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Cancer Susceptibility as a Cost of Reproduction and Contributor to Life History Evolution

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Reproduction is one of the most energetically demanding life-history stages. As a result, breeding individuals often experience trade-offs, where energy is diverted away from maintenance (cell repair, immune function) toward reproduction. While it is increasingly acknowledged that oncogenic processes are omnipresent, evolving and opportunistic entities in the bodies of metazoans, the associations among reproductive activities, energy expenditure, and the dynamics of malignant cells have rarely been studied. Here, we review the diverse ways in which age-specific reproductive performance (e.g., reproductive aging patterns) and cancer risks throughout the life course may be linked via trade-offs or other mechanisms, as well as discuss situations where trade-offs may not exist. We argue that the interactions between host–oncogenic processes should play a significant role in life-history theory, and suggest some avenues for future research.

Keywords: disease, sexual selection, reproduction, reproductive aging, neoplasia, transmissible cancer, senescence

INTRODUCTION

Natural selection shapes organisms to maximize reproductive fitness, and this phenomenon leads to pivotal trade-offs around which all life-history traits ultimately evolve (Williams, 1966; Rose and Mueller, 1993; Roff, 2001; Stearns, 2006; Harshman and Zera, 2007). Exploring the consequences of reproductive trade-offs on organisms has therefore been—and remains—a central topic in

evolutionary biology (Schaffer, 1974; Bell, 1980; Gustafsson et al., 1995; Hamel et al., 2010; Schwenke et al., 2016). There are numerous examples showing that the reproductive allocation of a given event correlates negatively with both short-term survival and/or future reproductive performance (Stearns, 2006; Hamel et al., 2010). Similarly, reproductive costs can be paid in the long run, through an earlier and or steeper actuarial and reproductive aging (Lemaître et al., 2015). Trade-offs between reproductive effort and subsequent survival can occur for a variety of reasons, one of them being that reproductive activities are energetically demanding, thus the amount of energy an individual allocates toward reproduction reduces its allocation to health maintenance (Kirkwood, 1977; Maklakov and Immler, 2016). For instance, reproductive activities and allocation to immune function are often mutually constraining: increased reproductive activity may limit immune performance, which in turn can enhance vulnerabilities to infections (Sandland and Minchella, 2003; French et al., 2007; Knowles et al., 2009; Fedorka, 2014; Schwenke et al., 2016). Allocation of resources away from soma to reproduction might also result in a decreased capacity to cope with damage caused by stress and toxicity, and/or be associated with detrimental by-products of metabolism, e.g., the production of damaging reactive oxygen species (Metcalfe and Monaghan, 2013, but see Blagosklonny, 2010). Finally, some of the genes selected for fitness conferring advantages during early life (e.g., increased reproductive output) may also have other functions; for example, carrying alleles that support reproduction may at the same time increase the risk of pathologies later in life (i.e., antagonistic pleiotropy) (Williams, 1957; Leroi et al., 2005; Madimenos, 2015; Austad and Hoffman, 2018; Gunten et al., 2018).

Apart from being a leading cause of human death worldwide, cancer is a biological process that appeared with the evolution of metazoans during the late Precambrian (Domazet-Lošo and Tautz, 2010; Nunney, 2013). Cancer occurs when individual cells become malignant, i.e., lose their normal cooperative behavior, become insensitive to host controls, proliferate in an uncontrolled fashion, and spread from primary tumors to surrounding tissues and then to distant organs (i.e., metastasis), thereby causing morbidity and potentially death (Hanahan and Weinberg, 2011). Chronological age is indisputably the most significant risk factor (in terms of incidence) for developing metastatic cancer, but it is also well established that oncogenic processes frequently exist at sub-clinical levels earlier in life (in humans and other animals, Folkman and Kalluri, 2004; Bissell and Hines, 2011; Madsen et al., 2017), and in fact represent a long continuum between precancerous lesions to invasive forms (Maley et al., 2017). Recent advances in oncology suggest that pathogens, parasites, viruses, or transposable elements may be the most common causes of cancer in wildlife, while second-hand smoke, nutritional challenges, breeding stress, UV radiation, and chemicals in the environment causing somatic mutations may be most important for pets and humans (Aktipis and Nesse, 2013; Giraudeau et al., 2018; Pesavento et al., 2018). Since cancer is observed in almost all branches of multicellular life, from *Hydra* to whales (Leroi et al., 2003; Aktipis et al., 2015; but see Azpurua and Seluanov, 2013; Fortunato et al., 2021), we hypothesize that cancer should be a major mediator of life-history trade-offs and a contributor to life-history evolution.

The short- and long-term fitness consequences of oncogenic manifestations early in life, at a life-history stage where individuals are expected to maximize their allocation of resources toward growth and reproduction, remain poorly documented (Vittecoq et al., 2013; Thomas et al., 2018). In addition, the precise reasons why oncogenic processes—depending on organs, individuals, and/or species— evolve at variable rates inside the body are not yet well understood, although there is clear evidence that a variety of internal and external parameters are important (e.g., sex, age, immune status, organ ecology and microenvironment, energetic capacity, stress, environment, Tevfik Dorak and Karpuzoglu, 2012; Henry et al., 2015; Thomas et al., 2016; Hochberg and Noble, 2017; DeGregori et al., 2018; Biro et al., 2020; Vibishan and Watve, 2020). Evolutionary ecologists have, until recently, largely neglected the importance of cancer cells for animal ecology (Thomas et al., 2017). There are more than 100 types of cancer (grouped into five major categories: carcinoma, sarcoma, myeloma, leukemia, and lymphoma) that can affect almost every part of the body (Weinberg, 2007). In addition to malignant tumors, multicellular organisms often harbor benign neoplasms (Boutry et al., 2022b). Benign neoplasms have received less attention than malignant tumors because they have less often obvious and serious impacts on the patient/host health, even if noticeable exceptions exist (see Boutry et al., 2022b for a recent synthesis).

Tumoral processes, especially malignant ones, can be detrimental to host fitness by imposing direct costs on it. For instance, malignancies affecting reproductive organs, like cervix, uterus, endometrial, ovary or testicular cancers, can severely compromise their host's reproductive potential by triggering reproductive aging or inducing infertility (Brinton et al., 2004, 2005; Paduch, 2006; Singh et al., 2011; Hanson et al., 2017). Another well-known direct cost of (notably metastatic) cancers on host fitness is due to their detrimental effect on survival. While the survival cost of cancer is largely documented for human and domestic animals, less information is available for wildlife species. Recent studies from zoo animals showed that cancerous processes are however widespread (see Vincze et al., 2022). The lack of information in the wild is likely due to the fact that tumor-bearing individuals, often in poorer condition than healthy ones, have increased probability to die early, being victims of predation or infections (Boutry et al., 2022a). Thus, cancer is indirectly costly when tumor-bearing individuals are considered within their ecosystems. Although experimental evidence would be welcome, it is also likely that tumor-bearing individuals should be less attractive for sexual partners, and/or will have lower ability to deliver good parental care (Vittecoq et al., 2015).

As with other fitness-reducing factors, evolutionary theory predicts that metazoans are under selective pressure to: (i) avoid the source of malignancies in the first instance, (ii) prevent tumoral progression once initiated, and finally (iii) alleviate the fitness costs if further cancer development is not preventable (Ujvari et al., 2016). These strategies necessarily involve immediate and/or long-term costs that are traded against other functions (Jacqueline et al., 2017a), even if the evolution

of cancer defenses is predicted to be variable between species, depending on their ecology. For instance, tumors are common in laboratory mice, but are rarely observed in wild populations. While this difference between natural and artificial environments may in part be due to differences in environmental exposure to cancer inducing agents, it also results from the fact that the average lifespan of a wild mouse (a prey species) is only a few months. While somatic mutations contributing to cancer in laboratory mice may be common, historically, there may have been little selection on immune processes that prevent, or slow cancer because wild mice rarely live long enough to experience tumor formation (Perret et al., 2020).

