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Telomeres, lifestyle, cancer, and aging

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Abstract

Purpose of review—There has been growing evidence that lifestyle factors may affect the health and lifespan of an individual by affecting telomere length. The purpose of this review was to highlight the importance of telomeres in human health and aging and to summarize possible lifestyle factors that may affect health and longevity by altering the rate of telomere shortening.

Recent findings—Recent studies indicate that telomere length, which can be affected by various lifestyle factors, can affect the pace of aging and onset of age-associated diseases.

Summary—Telomere length shortens with age. Progressive shortening of telomeres leads to senescence, apoptosis, or oncogenic transformation of somatic cells, affecting the health and lifespan of an individual. Shorter telomeres have been associated with increased incidence of diseases and poor survival. The rate of telomere shortening can be either increased or decreased by specific lifestyle factors. Better choice of diet and activities has great potential to reduce the rate of telomere shortening or at least prevent excessive telomere attrition, leading to delayed onset of age-associated diseases and increased lifespan. This review highlights the role of telomeres in aging and describes the lifestyle factors which may affect telomeres, human health, and aging.

Keywords

aging; cancer; lifestyle; oxidative stress; telomere

Introduction

Telomeres, the specific DNA–protein structures found at both ends of each chromosome, protect genome from nucleolytic degradation, unnecessary recombination, repair, and interchromosomal fusion. Telomeres therefore play a vital role in preserving the information in our genome. As a normal cellular process, a small portion of telomeric DNA is lost with each cell division. When telomere length reaches a critical limit, the cell undergoes senescence and/or apoptosis. Telomere length may therefore serve as a biological clock to determine the lifespan of a cell and an organism. Certain agents associated with specific lifestyles may expedite telomere shortening by inducing damage to DNA in general or more specifically at telomeres and may therefore affect health and lifespan of an individual. In this review we highlight the lifestyle factors that may adversely affect health and lifespan of an individual by accelerating telomere shortening and also those that can potentially protect telomeres and health of an individual.

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Structure and function of telomeres

Telomeres, the DNA–protein complexes at chromosome ends (Fig. 1), protect genome from degradation and interchromosomal fusion. Telomeric DNA is associated with telomere-binding proteins and a loop structure mediated by TRF2 protects the ends of human chromosomes against exonucleolytic degradation [1], and may also prime telomeric DNA synthesis by a mechanism similar to 'gap filling' in homologous recombination [2]. As shown in Fig. 2, telomere shortening occurs at each DNA replication, and if continued leads to chromosomal degradation and cell death [3]. Telomerase activity, the ability to extend telomeres, is present in germline and certain hematopoietic cells, whereas somatic cells have low or undetectable levels of this activity and their telomeres undergo a progressive shortening with replication (Fig. 2). Telomerases are reactivated in most cancers and immortalized cells. However, a subset of cancer/immortalized cells lack telomerase activity and maintain telomere length by alternative mechanisms, probably involving genetic (homologous) recombination [4], which is elevated in most immortal/cancer cell lines [5]. We have found that telomerase physically interacts with recombinase family of proteins and inhibitors of homologous recombination reducing telomere length in telomerase positive Barrett's adenocarcinoma cells (unpublished data from our laboratory). This suggests that recombinational repair is closely connected to telomere maintenance.

Telomere shortening, cancer, and aging

Telomeres shorten with age and rate of telomere shortening may indicate the pace of aging.

Telomere length decreases with age and may predict lifespan

Normal diploid cells lose telomeres with each cell division and therefore have a limited lifespan in culture. Human liver tissues have been reported to lose 55 base pairs of telomeric DNA per year [6]. Rate of telomere shortening in rapidly renewing gastric mucosal cells is also similar to that observed for liver tissue. The expression of stathmin and EF-1a, the biomarkers for telomeric dysfunction and DNA damage in a cell, increases with age and age-related diseases in humans [7,8]. Telomere length negatively correlates with age whereas the expression of p16, which increases in aging cells, positively correlates with age [7,8].

