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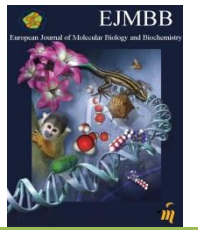

ARE TELOMERES --THE KEY TO IMMORTALITY?

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ABSTRACT
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.

INTRODUCTION

Telomeres, the specific DNA–protein structures found at both ends of each chromosome, protect genome from nucleolytic degradation, unnecessary recombination, repair, and inter chromosomal 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 [1]. 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 [2].

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Background

Telomeres, the DNA–protein complexes at chromosome ends 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 and may also prime telomeric DNA synthesis by a mechanism

similar to 'gap filling' in homologous recombination Telomere shortening occurs at each DNA replication, and if continued leads to chromosomal degradation and cell death . 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. 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, which is elevated in most immortal/cancer cell lines. 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.

Inside the nucleus of a cell, our genes are arranged along twisted, double-stranded molecules of DNA called chromosomes. At the ends of the chromosomes are stretches of DNA called telomeres, which protect our genetic data, make it possible for cells to divide, and hold some secrets to how we age and get cancer [3-5].

Telomeres have been compared with the plastic tips on shoelaces, because they keep chromosome ends from fraying and sticking to each other, which would destroy or scramble an organism's genetic information.

Yet, each time a cell divides, the telomeres get shorter. When they get too short, the cell can no longer divide; it becomes inactive or "senescent" or it dies. This shortening process is associated with aging, cancer, and a higher risk of death. So telomeres also have been compared with a bomb fuse. Like the rest of a chromosome, including its genes, telomeres are sequences of DNA — chains of chemical code. Like all DNA, they are made of four nucleic acid bases: G for guanine, A for adenine, T for thymine, and C for cytosine.

Telomeres are made of repeating sequences of TTAGGG on one strand paired with AATCCC on the other strand. Thus, one section of telomere is a "repeat" made of six "base pairs."

In white blood cells, the length of telomeres ranges from 8,000 base pairs in newborns to 3,000 base pairs in adults and as low as 1,500 in elderly people. (An entire chromosome has about 150 million base pairs.) Each time it divides, an average cell loses 30 to 200 base pairs from the ends of its telomeres. Cells normally can divide only about 50 to 70 times, with telomeres getting progressively shorter until the cells become senescent or die. Telomeres do not shorten in tissues where cells do not continually divide, such as heart muscle.

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. 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. 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. Telomere length negatively correlates with age whereas the expression of p16, which increases in aging cells, positively correlates with age.

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. Cawthon *et al* 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 [5-7].

DISCUSSION

Accelerated telomere shortening may increase the pace of aging

As a normal cellular process, telomere length decreases with age Telomere length in humans seems to decrease at a rate of 24.8–27.7 base pairs per year 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 Telomere length is affected by a combination of factors including donor age genetic, epigenetic make-up

and environment social and economic status exercise body weight and smoking Gender does not seem to have any significant effect on the rate of telomere loss When telomere length reaches below a critical limit, the cells undergo senescence and/or apoptosis

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 heart failure , diabetes increased cancer risk and osteoporosis The individuals whose leukocyte telomeres are shorter than the corresponding average telomere length have three-fold higher risk to develop myocardial infarction 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 Excessive or accelerated telomere shortening can affect health and lifespan at multiple levels. Shorter telomeres can also induce genomic instability by mediating interchromosomal fusion and may contribute to telomere stabilization and development of cancer 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 However, inhibition of telomere maintenance mechanisms and continued telomere shortening induces senescence and/or apoptosis in immortal/cancer cells.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 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 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 adultsImportance of having telomere in chromosome Without telomeres, the main part of the chromosome — the part with genes essential for life — would get shorter each time a cell divides. So telomeres allow cells to divide without losing genes. Cell division is necessary for growing new skin, blood, bone, and other cells [4-6].

Without telomeres, chromosome ends could fuse together and corrupt the cell's genetic blueprint, possibly causing malfunction, cancer, or cell death. Because broken DNA is dangerous, a cell has the ability to sense and repair chromosome damage. Without telomeres, the ends of chromosomes would look like broken DNA, and the cell would try to fix something that wasn't broken. That also would make them stop dividing and eventually die.

Telomeres get shorter each time a cell divide

Before a cell can divide, it makes copies of its chromosomes so that both new cells will have identical genetic material. To be copied, a chromosome's two DNA strands must unwind and separate. An enzyme (DNA polymerase) then reads the existing strands to build two new strands. It begins the process with the help of short pieces of RNA. When each new matching strand is complete, it is a bit shorter than the original strand because of the room needed at the end for this small piece of RNA. It is like someone who paints himself into a corner and cannot paint the corner.

