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Aggregating traditional cardiovascular disease risk factors to assess the cardiometabolic health of childhood cancer survivors: An analysis from the Cardiac Risk Factors in Childhood Cancer Survivors Study

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Abstract

Background—Childhood cancer survivors are at increased risk of cardiovascular disease (CVD), which may be associated with traditional CVD risk factors. We used CVD risk aggregation instruments to describe survivor cardiometabolic health and compared their results with sibling controls.

Methods—Traditional CVD risk factors measured in 110 survivors and 31 sibling controls between 15 and 39 years old were aggregated using Pathobiological Determinants of Atherosclerosis in Youth (PDAY) scores and the Framingham Risk Calculator (FRC) and expressed as ratios. The PDAY odds ratio represents the increased odds of currently having an advanced coronary artery lesion, and the FRC risk ratio represents the increased risk of having a myocardial infarction, stroke, or coronary death in the next 30 years. Ratios are relative to an individual of similar age and sex without CVD risk factors.

Results—The median PDAY odds ratio for survivors was 2.2 (interquartile range 1.3–3.3), with 17% N4. The median FRC risk ratio was 1.7 (interquartile range 1.0–2.0), with 12% N4. Survivors and siblings had similar mean PDAY odds ratios (2.33 vs 2.29, $P = .86$) and FRC risk ratios (1.72 vs 1.53, $P = .24$). Cancer type and treatments were not associated with cardiometabolic health. There was a suggested association for physical inactivity with PDAY odds ratios ($r = 0.17$, $P = .10$) and FRC risk ratios ($r = 0.19$, $P = .12$).

Conclusions—Cardiometabolic health is poor in childhood cancer survivors but not different than that of their siblings, highlighting the importance of managing traditional CVD risk factors and considering novel exposures in survivors.

Childhood cancer survivors are at increased risk of cardiovascular disease (CVD) relative to the general population for at least 45 years after their original cancer diagnosis.¹⁻⁵ Although this relative risk may decline with longer survival, the absolute increased risk of CVD in survivors may worsen because of age-related increases in the baseline incidence of CVD. In addition, the mechanisms responsible for the increased relative risk of CVD in survivors may change with longer survival.⁶

Radiation- and chemotherapy-induced vascular damage accounts for much of the increased risk of CVD in the first decades after cancer treatment, although endocrine and metabolic abnormalities may be responsible for a larger portion of this increased risk with longer survival.⁷⁻⁹ The importance of considering both treatment-induced vascular damage and traditional CVD risk factors was made clear in a study of 450 survivors with cardiac irradiation exposure.¹⁰ Of 42 survivors who developed coronary artery disease, at just a median of 9 years after diagnosis, all had at least 1 traditional CVD risk factor, and survivors with either high cholesterol or hypertension were 3 times more likely to develop coronary artery disease.

In the 1980s, reports began documenting an increased prevalence of obesity in survivors relative to healthy populations,¹¹ a result still found in contemporary cohorts.^{12,13} In 1996, Talvensaari et al¹⁴ found that survivors had lower fasting serum levels of high-density lipoprotein (HDL) cholesterol and higher levels of glucose relative to healthy populations. Additional studies confirmed these findings and found abnormalities to be associated with cranial irradiation and decreased growth hormone.¹⁵⁻¹⁹

Recently, studies have found increased clustering of traditional CVD risk factors in survivors of acute lymphoblastic leukemia treated with cranial or total body irradiation; however, this association was not seen in survivors of other cancer types, and these studies did not include noncancer controls.^{20,21} Another study with sibling controls found no difference between survivors and siblings but did find that total body irradiation was associated with risk factor clustering.²² Several studies have also reported an independent association between physical inactivity and risk factor clustering in survivors.^{20,22}

That obesity, dyslipidemia, and insulin resistance are modifiable risk factors for CVD has led to the creation of screening guidelines for survivors.^{23,24} The early identification and aggressive management of traditional risk factors will, it is to be hoped, reduce the overall CVD burden of survivors.²⁵ Combining traditional CVD risk factors into a single measure might help identify survivors needing more aggressive interventions and increase survivors' understanding of the importance of risk factor management.²⁶ Traditionally, risk aggregation instruments have only been available for older populations.^{27,28} Recently, however, 2 such instruments have been developed and validated for younger patients.^{29,30}

We used these new risk aggregation instruments to describe the cardiometabolic health of survivors who were part of a National Cancer Institute–funded cohort study and who had been evaluated for traditional CVD risk factors.³¹ Furthermore, we compared estimates of their cardiometabolic health with those of sibling controls and determined whether cancer type, cancer treatments, or physical inactivity was associated with their cardiometabolic health.