Thus, cancerous processes, through their direct costs on hosts and/or most often through the costs of host defenses, have the potential to impose life history tradeoffs (Aktipis et al., 2013; Brown and Aktipis, 2015; Muller, 2017). We discuss here the idea that malignant processes are crucial to consider when studying life-history traits because malignant dynamics—and hence their consequences on health and survival—are likely to be linked in multiple ways with the age-specific reproductive activities of organisms (see **Figure 1**). While there have been many review papers linking host evolutionary ecology to cancer (e.g., Peto's paradox), to our knowledge, our paper is the first to primarily focus on the associations between cancer and reproduction. This synthesis highlights the underestimated role of oncogenic processes in shaping the multiple facets of the age-specific reproductive biology of multicellular hosts.

GENES PROMOTING BOTH FERTILITY AND CANCER RISK

One mechanism that can link together reproduction with increased susceptibility to cancer is through genes that have direct effects on both. Like several other biological processes detrimental to health, malignant dynamics can also be embedded in the antagonistic pleiotropy theory (e.g., Crespi and Summers, 2006; Carter and Nguyen, 2011; Jacqueline et al., 2017a; Lemaître et al., 2020a). At the genetic level, for instance, some alleles that increase cancer risk as a secondary effect of their positive roles on reproductive success have been identified; a good example is the *Xmrk* melanoma-promoting oncogene in the fish *Xiphophorus cortezi* (**Figure 2**). Despite significant deleterious cancer-induced effects leading to a shorter lifespan, this oncogenic allele persists in natural populations presumably because it is also associated with a larger body size, which increases the individual's reproductive success through mate competition. This oncogene is also directly correlated with aggressive behaviors (Fernandez, 2010). In addition, the presence of melanoma on the male's caudal fin intensifies the spotted caudal melanin pattern, which increases female preference for these mates (Fernandez and Morris, 2008; Summers and Crespi, 2010).

Another example concerns mutations on the tumor-suppressing gene BRCA, which is responsible for DNA repair. While women carrying *BRCA1/2* mutations have higher cancer incidence and higher mortality, one study reported that *BRCA* mutation carriers born in Utah prior to 1930 had naturally higher fertility compared to controls (before the advent of modern contraception) (Smith et al., 2012; see however, Oktay et al., 2015; Daum et al., 2018). The precise mechanisms behind this phenomenon are not completely understood, and perhaps are simply the consequence of genetic bottlenecks. However, they could also involve a trade-off between cancer suppression and tolerance for invasive fetal cells (Aktipis, 2020). Placentation in female eutherian mammals, like cancer metastasis, is indeed an invasive process that involves the transplantation of cells into new environments. Females in these species would therefore be potentially more vulnerable to cancer (Kshitiz et al., 2019). This hypothesis seems to be supported at the interspecific level, since species of mammals with more invasive placentation such as felines and canines are also more vulnerable to malignancies (D'Souza and Wagner, 2014). However, Boddy et al. (2020) did not confirm this tendency, and found instead at the interspecific level a positive relationship exists between litter size and prevalence of malignancy. Beyond these examples, the search for positive selection signals on mutations occurring in cancer suppression genes seems to be promising for the identification of candidate genes responsible for both fertility enhancement and cancer risk (Kang and Michalak, 2015).

The fact that cancer genes are not purged by natural selection can also be driven by antagonistic coevolution processes that occur in cases of conflict between evolutionary agents (Graham, 1992; Crespi and Summers, 2006). Some of these conflicts are related to reproductive activities, e.g., parent–offspring conflict, maternal–fetal conflict, sexual conflict, and/or sexual selection (Haig, 2015). The genes involved in such dynamics generate evolutionary disequilibriums, molecular-level arms races, and tugs-of-war over cellular resources, and they may increase susceptibility to cancer as a pleiotropic by-product of their role(s) in antagonistic coevolution (Crespi and Summers, 2006). Situations of sexual conflict, i.e., when the fitness of one sex comes at the expense of the other sex, can occur when the genes involved in rapid cell proliferations—which allow rapid growth or wound healing—are due to sexual selection being more advantageous for fighting males than for females. The optimum trade-off between DNA repair and cell proliferation rate, which also relies on the *BRCA1* and *BRCA2* alleles (Yoshida and Miki, 2004), is therefore likely to vary between males and females, generating sexually antagonistic selection. Oncogenic consequences for females, such as breast and/or ovarian cancers, could result from a disruption of the trade-off via a BRCA gene mutation in a somatic cell, leading to proliferation with less-effective DNA repair. Total cancer risks arising from perturbations to maternally and paternally opposed growth regulation have yet to be determined (Frank and Crespi, 2011), but exploring this hypothesis with comparative analyses seems promising. In particular, considering species that vary in the intensity of male sexual selection relying on body size and aggressive fights could be of interest since the differential optimum values for the repair–proliferation trade-off between sexes are expected to be somewhat different.

It is also thought that genes contributing to gamete production (rate and/or quality) may use pathways that are highly beneficial for cancer cells able to co-opt or subvert them during somatic evolution. These pathways could allow rapid cell proliferation

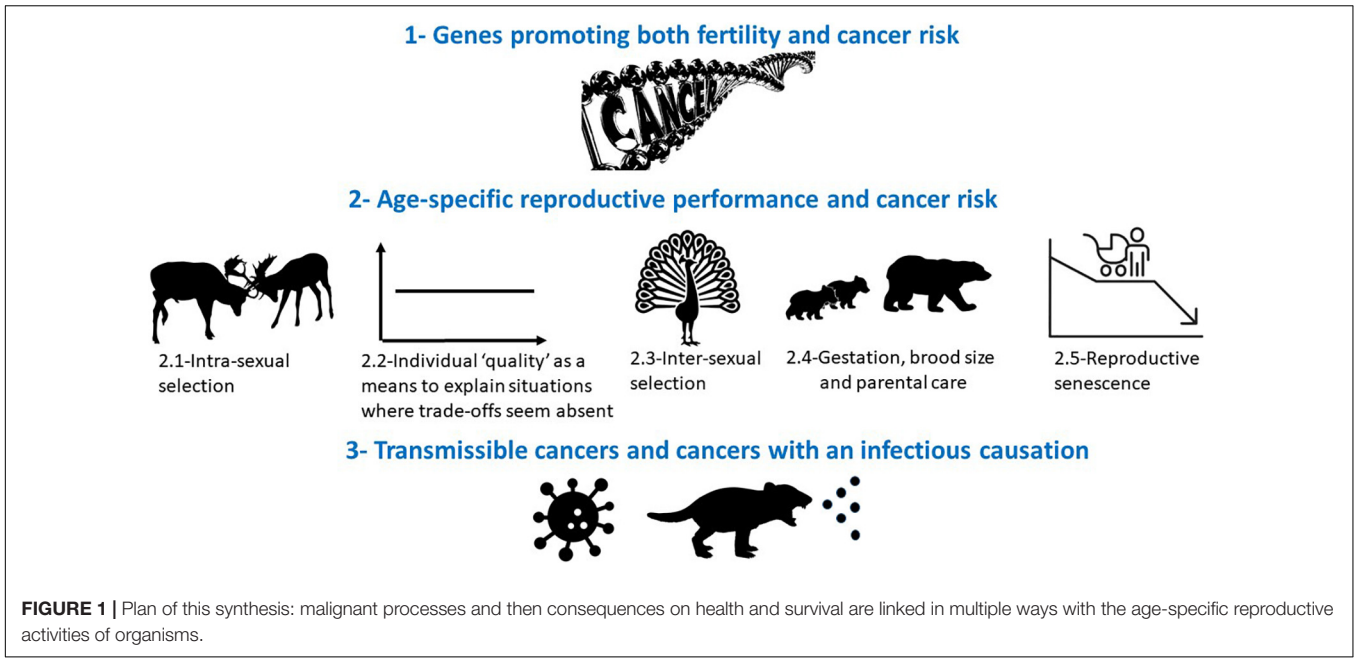

FIGURE 1 | Plan of this synthesis: malignant processes and then consequences on health and survival are linked in multiple ways with the age-specific reproductive activities of organisms.

