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REVIEW ARTICLE

The telomere paradox: Dual regulatory roles in aging and cancer

Telomer paradoksu: Yaşlanma ve kanserde ikili düzenleyici rol

Taha ALTUG[1], Fahri BAYIROGLU[2]

[1]Ankara Yıldırım Beyazıt University, Institute of Health Sciences, Department of Physiology, Ankara, Türkiye
[2]Ankara Yıldırım Beyazıt University, Faculty of Medicine, Department of Physiology, Ankara, Türkiye

Abstract

Aging and cancer are biologically interconnected processes shaped by genomic stability and cellular replicative capacity. Telomere dynamics occupy a central position at the intersection of these conditions. Progressive telomere shortening, driven by cell division and oxidative stress, activates a DNA damage response that induces replicative senescence or apoptosis once a critical threshold is reached. While this mechanism contributes to age-related tissue decline, it simultaneously functions as a tumor-suppressive barrier by limiting uncontrolled proliferation. However, in the presence of defective cell-cycle checkpoints, telomere dysfunction promotes chromosomal instability and malignant transformation. In contrast to telomere attrition, telomerase reactivation stabilizes chromosome ends and restores sustained proliferative capacity, thereby enabling replicative immortality—a defining hallmark of cancer. Although telomerase activity may theoretically support regenerative potential, it also facilitates tumor progression. Together, these context-dependent effects define the "telomere paradox," emphasizing the non-linear relationship between telomere length, telomerase activity, aging phenotypes, and cancer risk. This review integrates current knowledge on telomere structure, telomerase regulation, and shelterin-mediated protection within a conceptual framework linking telomere dynamics to both degenerative aging and oncogenic processes.

Keywords: Telomere, telomerase, aging, neoplasms, cellular senescence.

Özet

Yaşlanma ve kanser, genomik stabilite ve hücresel replikatif kapasite tarafından şekillendirilen biyolojik olarak bağlantılı süreçlerdir. Telomer dinamikleri bu iki olgunun kesişim noktasında merkezi bir rol oynamaktadır. Hücre bölünmesi ve oksidatif stres sonucu gelişen progresif telomer kısalması, kritik eşik aşıldığında DNA hasar yanıtını aktive ederek replikatif senesens veya apoptozu tetikler. Bu mekanizma yaşa bağlı doku fonksiyon kaybına katkıda bulunurken, aynı zamanda kontrolsüz proliferasyonu sınırlayan tümör baskılayıcı bir bariyer işlevi görür. Ancak hücresel kontrol noktalarının bozulduğu durumlarda telomer disfonksiyonu kromozomal instabiliteyi artırarak malign transformasyonu destekleyebilir. Telomer kısalmasına karşıt olarak telomerazın yeniden aktivasyonu, kromozom uçlarını stabilize ederek sürdürülebilir proliferatif kapasitenin yeniden kazanılmasını sağlar ve kanserin tanımlayıcı özelliklerinden biri olan replikatif ölümsüzlüğe olanak tanır. Telomeraz aktivitesi rejeneratif potansiyeli destekleyebilecek olmakla birlikte, aynı zamanda tümör progresyonunu da kolaylaştırabilir. Koşula bağlı bu çift yönlü düzenek, telomer uzunluğu ve telomeraz aktivitesinin yaşlanma fenotipleri ile kanser riski arasındaki doğrusal olmayan ilişkiyi tanımlayan "telomer paradoksu" kavramının temelini oluşturmaktadır. Derleme, telomer yapısı, telomeraz regülasyonu ve shelterin aracılı korunma mekanizmalarını, dejeneratif yaşlanma ve onkojenik süreçlerle bütünleştiren kavramsal bir çerçeve içinde ele almaktadır.

Anahtar Kelimeler: Telomer, telomeraz, yaşlanma, neoplazmlar, hücresel senesens.

