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Research Article

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Cardiovascular Risk Factors in Adult Survivors of Pediatric Cancer—A Report from the Childhood Cancer Survivor Study

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Abstract

Background: Childhood cancer survivors are at higher risk of morbidity and mortality from cardiovascular disease compared with the general population.

Methods: Eight thousand five hundred ninety-nine survivors (52% male) and 2,936 siblings (46% male) from the Childhood Cancer Survivor Study, a retrospectively ascertained, prospectively followed study of persons who survived 5 years after childhood cancer diagnosed from 1970 to 1986, were evaluated for body mass index of $\geq$30 kg/m^2 based on self-reported heights and weights and self-reported use of medications for hypertension, dyslipidemia, and impaired glucose metabolism. The presence of three or more of the above constituted Cardiovascular Risk Factor Cluster (CVRFC), a surrogate for Metabolic Syndrome.

Results: Survivors were more likely than siblings to take medications for hypertension [odds ratio (OR), 1.9; 95% confidence interval (95% CI), 1.6-2.2], dyslipidemia (OR, 1.6; 95% CI, 1.3-2.0) or diabetes (OR, 1.7; 95% CI, 1.2-2.3). Among these young adults (mean age of 32 years for survivors and 33 years for siblings), survivors were not more likely than siblings to be obese or have CVRFC. In a multivariable logistic regression analysis, factors associated with having CVRFC included older age at interview [$\geq$40 versus <30 years of age (OR, 8.2; 95% CI, 3.5-19.9)], exposure to total body irradiation (OR, 5.5; 95% CI, 1.5-15.8) or radiation to the chest and abdomen (OR, 2.3; 95% CI, 1.2-2.4), and physical inactivity (OR, 1.7; 95% CI, 1.1-2.6).

Conclusions: Among adult survivors of pediatric cancer, older attained age, exposure to total body irradiation or abdominal plus chest radiation, and a sedentary life-style are associated with CVRFC. *Cancer Epidemiol Biomarkers Prev; 19(1); 170–81. ©2010 AACR.*

Introduction

As childhood cancer survivors are being followed long-term, chronic health conditions directly related to their cancer therapies are being observed. Oeffinger et al. (1) recently reported that 30 years after diagnosis, almost three fourths of survivors followed through the Childhood Cancer Survivor Study (CCSS) were found to have at least one chronic health condition. Of interest, the risk of cardiovascular disease was ~10 times higher in cancer survivors than in siblings. In the general adult population, the risk of cardiovascular disease is significantly increased among individuals who have the cardiovascular disease risk factors (CVRF) that comprise the metabolic syndrome (MetS; ref. 2). MetS is a clustering of physiologic disturbances defined in slightly different ways by different medical and health care associations; however, each definition includes measures of obesity, hypertension, dyslipidemia, and insulin resistance (Table 1; refs. 3-6). Early diagnosis of MetS or its component risk factors has been advocated so that both medical and behavioral interventions may be used to prevent or reduce the associated cardiovascular sequelae.

There is a growing body of evidence that indicates that pediatric cancer survivors are at a greater risk of developing MetS or MetS component traits than are members of the general population (7-12). The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Pediatric, Adolescent, and Young Adult Cancers (COG Guidelines) delineate risk of late effects based on cancer therapeutic exposures (13). In the COG guidelines, MetS is a potential late effect after total body and cranial irradiation (7). Among component traits, obesity has been most thoroughly studied. It is observed more commonly among leukemia and central nervous system tumor survivors, particularly among females exposed to cranial irradiation at a young age (14-16). Dyslipidemia is described in adults treated with platinum agents (17). Hypertension is associated with renal damage secondary to either chemotherapy or radiation (17-19). Cardiac

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Table 1. Definition of MetS/CVRFC

	WHO 1999	EGIR 1999	NCEP/ATPIII 2001	IDF 2005	CCSS
Obesity	BMI, >30 kg/m^2 or waist to hip ratio Males: >0.9 Females:>0.85	Waist circumference Males: ≥94 cm Females: ≥80 cm	Waist circumference Males: >40 inches or >102 cm Females: >35 inches or >88 cm	Central obesity based on ethnic waist circumference	BMI, ≥30 kg/m^2
Hypertension	≥140/90 mm Hg or treatment	≥140/90 mm Hg or treatment	≥130/85 mm Hg or treatment	≥130/85 mm Hg or treatment	Taking medication for hypertension
Dyslipidemia	TG ≥150 mg/dl or HDL-C: Males <35 mg/dl Females<39 mg/dl	TG >177 mg/dl or HDL-C <40 mg/dl	TG ≥150 mg/dl HDL-C: Males <40 mg/dl Females <50 mg/dl or treatment	TG ≥150 mg/dl HDL-C: Males <40 mg/dl Females <50 mg/dl or treatment	Taking medication for dyslipidemia
Glucose	Diabetes or IGT or IR	Fasting plasma glucose ≥110 mg/dl but not diabetic	Fasting plasma glucose ≥110 mg/dl or treatment	Fasting plasma glucose ≥100 mg/dl or Type 2 DM	Taking medication for diabetes pills or insulin
Other	Microalbuminuria: overnight albumin >20 μg/min or albumin: Creatinne ≥30 mg/g				
Required for diagnosis	Diabetes, IGT or IR plus 2 or more of above. If normal glucose 3 of the above	Hyperinsulinemia or IR plus 2 of above	Any 3 or more	Central obesity based on ethnic waist circumference Plus 2 of the above	Any 3 or more

NOTE: Indicates treatment for the condition.