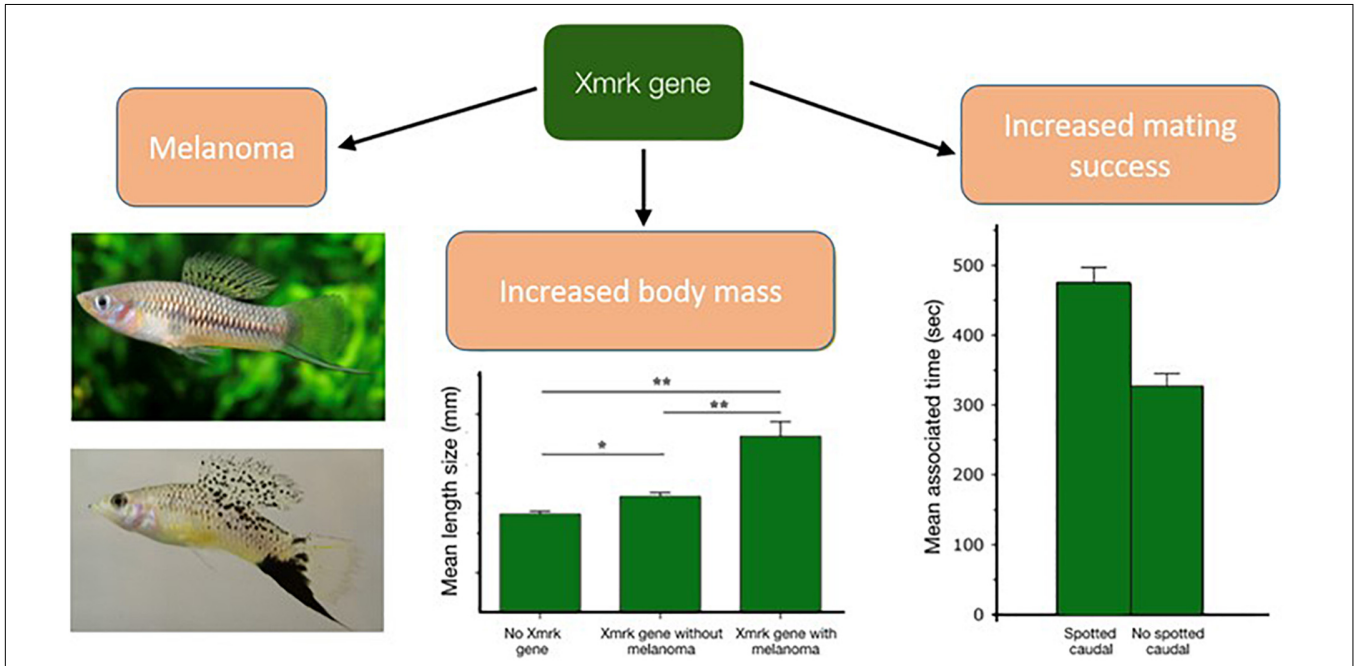

FIGURE 2 | Antagonistic pleiotropy and oncogenic congenital mutations: the *Xmrk* melanoma-promoting oncogene in the fish *Xiphophorus cortezi.* Sexual selection processes may sometimes favor cancer promoting oncogene alleles, as this is observed in the fish *Xiphophorus* developing melanoma (bottom Photo). Despite shorter lifespan due to the deleterious cancer-induced effects, the oncogenic *Xmrk* allele is not eliminated from natural populations of *Xiphophorus*, because several associated benefits early in life outweigh late costs (i.e., antagonistic pleiotropy). *Xmrk* allele is indeed associated to a larger body size and higher aggression, which increases individual's reproductive success through mate choice and competition for mates. The source and credit for the fish photos: Johnny Jensen (up) and Andre Fernandez (down). Figure modified from Fernandez and Morris (2008). $^{*}P < 0.05$, $^{**}P < 0.01$.

and/or avoidance of control by tumor suppressors or the immune system (Crespi and Summers, 2006). For example, *SPANX* genes in primates, which show evidence of strong positive selection, are involved both in spermatogenesis and in melanoma progression by promoting cancer cell growth (Kleene, 2005). More recent studies also support the hypothesis that some genetic pathways of spermatogenesis, whose evolution is governed by responses to sexual selection and intra-sexual conflict, are the same as those used by cancer cells to increase their survival and replication (genes such as *BRIP1*, *BUB1B*, *KTN1*, and *RANBP2*)

(Vicens and Posada, 2018). It has also been suggested that the CAG repeat region of the androgen receptor could be a locus of antagonistic pleiotropy in the context of sexual selection and sexual conflict (Summers and Crespi, 2008). Short repeats are associated with increased fertility at the phenotypic level, but there is also evidence that somatic evolution of malignant cell lineages during cancer progression are often associated with a repeated pattern of shortening of the CAG repeat, *a priori* because of positive selection among cell lineages.

AGE-SPECIFIC REPRODUCTIVE PERFORMANCE AND CANCER RISK

Intra-Sexual Selection

As mentioned before, antagonistic pleiotropy is when one gene has opposite effects on fitness at different ages, such that their effects are beneficial in early life, when natural selection is strong, but harmful at later ages, when selection weakens. In a theoretical study, Boddy et al. (2015) investigated the possible links between cancer risks and the level of intraspecific competition, assuming that an underlying resource-based trade-off between competitiveness and allocation into cancer defenses exists. As has been empirically observed (see Clocchiatti et al., 2016 for an example in humans), the model first showed that cancer prevalence is expected to be lower in females than in males, since mating competition usually has greater reproductive payoffs for males than for females (Clutton-Brock and Vincent, 1991) and also because of the immune-enhancing effect of estrogen (Taneja, 2018; even if the picture is more variable in humans, Mulder and Ross, 2019). Although experimental evidence is currently lacking, the higher male susceptibility is likely to be exacerbated when they grow faster and/or have to develop and maintain extravagant secondary sexual traits. This should theoretically be the case because the required higher cell proliferation itself increases cancer risk (especially in body areas with the greatest cellular divisions, e.g., testes cancer, antleromas). For instance, the insulin/insulin-like growth factor (IGF) signaling pathway to mTOR is essential for the survival and growth of normal cells but also contributes to the genesis and progression of cancer, increasing cell proliferation and anti-apoptosis processes (LeRoith and Roberts, 2003; Floyd et al., 2007). Another reason is because of a diversion of resources from somatic maintenance (e.g., DNA repair or immune defenses). A potential self-maintenance mechanism suffering shortfall could be the antioxidant machinery, when strenuous activity (e.g., mating competition, reproductive effort, maintenance of costly sexual signals) leads to an increased production of reactive oxygen species causing oxidative stress. Even if empirical data have not been always consistent, oxidative stress has been viewed as an important physiological costs of reproduction (Blount et al., 2016; Pap et al., 2018) and it is well known to participate in cancer development by promoting cancer initiation and progression through induced DNA damage, leading to mutagenesis, and by affecting DNA methylation patterns or the expression of oncogenes (Van Remmen et al., 2004; Kreuz and Fischle, 2016). Moreover, as recently highlighted by Ujvari et al. (in press), telomere dynamics could also occupy a pivotal position in these processes. Indeed, allocation toward the maintenance of costly sexual signals often alters oxidative metabolism (Hill, 2014), which can, in turn, provoke telomere erosion (Monaghan and Ozanne, 2018) and influence the emergence of oncogenic mutations. It is predicted that natural selection should favor the expression of secondary sexual traits over the cost of telomere dysfunction until the organism reaches its maximum reproductive potential, even if this is likely to promote malignant progressions beyond this (Taff and Freeman-Gallant, 2017; Pepke and Eisenberg, 2021). In a recent study, Wang et al. (2019) studied the genetic basis of antler regeneration in ruminants; antlers are among the fastest-growing bone in the animal kingdom. In red deer (*Cervus elaphus*), for instance, antlers regrow annually and reach up to 30 kg, with growth rates of ∼1.7 cm/day, which necessitates a rate of cell proliferation that surpasses classical cancerous tissue growth. Wang et al. (2019) found that the genes underlying the expression of these large sexual ornaments are among those that both promote and suppress cancer (**Figure 3**). Specifically, there was a higher correlation between the gene expression profiles of antlers and bone cancer such as osteosarcoma than between those of antlers and normal bone tissues, suggesting that antler growth and oncogenesis rely on similar developmental programs. Cancer is typically a pathology arising from perturbations to a precarious balance between strongly opposed growth promoters and growth repressors (Aktipis, 2020). However, these authors discovered that contrary to the situation in osteosarcoma, where neoplasms progress unchecked, antler growth was tightly regulated by the activity of cancer-controlling genes (both tumor-suppressing and tumor-growth-inhibiting genes), suggesting that antler growth is mechanistically equivalent to a controlled form of bone cancer growth. Cervids generally display a very low risk of cancer (Vincze et al., 2022). Ideally, the same genes promoting cancer prevention (tumor-suppressors like BRCA, TP53, BUB1, BUBR1, TGF-βRII, Axin, DPC4, p300, and PPARγ which generally play a role in controlling the cell cycle or DNA repair) would be selected for and likely conserved. However, they would share the same pathway used by cancerous cells because the same genes are used in cell division. Given that antlers are lost every year, we might speculate that this could potentially be a defense mechanism. In line with this hypothesis, a recent comparative analyses of cancer risk across almost 200 species of mammals highlighted that Artiodacyla such as Cervids are much less prone to cancer than other mammalian orders (Vincze et al., 2022).