INTRODUCTION

Aging is a universal and multifactorial biological process that unfolds at the level of cells, tissues, and organ systems. Even with advances in healthcare, nutrition, and lifestyle interventions, individuals typically experience progressive phenotypic and functional changes over time, including skin wrinkling, hair graying, immunosenescence, and reduced cardiopulmonary reserve (1). Historically, humanity has sought ways to slow aging and extend healthy life; in premodern traditions this aspiration included the pursuit of a "panacea," a hypothetical remedy believed to cure all diseases and prolong life indefinitely (2). Modern biomedicine frames these questions in mechanistic terms and increasingly focuses on extending healthspan rather than lifespan (3).

In this context, telomere biology has become a central

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pillar of contemporary aging research. The award of the 2009 Nobel Prize in Physiology or Medicine to Elizabeth Blackburn, Jack Szostak, and Carol Greider for discoveries concerning how chromosomes are protected by telomeres and the enzyme telomerase drew broad attention to the field. Translation of these discoveries has the potential to inform strategies for preventing or delaying diseases rooted in fundamental cellular processes and for improving long-term health outcomes (4).

It is widely accepted that genomic integrity and cellular function deteriorate progressively with age, culminating in irreversible functional decline. However, which genomic regions are preferentially affected, how damage accumulates over time, and why certain sequences are especially vulnerable remain incompletely understood. Accumulating evidence points to telomeres as a key locus of vulnerability and a major determinant of replicative capacity, supporting a telomere-centered framework for cellular senescence and organismal aging. Because age-related diseases affect diverse tissues and organs, they may appear independent of telomere biology; however, converging experimental and clinical observations support a unifying concept linking telomere dynamics to systemic disease susceptibility (4,5).

With ongoing cell division, telomeres progressively shorten, and this attrition limits replicative capacity by activating DNA damage responses and inducing cellular senescence, thereby contributing to age-associated pathologies and impaired tissue renewal (6). Beyond replicative erosion, telomere integrity is further compromised by oxidative stress and glycation, which accelerate telomeric DNA damage and are central drivers of aging biology (7). Telomere dynamics are not solely passive reflections of cell turnover but are actively shaped by regulatory pathways influencing telomerase activity, mitochondrial function, redox balance, and inflammatory signaling (8-10). Chronic psychosocial stress and impaired mitochondrial efficiency have been shown to suppress telomerase activity and accelerate telomere shortening over time, reinforcing the mechanistic link between stress biology and cellular aging (11). Importantly, accumulating evidence indicates that telomere attrition can be modulated by cellular programs and environmental exposures, highlighting the biological plasticity of telomere maintenance systems (12).

At the population level, telomere length appears to be influenced by modifiable lifestyle and psychosocial determinants, including nutritional patterns, habitual physical activity, sleep quality, social connectedness, psychological stress exposure, and adverse occupational environments, which collectively affect oxidative stress burden, systemic inflammation, and neuroendocrine regulation (7-10). Recent investigations have extended this framework to early-life programming, examining prenatal influences such as maternal stress and sleep disturbances during pregnancy. Although some studies suggest that elevated maternal stress or disrupted sleep may be associated with altered telomere length in offspring, larger population-based cohorts have yielded inconsistent findings. These heterogeneous results indicate that methodological variation, timing of assessment, and population-specific factors likely shape observed associations between maternal psychosocial exposures and early-life telomere dynamics (13,14).

Blackburn has noted that her early work began with the unicellular ciliate Tetrahymena, which she used as an experimental system to investigate chromosomes and their termini (5,15). In the early 1990s, telomeres were primarily recognized for their role in protecting chromosomal ends (16). Tetrahymena proved particularly informative because it contains a large number of short linear chromosomes, providing abundant telomeric substrates for biochemical and genetic interrogation (15).

This review summarizes telomere structure, telomerase regulation, and shelterin-mediated protection and proposes a conceptual framework for the telomere paradox, emphasizing the non-linear relationship between telomere length, aging phenotypes, and cancer risk.

Telomeres

Telomeres are specialized nucleoprotein structures located at the ends of linear chromosomes (17).

