Estrogen Receptor Positive			Estrogen Receptor Negative		
			# Case/ Control	OR (95%CI)[b, c]	P[d, e, f]	# Case/ Control	OR (95% CI) [b, c]	P[d, e, f]	# Case/ Control	OR (95% CI) [b, c]	P[d, e, f]	# Case/ Control	OR (95% CI) [b, c]	P[d, e, f]
COX2	rs689470	CC	410/618	1.00 (ref)	**0.001**	99/618	1.00 (ref)	0.83	131/262	1.00 (ref)	0.61	51/262	1.00 (ref)	0.46
		CT	39/17	3.05 (1.66–5.59)		5/17	1.41 (0.48–4.19)		168/325	1.05 (0.78–1.39)		77/325	1.18 (0.80–1.75)	
		TT	1/3	0.08 (0.00–3.11)		0/3			52/127	0.86 (0.58–1.28)		35/127	1.36 (0.83–2.21)	
		CT/TT *vs.* CC	40/20	2.60 (1.46–4.63)	**0.001**	5/20	1.17 (0.39–3.50)	0.78	220/452	1.00 (0.76–1.31)	0.84	112/452	1.23 (0.85–1.78)	0.28
COX2	rs5275	TT	179/279	1.00 (ref)	0.70	46/279	1.00 (ref)	0.90	62/119	1.00 (ref)	0.76	23/119	1.00 (ref)	0.06
		TC	214/288	1.11 (0.85–1.45)		47/288	0.96 (0.62–1.50)		175/337	0.97 (0.67–1.39)		65/337	0.98 (0.58–1.66)	
		CC	54/70	1.14 (0.75–1.72)		11/70	0.84 (0.41–1.74)		110/251	0.88 (0.60–1.30)		74/251	1.52 (0.90–2.56)	
		CC *vs.* TT/TC	393/567	1.08 (0.73–1.59)	0.71	93/567	0.86 (0.49–1.88)	0.66	237/456	0.90 (0.68–1.19)	0.47	88/456	1.54 (1.08–2.19)	**0.02**
COX2	rs2745557	GG	288/397	1.00 (ref)	0.51	68/397	1.00 (ref)	0.42	249/503	1.00 (ref)	0.93	130/503	1.00 (ref)	0.10
		GA	142/203	0.97 (0.74–1.28)		27/203	0.82 (0.51–1.33)		91/190	0.96 (0.71–1.29)		32/190	0.63 (0.41–0.96)	
		AA	19/37	0.70 (0.39–1.27)		9/37	1.43 (0.65–3.12)		10/21	1.10 (0.50–2.39)		4/21	0.77 (0.26–2.29)	
		GA/AA *vs.* GG	161/240	0.93 (0.72–1.21)	0.59	36/240	0.92 (0.59–1.43)	0.71	101/211	0.97 (0.73–1.29)	0.84	36/211	0.64 (0.43–0.96)	**0.03**
ALOX5	rs1369214	GG	141/190	1.00 (ref)	0.53	30/190	1.00 (ref)	0.92	70/156	1.00 (ref)	**0.01**	30/156	1.00 (ref)	0.20
		GA	226/310	1.03 (0.77–1.37)		51/310	1.06 (0.65–1.73)		157/367	0.96 (0.68–1.36)		82/367	1.15 (0.73–1.83)	
		AA	80/134	0.85 (0.59–1.22)		23/134	1.13 (0.62–2.04)		122/189	1.49 (1.03–2.15)		54/189	1.53 (0.93–2.51)	
		AA *vs.* GG/GA	367/500	0.83 (0.60–1.15)	0.26	81/500	1.09 (0.66–1.81)	0.74	227/523	1.53 (1.15–2.03)	**0.003**	112/523	1.38 (0.95–1.99)	0.09
ALOX5	rs7099874	GG	246/281	1.00 (ref)	**0.001**	40/281	1.00 (ref)	0.44	248/525	1.00 (ref)	0.56	131/525	1.00 (ref)	0.24
		GC	160/304	0.62 (0.47–0.80)		52/304	1.20 (0.77–1.88)		91/165	1.16 (0.86–1.57)		28/165	0.70 (0.45–1.09)	
		CC	40/48	0.96 (0.60–1.54)		11/48	1.59 (0.75–3.35)		9/19	0.84 (0.37–1.92)		6/19	1.26 (0.49–3.25)	
		GC/CC *vs.* GG	200/352	0.66 (0.51–0.85)	**0.001**	63/352	1.26 (0.82–1.93)	0.30	100/184	1.12 (0.84–1.50)	0.44	34/184	0.76 (0.50–1.15)	0.19
ALOX5AP	rs9579648	GG	319/441	1.00 (ref)	0.66	69/441	1.00 (ref)	0.82	235/473	1.00 (ref)	0.06	114/473	1.00 (ref)	0.74
		GC	121/177	0.94 (0.71–1.25)		31/177	1.08 (0.68–1.72)		99/217	0.97 (0.72–1.29)		47/217	0.92 (0.63–1.34)	
		CC	8/19	0.69 (0.29–1.62)		4/19	1.38 (0.45–4.20)		16/16	2.33 (1.13–4.82)		5/16	1.36 (0.49–3.82)	
		CC *vs.* GG/GC	440/618	0.70 (0.30–1.64)	0.42	100/618	1.35 (0.45–4.06)	0.60	334/690	2.36 (1.15–4.84)	**0.02**	161/690	1. 40 (0.50–3.90)	0.52
ALOX5AP	rs9315048	GG	256/388	1.00 (ref)	0.26	62/388	1.00 (ref)	**0.03**	173/354	1.00 (ref)	0.76	72/354	1.00 (ref)	0.37

(Continued)

TABLE 4 | Continued

Gene	SNP	Genotype	White						Black					
			Estrogen Receptor Positive			Estrogen Receptor Negative			Estrogen Receptor Positive			Estrogen Receptor Negative		
			# Case/ Control	OR (95%CI)[b, c]	$P^{d, e, f}$	# Case/ Control	OR (95% CI) [b, c]	$P^{d, e, f}$	# Case/ Control	OR (95% CI) [b, c]	$P^{d, e, f}$	# Case/ Control	OR (95% CI) [b, c]	$P^{d, e, f}$
		GT	164/220	1.17 (0.90–1.52)		30/220	0.90 (0.56–1.45)		141/294	0.96 (0.73–1.26)		70/294	1.15 (0.79–1.65)	
		TT	30/29	1.47 (0.84–2.55)		12/29	2.47 (1.19–5.15)		36/63	1.14 (0.73–1.80)		20/63	1.49 (0.85–2.63)	
		TT *vs.* GG/GT	420/608	1.38 (0.80–2.38)	0.24	92/608	2.56 (1.25–5.25)	**0.01**	314/648	1.17 (0.75–1.81)	0.49	142/648	1.40 (0.82–2.39)	0.22
ALOX12	rs3840880[g]	TT	154/187	1.00 (ref)	0.27	43/187	1.00 (ref)	**0.01**	79/159	1.00 (ref)	0.20	39/159	1.00 (ref)	0.07
		TG	217/316	0.87 (0.65–1.15)		51/316	0.75 (0.47–1.17)		154/345	0.90 (0.64–1.26)		93/345	1.05 (0.69–1.60)	
		GG	78/131	0.74 (0.52–1.07)		10/131	0.34 (0.16–0.70)		117/211	1.19 (0.83–1.70)		34/211	0.63 (0.38–1.06)	
		TG/GG *vs.* TT	295/447	0.83 (0.63–1.09)	0.18	61/447	0.62 (0.40–0.96)	**0.03**	271/556	1.00 (0.73–1.37)	0.99	127/556	0.89 (0.60–1.34)	0.59

[a]*Based 554 (87.0%) White cases and 517 (88.5%) Black cases with available data on ER status.*

[b]*OR, odds ratio; 95%CI, 95% confidence interval.*

[c]*Adjusted for age, family history of breast cancer in a first-degree relative, and proportion of European ancestry.*

[d]*P-trend for genetic dose response determined by coding genotypes as having 0, 1, or 2 variant allele, which was subsequently analyzed as an ordinal variable.*

[e]*P for heterogeneity from dominant or recessive models.*

[f]*All significant p-values were further adjusted for multiple comparisons using Bonferroni correction, with P <0.002 (0.05/30) considered statistically significant.*

[g]*Several SNPs on the ALOX12 gene, rs3840880, rs1126667, rs434473, rs1042357, were found in high LD with rs3840880 (r^2 >0.98) in White women, with a similar association pattern (**Supplemental Table 3**).*

inconsistent findings in studies of these SNPs in relation to breast cancer (39, 40). Further studies are needed to confirm the interrelationships of *COX2* genetic variants, menopausal status, tumor subtypes, and ancestry.

Like the COX pathway, studies have shown that 5-lipoxygenase (5LOX) and its metabolites are upregulated in multiple cancers and play a potential role in carcinogenesis (48). In this study, we identified several SNPs in the *ALOX5* and *ALOX5AP* genes that showed associations with overall breast cancer risk and differences by menopausal and ER status, in either White or Black women. The *ALOX5*-rs7099874 was associated with reduced risk in postmenopausal White women. Significant associations were observed for two *ALOX5 SNPs* (rs1369214 and rs1051713) and the *ALOX5AP*-rs9315045 in premenopausal Black women, and *ALOX5AP*-rs4293222 in postmenopausal Black women. The *ALOX5*-rs7099874 and *ALOX5AP*-rs9579648 were specifically associated risk of ER+ breast cancer, while *ALOX5AP*-rs9315048 were associated with risk of ER− cancer, in either White or Black women. These SNPs in relation to breast cancer were not well studied or reported in the literature, our findings provide some evidence of their potential role in breast cancer susceptibility and potential differences by menopausal and ER status.

ALOX12 and its metabolite, 12S-hydroxyeicosatetraenoic acid, have been implicated in influencing tumor transformation and progression (49, 50). A recent study showed an upregulation of ALOX12 in breast cancer cell lines and tumor tissues compared to their corresponding normal breast cells and tissues (51). We identified a group of SNPs (rs3840880, rs1126667, rs434473, rs1042357) that were found in high LD in Whites, but not in Blacks. Interestingly, we observed that these SNPs were significantly associated with overall breast cancer risk, specifically in postmenopausal White women only, and the associated reduced risk was stronger for ER− breast cancer. In addition, there is some evidence that the presence of minor alleles of the rs434473 was associated with early onset of natural menopause in White women (52), which may explain the lower breast cancer risk observed among these women. A previous study, however, suggested that rs434473 was associated with an increased risk, especially among women with regular nonsteroidal anti-inflammatory drug use (21). We also observed an increased risk of breast cancer with the major alleles of rs2292350 among post-menopausal White women. An association between this SNP and age at menopause has also been found in a population of Chinese women (53). Frequencies of these polymorphisms have been found to differ across populations, and future studies are needed to confirm these associations.

Several limitations warrant consideration. First, we selected a panel of candidate SNPs based on their potential functions from previous studies, other potentially important genetic variants may not be included in the current study. However, analysis of these common genetic variants in candidate pathways is a more focused method for increasing our knowledge of potentially important biological pathways in the etiology of breast cancer (54). Second, although this is a study with a large number of White and Black women, which allow us to examine racial differences for these genetic variants with breast cancer risk, our sample size was relatively limited when analyses were stratified by menopausal and ER status. Third, the majority of associations did not reach statistical significance after Bonferroni corrections for multiple comparisons, thus we cannot exclude the possibility of false positive findings. Lastly, as the SNP-breast cancer associations may be confounded by other potential risk factors, we examined whether inclusion of these factors as covariates change the risk estimate, and subsequently presented results from the multivariable-adjusted model to minimize residual confounding. Nevertheless, this study investigates the role of *COX* and *LOX* genetic variants in a large number of Black women, which addresses the unmet need to improve representation of Black populations in genomic breast cancer studies. Furthermore, SNP associations with breast cancer risk were found to differ between White and Black populations, especially when menopausal and ER statuses were considered. These findings may provide insights into the etiology of breast cancer, indicating areas for further research into reasons for breast cancer racial differences.

In conclusion, this study is among the first to examine genetic variants in genes involved in the COX- and LOX-related inflammatory pathways with breast cancer risk among both White and Black women. Our study suggests that genetic variants of these inflammation-related genes are associated with breast cancer, and that these associations and genotype distributions differ in subgroups defined by menopausal and ER status between White and Black women. As current research remains limited, additional studies are necessary to confirm these findings and explore the underlying molecular mechanisms.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

ETHICS STATEMENT

This study was approved by institutional review boards at the Roswell Park Comprehensive Cancer Center, the Rutgers Cancer Institute of New Jersey, Mount Sinai School of Medicine (now the Icahn School of Medicine at Mount Sinai), and participating hospitals in New York City. Signed informed consent was obtained from each participant prior to interview and biospecimen collection. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JM made substantial contributions to the interpretation of the data, drafted the manuscript, and revised it critically for important intellectual content. CA, EB, CCH, AO, GZ, TK and SY were essential to data collection and genotyping, interpretation of the data and manuscript writing. ZG made

substantial contributions to the conception, design, analysis, and writing the manuscript. 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/fonc.2021.679998/full#supplementary-material

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REVIEW
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A Review of Research on Disparities in the Care of Black and White Patients With Cancer in Detroit

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Racial disparities in cancer incidence and outcomes are well-documented in the US, with Black people having higher incidence rates and worse outcomes than White people. In this review, we present a summary of almost 30 years of research conducted by investigators at the Karmanos Cancer Institute's (KCI's) Population Studies and Disparities Research (PSDR) Program focusing on Black-White disparities in cancer incidence, care, and outcomes. The studies in the review focus on individuals diagnosed with cancer from the Detroit Metropolitan area, but also includes individuals included in national databases. Using an organizational framework of three generations of studies on racial disparities, this review describes racial disparities by primary cancer site, disparities associated with the presence or absence of comorbid medical conditions, disparities in treatment, and disparities in physician-patient communication, all of which contribute to poorer outcomes for Black cancer patients. While socio-demographic and clinical differences account for some of the noted disparities, further work is needed to unravel the influence of systemic effects of racism against Black people, which is argued to be the major contributor to disparate outcomes between Black and White patients with cancer. This review highlights evidence-based strategies that have the potential to help mitigate disparities, improve care for vulnerable populations, and build an equitable healthcare system. Lessons learned can also inform a more equitable response to other health conditions and crises.

Keywords: disparities, co-morbidities, cancer treatment, physician-patient communication, socio-economic

HIGHLIGHTS

An understanding of race-related factors underlying and maintaining health disparate outcomes is essential for developing interventions and initiatives that could reduce current inequalities in cancer care. Knowledge gained from research on racial health disparities can also help to eradicate disparities in the future.

INTRODUCTION

In the United States, there are significant racial disparities in cancer incidence and outcomes with higher incidence rates and worse outcomes occurring in Black compared to White populations across multiple primary cancer sites (1). Evidence suggests that these disparities result in large measure from inequitable social, economic, political, behavioral, and psychological processes, which disproportionately negatively impact outcomes among Black individuals with cancer (2). Numerous studies have evaluated the extent to which levels of socioeconomic status (SES), access to care, cancer treatment, and clinical communication contribute to racial health and healthcare disparities (3). While multiple causal pathways might explain in part why Black cancer patients have worse outcomes than their White counterparts, the major underlying force is arguably the legacy of various forms of racism against Black people in the US (4).

Systemic racism in the US began with the legal enslavement primarily of people from Africa and has pervaded medical practice over the last 300 years. Examples of racism in the US medical system range from unethical experimentation on coerced Black people to institutional practices in medical care that either exclude Black people entirely or systematically provide them with poorer treatment than White people (5–10). In an effort to understand and address Black-White health disparities, researchers in the Karmanos Cancer Institute's (KCI's) Population Studies and Disparities Research (PSDR) Program have conducted research over the past 30 years ranging from descriptive to evaluative and interventional. Our efforts to explore and better understand racial disparities in cancer incidence, care, and outcomes, along with efforts of our collaborators, are particularly relevant to our institution given our location in Detroit Michigan, a city with a majority of Black people.

In 2019, it was estimated that 69.6% of Michigan's 1,350,329 non-Hispanic Black population resided within the tri-county Detroit area with the largest proportion of the population (N=518,305) living in the city of Detroit, and the remainder (N=421,799) living in the suburban environs surrounding Detroit. According to Surveillance Epidemiology and End Results (SEER) data, between 2013 and 2017, Black compared with White individuals in Detroit had a disproportionate share of the burden of cancer, with incidence and death rates per 100,000 of 491.92 *vs* 489.01 and 195.25 *vs* 164.68 respectively (11). Our research on disparities has largely focused on populations in Detroit and the surrounding tri-county area. Further, given that KCI is one of the founding sites of the National Cancer Institute's SEER program, many of our studies and those of our collaborators include populations outside of the Detroit area.

In this review, we present a selection of research studies published on cancer disparities conducted by investigators in the KCI's PSDR program together with collaborators from several different institutions. After a thorough PubMed search of publications by PSDR investigators on racial disparities, we selected studies which focused on Black-White disparities in clinical presentation at diagnosis, treatment, and outcomes, as well as those that evaluated interventions designed to reduce or eliminate Black-White disparities. Given the critical juncture in race relations and health care equity in the US, the goal of this review is to summarize and critique published research and to provide a framework to shape future research that can lead to elimination of health disparities.

GENERATIONS OF DISPARITIES RESEARCH

The sections of the review generally follow the framework of Thomas et al. (12), which describes three generations of cancer disparities research ranging from descriptive, to analytical and interventional. First generation studies are those that both identify and document the existence of health disparities. Second-generation studies are analytic or evaluative, and attempt to assess variables that could potentially explain the noted disparities. Lastly, third generation studies have the goal of testing interventions that could serve as solutions to mitigate disparate outcomes. While the order of this review generally follows this overall framework, many of the studies cited span both first and second generations, and the section focused on physician-patient communication includes studies spanning all three generations of disparities research. We will conclude with a discussion of fourth generation research, the goal of which is to ultimately take action to eliminate disparities.

FIRST-GENERATION STUDIES: DOCUMENTING CANCER DISPARITIES

Black-White Disparities in Phenotypic Features at Diagnosis

Table 1 lists studies by PSDR investigators and their collaborators that identify and document disparities stratified by primary cancer type and show first-generation evidence that Black patients as compared with White patients present with more advanced and aggressive disease at diagnosis across cancer sites evaluated. In a survival analysis of 10,502 women with breast cancer using data from the Detroit Metropolitan Area (DMA)-SEER database, Black women were more likely to present with regional or distant stage disease (44.5%) compared to White women (36.5%) ($p < 0.00001$) (13). In another analysis of 1,700 women with early-stage breast cancer, using data from the Detroit and Los Angeles SEER registries, 16.1% of patients with stage 0 + 1 disease were Black and 75% were White, compared to stage II + III disease where 21.2% were Black and 62.4% were White (14). Similar results were reported for other primary cancer sites including a Detroit Metropolitan Area–SEER analysis of colorectal cancer (CRC) (15) and a study of young-onset CRC identified at 18-SEER sites, which showed that Black compared to White patients were less likely to be diagnosed with early-stage disease (16).

TABLE 1 | First-Generation Evidence of Black-White Disparities at Diagnosis.

Years of Study, Reference	Study Population	Clinical Presentation	Black Patients (%)	White Patients (%)	P-value
Breast Cancer					
12/2002- 1/2013, Lantz et al. (14)	DMA[2] + Los Angeles –	Stage (AJCC, TNM)[1]			<0.001
	SEER[3]	0 + I	16.1	75	(row
	N=1,700	II + III	21.2	62.4	percentage)
1988-1992, Simon and Severson (13)	DMA SEER	Stage (SEER)			<0.00001
	N=10,502	Local	53.6	62.7	
		Regional	38.2	33.1	
		Remote	6.3	3.4	
		Unknown	1.9	0.8	
		Tumor Size			<0.00001
		T1	46.5	62.3	
		T2	41.2	31.7	
		T3	11.0	5.3	
		T4	1.3	0.7	
		Histologic Grade			<0.00001
		1	3.2	4.3	
		2	15.3	14.4	
		3	27.1	16.6	
		4	2.7	1.5	
		Unknown	51.7	63.2	
1996-2005, Roseland et al. (17)	HFHS[4] N=2,387	Tumor Size			<0.001
		< 2 cm	56	66	
		2.1-5 cm	32	28	
		> 5 cm	9	4	
		Lymph Nodes			0.002
		Negative	66	72	
		Positive	34	28	
		Grade			< 0.001
		Well/moderate	51	63	
		Poor/undifferentiated	45	32	
		Hormone Receptor			<0.001
		ER/PR: Positive	64	75	
		ER/PR: Negative	30	19	
1994-1997, Du and Simon (18)	KCI[5]	Stage (TNM)			0.001
	N=588	I	42	51	
		II	47	46	
		IIIA	5	1	
		IIIB	6	2	
		Lymph Nodes +	39	36	0.563
		Hormone Receptor			<0.001
		ER+	52	73	
		PR+	49	65	
Holowatyj et al. (24)	SEER-18	Hormone Receptor			<0.0001
	N=134,639	ER+, PR +	8.2	73.2	
		ER+/PR-	12.9	68.7	
		ER-/PR+	19.9	59.7	
Holowatyj et al. (28)	DMA-SEER	21-Gene Recurrence Score			0.0004
	N=2,216	< 18	55.9	60.8	
		18-30	29.3	30.9	
		≥31	14.8	8.3	
Colorectal Cancer (CRC)					
1988-1992, Yan et al. (15).	DMA-SEER	Stage (TNM)			<0.001
	N=9,078	I + II	37.2	45.1	
		III	19.9	21.2	
		IV	27.6	22	
2000-2009, Holowatyj et al. (16).	SEER-18	Stage (ACJCC)			<0.001
	N=28,145	0	2.1	2.6	
		I + II	36.1	40.2	
		III	28.7	29.9	
		IV	27.1	21.7	
		Grade			<0.001
		I	7.1	8.2	

(Continued)

TABLE 1 | Continued

Years of Study, Reference	Study Population	Clinical Presentation	Black Patients (%)	White Patients (%)	P-value
		II	62.5	59.8	
		III	16.2	18.5	
		IV	1.1	1.3	
GYN Cancers					
2000-2013, Park et al. (30).	SEER -18	Stage (SEER)			
	N=76,241	Local	12.5	15.9	
	(ovarian)	Regional	8.5	8.7	
		Distant	68.7	67.6	
		Un-staged	10.4	7.8	
		Grade			
		Low	14.5	17.6	
		High	36.4	45.6	
		Unknown	49.1	36.9	
1988-1992	DMA-SEER	Stage (FIGO[6])			<0.001
Movva et al. (48)	N=1,036 (cervical)	I	48.9	59.6	
		II	19.6	18.2	
		III	12.7	8.8	
		IV	8.5	7.1	
2000-2011,Cote et al. (23)	SEER-18:	Stage (SEER)			
	N=120,513	Local	53	70	
	(uterine)	Regional	24	18	
		Distant	16	8	
		Unknown	4	4	
		Grade			
		Low	43	65	
		High	36	21	
		Unknown	20	14	
Prostate Cancer					
1988-1992, Schwartz et al. (27)	DMA-SEER	Grade (Localized)			<0.001
	N=8,679	Well	31	30	
		Moderate	43	47	
		Poor/Undifferentiated	18	14	
		Missing	8	9	
		Grade (Regional)			0.21
		Well	10	7	
		Moderate	44	49	
		Poor/Undifferentiated	37	37	
		Missing	10	7	
7/1990-12/1999	KCC	Clinical Stage			0.11
Powell et al. (53)	N=791	T1a-T1b	3.49	2.15	
		T1c	27.07	33.67	
		T2a	43.17	25.26	
		T2b	17.9	12.88	
		T2c	7.42	6.26	
		T3	0.44	0.18	
1992-2001	DMA-SEER N=1,056	Mean Tumor Volume (cc) by age group			
Powell et al. (25)		40-49	0.436	0.215	
		50-59	0.941	0.899	
		60-69	0.875	2.555	
		70-79	0.562	2.941	
		% Gleason Score (≤ 6) by age group			
		40-49	97	100	
		50-59	87	93	
		60-69	86	87	
		70-79	65	84	
1973-1994 (pre-PSA) and 1995-2005	SEER-18	% Gleason Score (by age group)			P<0.0001
(PSA)	N=Pre PSA 212,719	**40-49 years**			
Powell et al. (26)	Post PSA	2-6	45.4	52.4	
	309,793	7-10	54.6	47.6	
		50-59 years			

(Continued)

TABLE 1 | Continued

Years of Study, Reference	Study Population	Clinical Presentation	Black Patients (%)	White Patients (%)	P-value
		2-6-	37.6	44.8	
		7-10	62.4	55.2	
		60-69 years			
		2-6	32.4	37.4	
		7-10	67.6	62.6	
Other Primary Sites					
2002-2007	DMA-SEER:	Stage (AJCC)			0.03
Schwartz et al. (34)	N=951	I	72	65	
	Renal Cell Carcinoma	II	12	11	
		III or IV	13	20	

[1]*AJCC, TNM: American Joint Committee on Cancer, Tumor, Nodal, Metastases.*
[2]*DMA, Detroit Metropolitan Area.*
[3]*SEER, Surveillance, Epidemiology and End Results.*
[4]*HFHS, Henry Ford Health Systems.*
[5]*KCC, Karmanos Cancer Center.*
[6]*FIGO, Federation of Gynecology and Obstetrics Staging System.*

Data from single institutions in the Detroit Metropolitan area also showed disparities in stage at diagnosis. Together with their collaborators, researchers from the PSDR conducted studies using data from Henry Ford Health System (HFHS), a large integrated health center in Detroit, and the Karmanos Cancer Center (KCC), one of 54 National Cancer Institute designated Comprehensive Cancer Centers in the US.

In a study of Black-White differences in breast cancer survival among women diagnosed and treated at HFHS, the distribution of tumor size by race demonstrated that 66% of White women had tumors ≤ 2cm and 4% had tumors > 5 cm; however, the tumor size distribution for Black women was 56% and 9% respectively ($p< 0.001$) (17). Using data from the KCI, PSDR investigators demonstrated that Black women were also more likely to present with advanced disease at diagnosis (18).

Other first-generation evidence includes studies that describe Black-White disparities in tumor phenotypic characteristics in both SEER-based and single institution studies. Black compared to White cancer patients across multiple tumor types were more likely to present with higher-grade, and more aggressive disease (16, 19–22), and among individuals with endometrial cancer, Black patients were more likely to present with histologic subtypes associated with worse outcomes (20–23). In three hospital-based studies, Black women were more likely to present with triple-negative breast cancer (17, 18, 24), and in studies of prostate cancer, Black men were more likely to present with aggressive disease associated with higher Gleason grade and greater prostate gland volume (25–27). Similar patterns were seen in a study evaluating tumor genomic profiling in a Detroit Metropolitan Area-SEER analysis of women with early-stage hormone-sensitive breast cancer. The results from this analysis demonstrated higher recurrence scores in Black compared to White women, signifying a greater need for adjuvant chemotherapy (28).

These racial disparities in stage and tumor phenotype have been exemplified in reported racial disparities in overall survival over time. In an analysis of 25,997 women with breast cancer diagnosed through the Detroit Metropolitan Area–SEER registry between 1975-2001, successive historical cohorts (1975-1980 and 1990-1995) demonstrated a widening survival gap between Black and White women with breast cancer over time. This disparity pertained specifically to younger women who were not yet Medicare-eligible. In addition, disadvantages in access to radiation, chemotherapy, and hormonal therapy continued over time, particularly among Black women with lymph node-positive disease (data not shown in Table) (29). This information serves in a sense as a "natural experiment" in which it can be hypothesized whether changes in policy and interventions over time could have an influence on cancer survival and treatment. Lastly, in a SEER-18 study of ovarian cancer, Black compared to White women experienced poorer 5-year overall survival for each stage of disease (30).

Black-White Disparities in Co-Morbid Medical Conditions Among Patients With Cancer

In this section, we include studies of racial disparities in comorbidities among patients with cancer in order to identify factors that may place Black cancer patients at greater risk for poorer outcomes. In studies using data from both single institutions to multiple sites, PSDR investigators and collaborators found that Black compared to White cancer patients across multiple tumor types were more likely to be diagnosed with co-morbid medical conditions including hypertension (HTN) (18, 21, 22, 31, 32), diabetes (18, 32), heart disease (18), obesity (22, 33, 34), and chronic renal failure (34).

Table 2 lists studies suggesting that co-morbid medical conditions have a differential impact on cancer outcomes for Black and White patients with cancer. In a case-control study from the HFHS, metabolic syndrome was associated with prostate cancer risk in Black men with organ confined disease but not in White men (OR 1.82, 95% CI 1.02-3.23). Data from this study also suggested a possible protective influence of obesity for White but not Black men (OR 0.51, 95% CI 0.33-0.8) (32). Another analysis of Black ovarian cancer survivors from a large

TABLE 2 | The Impact of Co-Morbid Medical Conditions.

Years of study, Reference	Population	Outcome	Race Groupings	HR, 95% CI	Disparity
1999-2004, Beebe-Dimmer et al. (32)	HFHS[1] N=637 cases, 244 controls	Association between metabolic syndrome (MetS) and prostate cancer	MetS and prostate cancer:	Odds Ratio:	Metabolic syndrome associated with prostate cancer risk in Black men with organ confined disease. Obesity protective for White and not Black men.
			Black	1.71 (0.97-3.01)	
			White	1.02 (0.64-1.62)	
			Organ confined with MetS:		
			Black	1.82 (1.02-3.23)	
			White	1.01 (0.63-1.62)	
			Advanced with MetS		
			Black	0.93 (0.31-2.77)	
			White	1.17 (0.55-2.51)	
			Obesity		
			Black	1.15 (0.70-1.89)	
			White	0.51 (0.33-0.8)	
2010-2011, Bandera et al. (35)	AACES[2] N=492 cases, 696 controls All Black participants	Impact of BMI[3] 1yr pre-diagnosis and weight gain since age 18 on ovarian cancer risk	Ovarian cancer risk BMI ≥40	Odds Ratio 1.72 (1.12-2.66) Ptrend 0.03	Ovarian cancer risk associated with higher BMI and weight gain in study of Black postmenopausal women.
			Weight gain since age 18	1.52 (1.07-2.16) Ptrend 0.02	
2002-2007, Colt et al. (31)	USKCS[4] Cases: 843 White and 358 Black; Controls: 707 White and 519 Black	Role of hypertension in renal cell cancer incidence by race	HTN risk:	Odds Ratio	Higher risk of renal cell carcinoma for Black *vs.* White patients with HTN and consistent risk with prolonged or poorly controlled HTN.
			Black	2.8 (2.1-3.8)	
			White	1.9 (1.5-2.4)	
			Risk after 25 years of HTN:		
			Black	4.1 (2.3-7.4)	
			White	2.6 (1.7-4.1) Ptrend <0.001	
			Risk with poorly controlled HTN:		
			Black	4.5 (2.3-8.8)	
			White	2.1 (1.2-3.8) Ptrend<0.001	
Callahan et al. (36)	USKCS N=965 cases, 953 controls KPNC[5]: N=2162 cases, 21,484 controls	Race and gender-specific PAR% for hypertension and CKD based on race, age ≥50 years	Hypertension (USKC):	PAR%[6]:	Black compared with White patients had larger population attributable risk percent associated with HTN and chronic kidney disease.
			Black male	44.4% (24.7-64.1%)	
			White male	26.6% (14.2-39%)	
			Black female	50% (23.5-76.7%)	
			White female	28.5% (13.4-43.64%)	
			Hypertension (KPNC):		
			Black male	22.8% (1.6-44.1%)	
			White male	18.9% (13.7-24.1%)	
			Black female	39.8% (17.5-62.2%)	
			White female	27.4% (20.3-34.5%)	
			CKD[7] (USKC):		
			Black male	9.4% (4.0-14.8%)	
			White male	0.6% (-0.5-1.6%)	
			Black female	8.4% (1.9-14.9%)	
			White female	0.4% (-1.5-2.3%)	

(Continued)

TABLE 2 | Continued

Years of study, Reference	Population	Outcome	Race Groupings	HR, 95% CI	Disparity
			CKD (KPNC):		
			Black male	10.1% (4.6-15.5%)	
			White male	0.0% (-0.6-0.5%)	
			Black female	6.9% (1.5-12.4%)	
			White female	-0.3% (-0.8-0.1%)	
1986-1989 Silverman et al. (38)	SEER registries: Atlanta, Detroit, and New Jersey N=526 cases, 2,153 controls	Role of comorbidities in pancreatic cancer incidence by race	PAR %- smoking, diabetes, family history:	PAR%:	The known pancreatic risk factors accounts for some of the difference in risk for Black and White men, however a larger proportion of the difference in risk is accounted for by less known risk factors in Black and White women.
			Black male	46% (10-82%)	
			White male	37% (13-62%)	
			Black female	15% (13-43%)	
			White female	27% (4-49%)	
			PAR% adding heavy alcohol use, high BMI:		
			Black male	53% (13-93%)	
			White male	49% (23-74%)	
			Black female	88% (66-111%)	
			White female	47% (2-92%)	
2000-2005 Olson et al. (37)	SEER[8] Medicare: N=11,610 White, and 958 Black; age ≥ 66 years	Influence of co-morbidities on overall survival in endometrial cancer	OS[9]:	Multivariate	Black-white differences in OS and DSS in multivariable analysis remained after adjusting for co-morbidities
			Black *vs.* White	1.16 (1.05-1.28)	
			DSS[10]		
			Black *vs.* White	1.27 (1.08-1.49)	
1990-2005, Ruterbusch et al. (22)	HFHS N=627	Influence of comorbid conditions on survival: endometrial cancer	Black *vs.* White:	Multivariate	No Black-White differences in overall survival, but continued differences in disease specific survival after adjusting for clinical factors and co-morbid conditions
			Death from any cause	1.22 (0.94-1.57)	
			Death from endometrial cancer	2.27 (1.39-3.68)	
1996-2012, Cote et al. (21)	KCC[11]: N=97 White & 89 Black	Post-surgical outcomes, survival in very obese women (BMI ≥40): endometrial cancer	Overall Survival	Multivariate	Black-White difference in post-op complications but no differences in overall or disease-specific survival after adjusting for age, histology, FIGO stage and grade, treatment and comorbidities.
			Black *vs.* White	0.85 (0.36-2.03)	
			Disease specific survival		
			Black *vs.* White	0.95 (0.26-3.52)	

•*All statistics other than hazard ratios are indicated in the table.*
[1]*HFHS, Henry Ford Health System.*
[2]*AACES, African American Cancer Epidemiology Study.*
[3]*BMI, Body Mass Index.*
[4]*USKCC, US Kidney Cancer Study.*
[5]*KPNC, Kaiser Permanente Northern California.*
[6]*PAR%, Population attributable risk percent.*
[7]*CKD, Chronic kidney disease.*
[8]*SEER, Surveillance, Epidemiology and End Results Program.*
[9]*OS, Overall survival.*
[10]*DSS, Disease specific survival.*
[11]*KCC, Karmanos Cancer Center.*

multi-site epidemiological study, showed that BMI ≥ 40 and weight gain since age 18 were associated with higher odds of ovarian cancer (OR 1.72, 95% CI 1.12-2.66 for BMI; and OR 1.52, 95% CI 1.07-2.16 for weight gain) (35).

A study from the US Kidney Cancer Study (USKCS), which included Detroit as one of two sites, compared risk of renal cell carcinoma (RCC) among Black compared to White patients. Findings demonstrated a higher risk of RCC associated with history of HTN among Black compared to White patients (OR 2.8, 95% CI 2.1-3.8) (31). In an expansion of the USKCS analysis, which also used data from the Kaiser Permanente Northern California (KPNC) registry, the population-attributable risk percentages (PAR%) for HTN and RCC were highest among Black women followed by Black men, White women, and White men. The PAR% for RCC for chronic kidney disease for Black men and women was 7-10 times greater than for White women and men (36).

An analysis of the impact of co-morbid medical conditions on disparities in survival among Black and White women with endometrial cancer at the HFHS, found that Black women continued to have worse overall survival outcomes despite adjustment for co-morbid medical conditions (22). These findings were replicated in a similar analysis of SEER-Medicare linked data (37). In comparison, however, in a study of morbidly obese women with endometrial cancer from the KCC, there were no Black-White disparities in overall or disease specific survival, suggesting the possibility of more equal provision of care once women are part of a single medical care system (21).

Lastly, in a collaborative population-based case-control study of pancreatic cancer including patients from Detroit, Atlanta, and New Jersey, established risk factors (cigarette smoking, long-term diabetes mellitus, family history of pancreatic cancer) accounted for 46% of the risk of disease in Black men and 37% in White men, potentially explaining all but 6% of the excess risk among Black patients. Among women, when less accepted risk factors such as moderate/heavy alcohol consumption (>7 drinks per week) and elevated BMI (above the first quartile) were combined with established risk factors, 88% of the risk of disease in Black women and 47% in White women was explained, potentially accounting for all of the excess risk among Black women (38).

SECOND-GENERATION STUDIES: EXPLAINING DISPARITIES

The studies included in this section identify explanatory variables that might at least in part explain Black-White disparities as outlined below. PSDR investigators and collaborators assessed disparities using different outcome measures such as disparities in receipt of cancer-directed treatment, disparities in stage at diagnosis, disparities in rate of relapse, and disparities in survival including overall and disease-specific survival. The majority of studies utilized multivariable methods in order to determine the contribution of multiple potential confounders on racial disparities in outcomes.

Disparities in Cancer Treatment

Table 3 includes studies that evaluate racial disparities in cancer treatment and show mixed results across type of treatment, tumor type and institution. In an analysis of data on treatment for breast cancer from the KCC, no differences or disparities were found related to surgery or radiation, but Black women with regional stage disease were more likely to receive tamoxifen (OR 4.59, 95% CI 1.52-13.9) or chemotherapy (OR 3.10, 95% CI 1.09-8.81), suggesting the presence of other factors related to the need for more aggressive treatment among Black patients. In the same analysis, women with Medicare or Medicaid were more likely to have mastectomy compared to breast conserving surgery, suggesting that older women and women with lower income were less likely to take, or less likely to be offered, the more favored surgical option (39). In another analysis of early stage breast cancer at the HFHS, there were no racial differences in the receipt of adjuvant chemotherapy (OR 1.01, 95% CI 0.72-1.42) or in the timing of receipt of chemotherapy (OR 1.18, 95% CI 0.8-1.74) (40). Lastly, in an analysis of Black-White differences in breast cancer survival at the KCC, there were no racial differences in treatment received or the cost of care, suggesting similar provision of care despite race at a single institution (18).

In contrast however, racial disparities in treatment were consistently noted in studies of men with prostate cancer. In three SEER-based collaborative studies, Black compared to White men with prostate cancer were less likely to receive treatment for their cancer. In one study, Black men were less likely to receive any treatment for de-novo stage IV disease (41), or if they received treatment, more likely to have orchiectomy. In another study, Black men were less likely to receive treatment for local or regional stage disease and had worse survival (27). In the third study, Black men were more likely to choose observation only instead of active treatment (42).

In the HFHS study cited earlier, on the influence of co-morbidities on racial differences in outcome for women with endometrial cancer (**Table 2**), Black women were more likely to have no surgery (17% *vs.* 4%, p<0.001), and also more likely to need chemotherapy after surgery (27% *vs.* 20%, p=0.041), again potentially reflecting the more advanced stage and aggressive disease seen in Black women (data not shown in the table) (22). In summary, the studies cited in this section suggest that based on primary site, Black compared to White patients with comparable disease and stage may either be under-treated (less surgical intervention) or receive less desirable treatment (more mastectomy or orchiectomy). Other studies from single institutions show more comparable receipt of treatment across racial groups.

Disparities in Socioeconomic Status and the Impact on Cancer Outcomes

It is generally acknowledged that there are strong associations between variables that include patient social and economic characteristics, neighborhood characteristics, and cancer outcomes (43). Since individual measures of SES such as income, education and insurance are generally not available in larger population-based studies, PSDR investigators in

TABLE 3 | Studies focusing on Black-White differences in cancer-directed therapy.

Years of study, Reference	Population	Outcome	Race Groupings	HR, 95% CI	Disparity
1990-6 Banerjee et al. (39)	KCC[1] N=651	Racial differences in treatment –breast cancer	BCS[2]± RT[3] *vs.* Mastectomy ± RT White *vs.* Black (ref) Localized Regional tamoxifen White *vs.* Black (ref) Localized Regional Chemotherapy White *vs.* Black (ref) Localized Regional	Multivariate Odds Ratios 0.81 (0.4-1.65) 1.65 (0.65-4.16) 0.85 (0.35-2.07) 4.59 (1.52-13.9) 1.3 (0.52-3.26) 3.10 (1.09-8.81)	No racial differences in Breast Conserving surgery *vs.* mastectomy however Black women with regional stage disease more likely to receive tamoxifen or chemotherapy. Multivariate adjustment included race, hormone receptor status, tumor size and grade, positive nodes, age at diagnosis, SES, insurance, marital status and comorbidities.
1996-2005 Simon et al. (40)	HFHS[4] N=2234	Racial differences in the use of and timing of adjuvant chemo-therapy-Breast	Chemo Black White Chemo delay >60 days Black White	Multivariate Odds Ratio 1.01 (0.72-1.42) Ref 1.18 (0.8-1.74) Ref	No Black-White differences in use or timing of adjuvant chemotherapy after adjusting for age, tumor characteristics comorbidities, and SES variables.
1994-7 Du and Simon (18)	KCC N=588	Racial differences in patterns and costs of care, stage 1-3 - Breast	Surgery (Black *vs.* White): Lumpectomy Lumpectomy + RT Mastectomy + RT Chemotherapy Tamoxifen Mean 1-Year total treatment costs (Black *vs.* White)	 97% *vs.* 96% 82% *vs.* 76% 25% *vs.* 16% 41% *vs.* 42% 71% *vs.* 74% $16,348 vs. $ 15,120	No Black-White differences in treatment or cost of care at the KCC.
2004-14 Beebe-Dimmer et al. (41)	SEER[5]-Medicare N=8828	Treatment pattern by race - *de novo* stage IV prostate cancer; age ≥66yrs	No treatment: Black *vs.* White Orchiectomy: Black *vs.* White	Multivariable Odds Ratios 2.15 (1.7-2.71) 10.1 *vs.* 6.1%	Black *vs.* White men more likely to have no treatment and more likely to have orchiectomy.
1988-1992 Schwartz et al. (27)	DMA[6]-SEER: N=8679	Racial disparities in treatment, OS and DSS - prostate	Localized Black *vs.* White: Radical prostatectomy RT No treatment Regional Black *vs.* White: Radical prostatectomy RT No treatment	 16 *vs.* 26% 36 *vs.* 38% 48 *vs.* 36% (p,0.001) 26% *vs.* 47% 30% *vs.* 28% 44% *vs.* 24% (p<0.001)	Black *vs.* White men less likely to have radical prostatectomy and more likely to have no treatment.

(Continued)

TABLE 3 | Continued

Years of study, Reference	Population	Outcome	Race Groupings	HR, 95% CI	Disparity
2009-10 Xu et al. (42)	SEER-DMA N=260	Treatment choice for localized disease – prostate	Treatment choice: Black *vs.* White: Surgery *vs.* WW/AS[7] Radiation *vs.* WW/AS Radiation *vs.* surgery	Multivariable Odds Ratio 0.42 (0.05-0.31) 0.13 (0.02-0.69) 0.31 (0.06-1.63)	Black men were less likely than White men to have surgery or radiation compared to watchful waiting, however there were no differences in choice of surgery or radiation by race.

[1]*KCC, Karmanos Cancer Center.*
[2]*BCS, Breast conserving surgery.*
[3]*RT, Radiation therapy.*
[4]*HFHS, Henry Ford Health System.*
[5]*SEER, Surveillance, Epidemiology and End Results.*
[6]*DMA, Detroit Metropolitan Area.*
[7]*WW/AS, Watchful waiting/active surveillance.*

collaboration with other researchers assessed SES through linkage of geocoded residential addresses to sources of data for larger groups residing in standard geographic regions such as census tract (44) county, or census block, noting the potential for ecological fallacy (43, 45).

To account for differences in SES and other neighborhood characteristics, PSDR investigators used the deprivation index, which provides an estimate of the quality of living conditions at census tract levels. The deprivation index is based on the proportion of households without a vehicle; households without a telephone; population over the age of 16 that are unemployed; population living in a residence with more than 1 person per room; and population living below the poverty line (46). A composite index is calculated by adding the value of each of the variables divided by 5 to produce a single index value ranging from 0 to 1, with 0 representing no deprivation and 1 maximal deprivation (17). It should be noted that this method, while providing a broader context for individual SES, is not perfectly valid in that high-deprivation areas can include people of varying economic background (47).

Across a range of studies using data from single institutions or from the SEER registry, Black compared to White patients were more likely to have a primary residence in census tract areas documented as low SES or in areas where a lower proportion of the population had received higher education or had access to medical insurance (15, 17, 19, 40, 48, 49), or to reside in areas with higher measures of deprivation (17, 40, 49). In addition, as reported in one Detroit Metropolitan area-SEER study, Black breast cancer patients were more likely to reside in an area where hospitals provided more care for Medicare and Medicaid patients (13).

In studies using data from the KCC (18), pooled data from case-control studies (50), or from a large US study of postmenopausal women (51), Black compared to White patients had lower levels of educational achievement. In a Detroit Metropolitan Area-SEER analysis of colorectal cancer (CRC), Black compared to White patients were less likely to reside in a census tract area categorized as "professional" (16.5% vs. 42.5%, $p<0.001$) (15). In a study of women with estrogen and progesterone receptor negative breast cancer at the HFHS, Black compared to White women were ten times more likely to reside in an area with the highest level of deprivation (45.9% vs 4.4%, respectively $p< 0.001$) (49).

Table 4 lists studies that include SES as part of a multivariable model. In a Detroit Metropolitan Area -SEER study of racial differences in breast cancer survival, after adjustment for SES (based on census tract level data), and other predictors of survival including socio-demographic and clinical factors, White women with local- and regional-stage disease had better overall survival rates than Black women ($p<0.00001$); however, for women with distant-stage disease, there were no significant survival differences by race ($p=0.3$). In this analysis, racial differences in survival were only apparent up to 4 years after diagnosis, but not after 4 years ($p=0.6$). It is of note that the difference in survival for Black and White women in this analysis was more apparent among women at a younger age at diagnosis with a relative risk (RR) for women < 50 years at diagnosis

TABLE 4 | Racial Disparities Studies Which Include Socioeconomic Status as Part of Multivariable Model.

Years of Study, Reference	Population	Outcome	Race Groupings	HR, 95% CI	Disparity
1988-1992, Simon and Severson (13)	DMA[1] SEER[2] N=10,502	Overall Survival – Local, Regional and Distant Stage - Breast	Age < 50 Black White Age 51 + Black White	Multivariate RR 1.68 (1.27-2.23) Ref 1.33 (1.13-1.56) Ref	Blacks had worse overall survival particularly among younger women after adjustment for clinical factors and SES-based on census tract.
1988-1992, Yan et al. (15)	DMA-SEER N-9,078	Overall and disease-specific survival-Colo-rectal	Overall Survival Black White Disease specific Survival Black White	Multivariate HR 1.0 (0.92-1.09) Ref 1.06 (0.94-1.19) Ref	No Black-White differences in overall or disease specific survival after adjustment for clinical and SES-based on census tract.
1988-1992 Movva et al. (48)	DMA-SEER N=1,036	Overall Survival for stage I-IV - cervical cancer	Overall Survival Black White	Multivariate HR 1.12 (0.89-1.42) Ref	No Black-White differences in overall survival after adjustment for clinical factors and SES based on census tract.
1994-1997, Du and Simon (18)	KCC[3] N=588	Overall Survival and disease free survival -Stage I-III -Breast	Disease Free Survival Black White Overall Survival Black White	Multivariate HR 1.38 (0.85-2.26) Ref 1.06 (0.64-1.79) Ref	No Black-White differences in disease free or overall survival after adjustment for clinical factors and co-morbidities (insurance as proxy for SES but not included in the multivariable model)
1996-2005, Roseland et al. (17)	HFHS[4] N=2,387	Overall Survival – Stage I-III-Breast	Overall Survival Black White	Multivariate HR after adjustment for SES 0.97 (0.8-1.19) Ref	No Black-White overall survival differences after adjustment for SES based on disparity index
1996-2005, Roseland et al. (49)	HFHS N=542	Overall Survival ER/PR-, Stage I-III-Breast	Overall Survival Black White	Multivariate HR after adjustment for SES 1.26 (0.84-1.87) Ref	No Black-White overall survival differences only after adjustment for SES based on disparity index. After adjustment for clinical factors and treatment Blacks still had worse outcome.
1988-1992, Schwartz et al. (52)	DMA - SEER N=45,056	Regional + Distant *vs.* Local Stage at diagnosis-Breast, prostate, lung, colorectal and cervical.	Breast CA Black White Prostate CA Black White	Adjusted OR 1.30 (1.17-1.46) Ref 1.51 (1.35-1.70) Ref	Black race independently predicted advanced stage after adjustment for SES based on census tract for breast and prostate. No differences for lung, colorectal or cervical
12/2002-1/2013 Lantz et al. (14)	DMA + Los Angeles SEER N=1,700	Stage 0 + I *vs.* Stage II + III - Breast	Black White	Adjusted OR 0.79 (0.57-1.1) Ref	No Black-White differences in stage at diagnosis after adjustment for clinical factors, treatment, diagnostic method and SES-(only study with SES based on individual survey)
2000-2009, Holowatyj et al. (16).	SEER-18 N=28,145	Disease specific survival (age 20-49)-Colon and Rectal	Colon Black White Rectal Black White	Adjusted HR 1.35 (1.26-1.45) Ref 1.51 (1.37-1.68) Ref	Black-White differences in disease specific survival for young onset colorectal cancer after adjustment for clinical and treatment factors, and SES based on county-level poverty.

(Continued)

TABLE 4 | Continued

Years of Study, Reference	Population	Outcome	Race Groupings	HR, 95% CI	Disparity
1988-1992, Schwartz et al. (27)	DMA-SEER N=8,679	Influence of co-morbidity and SES on overall and disease specific survival for local and regional stage-prostate	Overall Survival	Adjusted HR	No overall survival differences for Black and White men with local or regional stage disease, however disease specific survival differences for men with local stage, after adjustment for treatment and SES-based on census tract.
			Local		
			Black	1.03 (0.96-1.11)	
			White	Ref	
			Regional		
			Black	0.90 (0.73-1.13)	
			White	Ref	
			Disease Specific		
			Local		
			Black	1.35 (1.17-1.65)	
			White	Ref	
			Regional		
			Black	0.83 (0.57-1.20)	
			White	Ref	
2002-2007 Schwartz et al. (34)	DMA-SEER: N=951	Overall survival -r renal cell carcinoma	OS:	Adjusted HR	No survival differences after adjustment for clinical, treatment factors, co-morbidities and SES based on deprivation index.
			Black	0.93 (0.65-1.35)	
			White	Ref	
			<65y at diagnosis		
			Black	1.14 (0.71-1.85)	
			White	Ref	
			Tumor ≤4cm:		
			Black	1.15 (0.67-1.98)	
			White	Ref	

[1]*DMA, Detroit Metropolitan Area.*
[2]*SEER, Surveillance, Epidemiology and End Results.*
[3]*KCC, Karmanos Cancer Center.*
[4]*HFHS, Henry Ford Health System.*

(RR,1.68, 95% CI 1.27-2.23), that was greater than the RR for women 51 and older at diagnosis (RR, 1.33, 95% CI, 1.13-1.56) (13). In other Detroit Metropolitan Area-SEER studies however, adjustment for SES at the census tract level accounted for all of the racial disparities in overall and disease specific survival for Black and White individuals with CRC (15), and overall survival for women with cervical cancer (48).

Similarly, results from single-institution studies showed no racial differences in survival after accounting for SES. These included a KCC study which showed no Black-White differences in breast cancer disease-free survival (HR 1.38, 95% CI 0.85-2.26) or overall survival (HR 1.06, 95% CI 0.64-1.75) (18), and in the HFHS analysis that showed no breast cancer survival differences after adjustment for neighborhood deprivation index (HR 0.97, 95% CI 0.8-1.9) (17). In a sub-analysis of Black and White women with estrogen and progesterone receptor negative breast cancer at the HFHS, there was also no overall survival disparity after adjustment for deprivation index (HR 1.26, 95% CI 0.84-1.87) (49).

However, other studies showed racial disparities even after controlling for economic and social factors. In a Detroit Metropolitan Area-SEER study after adjusting for SES based on census block, Black patients still had more advanced stage at diagnosis (regional or distant *vs.* local) among women with breast cancer (OR 1.30, 95% CI 1.17-1.46) and men with prostate cancer (OR 1.51, 95% CI 1.35-1.70) (52). However, differences in stage at presentation were not seen in an analysis of women with stage 0 to III breast cancer using the Detroit and Los Angeles SEER registries where after adjusting for SES based on individual questionnaire, and method of detection, there were no significant differences between Black and White women in diagnosis of stage 0+I disease *vs.* II+III (14).

In a SEER-18 site study of early onset CRC, after adjusting for SES based on the proportion of individuals below 200% of the poverty level at the county level as well as clinical and treatment factors, Black compared to White patients continued to have worse disease specific survival for both colon (HR 1.35, 95% CI 1.26-1.45) and rectal cancers (HR 1.51, 95% CI 1.37-1.68) (16). A Detroit Metropolitan Area–SEER prostate cancer study showed that after adjustment for SES based on census block data, there were no significant differences for Black and White men for overall survival; however, Black men with localized disease continued to have worse disease specific survival (HR 1.35, 95% CI 1.17-1.65) (27). Lastly, in a Detroit Metropolitan Area-SEER case-control study of RCC that adjusted for SES based on deprivation index and also adjusted for clinical factors and co-morbidity, there were no racial differences in overall survival (HR 0.93, 95% CI 0.65-1.35) (34).

Other studies that did not take into account SES showed varying results (not shown in Table). In a KCC analysis of men who had radical prostatectomy for clinically localized disease, after multivariable adjustment, Black men continued to have worse progression-free survival than White men (HR 2.35, 95% CI 1.63-3.4), p<0.0001 (53). Another study comparing the pre- to post-prostate screening era (PSA testing), another "natural experiment" over time, showed that Black men diagnosed in the pre-PSA era (1973–1994) had higher mortality than White men for all age groups; however this difference in survival disappeared in the post-PSA era (26).

In summary, PSDR investigators in collaboration with others have conducted a wide range of studies using data from either single centers in Detroit or across multiple sites using SEER or other larger data bases to better understand and explain racial health disparities. In general, the studies cited demonstrate that Black compared to White patients with cancer present with more advanced and biologically aggressive disease, are more likely to live in economically and socially deprived areas and are more likely to be diagnosed with co-morbid medical conditions which has the potential to hamper accessibility to optimal cancer-directed treatment. It is also possible that Black patients with co-morbid medical conditions are less likely to be offered treatment as a White person with the same co-morbidity.

While a number of studies have sought to evaluate factors such as differences in treatment or SES that might explain some of the disparities in cancer outcomes noted, these types of first- and second-generation disparities studies are largely descriptive and serve only to document the extent of the problem or identify potential factors underlying the disparities. Further, while controlling for SES is an accepted practice in studies of treatment disparities, two important caveats should be taken into consideration. First of all, SES disparities can be easily traced to legacies of institutional and structural racism and therefore controlling for SES is an attempt to control for one of the consequences of racism which remains unresolved. Secondly, in the process of controlling for disparities, researchers in a sense are creating a world where Black and White people have the same SES, which does not reflect reality.

PATIENT-PHYSICIAN COMMUNICATION AND DISPARITIES: FIRST, SECOND AND THIRD GENERATION STUDIES

In order to identify potential ways to address and intervene to reduce racial disparities, investigators in the PSDR in collaboration with other researchers, have conducted studies evaluating differences in clinical communication during patient-physician interactions with Black compared to White patients. In this section, we will present first-generation evidence of disparities in patient-physician communication and then second-generation studies looking at potential factors explaining these disparities and the impact of disparities on cancer outcomes. We will then describe third-generational interventional studies designed to mitigate these disparities in communication.

First-Generation Communication Studies

Clinical communication involving patients, their companions, and their providers plays a critical role in patient-centered care and outcomes (54, 55). Racial disparities in patient-physician communication are well-documented and have been associated

with racial disparities in cancer treatment and mortality (56, 57). In research that used video-recordings of patient-physician treatment discussions (after written consent) (58), PSDR researchers have investigated disparities in clinical communication during interactions between non-Black oncologists and their Black patients (59–62). They have also studied the influence of race-based attitudes (e.g., oncologist implicit racial bias, patient suspicion of medical care) on those interactions (61, 62).

As part of this research, PSDR researchers conducted a mixed-methods analysis of 109 video recordings to investigate patient and companion question-asking during interactions with oncologists. Findings showed that compared to White patients, Black patients asked fewer total questions, fewer direct questions, and were less likely to have a companion with them to contribute to question-asking and information-exchange. Findings from this research suggest that these differences in question asking may diminish the quality of information exchange during interactions with Black patients and that Black patients may receive less information from their oncologists (63).

A more recent study of video-recorded interactions between 114 Black patients and non-Black oncologists found that having a companion(s) during the interaction had a positive impact on patient-oncologist interactions. These included oncologists spending more time with the patient and using more patient-centered communication with patients who brought a companion (64). Given documented racial disparities in communication, the presence of companions may be especially beneficial to Black patients. Findings from these studies suggest that provider-level and system-level interventions may be used to encourage patients to participate actively in clinical interactions and to bring supportive companions to assist them in exchanging information with physicians. For example, oncologists could be trained to elicit patient questions and answer them directly and compassionately, and hospitals could encourage companion participation by facilitating video conferencing with companions who may not be able to attend visits.

Another study used linguistic discourse analysis to better understand communication about clinical trials in video-recorded interactions with Black and White patients and their medical oncologists. Findings showed that interactions with Black patients were shorter; the topic of clinical trials was less frequently mentioned; and, when clinical trials were mentioned, less time was spent discussing them (65). Differences were also observed in the discussion of some aspects of consent to clinical trials. Specifically, oncologists and Black patients spent less time discussing the purpose of the trial, risks and benefits, and alternatives to participating in the trial; however, they spent more time discussing the voluntary nature of trials (65). These findings are particularly problematic if this type of communication about clinical trials is the norm for Black patients with cancer (66) because it suggests that Black patients are not receiving adequate information to make an informed decision about participating in a clinical trial. These and similar findings led to intervention studies, described below, to improve the quality of communication during interactions in which clinical trials may be discussed.

Second-Generation Communication Research

Several investigations have focused on the influence of patient and physician race-based attitudes. With regard to physician race-based attitudes, PSDR investigators showed that oncologists with higher implicit bias (i.e. favoring White people) were more likely to have shorter interactions with Black patients than oncologists with lower implicit bias. Further, their communication was perceived by patients as less patient-centered and by patients and independent observers as less supportive with their Black patients. This in turn led to less patient confidence in treatment recommendations and greater perceived difficulty in completing treatment (61). With regard to patient race-based attitudes, using the Group-Based Medical Mistrust scale developed by a PSDR investigator (67), relationships were found between Black patients' group-based medical suspicion (67) and their attitudes about adherence and decisional control (62). Other work found that high levels of group-based medical suspicion among Black patients was associated with more negative evaluations of physicians and recommended treatment (68). Patient mistrust of medical care and lack of trust in physicians were also associated with not only how much Black patients spoke during medical interactions but also the valence of the words they used. High levels of patient mistrust was also associated with less favorable physician perceptions of Black patients, which, in turn, affected physician perceptions of how well these patients would tolerate treatments (68). A more recent study found that Black men with prostate cancer had higher levels of group-based medical suspicion than White men, and this race-based attitude was associated with less willingness to discuss clinical trials with their physicians (69). More current research is examining how patient and oncologist nonverbal communication may be associated with these race-based attitudes (70, 71).

Third-Generation Communication Interventions

In an attempt to mitigate these disparities in communication and the influence of race-based attitudes, PSDR investigators have developed and tested communication interventions. One type of low-cost and effective intervention tested has been question prompt lists (QPL). QPLs are simple communication tools designed to promote active participation in clinical interactions. QPLs are provided to patients before a clinical interaction and include a list of questions patients can consider asking their physician in a specific clinical context (72–75). Using a community engagement process to aid in its development, PSDR investigators created and tested a QPL for patients considering chemotherapy (76, 77). In a trial with 114 Black patients randomized to receive standard of care, a QPL brochure, or a QPL brochure and the assistance of a coach, video recordings of patient-physician interactions and post-interaction, patient surveys demonstrated that the QPL was feasible and acceptable. The QPL also increased observer coded patient active participation and information exchange in

treatment discussions with their medical oncologist (78). In ongoing studies, researchers are currently testing the effectiveness of a QPL designed to improve clinical trials discussions along with a companion intervention for oncologists (78), and an app-based QPL focused on cancer treatment costs (79).

TOWARDS FOURTH GENERATION DISPARITIES RESEARCH

The current paper has framed KCI research in the context of first-, second,- and third -generation disparities research. We are now laying the foundation for fourth-generation research, which is rooted in justice and action to eliminate disparities. Fourth generation research may be guided by public health critical race praxis (PHCR): "…a semi-structured process for conducting research that remains attentive to issues of both racial equity and methodologic rigor" (80). At the core of PHCR is race consciousness, which requires attention to racial dynamics within the research context as well as the outer world, and the role of racism in cancer health inequity (80).

