Premature aging in childhood cancer survivors (Review)

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Received September 13, 2022; Accepted October 26, 2022

DOI: 10.3892/ol.2022.13629

Abstract. Progress in medicine has increased the survival time of children suffering from cancer; >80% of patients survive for at least 5 years from the end of treatment. However, there are late effects of anticancer therapy, which accompany this success. Two-thirds of childhood cancer survivors (CCSs) have at least one late effect (any side effects or complications of anticancer treatment that appear months to years after the completion of treatment), e.g. endocrinopathies, cardiovascular diseases or subsequent cancers, and half of these late effects are serious or life threatening. These late consequences of childhood cancer treatment pose a serious health, social and economic problem. A common mechanism for developing a number of late effects is the onset of premature biological aging, which is associated with the early onset of chronic diseases and death. Cellular senescence in cancer survivors is caused by therapy that can induce chromosomal aberrations, mutations, telomere shortening, epigenetic alterations and mitochondrial dysfunctions. The mechanisms of accelerated aging in cancer survivors have not yet been fully clarified. The measurement of biological age in survivors can help improve the understanding of aging mechanisms and identify risk factors for premature aging. However, to the best of our knowledge, no single marker for the evaluation of biological or functional age is known, so it is therefore necessary to measure the consequences of anticancer treatment using complex assessments. The present review presents an overview of premature aging in CCSs and of the mechanisms involved in its development, focusing on the association of senescence and late effects.

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Key words: childhood cancer survivors, late effects, premature aging, aging-related diseases

1. Introduction

Owing to improvements in the diagnostics and treatment of childhood cancer, >80% of patients are cured (1). However, childhood cancer survivors (CCSs) are at risk of developing late effects (any side effects or complications of anticancer treatment that appear months to years after the completion of treatment). Approximately two-thirds of CCSs have at least one late effect of anticancer therapy, and nearly half of these late effects are serious or life threatening (1-4). Late effects can affect any organ or tissue and can occur at different time intervals after treatment (early, <5 years; late, 5-20 years; very late, >20 years) (5,6). Given the high number of CCSs (>500,000 in Europe in 2020) (1), these late effects are not only a medical, but also a social and economic problem.

2. CCSs and late effects

Several studies have already shown that numerous diseases develop much earlier in patients after cancer treatment compared with development in the general population (7-9). For example, at 20 years of age, CCSs have the same risk of developing a chronic disease as their siblings at 50 years of age (8). These patients are three times more likely to develop chronic diseases (e.g., subsequent neoplasms, cardiovascular diseases and endocrinopathies) compared with a control group of their siblings (8,9). In our recent study on CCSs (10), ultrasound sporadic renal angiomyolipomas were detected much earlier in CCSs (median age at diagnosis, 27.9 years) compared with that reported in the general population (50-60 years).

At 45 years of age, 95% of patients in remission have at least one chronic health problem (11). Late effects can be divided according to the type of organ or system disability and according to the type and extent of anticancer and/or supportive therapy used. Late effects can affect any organ or system (e.g., endocrine, cardiovascular, kidney, lung, gastrointestinal, hearing, eye, skin, neurocognitive and locomotor disorders), the most common of which are endocrinopathies, with the most severe, often lethal, including cardiovascular

diseases and subsequent cancers (1-4,12,13). Psychosocial consequences, which are often caused or increased by somatic damage, are also very important for the quality of life (1). Late effects therefore need to be investigated to elucidate their mechanisms; this will contribute to reducing late effect incidence rates and improving and individualizing screening.

A common mechanism of late effects is the premature biological aging of the individual. Biological aging is a heterogeneous process; it does not undergo the same rate of chronological aging and is the basis for the loss of physiological functions of the body and the increase in aging-related diseases over time (14,15). Biological aging is associated with the early onset of chronic diseases and leads to a higher risk of premature death of patients compared to the general population (8). Research has shown that cancer treatment leads to accelerated aging, which manifests as an increased risk of subsequent neoplasms or cardiovascular diseases in CCSs and in adult cancer survivors (16). Stelwagen *et al* (17) demonstrated that long-term testicular cancer survivors treated with cisplatin had accelerated vascular aging (increased vascular stiffness, increased ischemic and recovery time on digital cooling tests, and albuminuria), and Zhu *et al* (18) found the frequent appearance of aging-related conditions in breast cancer survivors. In another study, long-term childhood acute lymphoblastic leukemia (ALL) survivors demonstrated a late mortality that was more than three times higher than in the age-matched US population (19). In a study by Bøhn *et al* (20), one out of four long-term survivors of adolescent and young adult (AYA) cancer complained of chronic fatigue, and in a multicenter study in the UK (21), 85% of AYA cancer survivors complained of chronic fatigue 1 year after finishing therapy. The differences between these data are likely due to the method of evaluation and on the population of survivors themselves.

