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Review

Premature atherosclerotic cardiovascular disease in childhood cancer survivors

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ABSTRACT

Survival rates of childhood cancer have increased over the last 30 years, revealing a population with unique characteristics and risks. The effects of radiation and cardiotoxic chemotherapy predispose these children to both early and late cardiovascular disease. Cranial radiation also increases the likelihood of growth hormone deficiency, which leads to metabolic disturbances. Childhood cancer survivors are less likely to be active than their healthy siblings, and have a lower aptitude for physical activity. These issues are additive to the usual risks experienced by the general population, thereby significantly increasing the likelihood of premature cardiovascular disease. Early and regular screening and risk factor management in this population is recommended.

1. Introduction

Over 12,000 youth are diagnosed with cancer each year in the United States [1]. With improved treatments for childhood cancers, in the current era (1999–2006), 5-year survival rates have increased to 82% [2] resulting in over 325,000 childhood cancer survivors (CCS) in the United States [3] (1 in 600 children under the age of 14 years). This number is likely to increase as the incidence of the major childhood cancers continues to grow, in the face of ever-improving outcomes [3]. CCS are 8–10 times more likely to die from cardiac causes than age-matched controls [4,5]. Radiation therapy and some chemotherapeutic and biologic agents are known causes of cardiotoxicity, independently and especially in combination [6]. A report of necropsy studies in youth demonstrated severe stenosis in at least one coronary artery after >35 Gy of cardiac radiation [7]. Anthracyclines are widely used antineoplastic agents as they are very effective, yet are independently associated with elevated risk of early [8,9] and delayed cardiovascular (CV) disease and death [4,10]. The developing cardiovascular system of children is especially vulnerable to cancer therapy [11]. The most common long-term cause of non-cancer death in CCS is cardiac disease [5,6,12]. While congestive heart failure from anthracycline exposure and chest radiation therapy accounts for some deaths, most are related to traditional atherosclerotic cardiovascular disease (CVD) such as myocardial infarction, stroke, and other vascular diseases [6].

Adult cancer survivors demonstrate that these CV events are associated with the development of metabolic syndrome, insulin resistance, as is the case with atherosclerotic CVD in the general population, but with greater frequency and at a younger age. Many are asymptomatic even with severe coronary artery disease (CAD). Risk factors usually associated with aging such as obesity [13,14], hypertension [15–17], and diabetes mellitus [14] are noted prematurely after cancer therapy. We will focus on these factors and describe their prevalence, monitoring, and treatment in CCS.

2. Obesity

In non-cancer adult populations, premature CVD is closely associated with obesity [18]. Adults with increasing weight have an increased incidence of early CV events and death [18,19]. Currently in the United States, nearly 30% of youth are overweight and obese [20], which is associated with hypertension [21], low levels of high-density lipoprotein cholesterol (HDL-c) and elevated triglycerides [22,23], abnormal glucose metabolism [24], insulin resistance [23,25,26], inflammation [27–30], and functional abnormalities of the vasculature [31]. Children who are obese are likely to become obese adults, with insulin resistance [32] and lipid abnormalities [33]. CCS have been found to have an even higher incidence of obesity over the general population [34–36]. This has necessitated the establishment of simple yet reliable measurements of corporal adiposity. Body mass index, based on height and weight requires minimal training to perform, and is regularly employed to evaluate adiposity in adults and children, with good agreement in repeated measurements in adults [37–40]. Dual-energy x-ray absorptiometry (DXA) has been employed in research for its ease of acquisition and accuracy [41], and is now considered a "gold standard" for estimating body composition, but is mostly limited to research studies due to cost and complexity [42–46]. A number of studies in adult survivors of childhood cancers found no difference in rates of obesity compared to healthy siblings when using body mass index (BMI) [15], yet waist

