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# A Review of the Effects of Electromagnetic Fields on Telomere-Dependent Life Span in Human and Experimental Animal Models

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## ABSTRACT

**At current decade, electromagnetic fields (EMFs) and its beneficial or hazardous biological effects is subject of so many studies on human and animals. This paper reviews the effects of EMFs on telomere shortening throughout the life span of human and some animal models and also the importance of major antioxidants in reducing the damage caused by free radicals in the body under exposures. Some studies tried to show the role of oxidative stress in telomere shortening that inevitably directed biological experiments to the use of antioxidant vitamins for telomere stability. Based mainly on biological and epidemiological studies, *in vitro* experiments not only showed positive results with antioxidants, but *in vivo* studies are always getting attention, due to other biological factors that might influence the telomere shortening. Telomere length and telomerase activity assessed in animal cells, tissues and organs may determine telomere stability (off-again) and carcinogenesis (on-again) relationship and life span. In contrast to human, rodent telomeres are generally much longer and express telomerase in many tissues. The rapid death following reproduction observed in rodent especially mouse species is much different and so these model organisms are not a good representative of human aging mechanisms. However, the rat model might be more feasible than mice in studying the effect of oxidative stress and ageing. Animal models such as dogs, bird species, and cattle have been observed that does share more similarities in telomere and telomerase biology with humans, respectively. Although, investigations indicate that telomere length and telomerase activity can be a promising genetic biomarker for chronic oxidative stress caused by free radicals due to long-term exposure to environmental factors like EMFs as part of human daily lives, but there is a need for more research on the role of telomere shortening on inflammatory diseases progression, cancer and the various factors leading to cell senescence, such as heredity and other ageing.**

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## INTRODUCTION

Currently people live in an invisible but dangerous ocean of electromagnetic radiation. We believe that cellphones are unhealthy at any speed or we need to be aware of the adverse health effects of environmental factors so that we can have the choice of taking precautions against the exposures. There are critical following questions: What is the evidence that wireless and EMF radiations is dangerous and is disturbing biology and impacting our genetic material and DNA, our present functioning as well as potentially jeopardizing the health of future

generations? What mechanisms can explain the beneficial or hazardous biological effects and links to various conditions? How are the effects of EMFs on telomere shortening, telomerase activity and aging or life span? What is the importance of natural antioxidants, i.e., vitamins A, E and C in reducing the damage caused by free radicals in the body under exposures? Learn why use of time, distance and shielding in radiation protection is important and essential to preserve optimal functioning and fertility, while legal technological efforts are currently pursued to assure safer communications technologies. Hence, to response the questions, findings in this review can provide a better understanding of the subject matter and issues involved.

In this review, special attention is paid to the effects of environmental factors like EMFs on telomere attrition of human and some animal models and also the importance of natural antioxidants in reducing the damage caused by free radicals in the body under exposures.

## Detrimental effects of EMF on human and experimental animals

Nowadays, people are under exposure of various types of non-ionizing electromagnetic fields (EMF) that has increased due to wireless or the mobile handset and base station antennas. This new invisible environmental factor can affect gender, tissue density of the body, life span. The exposure levels to electromagnetic fields can penetrate the body and act on all the organs and tissues, altering the cell membrane potential and the distribution of ions and dipoles and therefore influencing the biochemical processes in the cell [1]. It has been reported that waves from the electromagnetic fields of cellular phones, can produce energy distribution and temperature in living tissues [2, 3]. In the long-term, these extremely low frequencies (ELFs) that are the International Telecommunication Union (ITU) designation for electromagnetic radiation (radio waves) with 3 to 30 Hz frequencies, and 100,000 to 10,000 kilometers wavelengths, respectively, cause some variations in the structure and biochemical properties of tissues [4, 5].

At current decade, EMFs and its hazardous or beneficial biological effects is subject of so many researches on human and animal models. In 2004-2005 some significant experiments has been conducted on the effects of EMFs on the nervous and endocrine systems [3, 5-7]. The results suggested that temperature is an important factor in the regulation of the release of endocrine hormones. For example, the activity of thyroid hormones increased under cold temperature and thyroid-stimulating hormone (TSH) secretion from the pituitary, and the release of T3 and T4 from the thyroid increased by acute psychological stress [8]. On the one hand, heat temperature is one of the wide varieties of factors which cause oxidative stress *in-vivo*.

