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ORIGINAL REPORT

Cardiovascular Status of Childhood Cancer Survivors Exposed and Unexposed to Cardiotoxic Therapy

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ABSTRACT

Purpose
To determine whether cardiovascular abnormalities in childhood cancer survivors are restricted to patients exposed to cardiotoxic anthracyclines and cardiac irradiation and how risk factors for atherosclerotic disease and systemic inflammation contribute to global cardiovascular status.

Methods
We assessed echocardiographic characteristics and atherosclerotic disease risk in 201 survivors of childhood cancer with and without exposure to cardiotoxic treatments at a median of 11 years after diagnosis (range, 3 to 32 years) and in 76 sibling controls.

Results
The 156 exposed survivors had below normal left ventricular (LV) mass, wall thickness, contractility, and fractional shortening and above normal LV afterload. The 45 unexposed survivors also had below normal LV mass overall, and females had below normal LV wall thickness. Exposed and unexposed survivors, compared with siblings, had higher levels of N-terminal pro-brain natriuretic peptide (81.7 and 69.0 pg/mL, respectively, *v* 39.4 pg/mL), higher mean fasting serum levels of non–high-density lipoprotein cholesterol (126.5 and 121.1 mg/dL, respectively, *v* 109.8 mg/dL), higher insulin levels (10.4 and 10.5 μU/mL, respectively, *v* 8.2 μU/mL), and higher levels of high-sensitivity C-reactive protein (2.7 and 3.1 mg/L, respectively, *v* 0.9 mg/L; $P < .001$ for all comparisons). Age-adjusted, predicted-to-ideal 30-year risk of myocardial infarction, stroke, or coronary death was also higher for exposed and unexposed survivors compared with siblings (2.16 and 2.12, respectively, *v* 1.70; $P < .01$ for both comparisons).

Conclusion
Childhood cancer survivors not receiving cardiotoxic treatments nevertheless have cardiovascular abnormalities, systemic inflammation, and an increased risk of atherosclerotic disease. Survivorship guidelines should address cardiovascular concerns, including the risk of atherosclerotic disease and systemic inflammation, in exposed and unexposed survivors.

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INTRODUCTION

Currently, more than 325,000 childhood cancer survivors live in the United States.[1,2] Survivors are at higher risk for chronic disease and premature death[3-5]; cardiovascular-related complications are of particular concern.[6-11] For 30 years after cancer treatment, survivors are eight times more likely to die from cardiac causes[3] and 15 times more likely to experience congestive heart failure (CHF)[4] than the general population. Even 45 years after diagnosis, their increasingly higher risk of cardiac death[8] is associated with exposure to cardiotoxic treatments (eg, anthracyclines, cardiac irradiation).[6-8]

In more than half of exposed survivors, cardiotoxic treatments are also associated with subclinical changes in left ventricular (LV) structure and function[12-16] that commonly include decreased LV wall thickness and increased LV systolic wall stress (afterload), which can progress to clinically relevant disease.[14,17] As a result, cardiac monitoring for early disease is recommended for survivors exposed to cardiotoxic treatments.[18] However, these recommendations do not include survivors unexposed to cardiotoxic treatments, who have yet to be systematically studied.

Survivors are also more likely to have traditional risk factors for atherosclerotic disease, including elevated cholesterol, obesity, and insulin resistance,[19-22] and regular screening and aggressive management of these risk factors are now recommended.[23] Increased systemic inflammation may promote atherosclerotic cardiovascular disease

and worsen treatment-related cardiac dysfunction, although these relationships are not well studied in survivors.

The Cardiac Risk Factors in Childhood Cancer Survivors Study, a National Cancer Institute–funded study, evaluated a large, representative cohort of survivors in western New York State.[24] We hypothesized that cardiovascular status would differ between survivors exposed and unexposed to cardiotoxic treatments and between both survivor groups and sibling controls.

METHODS

Participants

The protocol for the Cardiac Risk Factors in Childhood Cancer Survivors Study is detailed elsewhere.[24] Briefly, survivors were recruited from the Pediatric Long-Term Survivor Clinic at the University of Rochester (Rochester, NY) between 1998 and 2003. The clinic cared for survivors in a defined catchment area consisting of parts of the Finger Lakes region of New York State and northern Pennsylvania. Eligible survivors had received a cancer diagnosis 3 or more years before, were no longer receiving chemotherapy or radiation, and were without active disease. For each survivor, a sibling control (closest in age was preferred), without a history of cancer or serious illness, was invited to participate.

Information on cancer diagnosis and treatment was abstracted from medical records. All other information was collected during a single, daylong study visit that included echocardiography, fasting blood samples, and patient examinations. Values for total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, insulin, N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hs-CRP), homocysteine, the ratio of apolipoproteins A1 to B1, and insulin-like growth factor-1 (IGF-1) were determined in a Clinical Laboratory Improvement Amendments–approved laboratory (Strong Memorial Hospital Clinical Laboratory, Rochester, NY), except for hs-CRP, which was determined using the N High-Sensitivity CRP assay (Dade Behring, Newark, DE). Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters.