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circumference and visceral fat content were increased in some cancers [47–49]. Conversely, the Childhood Cancer Survivors Study, a large retrospective cohort study, demonstrated an increased incidence of obesity with an accelerated rate of increase in BMI when comparing adult survivors of acute lymphoblastic leukemia (ALL) to healthy controls [34]. In a study of 319 CCS during childhood, we compared the body composition of pediatric CCS to 208 healthy control subjects. As shown in Table 1, CCS were not significantly different from healthy controls in regards to weight, BMI, or BMI percentile, however, CCS had greater adiposity, demonstrated by waist circumference, ratio of waist-to-height, and percent fat mass (PFM_{DxA}) measured by DXA, while lean body mass (LBM) was significantly lower in CCS as a whole, and in leukemia survivors specifically, but not in survivors of solid tumors. Central nervous system (CNS) tumor survivors also demonstrated greater abdominal subcutaneous and visceral fat. BMI greater or equal to the 85th percentile for age and sex-specific criteria for overweight/obesity was similar between CCS and healthy control subjects (31.4 and 32.2% respectively), with significantly greater numbers of those with a waist circumference greater or equal to the 75th percentile in the CCS population compared to controls (11% vs. 6.7%; OR 2.1; 95% CI 1.4–3.2; $P < 0.001$). Waist-to-height ratio of greater or equal to 0.5, which predicts greater CV risk, was found in 24% of the CCS group compared to 11.2% of controls (OR 2.5; 95% CI 1.5–4.1; $P < 0.001$). Hypertension was not significantly different between CCS and controls (10.7% CCS vs. 7.2% controls, $P = 0.2$) [50].

As demonstrated in our pediatric study when evaluating adiposity, the tool employed may influence the prevalence of obesity. In this young population, waist circumference or body composition measures by DXA may be a more accurate measure of adiposity than BMI [50].

The pathophysiology of obesity in CCS is multifactorial, with genetic predisposition, female sex, history of cranial radiation, and history of exposure to steroids each adding to this risk [35,51–57]. By suppressing appetite and increasing energy expenditure, leptin, a cytokine produced by adipocytes, controls energy metabolism at the level of the hypothalamus [58,59]. Obese adults and children develop resistance to leptin, as evidenced by high leptin concentration in otherwise healthy individuals [60–63]. Abnormalities in leptin receptors, with high leptin concentrations have been found in CCS [64,65]. Late onset growth hormone (GH) deficiency, which can lead to obesity, can be a result of radiation exposure in the hypothalamic-pituitary axis [51,54,66–69]. GH plays a significant role in fat cell differentiation, fat cell size [67] and resistin concentrations [66], each of which help regulate insulin sensitivity [65]. With decreased levels of GH, CCS are at increased risk of insulin resistance, type 2 diabetes mellitus, and obesity [67–70]. Young adults who have undergone cranial radiation for ALL have an elevated risk of increased abdominal, visceral, and total adiposity; increased risk of metabolic syndrome; abnormal metabolism, and decreased lean body mass [71]. In our pediatric study of CCS we found a high prevalence of GH deficiency, which explained a large proportion of the increased adiposity in this cohort [72].

Some cancer patients experience cachexia, including fatigue, abnormal metabolism, weakness, and decreased lean body mass [50], which may predispose cancer survivors to premature CV disease similar to fetal malnutrition in healthy populations [73–78]. Prolonged and continuous courses of high-dose steroids, used in induction and intensification stages of cancer therapy, stimulate hunger and decrease lean body mass [52,56], and when that follows the muscle wasting and malnutrition of cancer, survivors will have a greater tendency for obesity later in life [6].

3. Hypertension

Hypertension, one of the criteria utilized to define metabolic syndrome [79,80], is a common risk factor for heart failure [81] and ischemic CAD in adults [82,83]. CCS are twice as likely as their healthy siblings to be hypertensive [15]. Hypertension is uncommon in children prior to diagnosis of cancer [84], yet during chemotherapy, some patients experience transient hypertension [85]. In a study of pediatric ALL patients, blood pressure returned to normal after therapy, with only 1% requiring antihypertensive medications [85]. Others found a similar pattern of hypertension during induction, but also found persistence of hypertension at the end of therapy, and systolic hypertension at 5 years from diagnosis [86]. In studies of patients undergoing allogeneic hematopoietic cell transplantation hypertension was reported in up to 70% within 2 years after transplantation, and persisted in 34% after 2 years [87]. Insulin resistance and obesity foster the development of metabolic syndrome [79,88], and the incidence of both is high in long-term survivors of childhood ALL [13,17,50]. In our pediatric study, blood pressure was not different between CCS and controls at a median of 10 years after therapy [50].

