

Aging and cancer: molecular facts and awareness for Turkey

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Abstract: Two important subjects concerning extension of the human life-span are biological aging processes and their relationship to diseases, and especially to the formation of cancer. It is clear that an aging population poses some challenges for developing countries. We set out to show the demographic structure of Turkey and to discuss the feasibility of decreasing the prevalence of cancer. We overviewed the literature on the relationship between biological aging and cancer formation, the environmental causes of cancer, and age-related characteristics of cancer in the elderly. In addition, some statistical data on the changing demography of Turkey were reviewed. It is seen that some predictions and preliminary preparations should be taken. However, in order to take precautions, first of all there must be a holistic approach from the causes to the consequences.

Key words: Biological aging, cancer, molecular mechanisms, environmental factors, age-related cancer characteristics, epidemiology, Turkey

1. Biological aging

Aging is a complex process influenced by multiple factors including biology and behavior as well as physical, social, and cultural aspects of the human environment. Additionally, these factors interact with each other. Aging starts biologically and then the other dimensions come. Biological aging is a time-related increase in an organism's intrinsic morbidity and mortality (Kirkwood and Austad, 2000; Adams et al., 2004; Hipkiss, 2007). Aging is universal and progressive and represents a steady decrease in physiological ability (Adams et al., 2004). It usually occurs after reproductive maturation and results from diminishing energy to maintain molecular fitness (Hayflick, 2000; Carnes et al., 2008). Age-related changes occur at different levels, caused by molecular damage that slowly overwhelms the defense, repair, and maintenance systems of the body. The result is an increase in generalized vulnerability at all levels of organization (Hipkiss, 2007). Cellular senescence has been proposed to contribute to organismal aging (Heemst, 2009).

Biological aging does not have a simple cause; instead, it is a very complex or multifactorial process. Mainly genetic and environmental factors influence the rate of biological aging (Adams et al., 2004; Carnes et al., 2008). Some cellular causes are telomere shortening, accumulation of mutations in nuclear DNA and mitochondrial DNA, effects of oxidants or free radicals (oxidative stress),

glycation (cross links), excess damaged proteins, and inadequate degradation of waste or increase in lipofuction within cells. These pathologies may cause age-related diseases. However, there is interindividual variation in the rate and nature of aging-associated diseases (Sander et al., 2008). These age-related diseases are the leading cause of death in developed/developing countries (Fontana, 2009). Among these diseases, there are cardiovascular diseases, cancers, neurodegenerative diseases, decreased resistance to infections, diabetes mellitus, and some others (Anisimov, 2001). These are named as totally age-associated pathologies or age-associated diseases. However, the distinctions between senescence and disease are blurred sometimes in biogerontology and medicine. Senescence and disease have some overlapping biological consequences (Carnes et al., 2008). Aging is not a disease, but it accompanies the decline in organ and body functions and indicates an increasing susceptibility to diseases such as cancer. During aging, the accumulation of genetic and epigenetic changes, the diminishing of telomere length, the progressive disruption of mechanisms for DNA repair, glucose metabolism regulation, cell cycle control, and stem cell renewal lead to the induction of senescence or apoptosis and loss of replicative capacity. These cellular dysfunctional mechanisms characterizing the aging process have also been found to be involved in carcinogenesis (Bassi et al., 2009). Actually, cellular

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senescence is a potent tumor suppressive mechanism. That is, there is damage or stress-induced cellular senescence in order to prevent risky cells from initiating tumorigenesis. Malignant tumorigenesis requires the genetic or epigenetic inactivation of at least one, and often both, of the tumor suppressor pathways, thereby enabling initiation of cancer cells to bypass the senescence checkpoint (Campisi et al., 2011).

2. Accompanying molecular mechanisms of aging and cancer

Aging and carcinogenesis share many molecular pathways. Aging includes a number of events at molecular, cellular, and physiological levels that also influence carcinogenesis. With the exception of germ cells and stem cells, most somatic cell types have a limited proliferative life-span. Indeed, this limitation may have evolved as a protective mechanism against cancer (Anisimov, 2009). However, the most significant risk factor for developing cancer is aging. The incidence of adult human cancers shows a relationship with age (Kennedy et al., 2012). Aging may increase or decrease the susceptibility of different cells or tissues to tumor development and may affect cancer initiation and progression in many ways (Anisimov, 2009; Hornsby, 2011). Therefore, growing older is a greater risk factor for developing cancer. About 80% of all cancers are diagnosed in people over 50. Thus, with the increase in the aging population, it is expected that cancer will become a more and more serious problem. Findings point out that some of the constantly active molecular mechanisms that defend cells from cancer transformation are increasingly disrupted with aging and may be involved in aging and in cancerogenesis (Bassi et al., 2009).

Cancer is the second cause of death in many developed countries (~25% of deaths) (Bassi et al., 2009; Fontana, 2009). Cancer is a complex multistep molecular genetic disease associated with the accumulation of multiple forms of DNA damage that cause a disorganization of cell proliferation and differentiation, and eventually tissue invasion and dislocation to distant sites. If not properly controlled through induction of senescence or apoptosis, accumulation of multiple DNA mutations in critical genes can disturb the cell proliferation process and progressive transformation of normal human cells into malignant tumor cells. Additionally, the surrounding microenvironment and the cell interactions between cancer cells play an important role in tumor cell proliferation, tissue invasion, and metastasis, which are ultimately responsible for ~90% of human cancer deaths (Longo et al., 2009). Cancer is relatively rare in young mammals, because they have more active tumor suppressor mechanisms. The incidence of malignant tumors increases with age, but patterns of age-related tumors are different for tissues (Anisimov, 2009).

With longer life-spans, there is increased risk for both DNA damage and long-term exposure to carcinogens. Therefore, older adults may have greater potential for accumulated molecular damage coexisting with age-related decreased cellular repair activity causing malignancies (Clough-Gorr et al., 2012). During their total life time, aging cells accumulate many DNA mutations and unrepaired lesions, defective mitochondria, progressively shortened telomeres, heterochromatic silencing, misfolded or carbonylated proteins, and oxidized biomolecules because of reactive oxygen species (ROS) (Kennedy et al., 2012).

