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Childhood Cancer Survivorship: An Update on Evolving Paradigms for Understanding Pathogenesis and Screening for Therapy-Related Late Effects

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Abstract

Purpose of review—Five-year survival for many childhood cancers approaches 80%, and there is a growing number of long-term survivors in the U.S.. These survivors are at risk for developing adverse health-related complications. We highlight recently published studies that provide new insight into the association between specific therapeutic exposures and late-occurring complications such as second malignant neoplasms, cardiovascular disease, endocrinopathies, and neurocognitive impairment.

Recent findings—The incidence for many long-term complications continues to increase with longer follow-up. Investigators have begun to explore the impact of aging and the role of genetic susceptibility as modifiers of risk in diseases where there is a clear association between therapeutic exposure and adverse outcome. Increased awareness of the importance of screening has set the stage for assessment of the impact of early detection for reduction of long-term morbidity and mortality among childhood cancer survivors at highest risk for therapy-related complications.

Summary—The long-term health-related burden in childhood cancer survivors is substantial. Recent studies exploring etiopathogenesis of treatment-related late effects have provided important information that will assist in ongoing efforts to develop personalized cancer care. Efficacious medical interventions are needed to help mitigate treatment-related complications in high risk survivors.

Keywords

Childhood cancer; Survivorship; Late effects; Genetics; Medical interventions

Introduction

Advances in treatment strategies for childhood cancer and supportive care have resulted in marked improvements in survival, with 5-year survival rates approaching 80%. [1] As of 2009, there were an estimated 363,000 survivors of childhood cancer in the U.S.; [2] of these approximately 24% have survived more than 30 years since their diagnosis, contributing to the growing number of long-term survivors of childhood and adult-onset cancer in the U.S.. [3] Unlike adults, children tolerate the acute effects of therapy relatively well. However, the

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use of chemotherapy, radiation, and/or surgery at an early age can contribute to complications that may not become apparent until years after completion of therapy. A recent article from the Childhood Cancer Survivor Study (CCSS) cohort reported that two out of three survivors will develop a chronic health condition, and more than one third will develop a condition that is severe or life-threatening.[4] The CCSS cohort consists of 14,357 five-year survivors of childhood cancer, diagnosed between 1970–1986 at one of 26 collaborating CCSS institutions, who completed a comprehensive questionnaire regarding a wide-range of health-related outcomes; 4,023 siblings were recruited to compare outcomes. [5] Overall, childhood cancer survivors were at an 8-fold increased risk of developing a severe or life-threatening health condition when compared to age- and sex-matched siblings. [4]

During the past three decades, research on survivorship issues has demonstrated well-established associations between specific therapeutic exposures and adverse outcomes such as subsequent malignant neoplasms, cardiopulmonary dysfunction, endocrinopathies, and neurosensory disorders (Table 1). Recognizing the need for a systematic plan for lifelong surveillance of health-related outcomes, the Children's Oncology Group (COG) developed risk-based exposure-related guidelines, designed for follow-up care of children who completed treatment for their malignancies.[6] The Guidelines and patient-directed informational "Health Links" can be downloaded from www.survivorshipguideline.org. We present here selected highlights from recently published studies that demonstrate how research is shedding new light on the etiopathogenesis and risk factors for some of the more commonly occurring late effects.

Second malignant neoplasms

Childhood cancer survivors are at risk for development of subsequent malignant neoplasms (SMN).[7–11**] This risk is approximately 10-fold greater than the general population, and an important health-related concern for the aging childhood cancer survivor population.[12] SMNs are the leading cause of treatment-related mortality in long-term childhood cancer survivors (standardized mortality ratio [SMR], 15.2; 95%CI 13.9–6.6).[13] Commonly reported solid SMNs include breast, thyroid, skin and brain cancer, and there is a strong and well-defined association with radiation exposure that is characterized by a latency that exceeds 10 years.[7] Other SMNs such as therapy-associated leukemia (t-MDS/AML) are notable for their shorter latency (typically <10 years from primary cancer diagnosis), and association with alkylating agents and/or topoisomerase II inhibitor chemotherapy.[7] Much of the information on incidence and risk factors for SMNs has come from studies involving large cohorts of survivors (CCSS,[5] British Childhood Cancer Survivor Study [BCCSS] [14]), followed >5 years from initial cancer diagnosis. These studies have found that for many SMNs such as solid cancers, the incidence continues to increase with longer follow-up, with no plateau of risk over time.[11**, 12] Importantly, survivors who develop a first SMN (SN1) are at an especially high risk of multiple occurrences of subsequent neoplasms, such that within 20 years from diagnosis of SN1, the estimated cumulative incidence of another neoplasm is 47%.[15*] Although not evaluated in the study, the experience of children with Li-Fraumeni syndrome (LFS) or retinoblastoma (Rb) would suggest that underlying genetic susceptibility (ie: *TP53* or *CHEK2* (LFS), *RBI* (Rb) gene alterations) may play a role in the development of multiple SMNs in a subset of childhood cancer survivors.