It has been reported that EMFs and MFs cause an increase in lipolysis and glycogenolysis in adipose tissue of rodent model and also an increase in hormones such as thyroxin, glucagon and cortisol of particular interest as a stress indicator secreted by the adrenal glands [7, 10, 11]. Based on human studies of Radon et al. [12] it has been reported that exposure to EMF increased serum cortisol [12]. Vangelova et al. [13] reported significant high levels of stress hormones such as cortisol levels of physiotherapists and nurses due to long-term EMF exposure. The elevated levels of cortisol as a number one of public health enemy, have been known for years that interfere with lower immune function, bone density and learning and memory, increase weight gain, cholesterol, blood pressure, heart disease etc. However, the number of investigations on the negative long/short-term effects of EMFs on endocrine glands are still limited [9].

According to the studies about of biological effects of EMF emitted from cellular phones (GSM: 900MHz) on laboratory animals, it is reported that 900 MHz EMF make to change the rate of some endocrine hormones in the rats [9] and hamsters [14], also, It makes oxidative stress in the rats and rabbits [14, 15]. Lotfi and Shahryar [13] had showed that EMFs emitted by cellular phone can change serum testosterone and lipid concentrations in exposed male hamsters. Some of the related studies with different frequencies of EMF and magnetic fields (MF) showed that Magnetic fields (MFs) and EMFs may cause decrease in total cholesterol and triglyceride of plasma in human and laboratory animals [16-20]. Also, these effects were more significant in longer time period in exposure to MF and EMF [17, 19]. Although there have been many studies in the case of biological effects of EMF with different frequency and time periods, unfortunately it hasn't been studied any possible direct effects of cellular phone EMF (GSM: 900 MHz) on plasma lipids rate such as cholesterol and triglyceride.

Evidences of the hazardous effect of cellular phones on male fertility are still equivocal as studies have revealed a wide spectrum of possible of testicular damage [21]. Shahryar et al. [14] had reported exposure to cellular phones EMF can elevate sex hormone (testosterone) in male hamsters and also can changes secondary sex ratio [22]. It seems that the effects of mobile phones and EMF on progesterone and stress hormone such as cortisol and especially on telomere shortening and life span were not clearly studied in rodent, while more studies were performed on birds or other animal models. Exposure to EMF was studied in poultry at pre-incubation [23], during-

incubation [24, 25] or post-incubation [26]. It has been well documented that when conditions were optimal, chick embryos developed normally and hatched in approximately 21 d [17], but hatchery factors includes turning, vital gas exchange, temperature, humidity and other environmental factors [28] have been shown to affect embryo growth.

The environmental factors that are critical to the development of the embryo occur during the incubation and hatching processes and any alterations in these processes influences the metabolism and growth of embryos with possible consequent at post-hatch life and affect finishing outcome via changes in the efficiency of nutrient metabolism and utilization [29-30]. At current decade, researchers have done focused on other environmental factors in hatching process such as light color [29], electric fields [30] and electromagnetic fields (EMF) [24, 25].

During rearing period, regardless to hazardous effects of fields, EMFs could apply as anti-coccidiosis agent [31]. During incubation, embryonic exposure to EMFs had detrimental effects on embryo development and hatching results [25, 32]. Along with negative effect of EMFs on development, various studies had reported significant [33] or not significant [34] effects of EMFs (50-60 Hz) on organ weight in mammalian models. It seems that late stage exposure to EMF caused slow proliferation and morphogenesis in liver [35]. As regards internal organs, in mammalian model, Erpek et al. [34] had reported that liver weight didn't have significant change in exposure to 50 Hz, 6 mT for two months, 2 h daily. In hatchery experiments, Shafey et al. [30] reported lower proportions of liver plus heart plus gizzard in chicks exposed to electric fields when compared with those of the control birds.

