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Telomeres, the loop tying cancer to organismal life-histories

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Abstract

Recent developments in telomere and cancer evolutionary ecology demonstrate a very complex relationship between the need of tissue repair and controlling the emergence of abnormally proliferating cells. The trade-off is balanced by natural and sexual selection and mediated via both intrinsic and environmental factors. Here, we explore the effects of telomere-cancer dynamics on life history traits and strategies as well as on the cumulative effects of genetic and environmental factors. We show that telomere-cancer dynamics constitute an incredibly complex and multifaceted process. From research to date, it appears that the relationship between telomere length and cancer risk is likely nonlinear with good evidence that both (too) long and (too) short telomeres can be associated with increased cancer risk. The ability and propensity of organisms to respond to the interplay of telomere dynamics and onco-genic processes, depends on the combination of its tissue environments, life history strategies, environmental challenges (i.e., extreme climatic conditions), pressure by predators and pollution, as well as its evolutionary history. Consequently, precise interpretation of telomere-cancer dynamics requires integrative and multidisciplinary approaches. Finally, incorporating information on telomere dynamics and the expression of tumour suppressor genes and oncogenes could potentially provide the synergistic overview that could lay the foundations to study telomere-cancer dynamics at ecosystem levels.

KEYWORDS
cell proliferation, mate-choice, parasites, parental effect, Peto's paradox, pollution, predator-prey interactions

1 | INTRODUCTION

Cancer appeared following the major transition of life from uni- to multicellularity during the late Precambrian, about 1 billion years ago (Aktipis et al., 2015; Domazet-Loso & Tautz, 2010). Multicellularity required the division of labour between cells and the evolution of reproductive altruism, where nonreproductive cells transmit their genes to future generations indirectly via those that are propagating by gametes (Szathmáry & Smith, 1995). However, these societies are vulnerable to cheater cells that fail to conform to their assigned

role, and exploit the society for their own reproductive benefit, that is, malignant, cancerous cells (Ducasse et al., 2015; Nunney, 2017; Box 1). Because multicellular organisms that are unable to control cheater cells prior to and during the reproductive period have reduced fitness, selection for enhanced anticancer mechanisms has been strong over the eons of evolution. This has yielded a diversity of within-individual cheat-prevention mechanisms operating at different levels ranging from genomes to cells and tissues, as well as the whole organism (Boutry et al., 2020; DeGregori, 2011; Nunney, 2013).

One of the key controls of cell proliferation in some mammals is suppression of telomerase expression and concomitant shortening of telomeres in somatic cells. Telomeres and replenishment of telomeric sequences via telomerase activity (Jafri et al., 2016) or other alternative pathways (Dilley & Greenberg, 2015; Sun et al., 2010) allow cell proliferation as they protect the end of chromosomes from fraying and sticking together. Maintaining telomere length (henceforth TL) above a critical length permits unlimited cell proliferation, which is one of the hallmarks of cancer (Hanahan & Weinberg, 2011), allowing malignant cell development and progression (Jafri et al., 2016). Concomitantly, limiting cell proliferation and thus inhibiting tumour formation via telomeric fail-safe, results in replicative senescence and in the progressive degradation of tissue function with advancing age (Weinstein & Ciszek, 2002). Evolutionary senescence theory predicts a balance between tissue repair and cancer suppression, that is, longer telomeres facilitating repair, shorter ones limiting cancer formation (Weinstein & Ciszek, 2002). In species experiencing a high likelihood of mortality and thus short lifespan due to environmental factors, the balance is proposed to shift towards relatively short telomeres, reduced tissue repair and reduced cancer risk; while in species where environmentally-driven mortality is less frequent and long lifespans are predominant, the balance is proposed to shift towards relatively longer telomeres, enhanced tissue repair, but concomitantly increased tumour risk (i.e., the reserve capacity theory by Weinstein & Ciszek, 2002, but see Risques & Promislow, 2018a).

Here, we review the literature and provide a perspective on how the ecology of organisms' shapes and drives the evolution of the complex relationships between TL, ageing and cancer development throughout life, within and across species. First, we provide a short overview of how telomeres can contribute directly to cancer development. Next, we discuss how the interconnected relationships between telomeres and cancer (henceforth "cancer-telomere dynamics") can shape organismal life history strategies.

2 | HOW TELOMERES CONTRIBUTE TO CANCER DEVELOPMENT

2.1 | Short telomeres and cancer development

Telomere shortening has been associated with repressing the emergence of cancer cells, as short telomeres present a barrier to cell proliferation (e.g., the Hayflick limit in human cells; Shay & Wright, 2000). With every somatic cell division, TL shortens slightly, and

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BOX 1 Definitions

Cancer: An abnormal growth of cells that has crossed basal membrane boundaries and/or spread into locations distant from the site of initiation.