The apparent lack of a correlation between sexual ornament size and cancer rate may be explained by mechanisms that offset the increased cancer risk. As possible supportive evidence, albeit in a different ecological context, Thomas et al. (2020) argued that strong ongoing artificial selection in domestic animals has sometimes resulted in extreme phenotypic responses favoring a higher incidence of cancer. However, there is also evidence for effective anti-cancer defenses in several domesticated animals, suggesting that artificial selection may also favor the evolution of compensatory anticancer defenses (see also Ibrahim-Hashim et al., 2020). More research in wild species, especially at the intraspecific level, would be necessary to evaluate how robust and

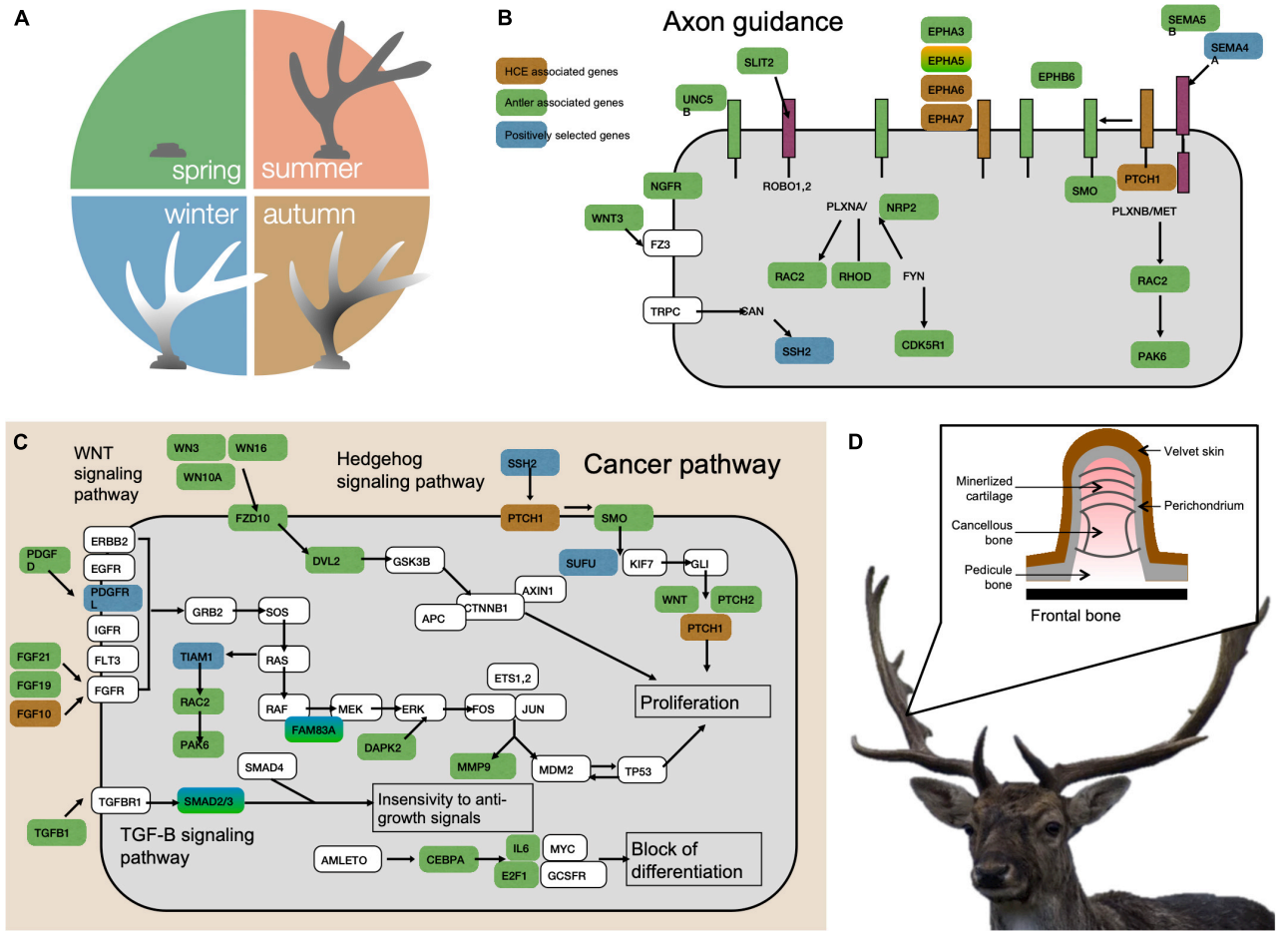

FIGURE 3 | Antler regeneration, neurogenesis and oncogenesis pathways. **(A)** Annual antler regeneration cycle in red deer. Antlers, after shed in winter regenerate in spring, and then grow most rapidly in summer. In autumn, they calcify and shed their velvet. For **(B)** (Axon guidance pathways) and **(C)** (Oncongenesis pathways): blue, genes positively selected in cervids; yellow, cervid-specific HCE associated genes; green, antler-specific expression genes. **(D)** Antler anatomy. **(C)** The anatomy of the antler. The source and credit for the red deer: Pixabay. Figure modified from Wang et al. (2019).

buffered these compensatory protections are. Indeed, because sexual selection processes may be intense in natural populations depending on the ecological contexts, it could be expected that animals benefiting from abundant resources might develop secondary sexual traits whose expression level is higher than that corresponding to their cancer defenses. A rapid evolution in this direction would then drive genotypes away from the optimum, which would result in an increased risk of cancer, at least until the species or population adapts to the changes (Abegglen et al., 2015; Boutry et al., 2020). Such kind of mismatch scenario could potentially be investigated in habitat when wildlife artificially benefits from excessive quantity of food. In humans, it is well established that good nutrition has promoted growth in recent decades, allowing individuals to grow taller (Grasgruber et al., 2014). However, it is also known that cancer risk increases with adult height, at least in part because the number of cells correlates positively with stature, while cancer defenses apparently remain the same (Nunney, 2018). It is unlikely that mechanisms will evolve to prevent large stature because of the sexual selection benefits associated with height in males (Stulp et al., 2013) as well as the reduced risks of obstetric complications in females (Guégan et al., 2000), and also because most oncogenic consequences will occur relatively late in life. However, such processes, at least in wild species, could result in positive feedback cycles in oncogene evolution, leading to improved tumor suppression, greater developmental precision and complexity, and further adaptive changes driving pleiotropic oncogene evolution (Crespi and Summers, 2006). Domestication of animals by humans may provide some support for the hypothesis that a mismatch between cancer risk and cancer defenses may promote malignant proliferation. For example, the artificial selection for size in dogs results in higher incidences of bone cancer in larger breeds compared to smaller ones (Grabovac et al., 2020) because selection for genes responsible for height (and hence a larger number of cells) was not accompanied by selection for more efficient cancer defenses (Thomas et al., 2020). In a related vein, pediatric cancers in humans most often concern three compartments, brain, blood and bone, that have undergone

rapid phenotypic changes in their developmental trajectories along the human lineage (Leroi et al., 2003). In current times, the risk of mismatch can also be exacerbated because anthropic activities result in higher pollution by mutagenic substances in ecosystems (Giraudeau et al., 2018) that—all things being equal—lead to unprecedented risks of cell derailment rates in organs that undergo intense cell divisions.