### Telomerase activity, Telomere shortening and aging

Telomerase is a ribonucleoprotein that is an enzyme which adds DNA sequence repeats ("TTAGGG" in all vertebrates) to the 3' end of DNA strands in the telomere regions, which are found at the ends of eukaryotic chromosomes. This region of repeated nucleotide called telomeres contains noncoding DNA and hinders the loss of important DNA from chromosome ends. As a result, every time the chromosome is copied only 100–200 nucleotides are lost, which causes no damage to the organism's DNA. Telomerase is a reverse transcriptase that carries its own RNA molecule, which is used as a template when it elongates telomeres, which are shortened after each replication cycle. Under normal circumstances, telomerase become shorter and shorter with each cycle of cell division. A sufficiently short telomere is believed to signal the cells to stop dividing. In the case of eukaryotic organisms, telomerases are composed of an accumulation of repeated defined nucleotide sequences (repeats), which for example contain the sequence TTAGGG in humans.

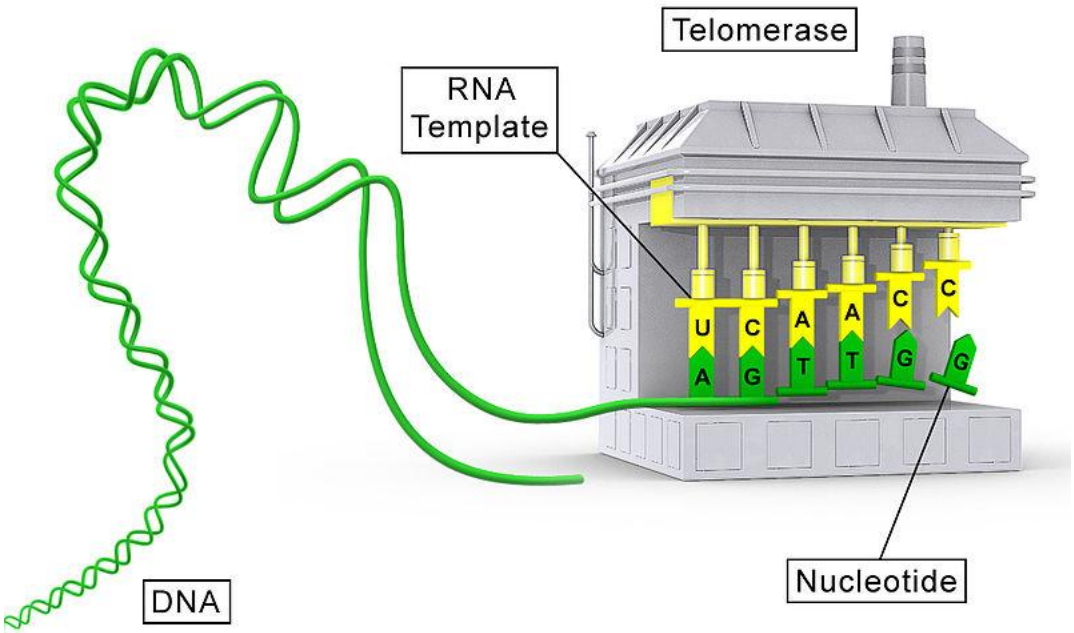


**Figure 1.** An illustration of a telomerase molecule. RNA-directed DNA polymerase. A conceptual diagram showing the protein component of telomerase (TERT) in grey and the RNA component (TR) in yellow [Author = Sierra Sciences, LLC (uploaded from intranet, February 19, 2009); Permission = Sierra Sciences has released this diagram under the Creative Commons]

Telomerase activity is expressed in most human tumor tissues but not in normal tissues except those of the germline (testes/ovaries). Stem cells of renewing tissues express very low levels of telomerase. Telomerase activity is occasionally detected in tissues adjacent to tumors possibly reflecting the presence of occult micrometastases.

It has been suggested that telomerase is responsible for the unchecked growth of human cancer cells. Unlike normal cells, in cancer cells telomerase appears to grant the cell immortality by maintaining telomere length so that the cell never receives a signal to stop dividing. The telomerase enzyme is an ideal target for chemotherapy because this enzyme is active in about 90 percent of human tumors, but inactive in most normal cells.

By contrast to stem cells and germ-line cells, telomeres in somatic cells shorten with each cell division leading to cellular senescence (ageing). The enzyme telomerase (cellular reverse transcriptase) is involved in telomere stability by synthesizing a new copy of the repeat by using its RNA template. Bodnar et al. [36] forced expression of telomerase in normal human cells by transfection of retinal pigment epithelial cells and foreskin fibroblasts with a vector encoding the human telomerase enzyme. Remarkably, these cells exhibited elongated telomeres, "divided vigorously", and proliferated at least 20 doublings beyond their normal life-span; in contrast, the control cells showed shortening of telomeres and senescence [36]. Thus, in typical somatic cells, human telomeres normally undergo shortening at each cell division, and when several kilobases of telomeric DNA is gone, cell division halts and senescence manifests.