Cheating cells: Cells that break shared rules in multicellular organisms (such as genetically encoded phenotypes or behaviours), and thus acquire fitness advantage (higher proliferation) for the cheater.

Chromatin: The combination of DNA and protein that makes chromosomes.

Chromothripsis: Also known as "chromosome shattering" is a single catastrophic event when first chromosomes fragment into many pieces and then DNA repair processes join the fragments back together in a random order.

Constitutive telomere length (TL): The length of telomeres in normal somatic tissues of individuals affected by cancer (vs. TL in their cancerous tissues).

Cooperation: Coordination of benefits and actions to facilitate shared goals to augment fitness of the larger ensemble, the organism.

Dicentric chromosomes: Abnormal chromosomes that contain two centromeres.

Kataegis: Several hundred base pairs long mutational clusters occurring in a small region of DNA in cancer genomes. Kataegis thought to result from DNA repair errors at the site of genome rearrangements.

Neoplasia: The formation of new, abnormal growth of tissue.

Oncogenesis: The complex, multistep process by which normal cells turn into cancerous cells, leading to cancer development.

Tetraploidization: Whole genome doubling resulting in chromosomal anomaly when normally diploid cells contain four copies of each chromosome (instead of two). Tetraploidization is frequent in solid tumours, leads to chromosomic rearrangements and is associated with poor cancer prognosis.

Tumour: Abnormal mass of tissue resulting from independent and unrestrained proliferation and growth of cells. Tumours that do not invade nearby tissues are benign, tumours that spread to neighbouring tissue and/or other parts of the body through the blood and lymph systems are malignant.

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once a critical length is reached, cell cycle arrest ensues and cell division ceases (cellular or replicative senescence). In vitro studies and investigation of familial and nonfamilial human cancer cases have provided support for telomere shortening being a barrier to tumorigenesis (Huang et al., 2013; Lorbeer & Hockemeyer, 2020;

Maciejowski & de Lange, 2017; Schmutz et al., 2020). On the other hand, in incipient cancer cells with ineffective cell cycle arrest, reduced TL can also lead to extensive genomic instability, that can promote cancer cell initiation and progression (Maciejowski & de Lange, 2017). Indeed, short telomeres have been observed in most solid cancers (Shay, 2016). Accumulation of cells harbouring chromosomes with short leucocyte telomeres (henceforth leucocyte telomere length [LTL]) with age has also been associated with increased cancer incidence in humans (reviewed in Willeit et al., 2010). However, a recent study did not find such association, but rather showed that short LTL with advancing age was associated with increased mortality risk from noncancer causes (Arbeev et al., 2020).

2.2 | Long telomeres and cancer development

The complex role of TL in cancer emergence is further demonstrated by studies showing association between cancer and constitutively short (reviewed in Savage et al., 2013) and long (Haycock et al., 2017) TL. The association of longer genetically determined LTL with higher risk of certain cancers (prostate, melanoma, thyroid, kidney, and genitourinary tumours) has been confirmed by recent genome-wide association studies (Codd et al., 2021; Giaccherini et al., 2021). The causal association between longer LTL and risk of several cancers may be explained by the theory proposed by Aviv et al. (2017), who suggested a modification of the two-hit hypothesis developed by Moolgavkar and Knudson (1981) and Meza et al. (2008). The two-stage clonal expansion model proposes the need of two mutational hits to occur for cancer formation: the first occurring at the stem-cell level resulting in a clone with replicative advantage, and the second mutational hits transforming the expanding clone into cancer (Aviv et al., 2017). According to Aviv et al. (2017), the first cancer initiating mutations occurring in stem cells are independent of TL, but the second hits that contribute to malignant transformation are TL dependent. Individuals with longer telomeres may face an increased risk of acquiring a second episode necessary for oncogenesis, due to the longer expansion phase before entering cellular senescence (Aviv et al., 2017).