Abbreviations: EGIR, European Group for the Study of Insulin Resistance; NCEP/ATP III, national Cholesterol Education Program Expert panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment panel III); TG, triglycerides; HDL, high density lipoprotein; IGT, impaired glucose tolerance; IR, insulin resistance; DM, diabetes mellitus.

disease is seen after treatment with anthracycline antibiotics or cardiac radiation (20, 21). In addition to the increased risk of MetS components, survivors of childhood cancers are reported to be at increased risk for cardiovascular morbidity/mortality when compared with noncancer controls (22, 23).

Because of the growing awareness that childhood cancer survivors are likely to be at increased risk of developing MetS and to suffer increased morbidity/mortality as a result of cardiovascular disease, the objective of this study is to use the large CCSS cohort to determine the prevalence of and factors associated with the development of Cardiovascular Risk Factor Cluster (CVRFC).

Materials and Methods

Subject Selection and Contact

The CCSS is a multi-institutional study of individuals who survived 5 or more years following treatment for cancer diagnosed during childhood or adolescence. Eligibility criteria for this study were as follows: (*a*) diagnosis of leukemia, central nervous system tumors (excluding craniopharyngiomas), Hodgkin lymphoma, non–Hodgkin lymphoma, kidney tumor, neuroblastoma, soft tissue sarcoma, or bone tumor; (*b*) diagnosis and initial treatment at one of the 26 collaborating CCSS institutions; (*c*) diagnosis date between 1970 and 1986; (*d*) age of <21 y at diagnosis; and (*e*) survival of ≥5 y from diagnosis. Survivors who had a recurrence or second malignancy were excluded from this analysis. CCSS protocol and contact documents were reviewed and approved by the Human Subjects Committee at each participating institution. Details of study design and cohort characteristics have been described elsewhere (24). Briefly, baseline data were collected for survivors and siblings using a 24-page baseline questionnaire in 1995 to 1996. The questionnaire was designed to capture a wide range of information including demographic characteristics, health habits, and frequency of diagnosed medical conditions. A follow-up questionnaire, Follow-Up 2000, was administered and

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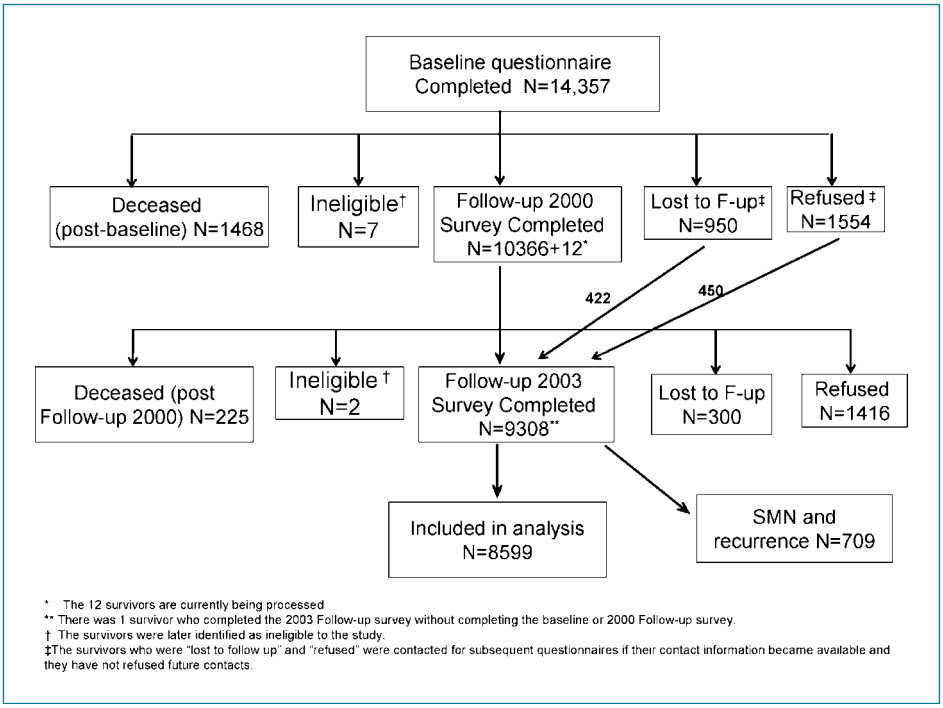

Figure 1. CCSS case participation.

included a request for updated information on cardiovascular disease outcomes. A second follow-up questionnaire, Follow-Up 2003, was administered between 2003 and 2005, updating health-related questions and medication use over the previous 2 y. Questionnaires are available on the CCSS Web site.[7]

