






ORIGINAL RESEARCH

Underdiagnosis and Undertreatment of Modifiable Cardiovascular Risk Factors Among Survivors of Childhood Cancer

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BACKGROUND: Determine the prevalence and predictors associated with underdiagnosis and undertreatment of modifiable cardiovascular disease (CVD) risk factors (hypertension, dyslipidemia, glucose intolerance/diabetes) among adult survivors of childhood cancer at high risk of premature CVD.

METHODS AND RESULTS: This was a cross-sectional study of adult-aged survivors of childhood cancer treated with anthracyclines or chest radiotherapy, recruited across 9 US metropolitan regions. Survivors completed questionnaires and in-home clinical assessments. The comparator group was a matched sample from the National Health and Nutrition Examination Survey. Multivariable logistic regression estimated the risk (odds ratios) of CVD risk factor underdiagnosis and undertreatment among survivors compared with the National Health and Nutrition Examination Survey. Survivors ($n=571$; median age, 37.7 years and 28.5 years from cancer diagnosis) were more likely to have a preexisting CVD risk factor than the National Health and Nutrition Examination Survey ($n=345$; $P<0.05$ for all factors). While rates of CVD risk factor underdiagnosis were similar (27.1% survivors versus 26.1% National Health and Nutrition Examination Survey; $P=0.73$), survivors were more likely undertreated (21.0% versus 13.9%, $P=0.007$; odds ratio, 1.8, 95% CI, 1.2–2.7). Among survivors, the most underdiagnosed and undertreated risk factors were hypertension (18.9%) and dyslipidemia (16.3%), respectively. Men and survivors who were overweight/obese were more likely to be underdiagnosed and undertreated. Those with multiple adverse lifestyle factors were also more likely undertreated (odds ratio, 2.2, 95% CI, 1.1–4.5). Greater health-related self-efficacy was associated with reduced undertreatment (odds ratio, 0.5; 95% CI, 0.3–0.8).

CONCLUSIONS: Greater awareness of among primary care providers and cardiologists, combined with improving self-efficacy among survivors, may mitigate the risk of underdiagnosed and undertreated CVD risk factors among adult-aged survivors of childhood cancer.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03104543.

Key Words: cancer survivors ■ cardiovascular risk factor ■ undertreatment

Five-year survival after a diagnosis of childhood cancer now exceeds 85% with an estimated half-million survivors of childhood cancer living in the United States.^{1,2} However, the excess risk of mortality

after 5-year survival remains considerable,³ with cardiovascular disease (CVD) the leading noncancer cause of premature mortality in this population.^{4,5} Attributable to cancer treatment-related exposures, survivors of

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CLINICAL PERSPECTIVE

What Is New?

- Although the prevalence of underdiagnosed cardiovascular disease risk factors (ie, hypertension, dyslipidemia, glucose intolerance/diabetes) was similar between adult-aged survivors of childhood cancer previously exposed to cardiotoxic cancer therapies and the general population, cancer survivors were nearly twice as likely to be undertreated for these conditions.

What Are the Clinical Implications?

- Greater awareness of the substantially increased risk of cardiovascular disease among cancer survivors and their health care providers, combined with increased health-related self-efficacy among survivors and more aggressive control of cardiovascular risk factors by providers, may mitigate this risk.

Nonstandard Abbreviations and Acronyms

CCSS	Childhood Cancer Survivor Study
MHLC	Multidimensional Health Locus of Control
NHANES	National Health and Nutrition Examination Survey

childhood cancer have a >5-fold increased risk of serious CVD and death, and a greater burden of modifiable CVD risk factors such as hypertension, dyslipidemia, and diabetes compared with the general population.^{4,5} These modifiable risk factors appear to be synergistic with the cardiotoxic effects of cancer treatments and potentiate survivors' risk of ischemic heart disease and heart failure more than they do in the general population.^{5,6} Survivors also tend to develop CVD risk factors at younger ages compared with siblings or the general population.^{7,8}

Given this high risk of CVD and associated mortality among childhood cancer survivors, early diagnosis and control of CVD risk factors are critical. Most adult-aged survivors of childhood cancer report only receiving general medical care not specific to their history of cancer.⁹ With the earlier onset of CVD risk factors compounded by limited knowledge of cancer survivor-specific screening guidelines among primary care providers,^{10,11} most high-risk survivors are not receiving recommended cardiovascular screening in a timely fashion.^{12,13} Therefore, underdiagnosis (ie, survivors with risk factors but unaware of them) and

undertreatment (ie, previously diagnosed risk factors but inadequately treated) are significant concerns for this growing high-risk population. Prior work in single institutional settings suggests that CVD risk factor underdiagnosis is common.^{8,14} To our knowledge, the degree of CVD risk factor undertreatment in this population has not been examined.

To address this gap in knowledge, we used a standardized clinical protocol to prospectively measure the prevalence of hypertension, dyslipidemia, and diabetes underdiagnosis and undertreatment among a national sample of adult-aged, long-term survivors of childhood cancer at high risk for premature CVD being recruited for a randomized clinical trial. We hypothesized that rates of underdiagnosis and undertreatment would be greater among survivors compared with a matched comparison group of adults without a history of cancer. We then examined predictors associated with a differential risk of underdiagnosis and undertreatment as potential targets for future intervention.

METHODS

Participants

The CCSS (Childhood Cancer Survivor Study) consists of 25 665 individuals diagnosed with cancer before age 21 years at 31 institutions in the United States and Canada between 1970 and 1999, and who survived at least 5 years following diagnosis.¹⁵ Detailed information about the original cancer diagnosis and treatment (chemotherapy agents and doses, radiotherapy fields and doses, surgeries) were abstracted from medical records. For this analysis, US-based CCSS participants who were aged ≥ 18 years, free of known ischemic heart disease or heart failure, and living within 50 miles of 9 major metropolitan areas were recruited as part of a randomized clinical trial testing whether a survivorship care plan telehealth intervention can improve cardiovascular outcomes among long-term survivors of childhood cancer (NCT03104543).¹⁶ Eligibility included being classified as having an increased risk of ischemic heart disease or heart failure ($\approx 10\%$ cumulative incidence or greater by age 50 years) per previously validated CCSS risk prediction models based on demographic information and cancer treatment exposures (ie, anthracycline or chest radiation exposure).^{17,18} This analysis includes participants recruited beginning September 2017 until April 2020, and with data available as of May 2020. Study procedures were approved by the institutional review boards at the Fred Hutchinson Cancer Research Center and St. Jude Children's Research Hospital. All participants provided informed consent before undergoing study procedures. Data used in this analysis, as with all CCSS data, can be requested through the CCSS resource (ccss.stjude.org).