2.3 | Short telomeres, gene expression regulation and cancer

Shortening of the telomere cap may, however, contribute to disease development and ageing long before evoking DNA damage responses, by regulating the expression of genes in the subtelomeric regions (Robin et al., 2014). When telomeres are long, chromosome looping brings them back to the chromatin, and hence they can influence the transcription of genes up to 60 Mb away from chromosome ends, a phenomenon termed telomere position effect (TPE) over long distance (TPE-OLD; reviewed in Vinayagamurthy et al., 2020). Due to the physical association with telomeres, genes in the subtelomeric regions, such as the reverse transcriptase gene (hTERT)—the

key component of the telomerase enzyme, get downregulated. Progressive shortening of telomeres throughout ageing leads to dissociation of the loop leading to gene activation, including hTERT. Telomerase is known to be reactivated in more than >90% of human cancers, and it has recently been shown to be under direct transcriptional control of a component of the telomere loop (telomeric repeat–binding factor 2, TRF2, Sharma et al., 2020). Shortened telomeres have also been demonstrated to have genome-wide epigenetic influence by altering DNA methylation, histone modifications and nucleosome positioning, and thus, to ultimately drive transitions in cell lineage commitment, for example, transdifferentiation or the epithelial-to-mesenchymal transition leading to cancer progression (reviewed in Harrington & Pucci, 2018).

2.4 | The antagonistic pleiotropic effect of telomere shortening on cancer development

Furthermore, replicative senescence paradoxically is a cancer defense that can promote cancer later in life (Cleal et al., 2018). This is a form of antagonistic pleiotropy since it is protective early in life through a limitation of cellular division either in case of oncogene activation or following telomere erosion (Campisi, 2001; Wright & Shay, 2001), but this tumour-preventive function over time also yields to reduced tissue regenerative capability that decreases the number of cells able to replace damaged cells. The reduced regeneration can favour cancer in old organisms because it promotes ecological niches within tissues suitable for malignant cells (Campisi, 2002; Capp & Thomas, 2020; Giaimo & d'Adda di Fagagna, 2012; Krtolica et al., 2001). Another antagonistic pleiotropic effect has recently been demonstrated: the loss of telomere protection may initiate telomere crisis, when telomere shortening leads to telomere fusions and the formation of dicentric chromosomes that drive genome instability (Artandi & DePinho, 2010). Dicentric chromosomes can alter normal chromosome segregation and DNA repair mechanisms resulting in chromosome shattering, mutation accumulation and genome duplications and thus, promote cancer progression via processes such as chromothripsis, kataegis and tetraploidization (Maciejowski & de Lange, 2017; Martínez & Blasco, 2017; Box 1). In conclusion, the relationship between TL and cancer risk is probably nonlinear with good evidence that both (too) long and (too) short telomeres can be associated with an increased cancer risk.

3 | A LIFE-HISTORY PERSPECTIVE: INDIVIDUAL LEVEL TELOMERE—CANCER DYNAMICS

Individuals often show substantial variation in their survival and reproductive prospects within a population, that is, the individual quality concept (Wilson & Nussey, 2010). High-quality individuals are expected to be larger (Naguib & Gil, 2005), show more elaborate secondary sexual traits (Vanpé et al., 2007), provide superior

parental care (Viblanc et al., 2020), able to mount stronger immune responses (Le Vaillant et al., 2015) and an improved ability to respond to environmental challenges (Forsythe et al., 2021). Telomere shortening with advancing age (Arbeev et al., 2020) has been associated with various physiological (e.g., Angelier et al., 2018) and life history parameters (e.g., Sudyka et al., 2014) as well as with altered breeding performance (e.g., Sudyka et al., 2019). Consequently, "the telomere–individual quality hypothesis" proposes that "long telomeres should be either directly or indirectly associated with better life-long performance, and thus, with higher individual quality" (Angelier et al., 2019). However, as discussed above, longer telomeres may enable more cell divisions and higher possibility to acquire cancer causing mutations throughout the life of an individual (Aviv et al., 2017). Tumour suppressor mechanisms, such as cell-cycle controls, DNA repair, programmed cell death, immune surveillance etc. (reviewed in Harris et al., 2017) may be able to counter the cancer initiating impact of longer telomeres. We, therefore, propose that the "telomere – individual quality hypothesis" should also include the effects of cancer suppression. Trade-offs between constantly eliminating premalignant lesions and other somatic functions may also alter the organism's resource allocation strategy (Boutry et al., 2020; Ujvari et al., 2016). Longer or shorter telomeres may decrease and/or increase the risk of cancer and thus necessitate the fine scale balancing of the organism's energy and physiological status. Below we propose a few perspectives on how the cancer-telomere dynamics could influence the individual quality framework.

3.1 | Rapid growth, body size and secondary sexual characteristics may influence telomere—cancer dynamics

Larger body size and conspicuous secondary sexual characteristics, such as ornamentation and colouring often provide fitness advantage, but may also impose costs on survival, due to energetic trade-offs between reproduction and survival, including the organism's allocation in combating cancer (Boddy et al., 2015). Faster growth can require shorter cellular generation times leading to faster telomere shortening (Monaghan & Ozanne, 2018; Pauliny et al., 2015) and the potential accumulation of mutations (Araten et al., 2005) that may initiate cancer development. Indeed, positive associations between higher growth rate and cancer risk have been observed in dogs and humans (Harris et al., 2017; Nunney, 2018).

