Cardiometabolic Risk in Childhood Cancer Survivors: A Report from the Children's Oncology Group

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ABSTRACT

Background: Childhood cancer survivors are at risk for cardiovascular disease. We assessed the burden of potentially modifiable cardiometabolic risk factors (CRF) among survivors compared with population-matched controls.

Methods: Survivors previously enrolled on Pediatric Oncology Group protocols 9404, 9425, 9426, 9754, and Dana-Farber Cancer Institute 95-01 from 1996 to 2001 with acute lymphoblastic leukemia/lymphoma, Hodgkin lymphoma, or osteosarcoma were prospectively assessed for the prevalence of CRFs and compared with an age, sex, and race/ethnicity-matched 2013 National Health and Nutrition Examination Survey (NHANES) population. We estimated future predicted cardiovascular risk based on general population (e.g., Framingham) and Childhood Cancer Survivor Study (CCSS) models.

Results: Compared with NHANES ($n = 584$), survivors [$n = 164$; 44.5% female, median age 28 years (range, 16–38 years); median 17.4 years (range, 13–22 years) since cancer diagnosis; median doxorubicin dose 300 mg/m^2; 30.5% chest radiation] had similar rates of obesity, diabetes, and dyslipidemia, but more prehypertension/hypertension (38.4% vs. 30.1%, $P = 0.044$). Survivors had fewer metabolic syndrome features compared with NHANES (≥2 features: 26.7% vs. 55.9%; $P < 0.001$). Survivors were more physically active and smoked tobacco less (both $P < 0.0001$). Therefore, general population cardiovascular risk scores were lower for survivors versus NHANES. However, with CCSS models, 30.5% of survivors were at moderate risk of ischemic heart disease, and >95% at moderate/high risk for heart failure, with a 9% to 12% predicted incidence of these conditions by age 50 years.

Conclusions: Childhood cancer survivors exhibited similar or better cardiometabolic and lifestyle profiles compared with NHANES, but nonetheless are at risk for future clinically significant cardiovascular disease.

Impact: Further strategies supporting optimal CRF control are warranted in survivors.

See related commentary by Mulrooney, p. 515

Introduction

With advances in the treatment of childhood malignancies, increasing numbers of children and adolescents diagnosed with cancer will become long-term survivors. Cardiovascular-related diseases, including heart failure, coronary artery disease, and cerebrovascular events, are leading causes of morbidity and mortality in childhood cancer survivors (1). Exposure to anthracycline chemotherapy and radiotherapy, such as radiation to the heart or brain, is associated with an increased risk of cardiovascular events and cardiovascular-related mortality in survivors, in a dose-dependent manner (1–4). Despite attempts to decrease the use and dose/volume of radiotherapy with the potential to damage the heart, this remains an important treatment modality. Strategies aimed at preventing anthracycline-associated cardiotoxicity include limiting cumulative exposure and using cardioprotective agents (1, 2, 5). However, anthracyclines remain critical in treating many pediatric cancers, such as high-risk leukemias, Hodgkin lymphoma, and sarcomas.

Cardiometabolic risk factors (CRF) relevant to the general population, such as hypertension, diabetes, obesity, and dyslipidemia, also contribute to an increased risk of cardiovascular disease in survivors (2, 4, 6) Some cancer-directed therapies may themselves predispose to the development of these traditional risk factors (1). We aimed to assess the burden of potentially modifiable traditional CRFs among young adult survivors previously treated on clinical trials that investigated the use of dexrazoxane in anthracycline-based regimens, and compare these results with population-matched controls.

Materials and Methods

Cancer survivors

Study participants were enrolled on the Children's Oncology Group (COG) follow-up protocol ALTE11C2 (NCT01790152), which seeks to determine the long-term health effects of dexrazoxane use in children, with a specific focus on cardiovascular health. Eligible ALTE11C2 participants included those previously enrolled and treated on legacy Pediatric Oncology Group therapeutic protocols P9404, P9425, P9426, and P9754, and Dana-Farber Cancer Institute Childhood ALL Consortium protocol 95-01 (high-risk arm), conducted from 1996 through 2001 (7–11). These frontline clinical trials featured upfront randomization to treatment with or without dexrazoxane