Methods

This substudy is part of the National Cancer Institute–sponsored Cardiac Risk Factors in Childhood Cancer Survivors Study, which has appropriate institutional review board approvals and written, informed consent.

The Cardiac Risk Factors in Childhood Cancer Survivors Study is described elsewhere.³¹ Briefly, survivors were recruited from the Pediatric Long-Term Survivor Clinic at the University of Rochester between 1998 and 2003. The clinic provides on-going follow-up care for survivors in the Finger Lakes region of New York and Pennsylvania. To recruit survivors not attending this clinic, we reviewed a list of all patients treated for childhood cancer at the University of Rochester, the provider for children with an oncological diagnosis in this region. Survivors were eligible if they had received a cancer diagnosis 3 years before, were no longer receiving cancer treatment, and were without active disease. For each survivor, a sibling control without a history of serious illness was invited to participate in the study, with the closest in age preferred.

Information on cancer diagnosis and treatment was abstracted from the medical records. All other information were collected during a single daylong study visit. Fasting blood samples were tested for traditional CVD risk factors including levels of total cholesterol, HDL cholesterol, and insulin. All tests were performed at the Strong Memorial Hospital Clinical Laboratory, Rochester, NY, which is in full compliance with the Clinical Laboratory Improvement Amendments. Blood pressure was recorded by Dinamap (GE Healthcare Critikon, Chalfont St. Giles, United Kingdom). Body mass index was calculated as weight in kilograms divided by the square of the height in meters. Physical inactivity was measured as self-reported hours of television watching per week.

Traditional risk factors for atherosclerotic disease—age, sex, non-HDL cholesterol, HDL cholesterol, current smoking status, hypertension, obesity, and hyperglycemia—were aggregated with Pathobiological Determinants of Atherosclerosis in Youth (PDAY) scores.²⁹ Each patient receives a score based on their risk factor profile that estimates the probability of currently having an advanced coronary artery lesion in either the left anterior descending artery (an American Heart Associate grade 4 or 5 lesion³²) or right coronary artery (any raised lesion covering at least 9% of the intimal surface). The PDAY scoring system uses a glycosylated hemoglobin level >8% to define hyperglycemia. Because this measure was not recorded in the Cardiac Risk Factors in Childhood Cancer Survivors Study, a fasting serum insulin level >18 μ U/mL was used; 12% of eligible survivors and 3% of siblings met this criteria.^{15,33-35}

The modified PDAY score is calculated by subtracting the points associated with age and sex from the above PDAY score. By the design of the PDAY scoring system, this modified PDAY score estimates the odds ratio of currently having an advanced coronary artery lesion in either the left anterior descending coronary artery or right coronary artery compared with an individual of similar age and sex without CVD risk factors. The odds for the individual without any modifiable CVD risk factors are estimated by the model. The PDAY probabilities and odds ratios were calculated for each subject between 15 and 34 years old, the age range for which the instrument was developed.

The Framingham Risk Calculator (FRC) uses a weighted combination of age, sex, total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, diabetes, and hypertensive treatment.³⁰ The FRC estimates expressed the 30-year risk, as a percentage, of experiencing a myocardial infarction, stroke, or coronary death. Because diabetes was not clinically diagnosed in the Cardiac Risk Factors in Childhood Cancer Survivors Study, a fasting serum insulin level >30 μ U/mL was used; 6% of eligible survivors and no siblings met this criteria.^{34,35}

The FRC also estimates an ideal 30-year risk of these events based on having no modifiable CVD risk factors.³⁰ The risk for the individual without any modifiable CVD risk factors is estimated by the model. An FRC risk ratio was created for each person by dividing the FRC

risk by the ideal risk estimated by the FRC. This FRC risk ratio represents the increased risk of having a myocardial infarction, stroke, or coronary death in the next 30 years relative to an individual of similar age and sex without CVD risk factors. An FRC risk and risk ratio were calculated for all subjects between 20 and 39 years old, the lowest end of the age range for which the instrument was developed.

