

Review

Ageing as an Important Risk Factor for Cancer

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Abstract. An ageing population is a typical feature of many developed countries across the world. Analyzed from a biomedical and philosophical point of view, this phenomenon is also a potential risk factor for social sustainability of communities. The association between ageing and cancer seems to be more than apparent. Therefore, the further increase of epidemic-like incidence of malignant tumors in a population can be expected in the near future. Elderly people usually suffer from age-dependent diseases, and such polymorbidity can seriously affect the treatment of malignant tumors. Such an impending situation may be associated with multiple medical, social and economic issues. This article summarizes data about the possible molecular mechanism influencing rapid spreading of tumors in the elderly population. Reduction of the activity of DNA repair machinery is a likely genetic cause. Besides this, even epigenetic mechanisms can influence this process. In this context, the role of cancer stroma in controlling multiple biological properties of tumors is a prospective target for translational research with potential therapeutic outcomes.

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Cancer Incidence Is Increasing Worldwide

The headlines of many articles inform us about epidemic incidence of cancer worldwide. It is disputable whether this reflects the truth or how much it reflects journalists' efforts to attract reader's attention to sensational information and thus improve the economical profit of their particular publication.

The epidemiologic data from the Czech Republic (and similarly from others) do indicate a remarkably high incidence of tumors (1, 2). According to the Czech Oncological Society (<http://www.linkos.cz/en>), almost 500,000 people suffer from cancer. About 80,000 new patients are diagnosed with cancer and 27,000 die from their disease each year. The majority of tumors were diagnosed in persons older than 55 years of age (3). This figure is alarming in the context of a country with population a little over 10 million citizens. There are many hypothetical explanations for this discouraging situation. One reason may be seen in the lifestyle, with a high caloric diet, stress, reduction of physical activity, exposure to pollution, frequently with a genotoxic effect. The progress in diagnostic technologies enabling effective screening of cancer and health authority-promoted campaigns may also be behind this high increase of incidence, because these diseases can now be diagnosed in very early stages. Such new screening strategies also improve the results of therapy, which is more effective and also completely curative at the early stages of cancer. Comparison of the demographic situation from other countries also suggests a relationship between ageing and cancer incidence.

An Ageing Population Influences Cancer Incidence

It is first necessary to determine the factors that facilitate an increase of life expectancy in many countries. Consequently,

Table I. *Examples of life expectancy and cancer death rate, worldwide.*

Country	Life expectancy (years)
Japan, Switzerland, San Marino, Italy, Singapore, Iceland, Andorra, Australia, Spain, Qatar ⁺ , Israel, Monaco, France, Sweden, Canada, Luxembourg, Cyprus, Norway, New Zealand, Netherlands, Austria, Greece, Ireland, South Korea, Finland, Germany, United Kingdom, Belgium, Malta, Slovenia, Portugal	>80
Kuwait ⁺ , Denmark, Chile, Costa Rica, Bahrain ⁺ , United States, Cuba, Czech Republic, Barbados, Colombia ⁺ , Brunei ⁺ , Croatia, Cook Islands, Panama ⁺ , Peru, Maldives ⁺ , Uruguay, Estonia, Poland, Slovakia, Bosnia/Herzegovina, Ecuador, Argentina, United Arab Emirates ⁺ , Turkey, Tunisia ⁺ , China, Venezuela ⁺ , Saudi Arabia ⁺ , Macedonia, Vietnam, Syria, Bahamas, Hungary, Saint Lucia ⁰ , Mexico ⁺	75-79
Kenya, Marshall Islands ⁰ , Afghanistan, Rwanda, Tanzania ⁺ , Liberia ⁺ , Mauritania ⁺ , Gambia ⁺ , South Africa, Djibouti ⁰ , Congo ⁺ , Malawi ⁺ , Benin ⁺ , Togo ⁺ , Ivory Coast ⁺ , Niger ⁺ , Uganda, Burkina Fasso ⁺ , Guinea ⁺ , Zambia ⁺ , Zimbabwe, Equatorial Guinea ⁺ , Nigeria ⁺ , Burundi, Cameroon ⁺ , Mozambique ⁺ , Chad ⁺ , Angola ⁺ , Mali ⁺ , Swaziland ⁺ , Lesotho ⁺ , Guinea-Bissau ⁺ , Somalia, D.R. Congo ⁺ , Central Africa ⁺ , Sierra Leone ⁺	45-60