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(10:1 mg/m^2 dose ratio of dexrazoxane:doxorubicin), except for P9754 (on which all patients received dexrazoxane; ALTE11C2 included a matched, non–dexrazoxane-exposed comparison group). This analysis included all ALTE11C2 participants enrolled between March 2014 and April 2019. Additional eligibility criteria for enrollment onto ALTE11C2 included being alive and in first complete remission, without history of progressive disease or hematopoietic cell transplantation (HCT), and no subsequent malignant neoplasm requiring additional cardiotoxic therapies. Although ALTE11C2 provided templated recruitment materials, research staff at participating COG sites had direct responsibility for approaching and enrolling potentially eligible participants. Research staff at participating sites also was responsible for verifying all eligibility criteria prior to enrollment onto ALTE11C2. The study provided honoraria to participants to fully cover the time and cost of study participation. All procedures were approved by the Central Institutional Review Board of the U.S. NIH and the Institutional Review Board of each participating institution. Written informed consent was obtained for each participant prior to study enrollment.

Comparison group

The National Health and Nutrition Examination Survey (NHANES) 2013–2014 dataset provided the source representing a general, contemporaneous, noncancer population for comparison purposes (12). This dataset was first limited to those ages 18 to 39 years with examination data and without a history of cancer ($n = 2{,}176$); individuals could have other comorbidities such as known hypertension, dyslipidemia, diabetes, heart failure, or ischemic heart disease. A random sample was then selected that matched the ALTE11C2 sample by 5-year age group, sex, and race/ethnicity ($n = 584$). The publicly available NHANES dataset does not contain geographic variables.

Measurements

For ALTE11C2, potentially eligible survivors were recruited by their original treating centers for a prospective, standardized clinical assessment. This included a comprehensive medical history focused on cardiometabolic health, including whether participants had known hypertension, dyslipidemia, and diabetes, and whether they were on medications for any of these conditions. Participants also had a standardized physical exam, including height, weight, waist circumference, resting blood pressure (four measurements, first discarded, average of remaining three), and ≥10-hour fasting blood draw (to assess lipid profile, glucose, and hemoglobin-A1c). Samples were blinded to dexrazoxane status and analyzed centrally. Participants completed a study questionnaire assessing their current quality of life [Short-Form-36 (SF-36), Version 2; ref. 13], family history of heart disease (14), physical activity, and tobacco smoking (12, 15). Participants also underwent two-dimensional echocardiography, with results to be reported separately (16).

Outcomes

Protocol definitions were as follows and reflect measured values: dyslipidemia, total cholesterol ≥200 mg/dL, high-density lipoprotein < 40 mg/dL, or triglyceride ≥ 150 mg/dL; obesity, body mass index of ≥30 kg/m^2; waist circumference elevated, ≥102 cm (males) or ≥88 cm (females); prediabetes, defined as fasting serum glucose of 100 to 125 mg/dL or hemoglobin-A1c of 5.7% to 6.4%; diabetes, defined as a fasting serum glucose ≥126 mg/dL or hemoglobin-A1c ≥6.5%; hypertension, defined as an average blood pressure measurement ≥130/80 mmHg; and prehypertension as an average blood pressure measurement of 120 to 129/<80 mmHg. The number of traits meeting metabolic syndrome criteria was determined among survivors and the NHANES group, as defined by Adult Treatment Panel (ATP) III classification, and included those currently receiving treatment for these conditions (Supplementary Table S1; ref. 17).

Adverse lifestyle factors included current tobacco smoking and not meeting Centers for Disease Control and Prevention (CDC) national guidelines for aerobic physical activity (defined as <75 minutes of vigorous physical activity/week, <150 minutes of moderate activity/week, or an equivalent combination; ref. 18).

We calculated the predicted cardiovascular risk expected among study participants using general population risk calculators including the 30-year Framingham risk score and longer-term risk prediction function, designed to estimate the extent of risk among young adults (full and hard lipid models). We also used the Pathological Determinants of Atherosclerosis in Youth (PDAY) Study Risk Score to estimate the risk of advanced atherosclerotic lesions (in the coronary arteries and the aorta). Supplementary Tables S2 and S3 present details regarding these general population risk calculators for reference purposes (19–21). To contrast results from these general population cardiovascular risk models, we also applied the Childhood Cancer Survivor Study's (CCSS) validated standard risk model to estimate survivor-specific risk of ischemic heart disease and heart failure accounting for cardiotoxic cancer treatment exposures (Supplementary Table S4; refs. 22, 23).