Regulation of telomerase activity is an area of intense investigation, but its exact mechanisms are not yet elucidated. The contribution to telomere loss by oxidative DNA damage senescence cells were found to contain 30% more oxidative modified guanine in their DNA. Since oxidative modifications and shortening by reactive oxygen species (ROS) leads to aging of the somatic cells, it is expected that antioxidants and reactive free radical scavengers may play a preventive role and possess anti-ageing properties. Additional evidence for the role of ROS in telomere shortening was associated with chronic oxidative stress and inflammation.

Various models (animal types) have been developed and applied to investigate the relationship between telomere length and oxidative stress. And future studies should investigate the genetic determinants of telomere shortening and stability and to assess the effects of environmental factors that increase oxidative stress and chronic inflammation.

### Antioxidant: Vitamins E and C

It has been recognized since the 1940s that vitamin E (α-tocopherol) is a powerful lipophilic antioxidant that is absolutely vital for the maintenance of mammalian spermatogenesis [37]. It is present in particularly high amounts in Sertoli cells and pachytene spermatocytes and to a lesser extent round spermatids [38].

Vitamin C (ascorbic acid) also contributes to the support of spermatogenesis at least in part through its capacity to reduce α-tocopherol and maintain this antioxidant in an active state. Vitamin C is itself maintained in a reduced state by a GSH-dependent dehydroascorbate reductase, which is abundant in the testes [39]. Deficiencies of vitamins C or E leads to a state of oxidative stress in the testes that disrupts both spermatogenesis and the production of testosterone [37].

Conversely, ascorbate administration to normal animals stimulates both sperm production and testosterone secretion [40]. This vitamin also counteracts the testicular oxidative stress induced by exposure to pro-oxidants such as arsenic, Bioaccumulation of polychlorinated biphenyl (PCBs) (Arochlor 1254), cadmium, endosulfan and alcohol [41-45]. Furthermore, endogenous ascorbate levels decrease dramatically when oxidative stress is induced in the testes by, for example, chronic exposure to lead, chromium, cadmium or aflatoxin [46-48]. Vitamin E has also been shown to suppress lipid peroxidation in testicular microsomes and mitochondria [49, 50] and to reverse the detrimental effects of oxidative stress on testicular function mediated by exposure to such factors as ozone, iron overload, intensive exercise or exposure to aflatoxin, polychlorinated biphenyls (PCBs), cyclophosphamide and formaldehyde [41, 45, 46, 51-55]. Furthermore testicular vitamin E levels have also been shown to fall significantly when oxidative stress is induced by exposure to pro-oxidant stimuli such as chromium [47]. Therefore, antioxidant nutrient supplementation especially vitamins E, C and A, selenium, zinc and chromium can be used to attenuate the negative effects of environmental factors as stress agents.

## DISCUSSION

### The role of oxidative stress in telomere shortening

These results and the role of oxidative stress in telomere shortening, inevitably directed biological experiments to the use of antioxidant vitamins in the prevention of telomere shortening [56]. Some studies supported this

suggestion. It was found that age-dependent telomere shortening in human vascular endothelial cells, *in vitro*, could be slowed down by an ascorbic acid derivative (ascorbate-2-O-phosphate). It led to an extension of the cellular life span and prevented cell-size enlargement (cellular indication of senescence) [57]. The same treatment of human embryonic cells with ascorbic acid phosphoric ester magnesium salt decreased the level of oxidative stress, prevented telomere attrition and extended the replicative life span of cells [58]. Another study *in vitro* by Yudoh et al. [59] chondrocyte senescence (risk for cartilage degeneration) has been used. These cells, chondrocytes, cultured in the presence of the oxidant H2O2 showed that oxidative stress induced telomere shortening and replicative senescence, but in the presence of ascorbate-2-O-phosphate the shortening was reduced [59].