Although potentially specific to certain populations (see for instance Trumble et al., 2014), testosterone in males has frequently been associated not only with a greater investment in mating behavior (Wingfield et al., 1990; Peters et al., 2008; Summers and Crespi, 2008; Dixson, 2015), but also (although still debated, Michaud et al., 2015) with a higher risk of prostate cancer (e.g., Alvarado, 2013 for males in human polygynous societies). This correlation potentially supports the hypothesis of a trade-off, where higher testosterone levels would allow males to engage in more short-term mating with different partners but at the cost of a higher long-term risk of prostate cancer. It is however, difficult to separate hormonal effects and higher exposure to sexually transmitted carcinogenic viruses also affecting prostate tissues, a risk that increases with the number of sexual partners (e.g., Moghoofei et al., 2019). Further research is needed to decipher the interactions between sexual hormones, the immune system, and cancer development in wild species. Promising models could be social species, especially those for which there are differential hormone levels and cancer risks between dominant and subordinate individuals (Jacqueline et al., 2017a).

Individual 'Quality' as a Means to Explain Situations Where Trade-Offs Seem Absent

Although trade-offs between reproduction and the ability to ward off cancer are expected based on long-standing life history theory (citations above), we should not always expect that reproductive costs are evident or detected. For example, investment into large antlers by Artiodactyla (discussed above) may not create detectible energy trade-offs and increased cancer risk if dominant individuals monopolize resources prior to breeding as is often the case in some species. That is, some individuals of high 'quality' possess abundant energetic resources that permit them to allocate energy to competing demands obscuring trade-offs. Similarly, some of the dramatic anti-cancer adaptations found in domestic animals (Thomas et al., 2020) may be also explained by the fact that abundant food permits simultaneous allocation of energy to reproduction and anti-cancer functions, again obscuring trade-offs. These views are consistent with theory showing that when variation in energy acquisition among individuals is greater than variation in allocation within individuals, competing life history traits will no longer be negatively correlated among individuals (van Noordwijk and de Jong, 1986). Indeed, reviews show energy expenditure on activity, reproduction and maintenance metabolism can often be positively correlated at the among individual level for domestic and laboratory reared animals (Biro and Stamps, 2008, 2010).

Inter-Sexual Selection

In addition to intra-sexual selection, inter-sexual selection through mate choice is central in the theory of sexual selection (Andersson and Simmons, 2006). For many years, it was expected females of many species chose to mate with old rather than young males, because older males often provide better resources (e.g., territories, parental care) and/or pass good genes on to their offspring (Brooks and Kemp, 2001). However, these theoretical predictions are now thoroughly revisited in the light of recent studies demonstrating the under-estimated occurrence of male reproductive aging, as well as the detrimental consequences of this process on female fitness (Lemaître and Gaillard, 2017; Monaghan and Metcalfe, 2019; Monaghan et al., 2020; Segami et al., 2021). Empirical studies suggest that female preference toward young males could be a pervasive mating tactic in the living world (e.g., Verburgt et al., 2011; Vanpé et al., 2019). Here, we propose that mating preferentially with younger males might also be adaptive in terms of a decreased cancer risk in the progeny. One reason is that males accumulate deleterious mutations in their germ-line at an ever-increasing rate as they age (Beck and Promislow, 2007), thereby reducing the quality of genes passed on to the next generation, which potentially favors cancer (e.g., see Choi et al., 2005 for an example that older paternal age increases the risk of breast cancer in female offspring). In addition, in several species – at least in humans and chimpanzees – sperm telomere length is positively correlated with male age, leading to a positive correlation between paternal age at conception and offspring telomere length (Eisenberg and Kuzawa, 2018; Eisenberg, 2019; Eisenberg et al., 2019). Longer telomeres in descendants of old fathers are likely to predispose the novel generation to a higher risk of cancer since cells have a greater chance to accumulate bad mutations before replicative senescence occurs and eliminates them (e.g., Aviv et al., 2017). Theoretical models aiming to predict age-based mating preferences in females based on the benefits-costs balance provided by both young and old partners should now fully consider the risk of cancer in the progeny. For instance, it may remain evolutionarily beneficial for females to produce a progeny whose lifespan will be shortened by cancer in species where old males provide more resources, especially if the cancer-induced death can occur relatively late in the life of offspring (i.e., once most of their reproduction has been achieved). In addition, given the heritability of height (Yang et al., 2010), further studies should also explore the possible oncogenic consequences for tall partner preference in humans.

Gestation, Brood Size, and Parental Care

In numerous species, reproduction is costly for females in terms of energy, nutrients, and metabolic adjustments, which may lead to faster aging and reduced longevity when reproductive effort increases (Westendorp and Kirkwood, 1998; Lemaître et al., 2015; Jasienska, 2020). Physiological consequences of elevated reproductive expenditure are also observed on biological markers of aging. For instance, in species for which males also have a high allocation of resources toward parental care, e.g., common terns (*Sterna hirundo*), where males are primarily responsible

for chick feeding, a negative association between reproductive success and telomere length is observed only in males (Bauch et al., 2016). The direct and/or indirect consequences of these kinds of reproductive costs on oncogenic process dynamics have not yet been fully explored for most species. Pregnancy in women, at least in Western populations, seems to have a dual effect on breast cancer risk (Hsieh et al., 1994). While full-term pregnancies in early life (<30 years) reduce breast cancer risk in the long-term (Albrektsen et al., 2005; Hurt et al., 2006), in the short term they boost the development of oncogene-activated cells into tumors and/or promote a metastatic cascade (Lambe et al., 2002; Lyons et al., 2011), which transiently increases cancer risk. The most common oncogenic progressions observed during pregnancy are malignant melanoma and lymphomas, leukemia, and breast, ovary, cervix, colon, and thyroid cancers (Pavlidis, 2002; Oduncu et al., 2003). The cancer risk is highest within the first 5 years after giving birth, and the risk of breast cancer in parous women is increased for more than 15–20 years compared with nulliparous women (Nichols et al., 2019). Multiple factors are likely responsible for this higher vulnerability to cancer during pregnancy, such as the strategic modulation of the maternal adaptive immune system during the first trimester and a relatively high inflammatory status (Fessler, 2002; Abrams and Miller, 2011; Lyons et al., 2011; but see Hové et al., 2021). The pathophysiology of cancer associated with pregnancy also includes factors like hormonal changes, permeability, and vascularization (D'Souza and Wagner, 2014; Hepner et al., 2019).

Enhanced reproductive effort through increased parental care has often been linked to concomitant or subsequent reduced immune-competence (Nordling et al., 1998), which in return should promote the proliferation of malignant cells (Jacqueline et al., 2017a). However, it seems likely in nature that reduced immunocompetence would first increase the frequency of infections that are detrimental to survival in the short term, long before malignant processes that escape immune-surveillance could have an effect of survival. The fact that detrimental oncogenic consequences in the wild are hidden because of deaths resulting from infectious processes does not mean that they are not significant, nor can we exclude the possibility that oncogenic consequences may interact with infectious dynamics (e.g., see Goldszmid et al., 2014; Jacqueline et al., 2017b, 2020). The oncogenic consequences resulting from trade-offs with enhanced parental care, if any, will be mainly observed in parasite- and predator-free environments such as zoos, provided breeding activities continue (see also Tanaka et al., 2020).