Statistical methods

Descriptive statistics are presented as frequencies and percentages. Unadjusted comparisons between survivors and NHANES were assessed using t-test (if the outcome was normally distributed), Wilcoxon rank sum (if the outcome was not normally distributed), χ^2, and Fisher exact (if the characteristic was rare, $n < 5$) tests. Categorical characteristics were also compared using logistic regression, calculating OR and 95% confidence intervals (CI). Measurements taken multiple times (blood pressure) were averaged and then assessed using regression weighted for the number of measurements. SF-36 scores were generated for the physical and mental components, accounting for current age and sex (13). Analyses were conducted using Stata (version 15). P values are two-sided, with values <0.05 considered significant. No adjustments were made for performing multiple statistical tests.

Results

In total, 164 survivors from 42 institutions enrolled on ALTE11C2 through April 2019 (**Table 1**), from among 431 potentially eligible survivors (38.1% participation rate; 0.7% active refusal rate; the remainder lost/passive nonresponders). Survivors had a median age of 28.3 years (range, 16–38 years), with median of 17.5 years (range, 13–22 years) since cancer diagnosis. The majority of participants (59.1%) had a diagnosis of acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LL); 35% had Hodgkin lymphoma. The median doxorubicin dose administered was 300 mg/m^2 (range, 100–600 mg/m^2; all participants were treated with doxorubicin). Compared with nonparticipants, participants were more likely to be female, White non-Hispanic, and to have received any cardiac radiotherapy, but did not differ by other demographic and clinical characteristics (Supplementary Table S5).

Comparing cardiometabolic parameters of survivors with the matched NHANES population, there were similar rates of obesity, dyslipidemia, and diabetes between groups, although fasting blood glucose, mean waist circumference, and hemoglobin-A1c were

Table 1. Demographic and treatment characteristics of childhood cancer survivors and NHANES comparison group.

Characteristics[a]	Survivors $N = 164$		NHANES $N = 584$	
Female sex	73	(44.5)	260	(44.5)
Current age, years (median, range)	28.9	(16–38)	28.0	(15–39)
White/non-Hispanic race/ethnicity	134	(81.7)	476	(81.5)
Time since diagnosis, years (median, range)	17.4	(13–22)	—	—
Age at cancer diagnosis, years (median, range)	11.3	(0–20)	—	—
Cancer diagnosis				
ALL	75	(45.7)	—	—
LL	22	(13.4)	—	—
Hodgkin lymphoma	58	(35.4)	—	—
Osteosarcoma	9	(5.5)	—	—
Doxorubicin exposure	164	(100)		
Cumulative doxorubicin dose, mg/m^2 (median, range)	300	(100–600)	—	—
Cranial radiotherapy exposure	97	(59.1)		
Chest radiotherapy exposure	50	(30.5)	—	—
Radiotherapy dose, Gy (median, range)[b]	22.1	(21.0–25.5)	—	—
Dexrazoxane exposure	86	(52.4)		

[a]*N* (%) unless otherwise specified.
[b]Among exposed.

significantly lower among survivors (**Table 2**). Prediabetes was identified in 9.9% of survivors compared with 15.8% of NHANES ($P = 0.06$). Survivors had higher mean systolic and diastolic blood pressures, and a higher frequency of measured prehypertension or hypertension [38.4% vs. 30.1%, $P = 0.04$; OR, 1.45 (95% CI, 1.01–2.08)]. However, a lower proportion of survivors met multiple metabolic syndrome-defining ATP III criteria (26.9% with ≥2 criteria and 11.9% with ≥3 criteria), compared with NHANES (55.9% ≥2 criteria and 18.7% ≥3 criteria; $P < 0.001$ and $P = 0.05$, respectively). There were no differences in the frequencies of known hypertension, dyslipidemia, or hypertension. Among survivors, cardiometabolic outcomes between ALL/LL versus Hodgkin lymphoma survivors did not significantly differ (Supplementary Table S6).