Of the 20,691 eligible 5-y survivors, 3,058 were lost to follow-up. Of those contacted, 14,357 (81%) agreed to participate and completed the baseline questionnaire. Figure 1 describes the participation rates for each CCSS survey. Retention in this cohort is high, with only a small percentage lost to follow-up or refusing further participation. Approximately 1% of survivors in this cohort die each year. Nearest-age siblings of randomly selected participants were also invited to participate as a nonmatched comparison population. Of the 5,857 siblings invited to participate, 3,899 siblings (67%) completed the baseline survey. Of the CCSS participants, 9,308 survivors and 2,951 siblings completed the second follow-up survey. Of these, our analysis included 8,599 survivors (excluding those who had a second malignancy or recurrence after the cohort entry due to potential lack of subsequent cancer treatment data) and 2,936 sibling (excluding those who had developed cancer due to lack of cancer treatment data) are included in this analysis. A comparison of the characteristics of the participants versus the nonparticipants has been described previously (24). In summary, a comparison was made of demographic and cancer-related characteristics between the participants and nonparticipants. The two groups were found to be very similar with regard to gender, cancer diagnosis, age at diagnosis, age at contact and type of cancer treatment. There was a slightly higher nonparticipation rate in the next of kin of those survivors who had died ≥5 y after diagnosis compared with the rates of survivors still living.

Cancer Treatment Information

Information relative to the original cancer diagnosis was obtained from treating institutions for all eligible cases. For all participants who returned a signed medical release, qualitative information on original cancer treatment was abstracted from the medical record for 42 specific chemotherapeutic agents; quantitative information was abstracted on a subset of 22 of these agents. Data were also obtained on the field(s) of radiation therapy. Radiation exposure (dichotomous yes/no variable) was defined as exposure to the brain, spine, chest, abdomen, total body irradiation (TBI), or other site (extremity).

Independent Variables

Information from the baseline survey includes demographic information (sex, race/ethnicity, date of birth) and previous cardiovascular events (arteriosclerosis, coronary heart disease, myocardial infarction, and stroke). Information about previous cardiovascular events were obtained from the Follow-Up 2000 survey. Variables from the Follow-Up 2003 survey include current age, current medication use, height and weight, health care visits in

[7] http://www.stjude.org/ccss

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the previous 2 y, smoking status, physical activity, and household income.

Outcome Measures

Our primary outcomes of interest for this analysis were the components and clustering of cardiovascular risk factors. CVRFC, our parallel definition for MetS, was defined as having at least three of the following four risk factors: obesity, hypertension, dyslipidemia, and diabetes mellitus or impaired glucose tolerance. Because the use of medications as documentation of MetS components is included in some definitions of MetS (Table 1), we used self-report of medications from the follow-up 2003 survey to classify participants as having or not having a particular component of the CVRFC. Our survey included a series of questions regarding the name and types of medicines taken regularly during the previous 2-y period. For this analysis, we looked at responses in the questionnaire regarding the medications/drugs taken regularly for (*a*) pills for diabetes, (*b*) insulin injections for diabetes, (*c*) medications for high blood pressure or hypertension, (*d*) medications to lower cholesterol or triglycerides, and (*e*) other prescribed drugs. The manner in which these questions were asked can be found at the CCSS Web site.[7] Individuals were considered to be taking the medication regularly if they reported either taking a medication consistently for >1 mo or for taking the medication ≥30 d or more in a year. Obesity was determined by calculating a person's body mass index (BMI) defined as kg/m^2 with a BMI of ≥30 kg/m^2 considered obese.

Data Analysis

The demographic and life-style characteristics of the survivors and siblings, and disease and treatment characteristics of the survivors, were tabulated to describe the survivor and sibling cohorts. To assess the relative prevalence of each CVRFs and CVRFC in survivors compared with siblings, odds ratios (OR) were estimated for having each CVRF or CVRFC at the time of survey, adjusting for age, sex, and ethnicity. To account for intrafamily correlation, generalized estimating equations with the logit link were used (25). To assess the associations of demographic and life-style factors, cancer treatment parameters, and current steroid use with each CVRF and CVRFC in survivors, we performed logistic regression analysis simultaneously assessing the effects of all these covariates, adjusting for age, sex, and ethnicity. To evaluate the association of cancer types (including sibling as a separate cancer type) with each CVRF and CVRFC, the generalized estimating equations analysis with the logit link adjusting for age, sex, and ethnicity was performed. The association between previously reported cardiovascular disease events and subsequent identification of CVRFC was explored using χ^2 tests. All analyses were done using the SAS software, version 9.1. All confidence intervals (CI) and statistical significance tests reported here are two sided.

Role of the Funding Source

The CCSS is funded through the National Cancer Institute (U24 CA55727). National Cancer Institute played no role in the design of the study; the collection, analysis, and interpretation of the data; the decision to submit the manuscript for publication; nor the writing of the manuscript.

Results

Characteristics of the Study Population

The demographic and life-style characteristics of the cancer survivors and the siblings, and the treatment characteristics of the cancer survivors, are shown in Table 2. Survivors were more likely than the siblings to be male (51.5% versus 46.4%) and to have annual household incomes of <$20,000 (11.4 versus 6.6%). Siblings were older and more likely to report participation in physical activity over the past month. The majority of the cohort members, both survivors and siblings, were white. Almost all of the survivors (89.8%) and siblings (89.0%) reported seeing a physician at some time during the previous 2 years. Prior cardiovascular events, defined as hardening of the arteries or arteriosclerosis, coronary heart disease, or myocardial infarction, were rare among both cancer survivors (1.0%) and siblings (0.3%). Radiation was included as part of the initial cancer treatment for 59.2% of the survivors, whereas 33.5% received anthracyclines of >100 mg/m^2 and 4.7% received platinum therapy.