3. Cell senescence

Cellular senescence serves an important role in aging; it is a process of permanent cell cycle arrest and involves the induction of specific phenotypic changes (22). Senescent cells stop dividing, enter the G0 phase and remain metabolically active (22). As cells undergo senescence in response to various stress stimuli, the whole process of senescence can be understood as a defense mechanism of the organism to prevent further growth of damaged cells (22,23).

There are two known pathways of cellular senescence: Replicative and premature/accelerated senescence. The observation that cells grown *in vitro* divide ~50 times and then stop dividing has led to the description of replicative senescence (24). This senescence is caused by telomere shortening (25). Premature/accelerated cellular senescence is independent of the length of the telomeres; in this pathway, cells respond to various negative stimuli such as oxidative stress or DNA damage (23). The difference between replicative and accelerated senescence is only in the stimulus to which the cells respond, its reaction is the same in both cases (23). When cell senescence is in response to a DNA-damaging stress stimuli, cells that are unable to undergo senescence and apoptosis due to mutations in genes important for their induction (e.g., $p14^{ARF}$, $p16^{INK4}$, RB1 and p53 pathways) will still divide and their daughter cells will suffer the same damage (26,27).

Several mechanisms [such as, epigenetic changes, accumulation of mutations, including mutations of mitochondrial DNA (mtDNA), and depletion of stem cells] contribute to aging and the development of aging-related diseases. Epigenetic changes include the accumulation of histone variants and aberrant histone modifications, changes in the accessibility of chromatin and deregulated expression of some microRNAs [e.g. expression of miR-99b-5p, miR-130b-5p, miR-505-5p and miR-425-3p are negatively associated with age (28)] that cause changes in gene transcription (29). The accumulation of mutations throughout life contributes to the biological changes that accompany aging (30), which may explain the increased risk of subsequent cancer and accelerated aging in CCSs (31). Mitochondrial genomes display a higher mutation rate compared with somatic genomes and are more sensitive to the genotoxic effects of anticancer therapy (32). mtDNA mutations can damage the mitochondria and thus reduce the ability of muscle cells to regenerate, which is one of the signs of old age (33). Stem cell compartments are depleted with age (34,35), but these cells can also undergo an accelerated aging process (36,37).

4. Biological age and its measurement

Biological age. To estimate accelerated aging in cancer survivors, the term called biological age was introduced, which predicts the risk of late effects more precisely than does chronological age (16). However, the assessment of biological age is difficult, and there is no consensus on its methodology. The so-called aging clocks are a set of signs that can predict biological age; epigenetic and proteomic aging clocks have been developed. The functional status and incidence of chronic diseases and geriatric syndromes can also be used to assess biological age (38).

Epigenetic clocks. Epigenetic clocks use markers based on different levels of CpG site methylation (e.g., Horvath's clock based on 353 CpG sites and Hannum's clock based on 71 CpG sites) detected in blood or tissues (39,40); results of these two clocks correlated with chronological age in relatively healthy individuals (39,40). Subsequently, Horvath's group developed another aging clock based on methylation (41). In the development of this clock, not only chronological data were used, but predictors of phenotypic age (for example, age at menopause, decline of the immune system and aging-related morbidity) were also taken into account. Therefore, it was assumed that this clock would better correlate with biological age, life expectancy and the incidence of aging-related diseases (41,42). Several other epigenetic clocks have been described (16). Furthermore, the methylation of some genes, including ELOVL2, FHL2 and PENK, have been shown to correlate well with biological age (43).

Several studies have found a correlation between an increased risk of cancer and biological age in the general population. Zheng *et al* (44) measured epigenetic age using Horvath's method and observed that an increase in epigenetic age was associated with an increased risk of developing any cancer within 3 years. In another study, Levine *et al* (45) found

that a 1-year increase in biological age measured by Levine's clock (based on methylation of 513 CpG sites) was associated with a 5% increase in the risk of lung cancer. Acceleration of biological age measured using Levine's clock was associated with an increased risk of invasive breast cancer, particularly in postmenopausal women (46). However, other studies have provided conflicting results. For example, an EPIC-Italy study found that men had a biological age-associated risk of colorectal cancer according to Horvath's clocks and the methylation levels of FHL2 CpG islands, but not according to Hannum's or Weidner's clocks, or according to the methylation levels of ELOVL2 CpG islands (47). In that study, an association with ELOVL2 methylation and breast cancer occurrence was observed in women, but no associations between any of the five clocks tested and colorectal cancer risk in women was found.