Accelerated telomere shortening in genetic disorder dyskeratosis congenital is associated with an early onset of several age-associated disorders and reduced lifespan. Telomerase activity, the ability to add telomeric repeats to the chromosome ends, is present in germline, hematopoietic, stem, and certain other rapidly renewing cells but extremely low or absent in most normal somatic cells. Transgenic induction of a telomerase gene in normal human cells extends their lifespan [9]. Cawthon *et al.* [10] showed that individuals with shorter telomeres had significantly poor survival due to higher mortality rate caused by heart and infectious diseases. Progressive shortening of telomeres leads to senescence, apoptotic cell death, or oncogenic transformation of somatic cells in various tissues. Telomere length, which can be affected by various lifestyle factors, may determine overall health, lifespan, and the rate at which an individual is aging [11•].

Accelerated telomere shortening may increase the pace of aging

As a normal cellular process, telomere length decreases with age [12,13]. Telomere length in humans seems to decrease at a rate of 24.8–27.7 base pairs per year [12,13]. Telomere length, shorter than the average telomere length for a specific age group, has been associated with increased incidence of age-related diseases and/or decreased lifespan in humans [10,14,15]. Telomere length is affected by a combination of factors including donor age [16], genetic, epigenetic make-up and environment [17–20], social and economic status

[21,22], exercise [21], body weight [12,23], and smoking [12,24]. Gender does not seem to have any significant effect on the rate of telomere loss [13]. When telomere length reaches below a critical limit, the cells undergo senescence and/or apoptosis [25,26].

Certain lifestyle factors such as smoking, obesity, lack of exercise, and consumption of unhealthy diet can increase the pace of telomere shortening, leading to illness and/or premature death. Accelerated telomere shortening is associated with early onset of many age-associated health problems, including coronary heart disease [27–29], heart failure [30], diabetes [31], increased cancer risk [32,33], and osteoporosis [34]. The individuals whose leukocyte telomeres are shorter than the corresponding average telomere length have three-fold higher risk to develop myocardial infarction [13]. Evaluation of telomere length in elders shows that the individuals with shorter telomeres have a much higher rate of mortality than those with longer telomeres [10]. Excessive or accelerated telomere shortening can affect health and lifespan at multiple levels. Shorter telomeres can also induce genomic instability [35,36] by mediating interchromosomal fusion and may contribute to telomere stabilization and development of cancer [36,37]. Consistently, telomerase activity in most cancer cells is elevated whereas telomere length is shorter, relative to corresponding control cells. We have shown that telomere length is shorter in cancer cell lines and primary cancer cells purified by laser capture microdissection [38,39]. However, inhibition of telomere maintenance mechanisms and continued telomere shortening induces senescence and/or apoptosis in immortal/cancer cells [38–46].

Several studies indicate that shorter telomeres are a risk factor for cancer. Individuals with shorter telomeres seem to have a greater risk for development of lung, bladder, renal cell, gastrointestinal, and head and neck cancers [32,33]. Certain individuals may also be born with shorter telomeres or may have genetic disorder leading to shorter telomeres. Such individuals are at a greater risk to develop premature coronary heart disease [13,28] and premature aging. Deficiency of telomerase RNA gene in a genetic disorder dyskeratosis congenita leads to shorter telomeres and is associated with premature graying, predisposition to cancer, vulnerability to infections, progressive bone marrow failure, and premature death in adults [47].

Impact of smoking and obesity on telomeres and aging

Smoking and obesity seem to have adverse effect on telomeres and aging.