Thomas et al. (12) assert: "In fourth-generation research, guided by PHCR, it is essential to remember that the goal is ultimately to take action to eliminate health disparities. In that context, the voice of community members is an absolute necessity. Fourth-generation research is deeply rooted in community and the racialized context of the populations who reside within them." The need for community voice in research guides KCI's Office of Cancer Health Equity and Community Engagement and its Michigan Cancer HealthLink program, which engages diverse populations throughout the state to build public interest, involvement, and community capacity to collaborate in cancer-related research. Michigan Cancer HealthLink is an academic-community partnership that uses a participatory research approach to facilitate collaboration between community members and researchers through an iterative process of problem definition, problem solving, and evaluation. Partnership activities also focus on skill development, resource mobilization, and relationship building. HealthLink is based on a network of Cancer Action Councils or CACs: groups of cancer survivors, caregivers, and advocates who use their local knowledge and expertise to reduce the burden of cancer in underserved communities. There are currently 9 CACs with over 100 members in six cities across four counties in Michigan, representing Black American, Arab American, young survivor, and LGBT+ communities (81).

Through Michigan Cancer HealthLink, we are setting the stage for fourth generation research to eliminate the disparities that disadvantage Black Americans. These efforts are informed by the principle of voice: the privileging of marginalized persons' contributions to discourses (81). The CACs are a key way to amplify the voices of Black Americans in our work. Using semi-structured methods, CACs identify and develop research priorities that they feel are most relevant to their specific communities. CACs also receive training in research methods to prepare them to actively partner with our researchers and contribute to development of research ideas, design, and implementation. In short, HealthLink is an infrastructure that supports action-oriented disparities research by building research capacity in Black American communities and soliciting different perspectives that can challenge, supplement, and even replace the traditional, academic perspectives that tend to dominate disparities work. As Ford et al. (80) assert, "[Voice] helps to illuminate disciplinary blind spots that are otherwise imperceptible from within a discipline's mainstream. It increases understandings of minorities' lived experiences, which improves operationalization of constructs, development of effective interventions and creation of an equitable society." As we apply a PHCR approach, we increasingly distance ourselves from the perspective that Black American communities are mainly environments that drive racial disparities in cancer risk, care, and outcomes. When viewed through the PHCR lens, these communities are vital hubs for resources, opportunities, partners, and solutions to achieve equity.

DISCUSSION

Researchers in KCI's PSDR, along with their collaborators, have spent the past three decades investigating racial disparities in cancer incidence, treatment, and outcomes among Black and White patients in Southeast Michigan, with a specific focus on the Detroit area, a city with a majority Black population. The studies document the pattern of more aggressive disease seen in Black compared to White cancer patients, as well as higher rates of co-morbid medical conditions and differences in treatment and communication, which have additional adverse effects on cancer outcomes. These findings suggest that in order to reduce or eliminate racial disparities in cancer outcomes, it is also of utmost importance to address larger questions of inequality inherent in the legacy of structural racism in the US, along with disparities across the spectrum of chronic comorbid and medical conditions, which have an disproportionately negative impact on Black people (4).

To date, abundant research on cancer disparities and inequities in health outcomes has been published, as exemplified by the recent review by Zevala et al. (82). This review includes a detailed description of disparities in cancer incidence, mortality, health care screening, treatment and tumor biology experienced by almost every racial and ethnic minority group in the United States, and across both common and uncommon cancers. Consistent with the research reported here, Zevala et al. provided explicit information on potential causative factors and steps needed to mitigate racial and ethnic disparities. Given the demographics of Detroit, our review focused on studies inclusive of Black and White cancer survivors outlining disparities similar to that experienced by other groups (82). Future work in the Detroit area should focus on structural racism and disparities in cancer care experienced by additional marginalized and minority groups in the region including the large Mexican and Arab American populations.

One prime example of structural racism is the status of residential housing in the US (4, 83). Black cancer patients are more likely to live in geographic areas with lower levels of aggregate SES, and consequently are faced with less access to high-quality medical care, resulting in lower quality of care. While structural racism may be difficult to address in the short term, providing transportation and easier access to care may be a first step with longer-term goals of equitable housing and insurance coverage. Recent efforts on the part of academic health centers including WSU and the KCI to better understand the underlying influence of social determinants on health care outcomes can provide new structures and options in which to train health care professionals to provide more equitable health care for all racial and ethnic groups (84, 85).

Other underlying reasons for Black-White health disparities include the legacy of fewer and lower quality medical services being available in the areas where many Black people live (5–7, 86); poor employment opportunities; and inadequate and unhealthy housing and inadequate or substandard education opportunities that have historically disadvantaged the Black community and have both directly and indirectly contributed to poor health care outcomes (86). Similarly, a historic loss of population for socioeconomic reasons or excess mortality from chronic health conditions has disproportionately burdened the Black population over time (87). Our research has demonstrated a few examples of "natural experiments" documenting the widening gaps in survival and treatment options for Black and White women with breast cancer over several birth cohorts (29), and a diminution in the prostate cancer mortality gap marked by the institution of PSA screening (26). Future work in Detroit should take advantage of other natural experiments such as new health care policies such as the Affordable Care Act, or other interventions that may shed light on how structural factors impact racial and ethnic differences in outcomes. In order to reduce Black-White disparities in cancer outcomes, we propose multi-level interventions such as community engagement, recruiting more diverse clinical staff (88), and conducting system-wide anti-racism training (85). Our research points to the benefit of interventions that are relatively easy to implement and could have an immediate impact on the quality of and better access to care, including Question Prompt lists, brief language-appropriate educational videos and the inclusion of Lay Health Advisors (89) and patient navigators as essential components of the health delivery system. Such efforts would also be easily adaptable to additional underserved populations.

At the KCI, the Detroit Research on Cancer Survivorship (ROCS) study is the only National Cancer Institute-funded survivorship cohort of Black cancer survivors in the US (90). Studies of this cohort (enrollment goal 5,000) are seeking to elucidate the specific influence of systematic and structural racism at the community and individual levels on the emotional and physical health, health and screening behaviors, and quality of life of Black cancer survivors (91–93) An understanding of race-related factors underlying and maintaining health-disparate outcomes is essential for developing interventions and initiatives that could reduce current inequalities in diagnosis, treatment, and survival, and improve the quality of cancer survivorship in Black men and women with cancer. Knowledge gained from research on racial health disparities among cancer patients and those with other medical conditions can also help to eradicate disparities in additional groups in the future.

AUTHOR CONTRIBUTIONS

SR: She conducted the pub med review of all of the articles included in the review, constructed the tables and helped edit and write the manuscript. LH: She wrote and organized the section on physician communication. She also was responsible for extensive editing. LP: Extensive editing with a focus on racial disparities and the physician communications section. KS: Extensive editing with a focus on the epidemiologic studies. FH: Extensive editing with a focus on the physician communications section. HT: She wrote the section on fourth generation research and edited the rest of the manuscript. JB: Editing with a focus on area based measures of SES. MC: Editing. AS: Editing and advise as to formatting and structure. SE: Extensive editing. Focused on the physician communication section. All authors contributed to the article and approved the submitted version.

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Endometrial Cancer Type 2 Incidence and Survival Disparities Within Subsets of the US Black Population

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Introduction: Endometrial cancer type 2 (EC2) carries a worse prognosis compared to EC type 1. EC2 disproportionately affects Black women among whom incidence is higher and survival is poorer compared to Whites. Here we assessed EC2 incidence and survival patterns among US Black ethnic groups: US-born Blacks (UBB), Caribbean-born Blacks (CBB), and Black Hispanics (BH).

Methods: We analyzed population-based data (n=24,387) for the entire states of Florida and New York (2005–2016). Hysterectomy-corrected EC2 incidence rates were computed by racial-ethnic group, and survival disparities were examined using Cox regression adjusting for tumor characteristics, poverty level, and insurance status.

Results: EC2 incidence rates were highest among UBB (24.4 per 100,000), followed by CBB (18.2), Whites (11.1), and Hispanics of all races (10.1). Compared to Whites, the age-adjusted cause-specific survival was worse for non-Hispanic Blacks (aHR: 1.61; 95%CI 1.52–1.71) and Hispanics of all races (aHR:1.09; 95% CI:1.01–1.18). In relation to Whites, survival was worse for non-Hispanic Blacks: UBB (aHR:1.62; 95%CI 1.52–1.74) and CBB (aHR:1.59; 95% CI:1.44–1.76) than for BH (aHR:1.30; 95% CI:1.05–1.61). Surgical resection was associated with a lower risk of death, while carcinosarcoma subtype and advanced stage at diagnosis were associated with a greater risk.

Conclusions: Although higher EC2 incidence and lower survival are observed among all African-descent groups, there are significant intra-racial differences among UBB, CBB, and BH. This heterogeneity in EC2 patterns among Black populations suggests an interplay between genetic and socioenvironmental factors.

Keywords: endometrial cancer, uterine cancer, Blacks, incidence, survival, Black Hispanic, Caribbean, US-born

INTRODUCTION

Uterine cancer incidence and mortality rates are increasing among US women (1, 2). Since 2016, cancer of the uterine body has been responsible for more than 10,000 deaths per year (3). Uterine cancer is diagnosed as endometrial cancer in 94% of cases, while 6% constitute uterine sarcomas (4). Endometrial cancer is quite heterogeneous and divided into the more often obesity-related -type 1 (EC1, representing low-grade endometrioid carcinomas) and EC type 2 (EC2, comprising carcinosarcoma, serous, clear-cell, mixed-cell, and high-grade endometrioid carcinomas) (5–7). -In contrast to EC1, which is associated with high 5-year survival, EC2 presents at a more advanced stage at diagnosis and is -associated with moderate to low survival after 5 years (7, 8).

Among upward-trending cancers, increasing incidence rates tend to exceed mortality rate increases because of better treatment modalities and earlier detection trends over time. This is not the case for uterine cancer, for which mortality is increasing faster than incidence (1, 2). This is a result of examining all subtypes of endometrial cancer as one homogenous group. EC1 is the more common type accounting for 60% of all new endometrial cancer cases, but it only accounts for a small proportion of endometrial-specific deaths (25%) (7). On the contrary, the less common EC2 accounts for nearly 75% of all endometrial cancer deaths (7). As previously shown, the incidence of the less common EC2 is increasing faster than EC1 (8), resulting in a shift in the severity of endometrial cancer overall. Confirming this complex trend, survival for all endometrial cancers combined has not shown an improvement in the last decades (2, 9).

In addition to the EC1 and EC2 heterogeneity, the epidemiology of uterine cancer on a population basis is further complicated by the difficulty in assessing the true population at risk. The prevalence of hysterectomy, a procedure commonly performed to treat fibroids, menorrhagia, and endometriosis, is currently decreasing although it has historically been the second most common gynecological surgical procedure after cesarean section (10, 11). In the US, the prevalence of this procedure differs substantially by geography and race, with Black women having a higher prevalence of hysterectomy (6, 12–14).

Despite that, Black women in the US share a disproportionately higher burden and mortality rate for endometrial cancer (1, 14), including a higher proportion of EC2 cases and worse survival for all EC2 subtypes in comparison to other races (7, 8).

EC2 is not a common cancer, and little is known in regard to the specific genetic and environmental factors that may impact its risk (incidence) and prognosis (survival). On a population basis, studies on incidence and survival of EC2 have been few, and none have scrutinized the intra-racial diversity in patterns among the most afflicted group in the US, women of African descent, particularly non-Hispanic Blacks. To our knowledge, only two publications have reported population-based rates of endometrial cancer among US Black populations (15, 16) including US-born, Caribbean-born, and African-born populations. One study has shown similar mortality rates for endometrial cancer across all three populations, which is suggestive of similar vulnerability between these populations (15). However, no research has studied incidence or survival for EC2, specifically in populations of African descent.

In this study, we aim to examine the incidence and survival of the more aggressive EC2 in the three largest racial-ethnic groups in the US, that is, non-Hispanic Whites, non-Hispanic Blacks, and Hispanics, and to explore the intra-racial differences in populations of African descent, namely, US-born Blacks, Caribbean-born Blacks, and Black Hispanics. The main hypothesis under study is that incidence and survival rates are different among all US Black populations, as well as between them and White and Hispanic women.

METHODS

Source of Data

Data for all EC2s diagnosed in the states of Florida and New York (2005–2016) with primary site codes C54.X and C55.9 and morphology codes 8000–8951 per the International Classification of Diseases for Oncology, third edition (ICD-O-3), were obtained from the respective state cancer registries. Cancer registries routinely record sociodemographic characteristics such as age, race-ethnicity, census tract poverty level, and insurance type; as well as tumor characteristics such as stage at diagnosis, morphology, and grade. Only the three main racial-ethnic groups were studied in the current study: non-Hispanic Whites, non-Hispanic Blacks, and Hispanics (of any race), from now on referred to as Whites, Blacks, and Hispanics, for simplicity. Consistent with previous studies, morphology was categorized according to previous studies as either EC1 (low-grade endometrioid) or EC2 (high-grade endometrioid, clear cell, mixed cell, carcinosarcoma, and serous) (5–8). For incidence calculations, unspecified high-grade adenocarcinomas (morphology code 8140) were proportionally allocated for each racial-ethnic and age-group into high-grade endometrioid, clear-cell, and serous carcinomas in Clarke et al. (14).

Classification of Populations of Non-Hispanic African Descent

Florida and New York data were chosen because these two states combined include 65% of the Caribbean-born Black population in the US (2.1 million) (17). For intra-racial (intra-Black) categorization among non-Hispanic Blacks, cases were classified as US-born Blacks or Caribbean-born Blacks based on country of birth, following previous work on these populations (15, 16). Country of birth missingness is a problem in cancer incidence data (18). In our datasets, 75% of all EC2 cases among non-Hispanic Blacks had a known birthplace. However, in order to conduct accurate population-based comparisons, the inclusion of all (100%) Blacks is necessary, given that most cases with "unknown" birthplace are in fact US- or Caribbean-born, had their birthplace been recorded. To overcome this problem, we assigned those with a missing birthplace to the categories of US-born Blacks, Caribbean-born Blacks, and other non-Hispanic Blacks (born in Africa, Europe, etc.) according to the majority group in the 5-year age group and area of residence of each case with missing country of birth. Census tract of residence was used in the case of

counties with more than 500,000 total population, and county of residence if the overall population in the respective county was less than 500,000.

Statistical Analyses

For the incidence analysis, we calculated hysterectomy-uncorrected and corrected endometrial cancer rates for all EC2s combined, as well as corrected rates by morphology subtype and racial-ethnic group for the entire 2005–2016 period. Detailed population denominators for each race-ethnicity by state were obtained from the US Census Bureau, using pooled single-year American Community Survey (ACS) data for 2005–2016 (17). Hysterectomy data were retrieved from the Biannual Behavioral Risk Factor Surveillance System (BRFSS) survey for 2006–2016 (19). Due to its biennial feature, hysterectomy prevalence was assumed the same for the BRFSS survey year and the immediately preceding year. For example, BRFSS 2006 hysterectomy data was used for 2005–2006 and 2016 data for 2015–2016. Hysterectomy-corrected denominators were estimated separately by state, racial-ethnic group, and for each 2-year period and then pooled for both states. BRFSS hysterectomy proportions were obtained for Whites, Blacks, and Hispanics (of any race) for the states of Florida and New York. For non-Hispanic Blacks, we also pulled hysterectomy prevalence for two additional geographic levels: 1) Metro statistical areas (MSAs) of New York-Newark-Jersey City and Miami-Fort Lauderdale-Pompano Beach; these MSAs are the areas that comprise sizeable proportions of both Caribbean-born Blacks and US-born Blacks, while in the states of Florida and New York outside of these MSAs, US-born Blacks nearly exclusively account for the total Black populations; and 2) the South Atlantic Censal Region States that includes Florida and the Northeastern Censal Region States that includes New York. The statewide hysterectomy proportions by age-groups were used for Whites, Hispanics, and Blacks (all combined).

Since BRFSS only provides proportions of hysterectomies for all non-Hispanic Blacks, to distinguish between US- and Caribbean-born, we proceeded as follows. First, for each state, we assumed that the hysterectomy proportion for US-born Blacks in both the MSA and the remaining area of each state outside the MSA was similar to that of Blacks in the larger Censal Regions (a population with a very large weight of US-born Blacks and very low weight of Caribbean-born Black populations). Based on this assumption, while taking into account the age-specific population proportions of both US- and Caribbean-born Blacks in each MSA from the ACS (17), and the total hysterectomy prevalence among Blacks in each MSA, we estimated the age-specific hysterectomy proportions for Caribbean-born Blacks. Incidence rates for all EC2 combined by subtype and by racial-ethnic groups were calculated per 100,000 persons, annualized, and age-standardized to the 2000 US Standard Population using 18 age-group bands. Gamma intervals modification was used to calculate 95% confidence intervals. Finally, we used negative binomial regression with adjustment for age to compare the incidence rates by racial-ethnic group and according to the period of diagnosis (2005–2010 *versus* 2011–2016).

For survival analysis, only the first primaries of EC2 diagnosed during 2005–2016 in both states were included. For each of the Black women for whom a specific Black ethnicity (US-born and Caribbean-born Black) was unable to be determined, the assignment was allocated to the larger of the two populations in the county/census tract of residence. In computing survival times, we used the presumed alive assumption (18), whereby cases that were not found as deceased on successive annual mortality linkages were censored on the last date covered, in this case, December 31, 2016. Cause-specific survival time was thus measured in months from the date of diagnosis until the date of death from uterine cancer, or December 31, 2016, whichever occurred first. Cases with death by a cause other than uterine cancer according to the SEER definition for site-specific cause-of-death (20) were censored at the time of death. Patients diagnosed with morphologies 8140 (adenocarcinoma not otherwise specified), those of unknown grade, and those diagnosed at autopsy only or by death certificate were excluded. Cause-specific Cox-proportional regression models for overall survival with socio-demographics, tumor, and treatment-related variables were fit for race-ethnicity as the main effect in each model. For any combination of variables, four different models were considered where only the race-ethnicity variable was changed based on different classifications and subgroups of Blacks. Adjusted hazard ratio (aHR), corresponding 95% confidence interval (CI), and p-value were calculated. For each model, we tested the proportionality assumption both visually with Kaplan-Meier survival curves by race-ethnicity and also by fitting time-varying Cox models and testing the time-varying terms in the models. All models satisfied the assumptions of proportionality except a very minor deviation for the model that included the race-ethnicity variable with Black groups only as can be seen in the Kaplan-Meier curve.

Lastly, for Black Hispanics, a unique group within Hispanics which is rarely studied, incidence rates were not estimated due to the current gross under-recognition of Black race among Hispanics (18), in which case, incidence rates on a population basis would be impossibly low. Previous surveys have found that Hispanics tend not to report a race as often as identifying a common ethnicity, Hispanic/Latino, and only one in every four Afro-Latinos report being of Black race (21). Notwithstanding this, we opted to show the relevant characteristics for Black Hispanics in both states when the race was known and to study survival comparisons between Black Hispanics and non-Hispanic Blacks (US-born and Caribbean-born), with the underlying knowledge that data for this group are incomplete and possibly subject to some degree of bias. This study is in compliance with the Florida Department of Health (DOH) Institutional Review Board and has been approved by the New York State DOH. Data management and statistical analyses were conducted using SAS v9.4 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 24,387 cases of EC2, which included 15,938 Whites, 5,260 Blacks, and 3,189 Hispanics, in FL and NY were analyzed. Among Black women, there were 3,568 US-born and 1,381 Caribbean-born Blacks. Only 353 Hispanics were recorded as

being of Black racial background. High-grade endometrioid was the leading EC2 morphological type among Whites (35%) and Hispanics (32%), followed by serous subtype (23 and 28%, respectively). For both non-Hispanic Blacks and Black Hispanics, the predominant morphological type differed with serous carcinoma being the leading type for US-born Blacks (34%), Caribbean-born Blacks (36%), and Black Hispanics (32%) (p=0.346). Carcinosarcoma was the second most common morphological type for US-born and Caribbean-born Blacks, and a similar proportion was found among Black Hispanics (26, 26, and 25%, respectively) (p=0.939) (**Table 1**). Proportions of carcinosarcomas were lower among Whites and Hispanics (17 and 18% respectively) (p<0.01). Localized stage at diagnosis was more common among Whites (47% localized and 16% distant stage) (p<0.01), whereas distant stage was disproportionately recorded among Blacks (36% localized and 22% distant). Whites were more likely to have private insurance, while Hispanics and Caribbean-born Blacks had higher proportions of Medicaid beneficiaries and uninsured. Black Hispanics and US-born Blacks had the highest proportion of women living in areas of high poverty (53 and 49%, respectively) in comparison to only 13% of White women (p<0.01).

Age-adjusted incidence rates (uncorrected and corrected for hysterectomy) for EC2, by racial-ethnic group, are shown in **Table 2**, as well as corrected rates for EC2 subtypes. Based on the hysterectomy-corrected rates, EC2 was nearly twice as common among US-born Blacks compared to Whites (Incidence Rate Ratio (IRR) 1.93 95%CI 1.70–2.20) when adjusted for period of diagnosis and age (**Table 2**). Caribbean-born Black rates were lower than for US-born Blacks but significantly higher than for Whites (IRR 1.34 95%CI 1.16–1.54). By subtype, US-born Blacks had the highest rates for all EC2 subtypes, but especially for serous carcinoma and carcinosarcoma, more than three times the rates of White women. Caribbean-born Blacks also had double the rates of these two subtypes as well as higher rates of clear cell compared to Whites. Rates of mixed-cell and high-grade endometrioid carcinomas were not elevated in relation to Whites. Overall, comparing the older (2005–2010) and more

TABLE 1 | Demographic and Clinical Characteristics of Endometrial Cancer Type 2 by Race-Ethnicity in Florida and New York (2005–2016).

	WHITES	HISPANICS		BLACKS		
	Total n	All Hispanics (any race)[a] n	Black Hispanics[b] n	All Blacks[a] n	US-born n	Caribbean-born[c] n
Total	15,938	3,189	353	5,260	3,568	1,381
Average Annual Population	22,283,445	7,784,296	345,330	5,996,582	4,571,526	1,121,738
% National Coverage of FL+NY	11.3%	15.3%	53.7%	14.9%	12.4%	65.1%
Median Age (years)	68	66	66	67	67	67
Age Range	23-105	24-100	33-96	23-100	23-100	32-100
Histology (p<0.001)[d]						
High-Grade Endometrioid	5,562 (34.9%)	1,025 (32.1%)	91 (25.8%)	1,163 (22.1%)	826 (23.2%)	279 (20.2%)
Clear Cell	827 (5.2%)	193 (6.1%)	17 (4.8%)	308 (5.9%)	212 (5.9%)	75 (5.4%)
Mixed Cell	3,222 (20.2%)	511 (16.0%)	45 (12.7%)	638 (12.1%)	415 (11.6%)	182 (13.2%)
Carcinosarcoma	2,648 (16.6%)	576 (18.1%)	87 (24.6%)	1,329 (25.3%)	909 (25.5%)	354 (25.6%)
Serous	3,679 (23.1%)	884 (27.7%)	113 (32.0%)	1,822 (34.6%)	1,206 (33.8%)	491 (35.6%)
Stage (p<0.001)[d]						
Localized	7,516 (47.2%)	1,372 (43.0%)	143 (40.5%)	1,904 (36.2%)	1,279 (35.8%)	489 (35.4%)
Regional	5,403 (33.9%)	1,144 (35.9%)	136 (38.5%)	1,959 (37.2%)	1,321 (37.0%)	531 (38.5%)
Distant	2,463(15.5%)	540 (16.9%)	59 (16.7%)	1,169 (22.2%)	800 (22.4%)	307 (22.2%)
Unknown	556 (3.5%)	133 (4.2%)	15 (4.2%)	228 (4.3%)	168 (4.7%)	54 (3.9%)
Insurance (p<0.001)[d]						
Private	7,434 (46.6%)	1,054 (33.1%)	104 (29.5%)	1,824 (34.7%)	1,264 (35.4%)	449 (32.5%)
Medicare	6,239 (39.1%)	951 (29.8%)	111 (31.4%)	1,762 (33.5%)	1,238 (34.7%)	433 (31.4%)
Medicaid	1,051 (6.6%)	841 (26.4%)	116 (32.9%)	1,131 (21.5%)	718 (20.1%)	334 (24.2%)
No Insurance	297 (1.9%)	154 (4.8%)	8 (2.3%)	219 (4.2%)	134 (3.8%)	72 (5.2%)
Unknown	917 (5.8%)	189 (5.9%)	14 (4.0%)	324 (6.2%)	214 (6.0%)	93 (6.7%)
Census Tract Poverty Level (p<0.001)[d]						
Very Low	3,973 (24.9%)	355 (11.1%)	27 (7.6%)	478 (9.1%)	324 (9.1%)	133 (9.6%)
Low	4,830 (30.3%)	532 (16.7%)	37 (10.5%)	718 (13.7%)	483 (13.5%)	191 (13.8%)
Medium	4,897 (30.7%)	977 (30.6%)	103 (29.2%)	1,539 (29.3%)	993 (27.8%)	458 (33.2%)
High	2,129 (13.4%)	1,314 (41.2%)	186 (52.7%)	2,494 (47.4%)	1,741 (48.8%)	596 (43.2%)
Unknown	109 (0.7%)	11 (0.3%)	0 (0%)	31 (0.6%)	27 (0.8%)	3 (0.2%)
State (p<0.001)[d]						
FL	6,906 (43.3%)	1,693 (53.1%)	113 (32.0%)	2,026 (38.5%)	1,483 (41.6%)	523 (37.9%)
NY	9,032 (56.7%)	1,496 (46.9%)	240 (68.0%)	3,234 (61.5%)	2,085 (58.4%)	858 (62.1%)
Treatment (p<0.001)[d]						
Chemotherapy	6,152 (38.6%)	1,295 (40.6%)	183 (51.8%)	2,520 (47.9%)	1,641 (46.0%)	689 (49.9%)
Surgery	14,488 (90.9%)	2,880 (90.3%)	309 (87.5%)	4,503 (85.6%)	3,036 (85.1%)	1,186 (85.9%)
Radiotherapy	6,072 (38.1%)	1,180 (37.0%)	129 (36.5%)	1,862 (35.4%)	1,245 (34.9%)	493 (35.7%)

[a]Includes all cases of this race-ethnicity, not just listed groups; [b]Top countries of birth: Cuba, Puerto Rico, Dominican Republic; [c]Top countries of birth: Haiti, Jamaica, Trinidad and Tobago; [d]p-value for chi-square tests comparing known categories among Whites, Black Hispanics, US-born Blacks, and Caribbean-born Blacks.

TABLE 2 | Age-adjusted[a] total and hysterectomy-corrected[b] incidence rates per 100,000 and rate ratios[c] with 95% confidence intervals by race-ethnicity in Florida and New York (2005-2016).

	Total (Uncorrected)	Hysterectomy-Corrected				
	EC Type 2 total	EC Type 2 total	High-Grade Endometrioid	Serous	Carcinosarcoma	Mixed Cell	Clear Cell
Rates							
WHITES	7.3 (7.2–7.5)	11.1 (10.9–11.2)	3.8 (3.7–3.9)	2.6 (2.5–2.6)	1.8 (1.7–1.9)	2.3 (2.2–2.4)	0.6 (0.5–0.6)
HISPANICS[d]	7.2 (7.0–7.5)	10.1 (9.8–10.5)	3.1 (2.9–3.3)	2.9 (2.7–3.1)	1.9 (1.7–2.0)	1.6 (1.5–1.7)	0.6 (0.5–0.7)
BLACKS[d]	14.2 (13.8–14.6)	23.5 (22.9–24.2)	4.9 (4.7–5.2)	8.4 (8.1–8.8)	5.9 (5.6–6.2)	2.8 (2.5–3.0)	1.4 (1.3–1.6)
US-born	14.8 (14.3–15.2)	24.4 (23.6–25.2)	5.3 (5.0–5.7)	8.6 (8.1–9.1)	6.2 (5.8–6.6)	2.8 (2.5–3.0)	1.5 (1.3–1.7)
Caribbean-born	12.6 (12.0–13.3)	18.2 (17.2–19.2)	3.7 (3.3–4.2)	6.7 (6.1–7.3)	4.6 (4.1–5.1)	2.2 (1.9–2.6)	1.0 (0.8–1.3)
Rate Ratios							
Period of Diagnosis: 2011–2016 *vs.* 2005–2010	–	1.07 (0.97–1.17)	0.86 (0.78–0.95)	1.27 (1.17–1.38)	0.98 (0.89–1.07)	1.35 (1.23–1.48)	0.89 (0.80–0.99)
WHITES	–	1	1	1	1	1	1
HISPANICS[d]	–	0.87 (0.77–0.98)	0.80 (0.78–0.95)	1.12 (1.01–1.25)	1.00 (0.88–1.13)	0.67 (0.60–0.76)	1.08 (0.92–1.27)
BLACKS[d]	–	1.83 (1.63–2.05)	1.22 (1.09–1.38)	3.12 (2.84–3.43)	3.07 (2.75–3.42)	1.17 (1.04–1.31)	2.50 (2.19–2.85)
US-born	–	1.93 (1.70–2.20)	1.34 (1.15–1.56)	3.38 (3.09–3.70)	3.41 (3.05–3.81)	1.25 (1.13–1.39)	2.69 (2.31–3.13)
Caribbean-born	–	1.34 (1.16–1.54)	0.83 (0.69–1.00)	2.34 (2.10–2.62)	2.29 (1.99–2.63)	0.93 (0.80–1.08)	1.61 (1.27–2.05)

[a]Age-adjusted to the 2000 U.S. Standard Population; [b]corrected for BRFSS survey-weighted estimates of hysterectomy prevalence; [c]negative binomial regression rate ratios adjusted for age and period of diagnosis; [d]includes all cases of this race-ethnicity; not just listed groups.

recent period (2011–2016), hysterectomy-corrected rates show a significant increase in serous and mixed-cell carcinomas in all populations combined and a decrease in high-grade endometrioid and clear-cell carcinoma (**Table 2**). Baseline rates by race-ethnicity for each period can be seen in **Supplementary Table 1**.

Table 3 shows the results of Cox multivariable survival analysis performed on 18,246 EC2s first primary cancers among Whites, Blacks, and Hispanics. At the end of follow-up, 5,945 had died of uterine cancer, 11,369 were alive, and 932 had died of other causes and were thus censored at the date of death. Surgical treatment was recorded for 90.9% of all cases, while 45.7% received chemotherapy, 40.9% radiotherapy, and only 1.0% had any record of hormone therapy. In model 4, the full model adjusting for all variables, treatment and stage at diagnosis were the most important determinants of survival. Surgical resection (aHR=0.39, 95%CI: 0.36–0.42) was associated with a 61% lower risk of death over time; increased survival was also observed for those who were treated with radiation therapy (aHR=0.76, 95%CI: 0.72–0.81) and chemotherapy (aHR=0.79, 95%CI 0.75–0.84). Additionally, distant stage at diagnosis resulted in a much higher risk of death (aHR=7.63, 95%CI: 7.02–8.29) compared to those women diagnosed at localized stage. By EC2 subtype (**Figure 1** and **Table 3**, Model 4), carcinosarcoma was associated with a two-fold higher risk of death (aHR=2.01, 95%CI: 1.87–2.16) compared to the reference high-grade endometrioid, while serous carcinoma was associated with a 15% higher risk of death (aHR=1.15, 95%CI: 1.06–1.23).

Cox regression models were extended to include intra-racial (US-born and Caribbean-born Blacks) and intra-ethnic groups (Black Hispanics). All Blacks combined showed an overall higher risk of death (model 1, aHR =1.61, 95%: 1.52–1.71) compared to Whites. However, this disadvantage was considerably reduced (model 2, aHR=1.22, 95%CI: 1.14–1.30) after adjustment for EC2 subtype, stage at diagnosis, and socio-economic and healthcare factors (poverty level, insurance, and treatment) in model 4. Among non-Hispanic Blacks, the results suggest some advantage for Caribbean-born Blacks with 8% lower endometrial cancer-specific survival (aHR=0.92, p=0.120) than US-born Blacks (**Table 3**, Model 4). Black Hispanics showed the lowest risk of death of all African-descent populations (**Figure 2**). After adjusting for all predictors, Black Hispanics had a 24% lower risk of death (model 4, aHR=0.76, 95% CI: 0.61–0.95) compared to US-born Blacks.

DISCUSSION

In this study, we analyzed population-based incidence and survival disparities specifically for EC2. This important subset of biologically heterogenous uterine cancers account for 75% of all deaths by endometrial cancer, require more aggressive treatment, and disproportionately affect Black populations. We found that the greater vulnerability of Blacks for EC2 reported previously extends to other women of African descent, regardless of region of origin and ethnicity. Black women not only have a higher incidence of EC2, especially of the more aggressive

TABLE 3 | Hazard ratios (HR adjusted for state of residence) for demographic, social, and clinical determinants of Endometrial Cancer Type 2 survival in Florida and New York (2005–2016).

Prognostic Factors	Model 1	Model 2	Model 3	Model 4
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Age				
15–44	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
45–54	0.97 (0.78–1.20)	0.96 (0.77–1.20)	1.03 (0.83–1.28)	1.08 (0.87–1.35)
55–64	1.43 (1.17–1.75)	1.27 (1.04–1.55)	1.48 (1.21–1.81)	1.47 (1.20–1.79)
65–74	1.35 (1.11–1.65)	1.20 (0.98–1.47)	1.44 (1.18–1.76)	1.44 (1.17–1.76)
75+	2.16 (1.76–2.64)	1.87 (1.53–2.29)	2.24 (1.83–2.75)	1.95 (1.59–2.40)
Histology				
High Grade Endometrioid	–	1 (Reference)	1 (Reference)	1 (Reference)
Clear Cell	–	1.21 (1.07–1.37)	1.07 (0.94–1.21)	1.04 (0.92–1.18)
Mixed high-grade	–	0.85 (0.78–0.93)	0.86 (0.79–0.94)	0.87 (0.80–0.95)
Carcinosarcoma	–	2.42 (2.26–2.60)	1.94 (1.80–2.08)	2.01 (1.87–2.16)
Serous	–	1.48 (1.37–1.58)	1.12 (1.05–1.21)	1.15 (1.06–1.23)
SEER Stage				
Localized	–	–	1 (Reference)	1 (Reference)
Regional	–	–	2.86 (2.67–3.07)	3.13 (2.91–3.36)
Distant	–	–	8.44 (7.85–9.09)	7.63 (7.02–8.29)
Unknown	–	–	3.38 (2.91–3.92)	1.66 (1.41–1.95)
Insurance				
Private Insurance	–	–	–	1 (Reference)
Medicare	–	–	–	1.15 (1.08–1.22)
Medicaid	–	–	–	1.07 (0.99–1.16)
No insurance	–	–	–	0.95 (0.82–1.11)
Unknown	–	–	–	1.07 (0.95–1.19)
Poverty Level				
Very Low	–	–	–	1 (Reference)
Low	–	–	–	1.03 (0.95–1.11)
Medium	–	–	–	1.01 (0.94–1.09)
High	–	–	–	1.08 (1.00–1.18)
Unknown	–	–	–	0.76 (0.53–1.09)
Chemotherapy				
No	–	–	–	1 (Reference)
Yes	–	–	–	0.79 (0.75–0.84)
Unknown	–	–	–	0.86 (0.72–1.02)
Surgery				
No	–	–	–	1 (Reference)
Yes	–	–	–	0.39 (0.36–0.42)
Unknown	–	–	–	0.78 (0.56–1.10)
Radiotherapy				
No	–	–	–	1 (Reference)
Yes	–	–	–	0.76 (0.72–0.81)
Unknown	–	–	–	0.73 (0.62–0.86)
Race/Ethnicity 1				
WHITES	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
BLACKS[a]	1.61 (1.52–1.71)	1.40 (1.32–1.49)	1.31 (1.23–1.39)	1.22 (1.14–1.30)
HISPANICS[a]	1.09 (1.01–1.18)	1.05 (0.97–1.14)	1.03 (0.95–1.12)	1.00 (0.92–1.08)
Race/Ethnicity 2[b]				
WHITES	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
US-born Blacks	1.62 (1.52–1.74)	1.42 (1.33–1.52)	1.36 (1.27–1.46)	1.25 (1.16–1.35)
Caribbean-born Blacks	1.59 (1.44–1.76)	1.36 (1.24–1.51)	1.23 (1.11–1.36)	1.14 (1.03–1.27)
Black Hispanic	1.30 (1.05–1.61)	1.15 (0.93–1.43)	1.05 (0.85–1.31)	0.98 (0.78–1.21)
Race/Ethnicity 3[b]				
US-born Blacks	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Caribbean-born Blacks	0.98 (0.88–1.09)	0.96 (0.86–1.07)	0.91 (0.81–1.01)	0.92 (0.82–1.02)
Black Hispanic	0.79 (0.63–0.98)	0.79 (0.63–0.99)	0.75 (0.60–0.94)	0.76 (0.61–0.95)

[a]*Includes all cases of this race-ethnicity; not just listed groups;* [b]*Hazard ratios obtained from separate models with only the mentioned racial/ethnic groups.*

subtypes (carcinosarcoma and serous carcinoma), but also have a lower overall survival for EC2. While a race-wide vulnerability for EC2 is evident among all Black populations, there are intra-racial differences that suggest socio-environmental factors also play a role in the incidence and survival outcomes of EC2.

In terms of incidence, US-born Blacks showed a significantly higher rate of EC2 than Caribbean-born Blacks, followed by Whites and Hispanics. Median age at diagnosis was similar between US- and Caribbean-born Blacks; age-specific incidence rates for all age bands were either similar or lower for Caribbean-

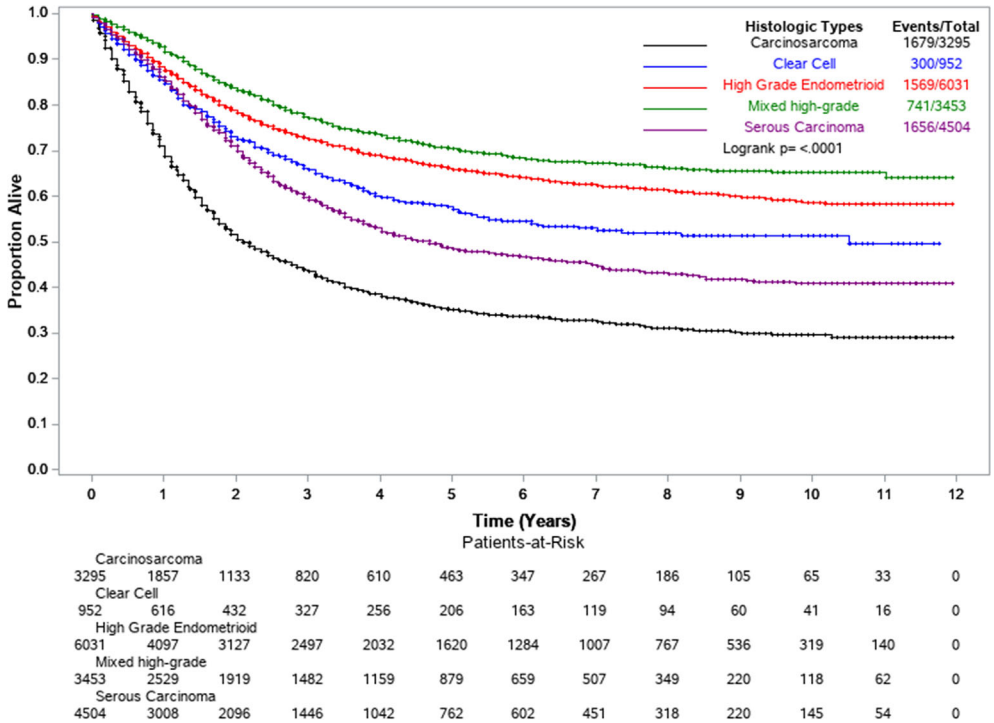

FIGURE 1 | Kaplan-Meier survival curves by EC2 histological subtypes. Florida and New York, 2005–2016.

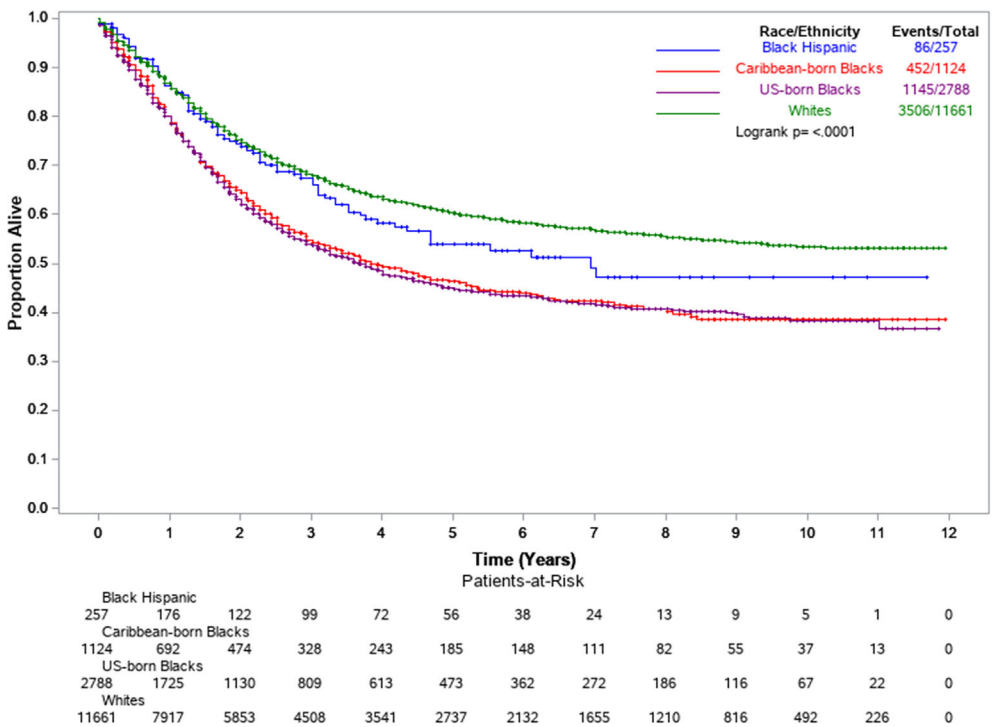

FIGURE 2 | Kaplan-Meier survival curves by select racial-ethnic groups. Florida and New York, 2005–2016.

born Blacks (data not shown). However, there were important differences by subtype. Rates of serous, carcinosarcoma, and clear-cell carcinoma were higher among both US- and Caribbean-born Blacks in relation to Hispanics and Whites. Yet, while US-born Blacks still retained the highest incidence of high-grade endometrioid cancers and mixed-cell endometrial cancers, there was no significant difference between Whites and Caribbean-born Blacks for these subtypes. These results suggest two things: first that the increased "Black" vulnerability is for non-endometrioid EC2 subtypes; second, that US-born Blacks carry a higher risk for all EC2 subtypes. Thus, socio-environmental factors among US-born Blacks may partly determine their excess risk in relation to Caribbean-born Blacks who share a related racial background. Some of these factors may include experiences of racial discrimination and stress across the lifespan which start from a younger age for those who are US-born Blacks, varying levels of socioeconomic status, the built environment, and the respective impact these may have on diet, fertility, contraception, body mass index, and hormonal factors, which can be implicated in the risk and survival for EC2.

Our knowledge of the epidemiology and especially risk factors for these subtypes is limited. Little is known about the influence of genetic differences, obesity, diet, parity, and hormones on each EC2 subtype. Obesity has been more strongly linked to EC1 than EC2 (22, 23), while hormonal factors are not distinctively different between EC1 and EC2 (24). In any case, the factors determining the excess occurrence of carcinosarcoma and serous carcinoma especially among Black populations are unknown.

Other important findings include the overall increase in EC2 rates among Whites and Blacks over time and serous carcinoma among all groups (**Supplementary Table 1**), which can only be described as an unfavorable trend. The upside is that carcinosarcoma, the subtype associated with the worst prognosis of all EC2s, did not show an increase between 2005–2010 and 2011–2016, in contrast to previous reports (6, 8).

Survival disadvantages for EC2 were observed for all minority populations in relation to Whites according to age-only adjusted models (Model 1): 62% higher risk of death for US-born Blacks, 59% for Caribbean-born Blacks, 30% for Black Hispanics, and 9% for all Hispanics combined. However, after adjustment for morphology (Model 2), the differences between Whites and Hispanics were no longer significant, and the HRs for all Black populations were substantially reduced. This decrease was in line with the observed higher proportions of subtypes with worse prognosis, among Black populations: carcinosarcoma and serous carcinoma. The disadvantage observed among US- and Caribbean-born Blacks was further attenuated by potentially modifiable factors such as stage at diagnosis as well as more established modifiable ones (treatment, insurance, and poverty level), presented in the fully adjusted model (Model 4). While the difference is not significant, the fully adjusted model suggests some advantages for Caribbean-born populations in relation to US-born populations. Advantages for majority foreign-born populations such as Black Hispanics and Caribbean-born compared to US-born Blacks may result from the described healthy immigrant effect (25). For those of Hispanic ethnicity, highly jointed family structures may increase social support as described by the concept of "familismo" which has previously been suggested to have a role in cancer survival (26). Interestingly, when comparing all Hispanics combined (Race-Ethnicity 1) and Black Hispanics (Race-Ethnicity 2) with non-Hispanic Whites, as the common reference category, the HRs differ in models 1 and 2 but are similar in model 3. This suggests that the initial worse prognosis for Black Hispanics in comparison to Hispanics overall can be largely attributed to their differing prevalence of endometrial cancer subtypes and stage at diagnosis. Our results agree with the only existing survival study on endometrial cancer among individuals of African descent (27) that also suggested that Caribbean-born Blacks had a lower risk of death compared to US-born Blacks; however, this was a hospital-based study. In our study, the survival difference is much smaller (8% lower risk of death in this population-based analysis *versus* 35% in the hospital-based study). Influences of educational level, family connection, social support, and treatment compliance on endometrial cancer survival have not been analyzed in these heterogeneous Black populations, particularly among Black Hispanics, who show an advantage in relation to US- and Caribbean-born Blacks in this study.

The most notable strength of our study is its true population-based nature given that all cases of EC2 recorded in both states were included. Moreover, all rates were hysterectomy-corrected. Both registries have high-quality data according to NAACCR certifications (28). The depiction of intra-Black variability is novel, and to our knowledge, this is only the second time population-based incidence rates for Afro-Caribbeans in the US have been estimated (29). Moreover, we describe the experience of Black Hispanics, a unique group often ignored because of its smaller population size. By pooling data from Florida and New York, the representation of the two smaller Black populations, non-Hispanic Caribbean-born and Black Hispanics, is particularly robust, encompassing 65 and 53%, respectively, of all potential individuals of these racial-ethnic groups in the country. Lastly, we include all women of Black race regardless of missing birthplace, previously shown to be a variable not missing at random, avoiding a common selection bias shown to impact survival estimates (18) and underestimate incidence rates. Using the entire population, we also avoid the selection bias linked to healthcare access, which has been associated with hospital-based studies (30).

This study is not without limitations. The assignment into either the US- or Caribbean-born Black category for those with a missing birthplace could have been an important limitation in incidence and survival analyses. However, analyses pre- and post-group assignment showed nearly identical differences between the two groups. As an example, the incidence ratio between US-born and Caribbean-born Blacks for EC2 using total corrected rates only decreased slightly from 1.37 (pre-assignment, considering only 75% of all non-Hispanic Blacks) to 1.34 (considering 100%) as shown in **Table 2** (post-assignment). Similarly, for survival, in a direct comparison between US-born Blacks and Caribbean-born Blacks, the aHR did not differ substantially from 0.98 in model 1 shown in **Table 3** (post-assignment) to 0.97 (95%CI 0.85–1.08) (pre-assignment). The hysterectomy prevalence for Caribbean-born

Blacks had to be estimated based on the metro areas of residence in contrast to areas where Blacks are mostly US-born. In terms of the survival analysis, the lack of clinical data on EC2 cases is a common limitation in cancer registry data. There is a lack of information on specific treatment modalities, such as specific surgical procedures performed, adherence, and completion of guideline-based care. Moreover, difficulties in follow-up can overestimate survival among foreign-born populations (18), which will somewhat underestimate the risk of death over time for Hispanics as a whole, including Blacks Hispanics, and Afro-Caribbeans. Additionally, other reported miscellaneous and unknown histologies of uterine cancer, which account for 3.0% for Whites, 4.3% for Hispanics, and 5.7% for Blacks, could correspond to EC2 and may underestimate an already high incidence for Black women. The increase in serous carcinoma among all populations could partly be due to better recognition of this subtype. Lastly, data on the molecular categorization of the various types of endometrial carcinoma and EC2 (POLE-ultramutated, microsatellite instability mutated, copy number high, and copy number low) (31) are not available in population-based cancer registries. However, studies evaluating associations between molecular signature and race-ethnicity mirror our findings, though further comprehensive study especially among these diverse populations of African descent is needed.

In conclusion, the need for research into EC2 subtypes, encompassing risk, and prognostic factors is a clear priority in the battle against this malignancy. Currently, from a clinical standpoint, therapeutic guidelines for the different subtypes of EC2 follow similar protocols despite the substantial differences in survival outcomes. The independent study and enrollment of these women with these cancers in clinical trials are made difficult since they are not common cancers. We found that all three Black populations analyzed had a higher risk of EC2 subtypes including serous, carcinosarcoma, and clear-cell carcinoma. Incidence and survival comparisons showed that US-born Blacks fared worse than other Black populations, thus emphasizing not only a genetic vulnerability common to all three populations but also socio-environmental factors that may constitute important modifiable factors in the battle against endometrial cancer. In this respect, research on epigenetic markers and related biological mechanisms, which may partly account for these differences, seems to be of particular interest for Black populations. There is a dearth of intra-racial and intra-ethnic health data for the US Black heterogeneous populations, which is surprising, given that this group bears a disproportionate burden of cancer morbidity and mortality (1, 2). Better knowledge of these intra-racial differences may allow us to find ways to better address endometrial cancer risk, early detection, and treatment challenges while enabling a better understanding of the epidemiology of this disease for all populations

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because restrictions from Florida and New York Departments of Health apply to the availability of these data. The authors themselves are unauthorized to share the individual-level data. The datasets are available by request with required approvals from the respective state cancer registry programs and Departments of Health. Requests to access the datasets should be directed to Florida Department of Health Cancer Registry Program and Florida Department of Health Institutional Review Board. Applications for data request are available from the FCDS Webpage (http://fcds.med.miami.edu/inc/datarequest.shtml). Researchers should contact the New York State Cancer Registry at nyscr@health.ny.gov.

AUTHOR CONTRIBUTIONS

PP was involved in the conceptualization, methodology, formal analysis, writing of the original draft, review and editing of draft, and supervision of the study. HM was involved in the formal analysis, review and editing of draft, and visualization. TK-S was involved in the methodology, resources, and review and editing of draft. BQ and MS were involved in the resources, formal analysis, and review and editing of draft. EK was involved in the study supervision and review and editing of draft. MS was involved in the formal analysis, review and editing of draft, and study supervision. 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/fonc.2021.699577/full#supplementary-material

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Interactions Between Adiponectin-Pathway Polymorphisms and Obesity on Postmenopausal Breast Cancer Risk Among African American Women: The WHI SHARe Study

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Background: A decreased level of serum adiponectin is associated with obesity and an increased risk of breast cancer among postmenopausal women. Yet, the interplay between genetic variants associated with adiponectin phenotype, obesity, and breast cancer risk is unclear in African American (AA) women.

Methods: We examined 32 single-nucleotide polymorphisms (SNPs) previously identified in genome-wide association and replication studies of serum adiponectin levels using data from 7,991 AA postmenopausal women in the Women's Health Initiative SNP Health Association Resource.

Results: Stratifying by obesity status, we identified 18 adiponectin-related SNPs that were associated with breast cancer risk. Among women with BMI ≥ 30 kg/m^2, the minor TT genotype of *FER* rs10447248 had an elevated breast cancer risk. Interaction was observed between obesity and the CT genotype of *ADIPOQ* rs6773957 on the additive scale for breast cancer risk (relative excess risk due to interaction, 0.62; 95% CI, 0.32–0.92). The joint effect of BMI ≥ 30 kg/m^2 and the TC genotype of *OR8S1* rs11168618 was larger than the sum of the independent effects on breast cancer risk.

Conclusions: We demonstrated that obesity plays a significant role as an effect modifier in an increased effect of the SNPs on breast cancer risk using one of the most extensive data on postmenopausal AA women.

Impact: The results suggest the potential use of adiponectin genetic variants as obesity-associated biomarkers for informing AA women who are at greater risk for breast cancer

and also for promoting behavioral interventions, such as weight control, to those with risk genotypes.

Keywords: obesity, adiponectin, postmenopausal breast cancer, African American women, single nucleotide polymorphism

INTRODUCTION

Obesity, defined as body mass index (BMI) of 30.0 kg/m^2 or greater, is a well-established risk factor for postmenopausal breast cancer risk (1, 2). It contributes about 10% of all postmenopausal breast cancer incidents in the United States (3). Obesity disproportionately affects African American (AA) women, where AA women have notably the highest prevalence of obesity and experience the continuing rise (4–6). This trend may reflect increased postmenopausal breast cancer incidence observed among AA women, whereas it has been stable for White women (2, 7–9). During 1999 through 2013, breast cancer incidence among women aged 50 to 59 years decreased slower among AA women (−0.1% per year) compared with White women (−1.7% per year). Furthermore, rates of breast cancer incidence among individuals aged 60 to 79 years increased for AA women, whereas the rates decreased for White women (8). The continuing trend of increased obesity in AA than White women explain the existing difference in breast cancer incidence and may results in widening the racial gap. Notwithstanding the strong epidemiologic evidence that differs considerably by race, biological mechanisms underlying the racial differences in the obesity and postmenopausal breast cancer is yet to be fully elucidated.

Adiponectin is a protein hormone that is secreted by adipose tissue playing a key role in regulating the metabolism of glucose and lipid, adipocyte inflammation, and cell proliferation (10, 11). Adiponectin levels are inversely associated with obesity (12, 13). In obesity, adiponectin resistance is increased with reduced expression of adiponectin receptors (*ADIPOR1* and *ADIPOR2*) in breast cancer cells (14, 15). Consequently, hypoadiponectinemia may predispose to breast cancer development by inhibiting cell apoptosis and enhancing cell proliferation through blocking several downstream signaling pathways, including AMP-activated protein kinase (AMPK) and mitogen-activated protein kinase (MAPK) signaling pathways (15, 16). Observational studies showed that adiponectin levels were lower in women with postmenopausal breast cancer compared to healthy women (17–19). Moreover, lower concentrations of adiponectin were found in AA postmenopausal women compared with White postmenopausal women (20). As such, adiponectin is emerging as a crucial adipokine in breast cancer development in women with obesity, and potentially explains the difference in the breast cancer incidence between AA and White women.

Only a few studies have identified genetic variants (i.e., single nucleotide polymorphisms [SNPs]) that were associated with functional and structural regulation of adiponectin and their association with breast cancer risk; but the findings were inconsistent and conducted mostly in population with European or Asian ancestry (21–25). In particular, rs1501299 in the adiponectin gene (*ADIPOQ*) was associated with an increased risk of breast cancer in some studies (21, 23), but not in others (22). No consensus could be reached for *ADIPOQ* rs2241766, where a positive, a negative, and no associations with breast cancer risk have been reported across different studies (21–24). Of these studies, one study was conducted in AA women reporting that only *ADIPOQ* rs1501299 was associated with increased breast cancer incidence (23). A pressing need remains to consider SNPs in other genes that were found to be associated with adiponectin levels including *CDH13* (26), *FER* (27), and *ARL15* (28) as the existing studies solely examined SNPs in adiponectin and its receptor genes. Investigating SNPs in the *ADIPOQ*, *ADIPOR1*, *ADIPOR2*, and other genes, and further examining the role of obesity in the association between the adiponectin-related SNPs and breast cancer risk could further shed light on the gene-obesity interrelated molecular pathway of adiponectin in breast cancer development.

The purpose of this study was to examine the effects of candidate SNPs that were previously confirmed by genome-wide association and independent replication studies of serum adiponectin levels on breast cancer risk among AA postmenopausal women, who are vulnerable to both high incidence of obesity and breast cancer risk, using a large prospective cohort study from the Women's Health Initiative (WHI) (23, 26, 27, 29–35). We hypothesized that the effects of candidate SNPs on breast cancer risk differs by obesity status, and therefore, investigated adiponectin-related SNPs that interact with obesity for their associations with breast cancer risk (**Supplementary Figure 1**).

METHODS

Study Population

The study included postmenopausal women aged 50 to 79 years enrolled in the WHI Clinical Trial and Observational Study that was conducted from 1993 to 2005. The details of its study design and method are described elsewhere (36, 37). Briefly, the WHI was designed to identify risk factors for major causes of morbidity and mortality and to develop prevention strategies for chronic diseases among postmenopausal women. Women were eligible for the WHI study if they were aged 50 to 79 years at the study enrollment; postmenopausal; and likely to reside in the same area for at least 3 years. Genome-wide genotype data have been collected on a subset of participants after obtaining additional consent for genetic studies. We included postmenopausal women enrolled in the WHI SNP Health Association Resources (SHARe) providing the molecular and genetic data of AA and Hispanic women (38).

For the purpose of our study, subjects must meet the following inclusion criteria to be included in the study analysis: the subjects (i) were AA postmenopausal women aged 50 to 79 years; (ii) without a diagnosis of cancer at the time of study enrollment (except non-melanoma skin cancer); and (iii) reported at least one of four physical measurements (i.e., height, weight, waist, and hip). Assuming that those who ended participation early are more likely to have incomplete outcome information leading to potential follow-up bias, the study excluded those who had been followed up for less than 1 year. In addition, individuals who had developed invasive breast cancer within the 1-year follow-up period were excluded to avoid the potential effects of reverse causation between obesity and invasive breast cancer risk.

Of 50,256 participants, a total of 8,380 identified their race or ethnicity as AA. We excluded 372 subjects who reported a diagnosis of any type of cancer at the time of enrollment, and two subjects who were missing information on all four physical measurements. Further, we excluded 15 participants who had developed invasive breast cancer within the 1-year follow-up period. There was no withdrawal or cessation of participation within the 1-year follow-up period. After applying the eligibility criteria, a total of 7,991 subjects were included in the analysis. Of 7,991 participants, 402 (5.0%) of the eligible women, greater than the breast cancer incidence of AA postmenopausal women in the US (9), developed invasive breast cancer (**Figure 1**).

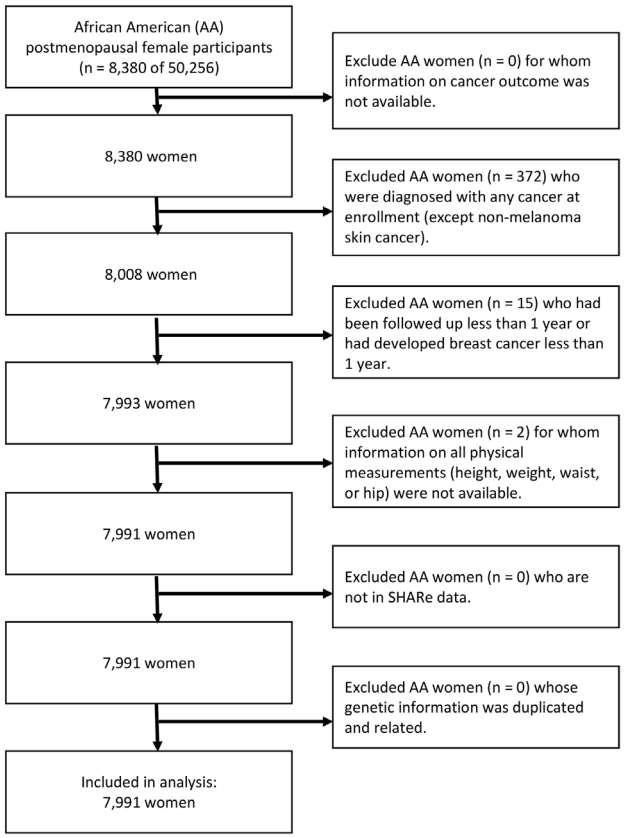

FIGURE 1 | Flow diagram of analytic cohort.

Breast Cancer Outcome

Self-reported invasive breast cancer cases were verified by adjudication of medical records in all participants of all phases of the WHI studies (39). As a result of the comprehensive outcome-assessment procedure, we did not have missing outcomes. Given that each type of breast cancer has distinct etiologies and prognoses for patients, the current study only included participants with primary invasive breast cancer. The participants were followed up from the date of enrollment to invasive breast cancer diagnosis, death, or end of follow-up.

Obesity Status: Body Mass Index, Waist-to-Hip Ratio, and Waist Circumference

We used three indices measuring body fat based on anthropometric measurements: BMI, waist-to-hip ratio (WHR), and waist circumference (WC). Each index was considered as a potential effect modifier to estimate its effect on the association between adiponectin-related SNPs and breast cancer among AA women. Also, these indices were each separately considered as a confounder of the relationship. Trained research personnel measured anthropometric measurements as continuous variables at the baseline (40). We used internationally recommended cutoff points for assessing adiposity-related risk (41, 42). BMI was categorized to define overall obesity with the following scale: underweight (< 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obesity (≥ 30 kg/m^2) (41). WHR used a cutoff of 0.85 (42), and WC used a cutoff of 88 cm in women to define abdominal obesity (41).