A recent report[11**] from the BCCSS found that the cumulative incidence of survivors developing an SMN increased steadily with sustained age from 1.6% at age 20 years to nearly 14% at age 60 years, compared to 8.4% expected at the latter age in the general population. The overall standardized incidence ratio (SIR) was four times more than

expected (SIR=3.9; 95%CI 3.6–4.2), and the absolute excess risk (AER) in survivors older than 40 years was highest for digestive and genitourinary SMNs (AER=5.9 [95%CI 2.5–9.3] and 6.0 [95%CI, 2.3–9.6] per 100,000 person-years, respectively. Especially sobering were the findings that by age 50, the incidence for colorectal cancer (CRC) for survivors treated with direct abdominopelvic irradiation was comparable to the risk in individuals with at least two first-degree relatives affected by CRC. Two additional studies[16,* 17*] have reported a high incidence of gastrointestinal cancers in childhood cancer survivors when compared to the general population, with the highest risk associated with abdominal radiation (SIR=11.2; 95%CI 7.6–16.4).[17*] This supports the current COG Guidelines recommendation that CRC surveillance for high risk survivors should begin at a much younger age (beginning 10 years after radiation or at age 35 years, whichever is later) than that currently recommended for the general population. A recent study[18**] has raised the possibility of host genetic susceptibility as a modifier of SMN risk. Investigators found two variants at chromosome 6p21 to be associated with radiation-induced SMNs in survivors of Hodgkin lymphoma. While these findings require further validation, they raise the possibility of novel gene-exposure associations that may help direct prevention strategies in survivors at highest risk for radiation-associated SMNs.

While it is well-recognized that radiation exposure largely contributes to the risk of solid SMNs, there is emerging evidence that chemotherapy may further modify the increasing risk over time. A report from the CCSS found that while children treated with abdominopelvic radiation were at the highest risk of gastrointestinal cancer, the overall risk among those not treated with radiation remained higher (SIR=2.4; 95%CI 1.4–3.9) than the general population; high-dose procarbazine (relative risk [RR]=3.2; 95%CI 1.1–9.4) and platinum chemotherapy (RR=7.6; 95%CI 2.3–25.5) independently increased the risk of gastrointestinal SMNs.[17] Another study evaluating risk of thyroid cancer reported a higher risk with alkylating chemotherapy exposure (RR=2.4; 95%CI 1.3–4.5), but only in radiation dose range <20 Gy, in which cell sparing likely predominates over cell killing.[19] These findings add to the evidence that chemotherapy alone may increase the risk of solid SMNs, which to date, was mainly thought to be related to prior radiation therapy.

Cardiovascular disease

Cardiovascular complications are a leading cause of therapy-related morbidity and mortality in long-term survivors of childhood malignancy.[20] These survivors are at a 15-fold increased risk of developing congestive heart failure (CHF) compared to age-matched controls.[4] There is a strong dose-dependent association between anthracycline exposure and risk of CHF; this risk is modified by younger age at exposure, female gender, and chest irradiation.[20] The cardiotoxicity may manifest as symptomatic CHF or asymptomatic functional cardiac abnormalities (ie: systolic or diastolic dysfunction) detected on imaging studies.[20] The incidence of CHF is below 5% with cumulative anthracyclines exposure of <300 mg/m²; the incidence approaches 20% at doses between 300 and 600 mg/m², and exceeds 35% for doses >600 mg/m². [20–22] A recent study of 5-year survivors of childhood cancer confirmed the previously reported exponentially increasing risk of CHF with anthracycline dose.[23**] CHF often develops years after cessation of therapy, and the incidence rises with follow-up.[20] Outcome following clinical CHF is poor; 5-year overall survival rate is <50%.[24, 25] Current estimates are that of the more than 363,000 childhood cancer survivors, nearly 60% will have been exposed to anthracyclines.[20]