CVRFs Among Survivors and Siblings

The distribution of each of the cardiovascular risk factors, individually and in three cluster combinations, is shown in Table 3 for both survivors and siblings. There was no difference in the prevalence of obesity in survivors (20.6%) compared with siblings (20.8%). However, hypertension, dyslipidemia, and diabetes were all more common among survivors than among siblings. After adjusting for age, ethnicity, and sex, survivors were ~1.9 (95% CI, 1.6-2.2) times more likely to be taking medication for hypertension, 1.6 (95% CI, 1.3-2.0) times more likely to be taking medications for dyslipidemia, and 1.7 (95% CI, 1.2-2.3) times more likely to be taking medications for diabetes than were members of the sibling comparison group. Nonetheless, survivors and siblings were equally likely to meet criteria for CVRFC (OR, 1.3; 95% CI, 0.9-1.9).

Associations between Demographics, Lifestyle, Treatment, and CVRFs

The associations between CVRFs and demographic, life-style, and treatment factors among the members of the survivor cohort are shown in Table 4, adjusted for all covariates in the table. In the adjusted model, when compared with white race/ethnicity, black race/ethnicity was associated with increased odds of obesity and hypertension. Older age at the time of questionnaire was associated with each CVRF and hypertension (i.e., P_{trend} for obesity = 0.015; P_{trend} for hypertension

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Table 2. Characteristics of the study population

	Survivors (*n* = 8,599)	Siblings (*n* = 2,936)
	N (%)	*n* (%)
Gender*		
Female	4,174 (48.5)	1,574 (53.6)
Male	4,425 (51.5)	1,362 (46.4)
Ethnicity*		
White	7,338 (85.3)	2,536 (86.4)
Black	327 (3.8)	64 (2.2)
Hispanic	349 (4.1)	82 (2.8)
Other/missing	585 (6.8)	254 (8.6)
Age at follow up questionnaire†		
<19 y	122	126 (4.3)
19-29 y	3,729 (43.4)	995 (33.9)
30-39 y	3,510 (40.8)	1,078 (36.7)
40-49 y	1,190 (13.8)	647 (22.0)
50+ y	48 (0.6)	90 (3.1)
Annual household income†		
<$20,000	977 (11.4)	194 (6.6)
$20,000-39,000	1,755 (20.4)	464 (15.8)
$40,000+	4,612 (53.6)	1,971 (67.1)
Not indicated	1,255 (14.6)	307 (10.5)
Health care visit in the previous 2 y†		
Yes	7,725 (89.8)	2,612 (89.0)
Smoking status†		
Current	1,402 (16.7)	583 (20.3)
Former	1,156 (13.7)	572 (20.0)
Never	5,859 (69.6)	1,711 (59.7)
Physical activity status†		
Reported leisure time physical activity in previous month	6,616 (77.0)	2,518 (85.7)
No leisure time physical activity in previous month	1,950 (22.7)	407 (13.9)
Did not indicate activity status	33 (0.3)	11 (0.4)
Current steroid use*†		
Yes	96 (1.1)	
Cancer diagnosis‡		
ALL	2,581 (30.0)	
AML	217 (2.5)	
Other leukemia	170 (2.0)	
Astrocytomas	649 (7.5)	
Medulloblastoma, PNET	234 (2.7)	
Other CNS tumors	167 (1.9)	
Hodgkin Lymphoma	1,006 (11.7)	
Non–Hodgkins lymphoma	673 (7.8)	
Kidney tumors	849 (9.9)	
Neuroblastoma	596 (6.9)	
Soft tissue sarcoma	755 (8.8)	
Ewings sarcoma	216 (2.5)	
Osteosarcoma	454 (5.3)	
Other bone tumors	32 (0.5)	
Age at diagnosis‡		
<5 y	3,573 (41.6)	
5-9 y	1,940 (22.6)	
10-14 y	1,690 (19.7)	

(*Continued on the following page*)

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Table 2. Characteristics of the study population (Cont'd)

	Survivors (n = 8,599)	Siblings (n = 2,936)
15-20 y	1,396 (16.2)	
Radiation‡		
None	2,740 (31.9)	
Medical record unavailable	763 (8.9)	
TBI	99 (1.2)	
Abdomen without chest	566 (6.6)	
Abdomen with chest	734 (8.5)	
Chest without abdomen	610 (7.1)	
Cranial with spinal	427 (5.0)	
Cranial without spinal	2,075 (24.0)	
Other radiation	585 (6.8)	
Anthracycline dose‡		
None	4,779 (62.6)	
<100 mg/m^2	296 (3.9)	
100-299 mg/m^2	1,223 (16.0)	
>300 mg/m^2	1,336 (17.5)	
Platinum exposure‡	367 (4.7)	
Cardiovascular events reported on baseline or First follow questionnaire *§		
Cardiac event‖	83 (1.0)	9 (0.3)
Hardening of the arteries of arteriosclerosis	34 (0.4)	3 (0.1)
Coronary heart disease	39 (0.5)	2 (0.1)
Myocardial infarct	46 (0.5)	5 (0.2)
Stroke	151 (1.8)	9 (0.3)

NOTE: The number of subjects may not add up exactly to the total of 8,599 survivors and 2,936 siblings due to a few missing values
Abbreviations: AML, acute myeloid leukemia; CNS, central nervous system.
*CCSS Baseline questionnaire.
†CCSS Follow-Up 2003 questionnaire.
‡CCSS Medical Record Abstraction Form.
§CCSS Follow-Up 2000 questionnaire.
‖Cardiac event include hardening of the arteries, myocardial infarction, and coronary heart disease (some events were duplicated in individual categories).