Adiponectin-Related SNPs

We conducted a candidate SNP approach, focusing on variants previously identified in GWA and replication studies of serum adiponectin levels (23, 26, 27, 29–35). Using the annotation file from the Affymetrix Genome-Wide Human SNP Array 6.0, we identified a total of 32 candidate SNPs (23, 26, 27, 29–35) and extracted them from the WHI SHARe dataset using the PLINK 1.9 software (**Supplementary Table 1**). Quality control was performed to exclude SNPs with a call rate less than 90%, a minor allele frequency less than 1%, and a Hardy-Weinberg equilibrium among AA women using a p-value cutoff of (38). We identified 3 SNPs in *ADIPOQ* (rs3774261, rs6444174, and rs6773957) that were in high linkage disequilibrium at a pairwise r^2 threshold of 0.80. Of the 32 candidate SNPs, 8 SNPs were located within or nearby *ADIPOQ* or adiponectin receptor genes (23, 29). The other 24 SNPs, which may support the function of transcriptional control structures or indirectly regulate adiponectin expression, were found within non-adiponectin–specific or uncharacterized genes (27, 29, 32, 33, 35, 43).

Statistical Analysis

Baseline characteristics were compared across breast cancer status using a chi-square test for categorical variables and a t-

test for continuous variables. We estimated hazard ratio (HR) and its 95% confidence intervals (CIs) for an effect of each SNP in predicting breast cancer development using a Cox proportional hazards regression model. Prior to fitting the model, the proportional hazard assumption was verified using the Schoenfeld residuals.

For each SNP, two sets of adjusted models were used, with the first adjusting for only age at baseline (Model 1) and the second adjusting for all covariates (Model 2). Covariates included in the analysis as potential confounding factors were measured at the baseline: age at baseline (year), family income (<$34,999, $35,000–$100,000, and ≥$100,000), employment status (yes *vs.* no), depressive symptom (depression scale ranging from 0 to 1 with a higher score indicating greater depressive severity), smoking status (ever smoke *vs.* no), age at menopause (year), number of pregnancies (never pregnant, 1 pregnancy, 2–4 pregnancies, and ≥5 pregnancies), exogenous estrogen use ever (yes *vs.* no), exogenous estrogen and progesterone use ever (yes *vs.* no), diabetic status (yes *vs.* no), dietary alcohol per day (gram), dietary total fat (gram), and physical activity (metabolic equivalent of task [MET] hours per week). We performed a complete case analysis excluding study participants with missing data in covariates. All 7,991 participants had data on age at baseline for fitting model 1, and a total of 6,121 participants (77%) were eligible for fitting model 2.

We compared crude and adjusted HRs to assess the effect of obesity as a confounding factor on the association between adiponectin-related SNPs and breast cancer risk. BMI, WHR, and WC are highly correlated, and thus, each index was entered individually in the regression models. A change greater than or equal to 10% indicates the presence of a confounding effect (44). For interaction analysis, two strategies were employed to assess the role of obesity on the relationship between adiponectin-related SNPs and breast cancer risk: (i) stratified analysis and (ii) analysis of the joint effects. The stratified analysis evaluates effect modification by comparing strata-specific HRs to one another and to the crude estimates. The analyses were performed separately for each index of obesity. Next, we calculated the relative excess risk due to interaction (RERI) to assess the joint effects of obesity and adiponectin-related SNPs on breast cancer risk on the additive scale with its 95% CIs obtained by the delta method (45). RERI equals 0 in the absence of additive interaction. Any departure from 0 indicates the presence of additive interaction. All statistical tests considered two-tailed p values less than 0.05 to be indicative of statistical significance. To account for the correction of multiple comparisons, we additionally applied the Benjamini and Hochberg procedure and controlled the false discovery rate at q-value of 0.05 in each adiponectin-related SNP (46). The R3.6.0 (dplyr, survival, epiR, and msm packages) was used.

RESULTS

Baseline Characteristics

Of 7,991 subjects, 402 (5.0%) reported developing breast cancer (**Table 1**). The overall mean age at the baseline was 60.9 years (SD, 6.8 years) with a mean follow-up year of 14.5 years (SD, 3.15 years). The mean BMI was 31.0 kg/m^2 (SD, 6.3 kg/m^2), the mean WHR was 0.82 (SD, 0.07), and the mean WC was 91.3 cm (SD, 13.3 cm). Characteristics of participants were generally balanced between those with and without breast cancer.

The Association Between Adiponectin-Related SNPs and Breast Cancer Risk

Among 32 adiponectin-related SNPs (**Supplementary Table 2**), three candidate SNPs were observed to have potential association between genotype and breast cancer risk (**Table 2**). Without adjusting for obesity, the heterozygous TC genotype of *OR8S1* rs11168618 (effect allele/reference allele: T/C) was correlated with a lower risk of breast cancer compared to the major CC genotype (HR, 0.65; 95% CI, 0.48–0.88) in model 1. The heterozygous TC genotype of *EIF4A2* rs266719 (T/C) decreased breast cancer risk compared with the major CC genotype in model 2 (HR, 0.65; 95% CI, 0.44–0.95). The heterozygous CA genotype of *KCNK9* rs2468677 (C/A) had increased breast cancer risk compared with the major AA genotype; however, it was found to be statistically significant only in model 2 with an additional adjustment for BMI (HR, 1.35; 95% CI, 1.00–1.80). After adjustments for multiple testing, those SNPs did not reach the significance level. Further, the assessment of confounding by BMI, WHR, and WC on the SNP-breast cancer relationship revealed that a confounding effect is unlikely to be a concern.

BMI, WHR, and WC as Effect Modifiers of the Association Between Adiponectin-Related SNPs and Breast Cancer Risk

Tables 3–**5** present analysis stratified by BMI (under/normal weight, overweight, and obesity), WHR (<0.85 *vs.* ≥0.85), and WC (<88 cm *vs.* ≥88 cm), respectively. The effects of obesity status on the relationship between several SNPs and breast cancer differed between strata. In model 1, the heterozygous TC genotype in *OR8S1* rs11168618 (T/C) was inversely associated with breast cancer risk among individuals with under/normal weight, overweight, WHR <0.85, and WC <88 cm. However, the significance was no longer observed in model 2. There was also a possible interaction of BMI ≥30 kg/m^2 with the heterozygous TC genotype in *OR8S1* rs11168618 (T/C) (RERI, 0.58; 95% CI, 0.35–0.80).

In relation to the *ADIPOQ* gene, the heterozygous CT genotype in rs6773957 (C/T) was negatively associated with breast cancer risk among individuals with under/normal weight by roughly 60% in model 2. An interaction between BMI ≥30 kg/m^2 and the heterozygous CT genotype was observed with a RERI of 0.62 with 95% CI of 0.32 to 0.92. Among those with WC <88 cm, the heterozygous CT genotype in rs6773957 (C/T) appeared to have a lower risk of breast cancer compared with the major CC genotype (HR, 0.65; 95% CI, 0.43–0.98). WC ≥88 cm showed an RERI of 0.47 with 95% CI of 0.33 to 0.62, suggesting super-additivity for the interaction between *ADIPOQ* rs6773957 (C/T) and WC. In addition, whereas effect alleles in *ADIPOR1* rs2232853 (T/C) were associated with an increased

TABLE 1 | Characteristics of participants by invasive breast cancer status.

	Total		Invasive breast cancer		No invasive breast cancer		
	(N = 7,991)		(N = 402)		(N = 7,589)		
	N	%	N	%	N	%	p[a]
Age group at baseline (year)							0.83
≤ 59	3,592	45	179	44.5	3,413	45	
60–69	3,423	42.8	177	44	3,246	42.8	
≥ 70	976	12.2	46	11.4	930	12.3	
BMI classification (kg/m2)							0.53
Underweight (< 18.5)	24	0.3	0	0	24	0.3	
Normal weight (18.5–24.9)	1,240	15.6	65	16.2	1,175	15.6	
Overweight (25–29.9)	2,681	33.8	127	31.7	2,554	33.9	
Obesity (≥ 30)	3,993	50.3	209	52.1	3,784	50.2	
WHR classification							0.27
< 0.85	5,342	67.1	259	64.6	5,083	67.2	
≥ 0.85	2,618	32.9	142	35.4	2,476	32.8	
WC classification (cm)							0.30
< 88	3,440	43.1	163	40.6	3,277	43.3	
≥ 88	4,534	56.9	238	59.4	4,296	56.7	
Family income ($)							0.40
< 34,999	3,767	50.2	178	47.1	3,589	50.4	
35,000–100,000	3,347	44.6	177	46.8	3,170	44.5	
≥ 100,000	390	5.2	23	6.1	367	5.2	
Employment status							0.78
No	4,201	56.1	207	55.3	3,994	56.1	
Yes	3,294	43.9	167	44.7	3,127	43.9	
Smoking status							0.81
No	3,900	49.3	195	48.7	3,705	49.4	
Ever smoke	4,006	50.7	205	51.2	3,801	50.6	
Number of pregnancies							0.71
Never pregnant	589	7.4	34	8.5	555	7.4	
1 pregnancy	795	10	44	11.1	751	10	
2–4 pregnancies	4,199	53	204	51.3	3,995	53.1	
≥ 5 pregnancies	2,339	29.5	116	29.1	2,223	29.5	
Exogenous estrogen use ever							0.17
No	5,336	66.8	281	69.9	5,055	66.6	
Yes	2,654	33.2	121	30.1	2,533	33.4	
Exogenous estrogen + progesterone use ever							0.25
No	7,059	88.3	348	86.6	6,711	88.4	
Yes	931	11.7	54	13.4	877	11.6	
Diabetic status							0.62
No	7,048	88.3	350	87.5	6,698	88.3	
Yes	935	11.7	50	12.5	885	11.7	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p[a]**
Age at baseline (year)	60.9	6.8	60.9	6.7	60.9	6.8	0.91
BMI (kg/m^2)	31	6.3	31.2	6	31	6.3	0.67
WHR	0.82	0.074	0.82	0.073	0.82	0.074	0.33
WC (cm)	91.3	13.3	91.8	12.4	91.2	13.3	0.40
Dietary alcohol per day (g)	2.4	9.01	1.9	5.4	2.4	9.2	0.30
Dietary total fat (g)	64.2	44.7	62.1	37.8	64.3	45	0.35
Depressive symptom[b]	0.047	0.141	0.044	0.127	0.048	0.142	0.60
Physical activity (METs hours per week[c])	9.84	12.7	9.6	12.5	9.9	12.8	0.68
Age at menopause (year)	46.6	7.3	46.9	7.8	46.6	7.3	0.44

BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; MET, metabolic equivalent of task.

[a]*From a chi-squared test for categorical variables and a t-test for continuous variables.*

[b]*Depression scale ranging from 0 to 1 with a higher score indicating a greater depressive severity.*

[c]*The intensity of physical activity is represented in a MET unit by measuring the amount of oxygen consumption during exercise.*

risk of breast cancer among White women (21), its association with breast cancer risk was not found among AA women.

For *FER* rs10447248 (T/C), women with BMI ≥30 kg/m^2 and the minor TT genotype had increased breast cancer risk in comparison to those with major CC genotype by approximately 2-fold in both model 1 (HR, 2.20; 95% CI, 1.08–4.49) and model 2 (HR, 2.53; 95% CI, 1.17–5.45). When we stratified the analysis by WHR status, different patterns were observed for the association between *FER* rs10447248 (T/C) and breast cancer risk. Carriers of the heterozygous TC genotype had

TABLE 2 | Associations of adiponectin-related SNPs and postmenopausal invasive breast cancer risk with or without adjusting for BMI, WHR, and WC.

		No adjustment for obesity status				Additional adjustment for BMI				Additional adjustment for WHR				Additional adjustment for WC			
		Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]	
Genotype	**brca/no**	**HR (95% CI)**	**P[c]**	**HR (95% CI)**	**P[c]**	**HR (95% CI)**	**P[c]**	**HR (95% CI)**	**P[c]**	**HR (95% CI)**	**P[c]**	**HR (95% CI)**	**P[c]**	**HR (95% CI)**	**P[c]**	**HR (95% CI)**	**P[c]**
rs266719																	
CC	306/5,671	1		1		1		1		1		1		1		1	
TC	41/1,036	0.74 (0.54–1.03)	0.07	**0.65 (0.44–0.95)**	**0.03**	0.74 (0.54–1.03)	0.07	**0.65 (0.44–0.95)**	**0.03**	0.74 (0.54–1.03)	0.07	**0.65 (0.44–0.96)**	**0.03**	0.74 (0.54, 1.03)	0.07	**0.65 (0.44, 0.95)**	**0.03**
TT	5/54	1.65 (0.68–4.00)	0.27	1.84 (0.68–4.95)	0.23	1.65 (0.68–4.00)	0.27	1.83 (0.68–4.94)	0.23	1.66 (0.69–4.02)	0.26	1.85 (0.69–4.98)	0.22	1.65 (0.68, 4.00)	0.27	1.84 (0.68, 4.95)	0.23
rs2468677																	
AA	81/1,841	1		1		1		1		1		1		1		1	
CA	188/3,353	1.27 (0.98–1.64)	0.08	1.33 (0.99–1.77)	0.06	1.28 (0.99–1.66)	0.07	**1.35 (1.01–1.80)**	**<0.05**	1.27 (0.98–1.64)	0.08	1.33 (0.99–1.77)	0.06	1.27 (0.98, 1.64)	0.08	1.33 (1.00, 1.77)	0.05
CC	83/1,569	1.20 (0.88–1.63)	0.25	1.14 (0.80–1.61)	0.47	1.21 (0.89–1.65)	0.22	1.15 (0.81–1.64)	0.43	1.20 (0.89–1.63)	0.24	1.14 (0.81–1.62)	0.45	1.20 (0.88, 1.63)	0.25	1.14 (0.80, 1.61)	0.47
rs11168618																	
CC	297/5,324	1		1		1		1		1		1		1		1	
TC	49/1,338	**0.65 (0.48–0.88)**	**0.01**	0.73 (0.53–1.01)	0.05	**0.65 (0.48–0.88)**	**0.01**	0.74 (0.53–1.02)	0.06	**0.65 (0.48–0.87)**	**<0.01**	**0.72 (0.52–1.00)**	**<0.05**	**0.65 (0.48, 0.88)**	**0.01**	0.73 (0.53, 1.01)	0.05
TT	6/102	1.02 (0.46–2.30)	0.96	1.08 (0.45–2.63)	0.86	1.01 (0.45–2.27)	0.98	1.08 (0.45–2.63)	0.86	1.02 (0.46–2.29)	0.96	1.09 (0.45–2.65)	0.85	1.02 (0.46, 2.30)	0.96	1.09 (0.45, 2.66)	0.84

Boldface text indicates statistical significance at P < 0.05.

Chr, chromosome; brca, invasive breast cancer; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; CI, confidence interval

[a]*Adjusted for age only.*

[b]*Adjusted for age, dietary alcohol (g), diabetes, dietary fat (g), depression scale, energy expenditure, employment status, ever smoking status, number of pregnancies, age at menopause, income status, unopposed estrogen use ever, unopposed estrogen + progesterone use ever.*

[c]*Results do not reach the significance level (q < 0.05) after adjustments for multiple testing with the Benjamini and Hochberg procedure.*

an elevated risk of breast cancer among WHR <0.85 compared with those with the major CC genotype (HR, 1.44; 95% CI, 1.09–1.90), whereas the reduced risk among WHR >0.85 (HR, 0.51; 95% CI, 0.31–0.86) in model 1.

DISCUSSION

Low circulating levels of adiponectin have been observed in obese individuals and women with postmenopausal breast cancer (12, 13, 17–19). Yet, the genetic mechanisms underlying the association between adiponectin and obesity in breast cancer risk have not been fully elucidated. Our study evaluated the association between genetic variants involved in regulating adiponectin circulating levels and breast cancer risk by obesity status among postmenopausal AA women. We found that heterozygotes of *OR8S1* rs11168618 (T/C) and *EIF4A2* rs266719 (T/C) were negatively associated with breast cancer risk, whereas the heterozygote of *KCNK9* rs2468677 (C/A) had an elevated risk. The crude estimates of breast cancer risk did not differ from the adjusted estimates, thus confounding by obesity is unlikely. The findings suggest that low circulating levels of adiponectin may serve as a risk factor for breast cancer, independent of obesity. Indeed, *in vivo* and *in vitro* studies have demonstrated a direct effect of adiponectin on breast cancer development with and without obesity environment (47). Increased levels of adiponectin attenuated cell proliferation in several breast cancer cell lines, including MCF-7 (48, 49), T47D (48, 50–52), SKBR3 (48), MDA-MB-231 (50, 51), and MCF-10A (53). Furthermore, transgenic mice with adiponectin injection reduced mammary tumorigenesis (50), whereas mice with reduced adiponectin expression led to earlier tumor onset and accelerated tumor growth compared to those with normal expression (54).

The evidence on the association of SNPs in *ADIPOQ* and *ADIPOR1* with breast cancer risk has been inconsistent (21–25). A previous study found that *ADIPOQ* rs17366568 influenced adiponectin plasma levels in non-Hispanic White women but not in AA women (55). In addition, women who carried effect alleles in *ADIPOR1* rs2232853 (T/C) were associated with increased risk of breast cancer in a case-control study that consists of predominantly White women aged 20 to 87 years (21). However, we did not find a significant correlation between this SNP and breast cancer risk among AA women aged 50 to 79 years. These results in part explain the existing racial variations between AA and White women in breast cancer incidence and adiponectin levels (2, 7–9, 20). The findings also support that different adiponectin-related genetic factors may contribute to the increased risk of breast cancer by race. Understanding racial differences in adiponectin-related SNPs by accounting for their associations with adiponectin levels and breast cancer risk is an important area for future research.

We also observed that SNPs in non-adiponectin-specific genes were associated with breast cancer risk, and these associations were modified by obesity. Individuals with the minor TT genotype of *FER* rs10447248 (T/C) and having BMI

TABLE 3 | Association between adiponectin-related SNPs and postmenopausal invasive breast cancer risk, by BMI status.

Genotype		Under/Normal Weight				Overweight					Obesity				
		Model 1a		Model 2b		Model 1a		Model 2b		RERI (95% CI)c	Model 1a		Model 2b		RERI (95% CI)c
	brca/no	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p		HR (95% CI)	p	HR (95% CI)	p	
rs2791553															
CC	106/2,050	1		1		1		1			1		1		
TC	191/3,329	0.71 (0.40–1.26)	0.24	0.63 (0.33–1.18)	0.15	1.53 (0.99–2.38)	0.06	1.37 (0.84–2.23)	0.20	0.57 (0.31–0.83)	1.04 (0.75–1.44)	0.83	0.99 (0.69, 1.43)	0.96	0.37 (0.19, 0.55)
TT	55/1,385	0.55 (0.24–1.23)	0.14	0.56 (0.23–1.35)	0.20	1.11 (0.62–1.99)	0.72	1.24 (0.67–2.29)	0.50	0.58 (0.25–0.92)	0.68 (0.43–1.07)	0.1	0.66 (0.40, 1.09)	0.1	0.15 (-0.26, 0.56)
rs4301033															
GG	236/4,455	1		1		1		1			1		1		
AG	99/2,049	0.92 (0.51–1.65)	0.79	0.94 (0.49–1.81)	0.86	0.73 (0.47–1.12)	0.15	0.73 (0.45–1.20)	0.22	–0.14 (–0.46 to 0.18)	1.05 (0.76–1.44)	0.78	1.12 (0.79, 1.61)	0.52	0.17 (-0.34, 0.69)
AA	17/249	0.54 (0.074–3.92)	0.54	0.64 (0.087–4.76)	0.67	1.82 (0.88–3.75)	0.11	2.12 (1.01–4.44)	<0.05	1.4 (–0.15 to 2.96)	1.18 (0.58–2.41)	0.66	1.4 (0.65, 3.03)	0.39	0.74 (0.001, 1.49)
rs266719															
CC	306/5,671	1		1		1		1			1		1		
TC	41/1,036	1.07 (0.55–2.08)	0.84	0.99 (0.47–2.06)	0.97	0.67 (0.38–1.20)	0.18	1.21 (0.77–1.90)	0.05	–0.61 (–1.15 to –0.069)	0.66 (0.40–1.08)	0.10	1.29 (0.89, 1.81)	0.10	-0.50 (-0.99, -0.01)
TT	5/54	0.00 (0.00 to Inf)	0.99	0.00 (0.00 to Inf)	0.99	0.79 (0.11–5.68)	0.82	1.34 (0.73–2.46)	0.89	1.17 (0.76–1.57)	2.71 (1.01–7.32)	0.05	0.99 (0.58, 1.70)	0.10	2.79 (2.38, 3.20)
rs3821799															
TT	112/2,140	1		1		1		1			1		1		
CT	169/3,330	0.55 (0.30–0.98)	0.04	0.42 (0.22–0.81)	0.01	1.44 (0.93–2.23)	0.10	1.49 (0.92–2.43)	0.11	0.77 (0.49–1.06)	0.93 (0.66–1.30)	0.66	0.86 (0.59, 1.25)	0.43	0.45 (0.13, 0.77)
CC	71/1,294	0.69 (0.33–1.46)	0.33	0.59 (0.26–1.34)	0.21	1.38 (0.81–2.37)	0.24	1.41 (0.78–2.57)	0.25	0.57 (0.18–0.95)	1.02 (0.68–1.54)	0.92	1.04 (0.66, 1.64)	0.88	0.37 (0.08, 0.65)
rs3774261d															
TT	110/2,123	1		1		1		1			1		1		
CT	166/3,263	0.59 (0.33–1.05)	0.07	0.40 (0.21–0.77)	0.01	1.24 (0.81–1.91)	0.32	1.24 (0.77–2.01)	0.38	0.67 (0.39–0.99)	1.02 (0.73–1.44)	0.89	0.99 (0.68, 1.45)	0.95	0.58 (0.28, 0.88)
CC	76/1,372	0.66 (0.31–1.39)	0.28	0.63 (0.29–1.37)	0.24	1.28 (0.76–2.14)	0.35	1.31 (0.74–2.32)	0.35	0.5 (0.14–0.86)	1.12 (0.75–1.69)	0.58	1.1 (0.69, 1.74)	0.70	0.4 (0.11, 0.68)
rs6444174d															
TT	249/4,940	1		1		1		1			1		1		
CT	90/1,658	1.39 (0.78–2.46)	0.26	1.82 (0.98–3.35)	0.06	0.7 (0.43–1.11)	0.13	0.76 (0.46–1.25)	0.28	–1 (–2.27 to 0.27)	1.26 (0.91–1.76)	0.17	1.22 (0.84, 1.76)	0.29	-0.52 (-2.78, 1.74)
CC	13/164	0.00 (0.00 to Inf)	1.00	0.00 (0.00 to Inf)	1.00	1.53 (0.62–3.76)	0.36	1.19 (0.37–3.82)	0.77	1.22 (0.72–1.72)	2.04 (0.99–4.18)	0.05	2.26 (1.04, 4.88)	0.04	2.42 (1.91, 2.93)
rs6773957d															
TT	104/2,034	1		1		1		1			1		1		
CT	171/3,349	0.55 (0.30–0.99)	0.05	0.39 (0.20–0.75)	0.01	1.3 (0.84–2.01)	0.24	1.32 (0.81–2.16)	0.27	0.74 (0.43–1.04)	1.05 (0.74–1.48)	0.78	1.04 (0.71, 1.53)	0.85	0.62 (0.32, 0.92)
CC	77/1,379	0.71 (0.34–1.47)	0.35	0.6 (0.27–1.32)	0.20	1.32 (0.78–2.23)	0.30	1.37 (0.77–2.45)	0.28	0.54 (0.17–0.92)	1.13 (0.75–1.71)	0.57	1.12 (0.70, 1.79)	0.63	0.44 (0.14, 0.74)
rs13434995															
AA	253/5,032	1		1		1		1			1		1		

(Continued)

TABLE 3 | Continued

Genotype		Under/Normal Weight				Overweight					Obesity				
		Model 1a		Model 2b		Model 1a		Model 2b		RERI (95% CI)c	Model 1a		Model 2b		RERI (95% CI)c
	brca/no	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p		HR (95% CI)	p	HR (95% CI)	p	
		1.69	0.07	2.2	0.01	1.13	0.56	1.14	0.59	–1.04	0.97	0.85	0.99	0.98	-1.29
GA	91/1,617	(0.96–2.97)		(1.19–4.07)		(0.75–1.72)		(0.71–1.82)		(–4.89 to 2.81)	(0.68–1.37)		(0.68, 1.46)		(-6.42, 3.83)
		3.94	0.02	7.14	<0.01	2.37	0.09	2.73	0.06	–3.66	0.3	0.23	0.41	0.38	-6.08
GG	8/115	(1.21–12.86)		(2.05–24.86)		(0.87–6.49)		(0.96–7.75)		(–48.02 to 40.71)	(0.042–2.16)		(0.057, 2.96)		(-18.10, 5.95)
rs10012953															
TT	238/4,540	1		1		1		1			1		1		
		0.75	0.36	0.91	0.77	1.03	0.87	1.06	0.80	0.19	0.99	0.95	1.13	0.51	0.22
CT	100/1,987	(0.40–1.39)		(0.47–1.77)		(0.70–1.54)		(0.68–1.64)		(–0.16, 0.53)	(0.71–1.37)		(0.79, 1.62)		(-0.18, 0.63)
		0.44	0.41	0.57	0.59	0.7	0.55	0.87	0.81	0.31	1.63	0.16	2.14	0.03	1.57
CC	13/230	(0.06–3.16)		(0.078–4.25)		(0.22–2.23)		(0.27–2.78)		(–0.30, 0.91)	(0.83–3.22)		(1.07, 4.25)		(0.30, 2.84)
rs10447248															
CC	245/4,881	1		1		1		1			1		1		
		1.46	0.20	1.6	0.14	1.01	0.98	1.12	0.62	–0.37	1.01	0.96	1.05	0.82	-0.49
TC	94/1,728	(0.82–2.57)		(0.85–3.01)		(0.66–1.52)		(0.71–1.75)		(–1.92 to 1.18)	(0.72–1.42)		(0.71, 1.53)		(-2.18, 1.20)
		1.7	0.47	2.2	0.30	0.98	0.97	0.41	0.37	–1.59	2.20	0.03	2.53	0.02	0.54
TT	13/152	(0.41–7.05)		(0.50–9.67)		(0.31–3.11)		(0.056–2.93)		(–3.89 to 0.72)	(1.08–4.49)		(1.17, 5.45)		(-10.66, 11.73)
rs998584															
CC	205/4,106	1		1		1		1			1		1		
		0.87	0.64	1	1.00	1.03	0.90	1.03	0.89	0.064	1.23	0.19	1.36	0.08	0.34
AC	129/2,313	(0.49–1.55)		(0.53–1.88)		(0.69–1.52)		(0.67–1.60)		(–0.23 to 0.36)	(0.91–1.66)		(0.97, 1.90)		(-0.38, 1.06)
		0.95	0.94	0.79	0.75	1.94	0.04	2.45	0.01	1.65	0.44	0.11	0.58	0.29	-0.28
AA	18/344	(0.29–3.10)		(0.18–3.36)		(1.02–3.67)		(1.27–4.72)		(0.32–2.98)	(0.16–1.20)		(0.21, 1.58)		(-1.04, 0.47)
rs11168618															
CC	297/5,324	1		1		1		1			1		1		
		0.37	0.03	1	0.05	0.52	0.02	0.67	0.20	0.35	0.87	0.49	1.01	0.77	0.58
TC	49/1,338	(0.15–0.93)		(0.54–1.86)		(0.30–0.91)		(0.42–1.05)		(0.03–0.68)	(0.59–1.29)		(0.71, 1.44)		(0.35, 0.80)
		0.76	0.79	0.73	0.83	0.97	0.97	1.22	0.70	0.38	1.1	0.87	0.89	0.95	-0.022
TT	6/102	(0.11–5.55)		(0.27–1.96)		(0.24–3.93)		(0.70–2.13)		(–0.90 to 1.65)	(0.35–3.45)		(0.53, 1.50)		(-1.24, 1.19)

Boldface text indicates statistical significance at P < 0.05.

Chr, chromosome; brca, invasive breast cancer; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; CI, confidence interval; NA, not applicable; RERI, relative excess risks due to interaction.

[a]*Adjusted for age.*

[b]*Adjusted for age, dietary alcohol (g), diabetes, dietary fat (g), depression scale, energy expenditure, employment status, ever smoking status, number of pregnancies, age at menopause, income status, unopposed estrogen use ever, unopposed estrogen + progesterone use ever.*

[c]*RERI and its 95% Cis were calculated for fully adjusted Cox models (aHR2) only*

[d]*High linkage disequilibrium (r2 > 0.80) was found between all pairs of these three SNPs in ADIPOQ.*

TABLE 4 | Association between adiponectin-related SNPs and postmenopausal invasive breast cancer risk, by WHR status.

Genotype		WHR < 0.85				WHR ≥ 0.85				RERI (95% CI)[c]
		Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]		
	brca/no	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	
rs4301033										
GG	236/4,455	1		1		1		1		
AG	99/2,049	1.02 (0.77–1.36)	0.90	1.03 (0.75, 1.43)	0.85	0.75 (0.49–1.14)	0.18	0.79 (0.50–1.25)	0.31	–0.31 (–1.08 to 0.45)
AA	17/249	1.55 (0.88–2.73)	0.13	**1.9 (1.04–3.46)**	**0.04**	0.84 (0.31–2.30)	0.74	0.99 (0.36–2.72)	0.99	–0.86 (–4.58 to 2.86)
rs10517133										
GG	293/5,679	1		1		1		1		
CG	56/1,027	0.8 (0.54–1.18)	0.26	0.86 (0.56–1.32)	0.49	**1.57 (1.04–2.39)**	**0.04**	1.37 (0.86–2.20)	0.19	0.55 (–0.26 to 1.35)
CC	3/52	1.32 (0.42–4.14)	0.63	1.06 (0.26–4.30)	0.93	0.00 (0.00 to Inf)	0.99	0.00 (0.00 to Inf)	0.99	NA
rs13434995										
AA	253/5,032	1		1		1		1		
GA	91/1,617	1.15 (0.86–1.55)	0.34	1.29 (0.93–1.78)	0.13	1.05 (0.69–1.60)	0.81	1.06 (0.67–1.67)	0.81	–0.2 (–1.60 to 1.20)
GG	8/115	1.92 (0.90–4.10)	0.09	**2.76 (1.23–5.96)**	**0.01**	0.44 (0.062–3.18)	0.42	0.52 (0.072–3.76)	0.52	–2.56 (–7.62 to 2.51)
rs10447248										
CC	245/4,881	1		1		1		1		
TC	94/1,728	**1.44 (1.09–1.90)**	**0.01**	**1.65 (1.21–2.24)**	**<0.01**	**0.51 (0.31–0.86)**	**0.01**	**0.46 (0.26–0.82)**	**0.01**	**–1.54 (–2.80 to –0.28)**
TT	13/152	1.67 (0.82–3.41)	0.16	1.74 (0.76–3.97)	0.19	1.59 (0.65–3.90)	0.31	1.42 (0.52–3.89)	0.50	–0.062 (–8.77 to 8.65)
rs11168618										
CC	297/5,324	1		1		1		1		
TC	49/1,338	**0.67 (0.46–0.97)**	**0.03**	0.79 (0.53–1.17)	0.24	0.61 (0.36–1.02)	0.06	0.59 (0.34–1.04)	0.07	–0.28 (–0.70 to 0.14)
TT	6/102	1.03 (0.38–2.78)	0.95	1.03 (0.33–3.23)	0.97	1.02 (0.25–4.11)	0.98	1.16 (0.28–4.76)	0.84	0.24 (–2.91 to 3.39)
rs10847980										
TT	192/3,629	1		1		1		1		
GT	130/2,635	1.07 (0.81–1.41)	0.65	1.03 (0.75–1.42)	0.85	0.78 (0.53–1.13)	0.19	0.69 (0.46–1.05)	0.08	–0.52 (–1.36 to 0.32)
GG	30/498	**1.7 (1.11–2.60)**	**0.02**	**1.73 (1.07–2.78)**	**0.02**	0.37 (0.14–1.01)	0.05	**0.31 (0.098–0.99)**	**0.049**	**–1.7 (–3.13 to –0.26)**
rs3865188										
TT	123/2,644	1		1		1		1		
AT	175/3,149	1.12 (0.84–1.48)	0.44	1.1 (0.80–1.51)	0.57	1.38 (0.92–2.05)	0.12	1.42 (0.92–2.20)	0.12	0.3 (–0.43 to 1.03)
AA	54/971	1.03 (0.69–1.54)	0.88	0.94 (0.59–1.50)	0.80	1.58 (0.93–2.69)	0.09	**1.81 (1.02–3.19)**	**0.04**	0.81 (–0.32 to 1.93)

Boldface text indicates statistical significance at P < 0.05.

Chr, chromosome; brca, invasive breast cancer; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; CI, confidence interval; NA, not applicable; RERI, relative excess risks due to interaction.

[a]*Adjusted for age.*

[b]*Adjusted for age, dietary alcohol (g), diabetes, dietary fat (g), depression scale, energy expenditure, employment status, ever smoking status, number of pregnancies, age at menopause, income status, unopposed estrogen use ever, unopposed estrogen + progesterone use ever.*

[c]*RERI and its 95% Cis were calculated for fully adjusted Cox models (aHR2) only.*

≥30 kg/m^2 had an elevated risk of postmenopausal breast cancer. FER tyrosine kinase increases NF-$\kappa\beta$ activation and signals interleukin-6 (IL-6) to regulate STAT3 phosphorylation (56, 57), which may explain its relationship with breast cancer risk through adiponectin and obesity. A decline in adiponectin secretion leads to overexpression of pro-inflammatory cytokines, including IL-6 and TNF-α, in an obese individual as a consequence of excess inflammatory response (58). The induction of TNF-α activates NF-$\kappa\beta$, which promotes breast cancer development (59, 60). IL-6 activates the Janus kinase-signal transducer and activator of transcription signaling pathway inducing the STAT3 dimer (58, 61, 62). This STAT3 dimer stimulates the transcription of genes strongly associated with the promotion of tumor growth and immunosuppression. This suggests that *FER* rs10447248 may predispose breast cancer by inducing NF-$\kappa\beta$ and IL-6 to trigger downstream signaling pathways.

TABLE 5 | Association between adiponectin-related SNPs and postmenopausal invasive breast cancer risk, by WC status.

Genotype		WHR < 0.85				WHR ≥ 0.85				RERI (95% CI)[c]
		Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]		
	brca/no	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	
rs266719										
CC	306/5,671	1		1		1		1		
		0.79	0.33	0.7	0.20	0.7	0.12	0.59	0.06	-0.14
TC	41/1,036	(0.49–1.27)		(0.41–1.21)		(0.45–1.10)		(0.34–1.03)		(-0.44, 0.16)
		0.00	0.99	0.00	0.99	**2.91**	**0.02**	**3.33**	**0.02**	**3.62**
TT	5/54	(0.00 to Inf)		(0.00 to Inf)		**(1.20–7.07)**		**(1.23–9.04)**		**(3.34, 3.90)**
rs3774261[d]										
TT	110/2,123	1		1		1		1		
		0.79	0.21	**0.64**	**0.03**	1.16	0.36	1.12	0.54	**0.43**
CT	166/3,263	(0.55–1.14)		**(0.43–0.97)**		(0.84–1.60)		(0.78–1.60)		**(0.28, 0.58)**
		0.99	0.99	0.89	0.62	1.14	0.52	1.15	0.53	0.19
CC	76/1,372	(0.64–1.54)		(0.55–1.43)		(0.77–1.69)		(0.74–1.78)		(-0.079, 0.47)
rs6773957[d]										
TT	104/2,034	1		1		1		1		
		0.78	0.19	**0.65**	**0.04**	1.21	0.26	1.19	0.34	**0.47**
CT	171/3,349	(0.54–1.13)		**(0.43–0.98)**		(0.87–1.67)		(0.83–1.71)		**(0.33, 0.62)**
		1.02	0.94	0.88	0.61	1.16	0.46	1.2	0.42	0.23
CC	77/1,379	(0.66–1.57)		(0.55–1.43)		(0.78–1.73)		(0.77–1.87)		(-0.034, 0.50)
rs13434995										
AA	253/5,032	1		1		1		1		
		1.26	0.22	1.31	0.20	1.01	0.91	1.09	0.63	-0.2
GA	91/1,617	(0.88–1.80)		(0.87–1.96)		(0.74–1.41)		(0.77–1.55)		(-1.39, 0.99)
		2.62	**0.02**	**3.65**	**<0.01**	0.55	0.41	0.7	0.61	-3.14
GG	8/115	**(1.15–5.98)**		**(1.57–8.47)**		(0.14–2.24)		(0.17–2.82)		(-8.86, 2.57)
rs13358260										
AA	338/6,525	1		1		1		1		
		1.88	**0.06**	**2.05**	**0.04**	0.59	0.29	0.5	0.24	**-1.6**
GA	14/233	(0.99–3.57)		**(1.03–4.06)**		(0.22–1.58)		(0.16–1.58)		**(-3.18, -0.008)**
		0.00	0.99	0.00	0.99	0.00	0.99	NA	–	NA
GG	0/5	(0.00 to Inf)		(0.00 to Inf)		(0.00 to Inf)				
rs592423										
AA	124/2,310	1		1		1		1		
		1.41	0.07	**1.6**	**0.03**	0.77	0.09	0.79	0.17	-0.97
CA	176/3,355	(0.97–2.04)		**(1.05–2.43)**		(0.57–1.04)		(0.57–1.11)		(-3.65, 1.72)
		1.01	0.98	0.84	0.59	0.84	0.39	0.91	0.68	0.004
CC	52/1,099	(0.59–1.72)		(0.44–1.60)		(0.56–1.26)		(0.58–1.42)		(-1.51, 1.52)
rs11168618										
CC	297/5,324	1		1		1		1		
		0.53	**0.01**	0.66	0.11	0.75	0.14	0.78	0.26	0.11
TC	49/1,338	**(0.33–0.87)**		(0.40–1.09)		(0.51–1.10)		(0.52–1.20)		(-0.14, 0.35)
		0.74	0.67	0.98	0.98	1.25	0.66	1.19	0.77	0.18
TT	6/102	(0.18–2.99)		(0.24–4.01)		(0.47–3.38)		(0.38–3.74)		(-1.47, 1.82)

Boldface text indicates statistical significance at P < 0.05.

Chr, chromosome; brca, invasive breast cancer; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; CI, confidence interval; NA, not applicable; RERI, relative excess risks due to interaction.

[a]*Adjusted for age.*

[b]*Adjusted for age, dietary alcohol (g), diabetes, dietary fat (g), depression scale, energy expenditure, employment status, ever smoking status, number of pregnancies, age at menopause, income status, unopposed estrogen use ever, unopposed estrogen + progesterone use ever.*

[c]*RERI and its 95% Cis were calculated for fully adjusted Cox models (aHR2) only.*

[d]*High linkage disequilibrium (r2 > 0.80) was found between these two SNPs in ADIPOQ.*

OR8S1 is an olfactory receptor (OR) that belongs to G protein-coupled receptors influencing tumorigenesis (63). An OR is most abundant in not only olfactory sensory neurons in an olfactory epithelium but is also found in tissues throughout the body. In the current study, the effect of *OR8S1* rs11168618 (T/C), which decreases adiponectin levels (33), was inversely associated with breast cancer risk. It has been reported that an activated OR 544 (*Olfr544*) increased adiponectin secretion in 3T3-L1 mouse adipocytes (64). In relation to breast cancer, *OR2B6* and *OR2W3* were ectopically expressed in breast cancer cell lines and breast cancer tissues making them potential biomarkers (65, 66). An activation of ORs in cancer cells promotes apoptosis and inhibits cell proliferation by inducing AMPK or MAPK signaling pathways (65, 67). Given the limited existing evidence on the role of ORs with adiponectin or different types of cancer, we can only speculate that activation

of ORs in adipose tissue has an indirect effect on lowering breast cancer risk through increasing adiponectin levels. To our knowledge, only the present study has evaluated *OR8S1* rs11168618 and breast cancer risk.

It is important to note the potential limitations that the study has. Although breast cancer outcome and anthropometric measurements were prospectively measured with strict ascertainment procedure, other variables included in the regression models were mainly obtained from the self-reported questionnaire at the time of enrollment, leading to recall bias. However, there was no difference in distributions of baseline characteristics among cohorts. Missing data were also unavoidable in this study. In particular, information on the family history of breast cancer had a low response rate of 37.4% reducing statistical efficiency of the estimates. Thus, we decided not to include family history of breast cancer to obtain sufficient power while sustaining a potential confounding effect. Low circulating adiponectin levels may contribute to a more aggressive phenotype of breast cancer, ER-negative breast cancer risk compared to ER-positive breast cancer risk (68). Also, reduced breast cancer risk was observed in women with increased high-molecular weight adiponectin levels and lower BMI (14). Nevertheless, we could not further analyze the data by molecular subtypes of breast cancer or by adiponectin isomers due to the small sample sizes. Lastly, the study was limited to postmenopausal AA women harming the generalizability of our results. Despite these drawbacks, we used one of the most extensive data on postmenopausal AA women and conducted the genetic association study of adiponectin concerning postmenopausal breast cancer risk. In many cases, genetic data of a minority racial or ethnic group are not readily available nor have a sufficient sample size to obtain a comfortable statistical efficiency of the estimates. In addition to finding the associations between candidate SNPs in adiponectin genes and breast cancer risk, the study considered other loci in non–adiponectin-specific genes Associated with regulating adiponectin expression. In doing so, we were able to identify genetic variants of circulating adiponectin levels that were not directly considered in previous studies but may predispose to breast cancer development.

In summary, our study evaluated the association between previously identified adiponectin-related SNPs and primary invasive breast cancer risk among AA postmenopausal women. We detected that several adiponectin-related SNPs interacted with obesity, altering the risk of postmenopausal breast cancer. As obese women have an approximately 30% increased risk in developing breast cancer compared with those with normal weight (69), weight management is recommended as breast cancer prevention strategies (70). In light of the evidence, such an intervention would be particularly beneficial to AA postmenopausal women who carry the risk alleles of the adiponectin-related SNPs. Also, the identified SNPs could be used as clinical and genetic predictors of breast cancer in conjunction with obesity for AA postmenopausal women. Future studies are warranted to incorporate genetic variants of other cytokines from adipocytes (e.g., leptin) to unravel the complexity of the underlying mechanisms between obesity and breast cancer risk among AA women. Also, comparing the effects of adiponectin-related SNPs across different racial/ethnic groups can contribute to better understanding of the racial disparity in breast cancer risk. Nonetheless, our findings may assist in reducing the persistent racial gap in breast cancer incidence between AA and White women by examining the role of obesity and adiponectin in postmenopausal breast cancer etiology that may differ by these racial groups.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in accordance with policies developed by the NHLBI and WHI in order to protect sensitive participant information and approved by the Fred Hutchinson Cancer Research Center, which currently serves as the IRB of record for the WHI. Data requests may be made by emailing helpdesk@WHI.org.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review boards of each participating clinical center of the WHI and the University of California, Los Angeles. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GN, Z-FZ, and SJ designed the study. GN and SJ performed the genomic data QC. GN performed the statistical analysis. Z-FZ, JR, HZ, and SJ participated in the study coordination and interpreted the data. SJ supervised the genomic data QC and data analysis and interpretation. SJ secured funding for this project. 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/fonc.2021.698198/full#supplementary-material

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Comparison of Radiomic Features in a Diverse Cohort of Patients With Pancreatic Ductal Adenocarcinomas

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Background: Significant racial disparities in pancreatic cancer incidence and mortality rates exist, with the highest rates in African Americans compared to Non-Hispanic Whites and Hispanic/Latinx populations. Computer-derived quantitative imaging or "radiomic" features may serve as non-invasive surrogates for underlying biological factors and heterogeneity that characterize pancreatic tumors from African Americans, yet studies are lacking in this area. The objective of this pilot study was to determine if the radiomic tumor profile extracted from pretreatment computed tomography (CT) images differs between African Americans, Non-Hispanic Whites, and Hispanic/Latinx with pancreatic cancer.

Methods: We evaluated a retrospective cohort of 71 pancreatic cancer cases (23 African American, 33 Non-Hispanic White, and 15 Hispanic/Latinx) who underwent pretreatment CT imaging at Moffitt Cancer Center and Research Institute. Whole lesion semi-automated segmentation was performed on each slice of the lesion on all pretreatment venous phase CT exams using Healthmyne Software (Healthmyne, Madison, WI, USA) to generate a volume of interest. To reduce feature dimensionality, 135 highly relevant non-texture and texture features were extracted from each segmented lesion and analyzed for each volume of interest.

Results: Thirty features were identified and significantly associated with race/ethnicity based on Kruskal-Wallis test. Ten of the radiomic features were highly associated with race/ethnicity independent of tumor grade, including sphericity, volumetric mean Hounsfield units (HU), minimum HU, coefficient of variation HU, four gray level texture features, and two wavelet texture features. A radiomic signature summarized by the first principal component partially differentiated African American from non-African American tumors (area underneath the curve = 0.80). Poorer survival among African Americans compared to Non-African Americans was observed for tumors with lower volumetric mean CT [HR: 3.90 (95% CI:1.19–12.78), p=0.024], lower GLCM Avg Column Mean [HR:4.75 (95% CI: 1.44,15.37), p=0.010], and higher GLCM Cluster Tendency [HR:3.36

(95% CI: 1.06–10.68), p=0.040], and associations persisted in volumetric mean CT and GLCM Avg Column after adjustment for key clinicopathologic factors.

Conclusions: This pilot study identified several textural radiomics features associated with poor overall survival among African Americans with PDAC, independent of other prognostic factors such as grade. Our findings suggest that CT radiomic features may serve as surrogates for underlying biological factors and add value in predicting clinical outcomes when integrated with other parameters in ongoing and future studies of cancer health disparities.

Keywords: radiomics, cancer disparities, pancreatic cancer, quantitative imaging, blacks

INTRODUCTION

Pancreatic cancer is the deadliest malignancy in the United States, with a 5-year relative survival rate of only 10% (1). Due to the lack of effective strategies for prevention, early detection, and treatment, pancreatic cancer is projected to become the second leading cancer killer by 2030 (2). Coinciding with the rise in pancreatic cancer diagnoses and deaths is a notable health disparity, with African Americans/Blacks having significantly higher pancreatic cancer incidence and mortality rates than Non-Hispanic Whites and Hispanic/Latinx (2–12). Biological reasons for these disparities are underexplored and often rely on biomarkers from tissue biopsies, which may not be representative of the entire tumor and its microenvironment. Easily accessible minimally invasive methods that can reflect tumor heterogeneity and correlate with clinical outcomes are urgently needed to advance personalized care for the racially and ethnically diverse population of patients diagnosed with pancreatic cancer each year.

Computed tomography (CT) images are routinely obtained as part of the diagnostic work-up for pancreatic cancer and can be repurposed to support quantitative imaging analyses (13). Radiomics refers to high-throughput extraction and analysis of quantitative features from standard-of-care medical images, many of which are "invisible to the human eye," to generate mineable data (14). Whereas standard "semantic" radiologic features are typically subjectively and qualitatively measured, computer algorithm-generated radiomic features such as tumor signal intensity, texture, shape, and volume have many advantages (15–21): they represent quantitative, objective measures; reflect tumor heterogeneity and subregional habitats; and are reproducible, stable, and strongly linked to clinical outcomes and underlying molecular data. Radiomic evaluations of pancreas CT scans have been conducted by our team (22–24) and others (15, 25–38), but to date none of these studies have focused on evaluating radiomic features present in pancreatic tumors from AA compared to other ethnic populations. Furthermore, we are unaware of published investigations that specifically compare racial and ethnic differences in radiomic features of different types of non-pancreas tumors. The objective of this study was to compare pretreatment CT radiomic features from a racially and ethnically diverse cohort of cases with pancreatic ductal adenocarcinoma (PDAC), the main histologic subtype of exocrine pancreatic cancers. The implications of this body of work could be far-reaching if radiomic features suggestive of a poor prognosis are identified in the pretreatment setting, in turn influencing clinical decision-making so that more aggressive treatments could be administered earlier to reduce disparities in historically underserved groups.

METHODS

Study Population

This retrospective cohort was derived from a radiological records database search of individuals with available pretreatment multiphase CT scans and a corresponding histologic diagnosis of PDAC. Cases were diagnosed and treated for PDAC at Moffitt Cancer Center and Research Institute (Tampa, Florida) between 1/2008 and 8/2018. Subjects were excluded if postcontrast venous phase CT imaging was not available or if pathology reports were not available. Race and ethnicity and other covariates were based on self-report. The final analytic dataset included CT images from 71 unique patients (**Table 1**). Ethics approval and written consent to participate were reviewed and approved by Advarra IRB (MCC# 19431; IRB #:Pro00024543).

CT Scanner Types, Acquisitions, and Procedures

CT exams were performed on different scanners as represented in **Table 2**, with most scans being performed on a Siemens Sensation 16 (n=31, 43.6%) (Siemens Healthcare, Erlangen, Germany). The post contrast venous phase series was used in this study due to the homogenous availability of this series within our cohort and the superior ability to visualize and segment tumors. The venous phase was generally acquired following weight-based Iopamidol 76% (Bracco Diagnostics Inc., Monroe Township, NJ, USA) dosing to achieve venous phase approximately 60 s post injection. Contrast dosing generally ranged from 75 ml for patients below 55 kg, to 150 ml for patients above 110 kg with gradient increases every 5 kg. Field of view (FOV) ranged from 299 to 500 mm × 299–500 mm based on patient size. The matrix was 512 × 512 for each exam. Slice thickness was 3.0 ± 0.3 mm. Mean venous phase voxel volumes were 1.61, 1.71, and 1.65 mm^3, for AA, H/L, and NHW, respectively (**Table 2**). At our institution, arterial phase bolus triggering is achieved *via* placement of the contrast

TABLE 1 | Select demographic and clinical characteristics of the pancreatic ductal adenocarcinoma CT radiomic study cohort (N=71).

	AA (n = 23)	H/L (n = 15)	NHW (n = 33)	Overall	P-value
Gender, N (%)					0.993
Female	12 (52.2%)	8 (53.3%)	17 (51.5%)	37 (52.1%)	
Male	11 (47.8%)	7 (46.7%)	16 (48.5%)	34 (47.9%)	
Age at diagnosis, mean (SD)	64.9 (10.2)	61.8 (12.7)	64.9 (10.1)	64.2 (10.6)	0.611
Vital status, N (%)					0.560
Alive	4 (17.4%)	5 (33.3%)	9 (27.3%)	18 (25.4%)	
Dead	19 (82.6%)	10 (66.7%)	24 (72.7%)	53 (74.6%)	
Smoking status, N (%)					0.971
Ever	11 (47.8%)	9 (60.0%)	17 (51.5%)	37 (52.1%)	
Missing	1 (4.35%)	0 (0.00%)	1 (3.03%)	2 (2.82%)	
Never	11 (47.8%)	6 (40.0%)	15 (45.5%)	32 (45.1%)	
Marital status, N (%)					0.516
Divorced	1 (4.35%)	3 (20.0%)	1 (3.03%)	5 (7.04%)	
Married	17 (73.9%)	10 (66.7%)	24 (72.7%)	51 (71.8%)	
Separated	2 (8.70%)	1 (6.67%)	1 (3.03%)	4 (5.63%)	
Single	1 (4.35%)	0 (0.00%)	2 (6.06%)	3 (4.23%)	
Unknown	0 (0.00%)	1 (6.67%)	1 (3.03%)	2 (2.82%)	
Widowed	2 (8.70%)	0 (0.00%)	4 (12.1%)	6 (8.45%)	
Primary site, N (%)					0.265
C241 Ampulla of vater	0 (0.00%)	0 (0.00%)	2 (6.06%)	2 (2.82%)	
C250 Pancreas Head	16 (69.6%)	12 (80.0%)	25 (75.8%)	53 (74.6%)	
C251 Pancreas Body	3 (13.0%)	1 (6.67%)	1 (3.03%)	5 (7.04%)	
C252 Pancreas Tail	0 (0.00%)	2 (13.3%)	4 (12.1%)	6 (8.45%)	
C257 Pancreas Other Specified	1 (4.35%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	
C258 Pancreas Overlapping	1 (4.35%)	0 (0.00%)	1 (3.03%)	2 (2.82%)	
C259 Pancreas, Not otherwise specified	2 (8.70%)	0 (0.00%)	0 (0.00%)	2 (2.82%)	
SEER Derived Stage, N (%)					0.257
Localized	2 (9.09%)	2 (18.2%)	6 (18.2%)	10 (15.2%)	
Regional, by direct extension only	4 (18.2%)	1 (9.09%)	5 (15.2%)	10 (15.2%)	
Regional, to lymph nodes only	4 (18.2%)	0 (0.00%)	0 (0.00%)	4 (6.06%)	
Regional, direct extension and lymph nodes	10 (45.5%)	6 (54.5%)	20 (60.6%)	36 (54.5%)	
Distant	2 (9.09%)	2 (18.2%)	2 (6.06%)	6 (9.09%)	
Tumor grade, N (%)					0.091
Well differentiated	1 (4.6%)	0 (0.0%)	2 (6.01%)	3 (4.35%)	
Moderately differentiated	8 (36.4%)	11 (78.6%)	20 (60.6%)	39 (56.5%)	
Poorly differentiated	6 (27.3%)	3 (21.4%)	8 (24.2%)	17 (24.6%)	
Not determined or Not available	7 (31.8%)	0 (0.0%)	3 (9.1%)	10 (14.5%)	
Clinical tumor size (cm), median (1st ~ 3rd quantile)	3.20 [2.65;4.68]	2.90 [2.40;9.05]	3.65 [2.42;16.0]	3.20 [2.50;9.60]	0.796
Pathological tumor size (cm), median (1st ~ 3rd quantile)	3.0 [2.3;4.7]	3.2 [3.0;4.9]	3.0 [2.5;4.9]	3.0 [2.5;5.2]	0.602
Regional nodes examined, median (1st ~ 3rd quantile)	16.0 [0.0;27.2]	26.0 [21.0;36.5]	17.0 [13.0;22.0]	18.5 [13.0;28.0]	**0.005**
Regional nodes positive, median (1st ~ 3rd quantile)	1.0 [0.5;2.5]	1.0 [0.0;5.5]	1.0 [0.0;2.0]	1.0 [0.0;3.0]	0.840
Survival time (months) median (1st ~ 3rd quantile)	15.0 [9.0;22.5]	24.0 [16.0;27.0]	31.0 [15.0;43.0]	22.0 [13.0;36.0]	**0.028**

AA, African Americans; H/L, Hispanic/Latinx; NHW, Non-Hispanic White; CT, computed tomography; SD, standard deviation; SEER, surveillance, epidemiology, end results program
Some numbers and percentages may not add up to the total due to missing data.
Statistically significant differences are noted in bold font.

tracking region of interest (ROI) over the abdominal aortic lumen at the level of the celiac trunk, with image acquisition triggered at a measured Hounsfield Unit density of 120, and venous phase ensues after a 30 s delay to achieve a 60 s venous phase.

CT Segmentation and Radiomic Feature Extraction/Reduction

Archived non-contrast and contrast-enhanced CT images were acquired from Moffitt's GE Centricity Picture Archiving and Communication System (PACS). Our experienced board-certified abdominal oncologic radiologists (JC and DJ) were blinded to patient characteristics and outcomes. For each case, the standardized imaging reporting template for PDAC staging (39) was completed to collect information on "semantic" qualitative-based radiologic features related to morphology, arterial and venous enhancement, and evaluation of extra-pancreatic structures. Whole lesion semi-automated segmentation was performed on each slice of the lesion on all pretreatment (within 3 months prior to treatment) venous phase CT exams using Healthmyne Software (Healthmyne, Madison, WI, USA). The venous phase was chosen in part because this phase was most consistent across all exams. To reduce feature dimensionality, 135 highly relevant non-texture (which measure tumor size, shape, and location) and texture features (which measure properties such as smoothness, coarseness, and regularity) were extracted from each segmented lesion and analyzed for the venous contrast phase. Additionally, CT specifications including scanner type, slice thickness, pixel size were recorded given the known variability that can occur with different scanners and settings (40, 41).

TABLE 2 | Scanner type and voxel volumes measured for the study cohort.

	AA (n = 23)	H/L (n = 15)	NHW (n = 33)	P value
Scanner model				0.512
Brilliance 64	1 (4.55%)	0 (0.00%)	0 (0.00%)	
Lightspeed pro 32	1 (4.55%)	1 (6.67%)	3 (9.09%)	
Lightspeed ultra	0 (0.00%)	1 (6.67%)	1 (3.03%)	
Lightspeed VCT	1 (4.55%)	0 (0.00%)	1 (3.03%)	
Sensation 16	13 (59.1%)	5 (33.3%)	13 (39.4%)	
Sensation 40	3 (13.6%)	3 (20.0%)	9 (27.3%)	
Sensation 64	3 (13.6%)	3 (20.0%)	6 (18.2%)	
Somatom definition AS	0 (0.00%)	2 (13.3%)	0 (0.00%)	
Voxel volume (mm^3), mean (range)	1.6 [1.4;1.8]	1.7 [1.6;2.0]	1.7 [1.4;2.1]	0.303

AA, African Americans; H/L, Hispanic/Latinx; NHW, Non-Hispanic White.

Statistical Analysis

Data analysis was performed to evaluate racial/ethnic differences in (a) study population characteristics, (b) CT procedures and standard NCCN imaging criteria, and (c) radiomic features. The Kruskal-Wallis test was used for continuous variables, and Chi-squared test or Fisher's exact test was used for categorical variables to compare the difference among racial/ethnic groups. Significant race/ethnicity-associated radiomic features were determined using a false discovery rate (42) at a threshold of 20%. Spearman correlation analysis was applied to evaluate the correlation between radiomic features. High correlated features were filtered out based on the absolute correlation coefficient above 0.9. Statistically significant radiomic features were summarized by principal component analyses (PCA) to derive a race/ethnicity-associated radiomic signature score as we described previously (43). Receiver operating characteristic (ROC) curve analysis was used to evaluate the prediction efficacy for race/ethnicity using the derived radiomic signature score. Cox proportional hazard regression was performed to evaluate the association between overall survival and each radiomic feature, including interaction terms between median-dichotomized radiomic features and race/ethnicity group (AA *versus* non-AA). Hazards ratios (HR) and 95% confidence intervals (CI) were estimated. Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up using the Kaplan–Meier method. Survival time was censored if patients were lost to follow up or after 4 years. Cox regression analysis was used to identify radiomic features independently prognostic for OS after adjustment for the following clinicopathological variables: age at diagnosis,

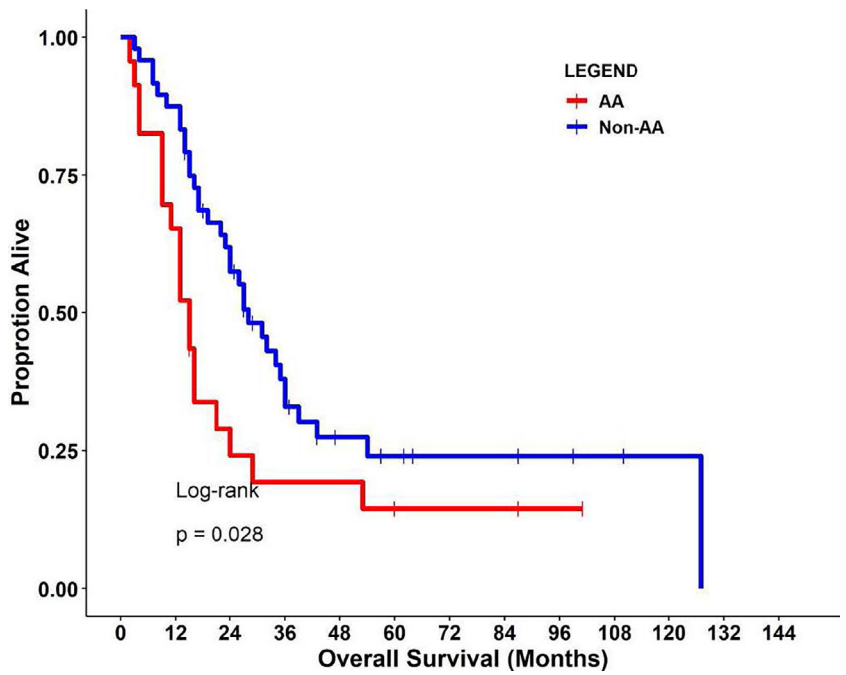


FIGURE 1 | Kaplan-Meier curves (log-rank test) of overall survival in the study cohort.

TABLE 3 | PDAC radiologic reporting template parameters for the study cohort.