2.1. Telomere length

One of the earliest observations on age-related decline in proliferative capacity of cells was described as the result of telomere shortening. In general, telomere dysfunction causes either senescence or crisis in human tissues and there is an association between telomere length and the markers of senescence in tissues *in vivo*. Telomere length is a major factor in the anticancer action of cellular aging (Hornsby, 2011). Telomeres stabilize the integrity of chromosomal ends. They compensate for incomplete semiconservative DNA replication at each chromosomal end. They protect against homologous recombination and nonhomologous end joining (Bassi et al., 2009; Sikora et al., 2011). When somatic cells divide, usually a short terminal telomeric repeat region of DNA is not replicated. This works as a kind of mitotic counter. The shortening of telomeres causes telomere dysfunction and a permanent inability for cell division occurs. Damage may also result from a susceptibility of telomeres to DNA damage from other causes such as oxidative stress (Hornsby, 2011). The critical shortening of telomeres limits cells to a particular division number. The cell detects this phenomenon as DNA damage and enters a cellular replicative senescence. The limited number of cell divisions plays an important role in cancer suppression. Telomere length is replenished by the telomerase. This enzyme is active in germ and stem cells. Most of the cancer cells bypass the protective phenomenon of senescence and become immortalized by telomere extension due to the overexpression of the telomerase enzyme. There is telomere maintenance activity in approximately 90% of cancers in almost all mammalian organisms. It may be thought that the shortening of the telomere and its restoring mechanisms is a trade-off between molecular pathways of aging and cancer (Bassi et al., 2009).

2.2. Genetic changes

Both nuclear DNA and mitochondrial DNA mutations play important roles in aging and age-related pathologies. Normally there are maintenance and repair systems to overcome molecular damage. Sometimes both mutations and disturbed DNA repair mechanisms may act synergistically in causing cancer. Some DNA damages

and wrong mitogenic signals can also cause cells to gain a senescent phenotype (Anisimov, 2009; Heemst, 2009). Biomarkers of cellular senescence in aging and age-related diseases are chromosomal instability and accumulation of DNA damage foci (Sicora et al., 2011). That is, genomic instability is a key mechanism of both aging and cancerogenesis. DNA damage at relatively low levels is efficiently repaired. However, somatic mutations accumulate in most organs and tissues. Aging and cancer are linked to DNA damage and damaged processing is linked to genome maintenance systems (Maslov and Vijg, 2009). When the balance between DNA damage and repair is disturbed, it can accelerate age-associated diseases. The loss of mitochondrial DNA integrity is also hypothesized to play an important role in the aging process. Especially in mitochondrial mutations, a hazardous cycle of oxidative damage induced by ROS production may play an important role in the aging process. MtDNA mutations have direct roles in initiation of carcinogenesis and also may have tissue susceptibility to metastatic potential (Figure 1) (Kennedy et al., 2012).

2.3. Epigenetic changes

Not only mutations but also epimutations are also important for aging and cancerogenesis. Epimutations or epigenomic alterations are heritable and stable changes in gene expression that do not affect the actual base pair sequence of the DNA. There are epigenetic changes in cellular senescence, aging, and age-related pathologies.

Epimutational damage causes stochastic changes in differentiated cells and this is one of the causes of the biological aging process (Maslov and Vijg, 2009). Somatic epigenetic inheritance depends on some enzymes that control methylation and histone acetylation in DNA. DNA methylation regulates chromatin stability and gene expression. The most important epigenetic changes are the silencing of tumor suppressor genes and repair genes and other genes involved in the control of cell cycle, senescence, detoxification, and apoptosis. Genome-wide hypomethylation was suggested as a step in carcinogenesis and promoter region methylation in the gene appears as an important mechanism of epigenetic inactivation of tumor suppressor genes (Anisimov, 2009; Bassi et al., 2009).

2.4. Oxidative stress

The ROS are extremely reactive molecules and can damage cellular components. ROS are generated and wiped out in cells. They are produced by mitochondrial metabolism, activation of nicotinamide adenine dinucleotide phosphate oxidase, peroxisomes, cytochrome P450 enzymes, nitric oxide synthase uncoupling, and the antibacterial oxidative burst of inflammatory cells. They also arise from exogenous sources, such as ultraviolet, ionizing radiations and genotoxic agents. ROS include superoxide anion, hydroxyl radicals, and hydrogen peroxide. These extremely unstable compounds perform genotoxic and cytotoxic activities through lipid peroxidation or protein damage and may cause DNA replication errors,

Somatic Mutations in Cancer

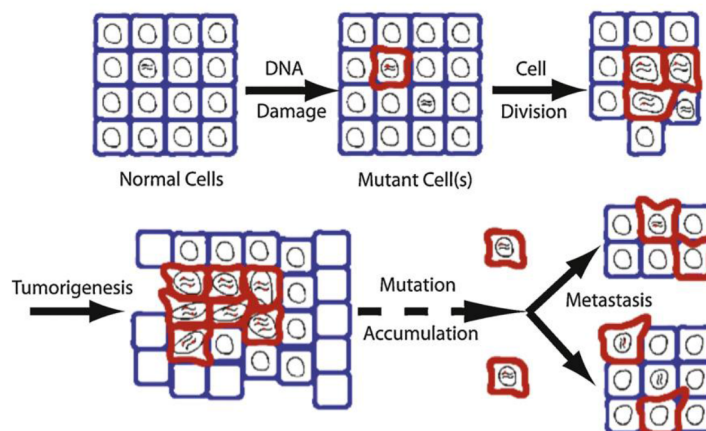


Figure 1. Accumulation of somatic mutations during cancer formation. During normal organismal aging, cells (blue) are continually exposed to DNA damaging events, which eventually results in cells harboring multiple mutations (red). Some mutations occur in regions of the genome that lead to uncontrolled cell proliferation. The acquisition of a mutator phenotype allows for more rapid somatic evolution that continually acts to select for cells able to bypass many of the defense mechanisms that limit unrestricted cell proliferation (from Kennedy et al., 2012).