Mechanisms required to generate impressive ornaments may also enable rapid cell proliferation (and accelerated telomere shortening) or lead to diversion of resources from somatic maintenance (DNA repair or immune defences), thus elevating cancer risk by increasing accumulation of somatic mutations (Boddy et al., 2015). As sexual signals have shown to provide honest indication of individual quality, including information on telomere dynamics (Taff & Freeman-Gallant, 2017), they may also indicate the individual's tumour suppressor capacity throughout its life.

3.2 | Reproduction, parental care and intergenerational transfer may influence telomere—cancer dynamics

Although telomeres have been proposed to be potential biomarkers associate with the cost of reproduction, a recent survey by Sudyka (2019) found limited experimental evidence for reproduction to cause telomere shortening. Nevertheless, correlative studies propose that direct and indirect conditions provided by the parent, such as exposure to maternal corticosterone (Haussmann et al., 2012), provisioning variations between parents (due to environmental conditions; Boonekamp et al., 2014 or behavioural differences; Adams et al., 2015), could affect offspring TL, and thus Viblanc et al. (2020) put forward the "telomere—parental quality hypothesis". Here, we propose to include the additional dimension of cancer suppression, as high-quality individuals and high-quality parenting can have a synergistic effect on telomere shortening and associated cancer emergence in offspring. Trade-offs between constantly eliminating premalignant lesions and other somatic functions, may also alter the organism's strategy as well as its ability to provide paternal care, and concomitantly influence offspring TL and fitness.

3.3 | Parasites, environmental condition and pollution may unbalance telomere—cancer dynamics

Despite the growing interest in infection–telomere interactions, there is considerable lack of knowledge and evidence on how this interaction may affect and contribute to increased cell proliferation and cancer initiation. The only empirical data on individual differences in TL (measured from ear biopsies) and capacity to respond to cancer so far arises from Tasmanian devils (*Sarcophilus harrisii*) and their transmissible cancer, Tasmanian devil facial tumour disease (DFTD). Positive association was found between TL and age at first infection with the transmissible clonal cell line, suggesting a later infection and decreased susceptibility to DFTD in individuals with longer telomeres (Smith et al., 2020). The authors proposed that either increased immune system function and/or protection against oxidative damage may underpin their observations. Attenuation of TL in immune cells and thus immune capacity (Haussmann et al., 2005), accumulation of senescent cells impairing wound repair at site of infection and secretion of proinflammatory modulators due to ageing may promote the establishment and growth of malignant cells as seen in fibroblast cells (Krtolica et al.,2001). In addition, DFTD in devils may potentially initiate significant oxidative damage, and thus individuals with longer telomeres may be able to sustain oxidative damage and senescence, and also control tumour growth better than individuals with shorter telomeres (Smith et al., 2020). Interestingly while female devils appear to be tolerating DFTD better than males and most tumour regressions have been observed in females (Ruiz-Aravena et al., 2018), no sex specific TL differences have so far been observed in Tasmanian devils (based on ear biopsies, Smith et al., 2020). While the studies on Tasmanian devils

demonstrate the association between TL and infection with a transmissible cancer and show that individuals with relatively long telomeres may have an advantage in immune capacity, tissue repair, and controlling tumour growth, further studies are needed to decipher the underlying mechanism and pathways.

The increased anthropogenic impacts on our environment is predicted to result in that the synergistic interaction between environmental stressors, parasites, telomere shortening and cancer development will be accelerated in the future (Giraudeau et al., 2018, 2019; Greaves, 2015; Meitern et al., 2020; Monaghan, 2014; Sepp et al., 2019). For example, inverse associations have been observed in TL and air pollution (Zhao et al., 2018), traffic noise pollution (Dorado-Correa et al., 2018) and chemical pollutants (Angelier et al., 2019; Blévin et al., 2016; Stauffer et al., 2017). It should be noted, however, that a significant portion of the literature published on this topic also found an absence of correlations between some pollutants and TL or shortening (Blévin et al., 2016; Grunst et al., 2020), or noted even opposite patterns (i.e., perfluoroalkyl substances [PFAS] in seabirds, for example Blévin et al., 2017; Sebastiano et al., 2020). To the best of our knowledge, no studies have ever investigated the association between pollution exposure, TL and cancer in any wild species. As human studies found associations between shortened telomeres and lung cancer development in areas with high levels of environmental radon (Autsavapromporn et al., 2018) and smoke exposure (Xue et al., 2020), investigating further this topic would be of great interest for wildlife ecologists. A recent study, however, investigating cancer defences in the urban habitat did not find any difference in the expression of cancer-related genes between urban and rural great tits (*Parus major*, Giraudeau et al., 2020). The lack of differences in anticancer defences between urban and rural birds may be the result of evolutionary mismatch as urban birds live in a highly oncogenic environment that they have not adapted to (Giraudeau et al., 2020). In urban environments, developing nestlings had shorter telomeres than in the rural population, and birds with short telomeres selectively disappeared at a higher rate during their first year of life in the city (Salmón et al., 2016, 2017). These results suggest that only individuals inheriting long telomeres and/or able to limit their shortening survive in urban environments that are known to present high levels of pollutants with negative effects on the antioxidant balance. It remains to be determined if this process influences the levels of defences against cancer (i.e., trade-offs of resource allocation) and/or the more direct relationships between telomeres and the development of cancer.