Parameter	AA (n = 20)	H/L (n = 14)	NHW (n = 33)	P value
Appearance (vs. parenchyma), N (%)				0.15
Hypodense	18 (90.0%)	11 (78.6%)	22 (66.7%)	
Isodense	2 (10.0%)	3 (21.4%)	11 (33.3%)	
Size (cm) [range]	2.6 [2.0;4.3]	2.6 [2.1;3.0]	2.5[1.8;3.1]	0.734
Location, N (%)				0.385
body/tail	5 (25.0%)	2 (14.3%)	4 (12.1%)	
head/neck	14 (70.0%)	12 (85.7%)	29 (87.9%)	
uncinate	1 (5.0%)	0 (0.0%)	0 (0.0%)	
Pancreatic duct narrowing/abrupt cutoff N (%)	16 (80.0%)	8 (57.1%)	26 (78.8%)	0.244
Biliary tree abrupt cutoff N (%)				0.729
absent	6 (30.0%)	5 (35.7%)	9 (27.3%)	
present	8 (40.0%)	3 (21.4%)	9 (27.3%)	
stent	6 (30.0%)	6 (42.9%)	15 (45.5%)	
Arterial evaluation				
Superior mesenteric artery (SMA) N (%)				
Solid soft tissue contact	7 (35.0%)	0 (0.0%)	1 (3.0%)	**0.002**
Hazy attenuation/stranding contact	4 (20.0%)	3 (21.4%)	4 (12.1%)	0.232
Focal vessel narrowing or contour irregularity	1 (5.0%)	0	0	0.309
Extension to first SMA branch	6 (30.0%)	2 (14.3%)	2 (6.1%)	**0.036**
Celiac axis N (%)				
Solid soft tissue contact	2 (10.0%)	0	0	0.092
Hazy attenuation/stranding contact	2 (10.0%)	1 (7.1%)	1 (3.0%)	0.591
Focal vessel narrowing or contour irregularity	0	0	0	.
Common Hepatic Artery (CHA) N (%)				
Solid soft tissue contact	3 (15.0%)	1 (7.1%)	1 (3.0%)	0.246
Hazy attenuation/stranding contact	3 (15.0%)	2 (14.3%)	2 (6.1%)	0.49
Focal vessel narrowing or contour irregularity	1 (5.0%)	0	0	0.309
Extension to celiac axis	1 (5.0%)	0	0	0.309
Extension to bifurcation of hepatic arteries	1 (5.0%)	0	0	0.309
Arterial variant N (%)				
Present	3 (15.0%)	3 (21.4%)	3 (9.1%)	0.515
Venous evaluation				
Main portal vein (MPV) N (%)				
Solid soft tissue contact	7 (35.0%)	2 (14.3%)	9 (27.3%)	0.398
Hazy attenuation/stranding contact	7 (35.0%)	2 (14.3%)	9 (27.3%)	0.398
Focal vessel narrowing or contour irregularity	8 (40.0%)	1 (7.1%)	4 (12.1%)	0.274
Superior mesenteric vein (SMV) N (%)				
Solid soft tissue contact	12 (60.0%)	3 (21.4%)	10 (30.3%)	0.055
Hazy attenuation/stranding contact	4 (20.0%)	4 (28.6%)	8 (24.2%)	0.846
Focal vessel narrowing or contour irregularity	8 (40.0%)	1 (7.1%)	5 (15.1%)	**0.033**
Extrapancreatic evaluation N (%)				
Liver lesions	3 (15.0%)	2 (14.3%)	3 (9.1%)	0.779
Peritoneal or omental nodules	1 (5.0%)	1 (7.1%)	1 (3.0%)	0.818
Ascites	1 (5.0%)	0	0	0.309
Suspicious lymph nodes	8 (40.0%)	3 (21.4%)	8 (24.2%)	0.385
Venous collaterals	5 (25.0%)	3 (21.4%)	4 (12.1%)	0.465

Possible program errors were observed when contouring inferior margin of mass for one H/L case having a tumor with a cystic component.
Three AA cases also do not have these parameters generated and are not included in this table.
PDAC, pancreatic ductal adenocarcinoma; AA, African American; H/L, Hispanic/Latinx; NHW, non-Hispanic White; cm, centimeters.
Bold font indicates a P value < 0.05.

gender, tumor size, tumor grade, and stage of disease. Statistical tests were two-sided and significant at alpha = 0.05. All statistical analyses were performed using the R 3.6.0 software (https://www.R-project.org).

RESULTS

Study Population Characteristics

This retrospective cohort included 71 individuals diagnosed and treated for PDAC at Moffitt Cancer Center and Research Institute (Tampa, Florida) frequency-matched on age-group (+/− 5 years) and gender. Select characteristics of the study population are shown in **Table 1**. There were 23 AA, 15 H/L, and 33 NHW represented, with a slightly higher percentage of females (52%, n=37). The average age at diagnosis was 64.2 years (standard deviation=10.6), and most patients had regional or distant disease. H/L cases had significantly higher numbers of regional nodes examined than AA and NHW (p=0.005), though node positivity was similar between groups (p=0.84). Finally, AA had a significantly shorter average survival time (15 months) compared to Non-AA populations (p=0.028) (**Figure 1**).

TABLE 4 | Radiomic features evaluated in this study and their univariate association with race/ethnicity.

	AA N = 23	H/L N = 15	NHW N = 33	P overall
anterior_posterior_length_mm mean[95%CI]	25.0 [18.0;28.5]	27.0 [17.5;30.0]	25.0 [19.0;28.0]	0.853
asphericity	0.22 [0.17;0.33]	0.22 [0.15;0.26]	0.17 [0.14;0.23]	0.090
coefficient_of_variation	0.34 [0.29;0.44]	0.38 [0.28;0.66]	0.49 [0.41;0.69]	**0.002**
cranial_caudal_length_mm	27.0 [19.0;32.0]	27.0 [21.0;30.5]	24.0 [19.0;35.0]	0.903
elongation	0.87 [0.71;0.93]	0.79 [0.68;0.87]	0.78 [0.68;0.88]	0.413
energy_intensity^2	5.27 [2.81;10.32]x10^9	4.30 [2.55;10.39]x10^9	4.34 [2.51;12.06]x10^9	0.964
energy_of_ct_number_hu^2	3.03 [1.41;6.67]x10^7	3.50 [1.49;6.98]x10^7	2.56 [0.83;5.51]x10^7	0.458
entropy_hu	6.70 [6.55;6.90]	6.70 [6.45;7.00]	6.90 [6.70;7.00]	**0.042**
flatness	0.58 [0.51;0.72]	0.62 [0.55;0.69]	0.65 [0.57;0.73]	0.626
glcm_avg_angular_second_moment	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.00 [0.00;0.00]	.
glcm_avg_column_mean	82.2 [68.0;93.9]	77.1 [46.1;90.7]	65.0 [42.7;81.7]	**0.021**
glcm_avg_column_standard_deviation	30.6 [28.1;40.5]	29.9 [24.7;37.6]	36.7 [31.2;43.9]	**0.037**
glcm_avg_column_var	943 [798;1760]	907 [611;1435]	1370 [973;2113]	0.062
glcm_avg_contrast	1207 [888;1637]	1087 [761;1529]	1580 [1051;2130]	0.055
glcm_avg_correlation	0.38 [0.28;0.42]	0.35 [0.28;0.40]	0.40 [0.34;0.43]	0.325
glcm_avg_dissimilarity	25.4 [22.5;28.8]	25.3 [21.1;28.8]	28.4 [25.2;33.0]	**0.031**
glcm_avg_energy	0.02 [0.02;0.03]	0.02 [0.01;0.03]	0.02 [0.02;0.02]	0.971
glcm_avg_entropy	11.5 [10.7;12.1]	11.5 [10.6;12.1]	11.5 [10.9;12.3]	0.966
glcm_avg_homogeneity	0.04 [0.04;0.05]	0.04 [0.04;0.05]	0.04 [0.03;0.04]	0.067
glcm_avg_row_mean	83.9 [67.2;93.8]	76.7 [40.1;90.5]	66.5 [41.0;79.5]	**0.027**
glcm_avg_row_standard_deviation	27.2 [24.5;30.9]	25.6 [22.5;31.8]	32.2 [26.4;35.2]	**0.014**
glcm_avg_row_var	741 [602;952]	656 [507;1010]	1039 [695;1237]	**0.014**
glcm_cluster_prominence†*	136 [59.5;274]	85.8 [47.0;185]	187 [93.9;368]	**0.035**
glcm_cluster_shade†*	-1.70 [-6.45;-0.05]	-1.40 [-2.55;2.10]	-1.40 [-4.50;6.30]	0.721
glcm_cluster_tendency†*	6.10 [4.20;7.40]	4.90 [3.65;7.75]	7.60 [5.20;8.70]	**0.029**
glcm_contrast†*	1.70 [1.55;2.00]	1.70 [1.30;2.15]	2.10 [1.50;2.80]	**0.040**
glcm_correlation†*	0.50 [0.45;0.60]	0.50 [0.40;0.60]	0.50 [0.50;0.60]	0.374
glcm_difference_average†*	1.00 [0.90;1.05]	1.00 [0.80;1.10]	1.10 [0.90;1.20]	0.096
glcm_difference_entropy†*	1.70 [1.70;1.85]	1.70 [1.60;1.90]	1.80 [1.70;2.00]	0.111
glcm_difference_variance†*	0.70 [0.70;0.90]	0.70 [0.60;0.90]	1.00 [0.70;1.20]	0.027
glcm_dissimilarity†*	1.00 [0.90;1.05]	1.00 [0.80;1.10]	1.10 [0.90;1.20]	0.096
glcm_first_measure_of_information_correlation†*	-0.10 [-0.15;-0.10]	-0.10 [-0.10;-0.10]	-0.10 [-0.10;-0.10]	0.702
glcm_inverse_difference†*	0.60 [0.60;0.60]	0.60 [0.60;0.65]	0.60 [0.60;0.60]	0.084
glcm_inverse_difference_moment†*	0.60 [0.55;0.60]	0.60 [0.50;0.60]	0.60 [0.50;0.60]	0.077
glcm_inverse_difference_moment_normalized†*	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	.
glcm_inverse_difference_normalized†*	0.90 [0.90;0.90]	0.90 [0.90;0.90]	0.90 [0.90;0.90]	0.717
glcm_inverse_variance†*	0.50 [0.50;0.50]	0.50 [0.50;0.50]	0.50 [0.50;0.50]	0.347
glcm_joint_average†*	6.90 [5.85;8.15]	6.20 [5.90;7.70]	7.30 [6.50;8.30]	0.335
glcm_joint_entropy†*	4.70 [4.50;4.90]	4.60 [4.30;4.95]	5.00 [4.70;5.20]	0.029
glcm_joint_maximum†*	0.10 [0.10;0.10]	0.10 [0.10;0.10]	0.10 [0.10;0.10]	0.331
glcm_joint_variance†*	2.00 [1.55;2.25]	1.60 [1.35;2.40]	2.30 [1.80;2.90]	0.027
glcm_second_measure_of_information_correlation†*	0.60 [0.50;0.70]	0.60 [0.50;0.65]	0.60 [0.50;0.70]	0.470
glcm_sum_average†*	13.7 [11.8;16.3]	12.4 [11.8;15.4]	14.5 [12.9;16.5]	0.347
glcm_sum_entropy†*	3.30 [3.10;3.40]	3.20 [2.95;3.50]	3.50 [3.20;3.60]	0.059
glcm_sum_variance†*	5.20 [3.75;6.40]	4.30 [3.30;7.00]	6.40 [4.80;7.90]	0.045
gldzm_grey_level_nonuniformity	41.6 [25.3;90.2]	44.7 [23.1;83.9]	42.3 [22.0;84.0]	0.827
gldzm_grey_level_nonuniformity_normalised	0.10 [0.10;0.20]	0.20 [0.10;0.20]	0.10 [0.10;0.10]	0.003
gldzm_grey_level_variance	5.60 [5.05;7.60]	6.20 [4.65;8.00]	7.60 [6.60;9.40]	0.012
gldzm_high_grey_level_zone_emphasis	50.5 [42.0;79.0]	48.8 [38.5;63.2]	53.6 [44.3;78.8]	0.442
gldzm_large_distance_emphasis§	2.50 [1.65;3.65]	2.70 [1.80;3.65]	2.70 [1.80;6.10]	0.709
gldzm_large_distance_high_grey_level_emphasis§	107 [71.6;192]	167 [80.7;216]	129 [87.8;267]	0.603
gldzm_large_distance_low_grey_level_emphasis§	0.10 [0.10;0.15]	0.10 [0.10;0.20]	0.10 [0.10;0.20]	0.584
gldzm_low_grey_level_zone_emphasis	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.972
gldzm_small_distance_emphasis§	0.80 [0.70;0.90]	0.80 [0.70;0.90]	0.80 [0.70;0.90]	0.964
gldzm_small_distance_high_grey_level_emphasis§	44.7 [37.1;50.3]	41.1 [25.2;48.7]	43.9 [36.6;65.0]	0.515
gldzm_small_distance_low_grey_level_emphasis§	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.00 [0.00;0.10]	0.665
gldzm_zone_distance_entropy	3.80 [3.55;4.35]	4.10 [3.60;4.55]	4.20 [3.80;4.60]	0.342
gldzm_zone_distance_nonuniformity	211 [98.3;270]	159 [92.8;272]	180 [120;242]	0.970
gldzm_zone_distance_nonuniformity_normalised	0.60 [0.50;0.70]	0.60 [0.50;0.70]	0.60 [0.40;0.70]	0.924
gldzm_zone_distance_variance	0.60 [0.20;1.05]	0.60 [0.30;1.05]	0.50 [0.30;1.50]	0.867
gldzm_zone_percentage§	0.10 [0.10;0.10]	0.10 [0.00;0.10]	0.10 [0.10;0.10]	0.135
glrlm_grey_level_nonuniformity‡	5986 [2823;10223]	6001 [2708;10739]	6170 [3615;13394]	0.841
glrlm_grey_level_variance‡	2.10 [1.75;2.70]	1.90 [1.50;2.95]	2.90 [2.00;3.40]	0.012

(Continued)

TABLE 4 | Continued

	AA N = 23	H/L N = 15	NHW N = 33	P overall
glrlm_high_grey_level_run_emphasis*	46.6 [36.7;68.3]	40.4 [37.1;60.9]	53.9 [43.2;71.9]	0.342
glrlm_normalized_grey_level_nonuniformity‡	0.20 [0.20;0.20]	0.20 [0.20;0.20]	0.20 [0.20;0.20]	0.567
glszm_grey_level_nonuniformity‡	41.6 [25.3;90.2]	44.7 [23.1;83.9]	42.3 [22.0;84.0]	0.827
glszm_grey_level_variance‡	5.60 [5.05;7.60]	6.20 [4.65;8.00]	7.60 [6.60;9.40]	0.012
glszm_high_grey_level_zone_emphasis‡	50.5 [42.0;79.0]	48.8 [38.5;63.2]	53.6 [44.3;78.8]	0.442
glszm_large_zone_emphasis‡	13080 [4011;36509]	12030 [3365;33727]	7602 [2833;30157]	0.742
glszm_large_zone_high_grey_level_emphasis‡	3.89 [1.81;22.75]x10^5	4.01 [1.81;17.93]x10^5	3.88 [1.46;12.94]x10^5	0.884
glszm_large_zone_low_grey_level_emphasis‡	344 [88.8;608]	226 [120;932]	174 [51.7;622]	0.530
glszm_low_grey_level_zone_emphasis‡	0.00 [0.00;0.10]	0.00 [0.00;0.10]	0.00 [0.00;0.10]	0.814
glszm_normalised_zone_size_nonuniformity‡	0.30 [0.30;0.35]	0.30 [0.30;0.40]	0.30 [0.30;0.40]	0.677
glszm_normalized_grey_level_nonuniformity‡	0.10 [0.10;0.20]	0.20 [0.10;0.20]	0.10 [0.10;0.10]	0.003
glszm_small_zone_emphasis‡	0.60 [0.50;0.60]	0.60 [0.60;0.60]	0.60 [0.60;0.60]	0.023
glszm_small_zone_high_grey_level_emphasis‡	29.8 [24.5;46.5]	31.4 [24.7;37.2]	33.1 [27.5;53.3]	0.388
glszm_small_zone_low_grey_level_emphasis‡	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.445
glszm_zone_percentage‡	0.10 [0.10;0.10]	0.10 [0.00;0.10]	0.10 [0.10;0.10]	0.135
glszm_zone_size_entropy‡	5.10 [4.80;5.50]	4.80 [4.65;5.35]	5.30 [5.00;5.50]	0.085
glszm_zone_size_nonuniformity‡	111 [46.7;169]	129 [34.4;172]	108 [63.4;190]	0.981
glszm_zone_size_variance‡	12621 [3911;35884]	11642 [3255;33387]	7458 [2756;29728]	0.742
hu_kurtosis	3.58 [3.24;4.16]	3.34 [3.13;4.08]	3.49 [3.13;4.06]	0.723
hu_skewness	-0.20 [-0.35;0.02]	-0.05 [-0.26;0.13]	-0.10 [-0.30;0.28]	0.486
hu_uniformity	66.2 [56.6;71.3]	62.0 [34.1;72.3]	50.6 [30.6;59.1]	0.002
hu_uniformity_acr	-33.30 [-65.15;-10.45]	-49.20 [-116.95;-1.35]	-85.70 [-117.80;-41.00]	0.061
maximum_ct_number_hu	175 [160;210]	190 [151;238]	181 [159;231]	0.999
median_ct_number_hu	83.0 [67.0;94.5]	78.0 [39.0;90.5]	67.5 [41.0;82.0]	0.045
mesh_compactness_1_mm	20.9 [14.4;31.1]	22.4 [16.5;33.4]	23.9 [16.6;34.2]	0.895
mesh_compactness_2_mm	0.55 [0.43;0.63]	0.56 [0.50;0.67]	0.62 [0.53;0.68]	0.092
mesh_sa_to_volume_ratio	0.32 [0.26;0.42]	0.31 [0.26;0.39]	0.29 [0.24;0.38]	0.804
minimum_ct_number_hu	-30.00 [-57.50;-14.00]	-39.00 [-83.00;-15.00]	-58.00 [-74.00;-46.00]	0.021
ngldm_dependence_count_percentage‡	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	.
ngldm_dependence_energy‡	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.034
ngldm_dependence_entropy‡	5.80 [5.75;6.15]	5.80 [5.70;6.10]	6.00 [5.80;6.20]	0.212
ngldm_dependence_nonuniformity‡	380 [192;771]	326 [167;675]	331 [187;747]	0.994
ngldm_dependence_variance‡	11.4 [9.85;12.7]	10.1 [9.75;14.6]	10.4 [7.90;12.4]	0.466
ngldm_gl_nonuniformity‡	895 [485;2395]	720 [406;2023]	767 [386;1999]	0.808
ngldm_gl_variance‡	2.00 [1.55;2.45]	1.70 [1.35;2.60]	2.70 [1.80;3.20]	0.013
ngldm_high_dependence_emphasis‡	56.1 [45.9;67.8]	58.8 [48.2;78.6]	51.6 [37.8;62.7]	0.361
ngldm_high_dependence_high_gl_emphasis‡	2250 [1966;3719]	2594 [1677;3588]	2946 [1948;4005]	0.964
ngldm_high_dependence_low_gl_emphasis‡	1.10 [0.85;1.70]	1.50 [0.80;2.40]	1.00 [0.80;1.50]	0.330
ngldm_high_gl_dependence‡	49.9 [36.2;69.2]	39.7 [37.0;62.2]	54.4 [45.4;68.9]	0.360
ngldm_low_dependence_emphasis‡	0.10 [0.10;0.10]	0.10 [0.10;0.10]	0.10 [0.10;0.10]	0.088
ngldm_low_dependence_high_gl_emphasis‡	5.10 [3.45;5.75]	4.40 [2.20;6.40]	5.30 [3.80;8.20]	0.186
ngldm_low_dependence_low_gl_emphasis‡	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.00 [0.00;0.00]	.
ngldm_low_gl_dependence‡	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.879
ngldm_normalized_dependence_nonuniformity‡	0.10 [0.10;0.10]	0.10 [0.10;0.10]	0.10 [0.10;0.10]	0.034
ngldm_normalized_gl_nonuniformity‡	0.20 [0.20;0.20]	0.20 [0.20;0.30]	0.20 [0.20;0.20]	0.008
rms_of_ct_number_hu	89.6 [71.4;97.0]	83.9 [49.3;94.8]	74.3 [50.5;87.2]	0.067
sphericity	0.82 [0.75;0.86]	0.82 [0.79;0.87]	0.85 [0.81;0.88]	0.084
standard_deviation_of_ct_number_hu	27.2 [24.6;30.9]	25.6 [22.7;31.8]	32.3 [26.4;35.3]	0.014
surface_area_mm^2	2077 [1241;3104]	2215 [1464;3284]	1771 [1408;3043]	0.879
transverse_length_mm	26.0 [20.0;33.0]	24.0 [22.5;31.5]	25.0 [19.0;29.0]	0.716
volume_mm^3	5522 [2863;11750]	6748 [3892;13092]	6075 [4018;12569]	0.919
volumetric_length_mm	34.0 [25.0;39.0]	35.0 [26.0;45.0]	31.0 [28.0;38.0]	0.810
volumetric_mean_of_ct_number_hu	83.9 [67.2;93.8]	76.7 [40.1;90.5]	66.5 [41.0;79.5]	0.027
wavelet_hhl_10th_percentile_hu	-4.80 [-5.80;-4.00]	-5.30 [-5.85;-4.70]	-5.2 0[-6.90;-4.30]	0.310
wavelet_hhl_90th_percentile_hu	4.90 [4.10;5.85]	5.30 [4.65;5.80]	5.30 [4.30;7.00]	0.454
wavelet_hhl_coefficient_of_variation	320 [-92.90;753]	114 [-379.00;175]	-80.70 [-454.90;244]	0.163
wavelet_hhl_energy_hu^2	5.90 [3.08;15.48]x10^4	1.04 [0.29;1.87]x10^5	9.86 [4.00;15.98]x10^4	0.707
wavelet_hhl_entropy	12.0 [11.2;13.3]	11.7 [10.9;13.1]	11.8 [11.1;13.2]	0.980
wavelet_hhl_excess_kurtosis	0.10 [0.00;0.25]	0.20 [0.10;0.40]	0.20 [0.10;0.50]	0.104
wavelet_hhl_interquartile_range_hu	5.10 [4.25;6.10]	5.40 [4.90;5.95]	5.60 [4.70;7.20]	0.466
wavelet_hhl_minimum_hu	-16.20 [-19.05;-12.35]	-19.50 [-23.70;-13.75]	-17.80 [-28.80;-14.40]	0.163
wavelet_hhl_maximum_hu	16.6 [11.6;18.2]	18.5 [15.3;22.7]	18.3 [14.0;26.5]	0.129
wavelet_hhl_mean_deviation_hu	3.00 [2.50;3.60]	3.30 [2.90;3.55]	3.30 [2.70;4.30]	0.321

(Continued)

TABLE 4 | Continued

	AA N = 23	H/L N = 15	NHW N = 33	P overall
wavelet_hhl_mean_hu	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.854
wavelet_hhl_median_deviation_hu	3.00 [2.50;3.60]	3.30 [2.90;3.55]	3.30 [2.70;4.30]	0.326
wavelet_hhl_median_hu	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.00 [0.00;0.10]	0.653
wavelet_hhl_quartile_coefficient_of_dispersion	45.7 [-105.15;289]	34.2 [-81.30;63.6]	63.6 [-66.20;179]	0.315
wavelet_hhl_range_hu	32.4 [24.0;38.0]	39.7 [28.8;50.5]	35.9 [28.3;54.8]	0.157
wavelet_hhl_robust_mean_deviation_hu	2.10 [1.75;2.50]	2.20 [2.00;2.50]	2.30 [1.90;3.00]	0.442
wavelet_hhl_rms_hu	3.80 [3.20;4.60]	4.30 [3.65;4.55]	4.30 [3.40;5.50]	0.254
wavelet_hhl_skeweness	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.419
wavelet_hhl_variance_hu^2	14.3 [10.2;20.9]	18.3 [13.3;20.6]	18.8 [11.6;30.2]	0.218

Some P values are missing because they were unable to be estimated.

AA, African American; H/L, Hispanic/Latinx; NHW, non-Hispanic White; MM, millimeters; CT, computed tomography; HU, Hounsfield Units; GLCM, gray level cooccurrence matrix; AVG, average; VAR, variance; GLDZM, gray level distance zone matrix; American College of Radiology; SA, surface area; NGLDM, neighborhood gray-level different matrix; GL, gray level; RMS, root mean square; HHL, high-pass high-pass and low-pass filters.

*†gray leveled image; *ibsi by slice with merging; ‡as volume with full merging; §with full merging.*

Bold font indicates a P value < 0.05.

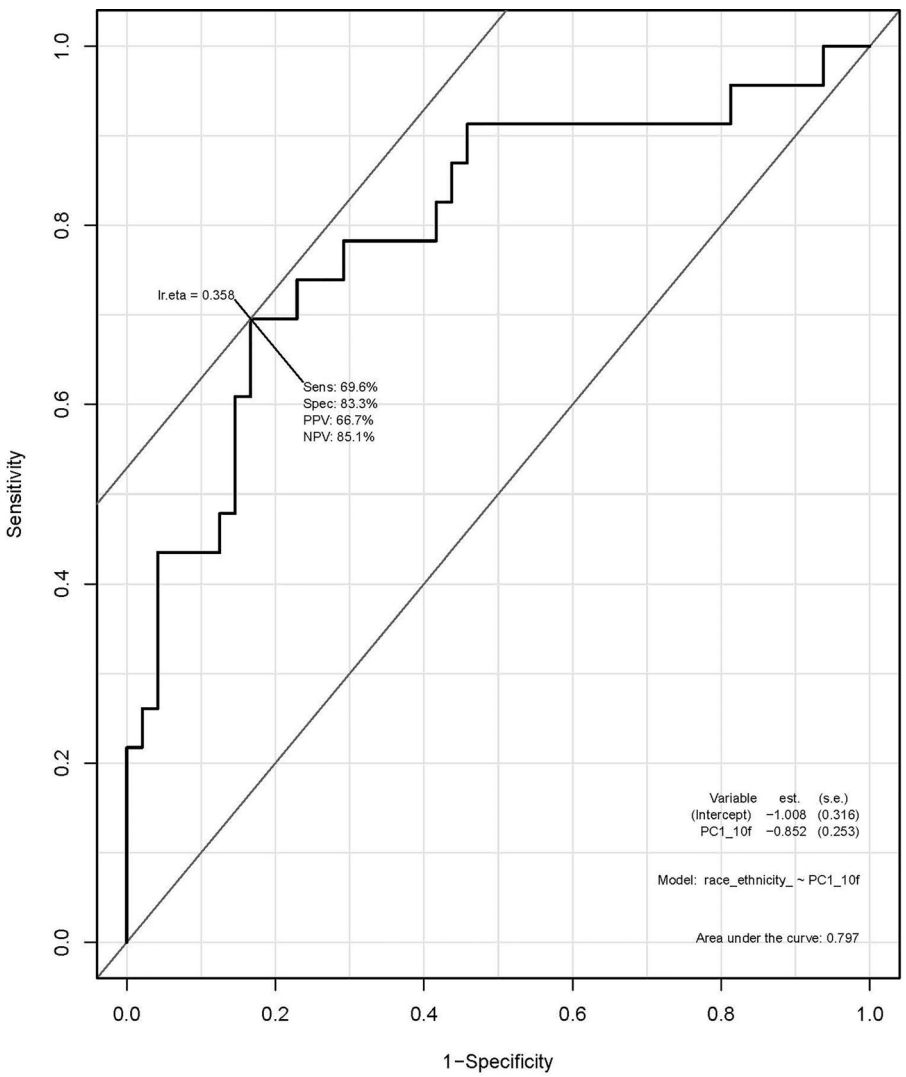


FIGURE 2 | Receiver operating characteristic (ROC) curve using principal component analysis to identify radiomic features predictive of race/ethnicity.

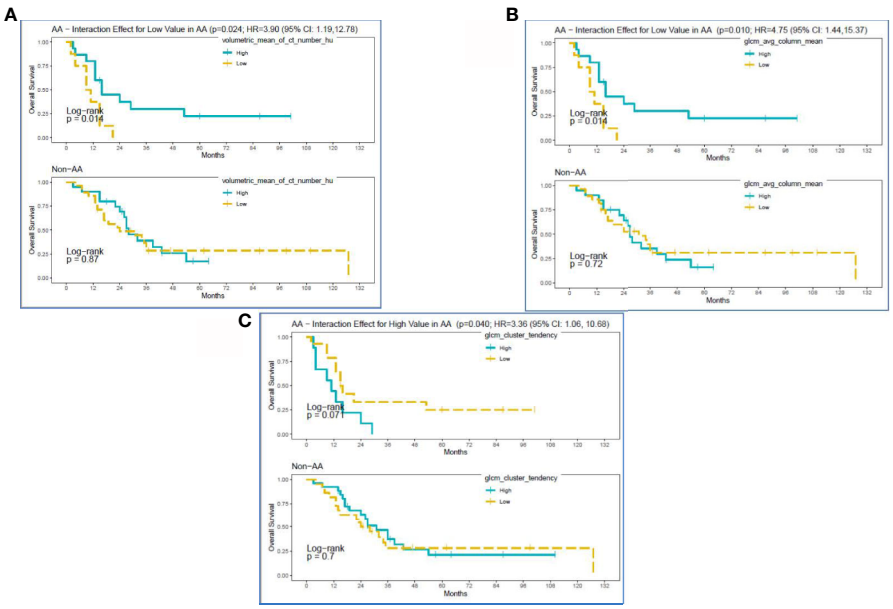


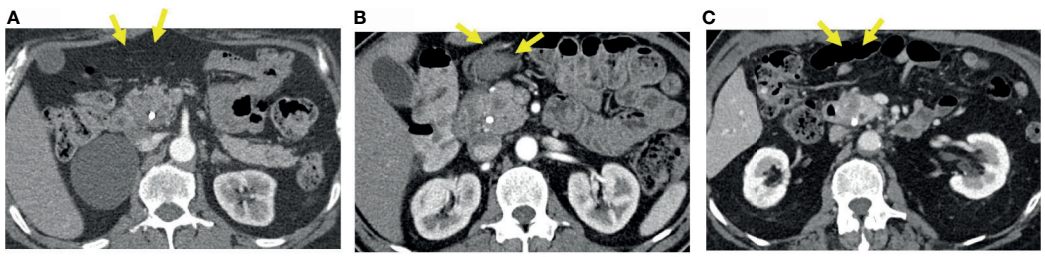
FIGURE 3 | Kaplan-Meier curves for significant interactions between radiomic features and overall survival among self-reported African American (AA) and Non-AA (Hispanic/Latinx, H/L; and Non-Hispanic White, NHW) groups according to **(A)** Volumetric Mean CT (HU), **(B)** GLCM Avg Column Mean, and **(C)** GLCM Cluster Tendency.

CT Procedures and Standard NCCN Imaging Criteria

No significant differences were observed between racial/ethnic groups in the scanner types used (p=0.512) or in the venous phase voxel volumes (p=0.303) (**Table 2**). Evaluation of standard imaging reporting criteria revealed three parameters that appeared to differ significantly between the three racial/ethnic groups. CT images from the AA group were found to have greater tumor involvement of the superior mesenteric vessels, as measured by degree of superior mesenteric artery (SMA) solid soft tissue contact (p=0.002), extension to the first SMA branch (p=0.036), and superior mesenteric vein (SMV) vessel narrowing and/or contour irregularity (0.033), when compared to NHW (**Table 3**).

Radiomic Features

A total of 135 textural and non-textural radiomic features were evaluated for their association with race/ethnicity. Kruskal-



- AA male 73y, moderately differentiated tumor grade
- Volumetric Mean of CT (HU) 58
- GLCM Avg Column Mean 58.1
- GLCM Avg Row Mean 57.8
- Deceased

- NHW male 61y, moderately differentiated tumor grade
- Volumetric Mean of CT (HU) 102
- GLCM Avg Column Mean 113.8
- GLCM Avg Row Mean 102
- Alive

- H/L male 73y, moderately differentiated tumor grade
- Volumetric Mean of CT (HU) 97.9
- GLCM Avg Column Mean 96.6
- GLCM Avg Row Mean 97.9
- Alive

FIGURE 4 | Axial venous phase CT images are presented in PDAC patients matched for tumor grade, gender, and age-group. Image **(A)** from an AA patient and shows a poorly defined hypoenhancing tumor marked by the yellow arrows. Image **(B)** in a NHW shows a similar radiologic appearance of the tumor but with significantly different radiomic tumor values. Image **(C)** in a Hispanic patient also had radiomic values different from the AA case. Note that a common bile duct stent is present in each of these patients.

Wallis test results indicated that 30 features were significantly associated with race/ethnicity (adjusted p<0.02; **Table 4**). Furthermore, 10 radiomic features were highly associated with race independent of tumor grade and included sphericity, volumetric mean Hounsfield units (HU), minimum HU, coefficient of variation HU, four gray level texture features, and two wavelet texture features (**Supplementary Table 1**). A multivariable model using principal component analysis to represent the radiomic signature yielded an area underneath the curve (AUC)=0.80 in differentiating AA *versus* non-AA (**Figure 2**).

Survival analysis identified the following non-correlated radiomic features with a significantly different survival difference between AA and non-AA (interaction effect between radiomic features and race with p<0.05): Volumetric Mean CT (HU) (HR: 3.90 (95% CI:1.19–12.78), p=0.024), GLCM Avg Column Mean (HR:4.75 (95% CI: 1.44,15.37), p=0.010), and GLCM Cluster Tendency (HR:3.36 (95% CI: 1.06–10.68), p=0.040) (**Supplementary Table 2**). Specifically, for Volumetric Mean CT and GLCM Avg Column Mean in tumors, low value of these radiomic features was associated with poorer survival among AA (**Figures 3A, B**). In contrast, survival curves overlapped between low and high groups of the radiomic features among non-AA. As a result, survival differences due to the radiomic features became differential between racial/ethnic groups (p=0.01–0.02). The GLCM Cluster Tendency (**Figure 3C**) had an opposite trend with high values associated with poorer survival among AA, but slightly improved survival among non-AA, leading to a significant differential survival difference between AA and non-AA (p=0.04). Furthermore, multivariate survival analysis indicated that Volumetric Mean CT (HU) and GLCM Avg Column Mean remain significantly associated with OS between AA and non-AA after adjustment for clinical-pathological features including age at diagnosis, gender, tumor size, tumor grade, and SEER-derived stage. Lower values of these radiomic features were associated with worse survival among AA (**Supplementary Table 3**).

Figure 4 reveals pretreatment CT images for three PDAC patients matched on tumor grade, gender, and age-group; lower radiomic values were observed among tumors from AA in volumetric mean CT HU and two GLCM texture features, compared to non-AA. These observations suggest that although the pancreatic tumors may appear similar on CT images, they reflect significantly different radiomic values associated with race/ethnicity and are predictive of overall survival.

DISCUSSION

We conducted the first investigation we are aware of to apply a radiomic approach to routine pretreatment CT scans from patients with PDAC to specifically explore associations with race/ethnicity and overall survival. Our analysis showed AA patients with low volumetric mean HU tumors had worse survival than similar tumors in non-AA. In PDAC, tumors with HU lower than surrounding pancreatic parenchyma have been correlated with worse outcomes (44). In our study, the low volumetric mean HU may be revealing a similar relationship to survival as the previously reported relative delta score, except that our measure is based in absolute HU as opposed to the delta score, which reflects relative differences in HU. Our analysis also demonstrated worse survival in AA patients having high coefficient of variation HU compared to similar tumors in non-AA, independent of key prognostic factors. The coefficient of variation HU is a reflection of tumor heterogeneity as it presents on CT based on voxel HU values, and it represents the standard deviation of the HU values within segmented tumors divided by the mean HU. Therefore, tumors with a wider range of different-appearing voxels within a tumor will have a larger coefficient of variation HU. In line with these findings, previous studies have shown that more heterogenous tumors are associated with high-grade dysplasia, resistance to anticancer therapies, and poorer prognoses (1, 45–48).

In this study, radiomics allowed us to preoperatively and non-invasively quantify the differences in appearance of pancreatic tumors across different racially and ethnically defined cohorts, even where the differences were not easy to visualize or describe qualitatively. We discovered multiple radiomic features that predict poor survival specifically in AA patients independent of other demographic and clinical factors. It is possible that these radiomic differences reflect inherent biological tumor differences specific to each ethnic group. Having potential poor prognostic biomarkers available in the pretreatment setting could influence clinical decisions and support earlier and more aggressive treatments that could reduce disparities for these underserved groups. Additionally, future studies correlating race/ethnicity-based radiomic features with tumor tissue-based biomarkers are needed to determine the capacity at which radiomics can be used in clinical decision-making workflows at the time of multidisciplinary tumor board.

We realize that the single-institutional retrospective design is prone to biases, but there is wealth in this exploratory investigation. Future prospective multicenter studies involving racially diverse cohorts of PDAC cases will be needed to continue to move PDAC disparities research forward. We plan to optimize and validate the most promising radiomic features and biomarkers in an independent cohort of AA PC cases using our multi-institutional Florida Pancreas Collaborative infrastructure (49). Furthermore, we plan to conduct a radiogenomic approach that integrates CT radiomic data with molecular biomarker data from pancreatic tumor tissue in order to uncover biological mechanisms to explain the disproportionate PDAC burden in AA.

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 Advarra IRB (MCC# 19431; IRB #: Pro00024543). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JP, DJ, and JC contributed to conception and design of the study. SV organized the database. JL and DT-C performed the statistical analysis. JP wrote the first draft of the manuscript, and JL, D-TC, DJ, and JC wrote sections of the manuscript. 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/fonc.2021.712950/full#supplementary-material

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ORIGINAL RESEARCH
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Access to Aboriginal Community-Controlled Primary Health Organizations Can Explain Some of the Higher Pap Test Participation Among Aboriginal and Torres Strait Islander Women in North Queensland, Australia

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Background: Aboriginal and Torres Strait Islander Community-Controlled Health Organisations (ACCHOs) provides culturally appropriate primary care for Aboriginal and Torres Strait Islander people in Australia. The population of North Queensland has a higher proportion of Aboriginal and Torres Strait Islander people, a greater population coverage of ACCHOs, and higher cervical screening participation than the Rest of Queensland. The association between regional differences in the use of ACCHOs for cervical screening and variations in screening participation among Aboriginal and Torres Strait Islander women is currently unknown.

Methods: This is a population-based study of 1,107,233 women, aged 20–69 years who underwent cervical screening between 2013 and 2017. Of these women, 132,972 (12%) were from North Queensland, of which 9% were identified as Aboriginal and Torres Strait Islander women (2% Rest of Queensland) through linkage to hospital records. Regional differentials in screening by Aboriginal and Torres Strait Islander status were quantified using participation rate ratios (PRRs) with 95% confidence intervals (CIs) from negative binomial regression models. Logistic regression was used to identify factors associated with Aboriginal and Torres Strait Islander women being screened at ACCHOs.

Results: Aboriginal and Torres Strait Islander women from North Queensland (*versus*) Rest of Queensland had higher odds of screening at ACCHOs after adjusting for age and

area-level variables. After adjustment for non-ACCHO variables, the regional differential in screening among Aboriginal and Torres Strait Islander women was significantly higher (PRR 1.28, 95% CI 1.20–1.37) than that among other Australian women [PRR = 1.11 (1.02–1.18)], but was attenuated on further adjustment for ACCHO variables, [PRR = 1.15, (1.03–1.28)] to become similar to the corresponding point estimate for other Australian women [PRR = 1.09, (1.01–1.20)]. However, the significant interaction between Aboriginal and Torres Strait Islander status and region ($p < 0.001$) remained, possibly reflecting the large cohort size. Screening participation increased with better access to health services for all women.

Conclusions: Improving access to primary health care for Aboriginal and Torres Strait Islander women, especially through ACCHOs, may reduce existing disparities in cervical screening participation. Further gains will require greater levels of local community engagement and understanding of the experiences of screened Aboriginal and Torres Strait Islander women to inform effective interventions.

Keywords: cervical cancer, Pap test, Aboriginal and Torres Strait Islander, inequalities, Australia

INTRODUCTION

Australian Aboriginal and Torres Strait Islander women experience a disproportionately high burden of cervical cancer (1, 2) despite a national population-based cervical screening program (NCSP) (3, 4) which, combined with high uptake of human papillomavirus vaccine (5), has led to population cervical cancer incidence and mortality rates in Australia being among the lowest worldwide (6).

On December 1, 2017, a renewed NCSP was implemented with five-yearly primary human papillomavirus (HPV)-based screening for women aged 25–74, replacing the original two-year Papanicolaou (Pap) test for those aged 20–69 years (4). Although both pathways involve clinical collection of a cervical sample suggesting that some of the factors impacting screening participation may be similar, this remains untested as the first population-based participation data for the renewed program will not be available until after 2022 (4).

National data on participation of Aboriginal and Torres Strait Islander women in the previous (Pap test based) NCSP are unavailable because pathology report forms, the primary source of information for cervical screening registers, did not routinely record Aboriginal and Torres Strait Islander status (1, 7). However, state-based studies using record linkage to identify Aboriginal and Torres Strait Islander women have reported substantially lower participation for Aboriginal and Torres Strait Islander women that have persisted over at least 10 years in Queensland, Australia (8–10). These studies also found that participation was higher among Aboriginal and Torres Strait Islander women, and other Australian women, living in North Queensland compared to the rest of the state (8, 9). North Queensland in this context refers to the northernmost and north west region of Queensland, including the cities of Cairns and Townsville, and has a distinctive regional character and identity (11). For example, in North Queensland, a higher proportion of the population are from more remote or disadvantaged areas, a lower proportion are from affluent areas, and a higher proportion identified as Aboriginal and Torres Strait Australians compared to total Queensland.

Compared to the Rest of Queensland, North Queensland has a higher proportion of the population who are identified as Aboriginal and/or Torres Strait Islander people (12) or who live in regional, remote, or disadvantaged areas (13). It also has a higher population coverage (14, 15) of Australian government-funded Aboriginal and Torres Strait Islander Community-Controlled Health Organisations (ACCHOs) (16). Ratios of ACCHO locations to populations are higher in north and western parts of Queensland and lower in the eastern parts of the state, particularly so for the south-east corner of the state (14). ACCHOs provide comprehensive, culturally appropriate, and accessible primary health care specifically for Aboriginal and Torres Strait Islander people (17, 18). They aim to be responsive to the needs of the local community and enable Aboriginal and Torres Strait Islander people's self-determination and empowerment (16, 18).

In Australia, cervical screening through the NCSP occurs mainly in primary care (with additional mobile health units) (1) and is provided at no cost for eligible women, though providers may charge a small service fee (19). Aboriginal and Torres Strait Islander women may either access mainstream or Aboriginal and Torres Strait Islander-specific primary health care services (mainly ACCHOs) (17). There is evidence that these services play a crucial role in delivering cervical screening (20, 21); in a semi-national clinical audit from 2005 to 2014, at least half of Aboriginal and Torres Strait Islander women who regularly attended these services had a two-yearly Pap test (21).

Previous studies have suggested that sustained participation in a program of continuous service improvement designed to identify and address barriers and facilitators to Pap smear screening led to higher cervical screening coverage among

Aboriginal and Torres Strait Islander women at ACCHOs (21, 22). Successful strategies included targeted culturally relevant health education, local community involvement, and establishment of specific women's health clinics with female practitioners (21, 22). Other facilitators include access to female practitioners and trained Aboriginal and Torres Strait Islander health workers to promote and perform screening tests which are associated with higher cervical (and breast) screening participation among screen-eligible Aboriginal and Torres Strait Islander women (23, 24). While enacting these enablers is important for long-term improvements in cervical screening, a more comprehensive understanding of the service and system level barrios (and facilitators) to screening is essential for the development of effective and culturally sensitive interventions to reduce the existing gap in cervical cancer incidence and mortality.

This population-based study used a large, linked dataset containing details of the cervical screening history and Aboriginal and Torres Strait Islander status of individual women to explore factors associated with attendance at ACCHOs for Pap tests among Aboriginal and Torres Strait Islander women living in North Queensland compared to the Rest of Queensland. We also quantified whether access to ACCHOs is associated with regional variations in five-year cervical screening participation among Aboriginal and Torres Strait Islander women and whether access to primary health care is associated with cervical screening among other Australian women.

METHODS

Ethical approval was obtained from the Queensland Metro South Human Research Ethics Committee (HREC/2018/QMS/44576). Data access and record linkage were approved by the office of the Director-General of Queensland Health, relevant data custodians, and the Queensland Data Linkage unit.

Regions

The geographical unit was the 2016 Statistical Area Level 2 (SA2) from the 2016 Australian Statistical Geography Standard, defined by the Australian Bureau of Statistics (ABS) as representing a community that interacts together socially and economically (25).

The North Queensland region was defined approximately as that part of Queensland north of latitude −20°. This region covers more than a third of the total land area (39% or 680,000 km^2) of Queensland (**Table 1**) and includes the major population centers of Cairns, Cooktown, Townsville, Mount Isa, and Charters Towers (**Supplementary File 1 Figure S1.1**). Based on 2016 SA2 boundaries, there are 80 SA2s that covered the entire North Queensland region without gaps or overlaps, each with varying land areas [median area 56 km^2, interquartile range (IQR): 9 to 945 km^2] and population (median: 5,924, IQR: 4,082 to 8,732).

The remaining area of Queensland, comprising 448 SA2s, (median area 12 km^2 IQR: 5 to 64 km^2; population median 8,191; IQR: 5,289 to 12,074) is referred to here as "Rest of Queensland".

TABLE 1 | Regional characteristics, Queensland, Australia 2017.

Region characterisitcs[1-7]	North Queensland	Rest of Queensland
Percent of geographical area covered	39.3	60.7
Percent of total Queensland population (persons)	11.4	88.6
Percent of population (persons) who…		
are Aboriginal and Torres Strait Islander	14.4	3.3
live in remote areas	11.4	0.9
live in major cities	0.0	72.2
live in disadvantaged areas	26.4	17.1
live in affluent areas	10.1	19.8
live within 30 min of a Pap test provider	96.1	98.7
live within 30 min of an ACCHO Pap test provider	85.0	80.8
live more than 1 h of an ACCHO Pap test provider	5.9	2.8
live within 30 min of a non-ACCHO Pap test provider	94.9	98.7
live more than 1 h of a non-ACCHO Pap test provider	1.6	0.04
Number of 2016 Statistical Area Level 2	80	448

ACCHO, Aboriginal Community-Controlled Health Organisation.
1. Census and population data were obtained from the Australian Bureau of Statistics.
2. Indigenous population data for Queensland was obtained from the Queensland Treasury.
3. Statistical Area Level 2 (SA2) from the 2016 Australian Statistical Geography Standard (ASGS).
4. Remote areas were defined by the Remoteness Areas 2016 classification (combines Remote and Very Remote).
5. 'Affluent areas' are the 20% of most advantaged Statistical Areas 2 (SA2s) and 'Disadvantaged areas' are the 20% of most disadvantaged SA2s as defined by the 2016 SEIFA Index of Relative Socioeconomic Advantage and Disadvantage obtained from the Australian Bureau of Statistics.
6. Pap test providers based on medical centers or general practitioner practices. One center or practice may have multiple health professionals who provide Pap tests.
7. Based on travel time from a SA2 (2016) at screening to geocoded residential street address of a Pap test provider.

Study Cohort

The study cohort comprised all female residents of Queensland, aged 20 to 69 years, who had a Pap test between January 1, 2013 and December 31, 2017. Aboriginal and Torres Strait Islander women in the NCSP were identified through linking the population-based Queensland Health Pap Smear Register (PSR), which during the study period collated all Pap tests performed state-wide (with the renewed NCSP there has been a transition to the National Cancer Screening Register), and the Queensland Hospital Admitted Patient Data Collection (QHAPDC) (26) that has accurate information on Aboriginal and Torres Strait Islander status (27).

Full details of the data extraction and record linkage process have been described previously (8). Briefly, records were extracted from the Queensland Health PSR for all Pap tests (and cervical-related histology tests) performed between January 1, 2012 and December 31, 2017 for women aged 15–69 years, who had not opted off the register. Records for all women who had been discharged at least once from public and private Queensland hospitals between April 1, 2000 (July 1, 2007 for private hospitals) and December 31, 2017 (inclusive) were

extracted from the QHAPDC for all women aged 15–69 years during the 2012–2017 calendar period. The two extracts were then linked using a combination of deterministic and probabilistic methods, including clerical review (26). Based on unpublished advice from the Linkage Unit, 81% of the Queensland Health PSR cohort was successfully linked to the QHAPDC.

Aboriginal and Torres Strait Islander status was determined using a standard majority-based algorithm (28, 29) with a woman in the Queensland Health PSR coded as Aboriginal and Torres Strait Islander if at least 50% of her linked QHAPDC records within the study period identified her as being Aboriginal and Torres Strait Islander. The 'majority-based algorithm' is one of four standard algorithms recommended by the Australian Institute of Health and Welfare (Australia's national agency for health and welfare related statistics) for the assignment of Indigenous status, thereby ensuring consistency both within and across administrative data sets (28, 29). All other linked women, and those who did not match to at least one QHAPDC record, were classified as other Australian. Information on the ethnicity of other Australian women was not available.

Previous sensitivity analyses (28, 29) indicated that the proportion of Aboriginal and Torres Strait Islander women in the linked dataset ranged from 2.3 to 2.5% based on four standard algorithms.

Geographical Area at Screening

Residential suburb and postcode for each Pap test record were mapped to the 2016 SA2 boundaries using population weighted geographic correspondence (30). If the address information for a given record was insufficient to assign the SA2, information from the closest (by date) record for the same woman with viable information was used. Women lacking geographical information for all records were excluded (n = 6,076, 79 Aboriginal and Torres Strait Islander).

Area-level socio-economic status (SES) was assessed using the 2016 census-based Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD) from the Australian Bureau of Statistics (31). The IRSAD is a composite measure of SES incorporating multiple measures of advantage and disadvantage including occupation, income, and education (31). Each SA2 was allocated an IRSAD score and then ranked into five quintiles of increasing disadvantage (**Table 2**). Remoteness was measured using the 2016 Remoteness Areas (32) classification, a purely geographic measure of relative access to services. The five remoteness areas were major cities, inner regional, outer regional, remote, and very remote. Each SA2 was categorized as having a low (<2.0%) or high (≥2.0%) proportion of Aboriginal and Torres Strait Islander women based on the 2016 Australian Census (33); 2.0% was chosen as the cut-off because this allocated approximately half the Aboriginal and Torres Strait Islander female population to each category.

Pap Test Providers

The term 'Pap test provider' is used in this paper to refer to the health care center where a Pap test was performed. A center may have multiple medical professionals who carried out Pap tests.

Information on the name and street address of Pap test providers was extracted from the Queensland Health PSR records for all women in the study cohort and geocoded to assign the corresponding SA2. Each unique provider (based on name and address details) was classified as an ACCHO if it matched with the published names and address details of an ACCHO in Queensland sourced from the National Aboriginal Community Controlled Health Organisation website (34) and links to the individual websites of all National Aboriginal Community Controlled Health Organisation members that were accessed from there. Unmatched geocoded providers were classified as non-ACCHO. Providers with missing address information and those located interstate, which could not be geocoded, were categorized as 'unknown'. Syntax searching in Stata was used during the matching process to consider the possibility of alternative spellings, synonyms, and abbreviations in the recorded provider information including Indigenous Health, IPHC, ACCHO, Aboriginal and Torres Strait Islander, Aboriginal & Torres Strait Islander Health, Aboriginal Health and ATSICHS, with this process refined through several iterations.

Geographical Information System software and a street network database were used to calculate road travel times from the centroid of residential SA2 of each woman at the time of screening to the geocoded location of the actual provider used for their Pap test. Corresponding travel times were also calculated from each provider to each of the 528 SA2s in Queensland to determine, for each SA2, the closest ACCHO or non-ACCHO facility. If both ACCHO and non-ACCHO health facilities were equidistant to a given SA2, the closest provider was set to ACCHO.

Estimated Resident Population

Population estimates for Queensland women by Aboriginal and Torres Strait Islander status, age, and SA2 across Queensland over the study period (35) were adjusted using age-specific hysterectomy fractions (1) to exclude women who had a hysterectomy from the population eligible for cervical screening. We used the same fraction for all women across all geographical areas because these fractions are not available by SA2 or by Aboriginal and Torres Strait Islander status (9). Although lower hysterectomy rates for Aboriginal and Torres Strait Islander women have been reported (36), the impact of this for our cohort is likely to be minimal given the younger age distribution for screened Aboriginal and Torres Strait Islander women (**Table 2**) and the lower hysterectomy rates among younger women (1).

We had no data on the catchment population for each of the providers, hence screening participation rates could not be calculated based on 'actual Pap test provider'.

Statistical Analysis

All statistical analyses were performed using Stata/SE (Version 16.1, Special Edition; Stata Corporation, College Station, TX, United States). Maps were generated using MapInfo Professional (version 16.0, Pitney Bowes, Stamford CT, United States).

TABLE 2 | Characteristics of screened women, Queensland 2013–2017 by region and Aboriginal and Torres Strait Islander status at time of first Pap test.

Variable	North Queensland (n = 132,972)		Rest of Queensland (n = 974,261)	
	Aboriginal and Torres Strait Islander (%) (n = 11,944)	other Australian (%) (n = 121,028)	Aboriginal and Torres Strait Islander (%) (n = 15,225)	other Australian (%) (n = 959,036)
Age group (years)				
20–29	33.8	24.3	36.6	23.4
30–39	26.3	23.9	24.7	24.4
40–49	21.3	22.6	20.5	22.6
50–59	12.5	18.0	12.4	17.5
60–69	6.1	11.2	5.8	12.1
Aboriginal and Torres Strait Islander female (%)[1]				
Low (<2.0%)	0.6	4.1	26.3	56.6
High (≥2.0%)	99.4	95.9	73.7	43.4
Area-level disadvantage[2]				
Most advantaged	0.7	4.8	8.0	23.5
Advantaged	5.5	20.1	14.4	24.2
Middle SES	14.5	23.5	17.1	20.7
Disadvantaged	25.1	27.8	24.7	16.0
Most disadvantaged	54.2	23.8	35.8	15.6
Remoteness[3]				
Major cities	0	0	52.8	74.3
Inner regional	0	0	32.9	20.6
Outer regional	59.6	92.3	10.7	4.2
Remote	18.2	5.9	1.5	0.5
Very remote	22.2	1.8	2.1	0.4
Actual Pap test provider[4,5]				
ACCHO	24.9	0.8	16.9	0.3
Non-ACCHO	60.2	90.9	72.2	93.3
Unknown	14.9	8.3	10.9	6.4
Closest Pap test provider[4,6]				
ACCHO	72.4	86.8	78.5	82.3
Non-ACCHO	18.0	1.5	0	0
Both	9.6	11.7	21.5	17.7
Number ACCHO providers[4,7]				
None	43.5	77.4	74.8	88.8
One	10.8	8.3	15.2	7.7
Two to four	23.1	11.6	9.2	3.3
Five or more	22.6	2.7	0.8	0.2
Number non-ACCHO providers[4,7]				
None	12.1	6.6	2.3	2.2
One	9.1	7.8	5.5	5.7
Two to four	29.7	32.5	22.1	22.1
Five to nine	30.5	27.5	31.5	37.5
10 or more	18.6	25.6	38.6	32.5
Travel time closest ACCHO provider[6]				
<30 min	80.9	86.4	76.8	81.7
30 min-1 hour	15.4	7.7	18.0	15.2
1-2 hours	3.4	5.3	3.9	2.9
2-5 hours	0.3	0.6	1.3	0.2
Travel time closest non-ACCHO provider[6]				
<30 min	81.2	96.9	95.9	98.4
30 min-1 hour	9.6	1.7	3.6	1.5
1-2 hours	1.4	0.1	0.5	0.1
2-5 hours	7.8	1.3	0	0

ACCHO, Aboriginal Community-Controlled Health Organisation; SES, socio-economic status.

1. Based on 2016 Australian Census.

2. Area-level disadvantage was defined by the 2016 SEIFA Index of Relative Socioeconomic Advantage and Disadvantage.

3. Remote areas were defined by the Remoteness Areas 2016 classification.

4. Provider refers to Pap test providers and are based on medical centers or general practitioner practices, that may have multiple health professionals who provide Pap tests.

5. Actual Pap test provider is the provider where a screened woman in the cohort had her first (index) Pap test during study period.

6. Based on travel distance from 2016 Australian Statistical Geography Statistical Area Level 2 (SA2) at screening to geocoded street address of a Pap test provider.

7. Number providers by 2016 Australian Statistical Geography Statistical Area Level 2 (SA2) at screening which is based on suburb and postcode of residence of a woman when screened.

Screening Participation

The outcome variable for this analysis was the cervical screening participation rate within the five-year time period of 2013 to 2017. Overall participation for the five-year screening interval of 2013–2017 was calculated as the age-specific number of screened women aged 20–69 divided by the estimated resident population [ERP, (**Supplementary File 1 Figure S1.2**), directly age-standardized (2001 Australian standard population). Estimates were calculated separately for Aboriginal and Torres Strait Islander women and other Australian women over the two regions: North Queensland and Rest of Queensland. Five-year intervals were chosen to be consistent with the current five-year screening interval for the NCSP (4). The participation rate measure is person-based, with a woman considered to have participated within the 2013–2017 time period if she was screened at least once during that time period. Women who had multiple screens within that 5-year time period were only counted once.

Regional Differential in Screening by Aboriginal and Torres Strait Islander Status

The regional differential (North Queensland *versus* Rest of Queensland) in five-year screening participation was quantified using negative binomial regression models, stratified by Aboriginal and Torres Strait Islander status. These models were chosen to account for extra-Poisson variation in the data. Details of the first (index) Pap test in the five-year study period were retained. The outcome variable was the number of screened women with the exposure variable being the corresponding population defined by age group and SA2.

Two models were fitted: the first was adjusted for region, age at screening, area-level SES, remoteness, and Aboriginal and Torres Strait Islander population (%). We further adjusted for ACCHO variables: closest Pap test provider type (ACCHO, non-ACCHO) and number of ACCHO providers (per screening SA2) as well as number of non-ACCHO providers (per screening SA2). Variables relating to travel time to closest ACCHO or non-ACCHO Pap test provider were not included in the final multivariate model because their inclusion did not improve model fit (*i.e.*, $p \geq 0.20$ for likelihood ratio tests of models with and without each variable). Their inclusion or exclusion also did not alter the magnitude and confidence intervals of the coefficients for the other key variables in the models.

All models were initially stratified by Aboriginal and Torres Strait Islander status, and then a combined fully adjusted model (non-ACCHO and ACCHO variables) including interaction terms between each variable and Aboriginal and Torres Strait Islander status was fitted to test whether individual effects were different for Aboriginal and Torres Strait Islander than other Australian women.

Results are presented as Participation Rate Ratios (PRRs) with 95% Confidence intervals (CIs) which were calculated by exponentiating the coefficients from the negative binomial models. Individual coefficients and interaction terms were assessed with the Wald test (significant if $p \leq 0.05$, two-sided).

Predictors of Screening at ACCHOs for Aboriginal and Torres Strait Islander Women

The study cohort for this separate analysis was restricted to Aboriginal and Torres Strait Islander women for whom there was sufficient locational information to classify the provider of their index Pap test as ACCHO or non-ACCHO. Logistic regression was then used to identify independent factors associated with Aboriginal and Torres Strait Islander women being screened at an ACCHO.

Models were developed in a stepwise manner, starting with the full model that included age, region, SES, remoteness, and Aboriginal and Torres Strait Islander female population (%). Variables were then dropped from subsequent models based on likelihood ratio tests ($p \geq 0.20$). Once dropped, each variable was given the opportunity to re-enter subsequent models.

Second-order interaction terms between each variable in the final main-effects multivariable model and region were also fitted to test whether effects varied by region.

Exponentiated coefficients from these models are presented as odds ratios (ORs) with 95% CI.

RESULTS

Regional Characteristics

In 2017, about 11.4% of the total population of Queensland lived in North Queensland. A higher proportion of the North Queensland population (than the Rest of Queensland) were Aboriginal and Torres Strait Islander people (14.4 *versus* 3.3%) and lived in remote (11.4 *versus* 0.9%) or disadvantaged (26.4 *versus* 17.1%) areas (**Table 1**). North Queensland also had a higher coverage of ACCHOs by population of Aboriginal and Torres Strait Islander women aged 20–69 years (**Supplementary File 1 Figure S1.3**). However, 10% of SA2s in North Queensland were at least 1 h travel time from their closest ACCHO compared to around 4% in Rest of Queensland.

Study Cohort

The initial cohort comprised 1,169,762 (28,530 Aboriginal and Torres Strait Islander) female residents of Queensland aged 20–69 years with known geographical information on address at screening who underwent a total of 2,396,250 Pap tests between January 1, 2012 and December 2017. For consistency with five-year screening rates, women who were screened in 2012 were dropped to give the final cohort of 1,107,233 women (27,169 Aboriginal and Torres Strait Islander) with 1,992,810 Pap test records.

Of these women, 132,972 (12.0% of cohort) lived in North Queensland with 233,019 Pap test records, of which 11,944 (8.9%) were identified as Aboriginal and Torres Strait Islander with 20,102 records. There were 974,261 women who lived in the Rest of Queensland, of which 15,225 (1.6%) were Aboriginal and Torres Strait Islander with 25,681 records (**Table 2**).

The proportion of Aboriginal and Torres Strait Islander women who had their index screen at an ACCHO was higher in North Queensland than the Rest of Queensland; with <1% of

other Australian women screened at an ACCHO (**Table 2**). Most women who screened at an ACCHO were Aboriginal and Torres Strait Islander (North Queensland 76%; Rest of Queensland 52%).

More than four out of five women (86% other Australian; 80% Aboriginal and Torres Strait Islander) had their index screen at their closest provider.

Screening Participation

Overall

Overall, Aboriginal and Torres Strait Islander women had significantly lower participation than other Australian women for both regions during 2013–2017 (**Supplementary File 2**). However, participation was higher for Aboriginal and Torres Strait Islander women in North Queensland than the Rest of Queensland. For example, the five-year participation rate was higher in North Queensland than Rest of Queensland by around 30% for Aboriginal and Torres Strait Islander women and 8% for other Australian women.

Regional Differential in Screening by Aboriginal and Torres Strait Islander Status

After adjustment for age, area-level SES, remoteness, and percentage of the female population who were Aboriginal and Torres Strait Islanders, Aboriginal and Torres Strait Islander women living in North Queensland were 28% more likely (PRR 1.28, 95% CI 1.20–1.37) to have participated in cervical screening than those from the Rest of Queensland. This regional differential was significantly higher than that for other Australian women (PRR = 1.11, 95% CI 1.02–1.18) with a significant interaction between Aboriginal and Torres Strait Islander status and region.