With longer follow-up of childhood cancer survivors, it has become apparent that lower cumulative doses of anthracyclines (<150 mg/m²) may place children at risk for cardiac compromise while others do not appear to be affected despite very high doses, raising the possibility that inter-individual variability in anthracycline pharmacodynamics may modify

risk of cardiotoxicity.[20] Using a biologically plausible candidate gene approach, investigators have begun to identify host polymorphisms that could alter metabolic pathways of anthracyclines. A recent report from the COG found that homozygosity for the G allele in carbonyl reductase-3 (*CBR3*) contributes to increased cardiomyopathy risk associated with low- to moderate-dose (1–250 mg/m²) anthracyclines, such that there seems to be no “safe dose” for patients homozygous for the *CBR3* V244M G allele.[26**] A subsequent study evaluating genetic modifiers of early- and late-occurring cardiotoxicity identified multiple variants of the *SLC28A3* gene as important modifiers of anthracycline-related cardiotoxicity risk.[27**] Many of these genomic variables, when fully established, could be important in facilitating the implementation of targeted primary prevention strategies.

Advances in non-invasive cardiac imaging have allowed investigators to identify a growing population of survivors who may be at risk for late occurring CHF, setting the stage for pharmacologic interventions to prevent progression to clinical CHF.[28, 29] Traditionally, monitoring of anthracycline-related cardiotoxicity has relied upon serial 2-dimensional (2D) echocardiography using resting left ventricular ejection fraction (LVEF) or shortening fraction (LVSF).[30] However, serial screening using echocardiography-derived LVEF/SF has increasingly been recognized as inadequate for detecting subtle changes in myocardial function. Often, at the point when changes in LVEF/SF are detected, functional deterioration proceeds rapidly and is often irreversible.[29–31] Cardiac magnetic resonance (CMR) has emerged as an alternative to traditional 2D echocardiography due to its superior intraobserver and interobserver reproducibility and ability to detect functional LV systolic changes at an earlier timepoint.[32] A recent report found that among survivors previously undiagnosed with cardiotoxicity, a substantial proportion had abnormal LVEF (32%) and cardiac mass (48%), defined as more than two standard deviations below the mean of normative CMR data.[33*] In fact, 2D echocardiography overestimated the mean LVEF for this population by 5%, and had a sensitivity of 25% and a false-negative rate of 75% for detection of LVEF <50%, a threshold that typically warrants cardiology referral for potential pharmacologic intervention.[33] It remains to be seen whether newer 2D echocardiographic measurements of myocardial remodeling (tissue doppler, strain) or 3D echocardiography can be successfully integrated into screening strategies in centers where CMR is either unavailable or cost-prohibitive.[34*]

Endocrine complications

Endocrine late effects after cancer therapy include problems with growth, weight, puberty and gonadal function, bone health, thyroid and adrenal function.[35] Studies evaluating endocrine-related complications in childhood cancer survivors have generally focused on specific outcomes, often limited to cohorts with single cancer diagnoses.[35] A recent single-institution study found that 57.6% of patients followed at a designated childhood cancer survivorship clinic had at least one endocrine condition, and 22.7% had multiple endocrine disorders.[36*] Commonly reported endocrine problems were weight related (under/overweight [31%]), abnormal gonadal function (25.2%) and growth disorders (19.4%).[36*] Survivors of hematopoietic cell transplantation (HCT) and children who were older during cancer treatment were at a significantly increased risk for having an endocrine complication.