Measurements

Participants completed a questionnaire assessing past medical history, including cardiovascular health and treatment, Morisky medication adherence scale,¹⁹ lifestyle habits per the Behavioral Risk Factor Surveillance System (ie, weekly minutes spent engaged in moderate and vigorous physical activity, average daily fruit/vegetable intake, and smoking/tobacco use),²⁰ health-related self-efficacy,²¹ and the Multidimensional Health Locus of Control (MHLC) scale, Form B.²² Adverse lifestyle behaviors were categorized as (1) not meeting national guidelines for moderate (≥ 150 min/wk) to vigorous physical activity (≥ 75 min/wk)²³; (2) eating < 5 servings of daily fruit/vegetable²⁴; and (3) currently smoking/using tobacco. Self-efficacy and MHLC were scored according to their respective published recommendations. Self-efficacy scores were converted to standardized T-scores using the developer's US adult reference population.

Participants then underwent a standardized clinical assessment at home. A trained examiner measured participants' standing height, weight, waist circumference, and resting blood pressure (seated, 3 measurements, each ≥ 3 minutes apart). For blood pressure, the highest systolic and diastolic values were then dropped, and the remaining values averaged. At the same visit, the examiner drew blood for a lipid profile, random glucose, and hemoglobin A_{1c}. To minimize barriers to participation, the study did not require participants to fast before the blood draw, but the duration of any fasting was recorded. The elimination of routine fasting before lipid testing is consistent with current clinical practice and recommendations.²⁵ National guidelines provided guidance on interpretation of non-fasting lipid and random glucose testing.^{25–29} Samples were shipped overnight to a central clinical laboratory (St. Jude Children's Research Hospital) and results provided within 1 business day of receipt.

Finally, to better quantify the degree of possible "white coat" or "masked" hypertension,³⁰ a random subset of participants also received a Bluetooth-enabled home blood pressure monitor (Omron 10 Series, Omron Healthcare, Lake Forest, IL) following their home visit and were asked to record 3 measurements per week over a 1-month period. Participants used the Eureka Research Platform, a National Institutes of Health-funded mobile health platform, to automatically and securely transmit these measurements to the study team for analysis.

Comparison Group

Individuals from the 2015 to 2016 National Health and Nutrition Examination Survey (NHANES) who underwent both the examination and standardized laboratory study components (n=9544) served as a

contemporaneous, noncancer population for comparison purposes.³¹ After excluding individuals with a history of cancer, heart failure, or ischemic heart disease, the remaining individuals (n=8650) were further limited to those who had $> 95\%$ completion of the selected examination and laboratory assays of interest in this analysis and frequency-matched with the CCSS study population by 5-year age group, sex, and race and ethnicity (0.6:1 ratio; n=345).

Outcomes Definitions

Underdiagnosis among both CCSS and NHANES participants was defined by (1) lack of any self-reported history of the target condition (hypertension, dyslipidemia, or diabetes); and (2) study measurements consistent with the condition based on established clinical guidelines. Specifically, the presence of possible undiagnosed hypertension was suspected based on cutoffs from the 2017 revised US guidelines if average systolic values were ≥ 130 mm Hg or average diastolic values ≥ 80 mm Hg.³⁰ These cutoffs were chosen given that study participants were predicted to have an $\approx 10\%$ or greater risk of ischemic heart disease or heart failure by age 50 years because of their treatment for childhood cancer. Dyslipidemia was suspected if low-density lipoprotein was ≥ 160 mg/dL or fasting triglyceride was ≥ 150 mg/dL (or if < 10 hours fasting, ≥ 200 mg/dL).^{27–29} Diabetes was suspected if fasting glucose was ≥ 126 mg/dL (or if < 8 hours fasting, ≥ 200 mg/dL) or hemoglobin A_{1c} $\geq 6.5\%$.²⁶ We also separately examined prediabetes if fasting glucose was 100 to 125 mg/dL (or if < 8 hours fasting, glucose 140–199 mg/dL) or hemoglobin A_{1c} was 5.7% to 6.4%.

While any participant who was previously undiagnosed is also technically undertreated, we specifically defined undertreatment in this study as occurring among those who self-reported being previously diagnosed with hypertension, dyslipidemia, or diabetes managed by either lifestyle modifications or medication therapy, but whose home visit measurement fell outside the commonly recommended therapeutic range: blood pressure $\geq 140/\geq 90$ mm Hg, low-density lipoprotein ≥ 160 mg/dL, fasting triglyceride ≥ 150 mg/dL (or ≥ 200 mg/dL if not fasting), or hemoglobin A_{1c} $\geq 7.0\%$. As a secondary outcome, among participants aged 20 to 60 years, we also estimated the 30-year risk of hard CVD events (coronary death, myocardial infarction, and stroke) on the basis of models developed for the general population.³²

Statistical Analysis

Univariate comparisons were assessed using *t* tests and chi-square tests. Comparisons of mean physiologic values between CCSS and NHANES used linear regression adjusted for the frequency-matched

variables (current age, sex, race or ethnicity). To examine the potential influence of participation bias, we also performed a sensitivity analysis in which we estimated underdiagnosis and undertreatment prevalence rates with inverse probability weights accounting for the distribution of sex, racial or ethnic status, history of hypertension requiring medications, and history of dyslipidemia requiring medications from the entire CCSS sample approached for this study ($n=1591$). Multivariable logistic regression, adjusting for current age, sex, and race or ethnicity, estimated the odds ratios (ORs) and the 95% CIs of any CVD risk factor underdiagnosis or undertreatment in CCSS compared with NHANES, and those associated with demographic and clinical characteristics within the CCSS population. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Reported P values were all 2-sided, with values <0.05 considered statistically significant. One of the authors (E.J.C.) had full access to all study data and takes responsibility for its integrity and the data analysis.

RESULTS

We approached 1591 survivors thought to be eligible on the basis of their most recent CCSS survey. Of these, 766 consented (48.1%), and after excluding those subsequently found to be ineligible ($n=29$), having missing questionnaires ($n=30$), not completing the home visit ($n=130$), having nonanalyzable blood samples ($n=1$), or withdrawing consent for the randomized clinical trial ($n=5$), 571 participants were available for analysis (Figure 1). Participants (56.9% women; 85.1% non-Hispanic White) had a median age of 37.7 years (range, 20.1–65.0) and were 28.5 years (range, 18.3–49.0) from their original cancer diagnosis (Table 1; survivor characteristics by individual cancer types shown in Table S1). Compared with NHANES, survivors were more likely to have a history of CVD risk factors (hypertension, 18.0% versus 11.0%; dyslipidemia, 14.0% versus 4.9%; diabetes, 6.5% versus 3.2%; all $P<0.05$). Although 68.3% of survivors ($n=390$) reported meeting national recommendations for physical activity, 67.6% ($n=386$) had at least 1 adverse lifestyle factor, with nearly one-quarter ($n=131$) having ≥ 2 adverse lifestyle factors. The NHANES sample was much less physically active and more likely to be current smokers compared with survivors. Finally, compared with participating cancer survivors, nonparticipating survivors were more likely to be men but did not otherwise appear to differ greatly by other demographic or clinical characteristics (Table S2).