European countries, *African countries*. Death rate from cancer per 100,000 persons: ⁺<100, ⁰data not available from World Life Expectancy (<http://www.worldlifeexpectancy.com>).

the links between ageing and its relationship to cancer will become more apparent. Life expectancy is progressively increasing worldwide, dramatically so in the course of the 20th century. The average human lifespan at the beginning of the 20th century was approximately 50-60 years of age and did not change until the beginning of the 1950s. Life expectancy increased in the following decades dramatically and has now reach around 80 years of age in many developed countries (4). The burden of mortality due to infectious diseases, which were the main cause of death until the middle of the 20th century, was significantly reduced after the massive introduction of sulfonamides and antibiotics to clinical practice. Cardiovascular diseases are still in the leading cause of death in many countries; however, associated mortality exhibits a decreasing tendency. Many patients survive longer due to the application of new therapeutic approaches (*e.g.* preventive cardiology) and novel procedures of interventional cardiology (5). This development has opened the way for expansion of malignant diseases in the elderly. Concerning the role of ageing, it is evident from Table I, that life expectancy over 75 years of age is very common in Europe, the Americas and in developed Asian countries. This life expectancy can reflect multiple aspects of human life, from lifestyle to climate. Above all, it also well reflects the wealth of a community. This latter aspect is primarily responsible for ease of the accessibility to medical care, including advanced medical technologies and modern therapeutics. Such communities or countries are also typically bearing the burden of high tumor incidence and associated mortality (<http://www.worldlifeexpectancy.com>). On the other hand, the lowest life span is seen in certain African countries. Despite the sparse population-based health data from these countries, the tumor incidence expressed as the death rate from cancer is significantly lower in comparison to countries with a high lifespan (6-8). Moreover, cancer-related mortality

can be influenced by other factors such as the high percentage of human immunodeficiency virus (HIV) positivity and acquired immunodeficiency syndrome (AIDS)-associated cancer. This situation can be further exemplified by colorectal cancer; where its incidence is higher in Southern Africa with a higher life expectancy than in other countries of this region (9). These type of data evoke many questions which can help in understanding the mechanisms influencing the increased cancer incidence in the elderly.

Biological Background of Ageing and Impact on Cancer Formation

Ageing is an integral aspect of the life of all organisms, including humans. It is not easy to define all the processes limiting our lifespan. The explanation of ageing is, usually, abstract. For example, according to the Encyclopaedia Britannica, ageing is defined as a number of progressive physiological changes in an organism that lead to senescence, or a decline of biological functions and of the organism's ability to adapt to metabolic stress (<http://www.britannica.com/science/aging-life-process>). Ageing itself is not a disease (10). It is the normal development of an individual (11). However, old age is associated with well-known, typical problems and related comorbidities (Table II) (12). On the cellular level, the ageing is associated with genomic instability, telomere attrition, epigenetic alterations, qualitative and quantitative changes of protein spectra, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communications (13, 14). These events result in the accumulation of irreparable damage to important processes in the body (15).

The age-altered stem cell can be a source of tissue/organ function failure or even cancer formation. It seems that the risk of developing cancer reflects the number of mitotic