Smoking may expedite telomere shortening and process of aging

Excessive telomere shortening can also lead to genomic instability [35,36] and tumorigenesis [36,37]. Consistently, the telomeres in most cancer cells are shorter relative to normal cells. Smoking is associated with accelerated telomere shortening [8]. The dosage of cigarette smoking is shown to negatively correlate with telomere length [8]. A dose-dependent increase in telomere shortening has been observed in blood cells of tobacco smokers [33,48]. A study conducted in white blood cells of women indicates that telomeric DNA is lost at an average rate of ‘25.7–27.7 base pairs’ per year and with daily smoking of each pack of cigarettes, an additional ‘5 base pairs’ is lost [12]. Therefore, the telomere attrition caused by smoking one pack of cigarettes a day for a period of 40 years is equivalent to 7.4 years of life [12]. Babizhayev *et al.* [11•] have proposed that telomere length can serve as a biomarker for evaluation of the oxidative damage caused by smoking and may also predict the rate at which an individual is aging. The authors also propose that oxidative damage leading to telomere shortening can be prevented by antioxidant therapy [11•]. In summary, the smoking increases oxidative stress, expedites telomere shortening, and may increase the pace of aging process.

Obesity is associated with excessive telomere shortening

Obesity is also associated with increased oxidative stress and DNA damage. Furukawa *et al.* [49] showed that the waist circumference and BMI significantly correlate with the elevated plasma and urinary levels of reactive oxygen species. Song *et al.* [8] have shown that BMI strongly correlates with biomarkers of DNA damage, independent of age. The obesity related increased oxidative stress is probably due to a deregulated production of adipocytokines. Obese KKAy mice display higher plasma levels of reactive oxygen species and lipid peroxidation, relative to control C57BL/6 mice [49]. The elevated levels of reactive oxygen species in obese mice were detected in white adipose tissue but not in other tissues, indicating that the oxidative stress detected in plasma could be attributed to oxidizing agents produced in the fat tissue. Moreover, the transcript levels and activities of antioxidant enzymes including catalase and dismutase were significantly lower in white adipose tissue of obese relative to control mice. The authors propose that a lack of antioxidant defense and elevated NADPH oxidase pathway in accrued fat probably led to increased oxidative stress in obese animals. Oxidative stress can induce DNA damage and may therefore expedite telomere shortening. Telomeres in obese women have been shown to be significantly shorter than those in lean women of the same age group [12]. The excessive loss of telomeres in obese individuals was calculated to be equivalent to 8.8 years of life, an effect which seems to be worse than smoking. Together these data indicate that obesity has a negative impact on telomeres and may unnecessarily expedite the process of aging.

Impact of environment, nature of work, and stress on telomeres and aging

Environment, nature of profession, and stress can also affect the rate of telomere shortening and health.

Exposure to harmful agents and nature of profession may affect telomere shortening

Hoxha *et al.* [50•] evaluated telomere length in the leukocytes derived from office workers and traffic police officers exposed to traffic pollution. Exposure to pollution was indicated by the levels of toluene and benzene. The investigators found that telomere length in traffic police officers was shorter within each age group, relative to telomere length in office workers. Similarly the lymphocytes of coke-oven workers, exposed to polycyclic aromatic hydrocarbons, had significantly shorter telomeres and increased evidence of DNA damage and genetic instability, relative to control subjects [51••]. Reduction in telomere length in these workers, although did not correlate with age and markers of DNA damage, significantly correlated with the number of years the workers were exposed to harmful agents. Telomere attrition has been associated with increased cancer risk [32,33] and coke-oven workers are at a greater risk to develop lung cancer. Telomere attrition in lymphocytes is also associated with aging [16]. Consistently, the reduced telomere length in the lymphocytes of coke-oven workers was also associated with hypomethylation of p53 promoter [51••], which may induce the expression of p53 [52], leading to inhibition of growth or induction of apoptosis [36]. Thus the exposure to genotoxic agents, which may induce damage to DNA in general or more extensively at telomeres, can increase cancer risk and pace of aging.