Traditional risk factors for atherosclerotic disease were aggregated, according to methods appropriate for age, with the modified Pathological Determinants of Atherosclerosis in Youth risk score, which predicts the risk of an advanced atherosclerotic disease lesion in a major coronary artery,[25] and by calculating the ratio of predicted-to-ideal risk estimated by the Framingham 30-Year Calculator for myocardial infarction, stroke, or coronary death.[26]

A cardiologist unaware of the participants' treatment status read two-dimensional and Doppler echocardiograms. The LV fractional shortening and rate-adjusted velocity of fiber shortening were calculated, and LV afterload was measured as meridional end-systolic wall stress.[27,28] Contractility was defined as the relationship between end-systolic wall stress and rate-adjusted velocity of fiber shortening with the LV stress-velocity index, a validated index incorporating afterload and independent of preload.[26,27] Heart rate and corrected QT interval were measured by electrocardiography.

Statistical Methods

Normal echocardiographic, height, and weight measurements vary in children by age, body-surface area, and sex. To adjust for these influences, *z* scores were calculated by dividing the difference between a participant's observed and normal predicted value by the standard deviation of normal values. Normal predicted echocardiographic values were calculated with a regression model using data from 296 patients from Children's Hospital Boston whose ages were similar to those of our patients (raw estimates provided in Appendix Table A1, online only).[27,28]

Wilcoxon rank sum or *t* tests were used to compare groups on continuous measurements. Fisher's exact test was used to compare proportions. All tests were two-tailed with an $\alpha = .05$. Because group comparisons were determined a priori, we did not adjust for multiple comparisons, so *P* values should be interpreted cautiously, given the large number of comparisons. Possible correlations between controls and their exposed and unexposed siblings were accounted for with generalized estimating equations. Additionally, analyses limited to matched survivor-sibling pairs were consistent in direction and magnitude with those reported (except non-HDL cholesterol in unexposed survivors). Correlations among serum biomarkers in survivors were assessed with Spearman's rank correlation coefficient (ρ). Correlations of NT-proBNP and hs-CRP with the echocardiographic characteristics were assessed using the partial Spearman's ρ correlation coefficient to remove the effect of the other biomarker. Data were analyzed with SAS, version 9.2 (SAS Institute, Cary, NC) and STATA, version 11.0 (STATA, College Station, TX).

Imbalances in age and sex between groups were adjusted using weighted propensity scores. Each participant's data were weighted by the inverse of the probability of being in a specific age and sex group, calculated with generalized logit models.[29-31] Sex-specific group values were adjusted for age using this approach. Weights were assessed for balancing and comparing groups.

The institutional review boards at the University of Rochester and University of Miami (Miami, FL) approved the protocol. Written informed consent was obtained from all participants or guardians, and assent was obtained from the participants when appropriate.

RESULTS

Participants

We analyzed 156 survivors exposed to cardiotoxic therapies, 45 survivors unexposed to these therapies, and 76 healthy sibling controls. Both survivor groups were older and more likely than controls to report taking medications, vitamins, or nutritional supplements (Table 1). Although few participants reported health conditions, cardiovascular disease was more common in the exposed survivors (CHF, n = 5; stroke, n = 2; myocardial infarction, n = 1). Unexposed survivors were older and longer from diagnosis than exposed survivors; median age at diagnosis in both groups was close to 6 years, and 90% of survivors received a diagnosis between 1976 and 1996 (Table 2). Exposed survivors were more likely than unexposed survivors to have had leukemia or lymphoma and been treated with a plant alkaloid, antimetabolite, corticosteroids, or asparaginase. Values for the comparisons that follow are age- and sex-adjusted estimates.

LV Structure and Function

Exposed survivors had below normal LV mass and wall thickness (Table 3) and had above normal LV afterload, which was also higher than in unexposed survivors. Compared with sibling controls and unexposed survivors, exposed survivors had impaired LV load–independent contractility and LV fractional shortening and lower systolic blood pressure. Exposed survivors also had a faster heart rate, a longer corrected QT interval, and higher serum levels of NT-proBNP than the other groups. Female exposed survivors had a longer corrected QT interval and higher serum levels of NT-proBNP; the mean (104.2 pg/mL) is consistent with cardiomyopathy.

Unexposed survivors had below normal LV mass overall and below normal wall thickness ($P = .07$), which was statistically significant in female survivors (Table 3). Unexposed survivors had normal LV load–independent contractility, fractional shortening, and systolic blood pressure but had higher levels of NT-proBNP than did sibling controls. Unexposed female survivors had lower LV wall thickness and higher serum levels of NT-proBNP; the mean (102.4 pg/mL) is consistent with cardiomyopathy (Fig 1).