spontaneous chemical changes in single- and double-strand DNA breaks, adducts, and crosslinks. Oxidative stress has some effects in cells such as accumulation of mutations in genes, telomere shortening, and damage in mitochondrial DNA. The free radical theory of aging was developed in 1956 by Harman and argues that aging results from ROS-generated damages (disputed by several authors), suggesting that prevention of oxidative stress may help to slow down the aging process. The antioxidative system includes many types of antioxidants, such as vitamins C and E, and enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. The antioxidative defense mechanism of the body protects cells from oxidative damage by scavenging harmful ROS. If the amounts of ROS exceed cellular antioxidative defense mechanisms, then the oxidative stress gets higher. Homeostasis of ROS is important and essential for life and it must be perfectly controlled. Intracellular high oxidative stress has 2 potentially significant effects; the first is to damage various cellular compounds and the second is to trigger the activation of specific cell-signaling pathways. Both effects may stimulate some cellular processes, aging, and the development of age-related diseases, such as cancer, because ROS are byproducts of energy production in mitochondria and can damage mitochondrial DNA over a short distance. Some mitochondrial damaged cells undergo programmed cell death, apoptosis. Accumulation of somatic mutations in mtDNA of tumor cells may also contribute to tumor growth. MtDNA damage may cause the insufficient expression of cellular components increasing the portion of disrupted, ROS-producing oxidative phosphorylation and eventually promoting the aging process and carcinogenesis. In the end, mitochondrial formation of ROS both causes and accelerates aging and cancer development. With age, the antioxidant system weakens and, therefore, oxidative damage is strengthened. There is evidence supporting a relationship between ROS and mutagenesis/carcinogenesis. Many cancer cells show increased production of ROS, and normal cells exposed to ROS show increased proliferation. Elevated ROS levels may also directly induce DNA damage, leading to genomic instability and cancer progression in the young (Anisimov, 2009; Bassi et al., 2009; Migliore and Coppede, 2009; Okada et al., 2012).

2.5. Apoptosis

Apoptosis is programmed and genetically controlled cell death. It can eliminate defective cells and protect organisms from malignancy. However, the proportion of apoptosis is important; a high proportion of apoptosis may give rise to aged phenotypes. Senescent cells have some characteristics such as increased ROS production, increased oxidative damage, reduced heat shock protein expression, increased glycation damage, accumulation of defective proteins,

and declined functions of apoptotic proteins. p53-related apoptosis is a protective mechanism against uncontrolled cell proliferation induced by oncogene activation. Apoptosis may play a protective role against cancer in some tissues, whereas cellular senescence may play a more protective role in other tissues. The decrease in apoptosis rate with age may promote cancerogenesis due to less efficient cellular signaling and regulation (Anisimov, 2009; Bassi et al., 2009).

2.6. Cell cycle control

Cell cycle checkpoints control the process in each cycle period to be accurately completed before progression. The genes of checkpoint proteins may be seen as a molecular link between aging process and carcinogenesis (Bassi et al., 2009). The tumor suppressor gene and its product p53 can implement antiproliferative effects in response to serious types of cell stress. Growth arrest, apoptosis, and cell senescence are some antiproliferative effects. In half of human tumors there are mutations within the p53 gene. Evidence indicates that tumors that have the wild-type p53 have other defects in the p53 pathway, which are also important in the development of cancer (Yi and Luo 2010). p53 can induce both apoptosis and cell cycle arrest. The decline in p53 response to stress at older ages may contribute to an increase in cancer incidence (Bassi et al., 2009). p53 may protect against cancer but at the cost of longevity; that is, individuals carrying alleles indicated in a low intensity of apoptosis are more vulnerable to cancer but less vulnerable to strokes or myocardial infarction (Yashin et al., 2009).

2.7. DNA repair mechanism

Cells are exposed to DNA damage continuously, via normal metabolic activities and environmental factors. DNA damage activates the defensive pathways of the cell by inducing multiple proteins involved in cell cycle checkpoints, DNA repair, protein trafficking, and degradation. DNA repair involves some constantly active processes by which a cell identifies and corrects DNA damage. The cell may enter 1 of 3 possible states: senescence, apoptosis, or unregulated cell division, which can cause cancerogenesis. Some genes that have been shown to influence organisms' life-span and cancer development are also involved in DNA repair pathways. Normally, the cell cycle checkpoint control pauses the cell cycle and gives time for the cell to repair DNA damage, and thus it prevents cancerous transformation. There is a link between DNA repair mechanisms, the aging process, and cancer. This is also shown by some hereditary DNA repair disorders. Additionally, there are some hereditary malignancies associated with reduced DNA repair function such as hereditary breast and colon cancer (Anisimov, 2009; Bassi et al., 2009).

2.8. Senescence-associated secretory phenotype

For malignant tumorigenesis, accumulation of somatic mutations and a suitable tissue milieu are necessary. A normal tissue microenvironment can suppress the ability of mutant cancer cells to proliferate. However, a tissue microenvironment may also gain a procarcinogenic state independently of the presence of tumor cells. An important procarcinogenic tissue milieu is age (Figure 2) (Campisi et al., 2011). The number of senescent cells in the body accumulates with time and those senescent cells are predominantly present at sites of age-related pathologies. Although most of the changes induced upon senescence are beneficial, in the long term, some of these changes may also have a negative impact on tissue functions and integrity, especially if senescent cells accumulate in high enough numbers. Senescent cells stay in permanent growth arrest with changed morphology and function. They usually gain a new phenotype with unusual secretory properties because of distinct changes in their gene expression pattern. Growth factors secreted by senescent cells may especially induce premalignant cells to malignant ones. Therefore, while beneficial for tumor suppression in the short term, induction of cellular senescence may have negative consequences later in life on the development of aging diseases. These are related to the hypermitogenic and secretory characteristic of senescent cells. These may cause, paradoxically, the development of late-life cancers (Heemst, 2009). Senescent cells secrete numerous chemokines, cytokines, growth factors, proteases,