Table II. *Problems typical of ageing.*

System	Problem
Nervous	Neurodegeneration Dementia Cognitive decline
Sensual	Eye disease (presbyopia, cataract, macular degeneration) Hearing loss
Cardiovascular	Atherosclerosis Heart disease
Locomotory	Sarcopenia Osteoarthritis Osteopenia
Metabolism	Diabetes mellitus

divisions of adult tissue stem cells (16). This hypothesis highlights the role of ageing on the increased cancer incidence in population because the number of stem cell divisions must clearly be higher in the elderly in comparison to the young. This idea also underscores the proposed role of cancer stem cells in tumor formation and spreading (17). It is now well understood that precise DNA repair is critical in stem cells (14), making them more resistant to DNA damage (18). On the other hand, adult tissue stem cells face genotoxic stimuli over decades. Once their DNA-repair capacity is exhausted and attenuated, the resulting genetic instability in stem cells can be causally associated with cancer formation in the elderly (14). The process of ageing can be well described in cells with damaged DNA-repair activity (19) (Figure 1). Longevity seems to be associated with higher capacity for gene repair, as is apparent in the comparison of short- and long-living organisms (20). However, aging is associated with a reduction of gene repair. This can be well demonstrated in the case of DNA polymerase $\delta 1$, which is very important for DNA replication and repair. Expression of this enzyme is significantly reduced during the course of ageing of an individual. It is three times lower in lymphocytes from donors aged 70 years in comparison to a 30 year-old person (21). Similarly, human dermal fibroblasts (HDFs) isolated from donors of different ages significantly differ in gene expression activity (22). HDFs from elderly donors exhibit lower production of extracellular matrix. This is well correlated to clinical signs of skin ageing. HDF transition to myofibroblast after cytokine stimulation is also lower than in the case of cells collected from young donors. This can be also correlated to well-documented clinical differences in wound healing. Similarly, the number of DNA strand breaks and time required for their repair is significantly influenced by ageing (22, 23). Double-strand DNA breaks can even participate to

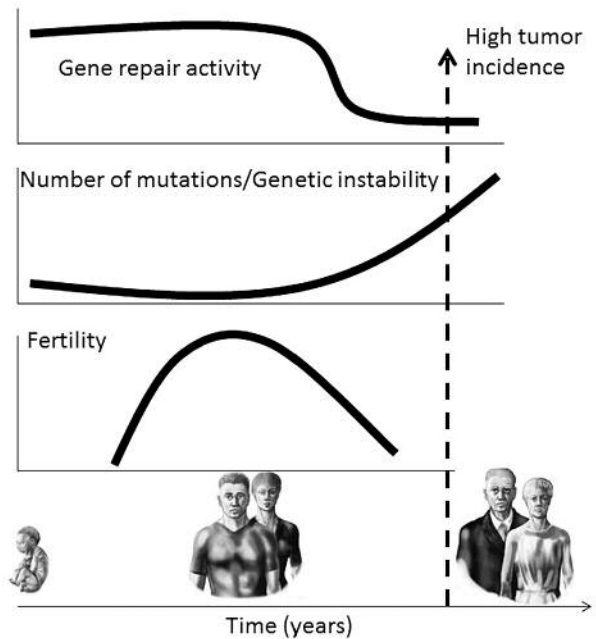


Figure 1. *Schematic presentation of temporal coincidence between reduction of capacity for DNA repair, increased number of mutations increasing genetic instability, fertile age and beginning of the period of high incidence of malignant tumors in humans.*

the loss of heterozygosity in the elderly and can be important for cancerogenesis (24, 25). The total number of mutations acquired during ageing is extremely high, and robust genomic technologies demonstrated that 3,000-13,000 genes per genome can be affected by 5,000-50,000 mutations (26). It is likely that such genomic alterations could be responsible for many health problems associated with ageing, such as neurodegeneration including Parkinson's and Alzheimer's disease (27, 28). The comparison of reduced DNA-repair activity, accumulation of mutations, cancer incidence and fertility seems to be interesting from a biological point of view (Figure 1). Accumulation of these alterations in tissue stem cells or cells forming their microenvironment can participate in the selection of aberrant clones that can give a rise to a malignant tumor (29, 30) (Figure 2). Genetically damaged stem cells as a potential cancer-initiating population are normally removed from the niche as demonstrated for example in hair graying, explained by the elimination of damaged melanocyte precursors (31). However, if this process of elimination is not successful, genetically unstable stem cells persist in their stem cell niche and their role in cancer initiation is highly probable (Figure 3). These genetic alterations can also significantly participate in the occurrence of cancer-related symptoms and comorbidities (Figure 3).