3.4 | Genetic and environmental factors have additive effect on telomere—cancer dynamics

Similar to other traits, individual differences in TL (Bauch et al., 2021; Dugdale & Richardson, 2018) and cancer susceptibility (Sepp et al., 2019; Ujvari et al., 2018) have both been shown to be influenced by environmental and genetic factors, thus an individual's quality and capacity to respond to cancer development and ageing

may be influenced by dynamic interactions between intrinsic and environmental factors, as already shown above. Loss of genetic diversity and inbreeding clearly have a negative impact on an organism's capacity to respond to internal and external challenges, and the combined effect of genetic and environmental impairment may accelerate telomere attrition and cancer development. Giraudeau et al. (2019) has proposed that telomere dynamics are not only an integrative mediator that assembles and relates the information about physiological status (e.g., oxidative stress levels, inflammation status and stress reactivity) to the potential pace-of-life strategy and lifespan of an individual, but also to be a messenger across generations, where offspring would receive information about the internal and external environment through the gametes. By expanding, the "telomere messenger hypothesis" (Giraudeau, Angelier, et al., 2019) to cancer, one can consider the possibility of telomeres not only being a mediator of cancer development during the lifespan of an organism, but also a predictor and emissary of the capacity of future generations to respond to malignant transformations.

4 | A LIFE-HISTORY PERSPECTIVE: TELOMERE AND CANCER DYNAMICS ACROSS SPECIES

Given the functional relationships linking telomere dynamics to the risk of developing cancer among organisms, we may predict that species-specific TL and dynamics might have—at least to some extent—evolved to buffer the risk of developing cancer (Gorbunova et al., 2014; Pepke & Eisenberg, 2021). So far, research performed on telomere dynamics and cancer prevalence at the interspecific scale have been limited and siloed with no cross-talk between these areas. In the following section, we will discuss how the recent advances in both fields can enrich each other and could lead to a unified life history view of the telomere-cancer conundrum.

So far, the most thorough comparison of TL and telomerase activity at the interspecific scale has been performed in mammals (Gomes et al., 2011; Pepke & Eisenberg, 2021). Using adult TL and telomerase activity measured in cultured fibroblasts of more than 60 species, (Gomes et al., 2011) documented a negative association between telomerase activity and body mass, which matches similar observations made across rodents (Gomes et al., 2011; Gorbunova & Seluanov, 2009). Based on the work of Gomes et al. (2011), it appears that small mammalian species are more efficient in maintaining or elongating their telomeres, which should ultimately increase the risk of uncontrolled cell proliferation. This size-dependent expression of telomerase is - at least at first glance - in line with the observations that large-bodied animals do not show higher cancer prevalence than small-bodied animals, the so-called "Peto's paradox" (Nunney et al., 2015). Indeed, while long-lived and large-bodied animals are particularly at risk of cancer development due to their larger number of somatic cells, and the higher number of potential cell replication, that could lead to the accumulation of cancer-causing mutations, the empirical evidence published so far suggest that these species do

not display higher prevalence of cancer (see Vincze et al., 2022 for a comparative analysis in mammals). The repression of telomerase in large species might constitute efficient anticancer defences and strategies to buffer the high cancer risk associated with large size (Risques & Promislow, 2018b).

However, the picture might not be so straightforward, as recently shown by Pepke and Eisenberg (2021), and various elements suggest that our understanding of cancer risk and telomere dynamics is still at its infancy. With the help of additional sensitivity analyses, Pepke and Eisenberg (2021) reanalysed the data set of Gomes et al. (2011) and also identified inverse association between TL and lifespan, as well as between TL and mass. The authors found that longer telomeres predict higher cancer risk across the studied species, thus supporting their hypothesis of shorter TL being the result of selection for cancer suppression in larger and longer lived species (Pepke & Eisenberg, 2021).