and insoluble components, and this new property is called the senescence-associated secretory phenotype (SASP). There are about 40 factors; some are involved in intercellular inflammatory signaling. SASP occurs in some proliferative cell types such as fibroblasts, endothelial cells, and epithelial cells. SASP can have striking autocrine and paracrine effects. The paracrine effects of senescent cells are the ability to alter the behavior of neighboring cells and the quality of the local tissue environment. The paracrine feature of SASP can have beneficial or harmful effects, depending on the physiological context. One of the beneficial effects is, of course, tissue repair. One detrimental effect is disrupting normal tissue structures and function, thereby promoting malignant phenotypes in nearby cells. (Campisi et al., 2011; Sikora et al., 2011). Normally, senescent cells are eliminated by the immune system. However, the aging immune system may become less capable of clearing senescent cells, and/or some senescent cells may escape from the immune system. In addition, the production of senescent cells increases with age and leads to an age-dependent acceleration of tissue damage. Some experiments have shown that both senescent cells and mutant premalignant cells accumulate highly with time. The accumulation of damaged and senescent cells during aging may be a source of some mobile proinflammatory cytokines that cause pathologies in both local and distal environments. Therefore, long-lasting inflammation may predispose organisms to various types of cancer (Campisi et al., 2011).

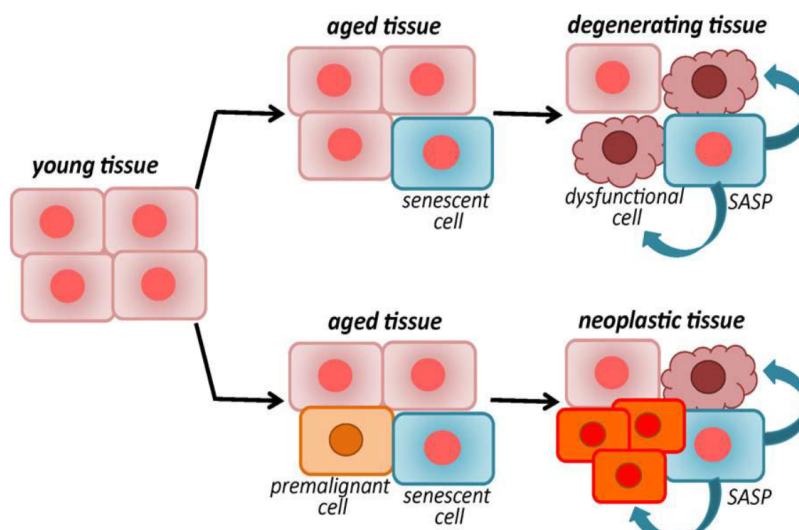


Figure 2. Senescent cells, by virtue of their SASP, may promote both the degenerative and neoplastic diseases of aging. Both senescent cells and preneoplastic cells increase with age in many tissues. The SASP of senescent cells can cause normal cells within tissues to lose optimal function, leading to tissue degeneration. The SASP can also cause premalignant cells to proliferate and adopt more malignant phenotypes, leading to full-blown cancer (from Campisi et al., 2011).

2.9. Stem cells

Adult stem cells are an in vivo source to replace the cells in high turnover tissues throughout the entire life-span. The regenerative capacity of an organism is determined by the ability and potential of its stem cells. Therefore, aging may be interpreted as signs of somatic stem cells aging. Some studies on stem cells have indicated that not only genetic and epigenetic alterations but also biochemical alterations affecting somatic cells might have a role in stem cell aging (Bassi et al., 2009). During aging, there is a reduction in stem cells, and this decline may indicate the relationship between cancer incidence and age. There is an exponential increase in the incidence of cancers with a peak around 80 years of age. All cancers show a decline in incidence after this age. Probably, the reduced number of stem cells limits the probability of generating the mutations turning a stem cell into a cancer cell in those late years. It is accepted that there is a balance between quantity and quality of stem cells, which ensures a natural life-span free of cancer and aging long enough for maturation and reproduction. The stem cells, which are still active in old age, may be functionally impaired because those inevitable errors of genome maintenance accumulate throughout the life-span. The increasing amount of mutations and epimutations in the proliferation-capable stem cells increases the risk of neoplastic transformation. However, some tissues accumulate mutations and epimutations and deplete stem cell populations at the same time. As we know, tissue regeneration is maintained by somatic stem cells; however, most malignancies are associated with tissues containing an active stem cell population (Figure 3) (Maslov and Vijg, 2009). Our stem cells also grow old as a result of mechanisms that prevent the development of cancer. The specific environment of a stem cell is called the niche and provides the adhesive support to maintain the stem cells within the tissue. During the aging process, the accumulation of mutations in the niche may cause disruption of the normal mechanisms. Mutations damage compartments of stem cells and in the end cause the aging of organs and the body. This disruption may cause pathological stem cell proliferation. The cancer stem cell hypothesis states that tumors contain a reservoir of self-renewal cells that share similar biological properties with normal adult stem cells (Bassi et al., 2009).