Lifestyle factors among survivors are depicted in **Table 3**. More survivors met CDC guidelines for physical activity [67.1% vs. 43.2% of NHANES population; OR, 2.7 (95% CI, 1.9–3.9)]. Fewer survivors reported a history of smoking [24.8% vs. 42.6%; OR, 0.5 (95% CI, 0.3–0.7)] or current tobacco use [13.0% vs. 28.9%; OR, 0.4 (95% CI, 0.3–0.6)]. Overall, survivors had lower odds of having one (OR, 0.40; 95% CI, 0.27–0.58) or two (OR, 0.15; 95% CI, 0.07–0.32) adverse lifestyle factors compared with NHANES.

Estimates of cardiovascular risks were made for survivors and the NHANES population (**Table 4**). Survivors had significantly lower mean risk scores compared with the NHANES when the Framingham full and hard cardiovascular risk lipid models were applied, and a younger Framingham heart age (all differences, $P < 0.05$). PDAY coronary artery and abdominal aorta scores also favored survivors versus NHANES, although differences did not meet statistical significance. However, if CCSS standard risk models were applied, 30.5% of survivors were at moderate risk of developing ischemic heart disease, and >95% of survivors were at moderate or high risk for developing heart failure, corresponding to a 9% to 12% predicted incidence of these conditions by age 50 years.

In quality-of-life assessments, survivors reported significantly better physical health compared with population norms (54.4 ± 7.5 SD vs. 50.0, $P < 0.001$), whereas mental health was similar (50.2 ± 9.7, SD vs. 50; $P = 0.82$). Among survivors, having a greater number of either metabolic syndrome traits or adverse lifestyle factors was associated with decreased self-reported physical health quality of life [coefficient −1.4 (95% CI, −2.6 to −0.28) and coefficient −2.8 (95% CI, −4.7 to −1.0), respectively], whereas associations with mental health quality of life were of borderline significance [coefficient −1.3 (95% CI, −2.8–0.1) and coefficient −2.3 (95% CI, −4.8–0.2), respectively; $P = 0.07$ for both].

We also explored cardiometabolic outcomes among survivors based on their original dexrazoxane assignment status. Among participants, 52% ($n = 86$) had been assigned to receive dexrazoxane. There were no statistically significant differences in cardiometabolic outcomes or estimates of cardiovascular risks between those assigned to receive anthracycline with or without dexrazoxane (Supplementary Table S7). Finally, cardiometabolic parameters were explored among survivors recruited from sites with ≥50% participation of eligible patients in the ALTE11C2 long-term follow-up study (survivors, $n = 68$) compared with sites with <50% participation (survivors, $n = 96$). Overall, participants enrolled from lower accruing sites had slightly worse cardiometabolic profiles compared with participants from higher accruing sites, although these differences were not statistically significant (Supplementary Table S8).

Discussion

Cardiovascular-related disease is a leading cause of morbidity and mortality in childhood cancer survivors (1). The development of risk factors for cardiovascular disease relevant to the general population, including hypertension, diabetes, obesity, and dyslipidemia, also contributes to increased risk in survivors (2, 4). In this study, young adult survivors exhibited similar cardiometabolic profiles as the matched NHANES population, with similar rates of obesity, diabetes, and dyslipidemia. Although overall, fewer survivors met multiple ATP III criteria for metabolic syndrome, survivors had higher blood pressures and an increased frequency of prehypertension/hypertension.

Differences in underlying oncologic diagnoses, definitions of metabolic syndrome, and the prevalence of metabolic syndrome in the general population can complicate comparisons of metabolic syndrome between studies, and varied ranges of metabolic syndrome prevalence have been reported among survivors (24). In a prospective analysis of the French Childhood Leukemia Survivor's cohort, Oudin

Table 2. Cardiometabolic parameters among childhood cancer survivors and NHANES comparison group.