They consist of repetitive DNA sequences bound by telomere specific proteins that collectively protect chromosome termini from being recognized as DNA double strand breaks, thereby preventing degradation, inappropriate repair, and end-to-end fusion. Although

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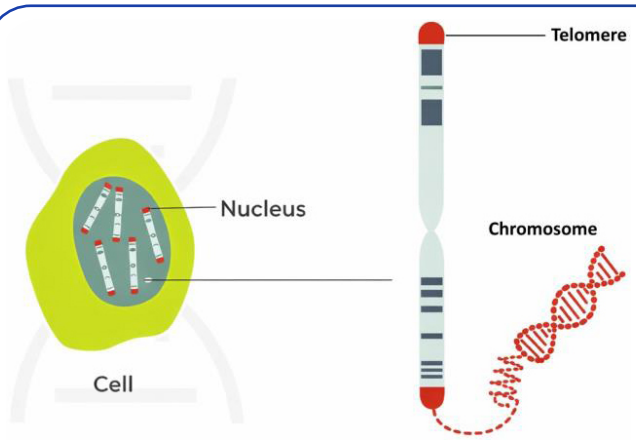

Figure 1. Chromosome and telomere architecture [Adapted from Blackburn (5)]

telomeres comprise less than one-ten-thousandth of total genomic DNA in human cells, they are essential for chromosomal stability and cellular viability (4).

In vertebrates, telomeric DNA is characterized by tandem repeats of the hexameric sequence (TTAGGG) on one strand paired with (CCCTAA)n on the complementary strand. Telomeres typically terminate in a 3-prime single-stranded, guanine-rich overhang of approximately 50–300 nucleotides, which facilitates the formation of higher order protective structures. Telomere length varies substantially between chromosome ends, between cell types, and among individuals; even within the same individual, different chromosome termini can exhibit marked differences in average telomere length (18).

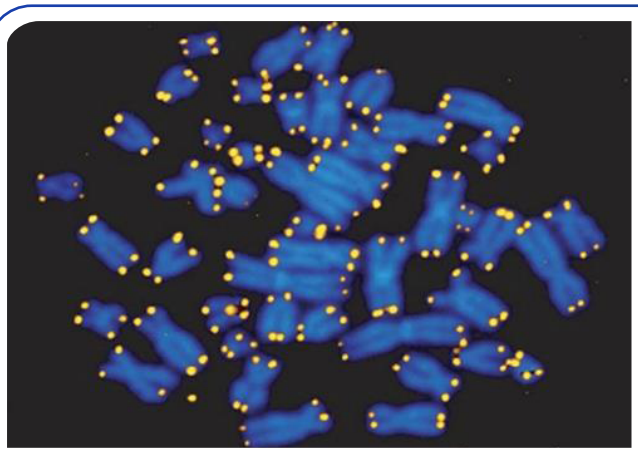

Figure 2. Telomeric repeats in a normal human lymphocyte visualized by quantitative fluorescence in situ hybridization (Q-FISH). Chromosomal DNA counterstained with DAPI is shown in blue and telomeres are shown in yellow (18)

Telomeres, together with their associated proteins, can adopt looped conformations (often referred to as T-loops) that help sequester the chromosome end and protect it from exonucleolytic degradation. Progressive telomere shortening occurs with each DNA replication cycle due to the end replication problem and nucleolytic processing. If unopposed, attrition can reach a critical threshold that triggers replicative senescence or apoptosis, effectively limiting the proliferative lifespan of somatic cells (19).

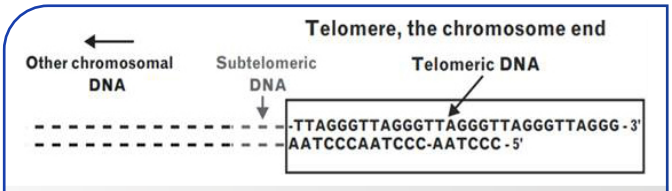

Figure 3. The conserved telomeric TTAGGG repeat interacts with specific proteins to form protective looped structures; progressive shortening with division can trigger replicative senescence or apoptosis (19).

In human nucleated blood cells, mean telomere length shows a pronounced age-associated decline, particularly in immune cell compartments, and displays substantial inter-individual variability at any given age. Early life hematopoietic expansion is thought to contribute to rapid initial shortening; the determinants of accelerated attrition later in life remain an area of active investigation (18).