< 0.0001; P_{trend} for dyslipidemia < 0.0001; P_{trend} for diabetes < 0.0001; and P_{trend} for any three risk factors < 0.001). Sedentary life-style was associated with CVRFC and each CVRF except dyslipidemia.

In terms of treatment modalities, exposure to >100 mL/m^2 of an anthracycline was associated with a 50% increase in the odds of hypertension. When compared with those who did not receive radiation, those who received cranial radiation were more likely to be obese and those that received >300 mg/m^2 of anthracyclines were less likely to be obese. Individuals who received either abdomen or chest radiation or were currently on steroid therapy showed increased risk for hypertension. Treatment for dyslipidemia was associated with TBI and radiation to the craniospinal axis, abdomen with chest, and chest alone. Diabetes was associated with TBI and radiation to the abdomen and radiation to both abdomen and chest. CVRFC was associated with TBI and combined abdominal chest radiation.

Associations between Diagnoses and CVRFs

Although treatment exposures and their association with CVRFs and CVRFC was the main focus of this analysis, in many nononcology clinical settings, specific cancer treatment data are often not available and only the cancer diagnosis is known. Therefore, the relative odds of the individual and clustered CVRF outcomes by cancer diagnosis, comparing survivors to the sibling comparison group, were estimated (Table 5). Most of these associations are driven by exposure to key treatment modalities or demographic/life-style factors. After adjusting for age, sex, and ethnicity, survivors of acute lymphoblastic leukemia (ALL) and astrocytoma were more likely than siblings to be obese. In contrast, survivors of Hodgkin lymphoma, kidney tumor, neuroblastoma, soft tissue sarcoma, and osteosarcoma were less likely than siblings to be obese. Survivors of many of the diagnostic groups (10 of the 14 diagnostic groups) were more likely than siblings to be taking medication for hypertension, with

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Table 3. Frequencies and percents, adjusted ORs, and 95% CIs comparing survivors to siblings on individual and combined CVRFs

	Survivors (*n* = 8,599)		Siblings (*n* = 2,936)		OR	95% CI	
	n	%	*n*	%			
Obese*	1,699	20.6	591	20.8	1.0	0.9	1.1
Currently taking medication for hypertension	761	8.8	168	5.7	1.9	1.6	2.2
Currently taking medication for dyslipidemia	448	5.2	117	4.0	1.6	1.3	2.0
Currently taking medication for diabetes	218	2.5	49	1.7	1.7	1.2	2.3
Any three risk factors (CVRFC)†	113	1.3	34	1.2	1.3	0.9	1.9

NOTE: OR, OR estimate adjusted for age, race, sex, and intrafamily correlation.
*Three hundred thirty-nine survivors and 89 siblings did not report height and/or weight and were thus removed from the obesity analysis.
†Five survivors and one sibling were removed from the CVRFC analysis due to lack of availability of the CVRFC information.

the greatest risk of reporting antihypertensive medication use among survivors of kidney tumors and osteosarcomas. Increased risk of dyslipidemia was found in survivors of medulloblastoma, Hodgkin, and non–Hodgkin lymphoma. ALL, acute myeloid leukemia, and neuroblastoma were associated with an increased risk for diabetes. Hodgkin lymphoma was the only diagnostic group significantly associated with meeting CVRFC criteria.

Associations between Previously Reported Cardiovascular Events and CVRFs

The associations between previously reported cardiovascular disease events (Follow-Up 2000) and current CVRFs (Follow-Up 2003) were evaluated for events reported at baseline and on the first follow-up survey. Among survivors, 83 reported cardiac events (coronary artery disease, atherosclerosis, or myocardial infarction) and 151 reported a history of stroke at either the baseline or the first follow-up questionnaire. All of these previously reported cardiac events, except for stroke, were associated with an increased risk of reporting CVRFC (three or four CVRFs) subsequently at second follow-up ($P = 0.003$).

Discussion

The primary focus of this study was to determine the risk of development of CVRFs and CVRFC after exposure to various cancer therapeutic modalities. Radiation therapy as opposed to chemotherapy was more strongly associated with the development of CVRFs, even after adjusting for other treatment exposures and demographic/life-style factors. In particular, exposure of large amounts of the torso to radiation, as in TBI and abdominal plus chest radiation, was strongly associated with many of the subsequent self-reported CVRFs and CVRFC. This may be due to radiation effects on either individual organs or the combined effects on multiple chest and abdominal organs.

In regards to chemotherapeutic exposures, moderate doses of anthracyclines were independently associated with hypertension, even after adjusting for other treatment exposures and demographic/life-style factors. In the analysis of demographic and life-style factors adjusted for treatment exposures, a striking progressive increase in the prevalence of each CVRF and CVRFC was noted with older attained age at the time of completing the questionnaire. Self-reported sedentary life-style remained associated with most CVRFs and CVRFC, independent of other demographic and treatment factors. These findings suggest that although factors known to be associated with CVRFs in the general population (i.e., age, sedentary life-style) remain important in cancer survivors, the risk of developing CVRF/CVRFC is also increased by selected prior therapeutic exposures. However, because many primary care clinicians do not know the specific cancer treatment modalities their patients received, CVRF and CVRFC was reported by cancer diagnoses and was compared with siblings. The associations of cancer diagnoses with CVRFs were not independent findings. Rather, these associations were likely dictated by the key cancer treatment exposures and underlying demographic data, such as older age at follow-up.