Parameter	Survivors[a] $N = 164$	NHANES[a] $N = 584$	*P* value
Body mass index, kg/m^2 (mean ± SD)	27.0 ± 6.0	28.2 ± 7.6	0.05
Body mass index category, *n* (%)			0.16
Underweight (<18.5 kg/m^2)	6 (3.7)	9 (1.5)	
Normal (18.5–24.9 kg/m^2)	69 (42.1)	214 (36.8)	
Overweight (25.0–29.9 kg/m^2)	47 (28.7)	178 (30.6)	
Obese (≥30 kg/m^2)	42 (25.6)	181 (31.1)	
Waist circumference, cm (mean ± SD)	91.5 ± 13.9	95.7 ± 17.5	0.006
Blood pressure, mm Hg (mean ± SD)			
Systolic	116.6 ± 12.3	114.3 ± 11.5	0.04
Diastolic	69.9 ± 9.3	68.0 ± 10.6	0.03
Blood pressure category, *n* (%)			0.13
Normal, < 120/80 mmHg	101 (61.6)	397 (69.9)	
Elevated/prehypertensive, 120–129/80 mmHg	31 (18.9)	85 (15.0)	
Hypertensive, ≥130/80 mmHg	32 (19.5)	86 (15.1)	
Known hypertension	5 (3.0)	33 (5.7)	0.18
Lipids			
Total cholesterol, mg/dL (mean ± SD)	180.7 ± 49.1	178.9 ± 38.5	0.61
Total cholesterol ≥200 mg/dL, *n* (%)	46 (28.8)	158 (27.8)	0.82
HDL, mg/dL (mean ± SD)	52.5 ± 12.7	50.1 ± 14.7	0.07
Low HDL, *n* (%)[b]	39 (23.8)	208 (35.6)	0.004
Triglyceride, mg/dL (mean ± SD)	130.1 ± 314.1	117.1 ± 146.0	0.56
Triglyceride ≥150 mg/dL, *n* (%)	30 (18.8)	46 (17.4)	0.72
Known dyslipidemia	6 (3.7)	19 (3.3)	0.78
Blood sugar			
Fasting glucose, mg/dL (mean ± SD)	89.7 ± 23.3	97.9 ± 20.0	<0.001
Hemoglobin-A1c, % (mean ± SD)	5.1 ± 0.7	5.2 ± 0.4	0.01
Prediabetes, *n* (%)	16 (9.9)	90 (15.8)	0.06
Diabetes, *n* (%)	4 (2.5)	9 (1.6)	0.50
Known diabetes	2 (1.2)	8 (1.4)	>0.99
Metabolic syndrome-defining criteria,[c] *n* (%)			
≥2 criteria	43 (26.7)	194 (55.9)	<0.001
≥3 criteria	19 (11.9)	73 (18.7)	0.05

Abbreviation: HDL, high-density lipoprotein.
[a]Column-based percentages presented unless otherwise stated; percentages exclude those with missing values.
[b]Males if <40 mg/dL and females if <50 mg/dL.
[c]ATP III criteria [≥3 meet formal metabolic syndrome definition: waist circumference >102 cm (males) or >88 cm (females); blood pressure ≥130/85 mm Hg; HDL <40 mg/dL (males) or <50 mg/dL (females), fasting triglyceride level ≥150 mg/dL, fasting glucose ≥100 mg/dL].

and colleagues reported that adult survivors of childhood leukemia [about half exposed to cranial and/or total body irradiation (TBI)] were at a greater risk of developing metabolic syndrome compared with the French population (25). The overall reported prevalence among survivors of 10% was similar to our study (11.9%), whereas the French comparison group demonstrated healthier profiles, with a metabolic

Table 3. Lifestyle factors among childhood cancer survivors and NHANES comparison group.

Lifestyle factor	Survivors[a] $N = 164$	NHANES[a] $N = 584$	*P* value
Tobacco smoking, *n* (%)			
History of smoking	40 (24.8)	240 (42.6)	<0.001
Current smoker	21 (13.0)	163 (28.9)	<0.001
Physical activity			
Meets CDC recommendations,[b] *n* (%)	108 (67.1)	252 (43.2)	<0.001
Total time, in moderate equivalents (minutes/week), median (IQR)	270 (90–630)	90 (0–360)	<0.001
Number adverse lifestyle factors, *n* (%)			<0.001
0	90 (56.6)	170 (30.1)	
1	60 (37.7)	284 (50.4)	
2	9 (5.7)	110 (19.5)	

[a]Percentages exclude those with missing values.
[b]CDC guidelines for aerobic activity: 150 minutes moderate-intensity aerobic physical activity or 75 minutes of vigorous-intensity physical activity, or an equivalent combination, each week.