Only a limited number of studies have followed the epigenetic age of CCSs. Epigenetic age acceleration (EAA) evaluated by Levine's clock increased in CCSs compared to controls (48). Higher EAA was observed particularly after chest, abdominal or pelvic radiotherapy, or after alkylating agent, glucocorticoid or epipodophyllotoxin therapy. Acceleration was also associated with hypertension, myocardial infarction, obesity, peripheral neuropathy and pulmonary obstruction or diffusion deficits (48), and EAA could be partly influenced by the lifestyle of survivors (for example, participating in physical activity, alcohol consumption and smoking) (48).

Proteomic aging clocks. Proteomic aging clocks are based on aging-related biomarkers in the blood measured using proteomic methods. Johnson *et al* (49) developed two versions of the proteomic aging clock: A 23-protein panel and an 83-protein panel. Both panels showed good correlations with chronological age. Tanaka *et al* (50) identified >200 proteins that are associated with age and developed a proteomic age clock that used only eight of those proteins, which correlated well with the chronological age of controls.

Markers of cell aging. To date, several markers of cell aging have been identified, such as $p16^{INK4a}$, $p16^{ARF}$, senescence-associated β-galactosidase, hyperphosphorylation of Rb1 and the levels of certain cytokines including, IL-6 and IL-8 (51-53). A case-control study found that an increase in $p16^{INK4a}$ expression in peripheral blood T-lymphocytes was associated with an increased risk of breast cancer (54). Sanoff *et al* (55) demonstrated that the expression of $p16^{INK4a}$ and ARF in peripheral blood T-lymphocytes increases immediately after chemotherapy and remains high for at least 1 year after treatment. This increase corresponded to ~15 years of chronological aging. Cellular age evaluated in terms of $p16^{INK4a}$ expression in peripheral blood T-lymphocytes was found to be >2 decades higher than chronological age in CCSs and AYA cancer survivors. Furthermore, 'frail' survivors had higher expression levels of $p16^{INK4a}$ than did 'non-frail' survivors (56). Higher expression levels of $p16^{INK4a}$ has also been associated with higher doses of chemotherapy prior to transplantation and with autologous hematopoietic stem cell transplantation (HSCT) in adult cancer survivors (57). The expression of $p16^{INK4a}$ in peripheral blood T-lymphocytes was higher in adult survivors of testicular germ cell cancer (both seminoma and non-seminoma) treated by chemotherapy compared with that in the matched controls (58). To the bets of our knowledge, similar information is not available for CCSs.

5. Premature aging in cancer survivors

One of the important signs of aging is frailty; for example, sarcopenia, decreased muscle strength, poor endurance, slow walking speed and low physical activity (59-61). Frailty was found in ~8% of CCSs who were >10 years post-cancer diagnosis and in their fourth decade of life (59). This increased to ~60% in older survivors of adult cancer who were >70 years old (60), whereas prevalence of frailty was ~10% in adults >65 years in various European, American and Asian populations (61). Frailty among cancer survivors is associated with a higher incidence of chronic diseases and mortality (62). A recent St. Jude lifetime cohort study showed that frailty in young adult cancer survivors is associated with decline in cognitive functions (63). The prevalence of frailty also depends on methodology (e.g., questionnaire, clinical examination and exercise testing) and on the definition of frailty itself (61,64). Childhood patients of brain tumors, bone tumors and Hodgkin lymphoma (HL) are at the highest risk of frailty (59,64). Brain, abdominal and pelvic irradiation, platinum cytostatic chemotherapy, HSCT, limb amputation and lung operations are also factors in the increased risk of frailty in CCSs (59,64,65). Female CCSs are frequently more frail than male CCSs (59,64). This can be partially explained by the sex-dependent acute toxicity of some cytostatics and their late effects (66). Furthermore, in the non-cancer population, frailty is more common in women than in men, which is thought to be due to the lower amount of muscle mass in women (61). Anticancer therapy-associated risk factors may be potentiated by lifestyle, such as smoking, obesity and low physical activity (59,64,67-69).

Osteoporosis and sarcopenia are additional signs of premature aging in CCSs. Decreased bone mineral density is common in CCSs (occurring in 9-18% of patients) and risk factors include ALL, brain tumors, HSCT, glucocorticoid therapy, radiation therapy, malnutrition and hypogonadisms and/or growth hormone deficiency (70). In two studies, Lee and Kim (71) and Lee *et al* (72) described an increased risk of cardiovascular diseases in male adult cancer survivors with sarcopenia, compared with those without and an almost three times higher risk of metabolic syndrome in both adult male and female survivors with sarcopenia.