In the general U.S. population, the prevalence of obesity and other adverse cardiovascular traits that make up the metabolic syndrome have increased dramatically among both adults and children in recent years (26, 27). Development of any of these traits during childhood or adolescence tracks into adulthood (28-30), and the presence of such traits increases the risk of future cardiovascular morbidity. A search of the literature (MEDLINE search terms "cancer survivor/survivorship," "metabolic syndrome," and/or "cardiovascular risk," English-language through December 2008; and selected bibliographies) identifies a variety of reports featuring both national

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survey data (31) as well as single institutional studies (32-35) including those that recruited a subset of CCSS participants (8). These studies suggest that cancer survivors may be at particularly increased risk of developing components of the MetS, although not all showed an increased risk of meeting the criteria for a diagnosis of MetS. Similarly, our study did not show an overall significantly increased risk of our MetS surrogate (i.e., CVRFC), although most survivor groups were at increased risk of one or more component traits compared with siblings. However, given the heterogeneity of childhood cancer cohorts, one advantage of our study compared with prior reports is our much larger sample size, which allowed more meaningful stratification by treatment, and demographic characteristics.

The underlying pathophysiology that predisposes toward development of CVRFs in the cancer survivor and the general population may be different. For example, obesity, considered by many to be the pathophysiologic driver of cardiovascular risk in the general population, was not more common overall in survivors compared with siblings, at least when determined using BMI. Other measures of central adiposity such as waist circumference and visceral fat content were not available to us, but have been noted to be increased in some, but not all, cancer survivor populations (8, 27, 34). However, even in the absence of obesity, other exposures and outcomes unique to cancer survivors may predispose toward the development of CVRFs. Chest and abdominal radiation may lead to an increased risk of cardiac and renal dysfunction including hypertension, possibly secondary to direct vascular injury and fibrosis (36). Growth hormone deficiency, often seen following cranial radiation and TBI, is associated with dyslipidemia, central adiposity, and altered carbohydrate metabolism (8, 37, 38). Many of these metabolic changes are inter-related and complex. For example, the growth hormone–deficient state has been associated with both increased and reduced insulin sensitivity (37). Interpretation of the data can be difficult as obesity per se blunts the growth hormone response to provocative testing in otherwise normal individuals. These exposures, along with selected chemotherapy effects (e.g., acute pancreatitis following asparaginase; insulin resistance associated with chronic high-dose steroid therapy) may ultimately contribute to an increased risk of diabetes (39, 40). Other chemotherapy agents, such as anthracyclines, have long been associated with an increased risk of cardiac dysfunction (13, 20), although anthracyclines specifically have not previously been associated with hypertension. Some studies of adult cancer patients have reported an association between platinum agents and hypertension (41), although this was not observed in our analysis.

This study has several methodologic limitations. The first is the creation of a definition for MetS that paralleled other definitions but accommodates the data available in the CCSS cohort. We tried to remain true to the four basic categories of risk: obesity, hypertension, abnormal lipids, and impaired glucose metabolism. MetS and its components are often under-recognized because these traits can be silent medical problems that require a visit to a physician, a physical exam, and laboratory analysis to be diagnosed. Although 89% of survivors and siblings reported a health care visit in the 2 years preceding completing the questionnaire, we are unable to ascertain if blood pressure, lipid analysis, and glucose metabolism tests were done at the time of the visit. In addition, our method of ascertainment required treatment for a CVRF and many survivors and siblings might have unrecognized or untreated CVRFs. There is potential bias in that survivors may have been more closely screened for CVRF and treated at a lower threshold because of their health care providers' awareness of their risk for cardiovascular disease. Another limitation is the self-reported heights and weights used for the calculation of BMI. However, because height and weight values were self-reported by both the survivors and siblings in this analysis, the likelihood of differential measurement bias is reduced (42). Self-reported medication histories obtained through questionnaires may be subject to misclassification and recall bias, but previous studies have shown reasonable agreement between medication self-report and medical records or pharmacy records. Better recall accuracy has been associated with antihypertensive medications, statins, and other chronic care medications compared with analgesics or antidepressants (43-47).

In addition, questionnaires designed to ask about medications for a specific indication, such as the CCSS questionnaire, are more sensitive than those with open-ended questions (44, 45). Accuracy was improved through confirmation that self-reported medications were correctly classified in the designated drug categories (e.g., medication for high blood pressure or hypertension, pills or insulin injection for diabetes, and medication to lower cholesterol or triglycerides, as well as review of all medications listed under other prescribed drugs). However, the use of self-report of medications as a proxy for disease is not standard and may result in underestimates and overestimates of the component traits of MetS.