The relationship between telomerase activity and body mass is not linear. In mammals, telomerase activity appears repressed in almost every species weighting more than 2 kg (Gomes et al., 2011; Gorbunova & Seluanov, 2009). Yet, cancer prevalence is predicted to increase as a function of both body size and lifespan over the entire range of life history strategies (Peto et al., 1977). In other words, large and long-lived species such as Proboscidea or Ceteacea are theoretically expected to display more cancer than any species of Cervids, although all species from these taxa are above the 2 kg threshold. However, observations made from zoo necropsies in 191 species of mammals highlight that cancer mortality risk is largely independent of both body mass and adult life expectancy across species (Vincze et al., 2022).

Other anticancer defences and strategies have been documented (Harris et al., 2017; Seluanov et al., 2018). These mechanisms, being shared across species or unique for a given species (Aviv et al., 2017) include for example the duplication of tumour suppressor genes (TP53) in elephants (Abegglen et al., 2015; Sulak et al., 2016), genes involved in DNA repair (proliferating cell nuclear antigen, PCNA) in whales (Keane et al., 2015), enhanced sensitivity to contact inhibition and slower cell proliferation in long-lived naked mole rats (Seluanov et al., 2009; Tian et al., 2018), and efficient prevention of damage caused by oxidative stress in long-lived bats (Zhang et al., 2013). Therefore, the relative influence of telomerase repression on cancer risk limitation is yet to be quantified as large species with telomerase activity might have also evolved additional tumour suppressor mechanisms. In mammals, some studies have shown telomere elongation in white blood cells and buccal mucosa (e.g., Fairlie et al., 2016; Hoelzl et al., 2016; Lemaître et al., 2021) and telomerase was detected in some tissues (e.g., in antlers of sika deer, *Cervus nippon*, Sun et al., 2010), and in cultured fibroblasts of several small-sized mammals (Gomes et al., 2011). One important step to take would therefore be to quantify telomerase activity across a wide range of biological tissues in mammals and other species. Moreover, evidence of telomerase activity throughout the lifespan and across various tissues have been reported in a long-lived seabird (Haussmann et al., 2005, 2007). We could thus predict that contrary

to mammals, large (and long-lived) birds might face a non-negligible risk in developing cancer. To test if the assumption is correct, it would be crucial to get accurate estimates of cancer prevalence among for example, long-lived sea birds. It is interesting to note that a recent study in common gulls reported a complex downregulation of the expression of eight cancer-related genes with age, a process that might be interpreted as a mechanism suppressing cancer risk for five of the genes but as increasing the risk for the three other genes differently expressed between young and old gulls (Meitern et al., 2020). An important note is, when considering telomerase activity in long-lived species and in association with cancer, that a detectable telomerase activity not necessarily result in telomere elongation as the enzyme has many other functions (e.g., inhibition of apoptosis in immune cells, enhancement of cellular inflammatory responses and maintenance of mitochondrial function, reviewed in Zheng et al., 2019).

Cancer risk should also depend on TL *per se*, as it determines the entrance of cellular senescence (Hayflick & Moorhead, 1961). So far, studies that have explored the diversity of TL and dynamics patterns across species have led to contrasted results and have unfortunately been focused only on birds and mammals. For instance, TL is negatively associated with maximum lifespan in mammals (Gomes et al., 2011), but not in birds (Criscuolo et al., 2021; Tricola et al., 2018). Importantly, oncogenesis is an age-dependent process with the risk of developing (most) cancers increasing with age (de Magalhães, 2013). Therefore, focusing on the species-differences in telomere attrition appears much more relevant in a cancer context than TL *per se*. In birds, the age-specific rate of decline in TL (measured in red blood cells) is negatively associated with maximum lifespan (Dantzer & Fletcher, 2015; Tricola et al., 2018). While a slower rate of telomere decline might thus constitute a mechanism to limit physiological ageing and thus a longer lifespan, it might also create a favourable ecosystem for cell proliferation at advanced ages, which in return might have promoted the evolution of diverse anticancer mechanisms in long-lived species (e.g., Abegglen et al., 2015; Vincze et al., 2022). Conversely, a steep rate of telomere attrition in short-lived species could rapidly lead to the accumulation of senescent cells at late ages, which might even be amplified in the presence of immune senescence (Ovadya et al., 2018), a widespread biological process in animals (Peters et al., 2019). This accumulation of senescent cells might contribute to the appearance of many age-related disorders in short-lived species but at the same time opens the door to the development of cancers (Mavrogonatou et al., 2020).