2.10. Inflammation

Low systemic inflammation is important in aging. It is known that the genes regulating the immune inflammatory responses are involved in longevity. Thus, inflammatory markers may be real predictors of mortality in the elderly. The proinflammatory status of the elderly causes functional decline and age-related diseases. In other words, these diseases may be initiated or worsened by systemic inflammation. Because of a low-grade activation

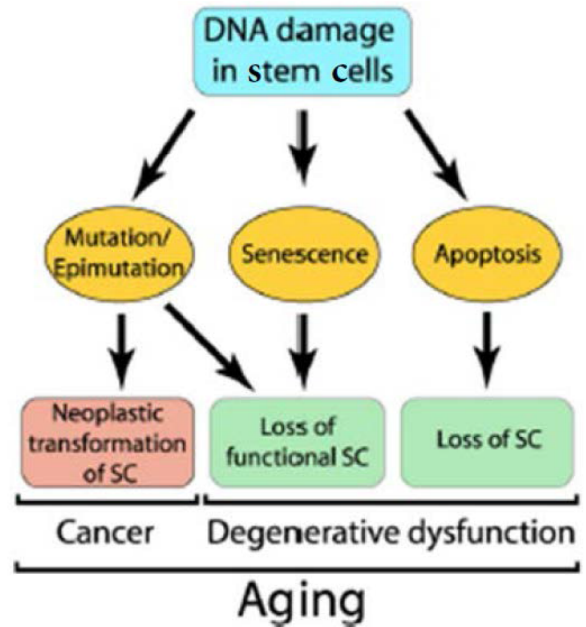


Figure 3. Hypothetical relationship among aging, cancer and stem cells (SC). Various endogenous and exogenous factors (e.g., ROS, replication errors, environmental hazards) cause DNA damage, also in stem cells. Among the cellular responses to DNA damage, apoptosis and senescence lead to attrition of stem cell populations, while DNA repair may lead to errors both increasing cancer risk and adversely affecting function. Hence, cancer and noncancer degenerative dysfunction can both be consequences of stem cells' responses to DNA damage (from Maslov and Vijg, 2009).

of the immune system by a lifetime of exposure to a variety of antigens/pathogens, levels of circulating inflammatory mediators may increase. Lifelong exposure to infections and inflammatory status may increase the risk of heart attacks, strokes, and cancer. People with genetic predisposition to a low inflammation characteristic have a reduced chance of developing age-related inflammatory diseases and an increased chance of becoming a centenarian. Centenarians and their children have a good chance of avoiding age-related diseases including cancers (Castel et al., 2007; Vasto et al., 2009). There is a strong association among chronic infection, inflammation, and cancer. ROS released at the site of inflammation play a role in carcinogenesis. Interleukin-6 (IL-6) is involved in immune response and inflammation. To cope with inflammation or as a strategy for the treatment of chronic inflammatory diseases, targeting IL-6 is thought to have therapeutic potential. The proinflammatory cytokine tumor necrosis factor (TNF)- α is also an important inflammation mediator. Some studies have reported that there is a high amount of it in autoimmune and inflammatory diseases, including the age-related ones, and that it does not provide longevity.

TNF- α is involved in the pathogenesis of cancer, mainly due to chronic inflammation, because it triggers DNA damage, angiogenesis, invasion, and metastasis. Regarding another interleukin, IL-10, genotypes producing low amounts of it seem to play a role in the susceptibility to inflammatory diseases. Conversely, genotypes producing high IL-10 are involved in the accession of longevity. It is thought that chronic inflammation caused by persistent infections by microorganisms may be a driving force in cancer development (Castel et al., 2007; Vasto et al., 2009).

Therefore, the relationship among the cellular pathways of senescence, apoptosis, and cancerogenesis is highly complex. Senescence and apoptosis are anticancer mechanisms that generally appear to promote aging, but adversely their failure is associated with cancer (Bassi et al., 2009). When senescence or apoptosis is blocked, cells continue to divide and may acquire further abnormalities, eventually going into crisis (Hornsby, 2011). Longevity may depend on a balance between tissue renewal mechanisms and tumor suppression. The trade-off between cancer and aging may result from the opposite ways of apoptotic and growth signaling pathways in cancer and aging cells (Yashin et al., 2009). As it is seen, there are many molecular and cellular parameters in studying and understanding biological aging and carcinogenesis. We know much about them but we still do not know enough, so studies must go on, first to understand and then to intervene.

3. Environmental effects on malignancy

Cancer is a complex group of diseases with a multifactorial etiology. Epidemiological data in cancer incidence have shown that environmental factors also have serious effects on the initiation, promotion, and progression of some cancers (Longo et al., 2009). There is evidence that life-long exposure to carcinogenic agents produces an overall increase in carcinogenic processes. Environmental exposures act on a variety of cancers. The term 'environment' includes all nongenetic factors (lifestyle factors, occupational exposures, infections, pollutants), and in the more narrow sense includes only air, water, soil, and food pollutants. About two-thirds of all cancers are linked to environmental causes. The most common environmental pollutants, namely air, water, and soil pollutants, are classified as the first group of carcinogens. Air pollutants include asbestos, tobacco smoke, household combustion of coal, and radon. Water pollutants include inorganic arsenic, cadmium, chromium, pentachlorobiphenyl, and radium. Soil pollutants include petroleum hydrocarbons and solvents (benzene), pesticides (formaldehyde), and heavy metals (nickel). A common approach is to describe the environment using 3 categories, consisting of personal behaviors, involuntary exposures, and occupational exposures (McGuinn et al., 2012). Environmental

and lifestyle factors such as ionizing radiations, UV radiations, air pollution, biocides, pesticides, metals, tobacco smoking, alcohol, and diet cause the additional production of oxidative stress and lead to carcinogenesis in the cells and body. Epigenetic changes may also occur due to environmental factors (Mena et al., 2009; Migliore and Coppede, 2009).

Oxidative stress is a pathophysiological mechanism in human pathologies. DNA base oxidation and mutations caused by ROS play a role in carcinogenesis, but they are also associated with the aging process. Hence, the additional actions of ROS are very important, and especially their effects on p53, cell proliferation, invasiveness, and metastasis. It is generally thought that cancer arises from a single cell, initiated by the mutation of some genes caused by random errors in DNA replication or a reaction of the DNA with free radicals or other chemical species (Mena et al., 2009). The increased risk of cancer in older adults is related to 2 age-linked processes. Because cancer is a multistep process, there are increased opportunities for DNA damage accumulation and longer exposure to several potential carcinogens as lives get longer. As a result, older adults may have greater risk for accumulated molecular damage coexisting with age-related decreased cellular repair activity, leading to malignancies (Vasto et al., 2009; Clough-Gorr et al., 2012).