Table 4. Estimated cardiovascular risks among childhood cancer survivors and NHANES comparison group.

Estimated risk	Survivors $N = 164$	NHANES $N = 584$	*P* value
Framingham 30-year risk			
Full cardiovascular risk, lipid model (mean ± SD)	7.6% ± 5.5%	9.2% ± 8.3%	0.02
Hard cardiovascular risk, lipid model (mean ± SD)	3.8% ± 3.5%	4.8% ± 5.3%	0.03
Predicted heart age (mean ± SD)	32.5 ± 4.6 years	33.7 ± 5.7 years	0.01
PDAY (mean ± SD)			
Coronary artery score	12.4 ± 6.9 points	13.3 ± 6.8 points	0.17
Abdominal aorta score	12.3 ± 5.7 points	13.3 ± 5.4 points	0.07
CCSS age 50-year risk, *n* (%)			
Ischemic heart disease[a]		n/a	
Low-risk	114 (69.5%)		
Moderate-risk	50 (30.5%)		
High-risk	0		
Heart failure[b]		n/a	
Low-risk	5 (3.0%)		
Moderate-risk	77 (47.0%)		
High-risk	82 (50.0%)		

Abbreviation: n/a, not applicable.
[a]Per "standard" model's predicted cumulative incidence of developing clinical ischemic heart disease by age 50 years, corresponding to 2% (low-risk), 12% (moderate-risk), and 20% (high-risk).
[b]Per "standard" model's predicted cumulative incidence of developing clinical heart failure by age 50 years, corresponding to 1% (low-risk), 9% (moderate-risk), and 12% (high-risk).

syndrome prevalence of 4.5% in contrast to the much higher prevalence in the NHANES population. In the CCSS, Armstrong and colleagues reported that adult survivors of childhood cancer had a similar prevalence of ≥ 2 CRFs (10.3%) compared with siblings (7.9%), but a higher prevalence of hypertension and dyslipidemia at 50 years of age, and a significantly higher incidence of late cardiac events (2).

Others have demonstrated an increased risk of metabolic syndrome among survivors, associated with higher body mass index at cancer diagnosis, older age at assessment, or a history of cranial radiation, abdominal radiation, or HCT with TBI (26–29). In our study, a lower proportion of survivors met multiple ATP III–defined metabolic syndrome criteria compared with the NHANES group, which could reflect the overall more favorable lifestyle habits of these survivors, despite high-risk treatment exposures (e.g., ALL/LL patients received cranial radiation). Survivors at particularly high risk of metabolic syndrome, such as HCT survivors treated with TBI, were not eligible for our study.

Although the similar cardiometabolic profiles of survivors and the control population are potentially reassuring, it is notable that this relatively young survivors' cohort had higher rates of prehypertension/hypertension. Although it is possible that this could be a chance finding secondary to multiple comparisons, in the general population, the association of hypertension with major cardiac events is well established (20). In survivors, hypertension has also been associated with an increased risk for major cardiac events, beyond the risk attributed to cancer-directed therapy, including an increased risk of cardiac mortality (2). Our results reinforce the importance of vigilance for prehypertension and hypertension in survivors, even in early adulthood.

In our study, survivors had more favorable lifestyle habits than the general population, including higher rates of meeting national recommendations for physical activity and lower rates of smoking tobacco. Prior studies also based on self-report have generally found that cancer survivors, both adult and pediatric, tend to be more inactive compared with noncancer comparison groups (30, 31). Therefore, it is possible that participants with healthier lifestyle profiles may have been more likely to participate in both the original clinical trials and/or the follow-up study. Nevertheless, regular exercise is associated with reductions in cardiovascular events and mortality in the general population (32, 33). In reports from the CCSS, Jones and colleagues showed that among survivors of pediatric Hodgkin lymphoma, vigorous exercise at baseline assessment was associated with a lower risk of subsequent cardiovascular events (34), and Scott and colleagues demonstrated that regular vigorous exercise and increased exercise over time were associated with a substantially decreased risk of mortality in adult survivors (35). Our findings regarding smoking are consistent with prior reports from the CCSS, the British Childhood Cancer Survivors Study, and other studies where survivors appear to have lower smoking rates compared with siblings and peers (36–38). Still, almost 25% of patients in our study had a history of smoking and 13% were current smokers, indicating a need for further efforts in smoking prevention and cessation.