Table 1. Demographic and Medical Characteristics of 201 Long-Term Survivors of Childhood Cancer, by Exposure to Cardiotoxic Cancer Therapy, and 76 Normal Sibling Controls

Demographic or Medical Characteristic	Exposed Survivors (n = 156)		Unexposed Survivors (n = 45)		Sibling Controls (n = 76)	
	No.	%	No.	%	No.	%
Demographic						
Female	82	52.6	19	42.2	35	46.1
Race						
White	138	88.5	40	88.9	71	93.4
African American	9	5.8	2	4.4	2	2.6
Other	9	5.8	3	6.7	3	3.9
Age at follow-up, years						
Median	17.4*		23.0†		15.1*†	
Range	5.9-39.7		8.0-32.8		5.3-45.9	
Health conditions at follow-up						
Irregular heartbeat	7	4.5	1	2.2	0	0
Congestive heart failure	5	3.2	0	0	0	0
Heart attack	1	0.6	0	0	0	0
High blood pressure	5	3.2	3*	6.7	0*	0
Stroke	2	1.3	0	0	0	0
Pericarditis	3	1.9	1	2.2	0	
Stiff or leaking heart valve	2	1.3	0	0	0	0
Genetic syndrome	0	0	0	0	1	1.3
Atherosclerosis	0	0	0	0	0	0
Structurally abnormal heart at birth	0	0	0	0	0	0
Rheumatic heart disease	0	0	0	0	0	0
Current smoker‡	9	12.2	3	11.1	2	8.7
Medications at follow-up						
Any current medication	71*	45.5	27†	60	19*†	25
Neurologic	11	7.1	3	6.7	1	1.3
Pain, anti-inflammatory	12	7.7	8*	17.8	3*	3.9
Pain, non-narcotic	10	6.4	7*	15.6	1*	1.3
Pain, narcotic	3	1.9	0	0	0	0
Thyroid	7	4.5	2	4.4	1	1.3
Sex hormone	10	6.4	5*	11.1	1*	1.3
Growth hormone	2	1.3	3*	6.7	0*	0
Allergy	9	5.8	5	11.1	4	5.3
Cardiac medication	6	3.8	0	0	1	1.3
GI	10*	6.4	6†	13.3	0*†	0
Antibiotic	4	2.6	2	4.4	0	0
Vitamins/nutritional supplements	28*	17.9	10†	22.2	1*†	1.3

*Values in the same row differ significantly at $P = .05$ by the Wilcoxon rank sum test.
†Values in the same row differ significantly at $P = .05$ by the Wilcoxon rank sum test.
‡Data are from participants 18 years of age or older to control for the effect of laws restricting smoking to this age or older. Sample sizes for this analysis are 74 exposed survivors, 27 unexposed survivors, and 23 sibling controls.

Table 2. Cancer Diagnosis and Treatment Characteristics of 201 Long-Term Survivors of Childhood Cancer, by Exposure to Cardiotoxic Therapy

Characteristic	Exposed Survivors (n = 156)		Unexposed Survivors (n = 45)		*P*
	No.	%	No.	%	
Cancer diagnosis					
Age at diagnosis, years					.22
Median	6.3		5.6		
Range	0-24.1		0-17.8		
Time since diagnosis, years					< .001
Median	10.0		15.0		
Range	3.3-31.6		5.1-25.6		
Year of diagnosis					.002
Median	1990		1985		
Range	1969 to 1998		1974 to 1997		
Cancer type					
Leukemia	63	40.4	6	13.3	< .001
Lymphoma	35	22.4	4	8.9	.05
Embryonal	31	19.9	11	24.4	.53
Sarcoma	15	9.6	10	22.2	.04
Brain	10	6.4	9	20	.02
Other	2*	1.3	5†	11.1	.006
Cancer treatment‡					
Anthracycline only	97	62.2	0	0	
Radiation to the heart only	22	14.1	0	0	
Anthracycline and cardiac radiation	37	23.7	0	0	
Cranial radiation	67	42.9	17	37.8	.61
Plant alkaloid	139	89.1	31	68.9	.002
Antibiotic (anthracycline)	134	85.9	0	0	
Alkylating agent	9	5.8	27	60	.86
Antimetabolite	89	57.1	11	24.4	< .001
Corticosteroid	83	53.2	11	24.4	< .001
Asparaginase	60	38.5	6	13.3	.001
Antibiotic (nonanthracycline)	20	12.8	3	6.7	.30
Topoisomerase II inhibitor	3	1.9	0	0	
Immunosuppressant	1	0.6	0	0	

*One germ cell cancer (0.7%) and one nonspecific cancer (0.7%).
†Three germ cell cancers (6.7%) and two nonspecific cancers (4.4%).
‡Drugs used in cancer treatment included the following: plant alkaloids: vincristine, vinblastine, and etoposide; antibiotics (anthracycline): doxorubicin, daunorubicin, idarubicin, and mitoxantrone; alkylating agents: dacarbazine, carmustine, melphalan, busulfan, carboplatin, cyclophosphamide, ifosfamide, mustard/nitrogen mustard/mechlorethamine, cisplatin, procarbazine, and thiotepa; antimetabolites: methotrexate, mercaptopurine, thioguanine, hydroxyurea, azacitidine, fluorouracil, and cytarabine; corticosteroids: prednisone, hydrocortisone, and dexamethasone; asparaginases: L -asparaginase, *Escherichia coli* asparaginase, *Erwinia* asparaginase, and pegaspargase; antibiotics (nonanthracycline): dactinomycin and bleomycin; topoisomerase II inhibitor: teniposide; and immunosuppressant: antithymocyte globulin.

Risk Factors for Atherosclerotic Disease and Related Measures

Both survivor groups were shorter than controls (Table 4). Mean BMI was higher in unexposed survivors than in exposed survivors and controls. Serum levels of IGF-1 were lower in all survivors than in controls.