While high reproductive investments can potentially result in increased cancer risks for individuals due to immediate trade-offs, it is also expected that natural selection can fix these problems on the long term. For instance, Brown and Aktipis (2015) suggested in a theoretical study that in cases of extended parental care, as well as with cooperative breeding systems, selection can favor cancer suppression into old age. At least for the proof of concept, artificial selection in the context of domestication illustrates that enlarging reproductive efforts may select for compensatory adaptations or additional defenses (Thomas et al., 2020). For example, while the ancestor of domesticated hens may live for 20–30 years and produce only small numbers of fertile eggs during a limited period of the year, strong artificial selection leading to the domesticated jungle fowl hen (*Gallus gallus domesticus*) has resulted in animals with a short lifespan and prolific daily ovulation and egg laying. Malignant ovarian cancer in domesticated chickens is frequent, but there is a five-fold variability between strains in the incidence of the disease (Johnson and Giles, 2006), suggesting that anticancer responses may have subsequently evolved in certain strains. Similarly, in dairy cows and goats that have been selectively bred for mammary gland growth and milk production, there is paradoxically a low occurrence of mammary tumors compared to domestic carnivores (Munson and Moresco, 2007), suggesting once again that anticancer mechanisms compensating for increased risks of lobular alveolar growth and hence malignancies have been concomitantly and/or subsequently selected. Further studies would be necessary to explore how relevant these phenomena are in wild species currently experiencing alterations in the reproductive biology because of climate change (e.g., Winkler et al., 2002; Pankhurst and Munday, 2011).

Reproductive Aging

The evolutionary ecology literature is replete of studies documenting reproductive aging (i.e., the decline in reproductive performance with increasing age, also coined reproductive aging) in females (see Holmes et al., 2003; Lemaître and Gaillard, 2017 for reviews). The decline in litter size from 10 years of age onward observed in Alpine marmot, *Marmota marmota* (Berger et al., 2015) constitutes one of the numerous examples of reproductive aging, and many other of reproductive traits (e.g., litter size, birth rate, juvenile survival) have been show to decrease with age. Nowadays, the common view is that female's reproductive aging is the rule rather than the exception, at least in endotherm vertebrates (more than 60% of the studies species in both birds, Vágási et al., 2021 and mammals, Lemaître et al., 2020b) even if reproductive aging trajectories remain highly variables both within and across species (Reid et al., 2010; Lemaître et al., 2020b). Reproductive aging is obviously particularly pronounced in species displaying menopause (see Péron et al., 2019), a cessation of the reproductive functions that occurs many years before death. In addition, there is now pervasive evidence that reproductive aging is common among males of various species. Indeed, while evidence that male fertilization efficiency decreases with age have been documented for a long time in human (see Johnson et al., 2015) and laboratory rodents (vom Saal et al., 1994), an increasing number of studies are now reporting male reproductive aging in semi-captive or wild populations of animals. Such decline in reproductive performance have been observed using reproductive success metrics (e.g., mating success, Raveh et al., 2010) but also the conspicuousness of secondary sexual traits (e.g., Perrot et al., 2016, or the quality of the ejaculates, Preston et al., 2011). However, while the study of reproductive aging is showing an unprecedent infatuation, the link between both reproductive aging and oncogenic processes are yet to be deciphered.

These two processes, reproductive aging and oncogenic processes, can share similar proximate origins. As emphasized in the sections above, an elevated reproductive expenditure

could be responsible for an increased risk of cancer (Boddy et al., 2015). Interestingly, there is compelling evidence that such substantial allocation to reproduction during early-life is also detrimental in terms of an earlier/stronger reproductive aging (e.g., Nussey et al., 2006 and Lemaître et al., 2014, for examples in females and males red deer, *Cervus elaphus*, respectively) and the physiological pathways that have been suggested to mediate the link between early- and late-life reproductive performance are strikingly similar to the one suggested to be involved in the reproductive effort-cancer trade-offs (e.g., oxidative stress, telomere attrition, see Kalmbach et al., 2015). However, this does not preclude any complex interactions between reproductive aging and oncogenic processes and understanding whether the occurrence of cancer is a cause, a consequence or is – to some extent – independent to the aging process remains a long-standing question (de Maghalaes, 2013; Thomas et al., 2018). Moreover, it is noteworthy that the cancer-reproductive aging dynamic is likely to be different between males and females for which the age-specific cancer rate of reproductive organs show striking differences (see de Maghalaes, 2013).

The various risk of cancers associated to the physiological pathways modulating the reproductive sequence (e.g., pregnancy in mammals) might have constituted a selected pressure on the evolution of reproductive aging patterns. For instance, it has recently been proposed (Thomas et al., 2019a) that menopause in humans (and in a few cetaceans) may have specifically evolved as an anticancer adaptation for some mismatches between the dynamics of oncogenic processes and natural anticancer adaptations that have occurred during recent evolutionary changes (**Figure 4**). While it is a natural phenomenon that oncogenic processes steadily accumulate in the body with age, pregnancies are unlikely to initiate cancers in an evolutionary stable context. However, mismatches in cancer defense levels can cause oncogenic processes to accumulate at higher rates, enhancing the growth of existing tumors and raising the risk of tipping the balance toward the initiation of uncontrollable metastatic cancers. Thus, after a given age, pregnancy could be associated with a higher probability of premature death due to metastatic cancers. The physiology of fertile women itself is also expected to favor malignant progression because several cancers also depend on hormones (estrogen and progesterone) for their growth (Aktipis et al., 2015; Aktipis, 2016; Atashgaran et al., 2016). Menopause could potentially have evolved as a "natural hormonal therapy" to prevent or alleviate the growth of malignancies before a fatal threshold is reached (Thomas et al., 2019a). If reproduction can contribute to an increase in oncogenic processes later in life, it is however, not the only nor even the most important contributor, and cancers remain common even after menopause and/or in nulliparous women (Gleicher, 2013; Einstein et al., 2015). This emphasizes how cancers must be viewed within multivariate life-history strategies and tradeoffs.

From this hypothesis, further fascinating directions (still debated in humans, e.g., Saadat, 2010) remain to be explored, such as the influence of offspring sex ratio on cancer risk, for example. All else being equal, sons in sexually dimorphic and polygynous species are often more costly to produce or rear than daughters (Bérubé et al., 1996; Whittingham and Dunn, 2000; Gibson and Mace, 2003; Cameron-MacMillan et al., 2007; Rickard et al., 2007). If male embryos more strongly foster the proliferation of existing malignant cells during pregnancy than female embryos, it could be expected that a sex ratio biased in favor of male progeny could, all else being equal, result in a higher overall maternal cancer risk and/or a higher risk of cancer at a younger age. The literature on this topic remains controversial at the moment (e.g., Hsieh et al., 1999; Wohlfahrt and Melbye, 2000; Saadat, 2010).

In addition, it would be particularly relevant to explore whether some of the mammalian species that show no decline in pregnancy rates with increasing age (e.g., white tailed-deer, *Odocoileus virginianus*) (DelGiudice et al., 2007) display a higher risk of cancers or have evolved alternative anti-defenses mechanisms to buffer cancer risk. This approach would also be relevant in ectotherm species that often show no decline (or sometimes even an increase) in fertility with age (e.g., Cayuela et al., 2020). Many studies are currently seeking to identify the biological properties enabling many ectotherm species to escape aging (e.g., Hoekstra et al., 2020 in reptiles). It has been notably highlighted that telomere dynamics can be particularly variable in these species (Hoekstra et al., 2020) with an absence of decline in telomere length with age (e.g., Ujvari and Madsen, 2009 in water python, *Liasis fuscus*). Whether this maintenance of telomere length with age is due to an increased expression of telomerase, which would in turn increased cancer risk is yet to be explored (Olsson et al., 2018) but would constitute a key support for a trade-off between the intensity of reproductive aging and the risk of cancer. Albeit limited, the bunch of empirical evidence compiled so far highlights that the risk of cancer is far from being negligible in ectothermic species such as reptiles (Madsen et al., 2017) which suggest that embracing this research path might be full of promises.