To confirm that the PDAY odds ratio and FRC risk ratio were less age dependent than the PDAY probability and FRC risk, as would be expected from their origin and methods of calculation, we assessed the correlations between age and these measures using Spearman ρ (online Appendix). Because the ratio measures depended less on age, they were deemed more appropriate for describing impaired cardiometabolic health and were analyzed further.

Because some survivors lacked a sibling control, mixed models were used to compare survivors and siblings. To assess the association of cancer type and the PDAY odds ratios and FRC risk ratios, analysis of covariance was used to adjust for age and sex. To assess the association of cancer treatments and the PDAY odds ratios and FRC risk ratios, a single linear regression model was used with all treatments of interest simultaneously included and adjusted for age and sex. To assess the association of physical inactivity and the PDAY odds ratios and FRC risk ratios in survivors, correlation coefficients were used as well as linear regression to adjust for age and sex with standardized regression coefficients (β s) reported.

The PDAY and FRC measures are reported as medians to describe the raw values and as means when from a statistical model. Because the PDAY odds ratio and FRC risk ratio were positively skewed (Figure 1), they were log transformed. Transformed variables were used in procedures assuming normality and estimates back transformed for reporting unless the β s are reported. α Was set at .05, and all tests were 2 tailed. Analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC), and figures were made using Stata version 9.2 (StataCorp LP, College Station, TX).

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Results

Of 201 survivors and 76 siblings enrolled in the Cardiac Risk Factors in Childhood Cancer Survivors Study, PDAY estimates could be calculated for 101 survivors and 31 siblings, and FRC estimates, for 73 survivors and 16 siblings (Table I). Of the 129 subjects without an estimate, 101 were <15 or >40 years old, and 28 were missing data for a specific risk factor. Roughly half of the survivors had an original cancer diagnosis of leukemia or lymphoma, and most were at least 10 years from cancer diagnosis (Table II).

Survivors had a median PDAY odds ratio of 2.2 (interquartile range [IQR] 1.25-3.30), and 17% of survivors had ratios >4 (Figure 1). Survivors had a median FRC risk ratio of 1.67 (IQR 1.00-2.00), and 12% of survivors had ratios >4 (Figure 1). Siblings had a median PDAY odds ratio of 2.2 (IQR 1.70-3.30), with 6% having ratios >4 and a median FRC risk ratio of 1.50 (IQR 1.00-2.00); none had ratios >4 (Figure 1). The difference in the proportion of survivors and siblings with ratios >4 was not statistically significant for the PDAY odds ratio ($P = .24$) or FRC risk ratio ($P = .35$).

Compared with siblings, survivors had similar mean PDAY odds ratios (2.32 vs 2.25, $P = .80$) and FRC risk ratios (1.70 vs 1.63, $P = .73$). After adjusting for age and sex, neither

PDAY odds ratios (2.33 vs 2.29, $P = .86$) nor FRC risk ratios (1.72 vs 1.53, $P = .24$) differed significantly between survivors and siblings. These results were consistent with analyses including only the survivorsibling pairs (online Appendix, Figure A3).

The PDAY odds ratios and FRC risk ratios of survivors of different types of childhood cancer did not appear to differ markedly (Table III) nor was the variance in either ratio explained by cancer type statistically significant. The PDAY odds ratios and FRC risk ratios of survivors were not strongly associated with specific cancer treatments (Table IV).

There was a suggested association for physical inactivity with the PDAY odds ratios and the FRC risk ratios ($r = 0.17$, $P = .10$ and $r = 0.19$, $P = .12$, respectively) even after adjusting for age and sex ($\beta = .16$, $P = .12$ and $\beta = 0.19$; $P = .10$, respectively).

Discussion

Our results show that PDAY scores and the FRC can be applied in survivors of childhood cancer to combine the results of recommended CVD risk factor screening. These estimates, based on traditional risk factors, suggest that many survivors have impaired cardiometabolic health and are at increased long-term risk of CVD, although for most survivors, this risk may not differ largely from that of their siblings. In addition, although this risk was not strongly associated with a specific cancer type or treatment, there was a trend toward an association with physical inactivity.