Fasting serum levels of non-HDL cholesterol were higher in all survivors than in controls and were even higher in exposed survivors than in unexposed survivors (Table 4). Both survivor groups had higher fasting serum insulin levels than did controls. Unexposed female survivors had higher fasting serum levels of non-HDL cholesterol and insulin than did unexposed males. Exposed male survivors had higher fasting serum levels of non-HDL cholesterol than did exposed females (Fig 1). When these traditional risk factors for atherosclerotic disease were considered in the aggregate, both survivor groups seemed to be at increased risk for cardiovascular disease (Table 4).

Systemic Inflammation

Serum levels of hs-CRP were similar in the survivor groups and higher in both survivor groups than in controls (Table 4). Exposed and unexposed female survivors had higher serum levels of hs-CRP than exposed and unexposed male survivors (Table 4).

Table 3. Selected Echocardiographic and Electrocardiographic Characteristics of 201 Long-Term Survivors of Childhood Cancer, With and Without Exposure to Cardiotoxic Cancer Treatments, by Study Group and Sex

	Total (Males and Females)						Males						Females						Male *v* Female, *P*		
	Exposed Survivors (n = 156)		Unexposed Survivors (n = 45)		Sibling Controls (n = 76)		Exposed Survivors (n = 74)		Unexposed Survivors (n = 26)		Sibling Controls (n = 41)		Exposed Survivors (n = 82)		Unexposed Survivors (n = 19)		Sibling Controls (n = 35)		Exposed Survivors	Unexposed Survivors	Sibling Controls
Characteristic	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE			
Echocardiographic characteristic, *z* score*																					
LV mass	−1.10†	0.10	−1.16†	0.18	−0.65‡	0.10	−1.06†	0.15	−0.87†	0.21	−0.38‡	0.11	−1.12	0.13	−1.60	0.30	−1.00‡	0.17	.77	.04	.002
LV end-diastolic posterior wall thickness	−1.15†	0.10	−1.02	0.18	−0.61‡	0.12	−1.11†§	0.15	−0.63	0.19	−0.55‡	0.14	−1.19†	0.13	−1.55†	0.30	−0.55‡	0.21	.68	.01	.99
LV end-diastolic dimension	−0.74	0.09	−0.93	0.17	−0.58‡	0.12	−0.68	0.13	−0.67	0.21	−0.30‡	0.15	−0.80	0.13	−1.29	0.24	−0.89‡	0.13	.52	.06	.003
LV thickness-to-dimension ratio	−0.31	0.11	−0.11	0.16	0.02	0.16	−0.21	0.16	0.08	0.21	−0.04	0.18	−0.40†	0.14	−0.39	0.27	0.26	0.26	.37	.17	.35
LV afterload (end-systolic wall stress)	−0.05†§	0.16	−0.72	0.28	−1.19‡	0.24	−0.07	0.22	−0.71	0.37	−0.77‡	0.35	−0.05†	0.24	−0.69	0.42	−1.40‡	0.29	.95	.96	.16
LV fractional shortening	0.55†§	0.14	1.60	0.36	1.73‡	0.24	0.62†	0.20	1.35	0.35	1.54‡	0.36	0.53†§	0.21	1.79	0.52	1.76‡	0.26	.75	.48	.62
LV load–independent contractility (stress-velocity index)	0.39†§	0.11	1.03	0.28	0.97‡	0.18	0.42	0.15	0.78	0.30	0.97‡	0.29	0.37§	0.16	1.32	0.41	0.95‡	0.23	.81	.29	.95
Blood pressure, *z* score																					
Systolic	0.06†§	0.09	0.48	0.16	0.35	0.11	0.25	0.14	0.54	0.23	0.57	0.15	−0.16	0.11	0.31	0.23	0.08	0.16	.02	.49	.02
Diastolic	1.12	0.08	1.21	0.13	1.23	0.11	1.24	0.12	1.11	0.17	1.37	0.12	0.98	0.10	1.23	0.21	1.04	0.16	.10	.64	.10
Electrocardiographic characteristics																					
Heart rate, beats per minute	82.53†	1.45	77.26	2.30	77.67	1.80	81.88†	2.16	74.32	3.59	75.63	2.13	83.31	1.87	80.84	2.41	81.00	2.62	.62	.13	.11
Corrected QT interval, milliseconds	407.01†§	1.80	398.66	3.50	400.75	2.37	403.96§	2.72	388.33	4.64	395.73	3.07	409.55	2.29	411.05	3.72	405.84	2.71	.12	< .001	.01
NT-proBNP, pg/mL	81.08†	7.90	69.25†	9.86	37.12	3.56	58.01†	7.41	37.79	6.81	35.32	4.36	104.32†	13.16	97.49†	15.17	40.92	6.29	.002	< .001	.46

Abbreviations: LV, left ventricular; NT-proBNP, N-terminal pro-brain natriuretic peptide.
*Total values were adjusted using a weighted propensity score technique for age and sex. Sex-specific values were adjusted using a weighted propensity score technique for age.
†The difference in the characteristic for either exposed or unexposed survivors versus sibling controls for either sex is significant at $P < .05$.
‡The difference in the characteristic for the sibling control group versus the Boston cohort, upon which the formulas to calculate the *z* scores for echocardiographic parameters were derived, is significant at $P < .05$.
§The difference in the characteristic for exposed versus unexposed survivors for either sex is significant at $P < .05$.