Telomerase

Telomerase is a specialized ribonucleoprotein reverse transcriptase that counteracts telomere attrition by adding telomeric repeats to chromosome ends. It is essential for long-term proliferative capacity and genomic stability in cell types that require extensive self-renewal. The enzyme contains a catalytic protein subunit, human telomerase reverse transcriptase (hTERT), and an intrinsic RNA component (hTR/TERC) that provides the template for repeat synthesis. In humans, telomerase activity is robust in germline cells, many stem/progenitor compartments, and most cancers, whereas it is typically low or undetectable in differentiated somatic tissues (20,21).

Evidence indicates that telomerase activity can be detected in select somatic contexts such as intestinal mucosa, thymus, and subsets of peripheral blood lymphocytes, consistent with their proliferative demands. In these settings, hTERT expression is generally low but

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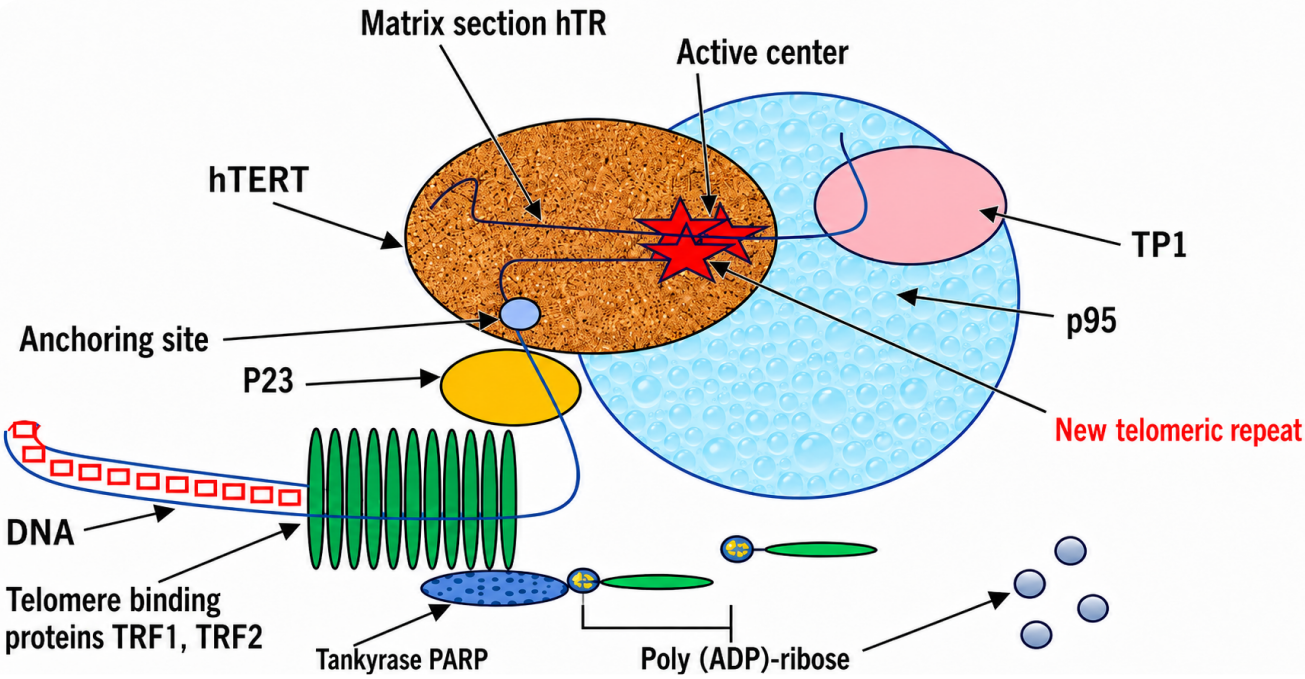

Figure 4. Schematic interaction of telomeric DNA with telomeric repeat binding factors (TRF1/TRF2) and associated components, including the catalytic subunit hTERT; PARP/tankyrase interactions are indicated (20)

measurable (20). Dysregulation of telomerase has been implicated in both malignant transformation and age-related degenerative conditions: telomerase reactivation supports cancer cell immortality, whereas insufficient telomerase activity can contribute to premature telomere shortening and increased vulnerability to chronic disease (7,21,22).