After further adjustment for closest Pap test provider type (ACCHO, non-ACCHO), number of ACCHO providers (per screening SA2), and number of non-ACCHO providers (per screening SA2), the regional differential for Aboriginal and Torres Strait Islander women was reduced to 15% (PRR = 1.15, 95% CI 1.03–1.28) (**Table 3** and **Figure 1**) similar to the corresponding point estimate for other Australian women. The significant interaction between Aboriginal and Torres Strait Islander status and region, however, remained, possibly reflecting the large cohort size.

For both groups of women, screening participation was lower in older women. For Aboriginal and Torres Strait Islander women only, participation was higher among those from remote areas or areas with higher Aboriginal and Torres Strait Islander female population (**Figure 1**). While for Aboriginal and Torres Strait Islander women, screening was higher among more disadvantaged women, it decreased with increasing disadvantage for other Australian women. The effect of age did not vary by Aboriginal and Torres Strait Islander status (**Table 3**), whereas the corresponding interaction term for SES, remoteness, or Aboriginal and Torres Strait Islander female population (%) were statistically significant.

Aboriginal and Torres Strait Islander women were 11% more likely to be screened if the closest Pap test provider was an ACCHO than a non-ACCHO (**Table 3**). Screening participation increased with better access to any Pap test provider (ACCHO, non-ACCHO) as measured by the number of corresponding providers (per screening SA2) for both Aboriginal and Torres Strait Islander and other Australian women.

Predictors of Screening at ACCHOs for Aboriginal and Torres Strait Islander Women

The study cohort for this analysis consisted of 24,590 Aboriginal and Torres Strait Islander women, who had their index Pap test either at an ACCHO or non-ACCHO in Queensland. Of these women, 10,606 (43.1%) women lived in North Queensland and 13,984 (56.9%) in Rest of Queensland.

After adjusting for age and area-level variables, Aboriginal and Torres Strait Islander women from North Queensland (compared to Aboriginal and Torres Strait Islander women in the Rest of Queensland) were 2.6 times more likely to have their index screen at an ACCHO (**Table 4** and **Figure 2**). Use of ACCHOs for Pap tests was also independently higher among older women and those from areas with higher Aboriginal and Torres Strait Islander female population (%) or disadvantaged areas. Those not living in outer regional areas were also more likely to be screened at an ACCHO (**Table 4**).

There was no statistical evidence that the effect of SES, the percent of the population who were Aboriginal and Torres Strait Islander or remoteness varied by region. However, the interaction between age group or SES and region was statistically significant. Increasing age was associated with higher odds of screening at an ACCHO only among Aboriginal and Torres Strait Islander women in Rest of Queensland, while those living in most disadvantaged areas were more likely to be screened at an ACCHO in North Queensland.

DISCUSSION

Cervical screening participation in 2013–2017 was higher among all women in North Queensland than among those in the Rest of Queensland. Although adjusting for ACCHO-related variables (closest Pap test provider type, number of ACCHO and non-ACCHO providers) reduced this regional difference among Aboriginal and Torres Strait Islander women, some regional variations remained, the magnitude of which was similar for Aboriginal and Torres Strait Islander and other Australian women. In other words, despite these adjustments, screening among Aboriginal and Torres Strait Islander women from North Queensland was still higher than the rest of the state. In addition, Aboriginal and Torres Strait Islander women from North Queensland were more likely to have their index Pap test at an ACCHO than those from Rest of Queensland even after adjustment for age and area-level factors.

This study indicates that access to ACCHOs may explain at least part of the regional variation in cervical screening participation for Aboriginal and Torres Strait Islander women in Queensland. There is evidence that physical access to ACCHOs and their coverage relative to Aboriginal and Torres

TABLE 3 | Participation rate ratios (PRR) [95% CI] for cervical screening by region, for Aboriginal and Torres Strait Islander women aged 20–69 years, Queensland, Australia, 2013–2017.

Variable	Adjusted Participation rate ratios [95% CI][1,2,3]		Interaction (Aboriginal and Torres Strait Islander status, variable) *p*-value[4]
	Aboriginal and Torres Strait Islander	other Australian	
Region	$p < 0.001$	$p = 0.011$	$P < 0.001$
Rest of QLD	1.00	1.00	
North QLD	1.15 [1.03, 1.28]	1.09 [1.01, 1.20]	
Age group (years)	$p < 0.001$	$p < 0.001$	$P = 0.072$
20–29	1.00	1.00	
30–39	0.90 [0.86, 0.95]	0.87 [0.84, 0.89]	
40–49	0.83 [0.78, 0.87]	0.81 [0.79, 0.84]	
50–59	0.72 [0.68, 0.77]	0.72 [0.70, 0.74]	
60–69	0.60 [0.56, 0.65]	0.59 [0.57, 0.61]	
Aboriginal and Torres Strait Islander female (%)[5]	$p < 0.001$	$p < 0.001$	$p < 0.001$
Low (<2.0%)	1.00	1.00	
High (≥2.0%)	1.09 [1.02, 1.17]	0.93 [0.89, 0.96]	
Area-level disadvantage[6]	$p = 0.033$	$p = 0.078$	$p < 0.001$
Most advantaged	1.00	1.00	
Advantaged	1.07 [0.97, 1.19]	0.91 [0.82, 1.00]	
Middle SES	1.04 [0.93, 1.16]	0.91 [0.81, 1.01]	
Disadvantaged	1.15 [1.02, 1.29]	0.89 [0.78, 1.01]	
Most disadvantaged	1.16 [1.03, 1.32]	0.84 [0.73, 0.97]	
Remoteness[7]	$p = 0.004$	*p= 0.056*	$p < 0.001$
Major cities	0.95 [0.86, 1.06]	1.09 [0.93, 1.27]	
Inner regional	0.91 [0.83, 0.99]	0.91 [0.79, 1.05]	
Outer regional	1.00	1.00	
Remote	1.31 [1.16, 1.49]	1.01 [0.79, 1.30]	
Very remote	0.89 [0.77, 1.02]	0.97 [0.75, 1.24]	
Closest Pap test provider[8,9,]	$p < 0.001$	$p = 0.062$	$p < 0.001$
Non-ACCHO	1.00	1.00	
ACCHO[10]	1.11 [1.03, 1.19]	0.93 [0.84, 1.00]	
Number ACCHO providers[8,11]	$p < 0.001$	$p = 0.019$	$p < 0.001$
None	1.00	1.00	
One	1.25 [1.13, 1.37]	1.19 [1.03, 1.36]	
Two to four	1.23 [1.10, 1.36]	1.15 [1.01, 1.36]	
Five or more	1.28 [1.04, 1.56]	1.43 [1.03, 1.99]	
Number non-ACCHO providers[8,11]	$p < 0.001$	$p = 0.013$	$p < 0.001$
None	1.00	1.00	
One	1.18 [1.02, 1.37]	1.13 [0.97, 1.33]	
Two to four	1.16 [1.02, 1.31]	1.13 [1.01, 1.30]	
Five to nine	1.16 [1.03, 1.32]	1.21 [1.05, 1.38]	
10 or more	1.39 [1.23, 1.58]	1.25 [1.09, 1.44]	

ACCHO, Aboriginal Community-Controlled Health Organisation; CI, confidence Interval.

1. Estimated using negative binomial models, with outcome being number of screened women and offset the number of eligible women.

2. P-values from Wald's joint test of coefficients for multivariate negative binomial regression.

3. Estimated from fully adjusted main effect negative binomial models stratified by Aboriginal and Torres Strait Islander status.

4. P-values from Wald's X^2 test for interaction effect from fully adjusted main-effects model with interaction term between each independent variable and Aboriginal and Torres Strait Islander status.

5. Based on 2016 Australian Census.

6. Area-level disadvantage was defined by the 2016 SEIFA Index of Relative Socioeconomic Advantage and Disadvantage.

7. Remote areas were defined by the Remoteness Areas 2016 classification.

8. Provider refers to provider of a Pap test and is based on medical centers or general practitioner practices that may have multiple health professionals who provide Pap tests.

9. Based on travel distance from 2016 (SA2) at screening to geocoded street address of a Pap test provider.

10. The category ACCHO includes those SA2's for which the closest Pap test provider is either an ACCHO or both (ACCHO, non-ACCHO).

11. Number providers by 2016 Australian Statistical Geography Statistical Area Level 2 (SA2) for a woman at screening.

Strait Islander population vary geographically across Australia (14, 15). In particular, there appear to be fewer ACCHOs (and other government-funded Aboriginal and Torres Strait-specific primary care organizations) in Central and Eastern Queensland, whereas higher population-based coverage of ACCHOs has been reported for North Queensland (14, 15).

The key goal of ACCHOs is to deliver comprehensive and culturally competent primary health care that is accessible and appropriate to the needs of Aboriginal and Torres Strait Islander people (17, 37). ACCHOs often employ Aboriginal and Torres Strait Islander health workers (37) and facilitate increased local community involvement, empowerment, and self-determination (16, 18).

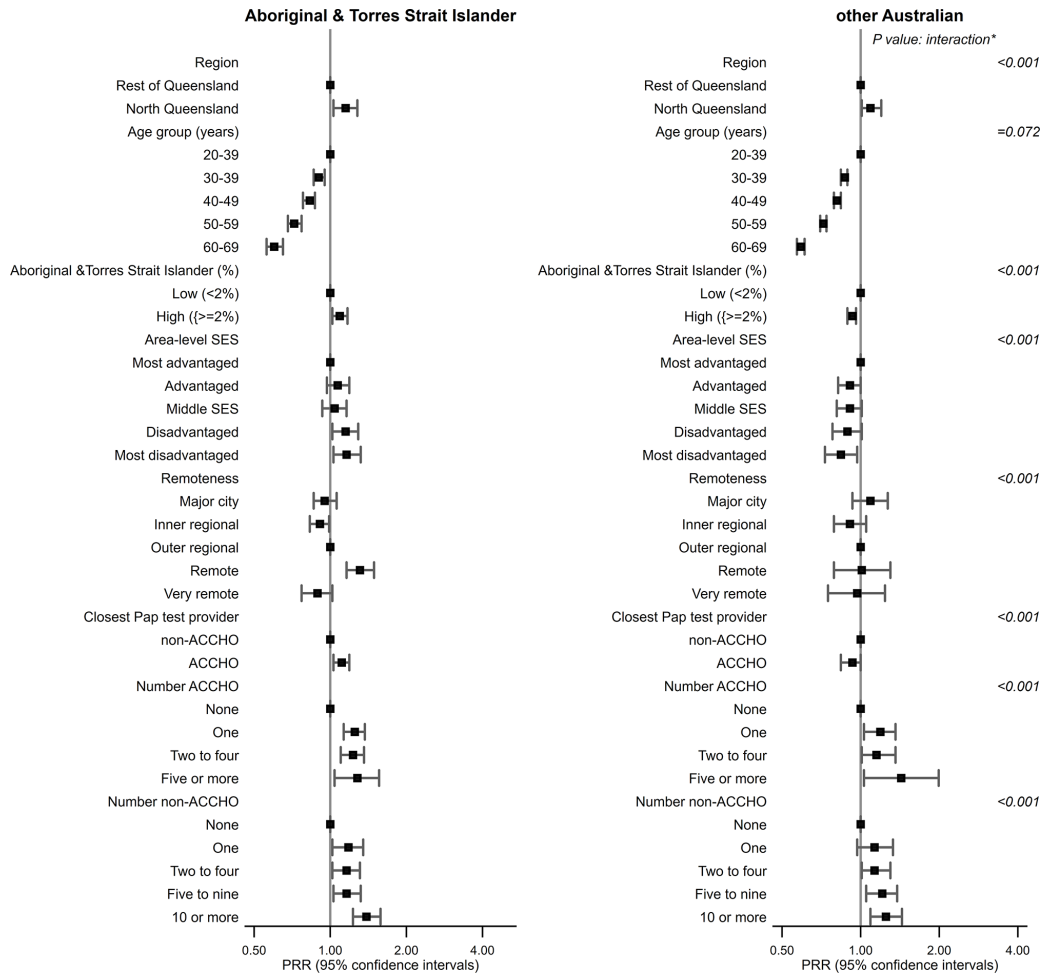

FIGURE 1 | Plot of participation rate ratios (PRRs) with 95% confidence intervals for factors associated with screening participation, by region and Aboriginal and Torres Strait Islander status, Queensland (QLD) 2013–2017. SES, socio-economic status; ACCHO, Aboriginal Community-Controlled Health Organisation; PRR, Participation Rate Ratios. *interaction term between Aboriginal & Torres Strait Islamder status and each variable.

Although there is a greater choice of screening providers in more urban areas, such services may not always be accessible or appropriate for Aboriginal and Torres Strait Islander women reflecting social, cultural, and system-level factors. Lower numbers of ACCHOs and other organizations providing primary health care specifically for Aboriginal and Torres Strait Islander people are also located in major cities compared to rural areas (17). By contrast, in remote and very remote areas, ACCHOs may be the only primary health care option for Aboriginal and Torres Strait Islander people (37), although only a very small proportion (4%) of other Australians are screened at an ACCHO. These factors may be reflected in the higher screening participation among Aboriginal and Torres Strait Islander women (but not other Australian women) from remote areas (*versus* major cities) in this study.

Moreover, while participation decreased with increasing disadvantage for other Australian women, consistent with overall higher cervical screening in affluent areas (4), the association was reversed for Aboriginal and Torres Strait Islander women. While we lack information to explore reasons for this differential in this study, the possible contribution of various initiatives for improving health of Aboriginal and Torres Strait Islander people from more disadvantaged areas (37, 38) should be explored in future studies.

While access to screening services for Aboriginal and Torres Strait Islander women through community driven and culturally informed health care organizations such as ACCHOs is likely to improve screening participation, other factors are also important. Although beyond the scope of this study, various geographical, organizational, and environmental factors have been previously associated with variations in cervical screening use across Aboriginal and Torres Strait Islander-specific primary health care services in Australia (21, 22). Moreover, a recent qualitative study designed to better understand the experiences of screened Aboriginal and Torres Strait Islander women suggested that in addition to personal factors (such as having

TABLE 4 | Participation rate ratios (PRRs) [95% CI] for cervical screening by region, for Aboriginal and Torres Strait Islander women aged 20–69 years, Queensland, Australia, 2013–2017.

	Adjusted Odds ratios ACCHO *versus* non-ACCHO (95% CI)[1,2,3] North Queensland
Region	$p < 0.001$
Rest of Queensland	1.00
North Queensland	2.57 [2.22, 2.98]
Age group (years)	$p < 0.001$
20–29	1.00
30–39	1.07 [1.00, 1.14]
40–49	1.16 [1.07, 1.26]
50–59	1.27 [1.16, 1.41]
60–69	1.31 [1.14, 1.50]
Aboriginal and Torres Strait Islander female (%)[4]	$p < 0.001$
Low (<2.0%)	1.00
High (≥2.0%)	1.56 [1.36, 1.78]
Area-level disadvantage[5]	$p < 0.001$
Most advantaged	0.87 [0.72, 1.05]
Advantaged	0.77 [0.68, 0.88]
Middle SES	0.65 [0.58, 0.71]
Disadvantaged	0.71 [0.66, 0.77]
Most disadvantaged	1.00
Remoteness[6]	$p < 0.001$
Major cities	3.26 [2.78, 3.82]
Inner regional	2.03 [1.73, 2.39]
Outer regional	1.00
Remote	2.03 [1.82, 2.25]
Very remote	1.77 [1.60, 1.96]

ACCHO, Aboriginal Community-Controlled Health Organisation; CI, confidence interval.
1. Estimated using fully adjusted main-effect logistic regression models.
2. P-values from Wald's joint test of coefficients for multivariate logistic regression.
3. ACCHO Aboriginal Community-Controlled Health Organisation (ACCHOs) are community-controlled health services designed to meet the primary healthcare needs of Aboriginal and Torres Strait Islander people.
4. Based on 2016 Census.
5. Area-level disadvantage was defined by the 2016 SEIFA Index of Relative Socioeconomic Advantage and Disadvantage.
6. Remote areas were defined by the Remoteness Areas 2016 classification.

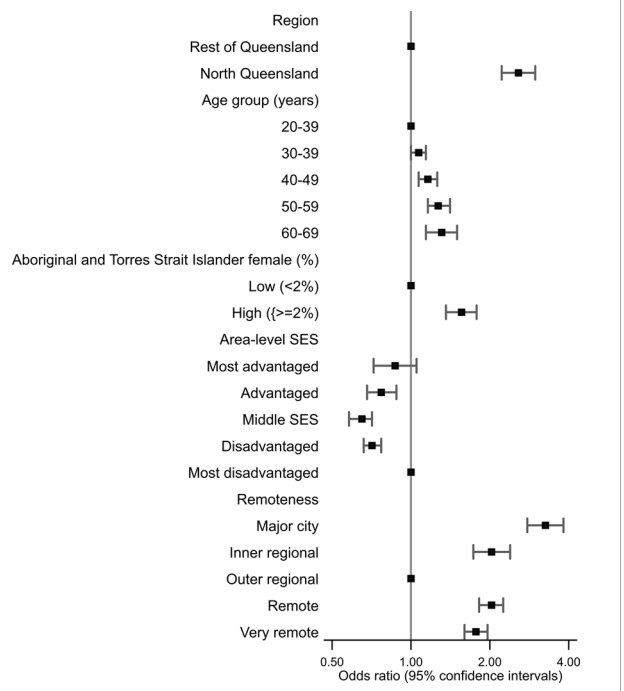

FIGURE 2 | Plot of odds ratios with 95% confidence intervals for factors associated with Aboriginal and Torres Strait Islander women attending an Aboriginal community-controlled health organization (ACCHO) for a Pap test, Queensland, 2013–2017.

control of their health), open discussion about screening and strong and trusting relationships with health professionals facilitated increased screening (39). This study also identified key logistical barriers to screening including competing demands, scheduling issues, and confidentiality concerns notably among rural health professionals. Proposed service-level strategies to improve screening participation included locally relevant community engagement, culturally tailored resources, flexible service provision, and better access to female (including Aboriginal and Torres Strait Islander) practitioners especially in rural areas (21, 22, 39). A greater understanding of systemic and local barriers (and enablers) impacting service delivery is crucial for ongoing innovations to maximize the role of ACCHOs in cervical screening for Aboriginal and Torres Strait Islander women. To be successful, any such initiative must be based on the perspectives and experiences of Aboriginal and Torres Strait Islander people as a core component.

It is likely that ACCHOs in remote areas employ more female health practitioners (16, 17) than urban areas. Greater availability of female especially Indigenous health practitioners and women's only health clinics have also been identified as enablers of cervical screening among Aboriginal and Torres Strait Islander women (22, 23, 39). Given that all North Queensland is deemed to be either outer regional or remote with no urban areas, it is plausible that higher screening participation reflects better access to female practitioners.

After full adjustment for provider-related variables, the regional differential in screening was similar for Aboriginal and Torres Strait Islander and other Australian women. The factors impacting higher cervical screening participation that were evident for both groups of women in North Queensland are unknown. While improving access to screening providers may help reduce existing disparities, further research is required to understand other facilitators and/or barriers to cervical screening in Australia. These are likely to include patient, provider, logistical and health system factors (40, 41). It is also important to better understand how to best facilitate access to and the acceptability of self-collection of samples for HPV-based cervical testing, which is currently only available to women aged 30 years and over who are either never-screened or are overdue for screening (by at least two years) (4).

Strengths and Limitations

Strengths of this study include the large population-based cohort with coverage until the end of the previous national cervical screening program in December 2017 and identification of screened Aboriginal and Torres Strait Islander women through

record linkage to inpatient hospital records. Pap test providers were identified as ACCHOs based on publicly available information sourced from the National Aboriginal Community Controlled Health Organisation website (34) and individual homepages of member organizations listed therein. Given that the National Aboriginal Controlled Health Organisation is the peak leadership body for all ACCHOs in Australia (34) provides some confidence that our search efforts were representative of available knowledge. Locational information on Pap test providers enabled us to determine the closest provider (at health service level) for each SA2 in Queensland.

Limitations include issues related to data-linkage issues (8–10), Aboriginal and Torres Strait Islander identification (8–10), numerator–denominator bias in that they were both sourced from different datasets, geographical mapping based on self-reported suburb and postcode rather than a validated full street address, and the well-documented challenges of accurately estimating the population of Aboriginal and Torres Strait Islander people (42, 43), although we used the best available published small-area population estimates (35). Moreover while Aboriginal and Torres Strait Islander identification in the QHAPDC database is considered to be adequate for research purposes (27), it is inevitable that some women would have been misclassified due to errors in record linkage process or incomplete self-identification. We also lacked capacity to look at screening participation separately for Aboriginal *versus* Torres Strait Islander women.

Our measure of accessibility was based on area-level travel time to closest Pap test provider. Not all women in our cohort would have had their Pap test at their closest provider; however given the high correlation between actual and closest Pap test increases confidence in reported estimates. There was no data on the catchment population for each provider to enable estimation of the screening participation based on the 'actual Pap test provider'.

This is an ecological analysis of a large population-based cohort of women who have participated in cervical screening, as such the SES measure used reflects the average level of disadvantage of the population living in each small area. These measures cannot be used to infer how individuals from the same area may differ from each other in their SES or how these differences are reflected in their screening behavior.

CONCLUSIONS

The difference in cervical screening participation among Aboriginal and Torres Strait Islander women in North Queensland *versus* Rest of Queensland was reduced after adjusting for ACCHO-related factors suggesting that access to ACCHO may explain some of the regional differential. That participation was higher among all women from North Queensland in areas with more Pap test providers suggests that creating more opportunities for cervical screening especially in areas with currently poor access to primary health care may be warranted. Prioritizing the involvement, collaboration, and self-determination of Aboriginal and Torres Strait Islander people in all aspects of implementation and service delivery is crucial for equitable screening participation. Better understanding of the experiences of screened Aboriginal and Torres Strait Islander women is also important to inform tailored interventions that overcome both logistical and systemic barriers to screening.

Patterns of health care utilization among Aboriginal and Torres Strait Islander women in Australia are relevant not only to the Australian context but also for Indigenous and other disadvantaged populations around the world when considering the extent of disparities in their access to health services and the possible factors contributing to them.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Data analyzed for this paper are not able to be shared on any publicly available repository due to legal and confidentiality requirements. Requests to access these datasets should be directed to Health Innovation, Investment and Research Office; Department of Health, Queensland Government; https://www.health.qld.gov.au/hiiro.

ETHICS STATEMENT

Ethical approval was obtained from the Queensland Metro South Human Research Ethics Committee (HREC/2018/QMS/44576). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

The authors PB, PD, JC and JA devised the project and the main conceptual ideas, PB coordinated the study. PD carried out the statistical analysis. PD drafted the manuscript. PB contributed to the original draft of the manuscript and all authors. PB, PD, LW, JC, GG, MW, and JA refined and approved the submitted version. 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/fonc.2021.725145/full#supplementary-material

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Racial and Ethnic Differences in the Financial Consequences of Cancer-Related Employment Disruption

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Introduction: Cancer-related employment disruption contributes to financial toxicity and associated clinical outcomes through income loss and changes in health insurance and may not be uniformly experienced. We examined racial/ethnic differences in the financial consequences of employment disruption.

Methods: We surveyed a national sample of cancer patients employed at diagnosis who had received assistance from a national nonprofit about the impact of cancer diagnosis and treatment on employment. We used logistic regression models to examine racial/ethnic differences in income loss and changes in health insurance coverage.

Results: Of 619 cancer patients included, 63% identified as Non-Hispanic/Latinx (NH) White, 18% as NH Black, 9% as Hispanic/Latinx, 5% as other racial/ethnic identities, and 5% unreported. Over 83% reported taking a significant amount of time off from work during cancer diagnosis and treatment, leading to substantial income loss for 64% and changes in insurance coverage for 31%. NH Black respondents had a 10.2 percentage point (95% CI: 4.8 – 19.9) higher probability of experiencing substantial income loss compared to NH White respondents, and Hispanic or Latinx respondents had a 12.4 percentage point (95% CI: 0.3 – 24.5) higher probability compared to NH White respondents, controlling for clinical characteristics (i.e., cancer type, stage and age at diagnosis, and time since diagnosis). Similarly, NH Black respondents had a 9.3 percentage point (95% CI: -0.7 – 19.3) higher probability of experiencing changes in health insurance compared to NH White respondents, and Hispanic or Latinx respondents had a 10.0 percentage point (95% CI: -3.0 – 23.0) higher probability compared to NH White respondents.

Discussion: Compared with NH White respondents, NH Black and Hispanic/Latinx respondents more commonly reported employment-related income loss and health insurance changes. Given documented racial/ethnic differences in job types, benefit generosity, and employment protections as a result of historic marginalization, policies to reduce employment disruption and its associated financial impact must be developed with a racial equity lens.

Keywords: financial toxicity, cancer, survivorship, productivity loss, employment

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INTRODUCTION

Almost half of over 16.9 million cancer survivors in the United States report cancer-related financial hardship, termed financial toxicity (1–3). This multidimensional construct encompasses material financial burden, altered care-seeking behaviors, and associated psychological distress stemming from medical costs, non-medical costs (e.g., transportation, childcare), and productivity loss (4, 5). Financial toxicity can have rippling effects over time, leading to medical debt, encounters with collection agencies, reductions in assets, and ultimately bankruptcy (4, 6–11). In addition, financial toxicity may cause patients to delay or forego treatment, including oral medications, as a way of coping with mounting costs (4, 12, 13). Clinically, these cumulative effects of financial toxicity are associated with worse health-related quality of life and psychological health (3, 14), higher symptom burden (15), and heightened mortality risk (16).

Over 40% of working age cancer survivors report cancer-related employment disruption, including retiring early, switching jobs, taking paid or unpaid leave, and reducing hours worked (17). Employment disruption is a significant contributor to cancer-related financial toxicity through loss of income, making it more challenging to keep up with other medical and non-medical costs, as well as loss of employer-based health insurance coverage (4, 18, 19). The effect of employment disruption on income is influenced by an individual's access to paid resources (e.g., sick leave, short- and long-term disability insurance) during time off (20). Given that workers in higher paying jobs are more likely to have robust benefits and protections, including paid leave and employer-subsidized health insurance (21, 22), the financial consequences of employment disruption have the potential to exacerbate existing socioeconomic and racial inequities.

Prior work has documented differences by race and ethnicity in cancer-related employment disruption, with Patients of Color more commonly reporting taking extended paid and unpaid leave, stopping work altogether, and reducing work hours (17, 19, 23, 24). Additional work has shown racial disparities in the prevalence of financial toxicity (2, 9, 13, 25), but no study to date has specifically examined racial/ethnic differences in the financial consequences of employment disruption. This study aims to fill this knowledge gap using data from a survey of individuals with cancer who received assistance from a national non-profit. It is particularly important to understand the nature of financial consequences of employment disruption in this high-risk and particularly marginalized group of patients.

MATERIALS AND METHODS

Participants and Recruitment

We used cross-sectional survey data collected by Patient Advocate Foundation (PAF), a national non-profit providing financial assistance and case management services to individuals with chronic or life-threatening illnesses. PAF administered the Impact of Disease Diagnosis on Employment survey electronically between October 2019 – November 2019 to a nationwide sample of participants who had received case management services or financial assistance from PAF between January 2018 and September 2019. This study population aims to represent patients with demonstrated healthcare access and/or affordability challenges. Participants were emailed the survey if they were no longer receiving services at the time of survey administration and opted in to receiving survey communications. PAF sent two reminder emails over the course of three weeks. Of all the email addresses sent a survey, 26% (N=3,352) completed the electronic survey. As there was no way to confirm the validity of all email addresses, it is possible that the denominator included people with invalid email addresses, thus contributing to the lower response proportion.

From this broader sample, we used survey responses to limit the analytic sample to participants who were employed (either full- or part-time) at diagnosis and self-reported a prior stage I-IV cancer diagnosis of any type (N=691). We excluded participants who were missing data for either of the two primary outcomes or for predictor variables included in the multivariable analysis with less than 10 missing responses (10.4%, 72/691). Excluded participants did not differ from the final analytic sample, with the exception of being more likely to have unknown race/ethnicity, cancer site, education, and insurance at diagnosis (**Supplemental Table S1**). The University of North Carolina Institutional Review Board deemed this secondary analysis as non-human subjects research.

Measurement of Financial Consequences of Employment Disruption

We operationalized our primary endpoint, financial consequences of employment disruption due to treatment, as the impact of cancer-related employment disruption on (1) household income and (2) health insurance coverage. We assessed the impact of employment disruption on household income by asking participants, "To what extent has this work disruption due to treatment negatively impacted your income?" Response options included "A great deal," "A lot," "A moderate amount," "A little," or "None at all". For analytic purposes, we collapsed response options to compare participants who reported "A great deal" or "A lot" of income loss to those who reported "A moderate amount" or less. We also asked participants to share the estimated amount of income loss monthly and the impact of this loss on household income and report these findings descriptively.

We assessed the impact of employment disruption on health insurance coverage by asking participants, "Did the change to your employment status impact your insurance coverage?" Response options included "Yes, I lost my insurance and am still uninsured," "Yes, I lost my insurance but eventually obtained insurance coverage again," "No," "Not sure/don't know." We compared all participants whose insurance coverage was affected (whether or not they obtained coverage again) to participants who did not lose coverage or were not sure. Among those participants who lost insurance and eventually obtained new coverage, we descriptively report on the type of new coverage obtained and how the cost and

coverage of this new plan compared to their plan prior to experiencing employment disruption.

Measurement of Resource Use

Among participants who reported taking what they considered to be a significant amount of time off work during treatment, we asked about the types of resources used during absences from work. Participants were given the following options and could select all that applied: Family Medical Leave Act (FMLA), Short Term Disability Insurance (STDI), Long Term Disability Insurance (LTDI), Sick leave, Paid time off/Vacation, Unpaid Leave, Other.

To account for trends in participant response options, we assigned participants to one of three groups on the basis of their self-reported resource use: Paid Leave Only, Paid and Unpaid Leave, Unpaid Leave/No Resources. Apart from FMLA, which provides individuals protected leave from work that may be unpaid or paired with paid leave, the remaining resource categories are clearly delineated as paid (STDI, LTDI, Sick Leave, PTO/Vacation) or unpaid (Unpaid Leave/No Resources). We thus categorized participants based on the distribution of their responses across all resource categories (e.g., a participant selecting Sick Leave and PTO/Vacation only would be categorized as using "Paid Leave Only"). Participants reporting using unpaid leave only or not reporting any resources were categorized as "Unpaid Leave/ No Resources."

Measurement of Covariates

The primary covariate in this analysis is self-reported race/ ethnicity. We collapsed race and ethnicity into the following categories based on how the data were collected: Non-Hispanic or Latinx (NH) White, NH Black, Hispanic or Latinx, Other, and Not reported. Due to small sample sizes, the "Other" category includes participants self-identifying as Asian (n=17), American Indian/Alaskan Native (n<10), Middle Eastern (n<10), Native Hawaiian/Other Pacific Islander (n<10), Caribbean Islander (n<10), and mixed race (n<10). Counts less than 10 are suppressed for confidentiality.

Other covariates included self-reported clinical, socioeconomic, and demographic characteristics hypothesized to be associated with the financial consequences of employment disruption. Clinical characteristics (age at diagnosis, time since first diagnosis, cancer site, cancer stage) were hypothesized to influence functional limitations impacting ability to work. Socioeconomic characteristics (full *vs.* part-time employment, education, health insurance status at diagnosis) were hypothesized to influence employment type/ demands influencing available accommodations and benefits, and demographic characteristics (gender, marital status) were hypothesized to influence social and financial supports and expectations.

Analytic Methods

We first assessed differences in sociodemographic characteristics by race/ethnicity, comparing percentage differences between each racial/ethnic group to NH White participants, as they comprised the majority of our sample. We then used logistic regression models to assess unadjusted and adjusted differences in our primary outcomes, impact of employment disruption on household income and health insurance, by race/ethnicity. In adjusted analyses, we first controlled for clinical characteristics only according to the National Academy of Medicine definition of racial/ethnic disparities (26). We then added in sociodemographic characteristics to assess the extent to which socioeconomic status may mediate these disparities. In the multivariable regression results, average marginal effects for each covariate can be interpreted as the average difference in the predicted probability of each outcome, holding all other covariates constant, across all observations in the analytic sample (27). Standard errors and confidence intervals (CIs) for the marginal effects were estimated by applying the Delta method using the "margins" command in STATA 16.1 (StataCorp, College Station, TX) (28). No collinearity in the final models was detected using a variance inflation factor threshold of five.

In a secondary analysis, we assessed the association of resource use with financial consequences of employment disruption using logistic regression controlling for clinical and sociodemographic characteristics. We assessed differences in the average marginal effects and their associated confidence intervals between participants in each resource use category (Paid Leave Only, Paid and Unpaid Leave, Unpaid Leave or No Resources). We also assessed differences in the percentage of respondents reporting each resource use category by sociodemographic characteristics. All analyses were conducted in STATA 16.1 (StataCorp, College Station, TX).

RESULTS

Participant Characteristics

Of the 619 participants included in the analytic sample, 63% were categorized as NH White, 18% as NH Black, 9% as Hispanic or Latinx, 5% as Other, and 5% as not reported. The majority of the sample was female (82%), employed full-time (*vs.* part-time) at diagnosis (83%), privately insured at diagnosis (71%), diagnosed between the ages of 41 and 60 years (59%), and diagnosed with a solid tumor cancer (77%). Compared to NH White participants, NH Black participants in this sample were more likely to be diagnosed at a younger age and to be single at diagnosis (**Table 1**).

Financial Consequences of Employment Disruption

Most of the sample (83%) reported having to take what they considered to be a substantial amount of time off work during cancer diagnosis and treatment. Over 64% of the sample reported that their income had been impacted substantially ("a great deal" or "a lot") as a result of cancer-related employment disruption. When asked to estimate the specific amount of income loss monthly, 50% of the sample estimated that their lost income was greater than $750 per month, and an additional 14% estimated lost income between $501 and $750 per month. Over 71% of the sample indicated that this loss of income had a substantial impact on their household income.

Almost one third (31%) of the sample reported that their cancer-related employment disruption impacted their

TABLE 1 | Descriptive statistics from a sample of employed patients with cancer who received assistance from a national non-profit, stratified by self-reported race/ethnicity (Oct – Nov 2019).

	Self-reported Race/Ethnicity				
	Non-Hispanic White	**Non-Hispanic Black**	**Hispanic/Latino**	**Other[1]**	**Not reported**
N=619	**392**	**110**	**56**	**33**	**28**
Gender					
Female	323 (82.4%)	94 (85.5%)	45 (80.4%)	25 (75.8%)	23 (82.1%)
Male	69 (17.6%)	16 (14.5%)	11 (19.6%)	8 (24.2%)	5 (17.9%)
Marital status					
Married or living with partner	182 (46.4%)	25 (22.7%)	27 (48.2%)	17 (51.5%)	11 (39.3%)
Single	93 (23.7%)	59 (53.6%)	18 (32.1%)	11 (33.3%)	10 (35.7%)
Divorced, widowed, or separated	117 (29.8%)	26 (23.6%)	11 (19.6%)	5 (15.2%)	7 (25.0%)
Full *vs* part-time employment					
Part-time	77 (19.6%)	14 (12.7%)	6 (10.7%)	2 (6.1%)	7 (25.0%)
Full-time	315 (80.4%)	96 (87.3%)	50 (89.3%)	31 (93.9%)	21 (75.0%)
Educational Attainment					
Two year college degree or less	220 (56.1%)	70 (63.6%)	37 (66.1%)	15 (45.5%)	15 (53.6%)
College degree (BA/BS) or more	153 (39.0%)	34 (30.9%)	19 (33.9%)	14 (42.4%)	12 (42.9%)
Other or not reported	19 (4.8%)	6 (5.5%)	0 (0.0%)	4 (12.1%)	1 (3.6%)
Insurance coverage at the time of diagnosis					
Private	270 (68.9%)	81 (73.6%)	44 (78.6%)	24 (72.7%)	19 (67.9%)
Public (Medicare, Medicaid, Military)	72 (18.4%)	15 (13.6%)	4 (7.1%)	8 (24.2%)	5 (17.9%)
Uninsured	28 (7.1%)	11 (10.0%)	5 (8.9%)	1 (3.0%)	2 (7.1%)
Other or not reported	22 (5.6%)	3 (2.7%)	3 (5.4%)	0 (0.0%)	2 (7.1%)
Age at diagnosis					
19-40 years old	57 (14.5%)	28 (25.5%)	12 (21.4%)	7 (21.2%)	4 (14.3%)
41-60 years old	222 (56.6%)	73 (66.4%)	31 (55.4%)	22 (66.7%)	18 (64.3%)
61 years or older	113 (28.8%)	9 (8.2%)	13 (23.2%)	4 (12.1%)	6 (21.4%)
Time since first diagnosis					
Within the last 12 months	49 (12.5%)	21 (19.1%)	8 (14.3%)	9 (27.3%)	4 (14.3%)
1 to 4 years ago	192 (49.0%)	56 (50.9%)	32 (57.1%)	15 (45.5%)	12 (42.9%)
5 or more years ago	151 (38.5%)	33 (30.0%)	16 (28.6%)	9 (27.3%)	12 (42.9%)
Cancer Stage					
Stage 1 or 2	146 (37.2%)	46 (41.8%)	17 (30.4%)	10 (30.3%)	7 (25.0%)
Stage 3 or 4	163 (41.6%)	46 (41.8%)	28 (50.0%)	17 (51.5%)	16 (57.1%)
Unknown	83 (21.2%)	18 (16.4%)	11 (19.6%)	6 (18.2%)	5 (17.9%)
Cancer Site					
Solid tumor[2]	294 (75.0%)	90 (81.8%)	46 (82.1%)	25 (75.8%)	21 (75.0%)
Blood[3]	70 (17.9%)	16 (14.5%)	5 (8.9%)	4 (12.1%)	5 (17.9%)
Not reported	28 (7.1%)	4 (3.6%)	5 (8.9%)	4 (12.1%)	2 (7.1%)

[1]*Other includes Asian (n=17), American Indian/Alaskan Native (n<10), Middle Eastern (n<10), Native Hawaiian/Other Pacific Islander (n<10), Caribbean Islander (n<10), and mixed race (n<10). Counts less than 10 suppressed for confidentiality.*

[2]*Solid tumor cancers include breast (n=366), prostate (n=27), colorectal (n=22), gynecologic (n=12), lung (n=12), head and neck (n<10), bone (n<10), bladder (n<10), gastrointestinal (n<10), liver (n<10), endocrine (n<10), sarcoma (n<10), skin (n<10), thyroid (n<10). Counts less than 10 suppressed for confidentiality.*

[3]*Blood cancers include myeloma (n=74), Non-Hodgkin's or Hodgkin lymphoma (n=15), leukemia (n=11).*

insurance coverage; the majority of these participants obtained insurance coverage again (88%; 168/192). Of those who obtained insurance coverage again, however, 55% reported that this coverage was more expensive and 38% reported that it covered fewer services (*versus* 13% reporting that it covered more, 38% reported that it covered roughly the same amount, and 11% unsure or missing). Almost 40% of those who obtained coverage again reported switching to Medicare; 18% obtained coverage through the health insurance exchange, 18% regained coverage through an employer, and 18% enrolled in Medicaid. The remaining 6% were not sure what type of health insurance they obtained or did not respond.

In unadjusted analysis, compared to NH White respondents, income loss was more commonly reported by NH Black (60% *vs*. 75%) and Hispanic/Latinx (60% *vs*. 75%) respondents. Similar trends were observed for the impact of employment disruption on health insurance coverage when comparing NH White respondents to NH Black (28% *vs*. 38%) and Hispanic/Latinx (28% *vs*. 38%) respondents.

Multivariable Analysis: Impact of Employment Disruption on Household Income

Holding all clinical characteristics constant, NH Black respondents had a 10.2 percentage point (95% CI: 4.8 – 19.9) higher probability of experiencing substantial income loss compared to NH White respondents, and Hispanic or Latinx respondents had a 12.4 percentage point (95% CI: 0.3 – 24.5) higher probability of experiencing substantial income loss compared to NH White respondents (**Figure 1** and **Table 2**). After adding socioeconomic and demographic characteristics to the model, the difference between NH Black and NH White

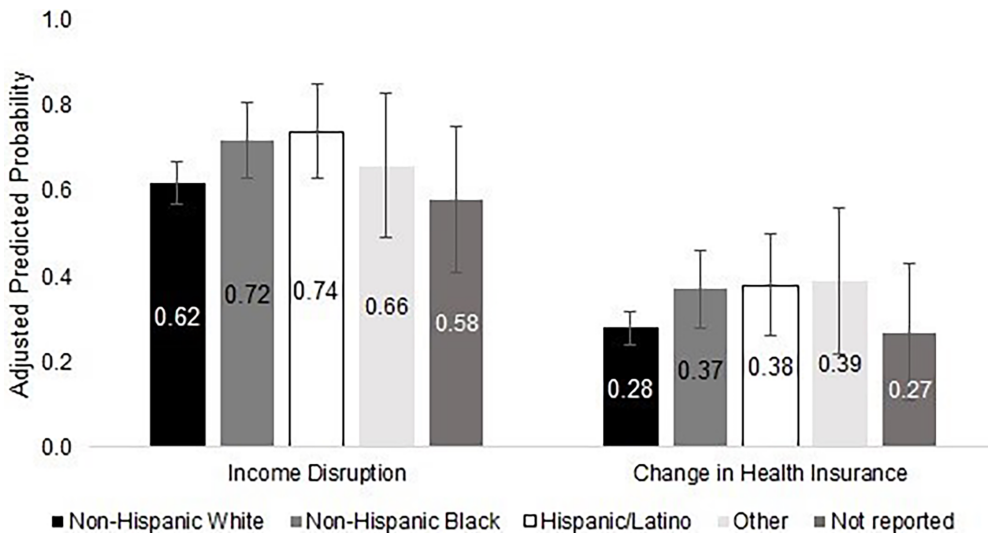

FIGURE 1 | Financial consequences of employment disruption in a sample of employed patients with cancer who received assistance from a national non-profit, stratified by race/ethnicity (Oct – Nov 2019) (N = 619). **Figure 1** shows the adjusted predicted probabilities of experiencing substantial income loss and a change in health insurance following employment disruption by race/ethnicity, controlling for clinical characteristics. Adjusted percentages are reported with 95% confidence intervals from the multivariable logistic regression using Delta-method calculated standard errors.

respondents was partially attenuated, with a marginal effect of 6.9 percentage points (95% CI: -3.2 – 17.0), but the difference between Hispanic or Latinx respondents and NH White respondents remained at 12.3 percentage points (95% CI: 0.4 – 24.2). Respondents who were younger, diagnosed with a higher cancer stage, diagnosed within the past year, diagnosed with blood (*vs*. solid tumor) cancer, non-married, employed full-time, and publicly insured or uninsured were more likely to experience income disruption (**Table 2**).

Multivariable Analysis: Impact of Employment Disruption on Health Insurance Coverage

Controlling for all clinical characteristics, NH Black respondents had a 9.3 percentage point (95% CI: -0.7 – 19.3) higher probability of experiencing changes in health insurance compared to NH White respondents, and Hispanic or Latinx respondents had a 10.0 percentage point (95% CI: -3.0 – 23.0) higher probability compared to NH White respondents (**Figure 1** and **Table 3**). When additional demographic and socioeconomic characteristics were added to the model, the observed racial/ethnic differences were further attenuated to 7.0 percentage points (95% CI: -2.5 – 16.6) and 5.0 percentage points (95% CI: -6.9 – 16.9) for NH Black and Hispanic or Latinx respondents, respectively. Respondents who were non-married, employed full-time, and privately insured were more likely to experience a change in health insurance. Additionally, respondents diagnosed with cancer at a higher stage, blood cancer (*vs*. solid tumor), and those diagnosed more than one year prior to the survey were more likely to have a change in health insurance. Respondents age 61 years or older at diagnosis (*vs*. 19-40 years) were less likely to experience a change in health insurance (**Table 3**).

Employment Leave Resource Use

Among the 510 participants who reported taking what they considered to be a significant amount of time off work, **Figure 2** shows the prevalence of resource use across each resource category. Paid leave (PTO or sick leave) was reported most commonly by 44% of the sample, followed by unpaid leave reported by 37%. Almost 30% of the sample used FMLA. Short-term disability insurance was used by 30% of the sample, and only 18% reported using long-term disability insurance. After categorizing participants according to their resource use patterns, 42% used unpaid leave only or reported no resource use, 41% used paid resources only, and 17% used a mix of paid and unpaid resources (**Figure 3**). After controlling for clinical and sociodemographic characteristics, compared to participants who used paid resources only during their time off work, participants who used unpaid resources had a 17.1 percentage poin (95% CI: 8.6 – 25.6) higher probability of reporting substantial income loss, and participants who used both paid and unpaid resources had a 14.1 percentage point (95% CI: 3.1 – 25.2) higher probability of reporting a change in health insurance (**Figure 3**).

In assessing patterns in resource use by sociodemographic characteristics, no substantial differences by race/ethnicity were observed (**Table S2**). Unsurprisingly, participants employed part-time at diagnosis more frequently used unpaid leave only compared to full-time employees. Participants with private insurance at diagnosis used paid leave only more often compared to publicly insured and uninsured participants, who were more likely to use unpaid leave only (**Table S2**).

TABLE 2 | Multivariable associations between patient characteristics and household income loss in a sample of employed patients with cancer who received assistance from a national non-profit (Oct – Nov 2019).

VARIABLES	Income Disruption[1]			
	Adjusted for Clinical Characteristics Only[2]		*Adjusted for Clinical & Sociodemographic Characteristics*[3]	
	Average Marginal Effect[4]	95% Confidence Interval	Average Marginal Effect[4]	95% Confidence Interval
Observations	**619**		**619**	
Race/Ethnicity (ref = NH White)				
NH Black	0.102	(0.004 – 0.199)	0.069	(-0.032 – 0.170)
Hispanic/Latinx	0.124	(0.003 – 0.245)	0.123	(0.004 – 0.242)
Other	0.039	(-0.133 – 0.211)	0.045	(-0.125 – 0.214)
Not reported	-0.034	(-0.217 – 0.149)	-0.025	(-0.204 – 0.154)
Clinical Characteristics				
Cancer Stage at Diagnosis (ref = Stage 1 or 2)				
Stage 3 or 4	0.162	(0.080 – 0.244)	0.139	(0.057 – 0.221)
Unknown stage	-0.032	(-0.142 – 0.078)	-0.020	(-0.128 – 0.088)
Cancer Site (ref = Solid tumor)				
Blood	0.121	(0.030 – 0.212)	0.137	(0.048 – 0.225)
Not reported	0.041	(-0.103 – 0.185)	0.032	(-0.111 – 0.174)
Age at Diagnosis (ref = 19-40 years old)				
41 - 60 years	-0.005	(-0.103 – 0.094)	0.003	(-0.097 – 0.103)
61 years or older	-0.159	(-0.281 – -0.036)	-0.147	(-0.274 – -0.020)
Time Since Diagnosis (ref = < 1 year ago)				
1 to 4 years ago	-0.122	(-0.222 – -0.022)	-0.104	(-0.206 – -0.001)
5 or more years ago	-0.188	(-0.294 – -0.082)	-0.163	(-0.273 – -0.053)
Sociodemographic Characteristics				
Gender (ref = Female)				
Male			-0.042	(-0.147 – 0.064)
Marital Status (ref = Married, Living with Partner)				
Single			0.091	(0.001 – 0.182)
Divorced, Widowed, or separated			0.098	(0.007 – 0.190)
Employment Status at Diagnosis (ref = Part-time)				
Full-time			0.115	(0.004 – 0.225)
Educational Attainment (ref = 2 year degree or less)				
College degree (BA/BS) or more			-0.061	(-0.137 – 0.015)
Other or not reported			-0.056	(-0.230 – 0.119)
Insurance Status at Diagnosis (ref = Private Insurance)				
Public (Medicare, Medicaid, Military)			0.107	(0.005 – 0.210)
Uninsured			0.202	(0.072 – 0.332)
Other or not reported			-0.026	(-0.199 – 0.147)

[1]*To what extent has this work disruption due to treatment negatively impacted your income? A great deal/a lot vs. A moderate amount/a little/none at all (referent).*
[2]*The first column includes results from a multivariable model controlling for clinical characteristics only, specifically cancer site, stage and age at diagnosis, and time since diagnosis.*
[3]*The second column includes results from a multivariable model additionally controlling for sociodemographic characteristics, specifically gender, marital status, employment status at diagnosis, educational attainment, and insurance status at diagnosis.*
[4]*Multivariable logistic regression used to estimate average marginal effects (95% confidence intervals reported in parentheses). Average marginal effects represent the average difference in the predicted probability of experiencing income disruption, or a change in health insurance, holding all other covariates constant, across all observations in the analytic sample.*

DISCUSSION

Our findings are in line with prior work documenting that underrepresented patients of color are more likely than NH White patients to experience cancer-related employment disruption. However, our work provides additional detail on the financial consequences of employment disruption in a sample of patients with documented financial need, elucidating one potential mechanism underlying heightened financial toxicity in patients of color (4, 13, 29). Specifically, we identified racial/ethnic differences in the financial consequences of employment disruption, particularly income loss and changes in health insurance coverage. Even after adjusting for clinical characteristics, differences in income disruption remained between NH White, NH Black, and Hispanic or Latinx individuals. Additionally, some clinical and sociodemographic characteristics, such as stage and insurance status at diagnosis, may be acting as mediators between race/ethnicity and employment outcomes due to the impact of systemic inequities on health and socioeconomic status. As programs and policies are instituted to address patient financial and employment concerns, we must pay explicit attention to racial equity to avoid exacerbating documented racial/ethnic disparities in financial toxicity (4, 13, 29). This may include developing policies to increase employment protections and expand insurance access and designing patient-centered navigation programs to overcome structural barriers to resources and employment protections (30, 31).

TABLE 3 | Multivariable associations between patient characteristics and employment-related changes in health insurance coverage in a sample of employed patients with cancer who received assistance from a national non-profit (Oct – Nov 2019).

VARIABLES	Change in Health Insurance[1]			
	Clinical Characteristics Only[2]		*Clinical & Sociodemographic Characteristics*[3]	
	Average Marginal Effect[4]	95% Confidence Interval	Average Marginal Effect[4]	95% Confidence Interval
Observations	**619**		**619**	
Race/Ethnicity (ref = NH White)				
NH Black	0.093	(-0.007 – 0.193)	0.070	(-0.025 – 0.166)
Hispanic/Latinx	0.100	(-0.030 – 0.230)	0.050	(-0.069 – 0.169)
Other	0.108	(-0.062 – 0.278)	0.131	(-0.035 – 0.297)
Not reported	-0.009	(-0.170 – 0.153)	0.010	(-0.153 – 0.173)
Clinical Characteristics				
Cancer Stage at Diagnosis (ref = Stage 1 or 2)				
Stage 3 or 4	0.12	(0.040 – 0.200)	0.103	(0.026 – 0.180)
Unknown stage	0.056	(-0.044 – 0.155)	0.044	(-0.053 – 0.142)
Cancer Site (ref = Solid tumor)				
Blood	0.195	(0.084 – 0.306)	0.179	(0.072 – 0.287)
Not reported	0.094	(-0.052 – 0.240)	0.059	(-0.077 – 0.196)
Age at Diagnosis (ref = 19-40 years old)				
41 – 60 years	-0.008	(-0.108 – 0.092)	-0.051	(-0.149 – 0.046)
61 years or older	-0.153	(-0.265 – -0.041)	-0.132	(-0.247 – -0.016)
Time Since Diagnosis (ref = < 1 year ago)				
1 to 4 years ago	0.147	(0.052 – 0.242)	0.146	(0.051 – 0.241)
5 or more years ago	0.139	(0.038 – 0.240)	0.116	(0.017 – 0.215)
Sociodemographic Characteristics				
Gender (ref = Female)				
Male			0.101	(-0.005 – 0.206)
Marital Status (ref = Married, Living with Partner)				
Single			0.088	(0.005 – 0.171)
Divorced, Widowed, or separated			0.123	(0.036 – 0.211)
Employment Status at Diagnosis (ref = Part-time)				
Full-time			0.141	(0.039 – 0.243)
Educational Attainment (ref = 2 year degree or less)				
College degree (BA/BS) or more			-0.068	(-0.140 – 0.003)
Other or not reported			-0.23	(-0.357 – -0.102)
Insurance Status at Diagnosis (ref = Private Insurance)				
Public (Medicare, Medicaid, Military)			-0.233	(-0.320 – -0.145)
Uninsured			-0.176	(-0.288 – -0.064)
Other or not reported			-0.031	(-0.208 – 0.146)

[1]*Did the change to your employment status impact your insurance coverage? Yes vs. No/Not sure (referent).*

[2]*The first column includes results from a multivariable model controlling for clinical characteristics only, specifically cancer site, stage and age at diagnosis, and time since diagnosis.*

[3]*The second column includes results from a multivariable model additionally controlling for sociodemographic characteristics, specifically gender, marital status, employment status at diagnosis, educational attainment, and insurance status at diagnosis.*

[4]*Multivariable logistic regression used to estimate average marginal effects (95% confidence intervals reported in parentheses). Average marginal effects represent the average difference in the predicted probability of experiencing income disruption, or a change in health insurance, holding all other covariates constant, across all observations in the analytic sample.*

The extent to which cancer impacts employment disruption is both a product of clinical and treatment characteristics (influencing how often patients must attend appointments and the symptoms/side effects experienced) (23, 32, 33), as well as characteristics of the work environment (influencing the accommodations and resources available to patients) (34, 35). Furthermore, the financial consequences of employment disruption, particularly income loss, are related to an individual's access to resources that may provide income continuity during time off from work (e.g., paid vacation or sick leave), supplemental income (e.g., short-term and long-term disability insurance), and job security and accommodations (e.g., Family Medical Leave Act, Americans with Disabilities Act). Differences by race/ethnicity in each of these domains may help to explain our findings that NH Black and Hispanic or Latinx patients with cancer were more likely than NH White patients to experience substantial income loss throughout diagnosis and treatment after controlling for clinical characteristics.

First, NH Black and Hispanic or Latinx individuals are more likely than NH White individuals to be diagnosed with advanced disease, which frequently requires more intensive and expensive treatments, and are therefore less likely to receive recommended treatments (36, 37). These documented disparities in clinical outcomes likely influence the intensity and longevity of required treatment, as well as the functional limitations associated with cancer and treatment side effects. Second, as a result of structural racism limiting the economic opportunities of People of Color in the United States, national data show that individuals identifying as Black race and those identifying as Hispanic or Latinx ethnicity are

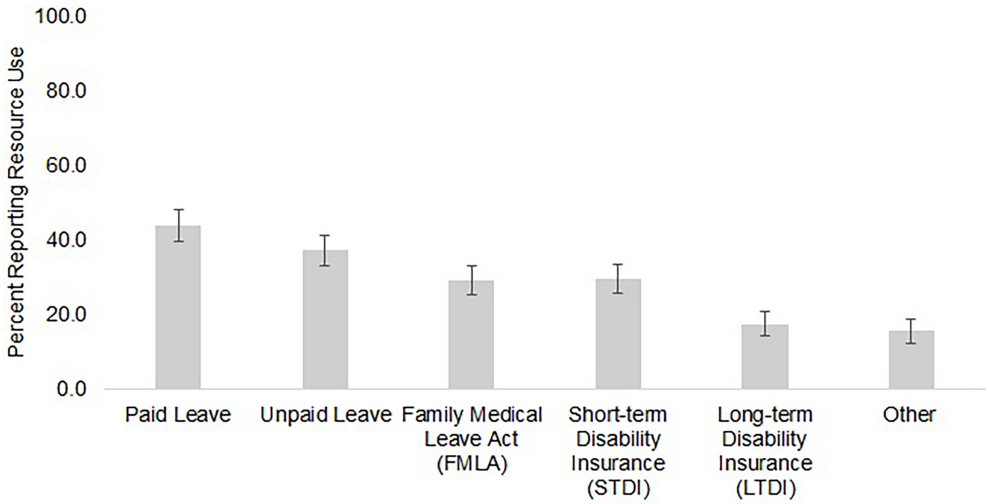

FIGURE 2 | Resource use among participants who reported taking a significant amount of time off work in a sample of employed patients with cancer who received assistance from a national non-profit (Oct – Nov 2019) (N = 510). **Figure 2** shows the percentage of participants reporting taking a significant amount of time off work who reported using each type of employment leave.

more likely than White individuals to work in service, production, and transportation occupations (38). Further, Hispanic or Latinx individuals are more likely than both White and Black individuals to work in construction and maintenance (38). These employment categories may offer less flexible schedules, hourly *versus* salaried payment arrangements, and less opportunity for remote work (23, 39, 40), all of which have been shown to be important accommodations to individuals undergoing cancer treatment (34, 35, 41). Third, access to more generous benefit policies, including disability insurance, paid time off, and employer-sponsored health insurance, is more common among individuals in higher earning jobs and more common among White workers *versus* workers of color in the United States (21, 22, 42). Differences in access to paid benefits by race and socioeconomic status have the potential to exacerbate disparities in the financial consequences of employment disruption.

The employment-related changes in health insurance observed in a third of this sample were most likely related to

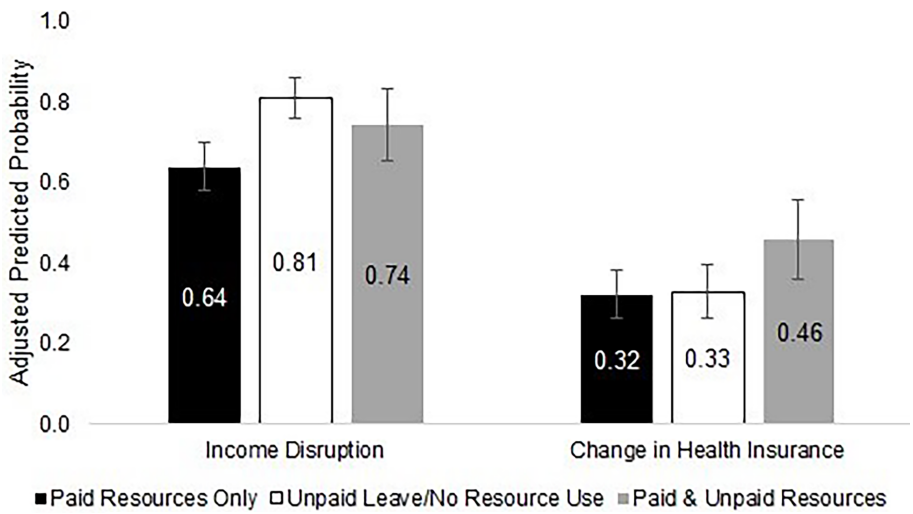

FIGURE 3 | Financial consequences of employment disruption by resource use among respondents taking a significant amount of time off work in a sample of employed patients with cancer who received assistance from a national non-profit (Oct – Nov 2019) (N = 510). **Figure 3** shows the percentage of participants reporting financial consequences of employment disruption (income loss and a change in health insurance) by the types of employment leave resources used after controlling for clinical and sociodemographic characteristics. Income loss was most commonly reported among those using unpaid leave only, whereas a change in health insurance was most commonly reported among those using both paid and unpaid resources.

the loss of private employer-sponsored health insurance (ESHI) due to extended time off, early retirement, or job loss. Thus, loss of health insurance was likely accompanied by a loss of income, compounding the experience of financial toxicity. Though we observed racial/ethnic differences in health insurance changes in unadjusted analyses, these differences were attenuated by sociodemographic characteristics, particularly marital status, employment status, and insurance status – all of which are related to the availability of and reliance on ESHI. Under FMLA, employers are required to continue offering ESHI throughout an employee's leave; however, employees may be responsible for continuing to pay their share of the premium, which would typically be deducted from their pay (43). This may be untenable for some patients taking unpaid leave with mounting medical bills. Further, if a patient must leave work altogether, the Consolidated Omnibus Reconciliation Act (COBRA) allows most employees to retain their ESHI coverage but requires them to pay the entire premium costs previously subsidized by the employer (44). Again, this additional cost may preclude patients from taking advantage of this protection.

These results have important implications for the development of programs and policies intending to equitably intervene on financial toxicity, particularly those focusing on the financial challenges caused by employment disruption. Oncology financial navigation, in which trained navigators assist patients with financial, insurance, and employment concerns throughout treatment, is one evidence-based approach to address systemic barriers to financial and employment resources (45–49). Given that challenges associated with income loss and changes in health insurance may develop over time, this analysis underscores the changing financial needs of patients over the continuum of their cancer treatment and care. This is in line with prior longitudinal work documenting the experience of financial toxicity over time (11, 41, 50, 51), though more work in this area is needed (52). As health systems, oncology practices, and non-profit organizations increasingly implement processes and programs to identify and address patient financial concerns (45–48), it is critical to routinely check-in with patients to assess changes in needs and ongoing eligibility for different assistance mechanisms.

Furthermore, financial navigation is most effective when targeted to patients at greatest risk of financial toxicity (47). Though our analysis was primarily focused on racial/ethnic differences in the financial consequences of employment disruption, the additional sociodemographic characteristics (e.g., marital status, insurance status, age, gender, education, employment status/type) associated with both income loss and changes in health insurance in our multivariable analyses were in line with those documented in the literature on cancer-related employment disruption to date (17, 53–56). Understanding the clinical and sociodemographic characteristics associated with employment disruption and financial hardship is important for ensuring that initiatives to ameliorate financial hardship are appropriately targeted (46, 47, 57, 58).