Telomerase counteracts telomere shortening

An enzyme named telomerase adds bases to the ends of telomeres. In young cells, telomerase keeps telomeres from wearing down too much. But as cells divide repeatedly, there is not enough telomerase, so the telomeres grow shorter and the cells age.

Telomerase remains active in sperm and eggs, which are passed from one generation to the next. If reproductive cells did not have telomerase to maintain the length of their telomeres, any organism with such cells would soon go extinct.

Telomeres and Cancer

As a cell begins to become cancerous, it divides more often, and its telomeres become very short. If its telomeres get too short, the cell may die. Often times, these cells escape death by making more telomerase enzyme, which prevents the telomeres from getting even shorter.

Many cancers have shortened telomeres, including pancreatic, bone, prostate, bladder, lung, kidney, and head and neck.

Measuring telomerase may be a way to detect cancer. And if scientists can learn how to stop telomerase, they might be able to fight cancer by making cancer cells age and die. In one experiment, researchers blocked telomerase activity in human breast and prostate cancer cells growing in the laboratory, prompting the tumor cells to die. But there are risks. Blocking telomerase could impair fertility; wound healing, and production of blood cells and immune system cells [6-8].

Role of telomeres in aging

Geneticist Richard Cawthon and colleagues at the University of Utah found shorter telomeres are associated with shorter lives. Among people older than 60, those with shorter telomeres were three times more likely to die from heart disease and eight times more likely to die from infectious disease.

While telomere shortening has been linked to the aging process, it is not yet known whether shorter

telomeres are just a sign of aging — like gray hair — or actually contribute to aging.

If telomerase makes cancer cells immortal, could it prevent normal cells from aging? Could we extend lifespan by preserving or restoring the length of telomeres with telomerase? If so, would that increase our risk of getting cancer?

Scientists are not yet sure. But they have been able to use telomerase in the lab to keep human cells dividing far beyond their normal limit, and the cells do not become cancerous.

If we used telomerase to "immortalize" human cells, we may be able to mass produce cells for transplantation, including insulin-producing cells to cure diabetes, muscle cells for treating muscular dystrophy, cartilage cells for certain kinds of arthritis, and skin cells for healing severe burns and wounds. An unlimited supply of normal human cells grown in the laboratory would also help efforts to test new drugs and gene therapies.

Telomere and other diseases

People with a disease named dyskeratosis congenita have telomeres that get short much more quickly than normal. These people endure premature aging and death. They face a higher risk of life-threatening infections, leukemia and other blood cancers, intestinal disorders, cirrhosis of the liver, and pulmonary fibrosis, a deadly stiffening of lung tissue. They also are more likely to endure gray hair, balding, poor wound healing, spots on the skin, intestinal disorders, softening of the bones, and learning disabilities. The implication is that telomeres may play a role in all those conditions, because they all involve tissues in which cells divide often. There also is some evidence linking shortened telomeres to Alzheimer disease, hardening of the arteries, high blood pressure, and type 2 diabetes [9-12].

Prospects for human immortality

Human lifespan has increased considerably since the 1600s, when the average lifespan was 30 years. By 2012, the average US life expectancy was nearly 79. Reasons for the increase include sewers and other sanitation measures, antibiotics, clean water, refrigeration, vaccines and other medical efforts to prevent children and babies from dying, improved diets, and better health care.

Some scientists predict average life expectancy will continue to increase, although many doubt the average will ever be much higher than 90. But a few say vastly longer lifespans are possible. Scientists say that if all processes of aging could be eliminated and oxidative stress damage could be repaired, "one estimate is people could live 1,000 year. 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 and tumorigenesis. Consistently, the telomeres in most cancer cells are shorter relative to normal cells. Smoking is associated with accelerated telomere shortening The dosage of cigarette smoking is shown to negatively correlate with telomere length A dose-dependent increase in telomere shortening has been observed in blood cells of tobacco smokers 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 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 Babizhayev *et al.* 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. 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.* showed that the waist circumference and BMI significantly correlate with the elevated plasma and urinary levels of reactive oxygen species. Song *et al.* 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. 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 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.

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.* 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 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 and coke-oven workers are at a greater risk to develop lung cancer. Telomere attrition in lymphocytes is also associated with aging. Consistently, the reduced telomere length in the lymphocytes of coke-oven workers was also associated with hypomethylation of p53 promoter which may induce the expression of p53, leading to inhibition of growth or induction of apoptosis 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 [12-15].