An emerging area of concern is the development of metabolic syndrome in long-term survivors of childhood cancer, defined as a cluster of health conditions which include: insulin resistance, overweight/obesity, hypertension, and dyslipidemia.[35, 37] This is especially problematic for survivors treated with cardiotoxic therapies such as anthracyclines and radiation, where certain components of metabolic syndrome (hypertension, insulin resistance) have been shown to substantially modify cardiovascular

disease risk.[25] A study in acute lymphoblastic leukemia survivors found the prevalence of metabolic syndrome to be 9.2%, with the highest prevalence noted in HCT survivors (18.6%).[38*] HCT with total body irradiation was associated with a higher rate of hypertriglyceridemia (odds ratio [OR]=4.5, $p=0.004$), low-level of high-density lipoprotein cholesterol (OR=2.5, $p=0.02$) and elevated fasting glucose (OR=6.1, $p=0.04$).[38] While the pathophysiology of therapy-related metabolic syndrome has not been elucidated, several investigators have proposed growth hormone (GH) deficiency as a critical modifier of risk, [37, 39] a finding validated in a subsequent cross-sectional study evaluating cardiovascular risk and insulin resistance in long-term survivors of childhood cancer.[40*]

Adult survivors of childhood cancer may also have reduced bone mineral density (BMD), as measured by DEXA scans.[35] Cancer treatments that interfere with bone accretion during adolescence and young adulthood are thought to increase the risk of osteoporosis and osteoporotic fractures later in life,[41] a notion that is not supported by a recent CCSS report.[42*] Known factors for reduced BMD in childhood cancer survivors include treatment with corticosteroids, radiation, methotrexate chemotherapy, and other endocrinopathies such as GH deficiency and hypogonadism.[35] As in previously described late effects, low BMD is likely a result of a combination of treatment-specific exposures and other host-environment interactions.[35, 43] A cross-sectional study of long-term cancer survivors revealed that in addition to treatment-related variables such as radiation and corticosteroids, lower levels of physical activity and higher daily television viewing time significantly increased the risk of osteopenia.[44**] The identification of modifiable risk factors such as physical inactivity may provide opportunities for the development of interventions for risk reduction in childhood cancer survivors at high risk for osteopenia in adulthood.

Neurocognitive sequelae

Neurocognitive complications can occur as a result of surgery and/or radiation to the brain, systemic therapy with high dose methotrexate, or intrathecal therapy.[45, 46] As a result, children with brain tumor, ALL, or non-Hodgkin lymphoma (NHL) appear to be at highest risk.[45, 46] In children treated with cranial radiation, neurocognitive deficits typically become apparent within 1–2 years following completion of therapy, and may be progressive in nature.[45, 46] Affected children may experience information-processing deficits resulting in academic difficulties, and are prone to problems with visual perceptual motor skills, receptive attention span, and expressive language. The reduction of cranial radiation dose for children with ALL and combined dose/field modification for children with brain tumors has resulted in a decrease in prevalence and severity of neurocognitive complications for children treated on contemporary protocols.[47–49] The evidence for neurocognitive complications due to chemotherapy alone is less established; described deficits are primarily restricted to attention, executive function, and complex fine-motor functioning.[49, 50]

For many long-term survivors of childhood cancer, neurocognitive deficits may affect the opportunities to participate in adult life roles, including their ability to find and maintain employment. A recent study examined the association of psychosocial, physical, and neurocognitive deficits with inability to work because of health or disability problems.[51*] Survivors with task efficiency and memory problems were more likely to report health-related unemployment or to work part-time. Employed female survivors with task efficiency, emotional regulation, and memory limitations were 20% less likely to report working in higher-skilled professional or managerial positions. The findings from this study suggest that interventions to improve employment outcomes for childhood cancer survivors should not only target physical health barriers to employment, but also include screening for mental health and neurocognitive problems.

Having poor neurocognitive function can also affect survivors' ability to access preventive care or engage in recommended physical activity. Survivors with neurocognitive problems in task efficiency are less likely to meet the Centers for Disease Control guidelines for weekly physical activity (RR=0.8, 95%CI 0.7–0.8) and less likely to engage in preventive health practices such as dental care (RR=0.92, 95%CI 0.9–1.0).[52*] While the etiology of many of these behavioral outcomes is likely to be complex, it is increasingly clear that certain subsets of cancer survivors may warrant closer surveillance for neurocognitive impairment so that proper interventions can be initiated prior to the development of additional adverse psychosocial and health-related complications.