Plasma levels of CRP, IL-1β, IL-6, advanced glycation end products (AGE) and the reduced/oxidized glutathione ratio were significantly higher in childhood HL survivors than in the matched controls (73). AGE accumulation leads to the subsequent activation of AGE receptors and the activation of intracellular pro-inflammatory signaling (73). These findings indicate that signs of inflammation and activation of antioxidant enzymes are one of the factors that contribute to aging, and may serve an important role in the development of late effects in CCSs (73). AGE are also responsible for alteration of the function and/or structure of secreted proteins, including fibrinogen, collagen and low-density lipoproteins (74).

Inflammation activates two important cytotoxic mediators, reactive oxygen species (ROS) and reactive nitrogen species (RNS), which damage cellular DNA (75). ROS

and RNS induce the production of cytokines and adhesion molecules and activate lymphocytes (76). Subsequently, this induces a chronic systemic inflammatory response known as 'inflamm-aging', which damages tissues by this increase in cytokines and activated lymphocytes (77). Inflamm-aging can involve any organ or tissue and is responsible for the development of osteoporosis, infertility, and metabolic and cardiovascular diseases (78). Metabolic syndrome occurs in about one in three CCSs, but its incidence can be influenced by lifestyle (79). Several studies have focused on the association of variants of different genes with metabolic syndrome in CCSs (80,81). Only one of these CCS studies observed a correlation between variants of the leptin receptor gene and obesity in women, especially those exposed to cranial irradiation, but no correlation was observed in men (81). The association of obesity with brain irradiation may suggest that growth hormone deficiency is involved in the development of metabolic syndrome (81). As such, it seems that in addition to genetic influences, several other factors serve roles in the development of metabolic syndrome in CCSs; however, further studies are necessary for clarification.

Peripheral blood mononuclear cells from CCSs showed less efficient oxidative phosphorylation, increased lipid peroxidation and increased lactate fermentation compared to matched controls (82). The age prediction model based on modifications of glucose catabolism in mononuclear cells showed that the predicted ages were higher compared with the actual ages; by contrast, the predicted ages of healthy controls were not very different from their actual ages (82).

Several studies in women (including prepubertal girls, AYA and in older premenopausal women) treated with chemotherapy showed decrease in anti-Müllerian hormone (AMH) levels during chemotherapy (83-85). Recovery of AMH levels was variable and, in some cases, low levels persisted. AMH levels provide information about ovarian reserve and may be a marker of ovarian aging (86). Female CCSs with a heterozygous genotype of rs1172822 in the BRSK1 gene had an increased risk of low AMH value. BRSK1 is thought to affect the secretion of gonadotropin-releasing hormone from the hypothalamus (87). Variants of cytochrome P450 (CYP450) enzymes that are important in drug metabolism affect the decrease in AMH levels in CCSs. For example, the CYP3A4*3 variant is associated with lower AMH levels, whereas CYP2B6*2 has a protective effect on the ovaries, which was manifested by higher AMH levels (88).

6. Mechanisms of premature senescence in CCSs

Premature aging in cancer survivors is caused by several mechanisms both at the cellular level and at the level of the whole individual. Cellular senescence in cancer survivors can be caused by chemotherapy, which may induce structural chromosomal aberrations, aneuploidy, polyploidy and endoreduplication, and/or by ionizing radiation, which generates single and double-strand DNA breaks. Studies detecting chromosomal abnormalities in the lymphocytes (89,90) and telomere shortening (65,75,91) in CCSs have been published. Childhood HL male survivors had a higher frequency of chromosomal breaks and gross chromosomal rearrangements that were random and complex compared with the healthy controls. This is consistent with genomic instability (89). Smith *et al* (90) detected a higher occurrence of translocation involving chromosome 4 in childhood and young adult HL survivors. The frequency of translocations was not significantly different between the group treated by radiation only and the group treated by combination of radiation and chemotherapy, but the latter group had a higher frequency of translocations (90). The CCSs of high-risk neuroblastoma (65), ALL (75) and a large group (2,427 CCSs) with different childhood cancers that included leukemias, lymphomas and solid tumors (91) had significantly shorter telomere length than the age- and sex-matched controls.