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 and may therefore cause increased oxidative damage to DNA and accelerated telomere shortening 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 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.

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.* 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 and the increased lifespan in such animals was associated with significantly longer telomeres in kidney. 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.* 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 Antioxidants can potentially protect telomeric DNA from oxidative damage caused by extrinsic and intrinsic DNA damaging agents.

Dietary restrictions have impact on health

Dietary restriction or eating less has an extremely positive impact on health and longevity. Reducing food intake in animals leads to reduced growth rate , 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]. The increased lifespan in such animals was associated with significantly longer telomeres in kidney. 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 the telomere

Song et al. 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. 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 non-athletes 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 [15-18].

Figure 1. Life expectancy at birth since last 4 decades Fig :Some factors in Aging

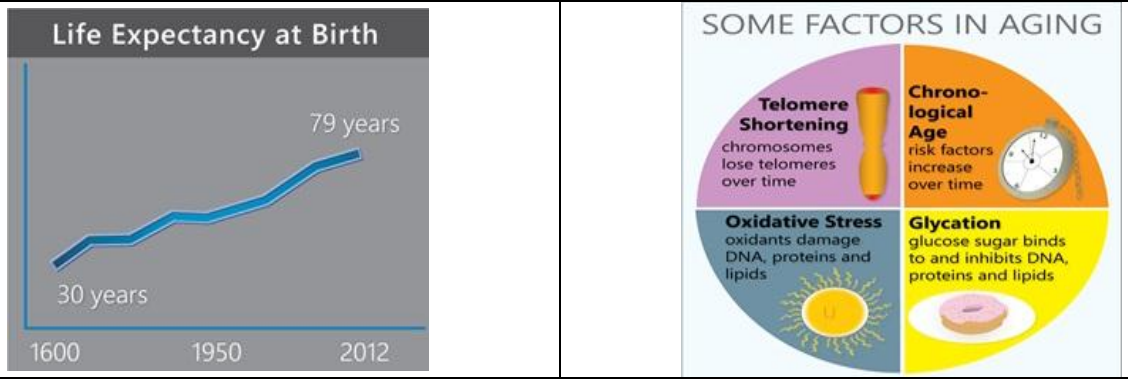
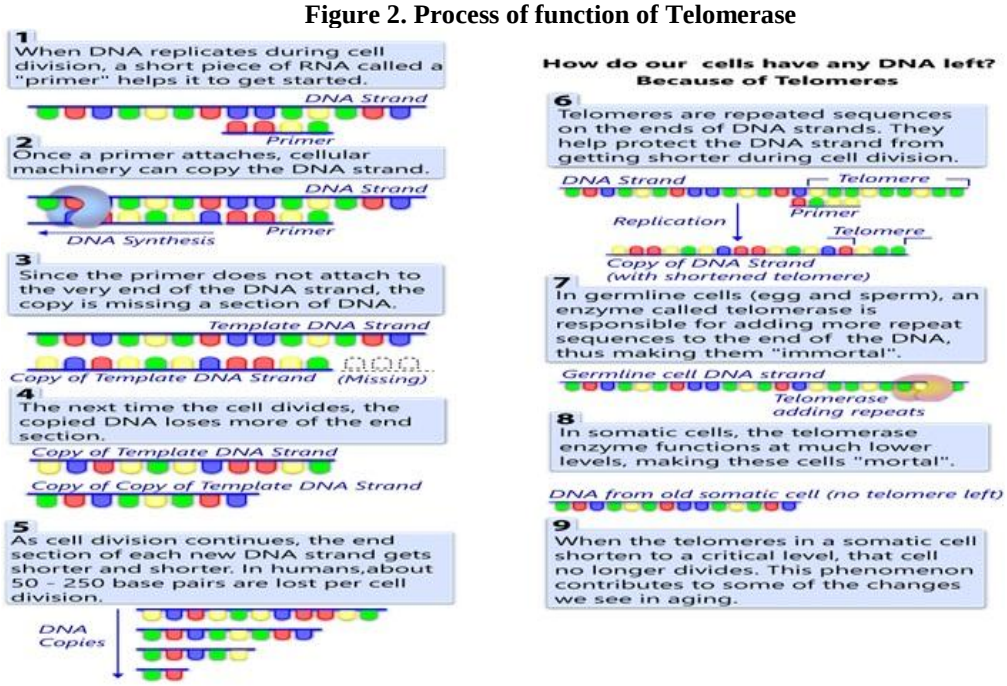


Figure 2. Process of function of Telomerase



CONCLUSIONS

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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