In this study, a significant proportion of survivors had either a PDAY odds ratio or an FRC risk ratio >4 , meaning that they were at least 4 times more likely to currently have a coronary artery lesion or to have CVD in the next 30 years than individuals of similar sex and age without CVD risk factors. This finding supports the current emphasis on promoting cardio-metabolic health in survivors and identifying at-risk survivors through screening²⁵ and is consistent with other studies showing increased risk factor clustering in some survivors.²⁰⁻²²

In addition, finding that physical inactivity trended toward an association with poor cardiometabolic health suggests that lifestyle interventions for survivors may reduce CVD risk in high-risk survivors and maintain a low-risk profile in those not yet at high risk.²⁵ This finding is consistent with other studies^{20,22} and may partially explain the lack of a strong association between cancer and treatment characteristics with cardiometabolic health.

The similar estimates of cardiometabolic health, which were based on traditional CVD risk factors alone, between survivors and siblings suggest that much of the increase in early CVD incidence in survivors may result from the direct effects of cancer treatment, such as treatment-induced vascular damage. The similarities in cardiometabolic health between survivors and siblings may also reflect a diluting of the difference in the prevalence of individual CVD risk factors by those similarly prevalent in survivors and siblings, such as smoking and hypertension.^{36,37}

The lack of a strong relationship between estimates of cardiometabolic health and cancer type or specific treatments likely reflects the pathophysiologic heterogeneity of the individual risk factors aggregated in these measures. Individual CVD risk factors are unlikely to be affected by the same cancer treatments or associated with the same pathophysiologic changes. Thus, specific treatment-to-risk factor associations are likely to be obscured by other unaffected risk factors in the aggregated measures. This finding underscores the need for a broad-based screening approach because poor cardiometabolic health does not appear to be limited to a specific survivor subgroup. As mentioned, this

finding may reflect the importance of lifestyle habits, such as diet and physical inactivity, on the development of traditional CVD risk factors in survivors.

These aggregated measures are clinically attractive, in part, because of their ability to provide information beyond the sum of their parts. Unlike counting the number of risk factors present, which requires ignoring variation above and below a specific point, risk aggregation instruments provide an objective and evidenced-based method of considering more subtle variations in risk. Furthermore, these measures provide a single estimate of cardiometabolic health. These measures make possible a baseline assessment of cardiometabolic health that can be followed over time to detect the development of elevated CVD risk.

Unlike the case for adults, where the absolute risks estimated by risk aggregation instruments represent outcomes of sufficient probability, immediacy, and importance to guide treatment decision making,³⁸ the absolute risks in adolescents and young adults are often very low and most strongly influenced by age, as opposed to cardiometabolic abnormalities. In these patients, ratios in which the absolute risk is expressed relative to the absolute risk if the patient had no cardiometabolic abnormalities may hold greater clinical value.

In addition to abnormalities in cardiometabolic health, the CVD burden of survivors is driven by novel mechanisms related to cancer treatment. Although radiation and certain chemotherapeutics cause vascular damage and are risk factors for CVD, they were not considered in the aggregation instruments used in this report.^{2,4,7,10} Survivors exposed to anthracyclines and cardiac radiation have subclinical cardiotoxicity, including reduced left ventricular wall thickness and increased left ventricular afterload.^{39,40} These changes may leave survivors less able to compensate for ischemic cardiac damage and more susceptible to CVD. However, effective treatments are lacking for these novel factors, limiting their value as screening targets.⁹

The risk aggregation instruments used in this study were developed in a nonsurvivor population. It is possible that CVD risk factors affect survivors differently. However, it seems unlikely that a history of childhood cancer would be protective, meaning any bias would likely underestimate cardiometabolic impairments. These risk aggregation instruments do not account for novel risk factors, which may further contribute to underestimation. The Cardiac Risk Factors in Childhood Cancer Survivors Study did not collect data on CVD end points, such as myocardial infarction, stroke, or coronary death, which are rare in younger populations, even those at relatively high risk.

For associations between cardiometabolic health and survivor characteristics, there was likely insufficient power to detect statistically significant differences. It is therefore not possible to exclude an association such as that between cranial irradiation and decreased cardiometabolic health because of a lack of statistical significance. However, the small size and heterogeneous nature of this population and the difficulty inherent in obtaining detailed clinical measurements decades after treatment mean larger samples are rare.

We propose that inexpensive risk aggregation instruments—the PDAY odds ratio and FRC risk ratio—can be used as an additional method for identifying survivors at elevated risk of CVD. These instruments may facilitate patient understanding of the possible benefits of risk factor modification, which could increase adherence to risk reduction strategies. Although there was no evidence that survivors are at greater risk of such impairment than their sibling controls, their increased risk relative to an ideal person underscores the importance of promoting cardiometabolic health in survivors who also appear to be at risk for CVD from treatment-related vascular and cardiac injury.