Compared with NHANES, cancer survivors had lower mean body mass indices (BMIs) and measures of central adiposity (Table 2). However, mean blood pressures, lipid values, and measures of glucose

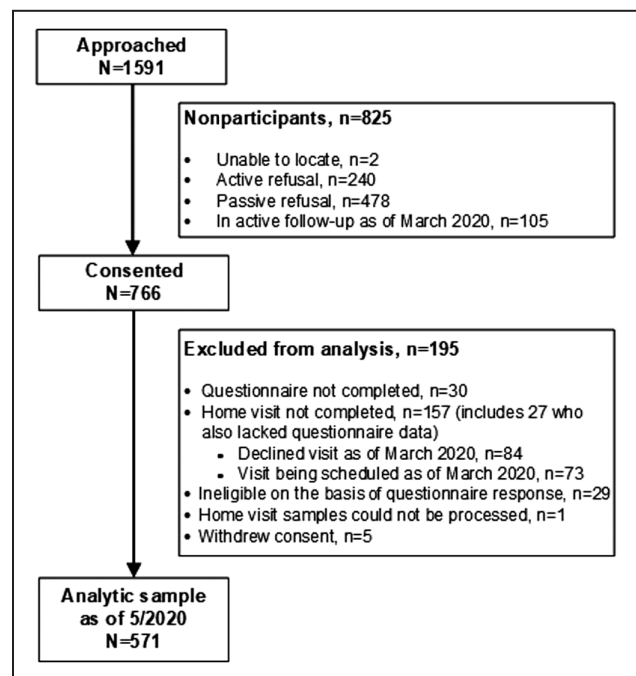


Figure 1. Consolidated Standards of Reporting Trials diagram.

Childhood cancer survivors were recruited between September 2017 and April 2020, when study procedures were halted because of COVID-19 pandemic-related restrictions in the United States.

tolerance were not consistently more favorable in one group versus the other. Based on models developed in the general population, the mean predicted 30-year risk of having a hard CVD event was lower among cancer survivors versus NHANES. Differences between cancer survivors and NHANES when stratified by underdiagnosis or undertreated status generally showed less favorable physiologic profiles among NHANES (Table S3). When physiologic parameters were compared within survivors alone, with and without any underdiagnosed or undertreated CVD risk factor, those with a possible underdiagnosed condition had greater BMI and waist circumference, along with worse mean blood pressures, cholesterol/triglyceride, blood glucose, and predicted hard CVD event risk. These differences were even greater among those with undertreated risk factors.

Overall, the proportion with potential CVD risk factor underdiagnosis was similar between cancer survivors ($n=155$; 27.1%) and NHANES ($n=90$; 26.1%; $P=0.73$). However, undertreatment was more common among survivors ($n=120$ [21.0%]) versus NHANES ($n=48$ [13.9%], $P=0.007$; OR, 1.8; 95% CI, 1.2–2.7). After weighting for potential characteristics associated with study nonparticipation, the prevalence rates of underdiagnosis and undertreatment among survivors were minimally altered: 27.4% and 20.1%, respectively. Survivors also remained at increased risk

Table 1. Characteristics of Childhood Cancer Survivors (CCSS) at High Cardiovascular Disease Risk and a Matched General Population Comparison Group (NHANES)

Characteristic, n (%)	CCSS N=571	NHANES N=345	P value
Female sex	325 (56.9)	187 (54.2)	0.42
Non-Hispanic White race and ethnicity	486 (85.1)	288 (83.5)	0.51
Median current age, y (range)	37.7 (20.1–65.0)	38.0 (20.0–64.0)	0.84
Median age at cancer diagnosis, y (range)	8.3 (0.01–20.8)	...	
Cancer diagnosis			
Bone cancer/sarcoma	86 (15.1)	...	
Central nervous system	59 (10.3)	...	
Kidney	55 (9.6)	...	
Leukemia	196 (34.3)	...	
Lymphoma	142 (24.9)	...	
Neuroblastoma	33 (5.8)	...	
Anthracycline exposure	441 (77.4)	...	
Chest radiation exposure	245 (43.1)	...	
History of hypertension	153 (26.8)	73 (21.2)	0.06
Currently on medications	103 (18.0)	38 (11.0)	0.004
History of dyslipidemia	191 (33.5)	75 (21.7)	<0.001
Currently on medications	80 (14.0)	17 (4.9)	<0.001
History of diabetes	52 (9.1)	13 (3.8)	0.002
Currently on medications	37 (6.5)	11 (3.2)	0.03
Lifestyle factors			
Physically active*	390 (68.3)	124 (35.9)	<0.001
≥5 cups daily fruits/vegetables	120 (21.0)	... [†]	
Current smoking/tobacco use	68 (12.5)	104 (30.1)	<0.001
Health care utilization			
Health insurance coverage	533 (93.3)	...	
Routine checkup within 1–2 years [‡]	517 (90.5)	...	
History of survivorship clinic attendance	262 (45.9)	...	

CCSS indicates Childhood Cancer Survivor Study; and NHANES, National Health and Nutrition Examination Survey.

*Reporting ≥150 minutes of moderate activity/week or ≥75 minutes of vigorous activity/week, or equivalent mixture of both.

[†]Not assessed by NHANES.

[‡]Defined as having had a checkup by a physician, physician assistant, or nurse practitioner within 1–2 years.

of undertreatment compared with NHANES even after adjusting for BMI and smoking status (OR, 2.0; 95% CI, 1.3–3.1).

In sensitivity analyses, examiner-measured blood pressure values were compared with self-measured values from home blood pressure monitoring (n=32

survivors; 50.0% female; median age, 38.0 years; median 14.5 measurements [range, 3–120] over 5 weeks). Overall, the average examiner-measured values tended to be lower compared with self-measured home monitoring (112/73 mm Hg versus 118/78 mm Hg) with fewer survivors (25.0% versus 31.3%) classified as hypertensive (ie, average value ≥130/≥80 mm Hg).

When the proportions of underdiagnosis and undertreatment among cancer survivors were examined for each CVD risk factor, potentially underdiagnosed conditions were identified in 18.9% for hypertension, 13.1% for dyslipidemia, and 0.7% for diabetes (but an additional 22.9% with potential prediabetes; Figure 2). Potential undertreatment was identified in 4.9% for both hypertension and diabetes, and 16.3% for dyslipidemia. Among survivors without a known history of a given CVD risk factor, 20% to 26% had examiner-measured values consistent with a possible new diagnosis of hypertension, dyslipidemia, or impaired glucose tolerance. Among survivors with a history of a given risk factor, the proportion with potential undertreatment ranged from 18.3% for those with hypertension to 48.7% and 53.8% for dyslipidemia and diabetes, respectively. Relatively few survivors had multiple underdiagnosed or undertreated risk factors (Table S4).