Conclusion

Research on survivorship-related issues has produced a wealth of knowledge regarding therapy-related risk factors for late effects. There is emerging data to suggest that genetic susceptibility could be an important modifier of these adverse outcomes. Future studies evaluating etiopathogenesis of late effects in survivors of childhood cancer will need to inform approaches for personalized cancer care that weighs treatment efficacy with the future risk for treatment-related complications. The promise for primary prevention notwithstanding, there is a growing childhood cancer survivor population that remains at risk for late effects due to past treatment exposures for their primary cancer. Randomized trials of medical interventions are needed to help identify novel approaches to mitigate many of the complications described in the current paper. Lastly, it is important to note that much of data presented on health-related outcomes is derived from children treated for malignancies prior to the mid 1990s. Future studies will need to evaluate the long-term impact of reduction in intensity of treatment for many childhood malignancies such as ALL, Hodgkin and non-Hodgkin lymphoma, Wilm's tumor, rhabdomyosarcoma, and certain CNS malignancies such as medulloblastoma. Information obtained from these studies will help caregivers in cancer treatment planning, counseling of families regarding late effects of therapy, and facilitate the ongoing modification of the current COG long-term follow-up screening recommendations.

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Key points

- Advances in the treatment of childhood cancer has contributed to a growing number of long-term survivors.
- Cancer treatment at an early age can lead to health-related complications that do not become apparent until many years after completion of therapy.
- Lifelong surveillance for complications such as second malignant neoplasms, cardiopulmonary dysfunction, endocrinopathies, and neurosensory deficits is necessary for survivors of childhood cancer.
- Ongoing research into etiopathogenesis and risk factors for late effects will set the stage for prevention strategies to mitigate adverse health-related outcomes in these survivors.

Table 1

Commonly occurring late effects in survivors of childhood cancer

Adverse outcome	Therapeutic exposures associated with increased risk	Highest risk factors
Subsequent malignant neoplasm		
Thyroid cancer	Radiation to the thyroid gland	Increasing dose up to 29 Gy, female sex, younger age at radiation
Skin cancer	Radiation therapy	Increasing dose
Secondary brain tumor	Cranial irradiation	Increasing dose, younger age at treatment
Breast cancer	Radiation to breast tissue	Increasing dose, decreased risk in women treated with alkylating agents
Therapy-related leukemia	Chemotherapy: alkylating agents, topoisomerase II inhibitors	Increasing dose of chemotherapeutic agents, older age at therapeutic exposure
Cardiopulmonary		
Cardiomyopathy/congestive heart failure	Anthracycline chemotherapy	High cumulative doses (>300 mg/m ²), female sex, <5 years at treatment, radiation involving the heart
Myocardial infarction	Radiation involving heart	Underlying risk factors for coronary artery disease (smoking, hypertension, dyslipidemia, obesity, diabetes)
Pulmonary fibrosis	Bleomycin chemotherapy, radiation to chest wall or lungs	Younger age at treatment, bleomycin dose >400 U/m ²
Endocrine and musculoskeletal		
Hypothyroidism	Radiation to the thyroid gland (neck, mantle, etc.)	Increasing dose, female sex, age at treatment
Hypogonadism	Alkylating agents, craniospinal irradiation, abdomino-pelvic irradiation, gonadal irradiation	Male sex, treatment during peripubertal or post-pubertal period in girls, higher cumulative doses of alkylators
Short stature	Cranial irradiation, corticosteroids, total body irradiation	Younger age at treatment, cranial radiation dose >18 Gy, unfractionated (10 Gy) total body irradiation
Obesity	Cranial irradiation	Younger age at treatment, female sex, cranial irradiation dose >20Gy
Osteopenia/ osteoporosis	Corticosteroids, craniospinal irradiation, gonadal irradiation, total body irradiation	Associated hypothyroidism, hypogonadism, growth hormone deficiency
Avascular necrosis	Corticosteroids, high-dose radiation to any bone	Dexamethasone, adolescence, female sex
Neurosensory		
Hearing loss	Cranial radiation, platinum-based chemotherapy	Younger age at treatment, increasing radiation and chemotherapy dose
Cataracts	Cranial irradiation, steroids	Higher radiation dose, combination of steroids and radiation
Neurocognitive deficits	Cranial irradiation, intrathecal methotrexate	Female sex, younger age (<5 years) at treatment, cranial irradiation and intrathecal chemotherapy