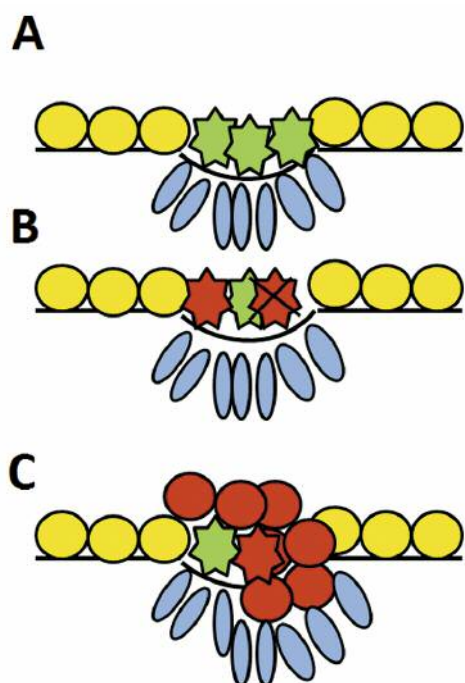


Figure 2. Model of the role of genetically altered stem cells in cancer formation. A: Normal tissue stem cells (green asterisks) located in their niche are supported by other cells, for example fibroblasts (blue oval cells). These tissue stem cells produce normal differentiated cells (yellow rings). B: When the stem cells are genetically altered (red asterisks), internal control mechanisms including immune surveillance try to remove them (crossed red asterisk) in order to prevent cancer formation. C: If their removal is not successful, these cells are cancer stem/initiating cells, the source of cancer origin and growth (red asterisk and rings). The cells originally supporting the stem cells will stimulate the growth and spread of the tumor.

Various cancer-specific genetic mutation signatures have been proposed. It is interesting in the context of this article that almost 75% of them are also seen in ageing (32, 33). This can be further well illustrated in clinical hematology, where a number of mutations of genes associated with leukemia was significantly elevated in 20% of healthy people aged over 90 years (34).

Summarizing the demographic, epidemiological and biological data, the life-time risk of developing cancer in Western societies is 50% (35).

Mutations and Epigenetics

During a lifetime, the human body encounters many exogenous stimuli resulting in mutagenic events. These can be due to physical factors (UV irradiation, X-ray *etc.*), or chemical substances (many food additives, air/water pollutants *etc.*). Regardless of their nature, they are

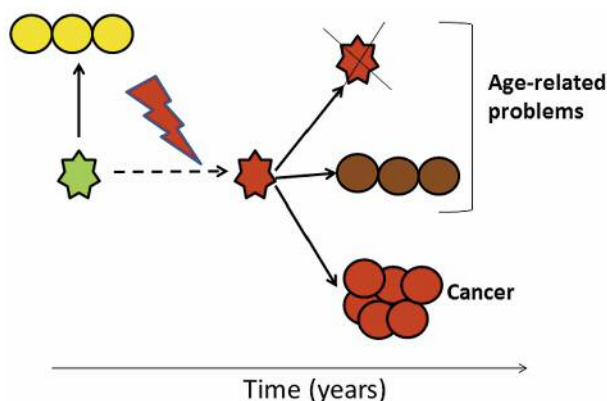


Figure 3. Model of the role of a genetically affected stem cell in the formation of age-associated symptoms and cancer. Normal tissue stem cells (green asterisk) produce normal functionally active cells (yellow rings). When these stem cells are genetically unstable due to accumulation of mutations (red asterisk), they are removed (crossed red asterisk), they produce functionally abnormal but non-tumor cells (brown circles) or cancer cells (red circles). A lack of cells arising from age-dependent removal of stem cells and the production of functionally abnormal differentiated cells can be responsible for ageing-associated problems.

associated with a genotoxic effect. Besides these exogenous mutagens, free radicals, such as highly potent superoxides, are produced by our own body as a by-product of metabolism. These reactive oxygen species can be considered as the main endogenous source of mutations. Once DNA errors are not repaired with a high accuracy and efficiency, they can be responsible for development of many major problems, including cancer. However, a certain frequency of errors occurring during DNA maintenance and replication in the cell cycle is naturally anticipated. Complicated cellular enzymatic machinery is, therefore, employed in their correction.