Characteristics associated with both underdiagnosis and undertreatment in cancer survivors included male sex, increased BMI, and the presence of ≥2 adverse lifestyle factors (Table 3). Additional characteristics associated with an increased risk of undertreatment included older current age (OR, 2.3–2.9) and a history of chest radiotherapy exposure (OR, 2.0; 95% CI, 1.3–3.1). Furthermore, survivors who reported greater health-related self-efficacy (OR, 0.5; 95% CI, 0.3–0.8) and those who scored higher on internal locus of control beliefs (OR, 0.7; 95% CI, 0.5–0.9) were less likely to be undertreated. In contrast, survivors who scored higher on external locus of control (powerful others) were more likely to be undertreated (OR, 1.5; 95% CI, 1.1–1.9). Secondary analyses that included these additional covariates concurrently (chest radiotherapy, adverse lifestyle factors, BMI, self-efficacy, and MHLC scales) showed similar results (Table S5). Finally, prior attendance at a survivorship (ie, long-term follow-up) clinic or having a recent routine checkup were not associated with a differential risk of underdiagnosis or undertreatment. Medication adherence was also not associated with a differential risk of undertreatment (data not shown).

DISCUSSION

Prior research from CCSS and other groups have shown that childhood cancer survivors are at

Table 2. Physiologic Measurements of Childhood Cancer Survivors (CCSS) at High Cardiovascular Disease Risk and the General Population (NHANES)

Outcomes,* n (%)	CCSS vs NHANES overall		CCSS only					
	CCSS N=571	NHANES N=345	P value†	No underdiagnosis or undertreatment N=323‡	Any underdiagnosis N=155‡	P value§	Any undertreatment N=120‡	P value§
BMI, kg/m ²	27.4 (6.4)	29.2 (7.2)	0.001	26.2 (6.0)	28.8 (6.9)	<0.001	29.4 (6.4)	<0.001
No. overweight 25–29 kg/m ² (%)	178 (31.2)	94 (27.3)	0.001	91 (28.2)	61 (39.4)	<0.001	36 (30.0)	<0.001
No. obese ≥30 kg/m ² (%)	160 (28.0)	136 (39.4)		72 (22.3)	49 (31.6)		50 (41.7)	
Waist circumference, cm	89.1 (15.6)	99.1 (17.0)	<0.001	85.7 (14.8)	93.1 (15.3)	<0.001	94.6 (15.4)	<0.001
No. with central adiposity (%)¶	182 (31.9)	190 (55.1)	<0.001	90 (27.9)	56 (36.1)	0.07	50 (41.7)	0.006
Systolic blood pressure, mm Hg	113.5 (12.6)	117.7 (13.7)	<0.001	109.7 (10.2)	118.7 (11.9)	<0.001	118.9 (15.2)	<0.001
Diastolic blood pressure, mm Hg	73.6 (8.9)	70.0 (11.0)	0.002	70.6 (7.0)	79.4 (8.4)	<0.001	75.9 (10.3)	<0.001
Total cholesterol, mg/dL	187.6 (40.2)	191.6 (42.0)	0.11	177.5 (30.4)	198.7 (46.7)	<0.001	211.0 (50.7)	<0.001
High density lipoprotein, mg/dL	52.3 (17.1)	54.3 (16.7)	0.04	56.9 (16.5)	48.9 (18.1)	<0.001	42.3 (10.5)	<0.001
Low density lipoprotein, mg/dL	105.4 (33.0)	114.3 (36.8)	<0.001	99.6 (25.7)	112.2 (36.7)	<0.001	119.1 (46.0)	<0.001
Triglyceride, mg/dL	155.5 (126.8)	111.2 (71.0)	<0.001	106.0 (50.7)	201.0 (156.1)	<0.001	265.1 (174.7)	<0.001
Blood glucose, mg/dL	90.7 (29.4)	103.2 (27.7)	<0.001	85.4 (16.7)	91.7 (36.7)	0.045	108.2 (45.1)	<0.001
Hemoglobin A _{1c} , %	5.6 (0.9)	5.4 (0.8)	0.004	5.4 (0.4)	5.6 (0.81)	0.005	6.3 (1.50)	<0.001
30-y hard CVD event risk, %[¶]								
Lipid model	9.9 (10.3)	11.7 (11.6)	0.02	6.5 (6.5)	10.9 (9.0)	<0.001	19.8 (14.5)	<0.001
BMI model	12.3 (12.8)	14.5 (14.3)	0.02	9.1 (10.0)	12.4 (10.9)	0.02	21.7 (16.8)	<0.001

BMI indicates body mass index; CCSS, Childhood Cancer Survivor Study; CVD, cardiovascular disease; and NHANES, National Health and Nutrition Examination Survey.

*Mean value (standard deviation) unless otherwise noted.

†Adjusted for sex, current age, and race and ethnicity, plus fasting duration (triglyceride and blood glucose only).

‡Numbers sum to >571 for CCSS, as some individuals had both at least 1 underdiagnosed condition and at least 1 undertreated condition (ie, hypertension, dyslipidemia, or diabetes/prediabetes); among NHANES, n=90 with underdiagnosis and n=48 with undertreatment.

§Compared against those with no underdiagnosed or undertreated hypertension, dyslipidemia, or diabetes.

¶Men ≥102 cm or women ≥88 cm.

‡Pencina et al, Circulation 2009³²; values shown are the mean risks (SD).