Interestingly, the concomitant increase in data availability on both cancer prevalence (e.g., (Vincze et al., 2022) and telomere dynamics (e.g., Remot et al., 2021) opens the door to promising studies in the field of comparative cancer biology. Yet, it is important to stress that much attention will have to be devoted on some methodological aspects that will be important to standardize. For instance, TL varies between tissues (e.g., in painted dragon lizards, *Ctenophorus pictus*, Rollings et al., 2019) and the likelihood to detect a decline in TL over the life course depends of the method of telomere measurement

(e.g., higher with the telomere restriction fragment [TRF] method and quantitative fluorescent in situ hybridisation [qFISH] methods than with quantitative PCR [qPCR] approach, see Remot et al., 2021 for a meta-analysis).

5 | CONCLUSIONS AND FUTURE DIRECTIONS

As emphasized throughout this review, while cancer and telomeres appeared to be clearly hand in hand at the cross-roads of trade-offs, the telomere-cancer dynamics is an incredibly complex and multifaceted process. The association starts not only when large tumours manifest, but rather early on as premalignant lesions emerge in the body of an organism. The abnormal proliferations are initiated and facilitated by short telomeres and further enabled by upregulation of telomerase enzyme resulting in unlimited potential for cell proliferation, while fuelled and supported by oxidative damage and inflammatory environments. The ability and propensity of individuals and species to respond to the oncogenic processes (from premalignant lesions to metastatic cancer), will depend on tissue environments, reproductive and life history strategies, environmental challenges (e.g., harsh climate, predation, etc.) and the evolutionary history of the species. Each step in these processes are the result of complex interactions and reciprocal feed-back effects (Thomas et al., 2017), and as such, the elucidation of the telomere-cancer dynamics requires integrative, multidisciplinary approaches.

The last decades have seen a burst in the publication of age-specific data on TL for a large number of species (see Remot et al., 2021 for a compilation). Species-specific data on cancer prevalence are now required to accurately establish the association between telomeres and cancer. This constitutes a real challenge in this field since no easily accessible blood biomarkers of cancers have been developed so far to diagnose cancer in wild vertebrates. Although high prevalence of cancer has been observed in some species, for example Tasmanian devils and belugas (*Delphinapterus leucas*; Madsen et al., 2017; McAloose & Newton, 2009), and particularly in polluted environments (Baines et al., 2021), detecting cancer in wildlife remains challenging. Tumours in wildlife are mostly detected during post-mortem surveys, that require histopathological examinations and do not allow early detection and monitoring of oncogenesis (Madsen et al., 2017). Noninvasive techniques, such as determining the ratio of heavy and light copper isotopes ($^{65}Cu/^{63}Cu$; Gourlan et al., 2019), proteome assays (Espejo et al., 2021), flow cytometry and molecular techniques (Bramwell et al., 2021; Burioli et al., 2019; Skazina et al., 2021) have been showing promising avenues for the noninvasive detection of cancer in captive felids, Tasmanian devils and bivalves, respectively (the two latter being cases of transmissible cancers). If one could step away from our vertebrate centred focus, bivalves could be potential study organisms to investigate the cancer and telomere dynamics. Abnormal proliferation of haemocytes, that is, disseminated neoplasia (DN, also referred to as haematopoietic or haemic neoplasia) has been documented for over 60 years and has been found in more than 20 Molluscan species, such as clams, mussels, oysters, and cockles (Barber, 2004; Carballal et al., 2015) and bivalve transmissible neoplasia (BTN) has now been observed in several species (Dujon, Gatenby, et al., 2020). Modelling predicts DN being widespread among bivalve marine populations (Bramwell et al., 2021). Neoplastic cells can be detected with various techniques from bivalve haemolymph and tissue samples (for protocols see Bramwell et al., 2021; Burioli et al., 2019; Skazina et al., 2021) and TL has also already been assessed in some species (Gruber et al., 2014). For research on vertebrates, promising alternatives include collaborations with zoos and wildlife health surveillance programmes that both perform thousands of necropsies with trained pathologists every year. Once these data on cancer susceptibility are accumulated, it should be possible to analyse whether the relationship between TL and cancer prevalence is linear or whether the risk of avoiding cancer is optimal for species displaying intermediate TL (and thus simultaneously buffering both the risk of cell proliferation and the accumulation of senescent cells). Moreover, as telomere dynamics, telomerase activity and cancer risk might all vary with body mass and maximum lifespan, appropriate control for allometric rules and pace of life will be required to decipher the link between telomere and cancer. For example, analysis by Gomes et al. (2011) showed that across the mammal phylogeny there is a negative association between telomerase activity and body size, while TL is negatively associated with longevity. Finally, cancer is a group of over 100 different diseases (Mukherjee, 2011) with great differences in cancer incidences across organs (Henson & Albores-Saavedra, 2004). Among many contributors, the number of stem cell divisions (Tomasetti & Vogelstein, 2015), the standing population size of an organ (Albanes & Winick, 1988; Roychoudhuri et al., 2006), the anatomic site (Noble et al., 2015) as well as the importance of each organ for survival until reproduction (Thomas et al., 2016) determine their vulnerability to cancer development. Therefore, the highly variable associations between cancer prevalence and TL may also differ between cancers in different tissues.