At chromosome ends, telomeric DNA is protected by the shelterin complex, comprising TIN2, TRF1, RAP1, TRF2, POT1, and TPP1. These proteins coordinate end protection, regulate access of DNA damage response (DDR) machinery, and control telomerase recruitment and processivity. In particular, POT1 binds single stranded telomeric DNA, whereas TRF1 and TRF2 bind double stranded repeats; TPP1 contributes to telomerase recruitment through interactions with hTERT and by facilitating alignment of the RNA template with the 3-prime overhang. Loss of shelterin components can uncap telomeres, triggering a DDR that enforces cell cycle arrest and prevents catastrophic chromosome fusion events, a major source of genomic instability (21).

Because telomerase is absent or expressed at very low levels in most normal somatic tissues, pharmacologic telomerase inhibition has been explored as a potentially selective anticancer strategy relative to conventional cytotoxic chemotherapy. Conversely, telomerase activation has been proposed as a potential therapeutic approach for certain telomere-shortening syndromes and age-related conditions, although such strategies require careful evaluation because of the inherent oncogenic risks associated with telomerase upregulation (21).

Telomeres and Cancer

Maintenance of tissue homeostasis in multicellular organisms requires tight regulation of cell proliferation, differentiation, and death. Cancer arises from the accumulation of genetic and epigenetic alterations that enable cells to proliferate uncontrollably, invade surrounding tissues, and metastasize to distant organs. One of the enabling hallmarks of malignant progression is the acquisition of replicative immortality, a process intimately linked to telomere maintenance mechanisms (23). Lifestyle factors such as smoking, chronic stress, physical inactivity, obesity, and exposure to environmental pollutants have been associated with accelerated telomere shortening and may contribute to the earlier onset of age-related diseases, including

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heart disease, heart failure, osteoporosis, diabetes, and cancer (19). The connection between telomere biology and oncogenesis was reinforced by observations that telomerase activity can be detected in approximately 90% of tumor samples, suggesting that telomerase reactivation is a common feature of human cancers (18).

Blackburn and colleagues described their 1978 discovery of tandemly repeated telomeric sequences in Tetrahymena and yeast as curiosity driven work with no obvious medical implications at the time (24). Subsequent identification of the human telomeric repeat in 1988 linked telomere biology directly to human aging and cancer research. Olovnikov's end-replication theory predicted progressive telomere shortening in somatic cells, later confirmed in telomerase-deficient human cell cultures. These findings established that critically short telomeres restrict proliferation, whereas telomerase reactivation restores replicative capacity, conferring a growth advantage to tumor cells (15).

Kim and colleagues developed the PCR-based telomeric repeat amplification protocol (TRAP) assay to sensitively measure telomerase activity in cell lines and tissues. Using this assay, they reported detectable telomerase activity in the vast majority of tumor derived or immortalized cell lines, whereas normal somatic cell cultures generally lacked detectable activity. Tissues for which both normal and tumor cell types were evaluated include skin, breast, lung, cervix, bladder, and prostate. Across all of these tissues, telomerase activity was consistently detected at high levels in tumor cells, whereas normal counterparts showed no detectable activity. Overall, these findings indicate that telomerase expression is present in most malignant tumor samples, consistent with tight repression in normal somatic tissues and activation during malignant progression (25).