Correlation Among Biomarkers for Cardiac Domains

Levels of NT-proBNP were not correlated with either hs-CRP or non-HDL cholesterol (Fig 2). Non-HDL cholesterol was moderately correlated with hs-CRP ($\rho = 0.35$, $P < .001$).

Correlation of Biomarkers for Cardiac Domains With LV Structure and Function

In exposed survivors, NT-proBNP was moderately correlated with LV dimension ($\rho = 0.25$, $P < .01$), afterload ($\rho = 0.27$, $P < .001$), and fractional shortening ($\rho = -0.24$, $P = .01$; Appendix Fig A1, online only). In unexposed survivors, hs-CRP was moderately correlated with LV mass ($\rho = -0.37$, $P = .02$), wall thickness ($\rho = -0.37$, $P = .02$), and dimension ($\rho = -0.32$, $P = .05$).

DISCUSSION

Both exposed and unexposed survivors had abnormalities in LV structure and function, traditional risk factors for atherosclerotic disease,

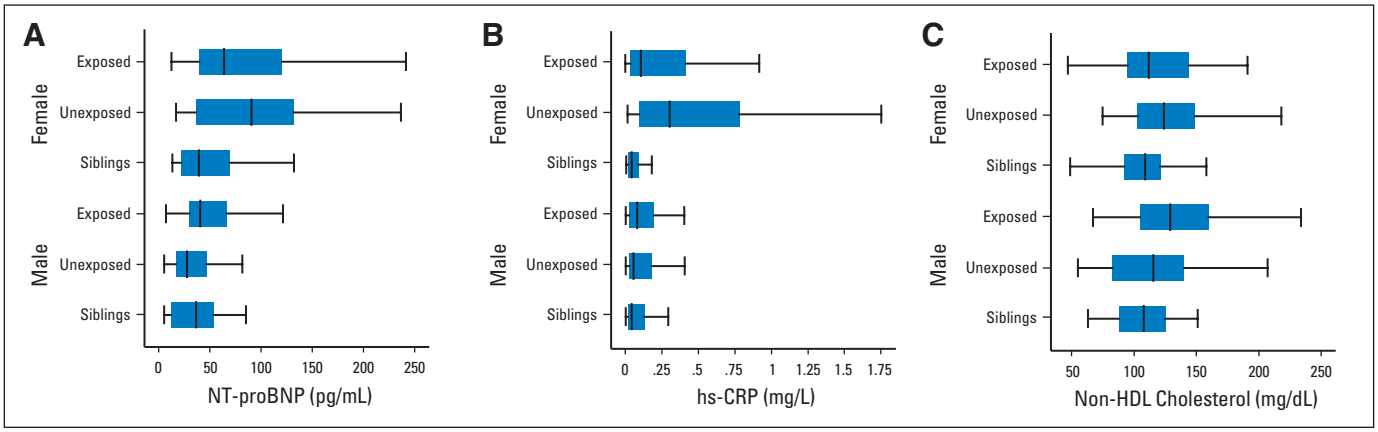

Fig 1. (A-C) Serum levels of cardiac biomarkers by cancer treatment history and sex. Box plots show the minimum, maximum, interquartile range (box), and median values for survivors of childhood cancer exposed or unexposed to known cardiotoxic treatments and for sibling controls, by sex. HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 4. Cardiac Risk Factors and Measures of Inflammation for Long-Term Survivors of Childhood Cancer, With and Without Exposure to Cardiotoxic Cancer Treatments, and Normal Sibling Controls, by Study Group and Sex