Stress increases the pace of telomere shortening and aging

The stress is associated with release of glucocorticoid hormones by the adrenal gland. These hormones have been shown to reduce the levels of antioxidant proteins [53] and may therefore cause increased oxidative damage to DNA [54] and accelerated telomere shortening [55]. Consistently, the women, exposed to stress in their daily life, had evidence of increased oxidative pressure, reduced telomerase activity, and shorter telomeres in peripheral blood mononuclear cells, relative to the women in the control group [56].

Importantly, the difference in telomere length in these two groups of women was equivalent to 10 years of life, indicating that the women under stress were at a risk for early onset of age-related health problems. Because telomere length may indicate an individual's biological age, the stress would adversely affect health and longevity.

Impact of diet, dietary restriction, and exercise on telomeres and aging

What we eat and how much we eat can significantly affect our telomeres, health, and longevity.

Impact of fiber, fat, and protein on telomeres

Cassidy *et al.* [57••] studied the association of leukocyte telomere length with various lifestyle factors in a relatively large group of women. Telomere length positively correlated with dietary intake of fiber and negatively associated with waist circumference and dietary intake of polyunsaturated fatty acids, especially linoleic acid. Reduction in protein intake of food also seems to increase longevity. Reduction in the protein content of food by 40%, led to a 15% increase in the lifespan of rats. The rats subjected to a protein-restricted diet early in life displayed a long-term suppression of appetite, reduced growth rate, and increased lifespan [58,59], and the increased lifespan in such animals was associated with significantly longer telomeres in kidney [58]. Consistently, the highest life expectancy of Japanese is associated with low protein and high-carbohydrate intake in diet. The source of protein also seems to be an important factor as replacing casein with the soy protein in rats, is associated with delayed incidence of chronic nephropathies and increased lifespan.

Dietary intake of antioxidants reduces the rate of telomere shortening

A study by Farzaneh-Far *et al.* [60] indicates that a diet containing antioxidant omega-3 fatty acids is associated with reduced rate of telomere shortening, whereas a lack of these antioxidants correlates with increased rate of telomere attrition in study participants. The authors followed omega-3 fatty acid levels in blood and telomere length in these individuals over a period of 5 years and found an inverse correlation, indicating that antioxidants reduce the rate of telomere shortening. Similarly, the women who consumed a diet lacking antioxidants had shorter telomeres and a moderate risk for development of breast cancer, whereas the consumption of a diet rich in antioxidants such as vitamin E, vitamin C, and beta-carotene was associated with longer telomeres and lower risk of breast cancer [61]. Antioxidants can potentially protect telomeric DNA from oxidative damage caused by extrinsic and intrinsic DNA damaging agents.

Dietary restriction reduces the pace of aging

Dietary restriction or eating less has an extremely positive impact on health and longevity. Reducing food intake in animals leads to reduced growth rate [58,59], reduced oxidative burden and reduced damage to DNA [59], and therefore keeps the animals in a biologically younger state and can increase their lifespan by up to 66% [59]. It has been shown that dietary restriction in rodents delays the onset of age-associated diseases and increases the lifespan. Rats subjected to a protein-restricted diet early in life displayed a long-term suppression of appetite, reduced growth rate, and increased lifespan [58,59]. The increased lifespan in such animals was associated with significantly longer telomeres in kidney [58]. Because oxidative stress can substantially accelerate telomere shortening, the reduction in oxidative stress by dietary restriction is expected to preserve telomeres and other cellular components.

Exercise may preserve telomeres and reduce the pace of aging

Song *et al.* [8] have demonstrated that duration of exercise inversely correlates with biomarkers for damage to DNA and telomeres and with p16 expression, a biomarker for aging human cell. Exercise can reduce harmful fat and help mobilize waste products for faster elimination, leading to reduced oxidative stress and preservation of DNA and telomeres. Werner *et al.* [62•] showed that exercise was associated with elevated telomerase activity and suppression of several apoptosis proteins, including p53 and p16, in mice. Consistently, in humans the leukocytes derived from athletes had elevated telomerase activity and reduced telomere shortening, relative to nonathletes [62•]. Exercise seems to be associated with reduced oxidative stress and elevated expression of telomere stabilizing proteins and may therefore reduce the pace of aging and age-associated diseases.