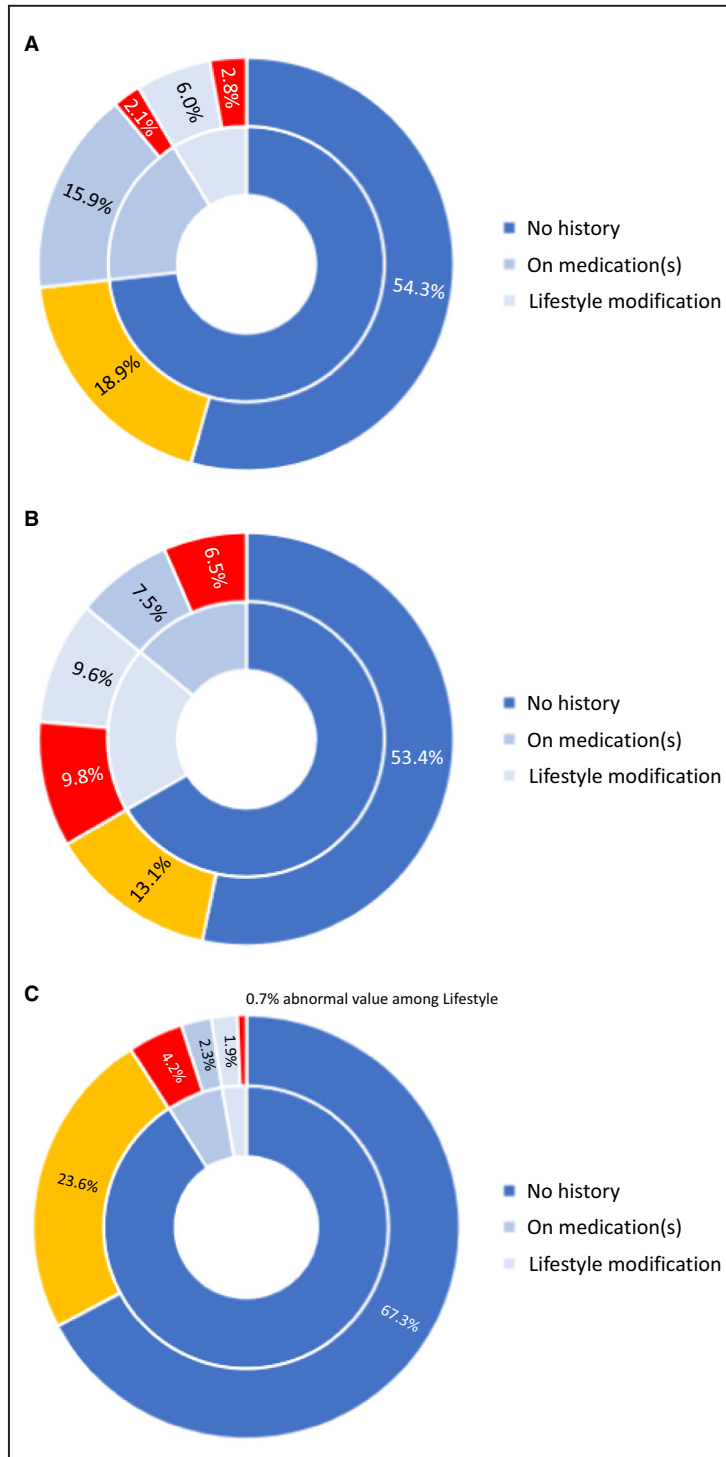


Figure 2. Sunburst charts showing the distribution of childhood cancer survivors (n=571) with normal and abnormal measurements corresponding to potential (A) hypertension, (B) dyslipidemia, and (C) glucose intolerance (diabetes and prediabetes).

The inner rings correspond to the proportions of survivors who reported no known history of the target cardiovascular risk factor (dark blue), survivors currently on medications (medium blue), and survivors with known risk factor but managed on lifestyle modification alone (light blue). The outer rings denote the proportion of survivors with a potentially underdiagnosed (gold) and undertreated (red) risk factor based on study measurements.

Table 3. Odds of Cardiovascular Disease Risk Factor Underdiagnosis or Undertreatment Among Childhood Cancer Survivors, Adjusted for Sex, Race/Ethnicity, and Current Age

Characteristic	Underdiagnosis N=155*		Undertreatment N=120*	
	OR (95% CI)	P value	OR (95% CI)	P value
Male vs female (ref)	1.8 (1.2–2.6)	0.003	1.9 (1.2–2.9)	0.004
Other races and ethnicities vs non-Hispanic White (ref)	0.7 (0.4–1.3)	0.30	0.9 (0.5–1.7)	0.72
Current age, y				
20–34	1.0 (ref)		1.0 (ref)	
35–39	1.0 (0.6–1.6)	0.94	2.3 (1.2–4.2)	0.009
≥40	0.9 (0.6–1.5)	0.78	2.9 (1.7–4.9)	<0.001
Anthracycline exposure vs none (ref)	1.5 (0.9–2.5)	0.12	0.7 (0.5–1.2)	0.22
Chest radiotherapy exposure vs none (ref)	1.0 (0.7–1.5)	0.88	2.0 (1.3–3.1)	0.002
Survivorship clinic attendance vs none (ref)	0.8 (0.5–1.2)	0.23	0.9 (0.6–1.4)	0.65
No routine vs routine checkup (ref)	1.3 (0.6–2.5)	0.50	0.6 (0.2–1.7)	0.37
No. adverse lifestyle factors [†]				
0	1.0 (ref)		1.0 (ref)	
1	1.1 (0.6–1.9)	0.72	1.4 (0.7–2.6)	0.34
≥2	1.8 (1.0–3.3)	0.06	2.2 (1.1–4.5)	0.03
Body mass index, kg/m ²				
<25	1.0 (ref)		1.0 (ref)	
25–29	2.3 (1.5–3.6) [‡]	<0.001	1.7 (1.0–2.9)	0.07
≥30			2.9 (1.7–4.9)	<0.001
High vs low health-related self-efficacy (ref) [§]	0.7 (0.5–1.1)	0.13	0.5 (0.3–0.8)	0.003
MHLC scale				
Internal	0.9 (0.7–1.2)	0.49	0.7 (0.5–0.9)	0.01
Chance	1.0 (0.8–1.3)	0.70	1.1 (0.8–1.4)	0.53
Powerful others	1.0 (0.8–1.3)	0.95	1.5 (1.1–1.9)	0.009

MHLC indicates Multidimensional Health Locus of Control; OR, odds ratio; and ref, referent.

*Compared with survivors without any cardiovascular disease risk factor underdiagnosis and undertreatment (n=323; referent).

[†]Consisting of physical inactivity, low fruit/vegetable consumption, and current smoking/tobacco use.

[‡]25–29 and ≥30 kg/m² categories combined as univariate analyses showed ORs 2.4 for both categories when compared with <25 kg/m².

[§]Defined as T-score ≥50 vs <50 (ref).

^{||}Modeled as a linear term with risk estimates reflecting the association with a 1-unit increase in the scale value.

increased risk of CVD, particularly among those with cardiotoxic cancer treatment exposures and those who develop subsequent CVD risk factors.^{4,5} The presence of these risk factors in conjunction with prior anthracycline or radiotherapy has been shown to have a synergistic effect on subsequent CVD risk, further emphasizing the need to mitigate potentially modifiable conditions in this high-risk population.^{5,6,33–35} In this analysis, we found that survivors at exceedingly high risk of premature CVD because of prior cancer treatment exposures had similar rates of CVD risk factor underdiagnosis as a matched general population sample. More than 90% of survivors in our study reported having health insurance and having had a routine checkup within the past 2 years, similar to rates reflective of the overall CCSS cohort.^{36,37} This is not dissimilar to recent national estimates showing that <10% of US adults

aged <65 years are uninsured.³⁸ However, survivors with a known CVD risk factor were nearly twice as likely to be undertreated compared with the general population.