There are also longstanding discussions about effect of small doses of *e.g.* radiation. The linear no-threshold model is a model formerly used in radiation protection. Firstly, it was used to quantify radiation exposure and based on this theory, regulatory limits of radiation were set. It assumes that the long-term, biological damage is directly proportional to the total obtained dose. On the other hand, some others highlight that a certain threshold must be overcome before the onset of adverse events. Furthermore, two principally competing theories on the effect of such small doses are postulated: the threshold model, which assumes that very small exposures are harmless, and the radiation hormesis model, which claims that radiation at very small doses can even be beneficial. The reality for small-dose exposures is still disputed and recent data are probably inconclusive (36). Despite this discussion, a parallel model can be applied to

ageing, where a high dose response would be comparable to effects seen in the elderly.

The role of mutagens seems to be even more complex. Besides resulting in genetic modifications, they are also very active in the control of epigenetic processes. These include *e.g.* DNA methylation and acetylation, as well as histone acetylation, influencing the activity of many genes. These are important for the transition from embryonic to fetal stage (37), from youth to old age, from normal tissue to cancerous tissue (38). From this point of view, DNA methylation may be important link between ageing, genome instability and cancerogenesis (39). The role of epigenetics in inactivation of gene repair can be well demonstrated in gastrointestinal tumors, as well as in the case of triple-negative breast cancer. The poor prognosis of a patient is associated with an inactivation of breast cancer 1 (*BRCA1*) by methylation of its gene promoter (40, 41). This gene can participate in DNA repair. Synergism of genetic instability induced by a reduction of activity of gene repair mechanisms with epigenetic mechanisms triggered by *e.g.* overproduction of reactive oxygen species can be important in cancer initiation and further progression (42). Modern large-scale genomic procedures, in combination with experimental and clinical research, can help us in understanding to this complex interplay.

Genetic Diseases as Models of Ageing and Cancer

DNA repair is very important for the maintenance of the integrity of an individual genome. It is also a significant aid for the prevention of serious, frequently fatal diseases, including cancer (43). DNA-repair activity seems to be attenuated during the course of ageing. From this point of view, it can be interesting to compare results of ageing with situations seen in diseases or syndromes associated with DNA-repair failure (44, 45). Diseases such as xeroderma pigmentosum, Werner syndrome, Lynch syndrome and Fanconi anemia can be considered paradigmatic examples. Association of these rare diseases with untimely occurring malignant tumors was the leading motif in their initial clinical description (30, 46-50).

The Hutchinson-Gilford progeria syndrome is caused by lamin A defect. Affected individuals suffer from premature ageing accompanied by all typical symptoms. Interestingly, patients with this disease also exhibit instability of the genome very similar to physiological ageing (51). Down syndrome induced by chromosome 21 trisomy is also accompanied by premature ageing and genetic instability associated with defective DNA repair (52, 53). A high incidence of acute myeloid leukemia in these patients was well documented (54). These data from well-defined genetic diseases suggests that a DNA-repair deficiency in the course of normal ageing can also result in increased risk of cancer in the elderly population (14).

Stroma as a Link Between Wound Healing and Cancer: Controlling Biological Behavior of Tumors