	Total (Males and Females)						Males						Females						Male *v* Female, *P*		
	Exposed Survivors (n = 156)		Unexposed Survivors (n = 45)		Sibling Controls (n = 76)		Exposed Survivors (n = 74)		Unexposed Survivors (n = 26)		Sibling Controls (n = 41)		Exposed Survivors (n = 82)		Unexposed Survivors (n = 19)		Sibling Controls (n = 35)				
Characteristic	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Exposed Survivors	Unexposed Survivors	Sibling Controls
Anthropometric measurements*																					
Body mass index, kg/m^2	23.1†	0.17	24.9‡	0.44	22.6	0.21	22.8‡	0.23	22.7	0.40	22.0	0.30	23.3†	0.26	27.3‡	0.82	23.0	0.28	.20	< .001	.02
Weight, *z* score	0.27‡	0.06	0.08‡	0.14	0.56	0.06	0.27‡	0.06	0.08‡	0.14	0.56	0.06	0.19‡	0.10	0.70	0.34	0.56	0.08	.49	.09	.99
Height, *z* score	−0.45‡	0.05	−0.44‡	0.1	0.18	0.05	−0.39†‡	0.07	−0.71‡	0.12	0.35	0.07	−0.53†‡	0.06	−0.02	0.17	−0.04	0.08	.13	< .001	< .001
Blood characteristics*																					
Non-HDL cholesterol, mg/dL	126.5†‡	1.17	121.1‡	2.15	109.8	1.41	135.6†‡	1.88	114.0	2.56	108.4	1.65	117.0†‡	1.25	130.5‡	3.52	111.8	2.33	< .001	< .001	.23
LDL cholesterol, mg/dL	103.4‡	0.97	100.8‡	1.92	92.9	1.20	108.8†‡	1.5	93.5	2.34	92.7	1.46	97.9†‡	1.18	110.1‡	3.08	93.2	1.90	< .001	< .001	.82
HDL cholesterol, mg/dL	51.3	0.37	50.0	0.80	50.5	0.46	47.8‡	0.45	46.8‡	0.84	50.1	0.52	54.6‡	0.57	53.3	1.43	51.0	0.85	< .001	< .001	.35
Insulin, μU/mL	10.4‡	0.27	10.5‡	0.65	8.2	0.21	10.9†‡	0.42	8.9‡	0.44	7.5	0.23	10.0‡	0.37	12.3‡	1.30	9.0	0.35	.10	.01	< .001
Apolipoprotein A1/B1 ratio	0.60‡	0.01	0.61‡	0.01	0.52	0.01	0.67†‡	0.01	0.57‡	0.01	0.53	0.01	0.55‡	0.01	0.67‡	0.02	0.51	0.01	< .001	< .001	.16
Homocysteine, μmol/L	7.2	0.07	7.3	0.14	6.9	0.14	7.4	0.11	7.5	0.20	7.1	0.17	6.9‡	0.09	6.9	0.18	6.5	0.15	< .001	.03	.02
IGF-1, ng/mL	213.7†‡	3.32	172.9‡	4.61	257.9	5.31	209.4‡	5.06	193.5‡	6.52	241.8	6.90	217.4†‡	4.43	150.3‡	6.17	277.7	8.18	.23	< .001	< .001
T_4, ng/dL	1.05†‡	0.006	1.12	0.13	1.18	0.03	1.04†‡	0.008	1.13‡	0.012	1.26	0.05	1.07	0.008	1.12‡	0.02	1.06	0.13	.008	.67	.15
TSH, μU/mL	2.24‡	0.05	2.41‡	0.20	1.94	0.06	2.14‡	0.06	1.93	0.09	1.81	0.06	2.33	0.08	2.86	0.41	2.22	0.14	.06	.03	.007
hs-CRP, mg/L	2.7‡	0.2	3.1‡	0.3	0.9	0.1	1.8‡	0.1	1.6‡	0.1	1.1	0.1	3.5†‡	0.3	4.9‡	0.5	0.7	0.01	< .001	< .001	.005
Atherosclerotic risk aggregation tools																					
Modified Pathological Determinants of Atherosclerosis in Youth risk score§	2.95‡	0.17	3.59†‡	0.26	2.07	0.20	3.81†‡	0.19	2.98‡	0.29	1.77	0.18	1.20†	0.10	2.90‡	0.27	0.89	0.14	< .001	.88	< .001
Ratio of Framingham calculator predicted-to-ideal 30-year hard cardiovascular disease risk‖	2.16‡	0.10	2.12‡	0.11	1.70	0.07	2.75†‡	0.17	2.05	0.10	2.12	0.06	1.70†‡	0.10	2.17	0.17†	1.02	0.05	< .001	.55	< .001

Abbreviations: HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IGF-1, insulin-like growth factor-1; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; T_4, free thyroxine; TSH, thyroid-stimulating hormone.

*Total values were adjusted using a weighted propensity score technique for age and sex. Sex-specific values were adjusted using a weighted propensity score technique for age.

†The difference in the characteristic for exposed versus unexposed survivors for either sex is significant at $P < .05$.

‡The difference in the characteristic for either exposed or unexposed survivors versus sibling controls for either sex is significant at $P < .05$.

§The modified Pathological Determinants of Atherosclerosis in Youth risk score measures the increased risk of having an advanced atherosclerotic disease lesion in a major coronary artery so that a 1-unit increase in the score is equivalent to a multiplicative change in the odds of having a lesion as a result of a 1-year increase in age.[24]

‖The ratio of Framingham calculator predicted-to-ideal 30-year risk of hard cardiovascular disease represents the increasing risk of having a myocardial infarction, stroke, or coronary death in the next 30 years, with the ratio representing the increased risk relative to the ideal.[25]

and systemic inflammation. Although several large observational studies have documented an increased risk of cardiovascular disease in survivors, they have focused on self-reported disease or death certificate data and have provided little information on the clinical course underlying these outcomes.[3-8] The cardiovascular-related abnormalities presented here support these findings and identify the processes likely underlying excess cardiovascular disease risk. Further, these findings suggest that this cardiovascular-related health burden will increase as this expanding population ages.

Even without exposure to cardiotoxic treatments, survivors had abnormal LV structure and function. Unexposed survivors had decreased LV mass in both sexes and decreased wall thickness in females, which are probably reflected by increased serum levels of NT-proBNP that accompany increased stress on the remaining LV cardiomyocytes. In addition, unexposed survivors had a higher mean BMI and higher fasting serum non-HDL cholesterol and insulin levels than controls. Aggregated, these risk factors increase the risk of atherosclerotic disease in unexposed survivors. Systemic inflammation, measured as hs-CRP, was also present and may exacerbate these abnormalities and the risk of atherosclerosis.