Appendix

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. The PDAY odds ratios and FRC risk ratios for 110 survivors of childhood cancer and 31 siblings.

Table 1

Characteristics of survivors of childhood cancer and siblings with cardiometabolic aggregated risk measures, by instrument

Characteristic	Cardiometabolic risk aggregation instrument					
	PDAY			FRC		
	Survivors (n = 101), n (%)	Siblings (n = 31), n (%)	P	Survivors (n = 73), n (%)	Siblings (n = 16), n (%)	P
Sex						
Male	46 (45)	15 (48)		31 (42)	9 (56)	
Female	55 (54)	16 (52)	.78	42 (58)	7 (44)	.32
Age at risk factor assessment, y						
15-19	36 (36)	15 (48)		— *	— *	
20-29	50 (50)	13 (42)		49 (67)	13 (81)	
30-39	15 (15)	3 (10)	.08	24 (33)	3 (19)	.10
Inactivity, TV h/wk						
0-9	46 (50)	18 (60)		36 (51)	10 (63)	
10-19	25 (27)	9 (30)		19 (27)	4 (25)	
20-29	6 (6)	1 (3)		4 (6)	1 (6)	
30-39	16 (17)	2 (7)	.03	11 (16)	1 (6)	.08

TV indicates television.

* The PDAY measures were calculated only for subjects between 15 and 34 years old, and FRC measures, only for subjects between 20 and 39 years old; the age ranges for which these instruments were developed.

Table II

Characteristics of survivors of childhood cancer with cardiometabolic aggregated risk measures, by instrument

Cancer characteristic	Cardiometabolic risk aggregation instrument	
	PDAY (n = 101), n (%)	FRC (n = 73), n (%)
Cancer diagnosis		
Leukemia	32 (32)	16 (22)
Lymphoma	23 (23)	22 (30)
Sarcoma	15 (15)	13 (18)
Brain cancer	14 (14)	11 (15)
Other	17 (17)	11 (15)
Treatment exposures		
Alkylating agent	60 (59)	48 (66)
Anthracyclines	58 (57)	36 (49)
Cranial irradiation *	51 (51)	29 (40)
Antimetabolite	47 (47)	28 (39)
Corticosteroids	46 (46)	31 (43)
Years from diagnosis		
3-10	34 (34)	16 (22)
11-20	55 (54)	38 (52)
21-31	12 (12)	19 (26)

* Fifty-one percent of those with PDAY estimates and 41% of those with FRC estimates received <18 Gy, with 22% and 28% receiving over 60 Gy, respectively.

Table III

Association of cancer diagnosis with CVD risk in survivors of childhood cancer, by risk aggregation instrument

Cancer diagnosis [†]	<u>Adjusted* group, mean (95% CI)</u>	
	PDAY odds ratio	FRC risk ratio
Leukemia	2.37 (1.87-3.00)	1.91 (1.44-2.53)
Lymphoma	2.25 (1.71-2.96)	1.65 (1.30-2.10)
Sarcoma	2.16 (1.53-3.04)	1.24 (0.90-1.71)
Brain cancer	2.71 (1.89-3.89)	2.00 (1.42-2.82)
Other	2.26 (1.64-3.12)	2.10 (1.49-2.96)

* Group means are age and sex adjusted using analysis of covariance.

[†]The F test for cancer diagnosis was not statistically significant for either the PDAY odds ratio ($P = .91$) or for the FRC risk ratio ($P = .17$), with P values representing the probability of finding the observed differences between cancer diagnoses groups were there no differences.

Table IV

Association of cancer treatments with CVD risk in survivors of childhood cancer, by risk aggregation instrument

Treatment	Adjusted* mean difference	
	PDAY odds ratio (<i>P</i> value)	FRC risk ratio (<i>P</i> value)
Cranial irradiation	0.48 (0.22)	0.15 (0.66)
Corticosteroids	−0.25 (0.54)	−0.38 (0.22)
Alkylating agent	−0.03 (0.93)	−0.11(0.73)
Antimetabolite	0.36 (0.44)	−0.19 (0.58)
Asparaginase	−0.22 (0.71)	0.50 (0.42)

* Mean differences between survivors with and without the treatment exposures are adjusted for age, sex, and the other treatments using linear regression. *P* values represent the probability of finding a difference as extreme as the observed difference was there no difference.