TRANSMISSIBLE CANCERS AND CANCERS WITH AN INFECTIOUS CAUSATION

At least for dogs and Tasmanian devils, infection by transmissible malignant cells can be viewed as a cost of reproduction. In the vast majority of cases, cancer is not a contagious disease and malignant cells die with their host. However, in at least nine independent cases, cancer cells have evolved the capacity to be horizontally transmitted: one cancer in dogs, two in Tasmanian devils (*Sarcophilus harrisii*), and seven in bivalve species (McCallum et al., 2009; Yonemitsu et al., 2019; Dujon et al., 2020; Garcia-Souto et al., 2022). In dogs, canine transmissible venereal tumor (CTVT) is indeed caused by a sexually transmitted cancer cell line that affects dogs worldwide (Strakova and Murchison, 2014). The tumors are usually localized on the external genitalia (penis and foreskin in males and vulva in females), and it spreads between individuals through sexual intercourse and licking and/or biting the affected areas. These transmissible cell lines appeared between 8,000 and 11,000 years ago (Strakova and Murchison, 2015; Ostrander et al., 2016).

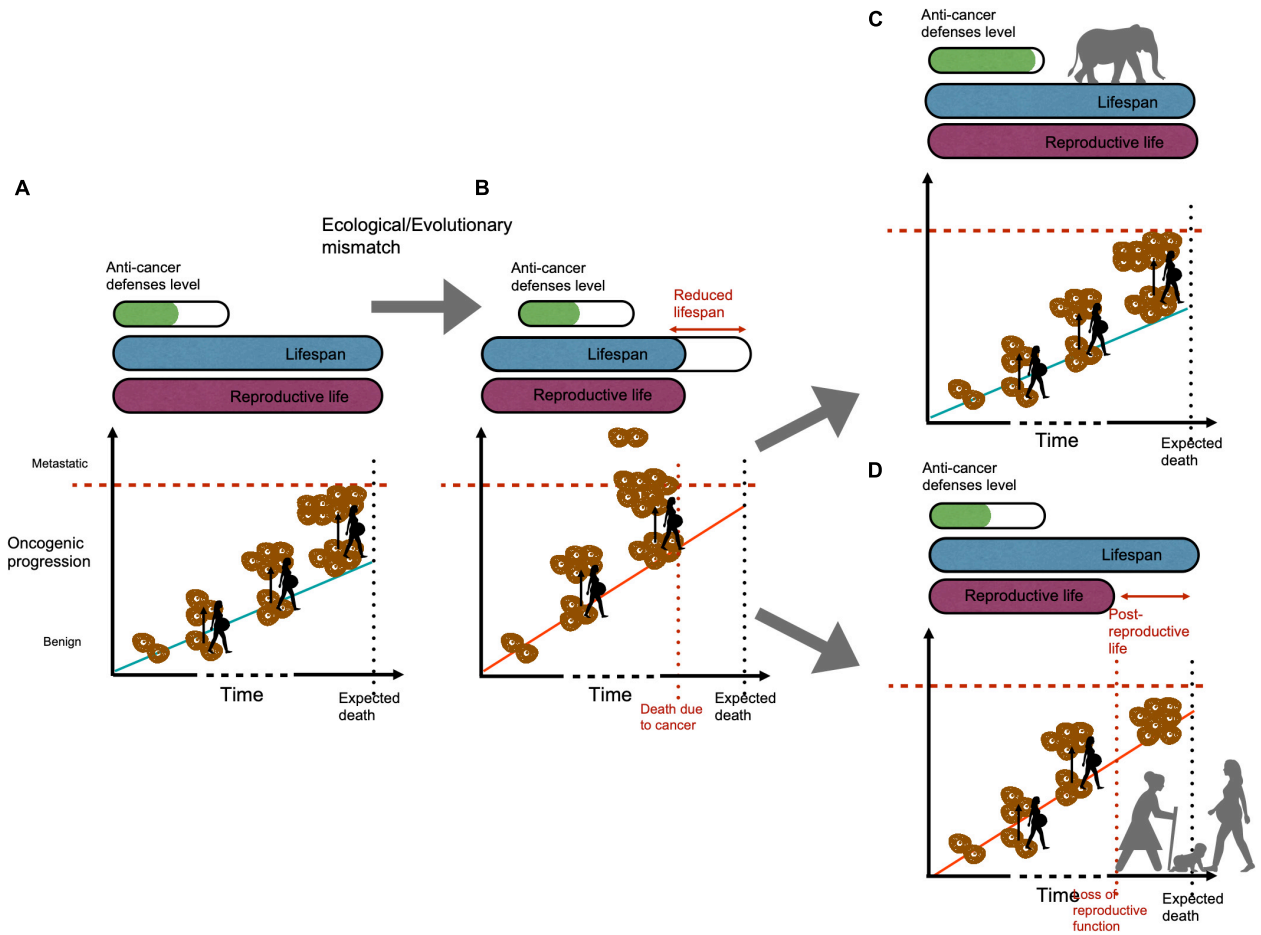

FIGURE 4 | Menopause as a possible (transient) adaptation to cancer risk following an evolutionary mismatch. **(A)** When cancer defenses are in alignment with malignant risks, oncogenic processes slowly accumulate through time, and even if pregnancy periods exacerbate their dynamics, the risk of metastatic cancers remains low. **(B)** Following an ecological and/or evolutionary mismatch, cancer defenses may become too weak given the novel cancer risks. Oncogenic processes accumulate rapidly, and this time reproductive episodes exacerbate metastatic cancer risks sooner in life for females, resulting in a short lifespan and a low fitness. From this situation, two evolutionary outcomes are possible, natural selection can (i) favor the evolution of better cancer defenses in these species (i.e., as in large animals such as whales and elephants), coming back to a situation comparable to **(A)**, here **(C)**, or (ii) favor females ceasing their reproduction prematurely to preserve their health and invest their energy/resources for their grandchildren **(D)**. In this later situation, female's fitness is higher than in **(B)** because of inclusive fitness. The **(D)** scenario could in theory be just a transient situation until other cancer defenses are selected (**A,C** examples). Figure modified from Thomas et al. (2019a).

Presumably as the result of this relatively long co-evolution with its hosts, CTVT rarely metastasizes and even displays a regressive stage (Das and Das, 2000; Martincorena et al., 2017). In Tasmanian devils, malignant cells are responsible for two cancers called devil facial tumor disease (DFTD), and devil facial tumor 2 (DFT2). It is not directly sexually transmitted, rather direct contact through biting is required, which frequently occurs during social interactions linked to reproduction. Infected individuals can still mate but they have reduced survival as a consequence of mating. DFTD was discovered in 1996 in northeastern Tasmania and has evolved into at least five clades (Hawkins et al., 2006; Kwon et al., 2020), whereas the second and independently emerged cancer, DFT2, was discovered in southeastern Tasmania at the d'Entrecasteaux Peninsula in 2014; (Pye et al., 2016; James et al., 2019; **Figure 5**). DFTD and DFT2 both induce large ulcerating tumors around the face and jaws, and DFT2 neoplasms are also frequently found in other parts of the body (James et al., 2019). DFTD, for which there is now a lot of information, is clearly fatal, with death usually occurring 9–12 months after the appearance of the first lesions with evidence of some individuals surviving up to 2 years (Wells et al., 2019). In only 25 years, the demographic cost of this transmissible cancer has been devastating, posing a serious conservation threat to the species, which is now classified as "Endangered" by the International Union for Conservation of Nature (Hawkins et al., 2008). While natural selection for less aggressive phenotypes could be expected in devils on the long term, it has not yet been observed, presumably because aggression is a trait associated with increased mating and breeding success in this species (Hamede et al., 2013). In evolutionary terms, it remains more