As expected,[12-16] exposed survivors had decreased LV mass and wall thickness, increased LV afterload, decreased LV load–independent contractility, and decreased LV fractional shortening. These changes likely reflect treatment-induced cardiovascular damage that kills cardiomyocytes and damages the remaining cardiomyocytes and progenitor cells. The normal LV end-diastolic dimensions accompanying these cardiovascular abnormalities and elevated serum levels of NT-proBNP indicate the restrictive nature of anthracycline- and radiation-induced cardiomyopathies. Longer corrected QT intervals in exposed survivors probably reflect cardiovascular damage and may worsen prognosis.[32,33] Exposed survivors also had reduced systolic blood pressure and increased heart rate, which may be early signs of reduced cardiac output and future CHF.

In another population of childhood survivors, increased LV afterload was significantly related to LV fractional shortening.[13] This relationship is confirmed here and extended to show that cardiomyopathy (higher NT-proBNP levels) is related to lower LV fractional shortening, as expected. In unexposed survivors, higher levels of generalized inflammation are associated with a smaller LV (lower mass, wall thickness, and dimension), suggesting that

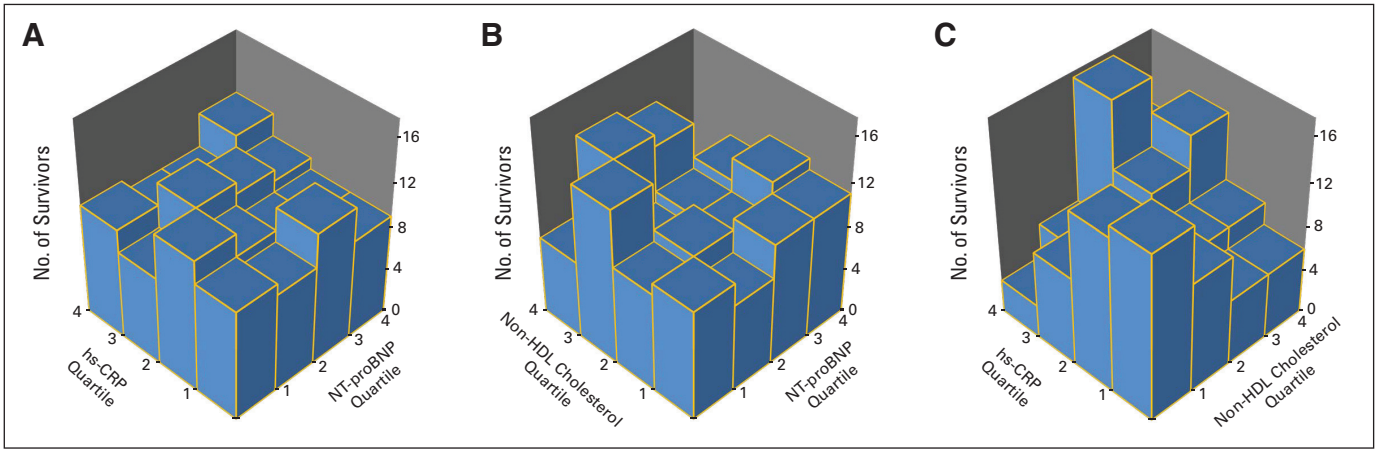

Fig 2. (A-C) Correlations between serum levels of cardiac biomarkers in survivors of childhood cancer. Bivariate histograms show the number of survivors of childhood cancer on the vertical axes in each quartile-quartile bin for the biomarker quartiles listed on the diagonal axes. Each bar represents the number of survivors who were in a specific quartile-quartile pair for each of the biomarkers listed on the two diagonal axes. The bars in any one row should add to the total in that quartile for the biomarker listed on the referent axis. Spearman's rank correlation coefficient and associated *P* value are also reported for the association between these biomarkers. HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide.

chronic inflammation may predispose survivors to develop restrictive cardiomyopathy.

Exposed survivors had higher fasting serum levels of non-HDL cholesterol and insulin. Systemic inflammation, as measured by hs-CRP, was also present and may exacerbate these cardiovascular abnormalities and the risk of atherosclerotic disease. Although increased cardiovascular mortality in childhood cancer survivors is consistent across studies, screening recommendations have not focused on concurrently identifying multiple causes of excess cardiovascular mortality. Instead, the focus has been on assessing LV function, not abnormal LV structure and cardiometabolic abnormalities. Our results support the need for comprehensive assessments of global risk for cardiovascular disease in all childhood cancer survivors. This recommendation is supported by the small correlations between serum levels of biomarkers across cardiac domains. Survivors with and without cardiac dysfunction, as reflected by being in a higher NT-proBNP quartile, were equally likely to be in a lower or higher quartile for non-HDL cholesterol and hs-CRP. Screening across a single cardiac domain will not identify all survivors at increased risk for cardiac disease.

The sex-related differences we found are consistent with reports indicating that female survivors are more vulnerable to cardiotoxic treatments.[13,34,35] Our study adds three findings to this relationship. First, sex is associated with several altered risk factors for atherosclerotic disease. Exposed male survivors had higher fasting serum levels of non-HDL cholesterol than did exposed females. However, among unexposed survivors, females had higher fasting serum levels of non-HDL cholesterol and insulin. Second, both exposed and unexposed female survivors had higher levels of hs-CRP. Third, unexposed female survivors were more likely to have altered LV structure and function, as indicated by decreased LV wall thickness and increased NT-proBNP levels, both indicating increased LV stress.