The degree of systemic arterial pressure elevation is dependent on the patient's cardiovascular status, age, type of cancer, and specific medication and dose used. Elevated blood pressures are present within hours of starting chemotherapeutic agents, and resolve rapidly when medication is discontinued [89]. The mechanism is thought to be a consequence of inhibiting the VEGF receptors, but is not completely understood. Arteriolar vasodilation after exposure to intrinsic nitric oxide is reduced by VEGF inhibition, which decreases concentrations of nitric oxide, resulting in vasoconstriction, increased peripheral systemic vascular resistance, and this leads to increased systemic blood pressures [90].

Some medications utilized for cancer treatment can directly cause renal damage (ifosfamide and methotrexate), leading to hypertension [91,92]. Abdominal radiotherapy, used in Wilms tumor, neuroblastoma, is associated with hypertension [15,93–95]. Hypertension in these cases may be due to renal artery stenosis induced by the radiation therapy, or

Table 1
Comparison of body composition between CCS and controls.

	CCS (n = 319)		Leukemia (n = 110)		CNS (n = 82)		Solid Tumors (n = 127)		Controls (n = 208)
	mean ± SE	p	mean ± SE	p	mean ± SE	p	mean ± SE	p	mean ± SE
Height (cm)	158.2 ± 0.6	**0.01**	156.4 ± 1.0	**<0.001**	156.2 ± 1.0	**0.04**	158.7 ± 0.9	0.31	159.9 ± 0.7
Weight (kg)	57.2 ± 1.1	0.85	55.4 ± 1.7	0.48	58.1 ± 2.0	0.39	55.4 ± 1.4	0.92	57.0 ± 1.2
Body Mass Index (kg/m^2)	22.4 ± 0.3	0.08	22.2 ± 0.5	0.15	23.1 ± 0.6	0.08	21.8 ± 0.5	0.68	21.8 ± 0.4
Body Mass Index Percentile	67.5 ± 2.0	0.51	68.0 ± 2.8	0.25	71.0 ± 3.2	0.71	64.6 ± 3.6	0.66	66.1 ± 2.4
Waist (cm)	73.1 ± 0.9	**0.02**	72.8 ± 1.2	**0.03**	74.7 ± 1.6	**0.01**	70.7 ± 1.1	0.67	71.1 ± 1.0
Waist (cm) to height ratio (cm)	0.5 ± 0.005	**0.001**	0.46 ± 0.007	0.06	0.48 ± 0.009	0.07	0.45 ± 0.008	0.36	0.4 ± 0.006
Percent Fat Mass (DXA)	28.1 ± 0.8	**0.007**	28.6 ± 1.1	**0.004**	29.9 ± 1.2	**0.002**	26.3 ± 1.4	0.52	25.9 ± 0.9
Lean Body Mass (DXA) (kg)	38.4 ± 0.5	**0.01**	37.0 ± 0.9	**<0.001**	37.3 ± 0.9	0.06	38.6 ± 0.8	0.37	39.9 ± 0.6
Abdominal visceral fat (CT) (cm^3)	22.3 ± 1.1	0.17	22.5 ± 1.3	0.09	25.5 ± 2.3	**0.01**	18.4 ± 1.2	0.51	21.0 ± 1.2
Abdominal subcutaneous fat (CT) (cm^3)	85.2 ± 4.5	0.07	83.5 ± 6.2	0.09	97.6 ± 8.5	**0.01**	73.1 ± 6.4	0.81	77.0 ± 4.9

All measures adjusted for age-at-study, gender, race, and Tanner score.
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