Another mechanism involved in the induction of cell senescence is epigenetic changes. Different patterns of DNA methylation were described in peripheral leukocytes from AYA HL survivors and from their unaffected twins (92). Daniel *et al* (76) observed altered DNA methylation in genes for immune response, inflammatory processes and oxidative stress in CCS T-cells >10 years after patients were treated with total body irradiation and HSCT.

Lipshultz *et al* (93) reported mitochondrial dysfunction as one of the signs of cell senescence in CCSs. The authors detected a higher mtDNA copy number per cell in childhood ALL survivors exposed to doxorubicin compared with those exposed to doxorubicin along with the cardioprotective dexrazoxane. Dexrazoxane acts by decreasing the formation of superoxide, and the authors suggested that this may represent persistent mitochondrial clonal expansion in response to early damage during doxorubicin administration, and dexrazoxane prevented doxorubicin-induced cardiac mitochondrial dysfunction by protecting oxidative phosphorylation activities and mtDNA integrity (93).

Another mechanism involved in premature aging in survivors is changes affecting the integrity of the entire individual, such as with endocrinopathies. For example, growth hormone deficiency was found in 12.5% of CCSs and in 46.5% of CCSs after radiotherapy involving the hypothalamic-pituitary region (70). This hormonal deficiency induces dysfunction in the insulin and insulin-like growth factor signaling pathway and the ability of cells to detect glucose, which is associated with increased risk of mortality and cardiovascular morbidity (62). Furthermore, luteinizing hormone/follicle stimulating hormone deficiency may participate in the premature aging reported in 6.5% of CCSs (70). The main risk factors are damage to the hypothalamic-pituitary region by a tumor, surgery and/or radiotherapy.

Other late effects in CCSs that mimic senescence are cognitive defects. These include, processing speed and executive functions, but attention and memory may also be affected (94). The risk factors for cognitive defects are a younger age at diagnosis, female sex and brain irradiation (94). Cognitive defects are accompanied by structural changes in the brain. Armstrong *et al* (95) described the correlation of memory impairment with decreased temporal lobe volume, white matter defects and changes of blood oxygen-dependent signaling in the hippocampus of survivors of childhood ALL after 24 Gy cranial radiotherapy but not at lower doses. Cerebrovascular dysfunction, and cardiac and pulmonary late effects can also be involved in cognitive defects through altered organ perfusion and hypoxia in childhood HL survivors (96).

7. Conclusions and future directions

Taken together, these studies indicate that anticancer therapy accelerates aging. However, the mechanisms of accelerated aging in cancer survivors are not yet fully understood. Measuring biological age in CCSs can help to improve the understanding of the biological mechanism of aging and to identify risk factors for premature aging. However, to the best of our knowledge, no single marker is currently known to assess biological or functional age. Therefore, a multilevel approach is needed to measure the aging-related consequences of anticancer therapy (97).

Owing to the increasing number of cancer survivors at risk of accelerated aging, the National Cancer Institute (US National Institutes of Health) organizes think tanks to design perspective strategies to prevent, slow or reverse the aging consequences of cancer and its treatment (98). To develop research on the late effects of CCSs, prepare guidelines for patient follow-up, spread awareness of CCS issues and enable CCSs to actively participate in care, PanCare was established (https: //www.pancare.eu). PanCare is a European network of experts, former pediatric cancer patients and their families, which aims to ensure that every cancer patient diagnosed in childhood and adolescence is provided with optimal long-term care after treatment. The PanCare project creates a common European platform for the care of this growing group of former pediatric oncology patients and for research projects in this area (99). PanCare studies also focus on understanding the risk of developing subsequent tumors and the risk of late mortality and morbidity in CCSs (100,101).

The present review summarizes the role premature aging plays in the development of late effects. Additional studies are needed not only to understand premature aging in CCSs but also how to prevent it. Aging-related consequences of cancer treatments would lead to anti-aging prevention and therapy. Physical training has been described to improve signs of frailty in CCSs (102). However, more data are needed to prepare training programs suitable for cancer survivors. It has been known for almost a century that caloric restriction prolongs life and delays aging-related pathology in laboratory animals (103). Evolutionarily conserved signaling pathways, such as mTOR, appear to mediate the anti-aging effects of diets, and the study of these pathways has contributed to the finding of molecular targets for pharmacological interventions (104). However, the suitability of these diets in cancer survivors for the prevention of accelerated aging is unclear.

Acknowledgements

Not applicable.

Funding

This study was supported by The Ministry of Health of the Czech Republic (grant no. AZV CR NV19-03-00245).

Availability of data and materials

Not applicable.

Authors' contributions

TE designed the review and completed the manuscript. JK and AZ performed the literature search and drafted the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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