These sex-related differences raise the possibility that although overall long-term cardiovascular mortality rates in survivors of either sex may be similar, the mechanisms underlying their increased risk, and thus their specific needs for intervention, may differ. Female survivors may be at increased risk of CHF, whereas male survivors may be at increased risk of atherosclerotic cardiovascular disease. This hypothesis is supported by Childhood Cancer Survivors Study data showing that during the first 30 years after cancer diagnosis, female survivors were 40% more likely to experience CHF but 40% less likely to experience myocardial infarction.[6] These mortalities may manifest at different times, with females having higher early cardiovascular-related mortality, as seen in this same cohort where females had a 40% increased cardiovascular-related mortality.[3]

Although studies of increased systemic inflammation in cancer survivors are limited,[36,37] increased values may help evaluate cardiovascular status. Systemic inflammation may worsen the cardiovascular status of many survivors who already have impaired LV structure and function.[38,39] Levels of NT-proBNP and hs-CRP may provide valuable information on the cardiovascular status of survivors and identify survivors in greatest need of further cardiovascular screening. Emerging evidence indicates that NT-proBNP levels within the range seen in both exposed and unexposed survivors are abnormal and associated with impaired cardiac function.[40-43] As in pediatric CHF, monitoring such markers may provide valuable information on worsening cardiovascular status.[44] Biomarker monitoring could possibly be incorporated into existing protocols for survivor follow-up.

Growth hormone deficiency may underlie many of these cardiovascular abnormalities and increases in risk factors for atherosclerotic disease.[45] Both survivor groups had lower serum levels of IGF-1 and lower height. Unexposed female survivors had lower serum levels of IGF-1 than did unexposed males and, as mentioned earlier, had higher fasting serum levels of non-HDL cholesterol and insulin, as well as thinner LV walls. These characteristics are consistent with the hypothesis that cranial radiation damages the hypothalamic-pituitary axis, with growth hormone deficiency occurring before other endocrinopathies and at lower radiation exposures.[46] A link between such damage and metabolic derangements has also been suggested.[19,37,47,48] Patients with growth hormone deficiency from other causes have altered cardiac status and lipid profiles.[49,50]

The psychosocial impact of survivorship may also lead to lifestyle behaviors, such as physical inactivity, that mediate the risk factor profiles reported here.[51,52] Systemic inflammation may be caused by

these factors or may be related to novel pathophysiologic pathways. Cancer treatments may also have a lasting effect on the immune system, leaving survivors with low-grade inflammation.

Current guidelines do not address cardiovascular screening in unexposed survivors,[18] but our results, in conjunction with recent studies,[6,7] suggest that screening for cardiac disease may be warranted. Screening may be less frequent in unexposed survivors, although the optimum frequency is unknown even for exposed survivors. Guidelines should also consider the possible effects of increased systemic inflammation and atherosclerotic disease risk in unexposed survivors.

Study outcomes, such as changes in LV structure and function and increased risk for atherosclerotic disease and systemic inflammation, reflect risk factors in the general population that have yet to be validated in survivors. As with other childhood cancer survivor studies where patients have not been observed throughout their entire life, the true clinical meaning and importance of statistically significant, subclinical changes detected by surrogate markers that are generally within the normal range can be questioned. For example, the specific cardiovascular consequences of a 10 to 15 mg/dL, statistically significant increase in serum non-HDL cholesterol in survivors are unknown. However, given the young age of the survivor population and the rarity of cardiovascular complications in younger patients, these intermediate outcomes are the most likely to provide information on their cardiovascular risks and may predict clinically important outcomes.[53] In the general population, even minor variations in serum cholesterol are strongly associated with cardiovascular disease mortality.[54]

The size of the differences in echocardiographic *z* scores in this study might seem small relative to those that guide daily clinical decisions by cardiologists, but they are consistent with those that independently predict mortality in children.[55,56] The sibling control group, against which comparisons are made, did display statistically significant differences in cardiac measurements compared with the Boston cohort. Although this might suggest that the sibling controls were abnormal relative to the Boston cohort against which *z* scores were calculated, we believe such differences reflect variability in echocardiographic practice rather than differences in cardiac status and underscore the importance of having had the survivor and sibling echocardiograms read by a single reader blinded to their cancer histories.[57]

Survivors of childhood cancer, regardless of exposure to cardiotoxic treatments, have cardiovascular abnormalities related not only to abnormal LV structure and function but also to increased traditional risk factors for atherosclerotic disease and systemic inflammation. Our findings suggest that all survivors have a higher long-term risk of cardiovascular diseases and may benefit from screening across several cardiovascular domains. Markers, such as serum cholesterol, NT-proBNP, and hs-CRP, may help identify patients in greatest need of more detailed cardiovascular assessment. Screening guidelines should consider including specific recommendations for survivors who did not receive cardiotoxic treatments, and future investigations should consider to what extent atherosclerotic disease and systemic inflammation exacerbate treatment-related cardiotoxicity. Evaluations limited to assessing LV fractional shortening are unlikely to identify all survivors at risk for premature cardiovascular disease from all causes.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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