Data on cardiovascular events were available from the baseline and first follow-up questionnaires. Realizing that the MetS components are often insidious diseases that can be present for months or years before diagnosis, there is likelihood that CVRFs ascertained in the Follow-Up 2003 questionnaire may have been present at the time of baseline and Follow-Up 2000 questionnaire. We analyzed the association of CVRFs ascertained at the Follow-Up 2003 questionnaire with the self-report of cardiovascular events at earlier time points and found a significant association. At the time of this evaluation, the CCSS cohort is still a relatively young adult cohort. We anticipate that the frequency of CVRFs, CVRFC, and cardiovascular events will increase with age. As the CCSS cohort ages, it will be important to continue to ascertain these outcomes to

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Table 4. ORs and 95% CIs of having individual or combined CVRFs for adult survivors of childhood cancer by demographic and life-style factors, cancer treatment parameters, and current steroid use

	Obesity		Hypertension		Dyslipidemia		Diabetes		Any three risk factors	
	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI
Sex										
Male (Reference)	1.0		1.0		1.0		1.0		1.0	
Female	1.1	1.0-1.3	0.9	0.7-1.0	0.5	0.4-0.6	1.2	0.9-1.6	0.8	0.5-1.2
Ethnicity										
White (Reference)	1.0		1.0		1.0		1.0		1.0	
Black	1.5	1.1-2.1	1.8	1.2-2.7	0.6	0.3-1.3	1.6	0.7-3.2	2.6	1.0-5.6
Hispanic	1.4	1.0-1.8	1.0	0.6-1.5	1.1	0.6-2.0	2.0	1.0-3.6	1.7	0.6-4.0
Other	1.0	0.8-1.3	0.9	0.6-1.3	1.2	0.8-1.7	1.1	0.6-1.8	0.8	0.3-1.9
Age at questionnaire										
<30 y (Reference)	1.0		1.0		1.0		1.0		1.0	
30-39 y	1.2	1.1-1.5	2.9	2.2-3.7	2.5	1.8-3.6	2.2	1.4-3.3	2.6	1.3-5.3
40+ y	1.4	1.1-1.8	6.6	4.7-9.4	5.6	3.6-8.8	4.9	2.6-9.3	8.2	3.5-19.9
Age at diagnosis										
15-20 y (Reference)	1.0		1.0		1.0		1.0		1.0	
<5 y	0.9	0.7-1.2	1.4	1.0-1.9	0.7	0.5-1.1	2.1	1.1-3.9	1.3	0.6-3.0
5-9 y	1.1	0.8-1.3	1.3	0.9-1.7	0.9	0.6-1.3	1.5	0.8-2.7	1.3	0.6-2.6
10-14 y	0.9	0.8-1.2	0.9	0.7-1.1	0.8	0.6-1.1	1.2	0.7-2.0	1.2	0.7-2.2
Annual household income										
$40,000+ (Reference)	1.0		1.0		1.0		1.0		1.0	
<$20,000	1.5	1.2-1.8	1.4	1.0-1.8	0.9	0.6-1.4	1.7	1.1-2.6	1.2	0.6-2.4
$20,000-39,000	1.5	1.2-1.7	1.2	1.0-1.5	1.0	0.7-1.3	1.1	0.8-1.7	1.3	0.8-2.2
Not indicated	1.2	1.0-1.5	1.3	1.0-1.7	1.0	0.7-1.4	0.9	0.5-1.4	1.0	0.5-2.0
Platinum										
No (Reference)	1.0		1.0		1.0		1.0		1.0	
Yes	0.5	0.4-0.8	1.3	0.9-1.9	1.2	0.7-2.0	1.2	0.5-2.4	0.9	0.2-2.7
Anthracycline dose										
None (Reference)	1.0		1.0		1.0		1.0		1.0	
<100 mg/m^2	1.0	0.8-1.4	0.8	0.4-1.3	1.0	0.5-1.8	1.7	0.8-3.4	1.6	0.5-4.2
100-299 mg/m^2	0.9	0.8-1.1	1.5	1.2-1.9	1.1	0.8-1.5	1.3	0.8-1.9	0.9	0.5-1.7
>300 mg/m^2	0.8	0.6-0.9	1.5	1.2-1.9	1.1	0.9-1.5	1.5	1.0-2.2	1.0	0.6-1.8
Radiation treatment										
No radiation (Reference)	1.0		1.0		1.0		1.0		1.0	
TBI	1.0	0.6-1.8	1.7	0.8-3.2	3.9	1.8-7.6	7.8	3.5-16.4	5.5	1.5-15.8
Abdomen no chest	0.7	0.5-0.9	1.9	1.4-2.6	1.3	0.7-2.1	2.5	1.4-4.2	1.9	0.7-4.2
Abdomen with chest	0.7	0.5-0.9	1.8	1.4-2.4	2.7	1.9-3.7	2.7	1.6-4.4	2.3	1.2-4.4
Chest no abdomen	1.0	0.8-1.3	1.5	1.1-2.0	1.9	1.3-2.8	0.7	0.3-1.5	1.2	0.5-2.7
Cranial with spinal	1.6	1.2-2.0	0.9	0.6-1.4	3.3	2.1-5.0	1.4	0.6-2.8	1.5	0.5-3.8
Cranial without spinal	2.0	1.7-2.3	0.7	0.6-0.9	1.3	0.9-1.8	1.4	0.9-2.2	1.2	0.6-2.3
Other radiation	1.1	0.8-1.4	0.9	0.6-1.2	1.6	1.1-2.4	1.4	0.7-2.5	1.2	0.4-2.6
MD visit past 2 y										
No (Reference)	1.0		1.0		1.0		1.0		1.0	
Yes	1.0	0.9-1.3	7.6	4.2-15.3	7.8	3.8-19.8	6.7	2.5-27.2	>999.9	5.6->999.9
Sedentary										
No (Reference)	1.0		1.0		1.0		1.0		1.0	
Yes	1.3	1.1-1.5	1.5	1.2-1.8	1.3	1.0-1.6	1.7	1.2-2.3	1.7	1.1-2.6