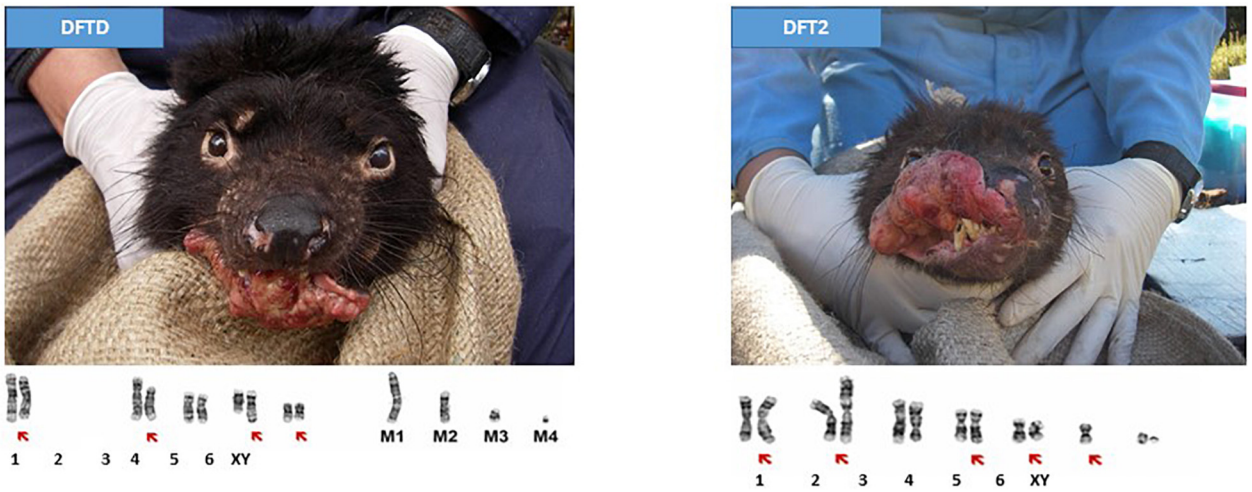

FIGURE 5 | Transmissible cancers in Tasmanian devils. Tasmanian devils with DFTD and DFT2 and the respective tumor karyotypes. Red arrows indicate chromosomes carrying cytogenetic abnormalities. The four marker chromosomes found in DFTD are labeled M1 to M4. Karyotypes from Pye et al. (2016).

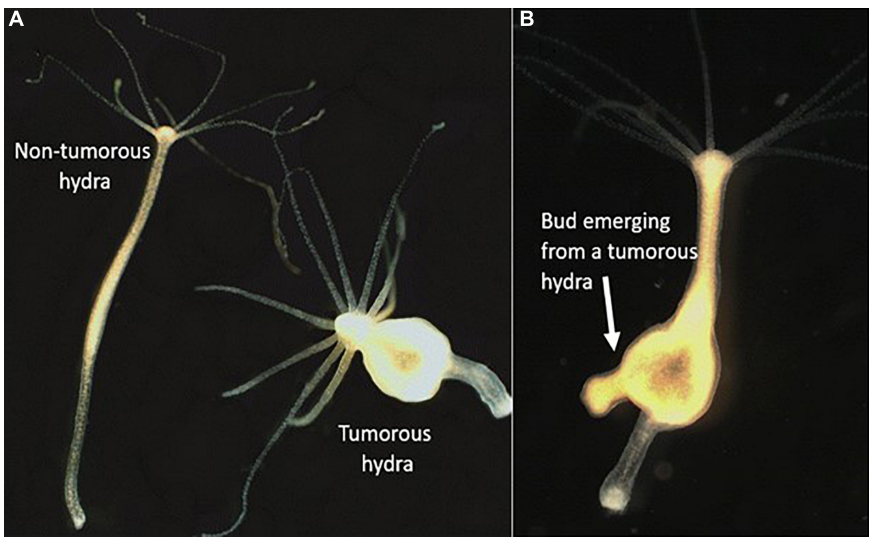

FIGURE 6 | Tumors in *Hydra oligactis*. **(A)** Non-tumorous and tumorous hydra. Neoplasia not only severely alter the polyp's body shape, but tumor-bearing individuals also show a shift in their microbiota and display a higher number of tentacles (Domazet-Lošo et al., 2014; Rathje et al., 2020). **(B)** Vertical transmission of tumoral cells in *Hydra oligactis*. After emergence, buds from tumorous hydra are morphologically similar to non-tumorous hydra, but after 4–6 weeks, they develop tumors as their parental polyp (Photo Justine Boutry).

beneficial to reproduce at a cost of developing and dying from DFTD than to remain healthy without reproducing. Interestingly, there is increasing evidence of tumor regressions in the wild, suggesting that devils are adapting to DFTD (Margres et al., 2018, 2020), and that a coexistence of devils and this transmissible cancer may be a long-term enzootic outcome (Wells et al., 2019; Hamede et al., 2020).

Reproduction can also be an opportunity for tumor cells to be vertically transmitted, from parent to offspring. Although rare, transmissions of cancer cells have been observed in humans from mother to fetus (Isoda et al., 2009; Greaves and Hughes, 2018). In addition, neoplastic leukemia cells arising in one monozygotic twin have been shown to transmit to the co-twin via intraplacental anastomoses (Clarkson and Boyse, 1971; Greaves et al., 2003). In the basal metazoan hydra (*Hydra oligactis*), tumor-bearing individuals (**Figure 6**) directly transmit tumoral cells to their offspring when reproducing asexually via budding (Domazet-Lošo et al., 2014). Given the omnipresence of oncogenic processes in multicellular organisms as well as the fact that transmissible cancer cells can have dramatic effects on their host's fitness (e.g., Tasmanian devils), Thomas et al. (2019b) argued that sexual reproduction may have been favored by natural selection over evolutionary time as a radical way to prevent the vertical transmission of cancer cells, since it allows

the offspring's immune system to be more efficient at recognizing and eliminating these cells [but see also Aubier et al. (2020)].

In addition to transmissible malignant cells, several cancers have an infectious causation, and a considerable proportion are transmitted during some step related to reproductive activity. Indeed, pathogens that have been recognized as etiological agents of cancers (e.g., herpes simplex viruses, cytomegalovirus, hepatitis virus, papilloma viruses, human immunodeficiency virus, Eskinazi, 1987) are usually transmitted by genital contact or intimate kissing (Ewald, 2009). For this category of malignancies, cancer risk is not surprisingly associated with increased sexual activity (e.g., Bosch et al., 1996; Hayes et al., 2000; Cooper et al., 2007; Gómez and Santos, 2007).

CONCLUSION

(1) Reproduction is a central activity for all living organisms, and is also associated with a diversity of costs that need to be considered for a full understanding of the selective landscape in which organisms live and evolve. While decades of research have focused on the identification and implications of these costs, little attention has been devoted to exploring how the schedule of reproductive activities over the life course may also influence malignant cell dynamics and cancer defenses that in turn affect health and survival.

(2) Most ecologists currently consider that reproductive events have little or no impact on oncogenic processes, but this has yet to be properly studied. One must also consider separately the trade-offs that are optimal in a Darwinian logic maximizing reproductive success, from those that are relevant in a public health perspective, for which disease risks occurring after the reproductive period matter too. Further studies would need to explore not only whether there are connections between reproductive costs and the dynamics of malignant processes, but also determine for different species and organs the "shape" of the relationship through time (e.g., linear, exponential, steps with thresholds).

(3) In addition, we need to improve our understanding of the potential interactions between different active evolutionary processes. We can consider birth weight as an example for which it has been established that high values are associated with higher cancer rates later in life. In humans, at least in the past, higher birth weights and/or size have been associated with fitness benefits, especially survival early in life under a wide range of environmental conditions. Certain genes could therefore mediate antagonistic pleiotropy, which is associated with the selection for enhanced birth weight due to survival benefits early in life at the expense of the later increased risk of cancer. Because of the same fitness benefits, this phenomenon could also have a maternal origin, e.g., by modifications to the level of resources available to the fetus during pregnancy and/or by choosing taller men as sexual partners.

(4) Finally, we also need to understand over the long term how these interactions may trigger the evolution of defense mechanisms that prevent and/or alleviate the detrimental effects of malignant cells on the fitness of breeding animals. Whether the directionality of the relationship between reproduction and cancer varies among individuals, populations, or species is poorly understood, but should be explored given that cancer dynamics can sometimes influence reproductive decisions, as is the case in *Drosophila* (see above sections). Research programs addressing these questions are particularly timely since modifications of environmental conditions by human activities have been associated with both alterations in the reproduction biology and increased cancer rates in wild populations. A better understanding of the dynamic interplay between age-specific reproductive activity and the dynamics of oncogenic processes remains a major goal for diverse research areas such as population dynamics, conservation biology, epidemiology, and public health.

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

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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