Characteristics associated with undertreatment included male sex, older age, history of chest radiotherapy, greater number of adverse lifestyle factors, and higher BMI. Notably, we found that survivors of childhood cancer predicted to be at high risk of future ischemic heart disease or heart failure were more likely to have a history of CVD risk factors compared with a matched general population sample despite reporting greater physical activity, less current smoking/tobacco use, and being less obese. These results highlight the need for clinicians caring for these young and middle-aged adult survivors to routinely screen for modifiable CVD risk factors at younger ages than in adults without cancer treatment risks, and to consider intervening

more aggressively when any are detected. Prior surveys of CCSS participants showed that nearly 60% of these adult-aged patients (mean age of 32 years at time of survey) received only general medical care, with <20% receiving risk-based, cancer survivor-focused care.⁹ The overwhelming site of care was community based, with <15% of participants still receiving care at a cancer center.⁹

For survivors of childhood cancer living in the United States, the primary evidence-based guidelines for long-term follow-up are generated and maintained by the Children's Oncology Group, a clinical trial network with >200 institutions, predominantly in North America. Current evidence-based recommendations from these guidelines include annual measurement of blood pressure for virtually all cancer survivors, and periodic (every 2 year) screening of lipid profiles and glucose metabolism among those exposed to abdominal radiation, or if comorbid CVD risk factors are present, including hypertension and being overweight/obese.¹² For survivors who received anthracyclines or chest radiation (stage A heart failure), routine echocardiography to monitor for early-onset cardiomyopathy also is recommended.^{13,39}

These recommendations differ from those for the general population. For example, the current US Preventive Services Task Force recommendation for young adults (aged <40 years) who are normotensive and without other apparent risk factors is to repeat blood pressure screening every 3 to 5 years.⁴⁰ While the US Preventive Services Task Force recommends periodic screening for diabetes and dyslipidemia in older adults (aged ≥40 years), particularly if overweight or obese, no recommendations have been made for younger adults.^{40–42} Interventions for those aged ≥40 years are typically based on 10-year cardiovascular disease risks as estimated by general population risk calculators.⁴³ Notably, 10-year risk estimates are typically not available for those aged <40 years. Furthermore, as was seen in this analysis, general population risk calculators also do not account for cardiotoxic cancer treatments and therefore likely underestimate CVD risk among cancer survivors.^{6,44}

Increasing primary care and cardiology provider awareness of cancer survivors' risks may help further reduce the likelihood of underdiagnosis and undertreatment. Surveys of family physicians and internists reported low knowledge of survivor-specific follow-up guidelines and low provider efficacy regarding needs of childhood cancer survivors.^{10,11} For childhood cancer survivors, a shared care model between primary care and survivorship specialists was endorsed by most primary care-based survey respondents. This included the provision of patient-specific follow-up recommendations (ie, survivorship care plans), which

has been recommended by the National Academy of Medicine.⁴⁵

In this study, CVD risk factor undertreatment was also more common among those with lower self-efficacy, external locus of control, and a belief that powerful others control health outcomes. Our findings in cancer survivors are consistent with associations reported in the general population for conditions such as diabetes, heart disease, and health-related lifestyle behaviors.^{22,46–48} For example, among patients with diabetes, higher self-efficacy was strongly associated with improved diet and physical activity as key components of improved diabetes self-management.⁴⁷ Similarly, internal locus of control has been associated with lifestyle behaviors that influence cardiovascular health.⁴⁸ These results suggest that interventions that increase survivors' health-related self-efficacy and improve their internal sense of control over health outcomes may also reduce undertreatment. Participants with an undertreated condition have since been randomized in an ongoing 1-year health promotion trial that tests a telehealth-delivered self-management intervention beginning with the review of a personalized survivorship care plan.¹⁶ This intervention will also attempt to improve primary care providers' self-efficacy toward survivorship care.

Adverse lifestyle factors remain important modifiers of subsequent CVD risk and mortality among childhood and adult cancer survivors.^{49–52} Even though cancer survivors in this and other studies may report healthier lifestyle profiles compared with the general population,^{53,54} a significant proportion of survivors remain inactive, use tobacco, and may benefit from a healthier diet. Prior research also suggests that cancer survivors, including survivors of childhood and adolescent cancers, are interested in and may be more motivated to pursue lifestyle changes following their cancer experience.⁵⁵

Our results should be interpreted with several limitations in mind. As our study participation was linked to an ongoing randomized clinical trial with a 1-year time commitment, our overall consent rate was 48%. This rate may have been higher without the COVID-19 pandemic, as some potentially eligible participants were still being actively approached when study visits had to cease. Aside from sex, nonresponders did not differ substantially from responders, and we did not find our estimates to be markedly altered when we weighted our sample for characteristics reflective of the entire study population. Although the participation rate may raise concerns about the generalizability of the cancer survivors in our sample, our use of an age, sex, race and ethnicity-matched general population comparison group strengthens the validity of our findings. Related to generalizability, we also acknowledge that the US population has become much more diverse in the

past 20 years, especially children and young adults. However, CCSS's overall racial and ethnic composition is reflective of the US population when study participants were diagnosed with cancer (1970–1999).⁵⁶

Another limitation is the potential for measurement error and misclassification of undertreatment status based on 1-time measurements. Clinically, the diagnosis of hypertension, dyslipidemia, and diabetes typically require repeat testing for confirmation. However, any misclassification should affect survivors and NHANES participants nondifferentially, and these methods, when applied to NHANES, have remained invaluable in providing estimates of health for the US population at large. For blood pressure, which may be subject to the greatest amount of moment-to-moment variability, our examiner-measured values did not appear to be higher than self-measured values.

In conclusion, CVD risk factor underdiagnosis and undertreatment among childhood cancer survivors at increased risk of heart disease was common. Greater awareness among survivors, primary care providers, and cardiologists, combined with increased self-efficacy among survivors and more aggressive control of these risk factors by providers, may mitigate this risk. However, whether survivors experience the same degree of risk reduction with tighter control of potentially modifiable risk factors as seen in general population clinical trials remains to be determined.

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Disclosures

None.

Supplemental Material

Tables S1–S5

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SUPPLEMENTAL MATERIAL

TABLE S1. Characteristics and physiologic measurements of childhood cancer survivors at high cardiovascular disease risk by original cancer diagnosis.