In conjunction with programmatic interventions, policies affording workers legal protections and disability resources are critically important to ensuring job retention throughout cancer treatment and into survivorship. Only 29% of respondents in our sample who took a significant amount of time off work reported using FMLA. FMLA offers up to 12 weeks of unpaid time off with job security for individuals working at a firm with more than 50 employees who meet specific criteria for hours worked and tenure (42, 43). Additionally, the Americans with Disabilities Act (ADA) requires employers to grant requests for reasonable accommodations to employees with specified conditions, including cancer. However, the ADA does not apply to firms with 15 or fewer employees, and the employer does not have to provide an accommodation if doing so would be an undue hardship, which is largely up to the employer's discretion (42, 59). As employees are increasingly hired in alternative contractual arrangements (60), attention must be paid to ensuring workers have equitable access to such legal protections (42). Furthermore, ensuring all patients are aware of these legal protections and have the skills and resources necessary to navigate these conversations with employers is a critical area of ongoing research to promote equity in employment outcomes (41, 61).

These findings must be viewed in the context of several limitations. The sample surveyed represents a financially vulnerable population who sought supportive services from a national non-profit; thus, conclusions drawn are not generalizable to the full US population of employed patients with cancer. The low survey response proportion also introduces the potential for selection bias if participants were more likely to respond if they had experienced extreme financial toxicity or employment disruption. This further reduces the generalizability of these study findings. As a result, it is likely that the prevalence of employment disruption, income loss, and changes in health insurance are higher in this population of patients with demonstrated financial need as compared to the broader population. However, we do not have reason to believe that this selection bias would influence the associations of patient characteristics with financial toxicity. The directional associations observed in our multivariable analyses are largely in concordance with a recent analysis of employment disruption among cancer survivors using nationally representative Medical Expenditure Panel Survey data (17). Additionally, it is critically important to understand the nature of financial needs in particularly marginalized, low-income individuals, such as those included in our sample. Future research should further investigate racial/ethnic differences in financial consequences of employment disruption in a nationally representative sample.

Another limitation is the use of self-reported measures for employment outcomes, which had not been validated in this population. Though most prior studies investigating this issue have relied on self-report (17, 19), there is a need for the validation of questionnaires and measures across diverse patient populations. Additionally, respondents' self-identified race and ethnicity were collapsed for analysis into four mutually exclusive categories due to sample size limitations. Therefore, we did not have enough data to draw meaningful conclusions about racial/ethnic differences in employment disruption between groups other than NH White, NH Black, and Hispanic or Latinx. We also did not have data on income at diagnosis, which has been shown to be associated with employment disruption in prior work (53). Instead, we used educational attainment as a proxy for baseline socioeconomic

status. The inclusion of income at diagnosis in our models controlling for clinical and sociodemographic characteristics may have further attenuated the racial/ethnic differences observed due to income potentially mediating the association of race/ethnicity with the financial consequences of employment disruption. Lastly, though we included stage at initial diagnosis in our models, we did not have information on potential stage progression. Thus, the stage data included may not fully represent a respondent's clinical context while experiencing employment disruption.

Among a national sample of patients with cancer in financial need who obtained assistance from a non-profit organization, NH Black and Hispanic or Latinx respondents were more likely than NH Whites to experience substantial income loss and changes in health insurance resulting from employment disruption. Policies and practices to address financial hardship, and specifically the financial consequences of employment disruption, must be developed with a racial equity lens to ensure that they recognize and address the systemic inequities leading to these observed differences.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because this data is owned by Patient Advocate Foundation and is subject to a Data Use Agreement. Requests to access the datasets should be directed to https://www.patientadvocate.org/.

AUTHOR CONTRIBUTIONS

CB: Conceptualization, Methodology, Formal analysis, Writing – Original draft preparation. SW: Conceptualization, Methodology, Supervision, Writing – Review and Editing. RA: Investigation, Conceptualization, Writing – Review and Editing. KG: Investigation, Conceptualization, Writing – Review and Editing. EA: Data Curation, Conceptualization, Writing – Review and Editing. EK: Writing – Review and Editing. LS: Conceptualization, Methodology, Supervision, Writing – Review and Editing. All authors contributed to the article and approved the submitted version.

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Colorectal Cancer Screening Prevalence and Adherence for the Cancer Prevention Project of Philadelphia (CAP3) Participants Who Self-Identify as Black

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Introduction: Colorectal cancer is the third leading cause of cancer-related deaths among Black men and women. While colorectal cancer screening (CRCS) reduces mortality, research assessing within race CRCS differences is lacking. This study assessed CRCS prevalence and adherence to national screening recommendations and the association of region of birth with CRCS adherence, within a diverse Black population.

Methods: Data from age-eligible adults, 50–75 years, (N = 357) participating in an ongoing, cross-sectional study, was used to measure CRCS prevalence and adherence and region of birth (e.g., Caribbean-, African-, US-born). Prevalence and adherence were based on contemporaneous US Preventive Services Task Force guidelines. Descriptive statistics were calculated and adjusted prevalence and adherence proportions were calculated by region of birth. Adjusted logistic regression models were performed to assess the association between region of birth and overall CRCS and modality-specific adherence.

Results: Respondents were 69.5% female, 43.3% married/living with partner, and 38.4% had <$25,000 annual income. Overall, 78.2% reported past CRCS; however, stool test had the lowest prevalence overall (34.6%). Caribbean (95.0%) and African immigrants (90.2%) had higher prevalence of overall CRCS compared to US-born Blacks (59.2%) (p-value <0.001). African immigrants were five times more likely to be adherent to overall CRCS compared to US-born Blacks (OR = 5.25, 95% CI 1.34–20.6). Immigrants had higher odds of being adherent to colonoscopy (Caribbean OR = 6.84, 95% CI 1.49–31.5; African OR = 7.14, 95% CI 1.27–40.3) compared to US-born Blacks.

Conclusions: While Caribbean and African immigrants have higher prevalence and adherence of CRCS when compared US-born Blacks, CRCS is still sub-optimal in the Black population. Efforts to increase CRCS, specifically stool testing, within the Black population are warranted, with targeted interventions geared towards US-born Blacks.

Keywords: screening, colon, disparities (health racial), immigrant health, colorectal cancer, African American, cancer, cancer prevention

INTRODUCTION

The American Cancer Society (ACS) estimates there will be about 147,950 new colorectal cancer (CRC) cases diagnosed in the US in 2020 and about 53,200 CRC deaths (1, 2). CRC is the third most frequently diagnosed cancer among Black men and women as well as the third-leading cause of cancer-related deaths (3). Further, racial disparities exist, with Non-Hispanic Blacks having the highest CRC incidence and mortality rates, when compared to other racial groups (3). Importantly, Blacks are a heterogeneous racial group and 10% of the US Black population are immigrants from the Caribbean and Africa (3, 4). Further, second generation immigrants make up an additional 8% of the population, subsequently making approximately 20% of Black population, immigrant-blacks and their children (5). Previous work has shown explicit differences in CRC mortality within the heterogeneous Black population in the US (6–8).

CRC is one of few cancers where mortality can be reduced 9–32% (9–14) with regular screening (1, 3, 15, 16). The U.S. Preventive Services Task Force (USPSTF) (16) and the ACS (15) have set guidelines for CRC screening (CRCS) for average-risk adults, ages 45–75, to ultimately reduce mortality. These recommendations include having a stool test within the last year, flexible sigmoidoscopy or computed tomography (CT) colonography in the last 5 years, or a colonoscopy within the last 10 years. While the importance of CRCS has been noted in the published literature, adherence to US CRCS guidelines (16) is not ideal and should be improved (17). While CRCS adherence appears similar between Whites and Blacks, the published literature provides evidence of an ethnic/racial disparity (18–27). Levels of adherence to any modality of CRCS (24–26), stool test [fecal occult blood test (FOBT) or fecal immunological test (FIT)] (18–20, 22, 23) and colonoscopy (19–23, 27), have been consistently higher in whites when compared to any other racial ethnic group.

Research assessing within race differences for CRCS prevalence and adherence is lacking. Therefore, using contemporaneous USPSTF guidelines at the inception of this research, this study determines the prevalence of CRCS and adherence to national screening recommendations among a heterogeneous population of Blacks, aged 50–75 years, participating in the Cancer Prevention Project of Philadelphia (CAP3). In addition, the association of region of birth (i.e., US, Caribbean or African born) and CRCS adherence was also assessed.

METHODS

This study used a subset of data from the ongoing CAP3 study for individuals recruited from September 2012 to August 2019. Methods for CAP3 have been described previously (28). Briefly, CAP3 recruited individuals in the Philadelphia metropolitan area, where the Black community is the largest minority group (~44% of the total population) (29) consisting of US-born, Caribbean-born, and African-born Blacks. This study was reviewed and approved by the Institutional Review Board at Fox Chase Cancer Center. All participants provided informed consent.

For the parent study, enrollment was limited to English speakers age 18+, who do not have a cancer diagnosis at the time of study enrollment. Having other comorbidities (i.e. hypertension, diabetes, etcetera), did not prevent study participation. For the current study, only individuals who were age eligible for CRCS (i.e., 50–75 years, the USPSTF recommendation in 2012 when the study was initiated) and responded to CRCS questions were included in the analysis (N = 357).

Data Collection

Questionnaires were administered *via* in-person interviews by trained research staff.

Measures

CRCS questions were adapted from the 2011 Behavioral Risk Factor Surveillance System (BRFSS) and the National Health and Nutrition Examination Survey (NHANES), both developed by the CDC (30, 31). Five questions in the CAP3 questionnaire provide data on CRCS-related prevalence and adherence. Specifically, participants were asked if they ever had a stool-based test and an endoscopic method of CRCS. If the individuals had received an endoscopic procedure, they were asked to specify whether it was flexible sigmoidoscopy or colonoscopy. The timing of each CRCS modality was also asked with the following response categories: within the past year (anytime less than 12 months ago); within the past two years (1 year but less than 2 years ago); within the past 3 years (2 years but less than 3 years ago); within the past 5 years (3 years but less than 5 years ago); within the past 10 years (5 years but less than 10 years ago); 10 or more years ago; don't know/not sure, and refused (31).

Country of birth, a single, open-ended question was asked of all participants. This variable was then categorized into a 3-level variable to describe ethnicity.

Demographic variables included: age, sex, marital status, education, income, and ethnicity. Other variables included: healthcare coverage, whether the respondent had health insurance; primary care provider status, whether the participant had someone they considered a primary care doctor; and routine physical (whether the participant had a routine physical in the last year). Length of time in the US represents the number of years each respondent has lived in the US.

Coding

Primary Outcome Variables

CRCS questions assessing stool test and two endoscopic modalities (i.e., colonoscopy or flexible sigmoidoscopy) were coded dichotomously as "yes" or "no" to reflect screening prevalence—whether people had ever had a stool test, colonoscopy, or any CRCS. A subsequent question was asked to determine time frame from last modality of CRCS, which were used to dichotomously code adherence variables as "never screened/overdue" or "adherent" based on the 2012 USPSTF guidelines (15, 16): stool test (in last year), colonoscopy (in last 10 years), and overall CRCS (stool test in last year, colonoscopy in last 10 years, or flexible sigmoidoscopy in last five years). Flexible sigmoidoscopy prevalence and adherence were not

explicitly assessed as it is rarely recommended in clinical practice (15) and very few people reported having the test (n = 9). However, the data for flexible sigmoidoscopy was included in the overall CRCS prevalence and adherence variables.

Independent Variable

Country of birth was recoded into a 3-level "region of birth" variable representing "US-born", "Caribbean-born", and "African-born". US-born included individuals that were born in the continental US and US territories around the world; Caribbean-Immigrants included individuals born in Barbados, Grenada, Guyana, Haiti, Jamaica, St. Lucia, and Trinidad and Tobago; lastly, African-Immigrants included individuals born in The Democratic Republic of the Congo, Liberia, Nigeria, Sierra Leone, Togo, and Uganda.

Sociodemographic Variables

The following categorical sociodemographic variables were included in analyses: age ("50–64" or "65+" years), sex ("male" or "female"), marital status ("married or member of an unmarried couple," "divorced, widowed or separated" or "never married"), annual household income ("less than $10,000 to 24,999," "$25,000 to 49,999," "$50,000 to 74,999," "$75,000+," and "don't know/not sure"), highest level of education ("<high school," "high school graduate" "some college," " college and beyond," and "don't know/ refused"), healthcare coverage ("yes" or "no"), having a primary care doctor ("yes" or "no") and having a routine physical ("within the last year" or greater than a year ago"). For regression analyses the following variables were recoded to have dichotomous responses: marital status ("married or member of an unmarried couple" or "divorced, widowed or separated, never married"), annual household income ("≤$50,000" or ">$50,000"), and highest level of education ("≤high school," or ">high school"). Length of time in the US, a continuous variable coded to represent years living in the US was also included in the analysis. For US-born Blacks this variable was coded as their age and for immigrants it was coded as length of time they have resided in the US.

Statistical Analysis

STATA version 13.1 was used to perform all statistical analyses. Descriptive statistics were calculated for the overall population of Blacks as well as stratified by self-reported region of birth. Fisher's exact or χ^2 tests were used to assess differences within the Black population; Fisher's exact test was used when respondent frequency was less than 5. Adjusted proportions for CRCS prevalence and adherence were calculated. Adjustment was done as appropriate based on established confounders in the literature (32–38) and the 10% change-in-estimate criterion (39). Specifically, marital status, level of education, income, healthcare coverage status, primary care provider (PCP) status, and having a routine physical within the last year were confounders and age, sex, and length of time in the US were included as covariates.

Adjusted logistic regression models were run for overall CRCS adherence and modality-specific CRCS adherence. Model specific adjustment was done as appropriate; methods previously described were used to determine covariates and potential confounders to be added to each modality-specific model. All odds ratios were deemed significant given the 95% confidence interval and $\alpha = 0.05$. Approximately 100 people were needed to detect a significant difference for overall CRCS and colonoscopy adherence at 80% power, with a two-tailed test with $\alpha = 0.05$.

RESULTS

Descriptive respondent characteristics are reported in **Table 1**. Overall, respondents were 69.5% female, 43.3% married or a member of an unmarried couple, and 38.4% made less than $25,000 a year and 81.2% had at least a high school diploma. Mean age for the entire study population is 59.7 years (standard error (SE) ± 0.37). Mean length of time in the US for Caribbean immigrants was 24.5 years (SE ±1.3) and 16.7 years for African immigrants (SE ±1.63). African and Caribbean immigrants were less likely to have health insurance when compared to US-born Blacks (63.0, 80.6 and 92.8%, respectively; p <0.001). This trend continued for having a primary care physician (78.3, 80.6, and 87.3%, respectively; p <0.001).

Adjusted CRCS prevalence and adherence to national CRCS guidelines are presented in **Table 2**. For ever having any type of CRCS, Caribbean immigrants (95.0%) and African immigrants (90.2%) had a higher prevalence when compared to US-born Blacks (59.2%) (p-value <0.001). While the entire study population had a low proportion of stool test adherence (12.9%), US-born Blacks had lower proportions of colonoscopy adherence (40.1%; p-value <0.001) and overall CRCS adherence (45.8%; p-value <0.001), when compared to Caribbean immigrants (80.3% colonoscopy, 51.4% overall CRCS) and African immigrants (82.1% colonoscopy, 80.6% overall CRCS).

Odds ratios for each adjusted model are presented in **Table 3**. The adjusted model for overall CRCS adherence, region of birth, our independent variable of interest, revealed that African immigrants were five times more likely to be adherent when compared to US-born Blacks (OR 5.25; 95% CI 1.34–20.6). Also, in the overall CRCS adherence model, individuals that did not have healthcare coverage were less likely to be adherent (OR 0.24; 95% CI 0.11–0.56). Length of time in the US was also associated with increased odds of overall CRCS adherence, where there are a 4% increased odds of overall CRCS adherence for each year spent in the US (95% CI 1.02–1.07). In the adjusted model for adherence to stool test, no variables of interest were revealed to be statistically significantly associated with adherence. However, it must be noted that length time in the US showed a marginal association (OR 1.01; 95% CI 0.98–1.05). The adjusted model for colonoscopy as a modality of CRCS revealed that Caribbean immigrants had a 6.84 increased odds (95% CI 1.49–231.5) and African immigrants had a 7.14 (95% CI 1.27–40.3) increased odds of adherence when compared to US-born Blacks. Not having healthcare coverage was associated with being 87% less likely to be adherent to colonoscopy (OR 0.13; 95% CI 0.04–0.43). Lastly, length of time in the US was associated with increased levels of adherence in this model as well. Specifically, for each year spent in the US, participants were 6% more likely to adhere to colonoscopy (OR 1.06; 95% CI 1.03–1.10).

TABLE 1 | Respondent characteristics (N = 357).

	Total* N = 357 N (%)	US-Born n = 208 N (%)	Caribbean-Born n = 103 N (%)	African-Born n = 46 N (%)	p-value
Age					0.468
50–64	269 (75.4)	155 (74.5)	76 (73.8)	38 (82.6)	
65+	88 (24.6)	53 (25.5)	27 (26.2)	8 (17.4)	
Sex					0.385
Male	109 (30.5)	68 (32.7)	26 (25.2)	15 (32.6)	
Female	248 (69.5)	140 (67.3)	77 (74.8)	31 (67.4)	
Marital Status					
Married or Member of Unmarried Couple	154 (43.3)	62 (29.9)	61 (60.0)	31 (67.4)	**<0.001**
Divorced, Widowed or Separated	119 (33.7)	78 (37.7)	28 (28.0)	13 (28.3)	0.171
Never Married	81 (23.0)	67 (32.4)	12 (12.0)	2 (4.3)	**<0.001**
Annual Household Income					
>$10,000–24,999	136 (38.4)	86 (41.7)	41 (39.8)	9 (20.0)	**0.024**
$25,000–49,999	85 (24.0)	50 (24.3)	24 (23.3)	11 (24.4)	0.980
$50,000–74,999	40 (11.3)	29 (14.1)	7 (6.8)	4 (8.9)	0.140
$75,000+	32 (9.0)	13 (6.3)	12 (11.7)	7 (15.6)	0.080
Don't Know/Refused	61 (17.3)	28 (13.6)	19 (18.4)	14 (31.1)	**0.017**
Highest Level of Education					
<High School	57 (16.0)	28 (13.5)	26 (25.2)	3 (6.5)	**0.006**
High School Graduate	111 (31.1)	70 (33.6)	32 (31.1)	9 (19.6)	0.175
Some College	80 (22.4)	59 (28.4)	19 (18.4)	2 (4.3)	**0.001**
College and Beyond	99 (27.7)	43 (20.7)	25 (24.3)	31 (67.4)	**<0.001**
Don't Know/Not Sure	10 (2.8)	8 (3.8)	1 (1.0)	1 (2.2)	0.419
Healthcare Coverage					**<0.001**
Yes	305 (85.4)	193 (92.8)	83 (80.6)	29 (63.0)	
No	52 (14.6)	15 (7.2)	20 (19.4)	17 (37.0)	
Primary Care Doctor					**<0.001**
Yes	324 (91.0)	199 (95.7)	89 (87.3)	36 (78.3)	
No	32 (9.0)	9 (4.3)	13 (12.7)	10 (21.7)	
Routine Physical					0.154
Within the last year	321 (90.4)	189 (91.7)	94 (91.3)	38 (82.6)	
>1 Year	34 (9.6)	17 (8.3)	9 (8.7)	8 (17.4)	
	Mean ± SE (Range)	**Mean ± SE (Range)**	**Mean ± SE (Range)**	**Years ± SE (Range)**	**p-value**
Time in US (years)	44.1 ± 1.11 (0.08–75)	59.7 ± 0.48 (50–75)	24.5 ± 1.30 (0.08–55)	16.7 ± 1.63 (2–43)	**<0.001**

**May not sum to 357 due to missing data. Boldface indicates statistical significance (p < 0.05). SE, standard error.*

DISCUSSION

To our knowledge, this is the first study to assess within race differences of overall CRCS and modality-specific CRCS, providing a unique perspective on screening patterns for the Black, heterogeneous racial group. We found that the prevalence of overall CRCS was high in this study population, however, adherence was not ideal. In addition, we found that when we disaggregated the Black population, Caribbean and African Immigrant Blacks had higher proportions of ever having colonoscopy and overall CRCS when compared to US-born Blacks. Further, immigrant Blacks had higher odds of being adherent to colonoscopy recommendations than US-born Blacks.

The overall adjusted CRCS prevalence for this study population was 78.2%, which is higher than the Healthy People 2020 benchmark of 70.5% (40) and prevalence of ever having CRCS reported from other national surveys (40, 41). Specifically, BRFSS and the National Health Interview Survey data from 2013–2018 report CRCS prevalence between 59.1 and 67.8% among Blacks (40, 41). However, data within these national surveys are not reported as granularly as our study; therefore, we are unable to compare prevalence by ethnic sub-groups. Overall, prevalence of stool test within this population was lower than colonoscopy, which is similar to published literature documenting colonoscopy is the most common screening modality, 74.9–84.2%, when compared to stool tests, 5.3–7.5%, from 2012, which is a similar time frame to the current study (41). Further, in a racially diverse population, Hawley et al. reported 37% of participants preferred colonoscopy, while 31% preferred a stool based test (42). Similarly, Palmer et al. found that 57% of individuals who self-identified as Black preferred colonoscopy over stool based testing (43). Our findings show US-born Blacks had lower proportions of both colonoscopy and stool based tests when compared to African and Caribbean immigrants (see **Table 2**). These data suggest a need for targeted intervention towards US-born Blacks to increase CRCS uptake overall, and interventions to increase stool based testing within the Black population as a whole.

The proportions of the study population who were adherent to modality-specific tests and overall CRCS were quite low overall and

TABLE 2 | Adjusted prevalence and adherence of colorectal cancer screening for the CAP3 study population (N = 357).

	Overall Sample N = 357% (95% CI)	US-Born N = 208% (95% CI)	Caribbean-Born N = 103% (95% CI)	African-Born N = 46% (95% CI)	p-value
PREVALENCE[a]					
Stool Test[c]	34.6 (29.2–40.6)	30.7 (21.0–42.5)	42.7 (25.9–61.4)	38.5 (17.4–65.1)	0.081
Colonoscopy[d]	65.2 (58.5–71.3)	41.7 (28.9–55.6)	90.9 (79.1–96.4)	84.7 (61.2–95.1)	**<0.001**
Any CRCS[e]	78.2 (72.4–83.1)	59.2 (44.4–72.4)	95.0 (86.0–98.3)	90.2 (71.4–97.1)	**<0.001**
ADHERENCE[b]					
Stool Test[f]	12.9 (9.0–18.1)	11.9 (6.0–22.3)	17.3 (6.5–38.7)	9.3 (1.6–38.7)	**0.0430**
Colonoscopy[g]	55.6 (48.1–62.8)	40.1 (27.9–54.7)	80.3 (57.1–92.6)	82.1 (54.3–94.6)	**<0.001**
Overall CRCS[h]	52.6 (46.6–58.5)	45.8 (33.6–58.5)	51.4 (35.8–66.9)	80.6 (60.0–92.1)	**<0.001**

CAP3, Cancer Prevention Project of Philadelphia; CI, Confidence Interval; CRCS, Colorectal Cancer Screening. Boldface indicates statistical significance (p <0.05).

[a]Respondent ever had a stool based test in their lifetime; respondent ever had a colonoscopy in their lifetime; respondent ever had a stool based test, colonoscopy or flexible sigmoidoscopy in their lifetime.

[b]Respondent had a stool based test within the last year; respondent had a colonoscopy within the last 10 years; respondent had a stool test within the last year, a sigmoidoscopy in the last 5 years, or a colonoscopy within the last 10 years.

[c]Adjusted for length of time in the US, marital status, healthcare coverage, if the participant had a PCP, and income.

[d]Adjusted for sex, length of time in the US, marital status, healthcare coverage, if the participant had a PCP, whether the participant had a routine physical in the last year, income, and education.

[e]Adjusted for length of time in the US, marital status, healthcare coverage, if the participant had a PCP, and income.

[f]Adjusted for sex, length of time in the US, marital status, healthcare coverage, if the participant had a PCP, income and education.

[g]Adjusted for length of time in the US, marital status, healthcare coverage, if the participant had a PCP, whether the participant had a routine physical in the last year, income and education.

[h]Adjusted for length of time in the US, marital status, healthcare coverage, if the participant had a PCP, whether the participant had a routine physical in the last year, and education.

in comparison to national data (44). For example, 2018 BRFSS reported that among Black respondents, 69.7% met USPSTF recommendations for testing (44), versus ~53% overall adherence in this study. In addition, stool test had the lowest adherence in our study population across all sub-groups (9.3–17.3%), which is similar to Daskalakis et al., Shavers et al., and James et al. where adherence proportions ranged from 8.5–17% study in Black CRCS studies and considerably lower than O'Malley et al. and Waghray et al. that reported adherence proportions at 29–30.9% (25, 45–48). This finding is not surprising in that stool test is recommended in clinical practice less often than colonoscopy (49–56). However, contrary to our hypothesis, Caribbean immigrants had significantly higher stool test adherence compared to US-born respondents and both Caribbean and African immigrants were significantly more likely to be up-to-date with colonoscopy compared to US-born respondents (80.3–82.1% vs. 40.1%). While seeing a primary care provider facilitates the process/initiation of CRCS and may increase CRCS uptake (57–59), this does not explain the differences we observed. Specifically, there were no differences in having a routine physical in the last year by ethnic sub-group. Further, a higher proportion of US-born Blacks reported having a primary care doctor and health insurance (see **Table 1**). While these are the data, it could be that there was differential over reporting of CRCS in our sample. While the published literature shows that self-report and medical record data for cancer screening measures generally coincide, ethnic and racial minorities tend to over-report screening more than their white counterparts (60–66). While these data offer insights for the aggregate Black population, ethnic sub-group data are not available; thus, it is unclear whether immigrant Blacks over-reported CRCS compared to US-born Blacks. Lofters et al. assessed self-reported validity in a diverse Canadian population and found that all immigrants were more likely to over-report when compared to Canadian naturals (67). Still, this data did not disaggregate the immigrant population to make a clear distinction as to what ethnic groups or countries compromised this group. Further work to examine the agreement of self-reported and actual CRCS within the Black population is warranted to determine the validity of our findings.

Adjusted logistic regression analyses revealed that African immigrants have a 7-fold increased odds of overall CRCS adherence compared to US-born Blacks and both Caribbean and African immigrants were more likely to be adherent to colonoscopy. In addition, not having health insurance was independently associated with reduced odds of adherence to overall CRCS and colonoscopy. Surprisingly, there was no association between having a regular PCP and overall CRCS adherence (**Table 3**). Higher adherence among immigrant Blacks was contradictory to our original hypothesis. This could be influenced by length of time in the US, which was independently associated with increased odds of overall CRCS and colonoscopy adherence, as well as medical mistrust. For example, the availability of screening programs in the immigrant home country may be non-existent, which is the case for a majority of Caribbean and African countries (68, 69). Thus, immigrants may take advantage of preventive screening that has been previously inaccessible to them. Relatedly, medical mistrust and/or distrust of the US health infrastructure among US-born Blacks (70–73) may explain why they are less likely to be adherent to overall CRCS and colonoscopy when compared to immigrant Blacks. A long history of mistreatment of US-born Blacks in medicine and health related research is documented most

TABLE 3 | Adjusted logistic regression for the association between region of birth and colorectal cancer screening adherence (N = 357).

	Overall CRCS Adherence[a,d] N = 350 OR (95% CI)	Stool Test Adherence[b,e] N = 333 OR (95% CI)	Colonoscopy Adherence[c,f] N = 235 OR (95% CI)
Region of Birth			
US	Ref	Ref	Ref
Caribbean	1.43 (0.52–3.93)	1.61 (0.43–5.96)	**6.84 (1.49–31.5)**
Africa	**5.25 (1.34–20.6)**	1.20 (0.18–7.80)	**7.15 (1.27–40.3)**
Sex			
Male	Ref	Ref	Ref
Female	0.76 (0.46–1.27)	0.67 (0.35–1.31)	1.56 (0.82–2.95)
Length of Time in the US			
	1.04 (1.02–1.07)	1.02 (0.98–1.05)	**1.06 (1.02–1.10)**
Marital Status			
Married/Member of Unmarried Couple	Ref		Ref
Divorced, Widowed or Separated	0.75 (0.45–1.25)		0.68 (0.35–1.34)
Healthcare Coverage			
Yes	Ref	Ref	Ref
No	**0.24 (0.11–0.56)**	0.67 (0.18–2.47)	**0.13 (0.04–0.43)**
Primary Care Provider			
Yes	Ref	Ref	Ref
No	0.68 (0.41–1.12)	0.55 (0.19–1.56)	0.92 (0.46–1.81)
Routine Physical			
Within the last year		Ref	
>1 Year		0.27 (0.03–2.18)	
Annual Household Income			
≥$50,000			Ref
<$50,000			1.57 (0.72–3.41)
Highest Level of Education			
≤High School		Ref	Ref
>High School		0.56 (0.29–1.07)	0.97 (0.51–1.86)

CRCS, Colorectal Cancer Screening; OR, Odds Ratio; CI, Confidence Interval. Boldface indicates statistical significance (p <0.05).

[a]*Adjusted for sex, length of time in the US, marital status, healthcare coverage and if the participant had a PCP.*

[b]*Adjusted for sex, length of time in the US, education, healthcare coverage, if the participant had a PCP, and whether the participant had a routine physical in the last year.*

[c]*Adjusted for sex, length of time in the US, marital status, income, education, healthcare coverage and if the participant had a PCP.*

[d]*Respondent had a stool based test within the last year.*

[e]*Respondent had a colonoscopy within the last 10 years.*

[f]*Respondent had a stool test within the last year, a sigmoidoscopy in the last 5 years, or a colonoscopy within the last 10 years.*

famously by the Tuskegee study of "Untreated Syphilis in the male Negro", and has left a lasting, negative impact on US-born Blacks (70, 74–76). Events of the past are further exacerbated by the current social climate (77) and the disproportionate rates in which diseases affect the Black community. This mistrust of the healthcare system may be more innate in US-born Blacks when compared to immigrant Blacks, because these types of social injustices are not as common in their home countries. Subsequently, immigrant Blacks may be more likely to place their trust in healthcare professionals than their US-counterparts (78).

Finally, while our adjusted analyses revealed a higher odds of adherence to overall CRCS and colonoscopy among immigrant Blacks when compared to US-born Blacks, crude analyses for CRCS (data not shown) showed that lower proportions of immigrant Blacks, were up-to-date on screening when compared to their US-born counterparts. Thus, CRCS interventions to increase coverage and utilization of healthcare are warranted to ensure CRCS uptake in the heterogeneous Black population.

This study provides novel CRCS findings within the heterogeneous Black population, which is a major strength of this work. For the first time, we report within race differences (i.e. US-born, Caribbean and African Immigrant Blacks) for overall and modality-specific CRCS prevalence and adherence; and examined the association of region birth with overall and modality-specific CRCS adherence. There is scant literature on CRC screening in immigrant populations of those identifying as Black; thus, this study provides insight and begins to address a gap in the literature. Immigrant health is an emerging topic in the literature and this paper provides novel information within this body of research. In addition to our unique study population, our survey instrument allowed us to code prevalence and adherence similarly to other national surveys (30, 31, 79) making the overall sample data for Blacks comparable to national reports.

While this paper provides insights on CRCS within a heterogeneous Black population, there are limitations. This study, like other survey-based studies, is subject to various types of biases. First, study participants had to recall the type of CRCS as well as the length of time since their last CRCS, which could bias our findings. For example, telescoping may have occurred, where respondents were likely to report their CRCS to be more recent than it actually was. Recall bias could also have contributed to misclassification of screening type, where respondents recalled the wrong screening type or the wrong date since their last CRCS. However, previous work has shown

that the two to three part nature of the CRCS questions used, which were identical to those in a validated, national based survey (31), reduced the likelihood of telescoping (80). Also, recall bias could have contributed to missing data on CRCS use (data not shown); however, it is highly unlikely that our findings were affected by these missing data because only about 1.1% (n = 4) of all CRCS data were missing. In addition, this study included volunteer participants; thus there are no non-responders for comparison. Further, the validity of self-reported CRCS is quite high compared to medical records (61–65, 81), which limits bias. Second, this survey was interviewer-administered, which may have introduced social desirability bias where respondents felt that they had to provide the interviewer with socially acceptable answers indicating they had screening in the appropriate timeframe. This type of bias would have subsequently led to non-differential misclassification bias (39), which likely would not have a significant impact on our findings. Third, our length of time in the US variable assumed that all US-born Blacks lived in the US their entire lives. Although the data on US expatriates are limited (82–84), approximately 9 million US-born individuals live abroad for 5–10 years. To explore whether this could have impacted our findings, we conducted a post-hoc sensitivity analysis based on a liberal assumption that 10% of US-born Blacks lived outside of the US for 5 years. Findings from this analysis assessing the association of region of birth with overall CRCS and colonoscopy were almost identical to the original analyses (data not shown). Fourth, cross-sectional studies generally have inherent limitations given unknown temporality; however, it was not an issue for these analyses, as region of birth preceded CRCS. Fifth, obtaining CRCS can be difficult (85–90); however, CRCS barriers, which include among other things, fear, logistics of the test, lack of information, time, and lack of physician recommendation were not assessed, which could impact our findings. Had we been able to incorporate CRCS barriers in our regression models, the odds ratios could have been attenuated towards the null. Limited generalizability, is also a limitation of this study. Participants in this study were a specific sample of persons who self-identified as Black of Philadelphia and as such are not necessarily representative of the CRC screening population in the US. This, data may only be comparable to cities that are also majority Black and have similar proportions of immigrant Blacks from Africa and the Caribbean. Aligned with this, while the region of birth variable included multiple countries across the Caribbean and Africa, it must be noted that the majority of Caribbean immigrants came from Haiti (69.9%), followed by Jamaica (19.4); and African immigrants came from Nigeria (67.4%) and Liberia (15.2%) (data not shown). Subsequently, the generalizability of this data to all immigrants from these regions is limited. Also, while we powered to observe significant differences between region of birth and overall CRCS and colonoscopy we were drastically underpowered to observe such differences for stool based CRCS. In order to observe a statistically significant difference between region of birth and stool tests, we would have need over 1,100 participants at 80% power, with a two-tailed test with $\alpha = 0.05$. Lastly, we did not differentiate between screening and diagnostic colonoscopy after stool-based CRCS. However, given the very low prevalence of stool test in our study population, it is likely that the majority of colonoscopies were for screening purposes and not diagnostic, subsequently having no meaningful effect on our findings.

In summary, self-reported overall adherence to CRCS and modality specific CRCS are sub-optimal among self-identified Blacks in Philadelphia. While immigrant Blacks were more likely to be adherent to colonoscopy when compared to US-Born Blacks, CRCS was still sub-optimal across all ethnic sub-groups, suggesting that interventions to increase adherence should be targeted to the entire US-Black population. This study provides the first data on CRCS and region of birth among a heterogeneous Black population that has historically been underrepresented in research. To advance CRCS research particularly in immigrant and traditionally underserved populations, future studies could assess CRCS in the expanded CAP3 population, which now includes populations in California and the Caribbean. In addition, future studies should explore CRCS barriers to better understand what might be influencing CRCS in heterogeneous Black populations and whether these barriers are nuanced by culturally specific factors.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Fox Chase Cancer Center Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EB and CR had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis study conception and design. CR is responsible for the original cohort study design. The subset analysis of CAP3 data was designed and conceptualized by EB. Statistical analysis and drafting of manuscript was done by EB. Critical revision of the manuscript for intellectual content was done by RJ. CR is responsible for study supervision, administrative, technical, and material support. All authors contributed to the article and approved the submitted version.

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Cancer Screening Knowledge and Behavior in a Multi-Ethnic Asian Population: The Singapore Community Health Study

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Background: Cancer has become the leading cause of mortality in Singapore and among other Asian populations worldwide. Despite the presence of National Cancer Screening programmes in Singapore, less than half of the population has had timely screening according to guidelines. The underlying factors of poor cancer screening rates and health outcomes among Asian ethnic groups remain poorly understood. We therefore examined cancer screening participation rates and screening behavior in a multi-ethnic Singapore population.

Methods: We collected data from 7,125 respondents of the 2015–2016 Singapore Community Health Study. Factors associated with cervical, breast, and colorectal cancer screening were evaluated using modified Poisson regression. Adjusted prevalence ratios were computed with 95% confidence intervals after adjusting for confounders.

Results: The mean age of the respondents was 57.7 ± 10.9 years; 58.9% were female and were predominately Chinese (73.0%), followed by Malay (14.2%), and Indian (10.9%). Less than half of the respondents in the recommended age groups had undergone cancer screening (cervical, 43%; breast, 35.1%; colorectal, 27.3%). Malay respondents were significantly less likely to screen as recommended for cervical (aPR = 0.75, CI = 0.65–0.86, $p < 0.001$), breast (aPR = 0.83, CI = 0.68–0.99, $p = 0.045$), and colorectal cancer (aPR = 0.55, CI = 0.44–0.68, $p < 0.001$), as compared to Chinese respondents. Respondents who had obtained lower secondary level education were 42% more likely to screen for cervical cancer (aPR = 1.42, CI = 1.23–1.64, $p < 0.001$), and 22% more likely to screen for breast cancer (aPR = 1.22, CI = 1.02–1.46, $p = 0.032$), compared to those with primary level education and below. Respondents with a household income ≥S $10,000/month were 71% more likely to screen for breast cancer (aPR = 1.71, CI = 1.37–2.13, $p < 0.001$), as compared with <$2,000/month.

Conclusions: Ethnicity and socio-economic status were significantly associated with lower uptake of cancer screening tests in Singapore. To improve the screening uptake among disadvantaged groups, a multi-faceted approach is needed that addresses the barriers to screening such as the adequacy of subsidy schemes and ethnic differences.

Keywords: behavior, breast cancer, cancer, cervical cancer, colorectal cancer, disparities, knowledge, screening

INTRODUCTION

GLOBOCAN estimated 18.1 million new cases and 9.6 million cancer deaths worldwide in 2018 (1). Approximately half of the global burden of cancer was attributed to Asia in part due to 60% of the global population residing there and is projected to continue increasing as life expectancy improves (1). Cancer is the leading cause of mortality among both native and immigrant Asians irrespective of their country of residence (2–6). Those residing in Western countries where they are the ethnic minority are more likely to present with advanced stages of cancer and to have lower cancer screening rates in comparison to non-Hispanic whites (2–6). A study in Canada demonstrated breast cancer screening disparities among immigrant women by world region of origin and found that South Asian women, which included Indians, had the lowest screened as recommended rate at 48.5%. East Asian and Pacific women, which included Chinese, had a screened as recommended rate of 61.1% (7). In another study in the United States, regression models showed that foreign-born women from Southeast Asia, which included Singaporean Chinese, Indian and Malays, were more likely to be unscreened for cervical cancer (13.7%) compared to US-born women (7.6%) (8). Studies conducted in Western countries are often too underpowered to distinguish different Asian ethnic sub-groups (9, 10). Singapore is an opportune country to explore cancer screening behaviors among Asian ethnic sub-groups due to the nation's large population of East Asians (Chinese), South Asians (Indians), and South East Asians (Malays).

In Singapore, cancer was the leading cause of death with 29.1% of total deaths in 2017 (11, 12). The Singapore Cancer Registry data showed that colorectal cancer (17.2%) had replaced lung cancer (14.8%) to become the most common cancer in men (13). Breast cancer (29.1%) and colorectal cancer (13.4%) remained the most common cancers in women (13). National Cancer Screening programmes have been launched to reduce morbidity and mortality in breast, cervical, and colorectal cancers. Through the Health Promotion Board (HPB), Singapore became the first Asian country to launch a population-wide national breast cancer screening programme in 2002 for females aged 50–69 years (14), which was shortly followed by the launch of a national cervical cancer screening programme in 2004 for females aged 25–69 years (15). From 2003, Singapore Cancer Society has been involved in large-scale opportunistic colorectal cancer screening. In 2011, HPB launched a national screening programme for colorectal cancer for individuals aged 50 and above (16). Although public awareness of screening and accessibility increased, the National Health Survey 2010 data showed that timely screening remained low with less than half of the population having had timely screening according to guidelines (17). Therefore, it is necessary to evaluate the progress of cancer screening.

This study aims to examine cervical, breast, and colorectal cancer screening behaviors in Singapore and identify how socio-demographic factors such as ethnicity and socio-economic status are associated with cancer screening rates. We will also examine the extent of the knowledge–behavior gap in cancer screening behavior. In doing so, we aim to better understand the determinants of cancer screening behaviors in the population of Singapore to improve screening programmes for the under-screened groups.

Abbreviations: aPR, adjusted prevalence ratio; CI, confidence interval; HPB, Health Promotion Board; FOBT, faecal occult blood test; NUS, National University of Singapore; SSHSPH, Saw Swee Hock School of Public Health.

METHODS

Study Population and Study Setting

Data used in this cross-sectional study was derived from the Singapore Community Health Study (CHS), a population health survey that was conducted in Queenstown and Bukit Panjang (18, 19) between April 2015 and August 2016. The surveyed districts were catchment areas for the National University Health System and resembled the age, gender, and ethnic distribution of the national population census (20). All Singaporean citizens and permanent residents aged 40 and above were eligible for participation in CHS. A total of 7,125 residents in this age group were interviewed (Bukit Panjang—4,906; Queenstown —2,219).

Data Collection

Recruitment in CHS occurred through community club events and advertisements (banners/posters) in residential blocks. All household members were eligible to participate in the study, which was voluntary and self-selected. Households also received invitation letters at least two weeks before being visited by a trained interviewer. A group of field work team members were required to pass an assessment after undergoing a minimum of three days of training by qualified staff from the University on consent-taking and administering the questionnaire before they were allowed to interview participants. A response rate could not be ascertained due to the multi-modal recruitment process.

Interviewer-administered standardized questionnaires were conducted in the preferred language and location of the

participant (own home or at the nearby Residents' Committee centre). A translator was arranged if required. Informed consent was taken from all participants.

The questionnaire explored socio-demographics (age, gender, ethnicity), socio-economic indicators (education level, household income, housing type), living arrangement (alone or with others), lifestyle practices including smoking and alcohol consumption, medical history (previous cancer diagnosis or any family history of any cancer) and cancer screening practices. Education level was categorized as primary [passing the Primary School Leaving Examination (PSLE)], lower secondary (years 1–3), secondary (passing the Singapore-Cambridge General Certificate of Education (GCE) Normal or Ordinary Level Examination), junior college (passing the GCE-Advanced Level Examination), polytechnic/arts institution (obtaining a diploma), and university (obtaining a degree, masters or PhD). For cervical cancer screening, the questions were: "Do you know what a Pap smear is?"; "Have you ever had a Pap smear test?"; "How long ago did you have your last smear done?". For breast cancer screening the questions were: "Do you know what a mammogram is?"; "Have you ever had a mammogram?", "How long ago did you have your last mammography done?". Finally, for colorectal cancer screening the questions were: "Have you ever had a blood stool test to determine whether the stool contains blood?"; "How long ago did you have your last blood stool test done?'; "Have you ever had either sigmoidoscopy or colonoscopy, an examination in which a tube is inserted in the rectum to view the colon for signs of cancer or other health problems?"; "How long ago did you have your last sigmoidoscopy or colonoscopy done?".

According to the screening guidelines of Singapore (21), the frequency of cervical and breast cancer screening was considered done as recommended if women aged 25–69 years reported having a Pap smear every 3 years, and if women aged 50–69 years reported having a mammogram every 2 years, respectively. Colorectal cancer screening was done as recommended if fecal occult blood test (FOBT) was done annually or sigmoidoscopy/colonoscopy was done once every 10 years for individuals aged ≥50 years.

Ethics approval was obtained from the National Health Group Domain Specific Review Board (2015-00095) as well as the National University of Singapore IRB (S-19-340).

Statistical Analysis

Baseline characteristics were reported as categorical variables and tabulated using proportions for the descriptive analysis. For estimating prevalence ratios in cross-sectional studies, Zou's method using multivariate modified Poisson regression with robust sandwich variance was chosen as the most viable statistical option as described in Lee's Practical Guide for Multivariate Analysis of Dichotomous Outcomes (22). This method was utilized to estimate the adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) using R packages lmtest v0.9-3.7 and sandwich v2.5-1. Variables identified as determinants of screening behaviors in previous studies (23–28) that proved to be significant in the univariate analysis for the respective cancer groups (*e.g.* age, ethnicity, education, household income, housing type, living arrangement, past history of any cancer, family history of any cancer, and frequent smoking) were used to adjust for potential confounding. The analysis was also stratified by family history. A P-value ≤0.05 was used to determine statistical significance. The knowledge–behavior gap was calculated as the difference in proportions between those that reported having knowledge of the screening test and those that ever did the screening test or screened as recommended. All analysis was performed using R version 3.6.2.

RESULTS

Respondents of the survey (N = 7,125) were mostly aged 40–69 years (85%) with a mean age of 57.7 ± 10.9 years and ethnically Chinese (73%) with a slight majority of females (58.9%) (**Table 1**). The age, gender, and ethnic distribution of our survey sample resembled the population census during the same time period (**Supplemental Figures 1**–**3**).

A majority of the screening-eligible female respondents reported having knowledge of Pap smear (80.0%) and mammography (93.6%). At least three quarters had ever been screened (cervical, 77.2%; breast, 75.2%); whereas, less than half had undergone screening as recommended (cervical, 43.0%; breast, 35.1%) (**Table 2**).

Nearly half of the eligible respondents (49.0%) had ever been screened for colorectal cancer, but only 27.3% had screened within the recommended time period. More respondents had ever had FOBT (42.9%) compared to colonoscopy or sigmoidoscopy (22.1%). Among female respondents aged 50–69 years, only 10.7% had screened for all three cancers (cervical, breast, colorectal) within the recommended time period.

Characteristics Associated With Female Cancer Screening (Cervical and Breast) Knowledge of Screening Test

In the multivariate analysis, Malay and Indian ethnicity and higher level of education were significantly associated with reporting having knowledge of the Pap smear test (**Table 3**).

Individuals of Malay (aPR = 1.17, CI = 1.12–1.22, $p < 0.001$) and Indian (aPR = 1.18, CI = 1.13–1.23, $p < 0.001$) ethnicity were more likely to report knowledge of Pap smear testing as compared with ethnic Chinese. In contrast, Malay women were less likely than Chinese women to report having knowledge of mammography (aPR = 0.92, CI = 0.88–0.96, $p < 0.001$) (**Table 3**).

All levels of education higher than primary school and below were significantly associated with self-reported knowledge of the screening tests even for those with only lower secondary school education. Compared with having attained at most primary school education, the prevalence of self-reported knowledge regarding Pap smear was already 47% higher at secondary school level education (aPR = 1.47, CI = 1.38–1.56, $p < 0.001$). Household income and housing type showed weaker associations with self-reported Pap smear knowledge.

TABLE 1 | Characteristics of the study population by cancer screening eligibility criteria*.

Characteristic	Total	Cervical Cancer Screening	Breast Cancer Screening	Colorectal Cancer Screening
	N = 7125 n(%)	N = 3584 n(%)	N = 2532 n(%)	N = 5281 n(%)
Age(years)				
40–49	1,842 (25.9)	1058 (29.5)	–	–
50–59	2,386 (33.5)	1447 (40.4)	1449 (57.2)	2384 (45.1)
60–69	1,830 (25.7)	1079 (30.1)	1083 (42.8)	1830 (34.7)
70–79	827 (11.6)	–	–	827 (15.7)
80 and above	240 (3.4)	–	–	240 (4.5)
Gender				
Female	4,197 (58.9)	–	–	3,135 (59.4)
Male	2,928 (41.1)	–	–	2,146 (40.6)
Ethnicity				
Chinese	5,203 (73.0)	2,584 (72.1)	1,893 (74.8)	4,029 (76.3)
Malay	1,014 (14.2)	563 (15.7)	381 (15.0)	720 (13.6)
Indian	777 (10.9)	371 (10.4)	231 (9.1)	473 (9.0)
Others	131 (1.8)	66 (1.8)	27 (1.1)	59 (1.1)
Education				
Primary and below	2,415 (33.9)	1,149 (32.1)	993 (39.2)	2,163 (41.0)
Lower secondary	1,414 (19.8)	705 (19.7)	552 (21.8)	1,176 (22.3)
Secondary	1,546 (21.7)	900 (25.1)	615 (24.3)	1,092 (20.7)
Junior College	391 (5.5)	182 (5.1)	102 (4.0)	247 (4.7)
Polytechnic/Arts Institution	637 (8.9)	309 (8.6)	143 (5.6)	320 (6.1)
University & above	719 (10.1)	338 (9.4)	126 (5.0)	280 (5.3)
Monthly household income ($S)				
<$2,000	2,185 (30.7)	937 (26.1)	754 (29.8)	1,882 (35.6)
$2,000–$3,999	1,586 (22.3)	845 (23.6)	534 (21.1)	1,069 (20.2)
$4,000–$5,999	953 (13.4)	511 (14.3)	316 (12.5)	590 (11.2)
$6,000–$9,999	734 (10.3)	380 (10.6)	205 (8.1)	400 (7.6)
≥$10,000	343 (4.8)	173 (4.8)	114 (4.5)	206 (3.9)
Housing type				
≤2-room public flat	384 (5.4)	156 (4.4)	113 (4.5)	308 (5.8)
3-room public flat	1,795 (25.2)	812 (22.7)	545 (21.5)	1,297 (24.6)
≥4-room public flat/private	4,945 (69.4)	2,615 (73.0)	1,873 (74.0)	3,675 (69.6)
Living arrangement				
Alone	399 (5.6)	162 (4.5)	138 (5.5)	352 (6.7)
With others	6,722 (94.3)	3,420 (95.4)	2,394 (94.5)	4,927 (93.3)
Past history of any cancer				
No	6,867 (96.4)	3,441 (96.0)	2,405 (95.0)	5,044 (95.5)
Yes	258 (3.6)	143 (4.0)	127 (5.0)	237 (4.5)
Family history of any cancer				
No	4,867 (68.3)	2,344 (65.4)	1,602 (63.3)	3,551 (67.2)
Yes	2,258 (31.7)	1,240 (34.6)	930 (36.7)	1,730 (32.8)
Frequent smoking[a]				
No	5,834 (81.9)	3,333 (93.0)	2,401 (94.8)	4,401 (83.3)
Yes	805 (11.3)	102 (2.8)	55 (2.2)	546 (10.3)
Frequent alcohol intake[b]				
No	4,931 (69.2)	2,762 (77.1)	1,961 (77.4)	3,605 (68.3)
Yes	559 (7.8)	134 (3.7)	86 (3.4)	403 (7.6)

*Based on recommended screening guidelines for selected cancers as defined by MOH guidelines: cervical cancer—Pap smear for sexually active females aged 25 to 69 years at least once every 3 years; breast cancer—mammography for females aged 50 to 69 years every 2 years; colorectal cancer—fecal occult blood test (FOBT) done annually or sigmoidoscopy/colonoscopy once every 10 years for individuals aged ≥50 years.

[a]Frequent smoking is defined as smoking cigarettes daily.

[b]Frequent alcohol intake is defined as having at least 1–4 servings per week.

Ever Screened

Education level and household income were significantly associated with ever having a Pap smear test (**Table 3**). In addition, women living with others (aPR = 1.30, CI = 1.11–1.53, p = 0.001) were 30% more likely to ever have a Pap smear compared with those living alone. Older age, higher education level, high household income, and having a more expensive housing type were significantly associated with ever having a mammogram, whereas Malay ethnicity was associated with a lower likelihood of ever having a mammogram (**Table 3**).

Among those who reported no knowledge of the screening tests (N = 711 for Pap smear; N = 161 for mammogram), 44.7% underwent screening with Pap smear (n = 318) and 26.1% with mammogram (n = 42). For Pap smear, respondents of Malay (aPR = 0.45, CI = 0.27–0.75, p = 0.002) and Indian (aPR = 0.36, CI = 0.16–0.82, p = 0.015) ethnicity were less likely to report this

TABLE 2 | Cancer screening test knowledge and participation rates.

	Number of respondents eligible for screening as recommended	Reported having knowledge of screening test[∓]	Those who had ever been screened	Those who had screened as recommended*
	Total (N)	n(%)	n(%)	n(%)
Pap Smear	3,584	2,872 (80.0)	2,763 (77.2)	1,539 (43.0)
Mammography	2,532	2,370 (93.6)	1,903 (75.2)	889 (35.1)
FOBT only	5,281	–	2,267 (42.9)	–
Colonoscopy/ Sigmoidoscopy only		–	1,167 (22.1)	–
FOBT/Colonoscopy/ Sigmoidoscopy		–	2,589 (49.0)	1,440 (27.3)
All of the above°	2,536	–	–	272 (10.7)

*Based on recommended screening guidelines for selected cancers as defined by MOH guidelines:
cervical cancer—Pap smear for sexually active females aged 25 to 69 years at least once every 3 years; breast cancer—mammography for females aged 50 to 69 years every 2 years; colorectal cancer—faecal occult blood test (FOBT) done annually or sigmoidoscopy/colonoscopy once every 10 years for individuals aged ≥50 years.
∓Due to limitations of the collected data, knowledge for colorectal cancer screening was not reported.
°Pap smear, mammography, and either FOBT or colonoscopy/sigmoidoscopy.

behavior compared to Chinese (**Supplemental Table 1**). The sub-group analysis was not reported for mammogram due to the small sample size.

Screened as Recommended

Participants of Malay ethnicity (aPR = 0.75, CI = 0.65–0.86, p < 0.001) and those aged 60–69 years (aPR = 0.73, CI = 0.64–0.83, p < 0.001) were significantly less likely to undergo Pap smear screening as recommended at least once every three years (**Table 3**). Socio-economic factors directly associated with screening as recommended were higher education level and higher household income. Respondents living with others (aPR = 1.81, CI = 1.31–2.52, p = 0.002) were 81% more likely to screen as recommended compared to those living alone. Similar to cervical cancer screening, Malay ethnicity (aPR = 0.83, CI = 0.68–0.99, p = 0.045) was observed to be less likely to screen for breast cancer as recommended compared to Chinese. Higher education and higher household income were also significantly associated with mammogram screening as recommended at least once every two years (**Table 3**). A higher proportion of respondents reported desirable cancer screening behavior among those who had any family history of any cancer in comparison with those without any family history (**Supplementary Table 4**).

Characteristics Associated With Colorectal Cancer Screening

Older age (60–79 years), higher education level, higher household income, past history of any cancer, and family history of any cancer were significantly associated with having ever screened for colorectal cancer by FOBT and/or scope (colonoscopy/sigmoidoscopy) (**Table 4**). Malay and Indian respondents as well as those who smoked daily were significantly less likely to be ever screened. The same variables that were significantly associated with having ever been screened by FOBT, colonoscopy, or sigmoidoscopy were also significantly associated with screening as recommended (**Table 4**).

A key difference was that among the ethnic groups, only Malay ethnicity (aPR = 0.55, CI = 0.44–0.68, p < 0.001), and not Indian ethnicity, remained significantly associated with a lower likelihood of screening as recommended.

We examined determinants of screening as recommended for all three cancers among eligible women aged 50–69. Higher level of education and higher household income were significantly associated with having screened as recommended for all three cancers, whereas Malay ethnicity (aPR = 0.53, CI = 0.33–0.84, p = 0.008) was significantly associated with a lower likelihood as compared with Chinese ethnicity (**Supplemental Table 2**).

Knowledge–Behaviour Gap

The gap between the percentage that reported knowledge of Pap smear and were ever screened with Pap smear was 2.8% (**Table 2**). For mammography, the gap was higher at 18.4%. Our multivariate analysis indicated the Malay ethnicity was in general less likely to exhibit cancer screening behavior compared with ethnic Chinese. The knowledge–behavior gap among the ethnicities was calculated using the difference in proportions between those that reported having knowledge of the screening test and those that ever did the screening test or screened as recommended. For ever having done the screening test, Malays had the largest knowledge–behavior gap with 13.1% for Pap smear and 26.5% for mammography (**Figure 1**).

Likewise, Malays exhibited the largest knowledge–behavior gap at 52.8% for having screened with Pap smear as recommended. For having screened with mammography as recommended, the gaps were similarly high across the three ethnicities—Chinese (59.4%), Malay (56.7%), Indian (56.7%).

DISCUSSION

Although screening recommendation guidelines vary slightly between countries, our screened as recommended participation rates fell behind other high-income East Asian countries such as Taiwan in 2016 (cervical, 72.1%; breast, 39.3%; colorectal, 40.7%) (29), and South Korea in 2014 (cervical, 66.1%; breast, 66.0%;

TABLE 3 | Adjusted prevalence ratio (aPR) estimates for characteristics associated with knowledge of and participation in cervical and breast cancer screening.

Characteristic	Cervical cancer[a]						Breast cancer[b]					
	Reported having knowledge of the screening test		Those who had ever been screened		Those who had screened as recommended*		Reported having knowledge of the screening test		Those who had ever been screened		Those who had screened as recommended**	
	aPR (95% CI)	p-value	aPR (95% CI)	p-value	aPR (95% CI)	p-value	aPR (95% CI)	p-value	aPR (95% CI)	p-value	aPR (95% CI)	p-value
Age (years)												
40–49	Ref		Ref		Ref							
50–59	1.01 (0.98–1.05)	0.50	1.00 (0.95–1.04)	0.92	0.91 (0.83–0.99)	0.037	Ref		Ref		Ref	
60–69	0.96 (0.91–1.01)	0.086	0.98 (0.93–1.04)	0.53	0.73 (0.64–0.83)	<0.001	1.00 (0.98–1.03)	0.73	1.13 (1.07–1.19)	<0.001	0.99 (0.87–1.13)	0.86
Ethnicity												
Chinese	Ref		Ref		Ref		Ref		Ref		Ref	
Malay	1.17 (1.12–1.22)	<0.001	0.97 (0.91–1.02)	0.26	0.75 (0.65–0.86)	<0.001	0.92 (0.88–0.96)	<0.001	0.79 (0.72–0.87)	<0.001	0.83 (0.68–0.99)	0.045
Indian	1.18 (1.13–1.23)	<0.001	1.03 (0.97–1.09)	0.40	1.03 (0.92–1.17)	0.59	0.99 (0.95–1.03)	0.61	0.94 (0.86–1.03)	0.20	1.03 (0.85–1.25)	0.74
Others	1.02 (0.93–1.12)	0.68	1.02 (0.92–1.15)	0.67	0.89 (0.69–1.16)	0.40	0.86 (0.73–1.02)	0.075	1.01 (0.83–1.22)	0.96	1.12 (0.71–1.75)	0.63
Education												
Primary and below	Ref		Ref		Ref		Ref		Ref		Ref	
Lower secondary	1.27 (1.18–1.36)	<0.001	1.22 (1.15–1.31)	<0.001	1.42 (1.23–1.64)	<0.001	1.07 (1.03–1.11)	<0.001	1.10 (1.02–1.19)	0.009	1.22 (1.02–1.46)	0.032
Secondary	1.47 (1.38–1.56)	<0.001	1.21 (1.14–1.29)	<0.001	1.40 (1.22–1.60)	<0.001	1.10 (1.07–1.14)	<0.001	1.13 (1.06–1.21)	<0.001	1.33 (1.12–1.57)	0.001
Junior College	1.43 (1.33–1.55)	<0.001	1.19 (1.09–1.30)	<0.001	1.30 (1.07–1.59)	0.009	1.11 (1.07–1.15)	<0.001	1.09 (0.97–1.22)	0.14	1.10 (0.82–1.48)	0.51
Polytechnic	1.48 (1.38–1.59)	<0.001	1.15 (1.06–1.25)	0.001	1.34 (1.14–1.58)	0.001	1.11 (1.07–1.15)	<0.001	1.15 (1.05–1.26)	0.004	1.19 (0.92–1.54)	0.19
University	1.48 (1.38–1.59)	<0.001	1.16 (1.07–1.26)	<0.001	1.44 (1.22–1.70)	<0.001	1.11 (1.07–1.16)	<0.001	1.15 (1.05–1.28)	0.005	1.31 (1.01–1.68)	0.039
Monthly household income ($S)												
<$2,000	Ref		Ref		Ref		Ref		Ref		Ref	
$2,000–$3,999	1.05 (1.00–1.11)	0.067	1.10 (1.04–1.17)	0.002	1.21 (1.06–1.37)	0.004	1.00 (0.97–1.04)	0.81	1.04 (0.98–1.12)	0.22	1.12 (0.95–1.32)	0.18
$4,000–$5,999	1.10 (1.04–1.16)	0.001	1.16 (1.09–1.24)	<0.001	1.28 (1.12–1.47)	<0.001	1.01 (0.98–1.05)	0.4	1.07 (0.99–1.16)	0.067	1.25 (1.03–1.50)	0.02
$6,000–$9,999	1.10 (1.05–1.17)	<0.001	1.20 (1.12–1.28)	<0.001	1.48 (1.29–1.71)	<0.001	1.00 (0.96–1.04)	0.98	1.02 (0.93–1.12)	0.63	1.18 (0.95–1.47)	0.14
≥$10,000	1.12 (1.06–1.19)	<0.001	1.25 (1.16–1.34)	<0.001	1.51 (1.28–1.79)	<0.001	1.01 (0.98–1.05)	0.41	1.20 (1.11–1.30)	<0.001	1.71 (1.37–2.13)	<0.001
Housing type												
≤2-room public flat	Ref		Ref		Ref		Ref		Ref		Ref	
3-room public flat	1.06 (0.93–1.20)	0.41	1.03 (0.88–1.20)	0.74	1.05 (0.79–1.40)	0.78	1.05 (0.97–1.14)	0.26	1.27 (1.05–1.53)	0.013	1.22 (0.84–1.77)	0.30
≥4-room public flat/ private	1.22 (1.07–1.38)	0.003	1.20 (1.04–1.39)	0.013	1.19 (0.90–1.57)	0.31	1.06 (0.98–1.15)	0.14	1.36 (1.13–1.63)	0.001	1.30 (0.91–1.87)	0.15
Living arrangement												
Alone	Ref		Ref		Ref		–		–	–	–	–
With others	0.99 (0.90–1.09)	0.86	1.30 (1.11–1.53)	0.001	1.81 (1.31–2.52)	0.002	–		–	–	–	–
Past history of any cancer												
No	–		–	–	–	–	Ref		Ref		Ref	
Yes	–		–	–	–	–	1.02 (0.98–1.05)	0.44	1.16 (1.08–1.24)	<0.001	1.69 (1.41–2.02)	<0.001

[a]*Multivariate modified Poisson regression model analyses were adjusted for age, ethnicity, education, monthly household income, housing type, and living arrangement.*

[b]*Multivariate modified Poisson regression model analyses were adjusted for age, ethnicity, education, monthly household income, housing type, and past history of any cancer. No significant characteristics were found to be associated with knowledge of mammography on univariate analysis.*

**Based on recommended screening guideline for cervical cancers as defined by MOH guidelines: Pap smear for sexually active females aged 25 to 69 years at least once every 3 years.*

***Based on recommended screening guideline for breast cancer as defined by MOH guidelines: mammography for females aged 50 to 69 years every 2 years.*

TABLE 4 | Adjusted prevalence ratio (aPR) estimates for characteristics associated with participation in colorectal cancer screening.