Therapeutic strategies targeting telomerase in cancer have been explored through multiple approaches (23,26,27). One experimental concept involves forcing telomerase to synthesize mutant telomeric DNA by altering the RNA template, thereby disrupting binding of sequence specific telomere protective proteins and functionally uncapping chromosome ends. In MCF-7 breast cancer cells, expression of mutant template telomerase RNA induced a robust apoptotic response, highlighting how telomere uncapping can engage potent cell death programs (28). An alternative strategy targets telomerase activity or telomere synthesis to enforce progressive telomere attrition until replicative senescence or apoptosis is triggered. This can be accomplished through dominant-negative hTERT variants that disrupt catalytic function or via agents that directly inhibit telomeric DNA elongation without altering telomerase ribonucleoprotein abundance. These interventions induce predictable telomere erosion followed by proliferative arrest and/or cell death (28). In vivo evidence further supports therapeutic targeting of telomerase RNA, as ribozyme-mediated knockdown in melanoma models significantly reduced pulmonary metastatic burden after systemic delivery (29).

The relationship between telomere length and cancer risk has been evaluated in large-scale population studies. In a comprehensive meta-analysis published in 2016, Zhu et al. evaluated data from 51 independent studies, including a total of 68,792 controls and 23,379 cancer cases (Table 1). They assessed the associations using either fixed effects or random effects models, depending on the level

Table 1. Cancer risk by telomere length: Pooled relative risk (95% CI) (30)

Cancer Type	Cases (Short/Total)	Controls (Short/Total)	Odds Ratio (95% CI)
Skin cancer	1448 / 2799	2596 / 4888	1.17 (0.83–1.66)
Tumors of urogenital system	1549 / 3160	1914 / 3803	0.99 (0.82–1.20)
Gastrointestinal tumor	2461 / 3937	2640 / 5146	1.62 (1.33–1.97)
Breast cancer	2205 / 4270	2530 / 4869	0.96 (0.78–1.19)
Lung cancer	1391 / 2806	1465 / 2821	0.91 (0.63–1.31)
Head and Neck cancer	286 / 509	499 / 1156	1.86 (1.23–2.82)
Lymphoma	258 / 561	283 / 561	1.31 (0.44–3.84)
Other types of cancer	12554 / 23379	34573 / 68792	1.10 (0.98–1.23)

Model: Random-effects (Mantel–Haenszel method), Heterogeneity: $Chi^2 = 581.36$; df = 61; $P < 0.00001$; $I^2 = 90\%$, Test for overall effect: $Z = 1.68$; $P = 0.09$

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of heterogeneity, and performed cancer type–specific analyses because heterogeneity varied substantially across different tumor types. Overall cancer risk was not significantly associated with telomere length; however, shorter telomeres were associated with increased risks of gastrointestinal tumors and head and neck cancer. Notably, in prospective studies, short telomeres were associated with a reduced risk of lung cancer. Dose response analyses also suggested a modest increase in overall cancer risk with shorter telomeres, with stronger effects for gastrointestinal and head and neck cancers (30).

The Telomere Paradox: A Dual Role in Aging and Cancer

Telomere biology exhibits a paradoxical relationship with aging and cancer. Progressive telomere shortening limits cellular proliferation, thereby acting as a tumor-suppressive mechanism by triggering replicative senescence and apoptosis (31). However, the same mechanism contributes to tissue degeneration, impaired regenerative capacity, and age-related functional decline. Conversely, telomerase reactivation prevents telomere attrition and supports tissue renewal, yet this advantage comes at the cost of enabling replicative immortality, a hallmark of malignant transformation (32,33). This duality positions telomere maintenance as a double-edged sword, where both excessively short and abnormally stabilized telomeres can increase disease susceptibility depending on cellular context, tissue type, and genetic background (30). Therefore, telomere length should not be interpreted as a linear biomarker of either aging or cancer risk, but rather as a context-dependent determinant shaped by oxidative stress, inflammation, lifestyle exposures, and telomerase regulation (34).