Animal experiments have shown that there are age-related differences in sensitivity to carcinogens in some tissues. Furthermore, some carcinogens may also affect aging. Chronic inhalation of tobacco smoke causes overproduction of free radicals and signs of aging. Lead exposure may contribute to arterial aging. Acceleration of aging by ionizing radiation is well known. Ionizing radiation and chemical carcinogens cause disturbances in the internal tissues, similar to those of normal aging, but at earlier ages. Carcinogenic factors generally cause a transition to an older level of function in metabolic processes and hormonal and immune status. This transition has different latent periods in the various tissues and systems of the exposed organism. Another well-known fact is that cells with the highest proliferative activity would be more likely to undergo malignant transformation. Carcinogens induce in vitro a flattened and enlarged cell shape and the protein named 'senescence-associated beta galactosidase', characteristics of senescent cells in mammals (Anisimov, 2009).

Some environmental risk factors such as smoking and lifestyle are modifiable, whereas others such as family history and race are not. The World Health Organization states an important estimation that more than 30% of cancer deaths in the general population can be prevented by modifying the risk factors. The effect of these factors may be magnified in older adults. Smoking is surely considered

to be the most important cause of preventable death in the world. Diet and physical activity are also modifiable risk factors in older adults. Primary prevention (tobacco avoidance, healthy diet, weight control, physical activity) as the main strategy related to lifestyle factors is very important to reduce multiple primary cancers (Clough-Gorr et al., 2012). The transforming of a normal cell into a tumor cell is a complex and multistage process. The first approach to reduce cancer risk is prevention, focused on the reduction of exposure to environmental carcinogens (Hodek et al., 2009; Longo et al., 2009).

New cancer cases are continuously rising and it is projected to rise worldwide by about 70% by 2030. Stopping smoking, reducing obesity and increasing physical activity, reducing consumption of alcohol, vaccination against hepatitis B and human papilloma viruses, safe sex, and the avoidance of environmental and occupational carcinogens and excessive sun exposure may all make significant contributions to cancer prevention (Table). Cancer is a global problem. However, there are different cancer types at regional and national levels. Interestingly, most cancers grow slowly and occur decades after initiation. The benefit of regional or national prevention strategies will only be seen decades after their initiation (Franceschi and Wild, 2013). Only 5%–10% of all cancer cases are due to transmitted familial genetic defects and

the remaining 90%–95% are due to environmental effects (Martin-Moreno et al., 2008; Gonzales et al., 2010). It is obvious that avoidance of environmental carcinogens may keep humans from developing cancer or decrease the risk of developing cancer. Therefore, because environmental carcinogenesis is preventable, everybody must be aware of these effects throughout the whole life-span.

4. Age-related cancer characteristics

Age-related pathologies are generally chronic and cause serious morbidity and mortality. Generally, age-related diseases are placed in 2 categories. The first is 'loss of function' diseases and the second is 'gain of function' diseases. Diseases in the first group are degenerative pathologies. These are caused by a loss of cellular or subcellular functions and tissue elements. Examples are neurodegenerative diseases, some cardiovascular diseases, macular degeneration, osteoporosis, and sarcopenia. Diseases in the second group are hyperplastic pathologies. These are caused by a gain in new cells and/or new cellular functions. Examples are some forms of hyperplasia and atherosclerosis. The most marked and deadly type of the gain of function disease is cancer (Campisi et al., 2011). As is known, carcinogenic processes take time and it is therefore likely that more tumors develop in the elderly. However, every type of cancer has its own age-dependent

Table. Risk factors for cancer that are also leading causes of disease burden globally or regionally and potentially modifiable (from Franceschi and Wild, 2013).

Risk factor	Minimal risk exposure	Cancer
Smoking	No smoking	Cancer of the lungs, upper aerodigestive tract, liver, pancreas, cervix uteri, bladder, and kidney and leukemia
Alcohol	No use	Cancer of the upper aerodigestive tract, liver, and breast
Overweight and obesity	BMI ≥ 21 SD 1 kg/m ²	Cancer of the colon, gallbladder, breast (postmenopausal), endometrium, and kidney
Physical inactivity	≥ 2.5 h/week	Cancer of the colon, rectum, breast, and prostate
Low fruit and vegetable intake	600 g/day SD 50 g	Cancer of the upper aerodigestive tract, stomach, colon, and lung
Urban air pollution	7.5 mg/m ³ for PM _{2.5} 1.5 mg/m ³ for PM ₁₀	Cancer of the lungs
Indoor smoke from solid fuels	No solid fuel use	Cancer of the lungs
Unsafe sex	No unsafe sex	Cancer of the cervix, anogenital tract, and oropharynx
Contaminated injections in health care setting	No contaminated injections	Liver cancer, non-Hodgkin lymphoma

BMI ≥ 21 body mass index; SD: standard deviation; PM: particulate matter.

tendency of incidence, and tumor behavior is never uniform at all ages (Anisimov, 2009; Okada et al., 2012). Nowadays we know many of the genetic and environmental effects that increase the risk of cancer development. However, the most important risk factor is advancing age, so cancer disproportionately affects the elderly (Campisi et al., 2011; Clough-Gorr, et al., 2012). There has been a significant increase in the mean life-span of the human population. It is suggested that for the increase in mean life-span achieved by the decrease in mortality at early ages, mankind pays at later ages with an increased risk of cancer (Anisimov, 2009).