Conclusion

Telomeres shorten with age and progressive telomere shortening leads to senescence and/or apoptosis. Shorter telomeres have also been implicated in genomic instability and oncogenesis. Older people with shorter telomeres have three and eight times increased risk to die from heart and infectious diseases, respectively. Rate of telomere shortening is therefore critical to an individual's health and pace of aging. Smoking, exposure to pollution, a lack of physical activity, obesity, stress, and an unhealthy diet increase oxidative burden and the rate of telomere shortening. To preserve telomeres and reduce cancer risk and pace of aging, we may consider to eat less; include antioxidants, fiber, soy protein and healthy fats (derived from avocados, fish, and nuts) in our diet; and stay lean, active, healthy, and stress-free through regular exercise and meditation. Foods such as tuna, salmon, herring, mackerel, halibut, anchovies, cat-fish, grouper, flounder, flax seeds, chia seeds, sesame seeds, kiwi, black raspberries, lingonberry, green tea, broccoli, sprouts, red grapes, tomatoes, olive fruit, and other vitamin C-rich and E-rich foods are a good source of antioxidants. These combined with a Mediterranean type of diet containing fruits, and whole grains would help protect telomeres.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 101–102).

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Key points

- Telomere length shortens with age.
- Rate of telomere shortening may indicate the pace of aging.
- Lifestyle factors such as smoking, lack of physical activity, obesity, stress, exposure to pollution, etc. can potentially increase the rate of telomere shortening, cancer risk, and pace of aging.
- Dietary restriction, appropriate diet (high fiber, plenty of antioxidants, lean/low protein, adding soy protein to diet), and regular exercise can potentially reduce the rate of telomere shortening, disease risk, and pace of aging.

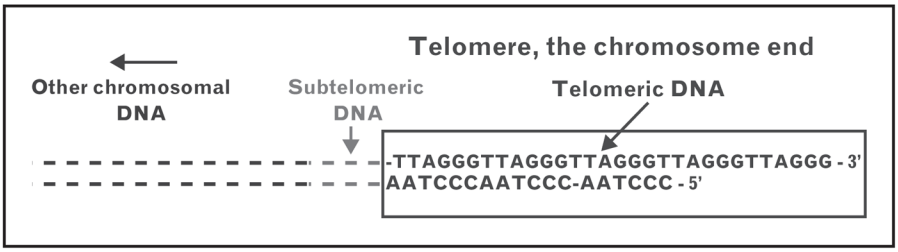

Figure 1. Telomeres, the DNA–protein structures which protect chromosomes

Our chromosomes end with repeats of conserved 'TTAGGG' sequence. These sequences interact with specific proteins and attain a looped conformation which protects chromosomal DNA from degradation. The length of telomeric DNA shortens with each cell division and when it reaches below a critical limit, the cell undergoes replicative senescence or apoptotic cell death. The length of telomeric DNA determines the lifespan of a cell in culture.