With more favorable lifestyle habits and a similar burden of CRFs, survivors had lower predicted cardiovascular risk when applying general population risk prediction models for cardiovascular disease compared with the NHANES group. However, a high proportion of survivors had moderate or greater risk of future serious cardiovascular disease as predicted by previously validated childhood cancer survivors–specific risk models. Our results emphasize the challenge of adopting general population risk scores in childhood cancer survivors, with the potential to underestimate their likely true risk. Clinicians should be aware of the limitation of applying general population risk prediction models to survivors based on the absence of incorporation of high-risk cancer treatment exposures, while recognizing the importance of traditional CRFs in the childhood cancer survivor population. The development of predictive models for survivors that optimally incorporate the risk associated with cancer-directed therapy and the interplay with traditional CRFs has the potential to better inform clinical monitoring and intervention strategies (39). Incorporation of lifestyle factors and patient-level laboratory and physiologic data such as blood pressure measurements and lipid levels, as well as

dexrazoxane utilization, may further optimize future risk models for childhood cancer survivors.

This analysis was conducted in the context of long-term follow-up after cancer treatment which included administration of anthracycline with or without dexrazoxane. The use of dexrazoxane has been shown to have a medium-term cardioprotective effect based upon echocardiographic assessment of left ventricular structure and function and serum cardiac biomarker concentrations (40, 41). In this assessment, we did not see differences in cardiometabolic parameters in survivors based on dexrazoxane exposure. ALTE11C2's long-term echocardiographic assessment results will be reported separately, with completion of primary study accrual. Defining the extent of potential long-term risk mitigation due to dexrazoxane cardioprotection could further improve childhood cancer survivor risk assessment.

A limitation of this analysis is the lower patient accrual at some sites, which may limit our results' generalizability toward childhood cancer survivors at large. Long-term follow-up of patients treated on legacy protocols poses challenges for recruitment decades later, particularly as most COG sites only follow patients through childhood and the majority of potential participants were not reachable. Current distance from participating sites or socioeconomic factors could have contributed to reduced participation. We attempted to mitigate any potential biases associated with differential recruitment by sex and race/ethnicity by matching on those characteristics in our NHANES comparison group. Furthermore, in assessing cardiometabolic outcomes among survivors recruited from sites with greater and lesser participation, no significant differences were found, lending support to the potential generalizability of results. Nonetheless, differential accrual remains a potential source of bias. It is also unlikely that a significant survival bias is contributing to a healthier than expected study population. A prior examination of COG and U.S. national death codes obtained for the original clinical trial populations for this study found that after more than 12 years of follow-up, among 132 deaths recorded from 1,008 patients, none were due to a primary cardiovascular cause (42). Of cardiovascular causes classified as secondary causes of death, these were reported in four individuals, all of whom died of their primary underlying cancer.

In conclusion, after more than 17 years since cancer diagnosis, young adult survivors had similar cardiometabolic profiles compared with general population controls. Survivors had higher rates of prehypertension/hypertension, reinforcing the importance of close attention to blood pressure monitoring and management, even in early adulthood. With more favorable lifestyle habits, survivors not only had a lower predicted cardiovascular risk when applying general population risk factor models for the subsequent development of clinically significant cardiovascular disease, but also had a moderate or greater risk of subsequent symptomatic cardiovascular disease predicted by childhood cancer survivor–specific risk models. Future research should focus on interventions that support optimal CRF control. The development of effective anticancer therapies with lower cardiotoxicity profiles should remain a priority. Meanwhile, intensive CRF control and lifestyle improvements among childhood cancer survivors are particularly warranted.

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Authors' Contributions

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