Deciphering the telomere-cancer dynamics across species is further hampered by individual and tissue-specific variations in the ageing process (including telomere maintenance and cancer suppression). For example, while no age-related telomere shortening has been observed in the longest-lived rodent, the naked mole-rat (*Heterocephalus glaber*), and the Mahali mole-rat (*Cryptomys hottentotus mahali*), age related senescence and telomere attrition have been documented in their close relative, the Damaraland mole-rat (*Fukomys damarensis*; Leonida et al., 2020). The effect of oxidative stress on TL has also been shown to be individual and tissue specific (Kim & Velando, 2015; Noguera et al., 2015), where certain groups of animals (e.g., different sex, or behavioural phenotypes) may have less affective antioxidant defences, or tissue types may have different adaptive antioxidant capacity (Cattan et al., 2008). Tissue-specific gene expression analyses across human tissues have also revealed a complex relationship between ageing, cancer and cellular senescence (Chatsirisupachai et al., 2019). While in most tissues, gene expression patterns change in the opposite direction in ageing and in

their corresponding cancers, in the thyroid and uterus the changes occur in the same directions. Chatsirisupachai et al. (2019) therefore concluded that "in general ageing processes might be opposite to cancer, the transcriptomic links between human ageing and cancer are tissue-specific". Similarly, the evolutionary ecology of organs has also been predicted to influence cancer development and progression (Thomas et al., 2016).

Future comparative studies should also attempt to investigate the telomere-cancer dynamics not only in a single representative species of a taxonomic group, but across several sister species with similar lifespan and body size. As shown by Vincze et al. (2022), cancer risk varies widely among taxonomic orders in mammals, associates with diet, but the mortality risk due to cancer is largely independent of body mass and adult life expectancy across species. By conducting TL analyses across broader taxonomic groups (and via controlling for phylogenetic relationships) one may discover more general patterns along the telomere-cancer dynamics axis and deciphers how life-history evolution shapes cancer resistance. If possible, additional tissue types (proliferative versus non-proliferative tissues) should also be targeted simultaneously, and experimental studies could investigate how decreasing antioxidant protection or increasing pro-oxidant generation influence mutation rates, TL and cancer markers (e.g., inflammatory signals, proliferations rates, contact inhibition). Longitudinal studies starting at young age and following individuals through their lifetime would allow detailed monitoring of how oxidative damage influences telomere attrition, inflammation and the emergence of premalignant lesions as individuals embark on their life history. Mate-choice experiments between healthy and cancerous individuals (with concurrent measurements of oxidative damage and TL) and follow up investigations of their reproductive output and fitness would be necessary to identify the signatures of natural and sexual selection. Experimental studies of Drosophila have shown that social behaviour alters cancer outcomes (Dawson et al., 2018), as well as female Drosophila accelerating their reproductive effort when affected by cancer (Arnal et al., 2017), but whether these phenotypic and reproductive adjustments coincide with shorter or longer telomeres (maintained by targeted retrotransposition of non-long terminal repeat (non-LTR) retrotransposons as Drosophila lack the telomeric repeat motives and telomerase observed in vertebrates, Casacuberta, 2017), higher or lower oxidative damage, remains to be answered.

Model systems where cancer can be experimentally induced could be used to look at the trade-offs between investing into somatic maintenance, reproduction, immune function and cancer suppressions, as well as how the microenvironment of tumours influence inflammation and ageing of a given species.

Finally, incorporating information on TL, antioxidant levels, tumour biomarkers (e.g., expression of tumour suppressor and oncogenes genes) from various species as well as ecological parameters (e.g., pollution levels, climate variables etc.) across ecosystems into a cancer-landscape ecology approach (Dujon et al., 2020) could potentially provide the synergistic overview that is needed in order to study cancer in ecosystems.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

No data was generated for this article.

BENEFIT-SHARING STATEMENT

A research collaboration was developed with the scientists contributing to the review article. More broadly, our group is committed to international scientific partnerships, as well as institutional capacity building.

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