The capacity for regeneration and wound repair seems to be negatively correlated with longevity from the phylogenetic point of view. On the contrary, cancer incidence is much higher in complex long-living organisms than in simple organisms with a short life expectancy (36). Despite this contrast, there are numerous similarities between the tissue healing/regeneration and cancer. This concept was postulated almost 30 years ago (55). Granulation tissues of wounds and tumor stroma are quite similar. They share similar morphology. Their gene-expression profiles are also remarkably overlapping. Both tissues are composed from activated fibroblasts (producing the extracellular matrix, growth factors and other cytokines and chemokines), inflammatory cells and immature capillaries (56-58). Interestingly, cancer-associated fibroblasts (CAFs) of tumor stroma produce pro-inflammatory cytokines/chemokines such as interleukin 6 (IL6), IL8 and chemokine (C-X-C motif) ligand 1 (CXCL1) (59). Similar products can also be released from specialized inflammatory cells. CAFs are thus important in maintaining the stability of the microenvironment within the tumor. This observation corresponds with the stimulatory role of chronic inflammation on cancer initiation seen in facultative precancerosis. Surprisingly, a secretory phenotype typical for inflammation is also frequently reported during ageing and in cellular senescence (11). Inflammatory cells represent also an important source of reactive oxygen radicals, with the above mentioned consequences (60). The positive effect of stromal cells on cancer progression was documented in many types of tumor, including tumors arising in the squamous stratified epithelium (61). Although the tumor stroma is morphologically not very rich in glioblastoma, it seems to be important for driving the biology even of this type of tumor (62). Moreover, CAFs isolated from other neuroectodermal tumors are able to stimulate invasiveness of glioblastoma cells *in vitro* (62). Pro-inflammatory cytokines/chemokines such as IL6, IL8 and CXCL1 were also described as having a very important influence on the intercellular crosstalk in other neuroectodermal tumors *e.g.* in malignant melanoma (63-65). Moreover, IL6, IL8 and CXCL1 were also found to be part of the gene signature of an aggressive malignant glioblastoma typical of old patients (66). In the context of this article, the role of these particular factors is most likely not tumor type-specific because these proteins also participate in intercellular interactions in squamous cell carcinoma. They are also seen in course of wound healing (57) and belong to so called senescence-associated secretory phenotype family (67).

Despite differences in anatomical tumor origin and type, cancer cells are frequently genetically altered and they vitally

require specific microenvironment support. This seems to be critical for cancer cell proliferation, as well as for the migratory activity of cancer cells and consequently metastasis formation. Stromal dominance can even actively drive cancer progression as in the case of dystrophic epidermolysis bullosa (68). The stroma here becomes very powerful due to chronic inflammation linked to hereditary epidermal fragility. In this case, synergistic cancer-supporting microenvironment and life-long inflammation upgrades even relatively non-aggressive cutaneous squamous cell carcinoma to a deadly disease, killing patients.

Paradigms Behind Cancer Biology and Ageing

Malignant tumors represent by nature a heterogeneous group of diseases. Despite the tumor type and anatomical origin, all tumors can, for the sake of simplicity, be divided into three main categories that can substantiate the final strategy for their prevention and therapy.

The first group is presented by hereditary cancer. *A priori* pathological mutation-bearing genetic material is transferred by gametes (for example *BRCA1* causing breast/ovary cancer or retinoblastoma protein 1 (*RBI*) in retinoblastoma) to offspring. Affected individuals acquire cancer usually in childhood or in early adulthood. Efficient genetic counseling and oncological screening in affected families can be crucially important in order to prevent the clinical manifestation of disease.

Secondly, cancer as an infectious disease is caused by viral infections human papilloma virus and uterine cervix carcinoma, hepatitis virus and hepatocellular carcinoma) or indirectly by bacterial infection (*Helicobacter pylori* and stomach cancer) or parasitic infestation (in case of chronic bilharziosis in urinary bladder carcinoma). Vaccine development and an effective nation-wide vaccination campaign along suitable clinical or laboratory screening can prevent of this type of disease.

However, the largest proportion of cancer cases is represented by sporadic tumors. This issue was thoroughly investigated in recent years (54), however, others immediately raised multiple objections against such simplification (69). Despite the ongoing florid discussion, ageing seems to be integral component in both the aforementioned concepts. Due to inherent genetic instability, ageing represents an implicit factor for cancer development. Cancer-affected elderly patients represent an immensely growing target population for cancer therapy in the near future. Limited capacity of DNA repair allowing successful editing of stochastically occurring mutations is further restricted in the elderly by associated epigenetic mechanisms. By extension, a generalized decrease in gene-repair capacity in the process of ageing might be regarded as an integral regulatory check-point of natural human

ontogeny. This mechanism ensures limits of an individual's existence after the accomplishment of individual reproduction and gene spreading (Figure 1) (70).