(*Continued on the following page*)

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Table 4. ORs and 95% CIs of having individual or combined CVRFs for adult survivors of childhood cancer by demographic and life-style factors, cancer treatment parameters, and current steroid use (Cont'd)

	Obesity		Hypertension		Dyslipidemia		Diabetes		Any three risk factors	
	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI
Smoking status										
Never (Reference)	1.0		1.0		1.0		1.0		1.0	
Former	1.1	0.9-1.3	0.9	0.7-1.2	0.8	0.6-1.1	1.3	0.9-2.0	0.9	0.5-1.6
Current	0.9	0.8-1.1	0.7	0.6-0.9	0.8	0.5-1.0	1.2	0.8-1.8	1.1	0.6-1.9
Current steroid use										
No (Reference)	1.0		1.0		1.0		1.0		1.0	
Yes	1.4	0.8-2.3	4.4	2.5-7.3	2.3	1.0-4.6	0.9	0.1-2.8	2.8	0.7-8.1

*Adjusted for all other variables in the model.

assess for stronger associations of demographic, life-style, and treatment factors with CVRFs and clustering. It will also be important to ascertain the risk for subsequent development of cardiovascular events in survivors who *a priori* are identified to have CVRFC.

The presence of MetS and its component parts are associated with significant morbidity and mortality from cardiovascular disease in the general population (48-50). Many of the recognized risk factors for the development of cardiovascular disease—obesity, hypertension, dyslipidemia, and physical inactivity—are amenable to behavioral/life-style and pharmacologic interventions. Ongoing follow-up in this cohort will show if the prevalence and severity of chronic health conditions remains disproportionately high in cancer survivors compared with the general population. It is hoped that the results of this study will encourage clinicians to emphasize to pediatric cancer survivors the importance of maintaining regular health care. In light of the high prevalence of chronic health conditions including cardiac disease and

Table 5. ORs and 95% CIs of having individual or combined CVRFs for adult survivors of childhood cancer by diagnosis, adjusted for sex, ethnicity, and age at questionnaire completion

	Obesity		Hypertension		Dyslipidemia		Diabetes		Any three risk factors	
	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI
Cancer diagnosis										
Siblings (Reference)	1.0		1.0		1.0		1.0		1.0	
ALL	1.6	1.4-1.8	1.4	1.1-1.7	1.2	0.9-1.7	2.0	1.4-2.9	1.4	0.8-2.5
AML	1.0	0.7-1.5	2.0	1.2-3.4	0.9	0.4-2.2	5.6	3.1-10.0	2.1	0.4-5.2
Other leukemia	1.1	0.8-1.7	1.9	1.0-3.4	0.4	0.1-1.6	2.3	0.9-5.7	0	NE
Astrocytoma	1.4	1.2-1.7	0.9	0.6-1.3	1.2	0.8-1.8	1.1	0.5-2.1	0.5	0-1.3
Medulloblastoma	1.4	1.0-1.9	1.7	1.0-2.9	5.9	3.8-9.1	1.9	0.8-4.6	3.1	0.8-6.8
Other CNS malignancy	1.1	0.7-1.6	0.8	0.4-1.7	1.3	0.6-2.7	2.1	0.8-5.2	1.2	0-3.5
Hodgkin Lymphoma	0.7	0.6-0.9	2.2	1.7-2.7	2.5	1.9-3.2	1.4	0.9-2.2	1.8	1.1-3.0
Non–Hodgkin Lymphoma	0.8	0.7-1.0	2.1	1.6-2.8	1.9	1.3-2.6	1.6	0.9-2.8	1.4	0.6-2.6
Kidney tumor	0.6	0.5-0.7	3.3	2.5-4.3	1.5	0.9-2.3	1.8	1.0-3.1	2.0	0.7-4.1
Neuroblastoma	0.7	0.6-0.9	2.0	1.3-2.9	0.9	0.4-1.7	2.4	1.3-4.4	0.4	0-1.3
Soft tissue sarcoma	0.7	0.6-0.9	1.7	1.3-2.3	0.9	0.6-1.3	1.2	0.7-2.2	1.4	0.6-2.6
Ewings sarcoma	0.8	0.6-1.1	2.3	1.5-3.5	1.7	1.0-2.9	1.9	0.8-4.2	1.5	0.3-3.2
Osteosarcoma	0.4	0.3-0.6	2.9	2.1-3.8	1.3	0.8-1.9	1.0	0.5-2.0	0.4	0-1.0
Other bone malignancy	0.5	0.2-1.6	1.2	0.4-3.7	1.0	0.2-4.2	1.4	0.2-10.1	1.8	0-7.0

*Adjusted for sex, race/ethnicity, current age, and intrafamily correlation in the model. NE, not estimable.

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associated increased rates of death, it behooves all health care providers to be proactive in the early recognition and treatment of cardiovascular risk factors in this population (1, 23, 51).

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