Progressive telomere shortening promotes replicative senescence and limits cellular proliferation, contributing to aging phenotypes and degenerative disorders (35). At the same time, telomere erosion acts as a tumor-suppressive barrier by restricting uncontrolled proliferation. In contrast, telomerase reactivation and alternative telomere lengthening (ALT) mechanisms

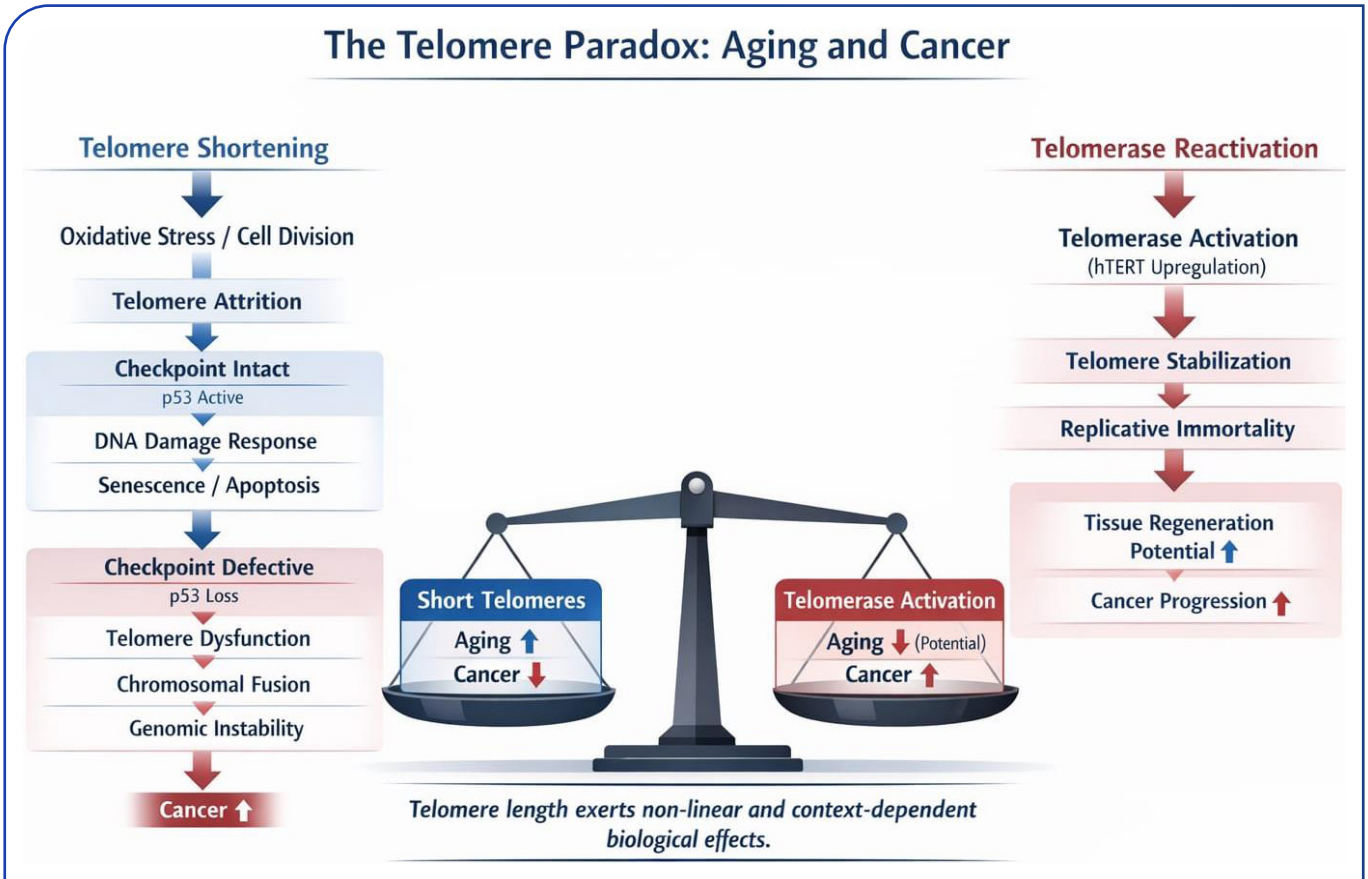

Figure 5. Conceptual model of the telomere paradox linking aging and cancer risk

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stabilize telomeres, enhance regenerative capacity, and promote cellular immortality, thereby facilitating oncogenesis (36). The net outcome depends on tissue context, oxidative stress burden, inflammatory status, and genetic predisposition (34).