Although *in vitro* experiments showed positive results with antioxidants, *in vivo* experiments are considered more important because other biological factor might influence the telomere shortening. Male and female rats were used for these types of experiments. Several oxidative stress markers were studied and the results showed that female rats exhibited longer telomeres than male rats. Expression levels of certain antioxidant enzymes, such as the mitochondrial antioxidant manganese superoxide dismutase (MnSOD), glutathione peroxidase (GPx) and glutathione reductase (GRx), in the renal cortex and medulla were found to be higher in female than in male rats. The explanation is that female rats have higher levels of estrogens, which enhance gene expression of MnSOD. The decreased antioxidant levels may be partially responsible for the age-related kidney telomere shortening [60, 61].

Proliferating fibroblasts exposed to buthionine sulfoximine, which depletes the antioxidant enzyme reduced glutathione (GSH, reduced Glutathione is a linear tripeptide, the molecule has a sulfhydryl (SH) group on the cysteinyl portion, which accounts for its strong electron-donating character), decreased telomerase activity, whereas repletion of cells with glutathione increased telomerase activity in a dose-dependent manner [62].

Italian researcher La Torre et al. in 1997 [63] found that the death of some cell lines was due to the sum of molecular damages caused by free radicals, and the subsequent loss of telomeric DNA. So short of the siRNA inhibition in cancer cells, what interventions can be affected for the health aspects? [64]. We have all heard of free radicals damage and on the contrary, health benefits of antioxidants. Science has progressed to the point that availability of antioxidants will allow the body to eliminate and or decrease the damage caused by free radicals (oxidative stress). Anti-oxidants are substances that are generally ingested and provide electrons to bind with dangerous free radicals and neutralize them in order for the body to dispose of them.

Different parts of the body are protected by different antioxidants. Structures containing lipids (fats) are mainly protected by the fat soluble vitamins A and E, whereas the water-soluble vitamin C helps us against free radicals in the blood, body fluids and within cells. If there was a method by which countless negatively charged ions could be delivered into your body (most of us aren't getting it from our cooked processed food diets anymore) would it not be totally beneficial. In the recent past, everyone was scrambling to find powerful anti-oxidants. The cause of aging, along with most of humanity's diseases, has been determined to be due, in large part, to actions of free radicals on our body.

We need to know which events speed up the pace of telomere shortening late in life although it can be associated with the cell's ability to withstand oxidative damage [65]. Meanwhile, the observed reduction in telomerase activity likely contributes to the acceleration in telomere erosion [67]. Therefore by the more antioxidants present in the body the less damage that occurs to the chromosome [68-71]. Telomere length is also directly related to life span and incidence of disease [72].

### Which animal models have more similarities in telomere and telomerase biology with humans?

In contrast to human, rodent telomeres are generally much longer and express telomerase in many tissues. Telomere shortening is broadly studied in mice, especially in telomerase knockout mice [73, 74]. However, it is only after 4-6 generations that telomere shortening becomes a critical issue in these mice, indicating mechanisms of carcinogenesis and ageing [75]. The rapid death following reproduction observed in rodent especially mouse species is much different and so these model organisms are not a good representative of human aging mechanisms, however, scientists noticed that rat telomeres do not have to be modulated to detect shortening, so the rat model might be more feasible than mice in studying the effect of oxidative stress and ageing. Telomere length assessed in Wistar rats in the kidney, liver, lung and brain may determine life span (longevity). It was found that male rats have shortened life span compared to females [76, 77]. Telomere length has been investigated in dogs, cats, bird species, horses, and cattle as animal models for applicability of the research to human telomere and telomerase activity. These animals have been observed that does share more similarities in telomere and telomerase biology with humans [78-90].

## CONCLUSION

People should be aware of the biological hazard and adverse health effects of EMFs as life stress. These studies have shown that electromagnetic fields as part of human daily lives can speed up the shortening of our protective telomeres and the ageing process because of chronic oxidative stress caused by free radicals, and people who rely on supplements and have a diet rich in major natural antioxidants or a good mixture of fruit and vegetables with high in antioxidants to help reduce the effects of these waves will live longer and healthier than those who don't.

However, although there is a long way to be able to assess the effects of environmental factors in life span, there is a need for more research on genetic determinants of telomere stability and other intrinsic and extrinsic factors leading to cell senescence and also the role of telomere shortening on inflammatory diseases progression, cancer and the various factors, such as heredity and other ageing.


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### Competing interests

The authors declare that they have no competing interests.

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