Cancers may have very different characteristics depending on the age of the patient. Generally, 2 types of mechanisms are involved: changes in the biology of tumor cells, and changes in the ability of the patient to sustain and stimulate tumorigenesis. There are usually age ranges for the occurrence of cancers. Some cancers such as leukemias, lymphomas, and ovarian cancers become more aggressive as age increases, and some others such as breast and lung cancers become more sluggish. As an example, late onset breast cancers grow more slowly and are biologically less aggressive than early onset ones. However, some cancers such as non-Hodgkin lymphoma in older adults have a worse prognosis than in younger individuals. Of course, age-related physiological changes are important and relevant to the biology and treatment of cancers. They may affect some parameters such as the tumor growth rate, the pharmacokinetics of drugs, and the risk of drug toxicity. Multiple illnesses are also related to pathophysiology, diagnosis, prognosis, treatment, and etiology. With advancing age, the ability to survive is inversely related to the number of comorbidities rather than to cancer. However, cause of death varies according to the type of the cancer. Ultimately, with improvements in cancer screening and treatment strategies, the risk of death from cancer has continuously decreased. However, there is another issue, which is that the risk of developing a second primary cancer is high (Clough-Gorr et al., 2012).

While tumor incidence generally increases with age, paradoxically tumor growth and metastasis decrease at a slower rate at later ages, but not all tumors display same manner. There are several mechanisms of age-related reduced tumor progression. These are decreased tumor cell proliferation, increased apoptotic cell death, decreased angiogenesis, and antitumoral immune response changes. Paradoxically, immunosenescence may create an environment that is unsuitable for tumor growth in older people. There are some problems in the treatment of elderly cancer patients, such as some multiple pathologies, higher susceptibility to surgical procedures, and higher sensitivity to the toxicity of the aggressive chemotherapeutic treatments. The increase in the aged

cancer patient population necessitates that oncologists become familiar with age-associated changes in organ physiology and with the impact of these changes on cancer treatment and toxicity (Leibovici et al., 2009).

Although the incidence of cancer increases with age, metastasis seems to be reduced with age. As a reason for this, age-related changes seem to moderate the aggressive nature of tumor proliferation or metastasis. In elderly patients who die of cancer, antemortem symptoms and autopsy observations suggest that the tumors were nonaggressive, extremely slow growing, and less symptomatic. There are some possible causes of age-related differences in tumor cells. Of course, all these factors relate oncology with gerontology. There are 2 types of factors for the age-associated changes in tumor incidence and malignancy. One is local and the other is humoral. These may be angiogenesis, wound healing, extracellular matrix, immune effector cells, hormones, growth factors/cytokines, nutrition, and reactive oxygen species. The structure of tumor vessels in old and young hosts is different. Angiogenesis-stimulating soluble factors change with age. The reduced sensitivity to angiogenic factors may be responsible for the age-related decline in tumor growth and expansion. Tumor angiogenesis is also dependent on immune function. Generally, the production of angiogenic factors and the body's response to them decline with age. Aging also influences extracellular matrix biosynthesis and extracellular matrix physiology may affect malignancy. Generally, tumors in older hosts contain more fibrous tissue. After fibrosis, angiogenesis in older hosts is inhibited. Fibrosis may also reduce invasiveness and metastasis. The age-associated decline in immune function is an important factor for the pathogenesis of tumor development in patients of middle and old age. The metastatic potential of cancer cells may depend partly on systemic soluble humoral factors found in the blood or the lymphatic stream. Whereas some tumors are dependent on hormones for their growth and expansion, malignancy of tumors may be influenced by age-associated changing hormone levels, such as thymic or glucocorticoid hormones. Some of their effects may modulate immune function. Likewise, cytokine and other growth factors are involved in tumor formation and metastasis. The dietary habits of elderly people may affect age-associated changes of the tumor phenotype. Dietary restriction may reduce tumor incidence and metastasis in cancer and prolong the survival time (Okada et al., 2012).

Higher cancer incidence with longer mean life-spans requires physicians to develop a better understanding of the epidemiology of cancer and aging. A greater understanding of cancer and aging will provide valuable opportunities to find treatment strategies that maximize survival and maintain quality of life in older cancer patients (Eser et al., 2010a; Clough-Gorr et al., 2012).

5. Epidemiology of cancer in Turkey

Survival time in developed and developing countries is increasing. This condition arises from several factors of high quality of life, such as good nutrition and living conditions and progression in health care. The increased incidence of cancer in people over 50–60 years old may actually be attributed to 2 factors. One is the aging of the population and the other is the diffusion of environmental carcinogenic agents (Longo et al., 2009; Mena et al., 2009; Eser et al., 2010a). In Europe, over 45% of all cancers occur in patients over 70 years of age. It is expected that 70% of all cancers will occur in people 65 years and over by the year 2020 (Leibovici et al., 2009). A total of 2.4 million new cancer cases were diagnosed in EU countries in 2008. The most-seen types of cancers were lung, colorectal, prostate, and breast. Because the population of Europe is aging, the rate of new cases of cancer is also expected to increase. Of course there are regional differences in cancer incidence in Europe. In 2008, the highest incidence rate for all combined cancer types was in North and West Europe; it was lower in some Mediterranean countries such as Turkey (OECD/European Union, 2010). Because the young population of Turkey is aging, an older demographic structure is appearing. Turkey's current life expectancy at birth is 75 and it will be 78 by the year 2023. The current 65+ age group population rate is 7.5% and it will be 20.8% by the year 2050 according to population projections by the National Institute of Statistics in 2013 (www.tuik.gov.tr). In Turkey, cancer incidence rates have also risen due to individual attitudes and environmental risk factors,

as in other countries (Figure 4). The distribution of new cancer cases by age group on the basis of 2005 data for Turkey is as follows: 1) The population of 60 years of age or older constitutes 49.8% of total new cases. New cases in this age group make up 41.7% of cases in women and 55.7% in men. 2) The population of 50 years of age or older constitutes 72.8% of total new cases. New cases in this age group make up 64.3% of cases in women and 79% in men. 3) The population of 40 years of age or older constitutes 87.5% of total new cases. New cases in this age group make up 83.4% of cases in women and 90.6% in men. These results clearly show that most cancers are observed in patients over 40 years of age in Turkey. The average life-span of the cancer patients is also increasing. In total, there are demographic transitions, increasing longevity, improvements in the registry system, early diagnosis, and more effective treatment methods. Therefore, cancer prevention policies at individual and country levels are very important. Cancer (21.1%) was the second highest cause of death after diseases of the circulatory system (37.9%) in 2012 in Turkey. Again, cancer (21.3%) continued to be the second highest cause of death after diseases of circulatory system (39.8%) in 2013. However, it is expected to increase in the following decades. Therefore, Turkey has to consider cancer control programs in the future. Cancer control programs first aim to reduce the consumption of tobacco products and reinforce healthy nutrition habits/avoidance of obesity by means of education or laws. Breast, cervical, colorectal, and stomach cancer screening programs, which have become more of an issue for Turkey, have also been introduced. In Turkey lung cancer is most frequent among