Factors such as improved hygiene standards, vaccination, efficient anti-infectious therapy, and improvements of interventional and preventive cardiology increase the life expectancy of many individuals, namely in developed countries with good accessibility to high quality medical care. This also leads inevitably to the fact that a substantially large proportion of people break such a set limit of "ontogenetically meaningful survival" living beyond their biological limits. Thus, ageing-associated cancer is a plausible mechanism securely ensuring population exchange.

However, there is a notably growing group of successful cancer-free elderly people such as centenarians. Of course, the overall genetic set-up and individual genetic variants associated with longevity are being intensively studied (71). The question of whether individual extreme long cancer-free survival is the consequence of mutations of putative master genes controlling and coordinating multiple aging-related pathways remains. It is necessary to mention here that these very old cancer-free people also frequently exhibit cancer-associated mutations in their genome but these mutations remain clinically silent (34). Results of these studies are extremely exciting for biologists, but they are naturally opening additional serious ethical as well as existential and philosophical considerations. Is it just a mistake of code which enables an individual to 'escape from the standards' or is there any additional value which might be transferred beyond their individual life?

Cancer and Ageing from a Socioeconomic Point of View

Longevity, ageing and death are fundamental topics traditionally attracting attention of people across various cultures. Treatises on these aspects of life are frequently a crucial component of many religious and philosophical systems. Ageing represents the factor that predetermines our biological existence with its multiple facets including medical problems such as high cancer incidence. Global rapid increase of the elderly population is frequently referred to as "the grey tsunami". In the scenario of increasing life expectancy worldwide, it is mandatory to identify the characteristics of a healthy aging phenotype. Nevertheless, the associated increased incidence of malignant tumors is also inevitably accompanied by numerous social and economic issues. Oncological care is complicated and psychologically exhausting not only for families, but also for the society as a whole. Modern anticancer therapy is fairly expensive in many cases. Combined data demonstrating the increasing lifespan of population and epidemic-like cancer statistics worldwide should warrant governmental bodies and

responsible healthcare authorities providing financial budgets necessary to cover the expenses associated with ageing-related cancer (72, 73).

Therapeutic Challenges

It is estimated that the proportion of people suffering from cancer will increase in the near future. This increase may be associated with serious medical, social and economic problems. These patients will suffer from many age-associated diseases frequently making them too vulnerable for usual surgery and classical aggressive anticancer therapy. Targeting of the cancer microenvironment can modulate the biological behavior of cancer cells. From this point of view, the therapeutic manipulation of the stroma represents a promising mode of adjuvant therapy. Inactivation of molecules participating in the crosstalk between tumor-forming cells seems to be promising therapeutic option. Failure in recruiting stromal elements could potentially be able to repair the low level of differentiation of malignant elements (56). The cancer stroma is strongly infiltrated by specialized inflammatory cells. Many of them significantly stimulate cancer cell proliferation and migration. Moreover, the whole cancer stroma exhibits a similar inflammatory secretory phenotype. Interestingly, well-known simple and inexpensive anti-inflammatory therapy can be useful in cancer treatment as well as in the prevention of the disease (74, 75). As an example from an *in vitro* experiment, acetylsalicylic acid is able to block breast cancer tumor-initiating cells as well as cancer cells by the inhibition of the transforming growth factor β /homolog to *Drosophila* protein, mothers against decapentaplegic protein 4 (TGF β /SMAD4) signaling pathway (76). However, the clinical relevancy of this finding must be verified by a carefully designed clinical study. The preventive application of selective anticancer drugs in ageing has also been proposed (77).

Conclusion

The trend for population ageing will become even more common in many countries worldwide, where it will closely track economic development. The increased incidence of cancer will demand attention of the governmental authorities to establish an adequate economic base necessary for the expensive treatment of numerous patients. This situation also sets a great challenge for the development of breaking innovations for cancer prevention and therapy.

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