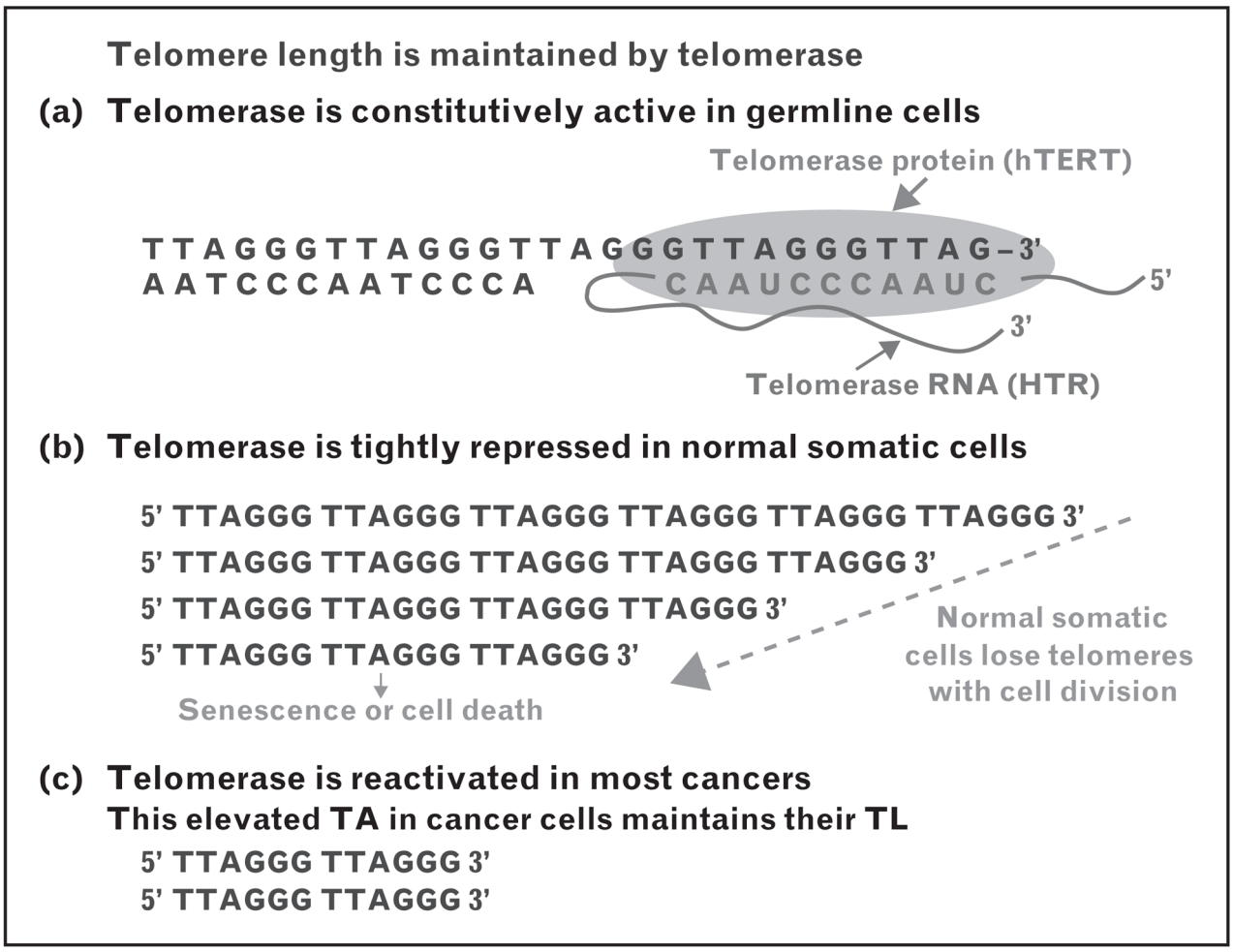

Figure 2. Length of telomeric DNA is important for lifespan of a cell

(a) Telomere length can be prevented from shortening by an enzyme Telomerase. Telomerase has a protein subunit (hTERT) and an RNA subunit (hTR). This enzyme is active in germline and stem cells and maintains their telomere length by adding 'TTAGGG' repeats to the ends of chromosomes. Therefore, telomeres do not shorten in these types of cells. (b) Telomerase is inactive in normal somatic cells. These cells, therefore, lose telomeres over time and when telomere length reaches below a critical limit, cells either senesce or die. (c) In the absence of appropriate signals for senescence or apoptotic death, continued cell division leads to severe telomere shortening and genomic instability. Although rare, but cells which survive this crisis, activate a telomere maintenance mechanism (either telomerase or homologous recombination-based ALT) and may become oncogenic. Therefore, most cancer cells have very short but stable telomeres. TA, telomere attrition; TL, telomere length.