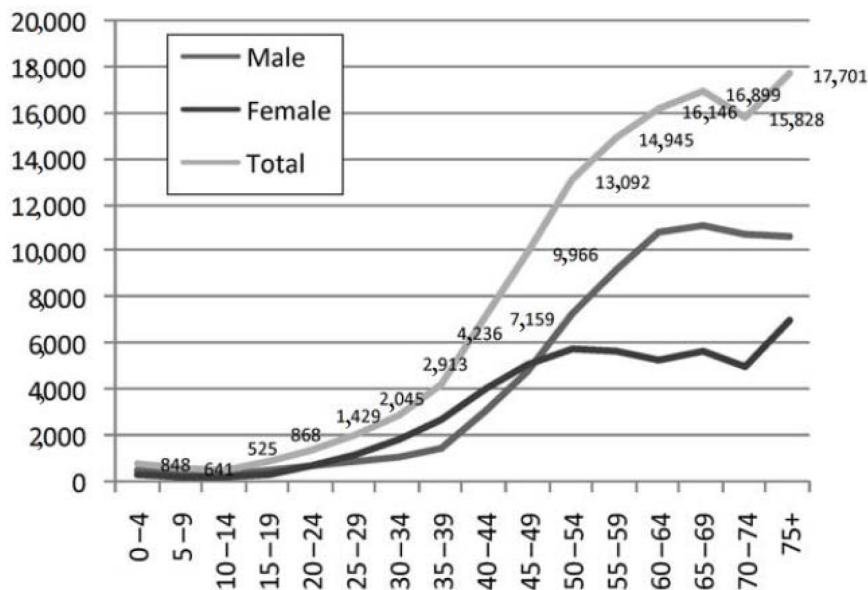


Figure 4. Cancer incidence (crude) in Turkey by age group in 2005 (from Yilmaz et al., 2011).

men and breast cancer is most frequent among women. Cancers of the stomach, colon and rectum, lung, liver, and esophagus are associated with the highest incidence worldwide, in addition to sex-specific malignancies of the female breast, uterus, and cervix and the male prostate (Yilmaz et al., 2011).

In Turkey, cancer, which was fourth among causes of death during the 1970s, has risen to second place following cardiac disease today. In 1991 the first active cancer surveillance registry was carried out in İzmir Province. Later other registries were established. In 2006, a total of 24,428 cancer cases (14,581 males and 9847 females) were reported by the combined 8 registries. They estimated that new cancer cases arise in 82,481 males and in 55,767 females a year in Turkey. The estimated age-specific and age-adjusted incidence rates for all cancers excluding nonmelanoma skin cancer in Turkey are 2101 per 100,000 among males and 1294 among females. In men, lung cancer was the first malignancy at 26.3% with 60.3 per 100,000, followed by prostate (10%), bladder (8.5%), stomach (6.8%), and colorectal (6.9%) cancer. In women, breast was the most common cancer (23.3%), followed by colorectal (8.1%), thyroid (6.2%), stomach (5.9%), and lung (5.2%) cancer. Although lung cancer was the most common cancer type for both sexes, it was seen at a rate over 7 times higher in men (60.3%) than in women (7.7%) (Eser et al., 2010b). Turkey's population is still young, with over half the population under 30 years of age. Turkey's population growth rate is 1.31 and cancer, with 170,000 new cases a year, has become one of the country's key public health problems. It is estimated that by 2030 cancer-related expenditures in Turkey will double, and 1.3 million people will be afflicted with cancer (www.tuik.gov.tr).

Longitudinal cohorts will be important in Turkey, as in other countries. In the last few years, some pilot studies have been published about age-specific incidence ratios of cancers, such as breast, melanoma, and colorectal cancers. All these studies have shown an increasing trend (Eser et

al., 2010a; Eser and Özdemir, 2012; Stillman et al., 2012). Turkey has a growing economy, but with the increasing of the aged population over 65 years, some socioeconomic and health problems are seen. It is obvious that cancer has become one of the major public health problems in Turkey in the last few decades. Cancers that have primary prevention and secondary prevention strategies constitute the major segment of cancers, which gives the opportunity to establish effective cancer control programs. The expected rise in cancer incidence and prevalence require well-designed and efficient cancer control programs in Turkey, as in other developed countries. First of all, existing programs must be improved and realized through well-planned and budgeted strategies in order to enhance the average survival and quality of life of cancer patients. In addition, reducing the financial burden of cancer treatment costs, which comes along with the increase in cancer incidence and prevalence, underlines the need in Turkey for efficient long-term new cancer scanning and control strategies.

6. Conclusion

In relation to aging and cancerogenesis, there are multifactorial effects. A country that has a young but aging population must investigate underlying mechanisms and prepare preventive studies more carefully and in an organized way. The message is thus clear not only for epidemiologists and population health experts but for everyone of all ages: understanding the facts surrounding the prevention of many forms of cancer is an important step in promoting individual and community health. At the same time, health professionals engaged in cancer research need to accept that they have a moral and ethical responsibility to promote translational practices whereby research findings are incorporated into practical actions that have beneficial outcomes for both individuals and society.

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