Characteristic	Those who had ever been screened by scope		Those who had ever been screened by FOBT		Those who had ever been screened by any three colorectal cancer tests		Those who had screened as recommended*	
	aPR (95% CI)	p-value	aPR (95% CI)	p-value	aPR (95% CI)	p-value	aPR (95% CI)	p-value
Age (years)								
50–59	Ref		Ref		Ref		Ref	
60–69	1.31 (1.14–1.50)	<0.001	1.16 (1.07–1.26)	<0.001	1.13 (1.06–1.22)	0.001	1.25 (1.12–1.40)	<0.001
70–79	1.55 (1.27–1.88)	<0.001	1.19 (1.05–1.34)	0.005	1.17 (1.05–1.30)	0.004	1.34 (1.14–1.59)	0.001
80 and above	1.60 (1.19–2.14)	0.002	1.17 (0.96–1.42)	0.12	1.20 (1.02–1.42)	0.032	1.14 (0.85–1.53)	0.38
Gender								
Female	Ref		Ref		Ref		Ref	
Male	1.11 (0.98–1.25)	0.10	0.98 (0.91–1.06)	0.70	1.02 (0.95–1.09)	0.54	1.08 (0.97–1.21)	0.14
Ethnicity								
Chinese	Ref		Ref		Ref		Ref	
Malay	0.51 (0.39–0.66)	<0.001	0.50 (0.42–0.58)	<0.001	0.50 (0.43–0.58)	<0.001	0.55 (0.44–0.68)	<0.001
Indian	0.78 (0.63–0.98)	0.034	0.73 (0.63–0.84)	<0.001	0.78 (0.68–0.88)	<0.001	0.92 (0.77–1.10)	0.36
Others	0.72 (0.42–1.23)	0.23	0.67 (0.47–0.97)	0.032	0.67 (0.48–0.92)	0.015	0.75 (0.48–1.19)	0.22
Education								
Primary and below	Ref		Ref		Ref		Ref	
Lower secondary	1.00 (0.84–1.19)	0.98	0.99 (0.89–1.11)	0.89	0.99 (0.90–1.09)	0.78	1.07 (0.92–1.24)	0.38
Secondary	1.32 (1.11–1.57)	0.002	1.20 (1.08–1.33)	<0.001	1.22 (1.12–1.33)	<0.001	1.25 (1.07–1.44)	0.004
Junior College	1.27 (0.99–1.63)	0.062	1.12 (0.95–1.31)	0.17	1.11 (0.96–1.28)	0.16	1.15 (0.92–1.44)	0.23
Polytechnic/Arts Institution	1.45 (1.16–1.81)	0.001	1.36 (1.19–1.55)	<0.001	1.33 (1.19–1.49)	<0.001	1.46 (1.21–1.76)	<0.001
University & above	1.41 (1.09–1.82)	0.008	1.37 (1.19–1.58)	<0.001	1.30 (1.14–1.48)	<0.001	1.41 (1.14–1.74)	0.002
Monthly household income ($S)								
<$2,000	Ref		Ref		Ref		Ref	
$2,000–$3,999	1.00 (0.84–1.18)	0.98	1.06 (0.96–1.17)	0.22	1.06 (0.97–1.15)	0.19	1.08 (0.94–1.25)	0.26
$4,000–$5,999	1.16 (0.96–1.40)	0.14	0.98 (0.87–1.11)	0.77	1.01 (0.91–1.13)	0.78	1.10 (0.94–1.30)	0.25
$6,000–$9,999	1.22 (0.98–1.51)	0.069	1.04 (0.91–1.18)	0.59	1.07 (0.96–1.20)	0.23	1.18 (0.98–1.41)	0.074
≥$10,000	1.47 (1.14–1.90)	0.003	1.20 (1.04–1.39)	0.013	1.18 (1.03–1.35)	0.014	1.30 (1.04–1.62)	0.021
Housing type								
≤2-room public flat	Ref		Ref		Ref		Ref	
3-room public flat	1.10 (0.82–1.46)	0.53	1.04 (0.86–1.26)	0.69	1.06 (0.89–1.25)	0.52	1.09 (0.84–1.42)	0.50
≥4-room public flat/private	1.10 (0.83–1.45)	0.50	1.21 (1.01–1.45)	0.038	1.18 (1.00–1.38)	0.049	1.24 (0.97–1.59)	0.093
Past history of any cancer								
No	Ref		Ref		Ref		Ref	
Yes	2.06 (1.74–2.45)	<0.001	1.20 (1.04–1.39)	0.013	1.36 (1.23–1.52)	<0.001	1.53 (1.28–1.84)	<0.001
Family history of any cancer								
No	Ref		Ref		Ref		Ref	
Yes	1.25 (1.11–1.42)	<0.001	1.08 (1.00–1.16)	0.048	1.10 (1.03–1.18)	0.004	1.20 (1.08–1.33)	0.001
Frequent smoking[a]								
No	Ref		Ref		Ref		Ref	
Yes	0.67 (0.52–0.87)	0.002	0.71 (0.60–0.83)	<0.001	0.73 (0.63–0.84)	<0.001	0.73 (0.59–0.90)	0.003

Multivariate modified Poisson regression model analyses were adjusted for age, gender, ethnicity, education, monthly household income, housing type, past history of any cancer, family history of any cancer, and frequent smoking.

**Based on recommended screening guidelines for colorectal cancer as defined by MOH guidelines:*

colorectal cancer—faecal occult blood test (FOBT) done annually or sigmoidoscopy/colonoscopy once every 10 years for individuals aged ≥50 years.

[a]Frequent smoking is defined as smoking cigarettes daily.

colorectal, 29.1%) (30). We also performed poorer compared to Western countries such as the United States in 2015 (cervical, 81%; breast, 71.6%; colorectal, 62.9%) (31) and the United Kingdom in 2017/18 (cervical, 71.4%; breast, 71.1%; colorectal, 57.7%) (32).

Compared to the cancer screening participation rates measured in the 2004 and 2010 national health surveys (17, 33), our screened as recommended participation rates did not indicate significant improvements (**Supplemental Table 3**). For example, the proportion of women who had gone for mammogram as recommended was 35.1% in our study, down from 39.6% in 2010. The proportion of Singapore residents who underwent colorectal screening as recommended was 27.3% in our study, up from 20.2% in 2010. Although the health promotion efforts over the years may have resulted in only modest changes in the screened as recommended participation rates, it is reassuring to observe that between 2004 and 2016, the ever screened rates have seen an upward trend (cervical, 70.1 *vs* 77.1%; breast, 54.2 *vs* 75.2%) in tandem with a downward trend in the size of the knowledge–behavior gap (cervical, 10.7 *vs* 2.8%; breast, 25.7 *vs* 18.4%). Improvements were also seen in colorectal cancer screening participation rates between 2004 and 2016 in ever screened with FOBT (17.3 *vs* 42.9%) and ever screened with sigmoidoscopy/colonoscopy (11.2 *vs* 22.1%).

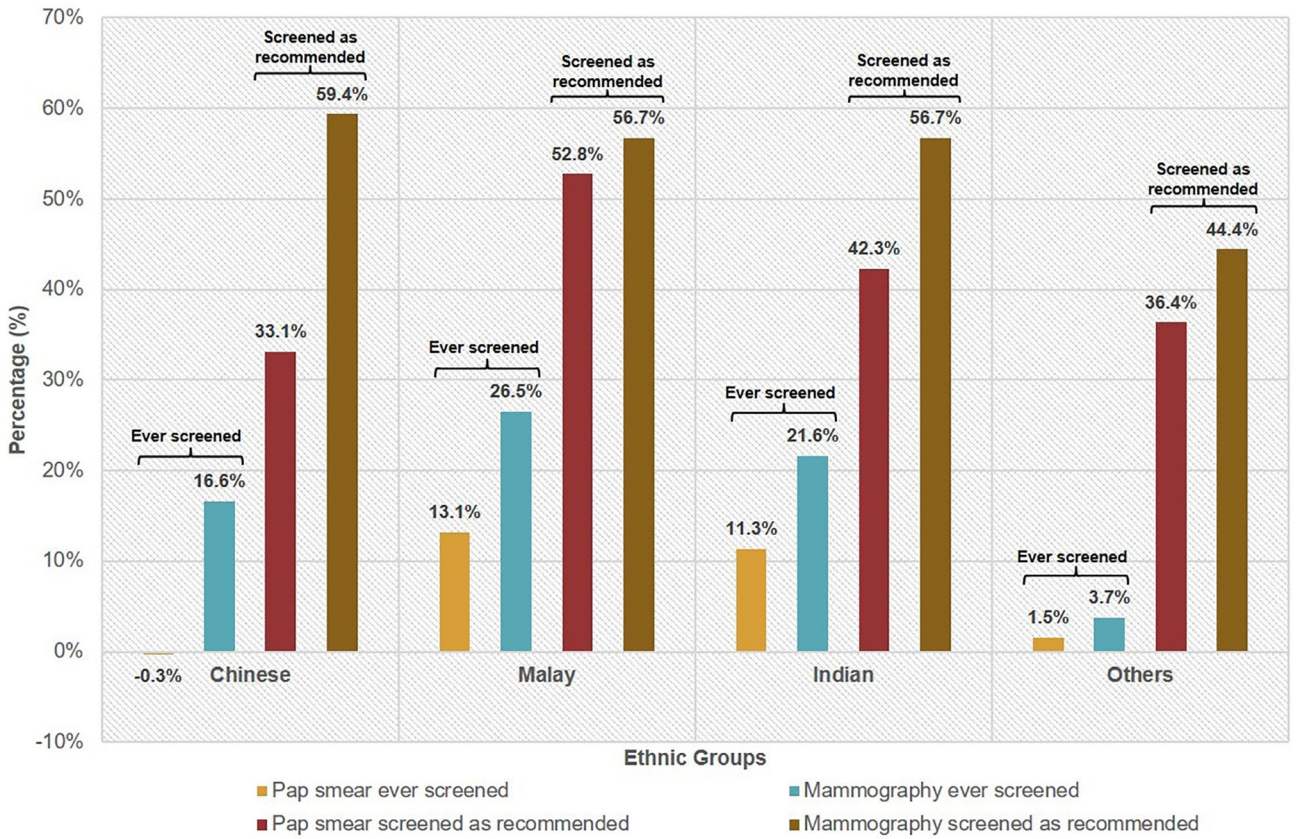

FIGURE 1 | Knowledge–behaviour gap[∓] of female cancer screening* by ethnicity. [∓]Knowledge–behaviour gap is defined as the difference in proportions between those that reported having knowledge of the screening test and those that ever did the screening test or screened as recommended. *Based on recommended screening guidelines for selected cancers as defined by MOH guidelines: cervical cancer—Pap smear for sexually active females aged 25 to 69 years at least once every 3 years; breast cancer—mammography for females aged 50 to 69 years every 2 years.

Our results demonstrate that screening knowledge and behaviors differ substantially by socio-economic status and ethnicity in Singapore. Higher educational level and household income were found to be significantly associated with screening as recommended for cervical, breast, and colorectal cancers. Malay ethnicity was associated with a lower likelihood of screening as recommended as compared with Chinese ethnicity. Cancer screening disparities associated with socio-economic status and ethnicity were reported in previous studies in Singapore (25–27, 34–38), as well as internationally (39, 40). However, limitations to the existing local literature include small sample sizes of the Malay and Indian ethnic minorities with oversampling of the Chinese ethnic majority, assessment of a single cancer screening modality, and age of the data. These limit the ability to generalize findings to the population and develop targeted population health interventions. Our study attempts to better estimate the true population effect sizes through our large representative sample size of 5,203 Chinese, 1,014 Malay, and 777 Indian respondents in the community setting.

Over the years, the Singapore Ministry of Health has endeavored to address the need to improve cancer screening participation rates, which culminated in the 2017 launch of the Enhanced Screen for Life Programme by the Health Promotion Board. This enabled eligible Singaporeans to screen for cervical, breast, and colorectal cancer from as low as $0–$5 per screening visit (41). Although affordability is an important consideration to address the socio-economic disparities, the continued low participation rates suggest there are additional barriers to address. A survey conducted at four polyclinics in Singapore reported that the most commonly cited reasons for not attending breast cancer screening programmes were lack of any breast problems, lack of time, and fear of pain (37). Another local mixed-methods study on barriers to breast and cervical cancer screening reported that fear of unnecessary treatments, ineffective treatments for early stage cancer, and low test sensitivity for early stage cancer were barriers to screening (28).

The proportion of those reporting having a family history of cancer was similar across cervical, breast, and colorectal cancer screening respondents; however, the association between a positive family history of cancer and cancer screening was only found to be significant among colorectal cancer screening respondents. While other studies have also reported this

association among Asian women (26, 42), local screening rates particularly among the higher risk first degree relatives of colorectal cancer patients continue to be low (43, 44). Barriers include poor understanding of the screening guidelines, lack of health promotion messaging by healthcare professionals, fear of the test and the diagnosis, scheduling difficulties, feeling invulnerable since young and asymptomatic, unawareness of genetic risk, and the high cost of colonoscopy (43–45). Risk perception should be emphasized in health promotion messaging among Asian ethnicities as perceived susceptibility to breast, cervical, and colorectal cancers was found to be the lowest among Asian women as compared with White, African American, and Latino women (42).

Observing past studies in tandem with our current study, there is a repetitive trend of Malay ethnicity being less likely to participate in cancer screening when compared to the Chinese ethnic majority and their Indian counterparts (17, 26, 27, 33, 46, 47). For female cancer screening, this may be partly explained by the knowledge–behavior gap demonstrated in our study. This gap may be linked to cultural beliefs among Asian women, which should be appropriately understood in order to craft effective policies and health promotion messages. Previous studies have reported cancer screening barriers related to social stigma, personal modesty, fatalistic attitudes, beliefs that breast cancer is a Western women-affliction, beliefs that mammograms cause cancer, and a preference to be unaware of a fatal disease diagnosis to postpone accompanying fears (28, 34, 37, 48–52). However, these findings are limited to predominantly Chinese respondents. In the neighboring country Malaysia with a high proportion of ethnic Malays, their National Health & Morbidity Survey in 2006 showed that only 7.9% of eligible women had underwent mammography as recommended, and only 12.8% had underwent Pap smear as recommended in 2011 (53). Malaysian studies have reported that Malay women are apprehensive about doing Pap smears especially if they are single or unmarried as it indicates sexual activity. A woman's partner or family members also hold great influence over decisions to screen due to strong family ties. Lack of knowledge among partners and male family members as well as perceived inaccessibility to a female health-care provider are commonly reported barriers (54–56). Similarly, the presence of male technicians/radiographers was found to be a barrier to mammogram screening (57).

The difference in the knowledge–behavior gap between ethnicities alludes to potential health literacy issues related to language barriers in Pap smear testing. Limited English proficiency and low health literacy among Asian women have been identified as barriers to cancer screening in several international studies where English is the predominant language (58–63). We also observed the phenomenon of Chinese women proceeding with Pap smear testing, despite not being fully aware of the purpose of the test. This may be linked to high trust among Chinese women towards their primary physician, which was reported by a study among Redhill residents in Singapore who were predominantly Chinese. Over half of the respondents rated trust towards primary care doctors and the medical profession as high or very high (64), which has been supported by other studies that reported high regard towards general practitioners in the Asian context (65, 66).

In our study, the knowledge–behavior gap was higher for mammography (18.4%) than for Pap smear (2.8%). Previous studies have suggested logistical and operational issues as reasons for the difference between uptake of Pap smear *versus* mammograms (34, 51, 52). The widespread availability of Pap smear tests as a bedside procedure in general practice clinics has made it readily accessible in contrast to the limited availability of mammography. In addition, most patients are able to state preferences or choose female doctors to perform the Pap smears; however, there is no freedom of choice for radiographer doing the mammograms. Having a male radiographer has been shown to be a barrier to screening in both Western and Asian cultures (67–70).

Strategies to further narrow the knowledge–behavior gap should include developing tailored cancer screening promotion campaigns for the Malay ethnic group, which can be done in close consultation with employers, religious, and community authorities to ensure the messages stay culturally relevant (71–77). To further incentivize cancer screening behavior, we must inculcate a culture of cancer screening through community screening initiatives so that they are seen as a form of social event (71, 78, 79). Targeted and frequent mass media campaigns have been shown to be effective in increasing awareness and compliance for cancer screening (71, 80, 81) as well as being frequently exposed to reminders with cues to action (23, 24, 71, 82, 83). Addressing polyclinic proximity and screening appointment logistics may contribute to improving mammography uptake (51). Further studies will need to be done on Malay-specific barriers and facilitators for screening across the three screening modalities as our analysis showed that only 10.7% screened as recommended for all three, and Malays had a higher propensity to not be screened. Existing studies in Singapore had predominantly Chinese respondents and focused on specific screening modalities (23–28). Further studies comparing cancer screening knowledge and behavior between Malays residing in Singapore *versus* Malays residing in Malaysia would help to elicit environmental and cultural influences.

Strengths and Limitations of the Study

Strengths of this study include a large sample population that resembles the overall age, ethnic, and gender distribution of the Singapore population (**Supplemental Figures S1–S3**) (84). Self-selection bias was minimized through the use of a door-to-door recruitment strategy. Misclassification due to interviewer bias, social desirability bias, or recall bias was reduced through the use of a standardized questionnaire consisting of closed-ended, easy to understand questions, simple response options, and trained interviewers that followed the designed question and answer format strictly. However, there are a few limitations to our study. As our survey questions were modelled after the National Health Survey to allow for comparisons, the questions

did not differentiate whether the tests were done for screening or diagnostic purposes. In addition, the questions did not differentiate if the participant was screening regularly as recommended or had coincidentally last screened in the recommended time period. As a result, the reported screened as recommended participation rates may be an overestimation of the true value. We were unable to corroborate the self-reported cancer screening data with objective data from medical databases. Another limitation was the inclusion criteria due to the interest of regional health system in targeting interventions on those aged 40 and above in their catchment area, which meant the cervical cancer screening age group from 25 to 39 years was unrepresented. Due to this targeted population, all household members who met the inclusion criteria were included in the Community Health Study; however, data on the proportion of households with more than one member who participated in the study were not available, and statistical analysis adjusting for such potential clustering effects was not performed.

CONCLUSIONS

Cancer screening knowledge and behaviors differ substantially between Asian ethnic sub-groups even within the confines of the island state of Singapore. Asian ethnicity represents a heterogeneous group with different religious and cultural traditions, and our results suggest that it is important to distinguish different ethnic sub-groups in future studies of screening behavior. Ethnic Malays are therefore, a key target population for further research and interventions to narrow the knowledge–behavior gap. Design of targeted cancer screening programmes and health promotion messaging by healthcare providers should include sensitivity to ethnic differences as well as female-specific cancer screening facilitators and barriers, which will help to further increase the uptake of cancer screening. The population-based cancer screening programmes are essential to Singapore's preventive health strategy. The availability of subsidized rates has allowed more members of the population to access cancer screening, but the overall cancer screening rates still remain low. Socio-economic factors such as educational and income level remain important aspects that policy makers and healthcare organizations should address to improve cancer screening.

DATA AVAILABILITY STATEMENT

The datasets used in this article are available from the corresponding authors on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Health Group Domain Specific Review Board (2015-00095) and the National University of Singapore IRB (S-19-340). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TC participated in the design of this study, performed the statistical analysis, interpreted the data, and drafted the manuscript. LT participated in the design of the Community Health Study, coordination, and data collection. RD is the principal investigator of the Community Health Study and participated in the manuscript revision of this study. WJS participated in the design of this study, the statistical analysis, interpretation of the data, and the manuscript revision. 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/fonc.2021.684917/full#supplementary-material

Supplementary Table 1 | Adjusted prevalence ratio (aPR) estimates for characteristics associated with those tested without knowledge of Pap smear. Multivariate modified Poisson regression model analyses were adjusted for age, ethnicity, education, monthly household income, housing type, and living arrangement. *Based on recommended screening guideline for cervical cancers as defined by MOH guidelines: Pap smear for sexually active females aged 25 to 69 years at least once every 3 years.

Supplementary Table 2 | Adjusted prevalence ratio (aPR) estimates for characteristics associated with screening as recommended for all three cancers. Multivariate modified Poisson regression model analyses were adjusted for age, ethnicity, education, monthly household income, housing type, living arrangement, past history of any cancer, family history of any cancer, and frequent smoking. *Based on recommended screening guidelines for selected cancers as defined by MOH guidelines: cervical cancer—Pap smear for sexually active females aged 25 to 69 years at least once every 3 years; breast cancer—mammography for females aged 50 to 69 years every 2 years; colorectal cancer–faecal occult blood test (FOBT) done annually or

sigmoidoscopy/colonoscopy once every 10 years for individuals aged ≥50 years. [a]Frequent smoking is defined as smoking cigarettes daily.

Supplementary Table 3 | Cancer screening participation rates in Singapore. NHS National Health Survey; CHS, Community Health Survey. Unless otherwise stated, the screening questions involved age groups 25–69 for cervical, 50–69 for breast, and 50 and above for colorectal. [¢]CHS 2016 age groups were 40–69 for cervical screening questions. [₸]The difference in proportion between knowledge of the cancer screening test and ever screened with the test.

Supplementary Table 4 | Cancer screening knowledge and participation rates, stratified by family history.

Supplementary Figure 1 | Age distribution in the survey sample in comparison to Singapore's population. **Based on Singapore SingStat 2016 Population Data ages 40 and above.

Supplementary Figure 2 | Gender distribution in the survey sample in comparison to Singapore's population. **Based on Singapore SingStat 2016 Population Data ages 40 and above.

Supplementary Figure 3 | Ethnic distribution in the survey sample in comparison to Singapore's population. **Based on Singapore SingStat 2016 Population Data ages 40 and above.

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Racial Disparities and Sex Differences in Early- and Late-Onset Colorectal Cancer Incidence, 2001–2018

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Background: Colorectal cancer (CRC) incidence rates have increased in younger individuals worldwide. We examined the most recent early- and late-onset CRC rates for the US.

Methods: Age-standardized incidence rates (ASIR, per 100,000) of CRC were calculated using the US Cancer Statistics Database's high-quality population-based cancer registry data from the entire US population. Results were cross-classified by age (20-49 [early-onset] and 50-74 years [late-onset]), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, American Indian/Alaskan Native, Asian/Pacific Islander), sex, anatomic location (proximal, distal, rectal), and histology (adenocarcinoma, neuroendocrine).

Results: During 2001 through 2018, early-onset CRC rates significantly increased among American Indians/Alaskan Natives, Hispanics, and Whites. Compared to Whites, early-onset CRC rates are now 21% higher in American Indians/Alaskan Natives and 6% higher in Blacks. Rates of early-onset colorectal neuroendocrine tumors have increased in Whites, Blacks, and Hispanics; early-onset colorectal neuroendocrine tumor rates are 2-times higher in Blacks compared to Whites. Late-onset colorectal adenocarcinoma rates are decreasing, while late-onset colorectal neuroendocrine tumor rates are increasing, in all racial/ethnic groups. Late-onset CRC rates remain 29% higher in Blacks and 15% higher in American Indians/Alaskan Natives compared to Whites. Overall, CRC incidence was higher in men than women, but incidence of early-onset distal colon cancer was higher in women.

Conclusions: The early-onset CRC disparity between Blacks and Whites has decreased, due to increasing rates in Whites—rates in Blacks have remained stable. However, rates

of colorectal neuroendocrine tumors are increasing in Blacks. Blacks and American Indians/Alaskan Natives have the highest rates of both early- and late-onset CRC.

Impact: Ongoing prevention efforts must ensure access to and uptake of CRC screening for Blacks and American Indians/Alaskan Natives.

Keywords: early-onset colorectal cancer, joinpoint analysis, National Program of Cancer Registries (NPCR), neuroendocrine tumors, racial disparities in cancer, Surveillance, Epidemiology, and End Results (SEER) program

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly occurring cancer in the United States (US) and the third leading cause of cancer mortality (1). CRC incidence rates have decreased since the mid-1980s, but this trend changed recently due to increasing rates of early-onset colorectal cancer (EOCRC), defined as CRC arising in individuals prior to age 50 (2). EOCRC rates have also increased worldwide, particularly in high-income countries (3). Recent CRC rates in 45-year-olds are similar to rates observed in 50-year-olds prior to the advent of routine CRC screening (1), which the US Preventive Services Task Force (USPSTF) first recommended in 1996 (4). Thus, the American Cancer Society (ACS) and the USPSTF have recently updated their guidelines to recommend screening beginning at age 45 (5, 6).

Established risk factors for late-onset CRC, including obesity (7–9), physical inactivity (10), smoking (8, 11), alcohol (12), and diet (12), have also been associated with EOCRC risk in some studies. However, known CRC risk factors do not fully explain the increasing rates of EOCRC (13), indicating there are likely undiscovered risk factors for EOCRC.

Non-Hispanic Black (NHB) Americans have had the highest incidence of CRC in the US since the 1990s, including EOCRC (1). NHBs and women of any racial/ethnic group are most likely to be diagnosed with tumors in the proximal colon, where detection—especially with sigmoidoscopy—is less likely (14–16). A recent study reported that rates of EOCRC have been increasing in both non-Hispanic White (NHW) and NHB Americans (17). However, the majority of studies to date have utilized data from Surveillance, Epidemiology, and End Results (SEER) Program, which only captures data from approximately 35% of the US population. The most recent rates of EOCRC by race/ethnicity, anatomic location, and histology for the entire US population have not been reported. In the present study, we examined US CRC rates from 2001-2018 by age, sex, race/ethnicity, anatomic location, and histology. The trends of EOCRC by these factors may provide clues as to the evolving etiology of EOCRC.

Abbreviations: ASIR, age-standardized incidence rate; ACS, American Cancer Society; AIAN, American Indian/Alaskan Native; APC, annual percent change; API, Asian/Pacific Islander; AAPC, average annual percent change; CRC, colorectal cancer; CIs, confidence intervals; EOCRC, early-onset colorectal cancer; IRR, incidence rate ratios; NPCR, National Program of Cancer Registries; NHB, non-Hispanic Black; NHW, non-Hispanic White; SEER, Surveillance, Epidemiology, and End Results; US, United States; USPSTF, US Preventive Services Task Force.

METHODS

Colorectal Cancer Data

We examined CRC incidence data from US Cancer Statistics, which includes data from the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) and the National Cancer Institute's SEER Program, spanning the years 2001 through 2018 (all available years) (18). The US Cancer Statistics database includes high-quality population-based cancer registry data from the entire US population, including all 50 states and the District of Columbia.

Incident primary CRC was defined by International Classification of Diseases for Oncology, Third Edition. Proximal colon cancer included cecum (C18.0), ascending colon (C18.2), hepatic flexure (C18.3), transverse colon (C18.4), and splenic flexure (C18.5). Distal colon cancer included descending colon (C18.6) and sigmoid (C18.7). Rectal cancer included rectum (C20.9) and rectosigmoid junction (C19.9). Overall CRC included these three anatomic locations in addition to overlapping lesions of the colon (C18.8), colon not otherwise specified (C18.9), and intestine not otherwise specified (C26.0). Colorectal adenocarcinomas were defined by ICD-O-3 histology codes (19, 20) 8140-8147, 8201, 8210-8213, 8220-8221, 8255, 8260-8265, 8310, 8323, 8331-8332, 8380, 8430, 8440, 8480-8481, 8490, 8550-8551, and 8570-8573. Colorectal neuroendocrine tumors were defined by histology codes 8013, 8240-8246, and 8249. EOCRC was defined as arising in adults 20-49 years of age, while late-onset CRC was defined as arising in persons 50-74 years of age (as the USPSTF only recommends selective screening after age 75) (6).

Statistical Analysis

Age-standardized incidence rates (ASIRs) and 95% confidence intervals (CIs) per 100,000 person-years were calculated for overall CRC, proximal colon, distal colon, and rectal cancer by age (20-49 and 50-74 years), sex, and race/ethnicity (non-Hispanic White, NHW; non-Hispanic Black, NHB; Hispanic; non-Hispanic American Indian/Alaska Native, AIAN; non-Hispanic Asian/Pacific Islander, API). We also examined overall CRC rates by histology (adenocarcinoma, neuroendocrine), age, and race/ethnicity. Rates were age-adjusted to the 2000 US standard population. Corresponding standard errors and 95% CIs were calculated (21). For 2001 through 2018, ASIRs were plotted on a semi-logarithmic scale to facilitate comparison of current rates and temporal trends (22).

To examine changes in ASIRs over time by anatomic location, age, and race/ethnicity, 2-year groupings (i.e., 2001-2002 and

2017-2018) were used. Joinpoint regression models were used to test whether a change in trend was statistically significant, using the Monte Carlo Permutation method (Joinpoint Regression Program, v4.8.0.1, Information Management Services, Inc., Calverton, MD). The joinpoint regression tested a linear model with no joinpoints and assessed if more joinpoints should be added based on statistical significance. In the models, we used a maximum of two joinpoints with a minimum of four years of data between joinpoints. The annual percent change (APC) and average annual percent change (AAPC) were calculated using the natural log-transformed rates based on each 2-year period (23). The 95% CIs were calculated using the parametric method.

To examine racial/ethnic disparities and sex differences in incidence rates, incidence rate ratios ($IRR=ASIR_1/ASIR_2$) and 95% CIs were calculated. Each racial/ethnic group was compared to NHWs; men were compared to women. The IRR is a measure of relative difference; a value of 1.0 corresponds to no difference in the rates.

Sensitivity Analysis

As the ACS and the USPSTF have updated their guidelines to recommend screening beginning at age 45 (5, 6), we conducted a sensitivity analysis to examine EOCRC trends in individuals less than 45 years of age. We also present data on CRC rates for all ages, <50 years, and ≥50 years.

RESULTS

The US Cancer Statistics database includes 2,585,621 CRC cases: 1,985,054 NHW, 298,735 NHB, 186,521 Hispanic, 14,806 AIAN, 83,820 API, and 16,685 Other/Unknown. For the main analyses, we excluded the CRC cases of Other/Unknown race/ethnicity.

Between 2001 to 2018, CRC rates among all ages decreased in all racial/ethnic groups and both sexes (**Supplemental Figure S1** and **Supplemental Table S1**). The overall CRC rates in NHWs decreased by 3.18% per year until 2011-2012, when the decrease in rates slowed to 1.80% per year; in NHBs, CRC rates decreased by 2.70% per year. In 2017-2018, CRC rates were 16% higher in NHBs and 6% higher in AIANs than in NHWs, while CRC rates were 10% lower in Hispanics and 20% lower in APIs compared to NHWs.

While overall CRC rates decreased between 2001 and 2018, EOCRC rates increased in NHWs, Hispanics, and AIANs, but remained stable in NHBs and APIs (**Figure 1**). However, early-onset distal colon and rectal cancer rates increased in all racial/ethnic groups. Similar temporal trends in EOCRC rates were observed for men (**Figure 1A**) and women (**Figure 1B**).

EOCRC incidence rates increased by 3.13% per year for AIANs, and by 1.62% per year for NHWs, and by 1.10% per year for Hispanics (**Table 1**), with a more rapid rates increased of 3.61% per year among Hispanics from 2013 to 2018. In NHWs, there were increases in early-onset rectal (AAPC=2.17), distal colon (AAPC=2.16), and proximal colon cancer (AAPC=0.44). In Hispanics, there were comparable increases. In AIANs, increases in rates of early-onset rectal (AAPC=4.04), distal colon (AAPC=3.07), and proximal colon cancer (AAPC=1.47) were greater than for NHWs, while the increases among APIs were smaller. The EOCRC trends were similar in men (**Supplemental Table S2**) and women (**Supplemental Table S3**), with the exception that early-onset proximal colon cancer decreased in NHB women (AAPC=-0.68). In the sensitivity analysis, trends were similar examining individuals aged 20-44 years (**Supplemental Figure S2** and **Supplemental Tables S4**) or <50 years (**Supplemental Table S5**), rather than 20-49 years.

Due to the significant temporal increase in EOCRC rates, AIANs had the highest EOCRC rates in 2017-2018 (ASIR=15.11 per 100,000), followed by NHBs (ASIR=13.26) and NHWs (ASIR=12.50; **Table 1**). The rate of early-onset proximal colon cancer was highest in NHBs (ASIR=4.70), while early-onset distal colon (ASIR=4.40) and rectal cancer (ASIR=7.12) rates were highest in AIANs. The rate of early-onset proximal colon cancer (ASIR=2.03) was lowest in APIs, while early-onset distal colon (ASIR=2.91) and rectal cancer (ASIR=4.07) rates were lowest in Hispanics.

Examining the racial/ethnic disparities in EOCRC, AIANs had a 21% higher incidence of EOCRC than NHWs, while Hispanics and APIs had a 20–23% lower incidence (**Table 1**). Due to increasing EOCRC rates in NHWs, racial disparities in incidence of EOCRC narrowed between NHBs and NHWs (2001-2002 IRR=1.33 to 2017-2018 IRR=1.06). However, NHBs still had a disproportionate burden of early-onset proximal colon cancer in 2017-2018 (IRR=1.59), compared to NHWs.

Rates of late-onset CRC (CRC in individuals aged 50-74 years) decreased during 2001-2018 in all racial/ethnic groups for both sexes (**Supplemental Figure S3**). As shown in **Table 2**, recent declines in late-onset CRC rates among NHWs (2011-2018 APC=-1.41) were less than among NHBs (AAPC=-2.48), Hispanics (AAPC=-1.77), and APIs (AAPC=-1.84), but racial/ethnic disparities in late-onset CRC incidence remain. Rates of late-onset CRC in NHBs were 29% higher and rates in AIANs were 15% higher, compared to NHWs. NHBs had a disproportionate burden of late-onset proximal colon (IRR=1.53), distal colon (IRR=1.22), and rectal cancer (IRR=1.04). AIANs also had a disproportionate burden of late-onset rectal cancer (IRR=1.21). APIs had lower rates of late-onset proximal colon cancer than NHWs (IRR=0.62) but higher rates of distal colon cancer (IRR=1.12). Rates of late-onset CRC were similar between Hispanics and NHWs. These late-onset CRC trends were similar in men (**Supplemental Table S6**) and women (**Supplemental Table S7**). In the sensitivity analysis, trends were similar examining individuals ≥50 years of age (**Supplemental Table S8**), rather than 50-74 years.

In **Tables 3**, **4**, rates of early- and late-onset CRC are shown by histology: colorectal adenocarcinoma accounted for 90.9% of all CRCs, while colorectal neuroendocrine tumors accounted for 4.1%. The majority (73.7%) of colorectal neuroendocrine tumors are located in the rectum; thus, only overall CRC rates are provided by histology. The rates and trends for CRC and colorectal adenocarcinoma were very similar (**Table 3**). The incidence of colorectal neuroendocrine tumors was about one-tenth of that of colorectal adenocarcinoma; for example, NHB rates of early-onset

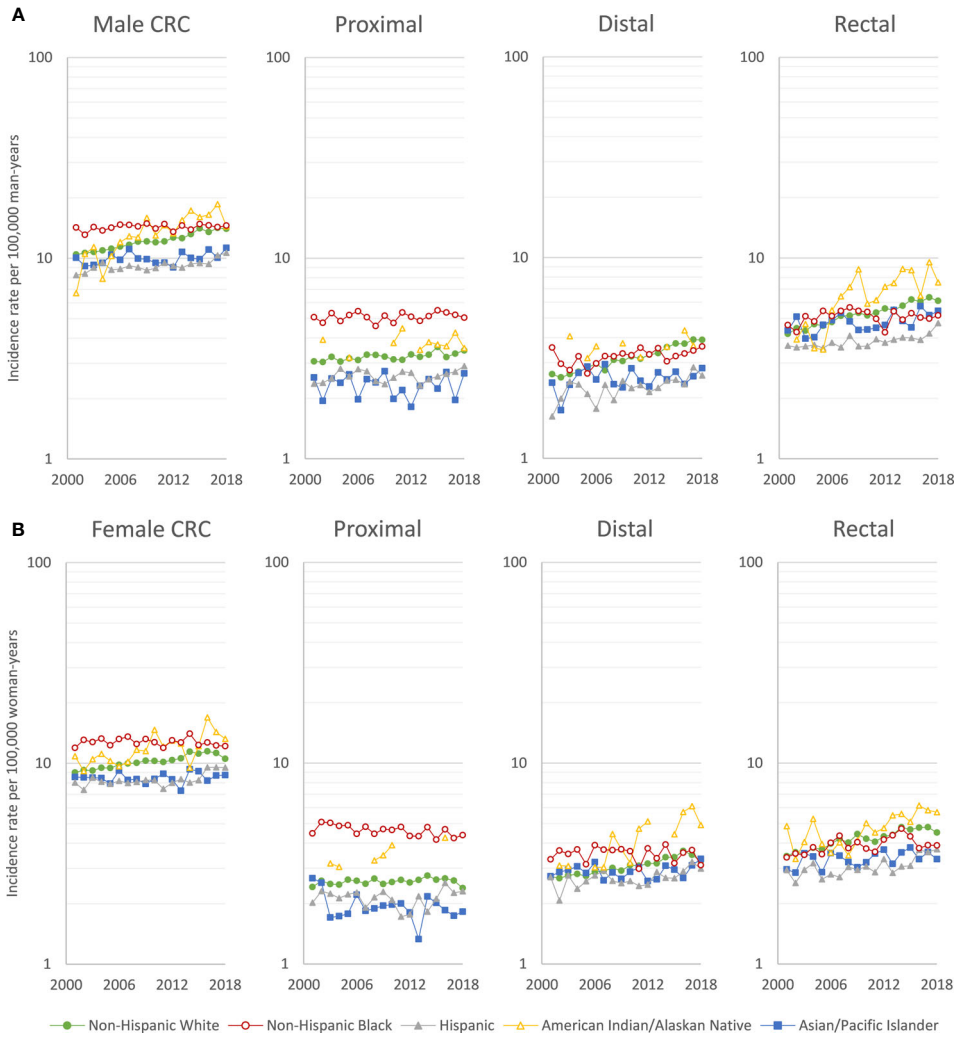

FIGURE 1 | Age-adjusted early-onset (20-49 years of age) colorectal cancer incidence rates per 100,000 person-years in **(A)** men and **(B)** women, US Cancer Statistics 2001-2018.

colorectal adenocarcinoma in 2017-2018 were 11.13 per 100,000 (**Table 3**), while rates of early-onset colorectal neuroendocrine tumors were 1.53 per 100,000 (**Table 4**). As shown in **Table 4**, rates of early-onset colorectal neuroendocrine tumors increased from 2001 to 2018 in NHWs by 2.22%, in NHBs by 1.97%, and in Hispanics by 1.87% per year. Rates of late-onset colorectal neuroendocrine tumors increased in NHBs by 1.95%, in Hispanics by 2.17%, in AIANs by 3.04%, and in APIs by 3.24% per year. The racial/ethnic disparities were more pronounced for colorectal neuroendocrine tumors (compared to colorectal adenocarcinoma), particularly for NHBs compared to NHWs. In 2017-2018, incidence was 2.35-times higher for early-onset and 3.26-times higher for late-onset colorectal neuroendocrine tumors in NHBs, compared to NHWs.

Sex differences were observed for both early- and late-onset CRC, with men having 16% higher rates of EOCRC and 44% higher rates of late-onset CRC (**Supplemental Figure S4**). At all ages, rates of CRC were higher in men than women for proximal colon and rectal cancer (**Figure 2**). For the ages of 25 to 44, however, women had higher rates of distal colon cancer than men. This sex difference in early-onset distal colon cancer incidence was present in every racial/ethnic group (**Supplemental Figure S5**). In men, the largest proportion of CRCs were rectal for both early- and late-onset disease (42.3% and 34.5%, respectively, data not shown). The exception was NHB men, who had equal proportions of EOCRC occurring in the rectum (35.7%) and proximal colon (35.7%); NHB men had highest proportion of late-onset CRC occurring in the proximal colon (39.6%). For women, the largest proportion of EOCRCs were rectal (38.7%), with the exception of NHBs who had the highest proportion of CRC occurring in the proximal colon (36.1%). The largest proportion of late-onset CRCs in women were proximal (42.4%), with the exception of APIs who had the highest proportion of CRC occurring in the rectum (34.3%).

TABLE 1 | Age-adjusted early-onset (20-49 years of age) colorectal cancer incidence rates per 100,000 person-years.

Age 20-49 Years	2001-2002					2017-2018					Trend 1 APC (%)	Trend 2 APC (%)	Joinpoint 1	AAPC (%)	AAPC 95% CI
	Cases	Rate	95% CI	IRR	95% CI	Cases	Rate	95% CI	IRR	95% CI					
All Colorectal Cancer															
Non-Hispanic White	17,299	9.82	(9.67, 9.97)	1.00	–	17,732	12.50	(12.32, 12.69)	1.00	–	1.62*			1.62*	(1.41, 1.82)
Non-Hispanic Black	3,794	13.05	(12.63, 13.47)	1.33	(1.28, 1.38)	4,137	13.26	(12.85, 13.67)	1.06	(1.02, 1.10)	0.05			0.05	(-0.24, 0.35)
Hispanic	2,247	8.00	(7.67, 8.34)	0.81	(0.78, 0.85)	4,629	10.02	(9.73, 10.31)	0.80	(0.78, 0.83)	0.28	3.61	2013-2014	1.10*	(0.14, 2.07)
American Indian/ Alaskan Native	186	9.32	(8.03, 10.76)	0.95	(0.82, 1.10)	290	15.11	(13.41, 16.95)	1.21	(1.08, 1.36)	3.13*			3.13*	(2.29, 3.98)
Asian/Pacific Islander	1,008	9.03	(8.48, 9.61)	0.92	(0.86, 0.98)	1,701	9.63	(9.18, 10.10)	0.77	(0.73, 0.81)	0.37			0.37	(-0.03, 0.78)
Proximal Colon Cancer															
Non-Hispanic White	4,888	2.78	(2.70, 2.86)	1.00	–	4,198	2.95	(2.86, 3.04)	1.00	–	0.44*			0.44*	(0.20, 0.67)
Non-Hispanic Black	1,408	4.85	(4.60, 5.11)	1.75	(1.64, 1.85)	1,462	4.70	(4.46, 4.95)	1.59	(1.50, 1.69)	-0.21			-0.21	(-0.53, 0.10)
Hispanic	641	2.28	(2.10, 2.46)	0.82	(0.75, 0.89)	1,176	2.55	(2.41, 2.70)	0.86	(0.81, 0.92)	-0.57	3.51	2013-2014	0.43	(-0.88, 1.77)
American Indian/ Alaskan Native	49	2.45	(1.81, 3.23)	0.88	(0.66, 1.17)	56	2.90	(2.18, 3.76)	0.98	(0.75, 1.28)	1.47			1.47	(-0.11, 3.07)
Asian/Pacific Islander	274	2.43	(2.15, 2.74)	0.88	(0.78, 0.99)	361	2.03	(1.82, 2.25)	0.69	(0.62, 0.77)	-0.57			-0.57	(-1.40, 0.26)
Distal Colon Cancer															
Non-Hispanic White	4,654	2.64	(2.56, 2.71)	1.00	–	5,137	3.63	(3.53, 3.73)	1.00	–	2.16*			2.16*	(1.91, 2.41)
Non-Hispanic Black	983	3.38	(3.17, 3.60)	1.28	(1.20, 1.37)	1,075	3.45	(3.25, 3.67)	0.95	(0.89, 1.02)	0.19			0.19	(-0.27, 0.66)
Hispanic	577	2.09	(1.92, 2.27)	0.79	(0.73, 0.86)	1,342	2.91	(2.75, 3.07)	0.80	(0.75, 0.85)	1.43*			1.43*	(0.60, 2.27)
American Indian/ Alaskan Native	52	2.60	(1.94, 3.41)	0.99	(0.75, 1.30)	85	4.40	(3.51, 5.44)	1.21	(0.98, 1.50)	3.07*			3.07*	(0.82, 5.37)
Asian/Pacific Islander	269	2.44	(2.16, 2.75)	0.93	(0.82, 1.05)	523	2.97	(2.72, 3.23)	0.82	(0.75, 0.89)	0.47			0.47	(-0.32, 1.27)
Rectal Cancer															
Non-Hispanic White	6,910	3.92	(3.83, 4.02)	1.00	–	7,732	5.45	(5.33, 5.58)	1.00	–	2.17*			2.17*	(1.87, 2.46)
Non-Hispanic Black	1,144	3.93	(3.70, 4.16)	1.00	(0.94, 1.07)	1,396	4.45	(4.22, 4.70)	0.82	(0.77, 0.86)	0.58			0.58	(-0.34, 1.50)
Hispanic	896	3.18	(2.97, 3.40)	0.81	(0.76, 0.87)	1,887	4.07	(3.89, 4.26)	0.75	(0.71, 0.79)	0.61	3.98	2013-2014	1.44*	(0.57, 2.32)
American Indian/ Alaskan Native	74	3.72	(2.92, 4.67)	0.95	(0.75, 1.19)	135	7.12	(5.96, 8.42)	1.30	(1.10, 1.55)	4.04*			4.04*	(2.87, 5.23)
Asian/Pacific Islander	423	3.77	(3.42, 4.15)	0.96	(0.87, 1.06)	763	4.34	(4.03, 4.65)	0.79	(0.74, 0.86)	0.93*			0.93*	(0.37, 1.50)

**Statistically significant at the 0.05 level.*

IRR, incidence rate ratio; CI, confidence interval; APC, annual percent change; AAPC, average annual percent change.

DISCUSSION

In recent years, incidence rates of EOCRC increased for NHWs, Hispanics, and AIANs. Incidence of EOCRC in AIANs increased by an average of 3.13% per year from 2001 to 2018. AIANs now have the highest rate of EOCRC, which is 21% higher than incidence of EOCRC in NHWs. NHBs have the second highest incidence of EOCRC; NHBs the highest incidence of late-onset CRC, which is 29% higher than incidence of late-onset CRC in NHWs. Rates of early- and late-onset colorectal neuroendocrine tumors are increasing in all racial/ethnic groups. Men have higher rates of CRC than women, with the exception of early-onset distal colon cancer.

The current study updates and expands recent US reports (1, 2, 16, 17), through interrogation of CRC rates by anatomic subsite, considering age, race/ethnicity, sex, and histology. A recent study, based on data from 1992-2014, reported increasing rates of early-onset distal colon and rectal cancer in NHWs and to a lesser extent NHBs. For early-onset proximal colon cancer, the prior study identified increasing rates for NHWs but

TABLE 2 | Age-adjusted late-onset (50-74 years of age) colorectal cancer incidence rates per 100,000 person-years.

Age 50-74 Years	2001-2002					2017-2018					Trend 1	Trend 2	Trend 3	Joinpoint 1	Joinpoint 2	AAPC	AAPC 95% CI
	Cases	Rate	95% CI	IRR	95% CI	Cases	Rate	95% CI	IRR	95% CI	APC (%)	APC (%)	APC (%)			(%)	
All Colorectal Cancer																	
Non-Hispanic White	121,306	126.08	(125.38, 126.78)	1.00	–	111,516	81.49	(81.00, 81.98)	1.00	–	-3.51*	-1.41*		2011-2012		-2.73*	(-3.10, -2.35)
Non-Hispanic Black	18,401	152.64	(150.38, 154.93)	1.21	(1.19, 1.23)	21,957	105.46	(104.05, 106.88)	1.29	(1.28, 1.31)	-2.48*					-2.48*	(-2.81, -2.15)
Hispanic	9,204	104.72	(102.53, 106.95)	0.83	(0.81, 0.85)	15,903	79.52	(78.27, 80.79)	0.98	(0.96, 0.99)	-1.77*					-1.77*	(-2.11, -1.42)
American Indian/Alaskan Native	754	108.23	(100.50, 116.40)	0.86	(0.80, 0.92)	1,283	94.12	(88.97, 99.49)	1.15	(1.09, 1.22)	-0.62*					-0.62*	(-1.14, -0.10)
Asian/Pacific Islander	4,177	95.28	(92.33, 98.30)	0.76	(0.73, 0.78)	6,800	70.03	(68.36, 71.73)	0.86	(0.84, 0.88)	-1.84*					-1.84*	(-2.02, -1.66)
Proximal Colon Cancer																	
Non-Hispanic White	46,241	47.53	(47.09, 47.96)	1.00	–	41,552	29.60	(29.31, 29.89)	1.00	–	-3.06*					-3.06*	(-3.32, -2.79)
Non-Hispanic Black	8,095	65.79	(64.31, 67.31)	1.38	(1.35, 1.42)	9,380	45.36	(44.43, 46.30)	1.53	(1.50, 1.57)	-2.56*					-2.56*	(-2.94, -2.18)
Hispanic	3,209	36.02	(34.73, 37.35)	0.76	(0.73, 0.79)	5,375	27.64	(26.90, 28.41)	0.93	(0.91, 0.96)	-1.78*					-1.78*	(-2.08, -1.48)
American Indian/Alaskan Native	256	35.64	(31.23, 40.48)	0.75	(0.66, 0.85)	419	31.04	(28.10, 34.21)	1.05	(0.95, 1.15)	-0.61					-0.61	(-1.58, 0.37)
Asian/Pacific Islander	1,128	26.54	(24.97, 28.18)	0.56	(0.53, 0.59)	1,757	18.23	(17.38, 19.11)	0.62	(0.59, 0.65)	-2.27*					-2.27*	(-2.65, -1.88)
Distal Colon Cancer																	
Non-Hispanic White	32,625	34.11	(33.75, 34.48)	1.00	–	26,647	19.76	(19.52, 20.01)	1.00	–	-4.70*	-1.20		2011-2012		-3.40*	(-4.00, -2.81)
Non-Hispanic Black	4,736	39.84	(38.68, 41.02)	1.17	(1.13, 1.20)	5,060	24.18	(23.51, 24.86)	1.22	(1.19, 1.26)	-1.71	-4.10*	-2.95*	2005-2006	2011-2012	-3.08*	(-3.31, -2.84)
Hispanic	2,531	28.61	(27.47, 29.79)	0.84	(0.81, 0.87)	4,039	20.00	(19.38, 20.64)	1.01	(0.98, 1.05)	-2.43*					-2.43*	(-2.95, -1.90)
American Indian/Alaskan Native	210	29.22	(25.24, 33.63)	0.86	(0.75, 0.98)	314	22.95	(20.45, 25.67)	1.16	(1.04, 1.30)	-1.19*					-1.19*	(-2.09, -0.28)
Asian/Pacific Islander	1,397	31.64	(29.95, 33.39)	0.93	(0.88, 0.98)	2,155	22.07	(21.14, 23.03)	1.12	(1.07, 1.17)	-2.21*					-2.21*	(-2.54, -1.89)
Rectal Cancer																	
Non-Hispanic White	37,177	38.32	(37.93, 38.71)	1.00	–	38,135	28.42	(28.13, 28.71)	1.00	–	-2.77*	-0.24		2011-2012		-1.83*	(-2.05, -1.62)
Non-Hispanic Black	4,445	36.61	(35.51, 37.73)	0.96	(0.93, 0.99)	6,218	29.69	(28.94, 30.45)	1.04	(1.02, 1.07)	-1.39*					-1.39*	(-1.75, -1.03)
Hispanic	3,014	34.30	(33.06, 35.58)	0.90	(0.86, 0.93)	5,661	27.66	(26.93, 28.40)	0.97	(0.95, 1.00)	-1.23*					-1.23*	(-1.66, -0.79)
American Indian/Alaskan Native	250	36.66	(32.27, 41.47)	0.96	(0.84, 1.08)	472	34.39	(31.31, 37.68)	1.21	(1.10, 1.32)	-0.12					-0.12	(-0.80, 0.56)
Asian/Pacific Islander	1,511	33.91	(32.17, 35.71)	0.88	(0.84, 0.93)	2,663	27.42	(26.38, 28.49)	0.96	(0.93, 1.00)	-1.20*					-1.20*	(-1.43, -0.97)

**Statistically significant at the 0.05 level.*

IRR, incidence rate ratio; CI, confidence interval; APC, annual percent change; AAPC, average annual percent change.

TABLE 3 | Age-adjusted early-onset (20-49 years of age) and late-onset (50-74 years of age) colorectal adenocarcinoma rates per 100,000 person-years.

All Colorectal Cancer	2001-2002					2017-2018					Trend 1	Trend 2	Joinpoint 1	AAPC	AAPC 95% CI
	Cases	Rate	95% CI	IRR	95% CI	Cases	Rate	95% CI	IRR	95% CI	APC (%)	APC (%)		(%)	
20-49 Years															
Non-Hispanic White	15,641	8.87	(8.73, 9.01)	1.00	–	16,093	11.36	(11.18, 11.53)	1.00	–	1.69*			1.69*	(1.50, 1.89)
Non-Hispanic Black	3,273	11.26	(10.88, 11.65)	1.27	(1.22, 1.32)	3,465	11.13	(10.76, 11.51)	0.98	(0.94, 1.02)	-0.02			-0.02	(-0.30, 0.25)
Hispanic	1,962	7.01	(6.70, 7.34)	0.79	(0.75, 0.83)	4,048	8.78	(8.51, 9.05)	0.77	(0.75, 0.80)	1.05*			1.05*	(0.43, 1.68)
American Indian/ Alaskan Native	166	8.33	(7.11, 9.70)	0.94	(0.81, 1.09)	258	13.42	(11.82, 15.16)	1.18	(1.04, 1.34)	3.07*			3.07*	(2.31, 3.83)
Asian/Pacific Islander	888	7.96	(7.44, 8.50)	0.90	(0.84, 0.96)	1,502	8.51	(8.09, 8.96)	0.75	(0.71, 0.79)	0.35			0.35	(-0.06, 0.75)
50-74 Years															
Non-Hispanic White	115,547	118.15	(117.47, 118.84)	1.00	–	101,799	74.26	(73.80, 74.73)	1.00	–	-3.72*	1.54*	2011-2012	-2.91*	(-3.28, -2.53)
Non-Hispanic Black	15,905	138.59	(136.43, 140.77)	1.17	(1.15, 1.19)	18,810	90.32	(89.02, 91.64)	1.22	(1.20, 1.24)	-2.82*			-2.82*	(-3.13, -2.51)
Hispanic	8,109	96.14	(94.04, 98.28)	0.81	(0.80, 0.83)	14,163	71.02	(69.83, 72.22)	0.96	(0.94, 0.97)	-1.97*			-1.97*	(-2.33, -1.61)
American Indian/ Alaskan Native	692	98.44	(91.05, 106.25)	0.83	(0.77, 0.90)	1,170	85.75	(80.84, 90.88)	1.15	(1.09, 1.22)	-0.74*			-0.74*	(-1.17, -0.30)
Asian/Pacific Islander	3,727	88.30	(85.46, 91.21)	0.75	(0.72, 0.77)	6,050	62.24	(60.66, 63.84)	0.84	(0.82, 0.86)	-2.12*			-2.12*	(-2.26, -1.98)

**Statistically significant at the 0.05 level.*

IRR, incidence rate ratio; CI, confidence interval; APC, annual percent change; AAPC, average annual percent change.

TABLE 4 | Age-adjusted early-onset (20-49 years of age) and late-onset (50-74 years of age) colorectal neuroendocrine rates per 100,000 person-years.

All Colorectal Cancer	2001-2002					2017-2018					Trend 1	Trend 2	Joinpoint 1	AAPC	AAPC 95% CI
	Cases	Rate	95% CI	IRR	95% CI	Cases	Rate	95% CI	IRR	95% CI	APC (%)	APC (%)		(%)	
20-49 Years															
Non-Hispanic White	755	0.43	(0.40, 0.47)	1.00	–	924	0.65	(0.61, 0.69)	1.00	–	2.22*			2.22*	(1.50, 2.94)
Non-Hispanic Black	272	0.93	(0.82, 1.05)	2.14	(1.86, 2.46)	480	1.53	(1.39, 1.67)	2.35	(2.11, 2.63)	1.97*			1.97*	(0.45, 3.51)
Hispanic	129	0.44	(0.37, 0.53)	1.02	(0.85, 1.23)	330	0.70	(0.63, 0.78)	1.08	(0.95, 1.23)	1.87*			1.87*	(0.22, 3.54)
American Indian/Alaskan Native	–					21	1.13	(0.70, 1.73)	1.75	(1.13, 2.69)	–			–	
Asian/Pacific Islander	78	0.70	(0.55, 0.87)	1.61	(1.28, 2.04)	139	0.78	(0.66, 0.92)	1.20	(1.01, 1.44)	0.79			0.79	(-0.96, 2.56)
50-74 Years															
Non-Hispanic White	2,318	2.36	(2.27, 2.46)	1.00	–	3,634	2.87	(2.77, 2.97)	1.00	–	0.79			0.79	(-0.21, 1.79)
Non-Hispanic Black	735	6.12	(5.68, 6.58)	2.59	(2.38, 2.81)	1,949	9.36	(8.95, 9.79)	3.26	(3.09, 3.45)	1.95*			1.95*	(0.84, 3.07)
Hispanic	262	2.92	(2.57, 3.30)	1.24	(1.09, 1.40)	870	4.11	(3.84, 4.40)	1.43	(1.33, 1.54)	2.17*			2.17*	(1.01, 3.33)
American Indian/Alaskan Native	22	2.67	(1.66, 4.09)	1.13	(0.74, 1.72)	47	3.53	(2.58, 4.70)	1.23	(0.92, 1.64)	3.04*			3.04*	(0.83, 5.30)
Asian/Pacific Islander	154	3.41	(2.89, 4.00)	1.44	(1.23, 1.70)	483	5.05	(4.61, 5.53)	1.76	(1.60, 1.94)	8.67	0.11	2007-2008	3.24*	(0.35, 6.21)

**Statistically significant at the 0.05 level.*

IRR, incidence rate ratio; CI, confidence interval; APC, annual percent change; AAPC, average annual percent change.

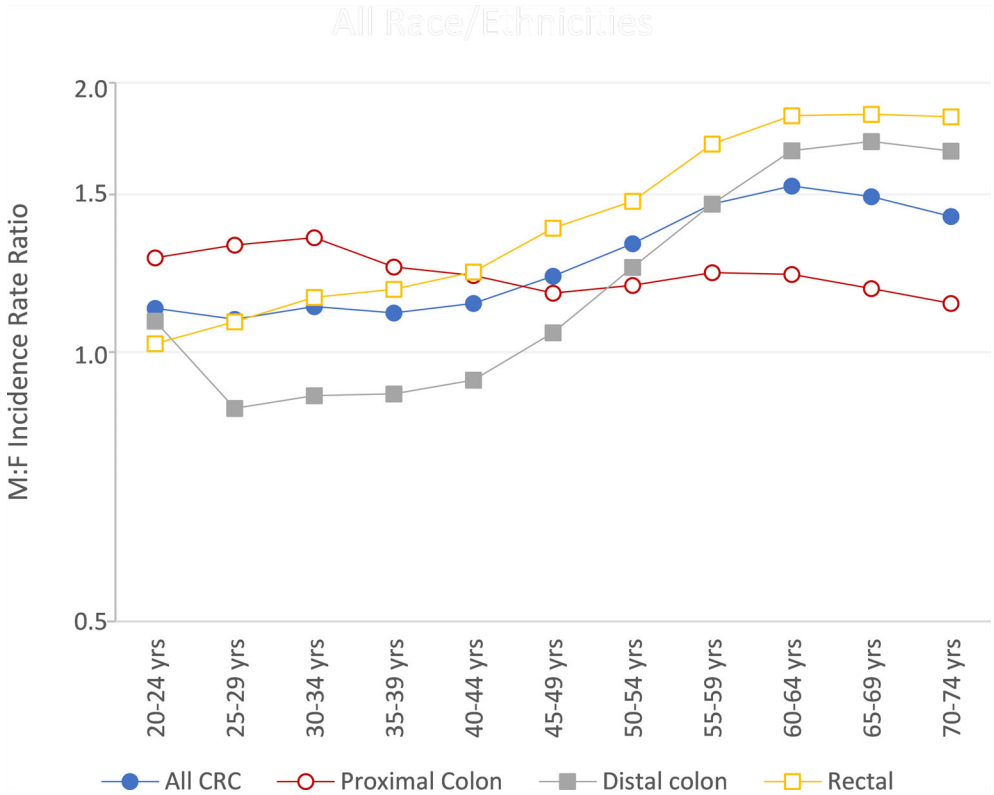

FIGURE 2 | Colorectal cancer male-to-female (M/F) incidence rate ratios by age and subsite, US Cancer Statistics 2001-2018.

decreasing rates for NHBs (17). Similarly, we report that increasing EOCRC rates in NHWs were driven predominately by large increases in distal colon and rectal cancer. However, we also report rates of early-onset distal colon cancer have increased in Hispanics and AIANs, while rates of early-onset rectal cancer have increased in Hispanics, AIANs, and APIs. Additionally, we found that in recent years early-onset proximal cancer increased among NHWs, Hispanics, and AIANs. We did not find that rates of any EOCRC were increasing in NHBs. Similar to the prior report (17), rates of early-onset proximal cancer have decreased in NHBs, specifically in NHB women. Another recent report, based on data from 1995-2016, reported that the increasing rates of EOCRC in NHWs resulted in recent EOCRC being equivalent between NHWs and NHBs (2). We found that EOCRC rates were similar between NHWs and NHBs, but EOCRC rates remain higher in NHBs.