Characteristics and measurements*	Acute lymphoblastic leukemia N=146	Other leukemia N=50	Bone cancer / sarcoma N=86	Central nervous system N=59	Hodgkin lymphoma N=95	Non-Hodgkin lymphoma N=47	Kidney N=55	Neuroblastoma N=33
Female sex (%)	79 (54.1%)	35 (70.0%)	54 (62.8%)	28 (47.5%)	47 (49.5%)	22 (46.8%)	38 (69.1%)	22 (66.7%)
White non-Hispanic race/ethnicity (%)	122 (83.6%)	42 (84.0%)	72 (83.7%)	53 (89.8%)	78 (82.1%)	43 (91.5%)	48 (87.3%)	28 (84.8%)
Median current age, y (range)	38.3 (21.5-62.5)	35.6 (21.6-59.4)	40.3 (20.1-59.4)	34.5 (23.8-55.2)	42.9 (26.9-65.0)	38.1 (27.4-58.3)	33.4 (22.1-56.2)	31.7 (20.4-42.4)
Median cancer diagnosis age, y (range)	4.9 (0.2-19.7)	6.8 (0.1-17.3)	13.5 (0.2-20.1)	8.8 (0.5-16.2)	14.2 (3.4-20.8)	9.8 (1.4-18.6)	3.7 (0.5-17.3)	0.9 (0.0-17.6)
Chest radiation exposure (%)	32 (22.1%)	16 (32.0%)	17 (20.0%)	59 (100.0%)	73 (76.8%)	9 (19.1%)	23 (42.6%)	16 (48.5%)
History of hypertension (%)	37 (25.3%)	17 (34.0%)	25 (29.1%)	14 (23.7%)	27 (28.4%)	12 (25.5%)	12 (21.8%)	9 (27.3%)
Currently on medications	24 (64.9%)	10 (58.8%)	20 (80.0%)	9 (64.3%)	21 (77.8%)	9 (75.0%)	7 (58.3%)	3 (33.3%)
History of dyslipidemia (%)	53 (36.3%)	18 (36.0%)	32 (37.2%)	23 (39.0%)	34 (35.8%)	11 (23.4%)	14 (25.5%)	6 (18.2%)
Currently on medications	23 (43.4%)	8 (44.4%)	11 (34.4%)	9 (39.1%)	19 (55.9%)	4 (36.4%)	3 (21.4%)	3 (50.0%)
History of diabetes (%)	14 (9.6%)	6 (12.0%)	7 (8.1%)	2 (3.4%)	7 (7.4%)	5 (10.6%)	7 (12.7%)	4 (12.1%)
Currently on medications	10 (71.4%)	4 (66.7%)	5 (71.4%)	2 (100.0%)	6 (85.7%)	3 (60.0%)	4 (57.1%)	3 (75.0%)
Lifestyle factors (%)								
Physically active [†]	110 (75.3%)	34 (68.0%)	56 (65.1%)	36 (61.0%)	63 (66.3%)	32 (68.1%)	39 (70.9%)	20 (60.6%)
≥5 cups daily fruits/vegetables	31 (21.2%)	8 (16.0%)	12 (14.0%)	11 (18.6%)	21 (22.1%)	11 (23.4%)	21 (38.2%)	5 (15.2%)
Current smoking/tobacco use	15 (10.3%)	6 (12.0%)	4 (4.7%)	4 (6.8%)	10 (10.5%)	1 (2.1%)	6 (10.9%)	2 (6.1%)
Healthcare utilization (%)								
Health insurance coverage	133 (91.1%)	45 (90.0%)	85 (98.8%)	57 (96.6%)	85 (89.5%)	43 (91.5%)	53 (96.4%)	32 (97.0%)
Routine check-up within 1-2 years [‡]	127 (87.0%)	44 (88.0%)	79 (91.9%)	57 (96.6%)	87 (91.6%)	40 (85.1%)	52 (94.5%)	31 (93.9%)
History of survivorship clinic attendance	70 (51.5%)	28 (62.2%)	42 (51.2%)	23 (43.4%)	32 (36.8%)	24 (53.3%)	26 (50.0%)	17 (56.7%)
BMI, kg/m ²	28.3 (6.4)	26.1 (5.7)	26.3 (5.7)	27.1 (7.1)	27.6 (5.7)	27.8 (6.9)	26.7 (5.3)	29.4 (9.6)
No. overweight 25-29 kg/m ² (%)	44 (30.1%)	12 (24.0%)	37 (43.0%)	18 (30.5%)	30 (31.6%)	16 (34.0%)	15 (27.3%)	6 (18.2%)
No. obese ≥30 kg/m ² (%)	50 (34.2%)	13 (26.0%)	13 (15.1%)	13 (22.0%)	30 (31.6%)	13 (27.7%)	16 (29.1%)	12 (36.4%)
Waist circumference, cm	90.8 (16.6)	87.0 (14.0)	88.7 (16.6)	88.4 (15.3)	91.3 (13.9)	88.8 (16.7)	82.3 (11.5)	91.9 (17.3)
No. with central adiposity (%) [§]	57 (39.0%)	16 (32.0%)	23 (26.7%)	21 (35.6%)	30 (31.6%)	13 (27.7%)	9 (16.4%)	13 (39.4%)
Systolic blood pressure, mmHg	113.8 (14.2)	111.0 (8.0)	112.3 (12.3)	114.0 (12.4)	115.4 (13.5)	113.7 (11.2)	112.0 (11.7)	115.3 (13.0)
Diastolic blood pressure, mmHg	73.9 (9.4)	73.4 (7.2)	74.0 (8.7)	72.8 (9.6)	73.3 (8.8)	73.7 (9.2)	73.4 (8.4)	73.2 (9.0)
Total cholesterol, mg/dL	184.0 (40.3)	190.9 (38.5)	192.3 (44.9)	202.8 (49.4)	189.5 (35.7)	185.0 (36.9)	178.3 (33.3)	172.9 (29.0)
High density lipoprotein, mg/dL	49.9 (15.0)	52.1 (15.2)	54.7 (19.4)	48.7 (16.6)	56.0 (19.8)	54.1 (20.8)	52.9 (14.2)	48.5 (9.3)
Low density lipoprotein, mg/dL	101.2 (31.8)	109.8 (34.6)	106.5 (36.3)	119.2 (40.4)	106.1 (30.6)	104.3 (31.3)	99.2 (27.8)	99.9 (23.2)
Triglyceride, mg/dL	162.8 (127.4)	151.9 (109.9)	162.8 (111.8)	181.8 (162.2)	147.4 (140.5)	152.6(164.6)	135.8 (74.2)	123.0 (59.1)
Blood glucose, mg/dL	87.7 (29.3)	92.2 (21.7)	92.5 (28.8)	88.9 (26.1)	93.9 (39.7)	92.4(20.5)	88.1 (24.6)	92.2 (31.6)
Hemoglobin A1c%	5.6 (1.1)	5.6 (0.8)	5.5 (0.7)	5.5 (0.5)	5.8 (1.0)	5.5 (0.8)	5.6 (0.6)	5.6 (0.6)

* Mean value (standard deviation) unless otherwise noted

[†] Reporting ≥150 minutes of moderate activity/week or ≥75 minutes of vigorous activity/week, or equivalent mixture of both

[‡] Defined as having had a check-up by a physician, physician assistant, or nurse practitioner within 1-2 years

[§] Males ≥102 cm or females ≥88 cm

TABLE S2. Demographic and clinical characteristics of participating versus non-participating cancer survivors recruited from the Childhood Cancer Survivor Study (CCSS) cohort.

Characteristic (%)	Participants		Non-participants N=825	Overall CCSS cohort* N=24,730
	All consented N=766	Complete data N=571		
Female sex	428 (55.9%)	325 (56.9%)	365 (44.2%)	11,544 (46.7%)
White non-Hispanic race/ethnicity	641 (83.7%)	486 (85.1%)	669 (81.1%)	20,233 (81.8%)
Median current age, years (range)	37.3 (20.1-65.0)	37.7 (20.1-65.0)	37.7 (19.7-64.9)	40.8 (19.1-69.5)
Median age at cancer diagnosis, years (range)	8.6 (0.01-20.9)	8.3 (0.01-20.8)	7.3 (0.00-20.7)	6.8 (0.0-21.0)
Cancer diagnosis				
Bone cancer / sarcoma	116 (15.1%)	86 (15.1%)	136 (16.5%)	3684 (14.9%)
Central nervous system	69 (9.0%)	59 (10.3%)	80 (9.7%)	4173 (16.9%)
Kidney	80 (10.4%)	55 (9.6%)	72 (8.7%)	2233 (9.0%)
Leukemia	251 (32.8%)	196 (34.3%)	255 (30.9%)	7699 (31.1%)
Lymphoma	205 (26.7%)	142 (24.9%)	215 (26.0%)	5077 (20.5%)
Neuroblastoma	45 (5.9%)	33 (5.8%)	67 (8.1%)	1864 (7.5%)
Anthracycline exposure	601 (78.9%)	441 (77.4%)	638 (78.1%)	10856 (48.1%)
Chest radiation exposure	315 (41.4%)	245 (43.1%)	329 (40.1%)	5430 (24.6%)
History of hypertension requiring medications [†]	107 (14.0%)	79 (13.8%)	85 (10.3%)	2990 (12.1%)
History of dyslipidemia requiring medications [†]	85 (11.1%)	70 (12.3%)	78 (9.5%)	2108 (8.5%)
History of diabetes requiring medications [†]	29 (3.8%)	23 (4.0%)	33 (4.0%)	1061 (4.3%)
History of tobacco use [†]	252 (32.9%)	175 (30.6%)	280 (33.9%)	7958 (32.2%)