observations support the concept that telomere length should be interpreted as a dynamic and context-dependent biomarker rather than a universal predictor of aging or malignancy (39,40). This non-linear model may help explain why population-based studies report

Table 2. Context-dependent relationship between telomere length, aging, and cancer

Telomere Status	Cellular Outcome	Aging Consequence	Cancer Risk Consequence	Clinical/Population Evidence
Physiological telomere length	Normal replication capacity	Normal tissue renewal	Baseline cancer risk	Healthy population distribution
Moderately shortened telomeres	Reduced proliferative reserve	Early tissue aging, immunosenescence	Variable (context-dependent)	Seen in aging immune compartments
Critically short telomeres	Senescence/apoptosis, DDR activation	Degeneration, stem cell exhaustion	Reduced risk initially (growth arrest barrier)	Tumor-suppressive checkpoint
Critically short telomeres + defective checkpoints (e.g., p53/Rb loss)	Chromosomal fusion and instability	Accelerated aging phenotypes	Increased risk (instability-driven transformation)	Observed in many premalignant contexts
Telomerase reactivation (hTERT upregulation)	Replicative immortality	Possible regeneration advantage	Increased risk (hallmark of cancer)	Telomerase active in ~90% tumors (approximate)
ALT activation	Telomere stabilization via recombination	Unclear systemic aging effect	Increased risk in a subset of tumors	ALT reported in subsets such as sarcoma and glioma
Long telomeres in somatic tissues	High proliferative potential	Potential delayed senescence	May increase risk in some cancers	Mixed results across population studies
Oxidative stress-driven shortening	DNA damage plus telomere erosion	Aging acceleration	May increase initiation risk	Linked to smoking, obesity, chronic stress in observational studies

Telomere Length as a Non-Linear Biomarker

Although telomere shortening is widely considered a biomarker of biological aging, evidence suggests that the relationship between telomere length and cancer risk is not linear (37). Extremely short telomeres may reduce tumor development by enforcing senescence, whereas intermediate shortening combined with impaired DNA damage checkpoints may promote chromosomal instability and malignant transformation (38). Furthermore, telomerase reactivation, while potentially beneficial for cellular longevity, supports replicative immortality and tumor progression. These heterogeneous associations between telomere length and cancer risk across tumor types.

CONCLUSION

Since their initial description, telomeres have remained central to biological research because of their essential role in safeguarding chromosome ends and regulating cellular replicative capacity. Accumulating evidence has firmly linked telomere attrition and telomerase regulation to fundamental mechanisms underlying both aging and carcinogenesis. Although oxidative stress, glycation, and other forms of molecular damage contribute to

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telomere erosion and age-related functional decline, telomere dynamics provide an integrative framework that connects cell division history with senescence, tissue homeostasis, and genomic stability. Importantly, the relationship between telomere length and cancer is neither linear nor uniform, as population-based studies reveal substantial heterogeneity across tumor types.

Critically short telomeres may function as tumor-suppressive barriers under intact checkpoint control, yet promote genomic instability when cellular safeguards fail. Conversely, telomerase reactivation stabilizes telomeres and sustains proliferative capacity, enabling replicative immortality while potentially influencing regenerative processes. These dual and context-sensitive effects define the telomere paradox, emphasizing that telomere biology must be interpreted within specific cellular and disease contexts. Clarifying this dynamic balance will be essential for translating telomere- and telomerase-targeted strategies into safe and effective interventions for age-related disorders and cancer.

Future Perspectives

Future research should focus on resolving the heterogeneity underlying telomere length–cancer associations by integrating tissue-specific telomere dynamics, telomerase activity profiling, genetic background, and environmental exposures. Particular attention should be directed toward defining the critical thresholds at which telomere shortening shifts from functioning as a tumor-suppressive barrier to acting as a driver of genomic instability and malignant progression.

The conceptual framework proposed in this review provides a basis for examining these transitions within the context of telomere duality. The development of safe telomerase-modulating strategies will require carefully balancing potential regenerative benefits against oncogenic risk, underscoring the importance of precision medicine–based approaches in targeting telomere biology.

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