Risk factors for late-onset colorectal adenocarcinoma, which accounts for the majority of CRC, are well researched including obesity (7–9), physical inactivity (10), smoking (8, 11), alcohol (12), and diet (12). The few studies of colorectal neuroendocrine tumors (24–26) raised the possibility that alcohol, metabolic syndrome, and cholesterol levels may be associated with an increased risk. A recent report, using the SEER Program database, reported that rates of neuroendocrine tumors, including colorectal, have increased (27), and that neuroendocrine tumors were more likely to occur in non-White racial/ethnic groups (27), especially distant-stage gastrointestinal neuroendocrine tumors. Another study, also based in the SEER Program database, reported that early-onset colorectal neuroendocrine tumors have increased more rapidly than early-onset adenocarcinomas (28), but did not consider these trends by race/ethnicity or for late-onset CRC. We found that rates of early-onset colorectal neuroendocrine tumors are rapidly increasing, including in NHBs for whom rates of early-onset colorectal adenocarcinoma are not increasing. We also found that rates of late-onset colorectal neuroendocrine tumors are increasing, while rates of late-onset colorectal adenocarcinomas are decreasing in all racial/ethnic groups.

One postulated risk factor for EOCRC is the gut microbiota, which has complex, multifactorial influences (e.g., diet, pathogens, stress, medications, tobacco/alcohol use, physical activity, genetics) (29) and has been reported to vary by race/ethnicity (30) and sex (31). Additionally, gut microbiome profiles have been reported to differ by CRC molecular subtype (32), which differ by anatomic location (33). A recent study supported the influence of the microbiota on EOCRC, reporting that the microbiome within tumors arising before age 45 were more likely to include *Fusobacterium nucleatum*, which promotes colorectal tumorigenesis in the tumor microenvironment by suppressing the immune response, and less likely to include *Moraxella osloensis* than tumors arising after age 65 (34). Identification of

microbial profiles specific to EOCRC may yield insights into the etiology of EOCRC and inform novel therapeutics and cancer screening strategies (34).

Historically, NHBs have had the highest rates of CRC in the US, including EOCRC (1, 17). We found that AIANs now have the highest rates of EOCRC and the second highest rate of late-onset CRC. AIANs have long had high rates of CRC, with the highest CRC rates in the US reported among ANs (35, 36). This could be in part due to higher prevalence of risk factors in the AIAN population (e.g., poor diet, vitamin D deficiency, smoking, obesity, diabetes, and *Helicobacter pylori* infection) (36–40), but it is likely that discrimination, historic healthcare administration policies, and structural challenges also play a major role (41). Perceived racial/ethnic medical discrimination has been linked with lower receipt of preventive cancer screening, including CRC screening (42), and nearly a quarter of AIANs report experiencing discrimination when accessing healthcare (43). Regardless of whether AIANs have other health insurance, including Medicare, the Indian Health Service is the primary federal agency that fulfills the US government responsibility to provide healthcare services to AIANs (44, 45). The Indian Health Service spends approximately half the amount per capita on healthcare for AIANs compared to per capita expenditures for federal inmates or Medicaid recipients (41). In 2016, the Indian Health Service reported that less than 40% of screening aged individuals had received appropriate CRC screening (i.e., stool testing in the past year, using a fecal occult blood test [FOBT] or a fecal immunochemical test [FIT]; flexible sigmoidoscopy in the past 5 years; or colonoscopy in the past 10 years) (46). The lack of screening for and removal of adenomas, the precursors to most colorectal adenocarcinomas, could result in higher incidence rates of late-onset CRC. Due to the logistics of endoscopy locations and resource availability, the primary mode of CRC screening in the Indian Health Service tends to be stool testing. Current guidelines from the US Multi-Society Task Force of Colorectal Cancer recommend colonoscopy every 10 years or FIT annually as the first-tier CRC screening tests (47). FIT tests are more acceptable than colonoscopy to most individuals (48), but adherence to an annual regimen and lower endoscopic follow-up for abnormal results can be challenging —especially for ANs, many of whom live in remote areas where access to endoscopy can require long-distance, high-cost air travel (49, 50). Further, the Indian Health Service is not health insurance. If endoscopy is not available at an Indian Health Service or tribal facility, it can be purchased through Contract Health Services. However, a lower endoscopy is not considered a high priority referral and could be denied, potentially impacting rates of both early- and late-onset CRC (45). Current strategies to increase screening in the AIAN population include close partnerships with the community to distribute culturally-sensitive information on CRC screening and implementation of patient navigation and provider education (49, 51, 52). Specific projects have trained mid-level healthcare providers (e.g., physician assistants and nurse practitioners) in rural areas to provide lower endoscopy (49) and mailed FIT kits to individuals with diabetes or pre-diabetes (51).

NHBs have the second highest rate of EOCRC and the highest rate of late-onset CRC. While the racial disparity between NHBs and NHWs in incidence of EOCRC has narrowed, this is due to increasing rates in NHWs, not to decreasing rates in NHBs. Due to the large increases in the overall EOCRC rate (primarily driven by the increases in rates of colorectal adenocarcinoma in NHWs), there is intense interest in understanding EOCRC etiology. In addition to the microbiome, discussed above, obesity is a primary risk factor of interest for EOCRC. Recent literature has shown conflicting results for an obesity–EOCRC association, with a study from a primarily NHW population showing an obesity is associated with an increased EOCRC risk (9) and a study from a primarily NHB population showing no association (53). Thus, obesity may not explain the high rates of EOCRC in NHBs. Another potential risk factor that has received little attention to date is increased levels of stress in younger birth cohorts (13, 54). One study has reported that perceived stress is associated with an increased risk of CRC (55), potentially through stress inducing genetic, epigenetic, microbial, and immune alterations (13). If stress increases EOCRC risk, this could disproportionately affect NHBs, compared to NHWs, as NHBs face additional stressors due to systemic, institutional, and individual racism. NHBs report experiencing the highest levels of both general racism (56%) and health care racism (13%) (56).

Disparities in CRC incidence between NHBs and NHWs persist after adjusting for risk factors and socioeconomic status (57). Further, in populations where the access to care is expected to be similar between racial/ethnic groups (e.g., active-duty military or veterans), the disparities in CRC incidence are even more pronounced (58–62). Thus, high rates of late-onset CRC in NHBs may be driven by social determinants of health and structural racism, which together with historic abuse and exploitation of NHB individuals (63) can hinder receipt of preventive screenings (64, 65). A recent study demonstrated that when NHB patients received care from NHB physicians, patients received more preventive services and had more trust in the healthcare system and patient-provider communication increased (65). The proportion of physicians who are NHB does not reflect the proportion of NHBs in the US population (66). Thus, pipeline programs for under-represented minorities to enter into healthcare careers are necessary to create a healthcare workforce that reflects the population it serves (64, 67). In addition, all physicians should receive training in implicit bias, cultural competency, and patient centeredness and practice in operationalizing these skills to improve communication with patients of different racial/ethnic groups (64, 68, 69).

Across all racial/ethnic groups, men have higher rates of CRC, and the sex differences in rates increase with age. In 2018, men and women had nearly equivalent rates of CRC screening (2). Thus, the higher rates of CRC in men are primarily attributed to modifiable risk factors that differ by sex—diets high in red meat, alcohol consumption, smoking, and visceral adiposity (70). However, the sex difference noted in the screening-aged population could also be due, in part, to some men reporting embarrassment and offense with CRC screening, which healthcare providers should be cognizant of when promoting CRC screening to men (71, 72).

In women, proximal colon cancer is the predominate type of late-onset CRC. Proximal colon cancers are more likely than distal colon or rectal cancer to have high microsatellite instability (MSI) (33, 73, 74), which is hypothesized to be partially due to high

estrogen levels. A recent study demonstrated that proxies of higher estrogen levels, including pregnancy, oral contraceptive use, and menopausal hormone therapy use, were associated with lower risk of MSI-high CRC in women (75). Thus, the predominance of late-onset proximal colon cancer in women may be partially due to declining estrogen levels. Proximal and distal colon cancer have different embryologic origins—the embryonic midgut and hindgut, respectively, which may also partially explain the molecularly distinct profiles and presentation of these cancer types (74).

The new ACS and USPSTF guidelines recommend screening beginning at age 45 (5, 6). However, rates of EOCRC are continuing to increase in individuals under age 45. Thus, additional research should focus on underlying causes and identifying predictors of EOCRC to determine if certain groups should be screened prior to age 45. For individuals aged 45 to 50 years, consistent messaging and access to healthcare are needed to ensure that these individuals obtain CRC screening, especially in AIAN and NHB communities. Flexible sigmoidoscopy, which only evaluates the distal colon and rectum, has been suggested as a screening tool for EOCRC (14, 76). However, proximal colon cancer is the predominant form of both early- and late-onset CRC in NHB men and women. Thus, NHBs should ideally receive a colonoscopy screening to fully evaluate the proximal colon.

The strength of this study is use of the US Cancer Statistics database (covering 99% of the US population) versus the more commonly used SEER Program database (covering up to 35% of the US population). Use of high-quality population-based cancer registry data from the entire US population allowed us to comprehensively explore racial/ethnic disparities and sex differences. Hispanic ethnicity may have been incorrectly classified for some individuals, as the US Cancer Statistics database uses the North American Association of Central Cancer Registries Hispanic Identification Algorithm (77). However, this algorithm has been shown to have high sensitivity (92.9), specificity (98.0), and positive predictive values (95.6) (78). We did not adjust for delayed data reporting, beyond the standard 2-year delay. However, delay in case reporting has been shown to be minimal for CRC, with 97% of cases reported using the standard 2-year delay (79). In addition, there is underreporting due to lack of data from Veterans Affairs hospital patients during some years, but the impact on CRC rates is minimal (80). Finally, a limitation of all cancer registry data is that no information is available on individual risk factors, including genetic predisposition to CRC which is particularly relevant for EOCRC. Thus, we were unable to adjust for individual-level factors.

Future research should focus on identifying risk factors and predictors of EOCRC to determine if there are high-risk groups that should be targeted for screening prior to age 45. Additional research is also needed to determine the etiology of colorectal neuroendocrine tumors, as rates of both early- and late-onset are increasing. Recent increases in EOCRC, primarily driven by increasing rates in NHWs, have elicited intense interest in understanding the underlying etiology of EOCRC. However, studies examining EOCRC etiology need to make certain that racial/ethnic minorities are included, to ensure that these studies can be used to mitigate racial/ethnic disparities in EOCRC. Ongoing prevention efforts must ensure access to appropriate CRC screening for AIANs and NHBs.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/cancer/uscs/public-use/obtain-data.htm.

AUTHOR CONTRIBUTIONS

JLP participated in the conception, design, and analysis of the study; and drafted the manuscript. LEB participated in the conception, design, and analysis of the study; and provided critical revision of the manuscript for important intellectual content. SWA participated in the design of the study and provided critical revision of the manuscript for important intellectual content. AAF participated in the design of the study and provided critical revision of the manuscript for important intellectual content. JRP participated in the design and analysis of the study and provided critical revision of the manuscript for important intellectual content. LR participated in the conception and design of the study, assisted in drafting the manuscript, and providing revisions of important intellectual content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Synergistic Effects of Genetic Variants of Glucose Homeostasis and Lifelong Exposures to Cigarette Smoking, Female Hormones, and Dietary Fat Intake on Primary Colorectal Cancer Development in African and Hispanic/Latino American Women

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Background: Disparities in cancer genomic science exist among racial/ethnic minorities. Particularly, African American (AA) and Hispanic/Latino American (HA) women, the 2 largest minorities, are underrepresented in genetic/genome-wide studies for cancers and their risk factors. We conducted on AA and HA postmenopausal women a genomic study for insulin resistance (IR), the main biologic mechanism underlying colorectal cancer (CRC) carcinogenesis owing to obesity.

Methods: With 780 genome-wide IR-specific single-nucleotide polymorphisms (SNPs) among 4,692 AA and 1,986 HA women, we constructed a CRC-risk prediction model. Along with these SNPs, we incorporated CRC-associated lifestyles in the model of each group and detected the topmost influential genetic and lifestyle factors. Further, we estimated the attributable risk of the topmost risk factors shared by the groups to explore potential factors that differentiate CRC risk between these groups.

Results: In both groups, we detected IR-SNPs in *PCSK1* (in AA) and *IFT172*, *GCKR*, and *NRBP1* (in HA) and risk lifestyles, including long lifetime exposures to cigarette smoking and endogenous female hormones and daily intake of polyunsaturated fatty acids (PFA), as the topmost predictive variables for CRC risk. Combinations of those top genetic- and lifestyle-markers synergistically increased CRC risk. Of those risk factors, dietary PFA intake and long lifetime exposure to female hormones may play a key role in mediating racial disparity of CRC incidence between AA and HA women.

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Conclusions: Our results may improve CRC risk prediction performance in those medically/scientifically underrepresented groups and lead to the development of genetically informed interventions for cancer prevention and therapeutic effort, thus contributing to reduced cancer disparities in those minority subpopulations.

Keywords: glucose homeostasis, random survival forest, attributable risk, smoking, endogenous estrogen, polyunsaturated fatty acid, colorectal cancer, African and Hispanic/Latino American women

INTRODUCTION

Although cancer mortality has declined throughout all racial/ethnic groups since 1971 when the National Cancer Act, known as the "War on Cancer", began, cancer health disparities still exist in the form of higher cancer incidence and mortality among the racial/ethnic minorities (1). In particular, colorectal cancer (CRC) incidence and death rates in African American (AA) women are highest among all racial/ethnic female groups and, compared with white women, 20% and 35%, respectively, were higher during 2012–2016 (2, 3). Also, in the 2 largest minorities, AA and Hispanic/Latino American (HA) women, CRC is the third leading cause of cancer diagnosis and related death (3, 4).

The risk for CRC development increases in older women. For example, approximately 90% of new CRC cases occur in women 50 years old and older (2), and one of the main risk factors is excessive adiposity (5, 6). Specifically, among AA and HA postmenopausal women of at least age 50 years, our preliminary analysis (**Table S1**) of abdominal adiposity (measured by waist circumference and waist-to-hip ratio) supported the role of obesity in increased risk for CRC, despite insufficient statistical power. For the major biologic mechanism of colorectal tumorigenesis due to obesity, insulin resistance (IR) or glucose intolerance has been thought to play a key mediating role (7, 8). Specifically, increased levels of glucose and insulin, reflecting IR, which interacts with obesity, promoted colorectal epithelial proliferation (9); the elevated insulin levels stimulated the growth of CRC in both cell lines (10) and an animal model (11). IR promotes mitosis by overexpressing insulin receptors and insulin-like growth factor 1 receptors and by dysregulating downstream cellular signaling cascades, resulting in enhancement of cellular anabolic status and increased anti-apoptosis and cell proliferation (12, 13). IR may thus initiate and facilitate CRC cell growth. However, studies focusing on AA and HA women for IR in relation to CRC risk are lacking. One study of DNA methylation in association with CRC among AAs (mainly women) (14) revealed aberrant methylation of CpG islands in the genes that are involved in an insulin network, suggesting the critical role of IR in AA women's colorectal carcinogenesis. Also, the preliminary results (**Table S1**) in AA and HA women from our analysis of the fasting glucose and insulin levels (FG and FI) indicated that increased levels of both molecules (particularly glucose) were associated with higher risk for CRC in both groups, but these findings lacked sufficient power to reach significance.

Considering that the systemic development of IR can be influenced by not only environmental (15–17) but also genetic factors (18, 19), studying genomic markers that explain variations of glucose and insulin concentrations may provide more confirmatory understanding of those concentrations' role in CRC development. The effort to detect genetic variations of IR has been made in extensive genomic studies, but they mostly focused on whites. AAs and HAs are thus underrepresented in genetic/genome-wide studies of IR. Uncovering IR-specific genetic signatures in these large minorities may advance the understanding of the biology of IR regulation and further, as cancer biomarkers, improve the prediction ability for CRC risk. It can also promote the development of genetically focused, tailored interventions for CRC preventive and therapeutic efforts.

For this reason, we conducted a genomic study of IR and, with validated IR-specific genetic variants, tested for the association with CRC risk specifically focusing on AA and HA postmenopausal women. Since the allele frequencies of modeled genotypes and their effects on IR and CRC are race/ethnicity specific, we conducted our genomic study separately within AA and HA women. We examined more than 780 IR single-nucleotide polymorphisms (SNPs) that have been detected as top genetic signals in the largest and independent genome-wide association (GWA) studies (20–25). With the IR-SNPs validated in our datasets, we tested for the association with CRC development.

Moreover, although obesity is most prevalent in both AA and HA women of all racial/ethnic groups (26), and the diabetes rates within those 2 minority groups are higher than they are in whites (27), CRC incidence is more prevalent in AA women than in HA women (3, 28). Our preliminary analysis also supported this phenomenon [hazard ratio $(HR)_{HA\ vs.\ AA} = 1.85$, 95% confidence interval (CI): 1.08 – 3.18] (**Figure S1**); this suggests the potential role of other lifestyle factors (e.g., diet, smoking, alcohol, female hormones) that are also associated with CRC risk (2, 29–38) in mediating the racial/ethnic differences in CRC risk. Therefore, we incorporated these CRC-associated lifestyle factors with IR genetic markers that we validated for their associations with IR and CRC risk and established risk-prediction models in AA and HA women. By computing the risk prediction for each variable for CRC risk, we detected the most influential genetic markers and lifestyle factors. We next estimated the prediction ability and accuracy of those risk factors, both singly and combined. We further computed to what extent genetic and lifestyle factors, separately and together, influence the development of CRC in each racial/ethnic group [i.e., population attributable risk (PAR)]. Eventually, we estimated an attributable risk (AR) for the common risk factors across the 2 groups to explore potential factors that may play a key role in differentiating the risk for CRC between groups.

MATERIALS AND METHODS

Study Subjects

Our study subjects were AA and HA postmenopausal women who had been enrolled in the SNP Health Association Resource (SHARe), which is a prospective cohort of the minorities as a part of Women's Health Initiative Database for Genotypes and Phenotypes (WHI dbGaP) Harmonized and Imputed GWA Studies with the aim of revealing genes/genetic variants in association with quantitative traits with enhanced statistical power in those racial/ethnic minorities. Details of the study design and rationale have been described elsewhere (39–41). In brief, healthy women were recruited at 40 WHI-designated clinical centers across the United States from 1993 through 1998 if they were 50–79 years old, postmenopausal, and expected to stay near the clinical centers for at least 3 years after enrollment. Women were excluded if they had any medical conditions associated with predicted survival of less than 3 years in the judgment of the clinical center physician. They had been further enrolled in the WHI dbGaP study if they had met eligibility for data submission to the dbGaP resource and provided DNA samples. Participants provided written informed consent at enrollment. Among 10,818 women (7,470 AA and 3,348 HA) who reported their race or ethnicity as AA or HA, we applied exclusion criteria as follows: genomic data quality control (QC); a history of diabetes; a diagnosis of any cancer type at enrollment; and less than 1-year follow-up. Ultimately, our study cohort contained 6,678 women (4,692 AA and 1,986 HA). After enrollment, they had been followed through August 2014, with a median follow-up of 15 years at the end point. By their last follow-up, 89 women [73 (1.5%) AA and 16 (0.8%) HA] had developed primary CRC. The institutional review boards of the WHI participating clinical centers and the University of California, Los Angeles approved our study.

Selection of IR SNPs

We employed data to select IR-specific SNPs from the publicly available genomic resource on glycemic traits, the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC; www.magicinvestigators.org) (20–23). MAGIC had analyzed FG and FI as continuous variables. We also used 2 other GWA-based data resources for racial/ethnic minorities. One (24) detected SNPs associated with FG in a 500-kb linkage disequilibrium (LD) block, and the other (25) found functional SNPs for glucose intolerance. Among a total of 1,344 FG-SNPs and 313 FI-SNPs identified in these studies, 689 FG and 91 FI SNPs for AA women and 692 FG and 92 FI SNPs for HA women are available in our SHARe dbGaP study, among which 94 FG and 8 FI SNPs for AAs and 168 FG and 1 FI SNPs for HAs were validated with a relevant phenotype.

Genotyping and Phenotyping

We extracted genotyping data for the study subjects from the WHI dbGaP SHARe database. Details of genotyping information have been reported (39, 41). DNA samples were obtained from the subject blood samples at baseline and genotyped with Affymetrix 6.0 (Affymetrix, Inc., Santa Clara, CA) at the Fred Hutchinson Cancer Research Center in Seattle, WA. Genomic data were normalized to Genome Reference Consortium Human Build 37, imputed with the 1000 genomes reference panels, and harmonized *via* pairwise concordance among samples across WHI GWA studies. We compared the self-reported ethnicity with genetic principal component (PC). If any discrepancy or admixed participant was found, the subject was labeled as being genetically inconsistent; no one in the SHARe data was identified whose genetic ethnicity was inconsistent. We conducted genomic data QC, filtering out those SNPs with a missing-call rate of ≥ 2%, a Hardy-Weinberg equilibrium of $p < 1E{-}04$, and $\check{R}^2 <$ 0.6imputation quality (42). Further, we excluded those individuals with unexpected duplicates, first- and second-degree relatives, and outliers defined by our genetic PC analysis.

Blood samples after fasting were derived from each subject at baseline by trained phlebotomists. Serum levels of glucose and insulin were measured using the hexokinase method on a Hitachi 747 instrument (Boehringer Mannheim Diagnostics, Indianapolis, IN) and using a radioimmunoassay method (Linco Research, Inc., St. Louis, MO), respectively, with average coefficients of variation of 1.28% and 10.93%, respectively.

Lifestyle Factors and Cancer Outcome

To select CRC-associated lifestyle factors, we performed a literature review (2, 29–38, 43–46) particularly focusing on AAs and HAs. On the basis of our review, we extracted the following lifestyle variables from the SHARe database: age at enrollment; family history of CRC (genetic inheritance); lipid metabolic profiles; anthropometric measures (body mass index [BMI], waist circumference, and waist-to-hip ratio); physical activity; alcohol intake (daily dietary alcohol intake and history of alcohol intake); smoking (number of years as a regular smoker and number of cigarettes smoked daily); nutrition (dietary fiber; daily fruits and vegetables; percent calories from protein; percent calories from saturated and mono- and polyunsaturated fatty acids [SFA, MFA, and PFA, respectively]; dietary calcium; vitamin K; and total sugars); age at menopause; and duration of oral contraceptive (OC) use. Additionally, we included in our data analysis the following variables: demographic and socioeconomic variables (education; marital status; and employment); comorbid conditions (depressive symptoms; cardiovascular disease ever; and hypertension ever); and other reproductive histories (age at menarche; number of pregnancies; duration of breast feeding; oophorectomy and/or hysterectomy; and unopposed/opposed exogenous estrogen use). All the aforementioned variables had been obtained at baseline from subjects *via* self-administered questionnaires, except weight, height, and waist/hip circumferences, which had been measured by trained clinical staff. The WHI coordinating clinical centers monitored all the data collection processes. By using those 35 selected variables, we further conducted preliminary univariate and stepwise/multiple regressions in association with CRC risk and checked multicollinearity between variables.

A diagnosis of primary CRC in the study subjects was confirmed *via* a centralized review of medical records and

pathology and cytology reports by the WHI committee of physicians, who followed the National Cancer Institute's Surveillance, Epidemiology, and End-Results guidelines (47). The time between enrollment and CRC diagnosis, censoring, or study end-point was computed, first in days, and then converted to years.

Statistical Analysis

We conducted linear and Cox proportional hazards regressions to estimate the relationship of GWA-based IR-SNPs with naturally log-transformed FG (mg/dl)/FI (μIU/ml) and with CRC risk, respectively, after confirming that the assumptions for each were met. Both regression analyses were adjusted for age and 10 genetic PCs that account for racial/ethnic ancestry variations. A 2-tailed $p < 0.05$ for validation tests of FG/FI and association tests with CRC risk was considered nominally significant. After the Bonferroni correction for multiple comparisons, $p < 7E-05$ for FG, $p < 5E-04$ for FI, and $p < 5E-04$ (in AAs) and $p < 3E-04$ (in HAs) for CRC risk were considered statistically significant.

With those SNPs validated for their association with relevant phenotype and CRC risk and the selected lifestyle factors, we conducted a Random Survival Forest (RSF) analysis. RSF is a tree-based ensemble machine-learning method that accounts for the nonlinear effects and high-order interactions among variables (48); it has outperformed traditional prediction models, successfully yielding more accurate predictions (49–53). The 2 key predictive values generated from the RSF model are minimal depth (MD); those variables with a small MD are highly predictive, and variable importance (VIMP); those variables with a larger VIMP are more predictive (48, 54). RSF creates a tree from the bootstrapped samples by maximizing survival differences across daughter nodes and, by repeating this process numerous times (n = 5,000 trees in this study), generates a forest of trees. Using the out-of-bag (OOB) data, we first computed the prediction error and next, the OOB concordance index (c-index = 1 – prediction error), which is conceptually similar to the area under the receiver operating characteristic (ROC) curve (AUC) (55, 56).

We applied a multimodal RSF approach in the AA and HA groups to detect the most influential predictors for CRC risk among the SNPs and lifestyle factors. In a separate RSF analysis within genetic markers and lifestyle variables, we first compared the 2 key predictive values, MD and VIMP, in the plot. Next, we computed the incremental error rate of each variable within the nested sequenced RSF models. Last, we estimated the drop error rate in each variable ranked by MD in the nested models to detect variables that contribute to reducing the prediction error rate. By using the identified topmost influential SNPs and lifestyle factors, both singly and combined in each group of women, we further estimated the OOB c-index within the nested RSF model and plotted an ROC curve (57) to quantitatively measure their prediction performance. Further, we estimated the combined effect of the topmost genetic and lifestyle predictors on CRC risk using Cox regression in each racial/ethnic group. After a 2-tailed p value was corrected for multiple comparisons *via* the Benjamini-Hochberg method, a 5% false discovery rate (FDR) was considered statistically significant. Eventually, by using the most predictive variables in each group, we computed the PAR percentage (58) to determine the extent to which CRC cases in the group are attributed to genetic and lifestyle factors, singly and in combination. Last, we identified common variables from the most influential variables among the AA and HA women, and by estimating the AR percentage for each variable (59), we explored what variable(s) may contribute to the racial difference in CRC incidence between the groups. Multiple R packages were used (R v4.0.4, pROC survival, survivalROC, randomForestSRC, ggRandomForests, ggplot2, ggthemes, and gamlss).

RESULTS

Between the 94 FG and 8 FI SNPs in AA women (**Tables S2A, B**) and the 168 FG and 1 FI SNPs (**Tables S3A, S2B**) in HA women, which were validated with a relevant phenotype nominally and after multiple comparison corrections, 35 FG SNPs overlapped, while none of the FI SNPs were shared by the AA and HA groups. In the analysis of those validated SNPs for their association with the risk of CRC development, 10 SNPs in AA women (**Table S2C**) and 27 SNPs in HA women (**Table S3C**) were significant nominally and after multiple comparison correction. Of note, they were all identified among the FG SNPs and were not shared by the 2 groups: the FG SNPs of AAs were from the chromosomes 5 and 7, whereas the FG SNPs of HAs were from chromosome 2. Using those SNPs validated with the phenotype and CRC outcomes in each group of women, we proceeded to the next step, RSF analysis.

Multimodal RSF Analysis of Validated SNPs and Selected Lifestyle Factors

To detect the topmost influential genetic and lifestyle factors in each racial/ethnic group within the RSF prediction model, we adapted a multimodal approach. In separate RSF models within the SNPs and selected lifestyle factors, we first generated a plot of 2 prediction measures, the MD and VIMP (**Figure 1**). In agreement with high ranks between the 2 values in AA women, we detected 1 genetic and 6 lifestyle factors as the topmost predictive variables for CRC risk (**Figures 1A, B**): *PCSK1* rs9285019 and years as a regular smoker, percent calories from PFA/day, dietary total sugar intake, age at enrollment, age at menopause, and duration of OC use. Next, we computed the incremental and drop error rates of each SNP and lifestyle variable arranged by MD in the nested sequenced RSF models (**Tables S4A, B**), detecting the same set of the topmost 1 genetic and 6 lifestyle variables, which contributes substantially to reducing the prediction error rate. By using these topmost predictive variables, we further estimated a c-index and AUC (**Table 1**) and plotted them (**Figure 2A**), confirming those top variables' prediction ability. Specifically, in the c-index plots for the SNP (**Figure 2Aa**) and lifestyles (**Figure 2Ac**), which were ordered by MD rank, those topmost genetic and lifestyle variables were distinctive to improve prediction ability compared with the rest of the variables. The AUC estimations

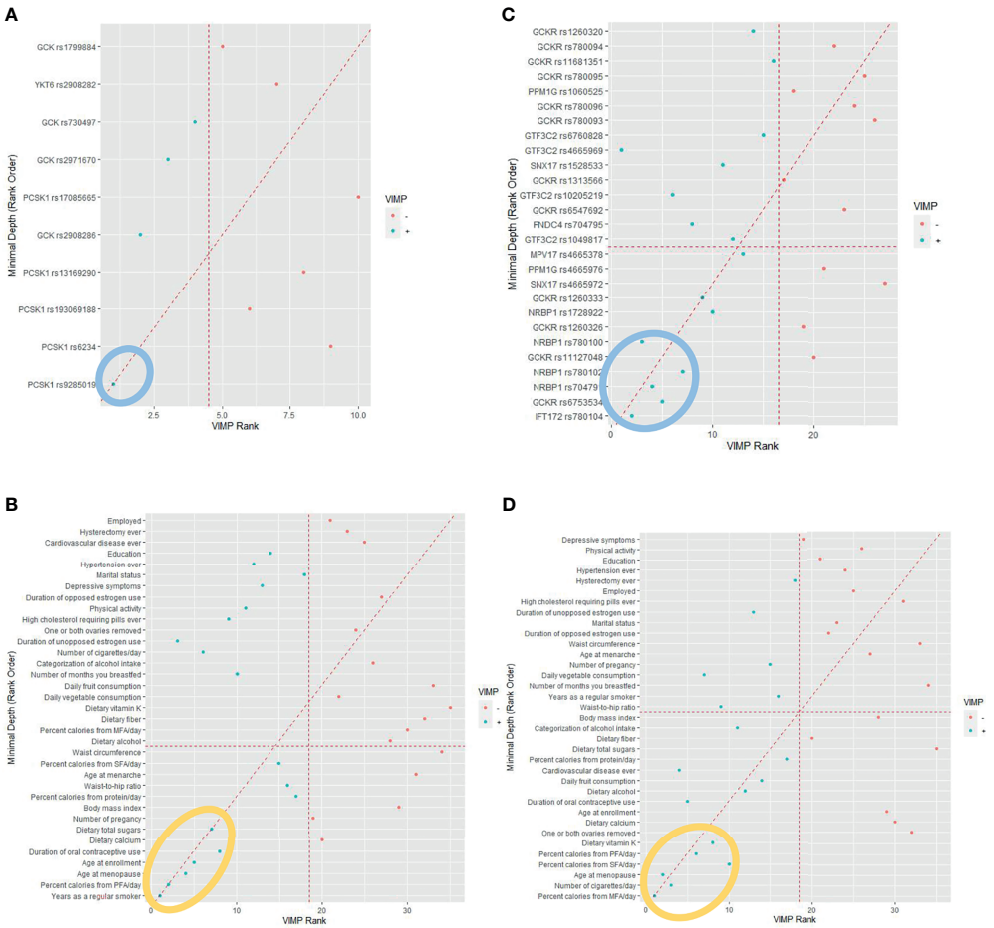

FIGURE 1 | Random survival forest comparing rankings between minimal depth and variable of importance (VIMP). **(A)** African American women. (Note: The 1 genetic marker within the blue oval was identified as the topmost influential predictor. **(B)** African American women. (MFA, monounsaturated fatty acid; PFA, polyunsaturated fatty acid; SFA, saturated fatty acid. Note: The 6 lifestyle variables within the orange oval were identified as the topmost influential predictors. **(C)** Hispanic American women. (Note: The 5 genetic markers within the blue oval were identified as the topmost influential predictors. **(D)** Hispanic American women. (MFA, monounsaturated fatty acid; PFA, polyunsaturated fatty acid; SFA, saturated fatty acid. Note: The 6 lifestyle variables within the orange oval were identified as the topmost influential predictors).

for those topmost genetic and lifestyle variables each presented results similar to those from the c-index estimation (**Figures 2Ab, 2Ad**). The combination of the gene- and lifestyle-specific AUC yielded 0.647 (95% CI: 0.587 – 0.708) (**Figure 2Ae**), revealing that the topmost lifestyle variables were more substantial contributors to the prediction performance than the top genetic marker was.

We applied the same approach to the group of HA women to find their topmost influential variables. We detected 5 SNPs and 6 lifestyles in agreement with high ranks between MD and VIMP (**Figures 1C, D**) and, by computing the incremental/drop error rate of each genetic and lifestyle variable (**Tables S4C, D**), we identified those same topmost genetic and lifestyle variables. Due to the high LD ($r^2 > 0.5$) within the detected topmost 5 SNPs, we determined 3 SNPs (*IFT172* rs780104, *GCKR* rs6753534, and *NRBP1* rs704791) as the final influential genetic markers and carried them over to the c-index/AUC estimation (**Table 1** and **Figure 2B**). The topmost lifestyle variables identified in the HA women were similar to those detected in the AA women, but more variables were involved: dietary fat intake (SFA/MFA) and dietary vitamin K intake. The c-index and AUC measures from a separate analysis within these topmost SNPs (**Figures 2Ba, Bb**) and lifestyle factors (**Figures 2Bc, Bd**) also indicated their prediction ability. The AUC from the SNPs and lifestyles together was 0.830 (95% CI 0.721 – 0.939) (**Figure 2Be**), in which those top genetic factors contributed more profoundly to the prediction ability than the top lifestyle factors did; this pattern differs from that observed in AA women.

The Detected Topmost SNPs and Lifestyle Factors: Combined Effects on CRC Risk

By using the topmost influential IR-SNPs and lifestyle variables in each racial/ethnic group, we implemented the machine-learning process using the RSF model to compute the

TABLE 1 | Predictive measures C-index and AUC of the topmost genetic and lifestyle factors in association with colorectal cancer risk.

	African American women			Hispanic American women		
Type of variable	**Topmost influential variables***	**C-index**	**AUC (95% CI)**	**Topmost influential variables***	**C-index**	**AUC (95% CI)**
SNP	*PCSK1* rs9285019	0.4715	0.561 (0.491 – 0.631)	*IFT172* rs780104	0.7064	0.798 (0.688 – 0.907)
				GCKR rs6753534	0.8175	
				NRBP1 rs704791	0.8048	
Lifestyle factors	Years as a regular smoker	0.5023	0.627 (0.566 – 0.689)	% calories from MFA/day	0.5979	0.675 (0.526 – 0.823)
	% calories from PFA/day	0.5356		Number of cigarettes/day	0.5245	
	Age at menopause	0.5486		Age at menopause	0.5655	
	Age at enrollment	0.6014		% calories from SFA/day	0.5836	
	Duration of OC use	0.6223		% calories from PFA/day	0.5896	
	Dietary total sugars	0.6301		Dietary vitamin K	0.5721	
SNP + Lifestyle factors	1 SNP + 6 lifestyle factors		0.647 (0.586 – 0.708)	3 SNPs + 6 lifestyle factors		0.830 (0.721 – 0.939)

AUC, area under the receiver operating characteristic curve; CI, confidence interval; C-index, concordance index; MFA, monounsaturated fatty acid; OC, oral contraceptive; PFA, polyunsaturated fatty acid; SFA, saturated fatty acid; SNP, single-nucleotide polymorphism.

**Topmost predictive variables were selected on the basis of random survival forest analysis with a multimodal approach.*

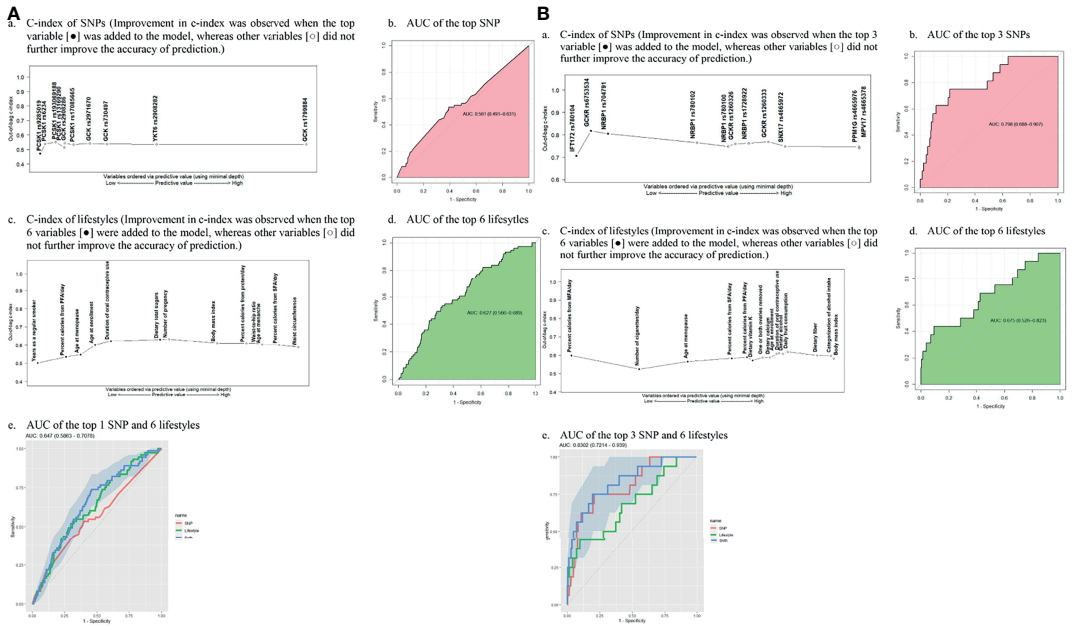

FIGURE 2 | Out-of-bag concordance index (C-index) and area under the receiver operating characteristic curve (AUC) for the topmost genetic and lifestyle factors (MFA, monounsaturated fatty acid; PFA, polyunsaturated fatty acid; SFA, saturated fatty acid SNP; single-nucleotide polymorphism **(A)** African American women. **(a)** C-index of SNPs (Improvement in c-index was observed when the top variable [•] was added to the model, whereas other variables [O] did not further improve the accuracy of prediction. **(b)** AUC of the top SNP **(c)** C-index of lifestyles (Improvement in c-index was observed when the top 6 variables [•] were added to the model, whereas other variables [O] did not further improve the accuracy of prediction.) **(d)** AUC of the top 6 lifesytles **(e)** AUC of the top 1 SNP and 6 lifestyles **(B)**. Hispanic American women. **(a)** C-index of SNPs (Improvement in c-index was observed when the top 3 variable [•] was added to the model, whereas other variables [O] did not further improve the accuracy of prediction.) **(b)** AUC of the top 3 SNPs **(c)**. C-index of lifestyles (Improvement in c-index was observed when the top 6 variables [•] were added to the model, whereas other variables [O] did not further improve the accuracy of prediction.) **(d)** AUC of the top 6 lifestyles **(e)** AUC of the top 3 SNP and 6 lifestyles.

cumulative predictive CRC incidence rate by adjusting for confounding variables and a nonlinearity effect of the variable on CRC incidence (**Figure 3**). In the AA group, the risk genotype and risk lifestyles were defined according to their cutoff values, which were determined by their risk distribution in the plot: *PCSK1* rs9285019 TC+CC; ≥ 20 years as a regular smoker; ≤ 6.8% of daily calories from PFA; age > 42 years at menopause; age between 56 and 79 years at enrollment; 5–37 years of OC use; and > 60.5 g of total dietary sugar intake. In the HA group, *IFT172* rs780104 GG, *GCKR* rs6753534 CC, and *NRBP1*

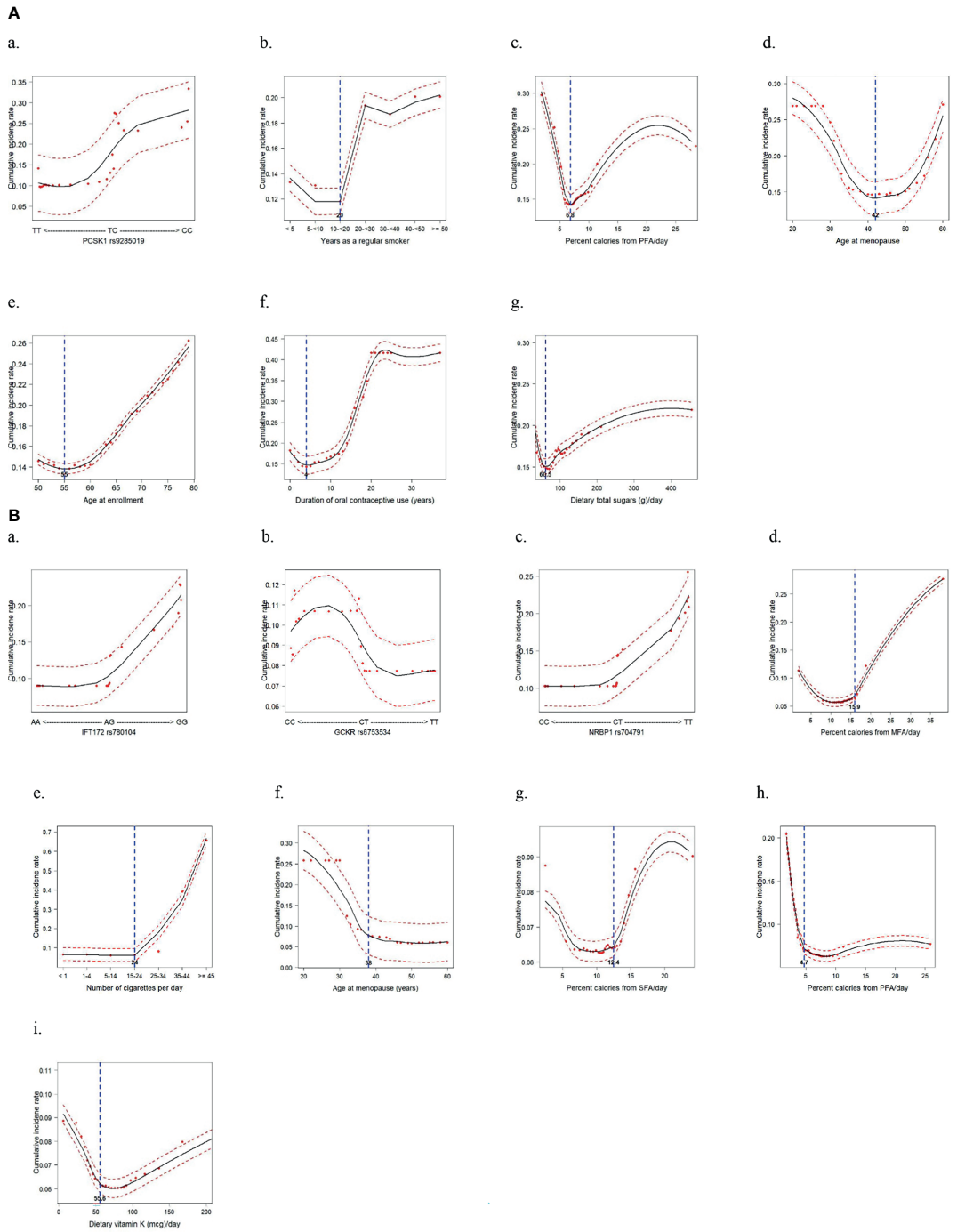

FIGURE 3 | Cumulative incidence rate of colorectal cancer for the topmost predictive genetic and lifestyle variables selected from a random survival forest analysis (Dashed red lines indicate 95% confidence intervals. **(A)** African American women: 1 genetic and 6 lifestyle factors. **(B)** Hispanic American women: 3 genetic and 6 lifestyle factors.

rs704791 TT were determined to be the risk genotypes. Also, > 15.9% of daily calories from MFA; ≥ 25 cigarettes smoked daily; age ≤ 38 years at menopause; > 12.4% of daily calories from SFA; ≤ 4.7% of daily calories from PFA; and ≤ 55.6 mg of dietary vitamin K were defined as the risk lifestyles. It is noteworthy that in both groups, a greater daily intake of calories from PFA was shown to be a protective factor against CRC development. Interestingly, prolonged exposure to female hormones (i.e., late

menopause and/or longer OC use) was revealed to be a risk factor for CRC development among the AA women, but in the HA women it was a protective factor.

Having categorized those topmost SNPs and lifestyle variables accordingly, we first investigated their individual risks for CRC (by adjusting for the others), thus confirming their single effects on CRC risk (**Table S5**). Indeed, the effect magnitude of the individual SNPs was much greater in the HA group than it was in AA group; this corresponded with the finding of the greater influence of those topmost SNPs on the AUC in the HA than in the AA women. Also, whereas most lifestyle variables were not significant after accounting for the others in the AA group, some of the lifestyle variables in the HA group were significant, having a substantial effect on CRC risk.

Next, we tested for the combined effect of the topmost influential SNPs and lifestyle variables, both singly and together, on the risk for CRC. Referring to the analysis of the number of combined lifestyles in relation to CRC risk (**Figure S2A**) in AA women, we combined the AA women with 5 or 6 risk lifestyles and compared their risk with that of the AA women with ≤ 4 risk lifestyles. This yielded an approximately 3 times increased risk for CRC in this high risk–lifestyle group (**Table 2**). Further, we combined the risk genotype and lifestyle factors to test for their synergistic effect on increasing risk for CRC. Compared with the women without either of genetic and lifestyle factors, the AA women with both risk factors were associated with a 4-times higher risk for developing CRC, suggesting a gene–lifestyle dose-response relationship in both additive and multiplicative interaction models (HR of G×E = 1.08). In the HA women, stronger effects of SNPs and lifestyle factors, in each combination, were observed (**Table 3**): about 10 times higher risk for CRC among those with 2 or 3 risk alleles than among those with none or 1 risk allele; and about 7 times greater CRC risk among those with 3 risk lifestyles than among those with ≤ 2 risk lifestyles. The maximum number of lifestyle combinations was 3, and they were categorized on the basis of CRC risk distribution by the number of combined lifestyles (**Figure S2B**). Consistent with our findings of the AA women, the HA women who had both risk genotypes and risk lifestyles had greater and much stronger (> 58 times) risk for CRC than did those who did not have either of them (**Table 3**). This also suggests that the most-predictive genetic and lifestyle factors in combination synergistically increased the predictability of CRC risk in both additive and multiplicative interaction models (HR of G×E = 1.38).

PAR Percentage for the Combined Topmost Variables in Each Group and AR Percentage for the Variables Common to Both Groups

In the estimation of PAR percentage from the topmost genetic and lifestyle variables in AA women, 23% of their CRC cases were attributed to one top SNP, and 33% were attributed to lifestyle factors in combination. Further, 45% of the CRC cases in AA women were attributed to those genetic and lifestyle factors combined, implicating that almost half of the cases could have been prevented if they would not have had such risk factors (**Table 2**). In HA women, 67% of the CRC cases was attributed to genetic factors, and 26% was attributed to risk lifestyles. When the top genetic and lifestyle factors were combined, about 70% of the CRC cases could have been prevented if they had not possessed such risk factors (**Table 3**).

In addition, we detected 3 common lifestyle factors among the topmost influential markers shared by the AA and HA women: smoking, age at menopause, and daily calorie intake from PFA (**Table 4**). The AR percentages from smoking between the groups were similar, but those from age at menopause and dietary PFA intake were 2 times and 4 times higher, respectively, in the HA than they were in the AA women. The

TABLE 2 | African American women: combined effect of risk genotypes and risk lifestyles on colorectal cancer risk and population-attributable risk percentage.

Number of risks	n	HR (95% CI)	*p*	PAR (%)[†]
Risk genotypes[£]				
0	2,756	reference		22.9
1	1,936	**1.64 (1.03 – 2.59)**	**0.0356**	
Risk lifestyles[¶]				
0	3,097	reference		33.6
1	1,595	**2.61 (1.65 – 4.15)**	**4.66E-05**	
Risk genotypes plus lifestyle factors[§]				
0	1,859	reference		44.9
Risk genotypes only	1,238	1.51 (0.75 – 3.02)	0.2450	
Risk lifestyles only	897	**2.46 (1.25 – 4.83)**	**0.0088***	
Both risks of genotypes and lifestyles	698	**4.02 (2.12 – 7.60)**	**1.95E-05***	
p_{trend}			**1.00E-04**	

CI, confidence interval; HR, hazard ratio; PAR, population attributable risk. Numbers in bold face are statistically significant.

[†]PAR(%) reflects, in total African American women, a risk of colorectal cancer attributable to the risk genotypes and the risk lifestyles, both singly and in combination.

[£]The number of risk genotype (PCSK1 rs9285019 TC+CC) was defined as follows: 0 (none) vs. 1 (1 risk allele).

*[¶]The number of lifestyles (≥ 20 years as a regular smoker, ≤ 6.8% of calories from polyunsaturated fatty acid/day, > 42 years old at menopause, 56–79 years old at enrollment, 5–37 years of oral contraceptive use, and > 60.5 g of dietary total sugars) was determined on the basis of analysis for the combined lifestyle factors (**Figure S2A**) and defined as follows: 0 (null/1/2/3/4 risk lifestyles) vs. 1 (5/6 risk lifestyles).*

[§]The combined number of risk genotypes and risk lifestyles was based on risk genotype defined as 0 (none) and 1 (1 risk allele), and risk lifestyles defined as 0 (null/1/2/3/4 risk lifestyles) and 1 (5/6 risk lifestyles). The ultimate number of risk genotypes combined with risk lifestyles was defined as 0 (no risk genotypes and risk lifestyles); and risk genotypes (only risk genotypes) and risk lifestyles (only risk lifestyles), separately and together.

**p values with false discovery rate < 0.05 are shown after multiple comparison corrections via the Benjamini-Hochberg method.*

TABLE 3 | Hispanic American women: combined effect of risk genotypes and risk lifestyles on colorectal cancer risk and population-attributable risk percentage.

Number of risks	n	HR (95% CI)	*p*	PAR (%)[†]
Risk genotypes[£]				
0	1,495	reference		66.8
1	491	**9.57 (3.08 – 29.67)**	**9.20E-05**	
Risk lifestyles[¶]				
0	1,850	Reference		26.2
1	136	**6.63 (2.30 – 19.11)**	**0.0005**	
Risk genotypes plus lifestyle factors[§]				
0	1,394	Reference		
Risk genotypes only	456	**8.55 (2.27 – 32.24)**	**1.53E-03***	73.3
Risk lifestyles only	101	4.97 (0.52 – 47.76)	0.1653	
Both risks of genotypes and lifestyles	35	**58.76 (13.15 – 262.68)**	**9.73E-08***	
p_{trend}			**2.00E-06**	

CI, confidence interval; HR, hazard ratio; PAR, population attributable risk. Numbers in bold face are statistically significant.

[†]PAR(%) reflects, in total Hispanic African women, a risk of colorectal cancer attributable to the risk genotypes and the risk lifestyles, both singly and in combination.

[£]The number of risk genotypes (IFT172 rs780104 GG; GCKR rs6753534 CC; and NRBP1 rs704791 TT) was defined as follows: 0 (none/1 risk allele) vs. 1 (2/3 risk alleles).

*[¶]The maximum combined number of lifestyles (> 15.9% of calories from monounsaturated fatty acid [FA]/day, ≥ 25 cigarettes/day, ≤ 38 years old at menopause, > 12.4% of calories from saturated FA/day, ≤ 4.7% of calories from polyunsaturated FA/day, and ≤ 55.6 mg of dietary vitamin K) was 3. The number of lifestyles was determined on the basis of analysis for the combined lifestyle factors (**Figure S2B**) and defined as follows: 0 (null/1/2 risk lifestyles) vs. 1 (3 risk lifestyles).*

[§]The combined number of risk genotypes and risk lifestyles was based on risk genotypes defined as 0 (none/1 risk allele) and 1 (2/3 risk alleles), and risk lifestyles defined as 0 (null/1/2 risk lifestyles) and 1 (3 risk lifestyles). The ultimate number of risk genotypes combined with risk lifestyles was defined as 0 (no risk genotypes and risk lifestyles); and risk genotypes (only risk genotypes) and risk lifestyles (only risk lifestyles), separately and together.

**p values with false discovery rate < 0.05 were shown after multiple comparison corrections via the Benjamini-Hochberg method.*

TABLE 4 | Colorectal cancer attributable risk for the lifestyle factors detected as the topmost predictive variables in both African American and Hispanic American women.

Overlapped variables:the topmost predictors	African American Women AR (%)	Hispanic American women AR (%)
Smoking[†]	61.7	87.4
Age at menopause	28.2	57.1
percent calories from PFA/day	12.7	48.9

AR, attributable risk; PFA, polyunsaturated fatty acid.

[†]The modeled variable for smoking factor is years as a regular smoker in African American women and the number of cigarettes smoked daily in Hispanic American women.

HA women's long lifetime exposure to female hormones tended to be protective, and the threshold of daily PFA intake to prevent CRC risk was less than the AA women's (5% *vs*. 7%, respectively). Altogether, we postulate that these 2 lifestyle factors play an important role in mediating the difference in CRC risk between AA and HA women.

DISCUSSION

Despite some improvement in healthcare disparities between different racial/ethnic categories in cancer medicine, disparities in cancer genomic science still exist for AA and HA women, the 2 largest minorities of the U.S. population, which are underrepresented in collection, aggregation, and analysis of genomic data for studies of cancer risk factors. Here we focused on AA and HA postmenopausal women to examine genetic markers of IR, one of the main biologic mechanisms of colorectal carcinogenesis, by using an extensive set of GWA-based IR SNPs. In addition to these genetic factors, by incorporating CRC-associated lifestyle variables to establish the CRC risk prediction model for each racial/ethnic group, we detected the topmost influential genetic and lifestyle factors. The combined topmost genetic- and lifestyle-specific markers revealed a synergistic effect on increasing the CRC risk by explaining a considerable portion of their cancer risk. Thus, constructing CRC risk profiles with those topmost markers substantially improved the risk-prediction performance. We believe that these results could be used in the development of genetically focused interventions for cancer prevention and therapeutic effort, and allow progress toward reducing cancer disparity in those minorities.

Most of the topmost FG-SNPs we detected are found in the intronic and intergenic regions of genes that play well-established roles in modulating glucose metabolism, implicating that these genetic variations may influence glucose homeostasis. In AA women, the genetic variant in the *PCSK1* gene was associated with FG concentration as well as increased risk for CRC. The *PCSK1* gene encodes prohormone convertase 1/3, which mediates the cleavage of proinsulin in the process of insulin biosynthesis. Thus, that gene mutation leads to the loss-of-function defect in insulin production, eventually resulting in impaired glucose tolerance (60–63). Further, the mutation of this gene is associated with carcinogenesis and enhanced cancer growth, particularly in the liver metastasis of primary CRC cells (64), suggesting the involvement of the convertases in the selective process of liver metastasis. To the best of our knowledge, ours is the first report of the *PCSK1* gene variation's association with primary CRC risk, particularly in AA women.

Of the topmost FG-SNPs detected in HA women, the genetic variant of *GCKR* was associated with a higher FG concentration and increased CRC risk. The *GCKR* regulates the activity of glucokinase in liver and pancreatic islet cells (65). For example, when circulating glucose level is low, *GCKR* forms an inactive complex with glucokinase, inhibiting glycolysis (66). Thus, a high degree of inhibition of this enzyme by *GCKR* can result in high FG levels. The genetic variation of *GCKR* in association with FG concentrations was previously reported in AAs (24) but not in HAs. Also, the *GCKR* variation has been associated with the risk of pancreatic cancer (67) and the prognosis of metastatic gastric cancer (68), but no published study so far has examined its association with CRC risk. Therefore, our findings of FG and CRC risk in HA women are meaningful and warrant replication in further studies with independent datasets. In addition, *NRBP1*, which encodes multidomain putative adapter proteins (69), has an anti-tumor role against CRC tumorigenesis and progression, as an *in vivo*/*in vitro* study (70) showed that the higher expression of *NRBP1* inhibited CRC cell proliferation and anti-apoptosis and correlated with better prognosis. *NRBP1* regulates the apoptotic pathway by inhibiting *Jab1*-mediated *JNK* signaling, which is essential in gene translation and regulation of cellular apoptosis (70–72); it may thus play a key role in suppressing CRC tumorigenesis. Supported by these earlier findings, our study reported that the variation of the *NRBP1* gene increased the risk of CRC, specifically in HA women. Last, the genetic variants of *IFT172* that encodes a subunit of the intraflagellar transport subcomplex *IFT-B*, which is necessary for ciliary assembly and maintenance, have been associated with ulcerative colitis and Crohn's disease (73), but their associations with CRC risk, as detected in our study, have not been previously reported, warranting future replication studies.

Among the 3 topmost influential factors shared by the AA and HA groups, the effect of smoking on CRC risk was strongest in both groups. As revealed in a recent Mendelian randomization study (31), prolonged lifetime exposure to cigarette smoking is positively associated with CRC risk. The carcinogens emitted by tobacco smoke into the digestive system and bloodstream promote tumorigenesis in colorectal mucosa (74). In particular, AA individuals tend to have higher total equivalents of nicotine per number of cigarettes smoked daily than individuals of other racial/ethnic groups, and their CRC screening rate is lower in active smokers than in never smokers (75); thus, screening in the high-risk group (active/longer-term regular smokers) is strongly recommended.

Both groups in our study had greater risk for CRC when they had lower daily intake of PFAs. Previous studies (29, 76) support our finding, by reporting that the decreased proportions of red blood cell PFAs and less intake of PFAs were associated with increased CRC incidence. PFAs have been shown to suppress pro-inflammatory cytokine production (77) and reduce triglycerides and low-density lipoprotein particles (78), which are key mediators in carcinogenesis. In our HA women, the CRC risk attributable to low PFA intake was more substantial than it was in our AA women. However, the HA women had a lower threshold of daily PFA intake than AA women in preventing CRC development. Altogether, the effect of less strict requirement of PFA intake in HA women may override their more sensitive influence of low PFA intake on CRC risk and thus, contribute to the lower CRC incidence in HA than in AA women.

Further, older age at menopause is an important risk factor for CRC development in postmenopausal women (79–81), suggesting that longer lifetime exposure to endogenous estrogen may increase the CRC risk. However, in our analysis of HA women, their longer-term exposure to female hormones tended to be protective against CRC risk, even after adjusting for a history of oophorectomy; this suggests a follow-up functional mechanism study in this racial/ethnic subpopulation. Similar to that of PFA intake, this protective role of prolonged lifetime exposure to female hormones in HA women may outweigh the greater effect of short-term hormone exposure on CRC risk than AA women had, explaining in part their lower CRC incidence compared with that of AA women.

Our data on smoking were self-reported, so our results may have been subject to misclassification bias. However, a previous study found high reliability of self-reported assessment of active smoking (82). Also, our RSF analysis may overfit the model with multiple tasks, warranting the conduct of replication studies with independent datasets. We examined AA and HA postmenopausal women, so our findings may not be generalizable to other racial/ethnic populations.

Overall, our study indicates that GWA-level IR SNPs combined with the lifestyle factors of smoking, lifetime exposure to endogenous female hormones, and dietary fat intake synergistically increased the risk for CRC, and the prediction ability and accuracy of these factors was notable. Of those risk factors, dietary intake of PFAs and lifelong exposure to female hormones may play a key role in mediating the racial disparity of CRC risk between AA and HA women. Our findings may improve CRC risk–prediction performance in these medically and scientifically underrepresented subpopulations, and by emphasizing the promotion of genetically informed preventive interventions (e.g., smoking cessation, higher PFA intake) and encouraging CRC screening of individuals who are at high risk owing to particular risk genotypes and behavioral patterns, our results may contribute to reduced cancer disparity in those minorities.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: The data that support the findings of this study are available in accordance with policies developed by the NHLBI and WHI in order to protect sensitive participant information and approved by the Fred Hutchinson Cancer Research Center, which currently serves as the IRB of record for the WHI. Data requests may be made by emailing helpdesk@WHI.org.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review boards of each participating clinical center of the WHI and the University of California, Los Angeles. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SJ, ES, MP, HY, and JP designed the study. SJ performed the genomic data QC. SJ performed the statistical analysis and SJ, ES, MP, HY, and JP interpreted the data. JP and ES supervised the genomic data QC and analysis and participated in the study coordination. JP oversaw the project. SJ secured funding for this project. All participated in writing and editing the paper. 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/fonc.2021.760243/full#supplementary-material

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