* Not known to be deceased as of January 1, 2019

[†] Based on responses to prior Childhood Cancer Survivor Study questionnaires

TABLE S3. Physiologic measurements of childhood cancer survivors (CCSS) at high cardiovascular risk compared with the general population (NHANES), stratified by cardiovascular disease risk factor underdiagnosis and undertreatment status.

Outcomes*	No underdiagnosis or undertreatment			Any underdiagnosis			Any undertreatment		
	CCSS N=323 [†]	NHANES N=218 [†]	P-value [‡]	CCSS N=155 [†]	NHANES N=90 [†]	P-value [‡]	CCSS N=120 [†]	NHANES N=48 [†]	P-value [‡]
BMI, kg/m ²	26.2 (6.0)	28.2 (7.2)	0.01	28.8 (6.9)	30.7 (6.7)	0.02	29.4 (6.4)	31.7 (7.0)	0.14
No. overweight 25-29 kg/m ² (%)	91 (28.2%)	52 (23.9%)	0.02	61 (39.4%)	33 (36.7%)	0.06	36 (30.0%)	11 (22.9%)	0.35
No. obese ≥30 kg/m ² (%)	72 (22.3%)	75 (34.4%)		49 (31.6%)	40 (44.4%)		50 (41.7%)	28 (58.3%)	
Waist circumference, cm	85.7 (14.8)	95.8 (17.0)	<0.001	93.1 (15.3)	103.8(15.2)	<0.001	94.6 (15.4)	107.7 (15.4)	<0.001
No. with central adiposity (%) [§]	90 (27.9%)	109 (50.0%)	<0.001	56 (36.1%)	54 (60.0%)	<0.001	50 (41.7%)	34 (70.8%)	0.001
Systolic blood pressure, mmHg	109.7 (10.2)	112.3 (9.1)	0.001	118.7 (11.9)	126.0 (13.8)	<0.001	118.9 (15.2)	131.5 (17.8)	<0.001
Diastolic blood pressure, mmHg	70.6 (7.0)	66.9 (8.9)	<0.001	79.4 (8.4)	74.6 (12.7)	<0.001	75.9 (10.3)	78.3(11.2)	0.26
Total cholesterol, mg/dL	177.5 (30.4)	176.7 (32.7)	0.73	198.7 (46.7)	216.0 (45.1)	0.01	211.0 (50.7)	226.5 (39.6)	0.02
High density lipoprotein, mg/dL	56.9 (16.5)	58.9 (17.4)	0.10	48.9 (18.1)	45.2(10.4)	0.07	42.3 (10.5)	49.7(13.2)	<0.001
Low density lipoprotein, mg/dL	99.6 (25.7)	101.1 (27.8)	0.41	112.2 (36.7)	135.5 (40.6)	<0.001	119.1 (46.0)	145.0 (35.5)	<0.001
Triglyceride, mg/dL	106.0 (50.7)	76.8 (35.5)	<0.001	201.0 (156.1)	173.5 (78.0)	0.15	265.1 (174.7)	166.0 (74.0)	0.001
Blood glucose, mg/dL	85.4 (16.7)	97.7 (10.5)	<0.001	91.7 (36.7)	109.4 (42.4)	0.001	108.2 (45.1)	118.9 (36.8)	0.054
Hemoglobin A1c%	5.4 (0.4)	5.2 (0.4)	<0.001	5.6 (0.81)	5.6 (1.2)	0.54	6.3 (1.50)	5.9 (1.1)	0.24

* Mean value (standard deviation) unless otherwise noted

[†] Numbers sum to greater than 571 and 345 for CSS and NHANES, respectively, as some individuals had both at least one underdiagnosed condition and at least one undertreated condition

[‡] Adjusted for sex, current age, and race/ethnicity

[§] Males ≥102 cm or females ≥88 cm

TABLE S4. Distribution of underdiagnosed and undertreated conditions among childhood cancer survivors.

No. under-diagnosed conditions	No. undertreated conditions				Total
	0	1	2	3	
0	323	79	13	1	416
1	111	26	1	0	138
2	16	0	0	0	16
3	1	0	0	0	1
Total	451	105	14	1	571

TABLE S5. Odds of cardiovascular disease risk factor undertreatment among childhood cancer survivors, adjusted for sex, race/ethnicity, current age, chest radiotherapy, adverse lifestyle factors, body mass index, self-efficacy, and MHLC scales.

Characteristic	Undertreatment N=120*	
	OR (95% CI)	P-value
Male vs. female (ref)	1.5 (0.9-2.5)	0.11
Other vs. non-Hispanic White (ref)	1.5 (0.9-2.5)	0.11
Current age, years [†]	1.4 (1.0-1.9)	0.04
Chest radiotherapy exposure vs. none (ref)	2.0 (1.2-3.4)	0.009
No. adverse lifestyle factors [‡]		
0	1.0 (ref)	
1	1.4 (0.7-2.8)	0.38
≥2	1.9 (0.9-4.2)	0.10
Body mass index, kg/m ²		
<25	1.0 (ref)	
25-29	1.9 (1.0-3.6)	0.06
≥30	3.1 (1.7-5.8)	<.001
High vs. low health-related self-efficacy [§]	0.5 (0.3-1.0)	0.03
MHLC Scale		
Internal	0.6 (0.4-0.9)	0.03
Chance	0.8 (0.6-1.2)	0.25
Powerful others	1.7 (1.2-2.5)	0.005

CI, confidence interval; MHLC, Multidimensional Health Locus of Control; OR, odds ratio; ref, referent

* Compared with survivors without any cardiovascular disease risk factor underdiagnosis and undertreatment (n=323; referent)

[†] Modeled as a linear term with the following categories: 20-34, 35-39, and ≥40 years

[‡] Consisting of physical inactivity, low fruit/vegetable consumption, and current smoking/tobacco use

[§] Defined as T-score ≥50 vs. <50 (ref)

^{||} Modeled as a linear term with risk estimates reflecting the association with a one unit increase in the scale value