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Comprehensive Echocardiographic Detection of Treatment-Related Cardiac Dysfunction in Adult Survivors of Childhood Cancer

Results From the St. Jude Lifetime Cohort Study

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ABSTRACT

BACKGROUND Treatment-related cardiac death is the primary, noncancer cause of mortality in adult survivors of childhood malignancies. Early detection of cardiac dysfunction may identify a high-risk subset of survivors for early intervention.

OBJECTIVES This study sought to determine the prevalence of cardiac dysfunction in adult survivors of childhood malignancies.

METHODS Echocardiographic assessment included 3-dimensional (3D) left ventricular ejection fraction (LVEF), global longitudinal and circumferential myocardial strain, and diastolic function, graded per American Society of Echocardiography guidelines in 1,820 adult (median age 31 years; range: 18 to 65 years) survivors of childhood cancer (median time from diagnosis 23 years; range: 10 to 48 years) exposed to anthracycline chemotherapy (n = 1,050), chest-directed radiotherapy (n = 306), or both (n = 464).

RESULTS Only 5.8% of survivors had abnormal 3D LVEFs (<50%). However, 32.1% of survivors with normal 3D LVEFs had evidence of cardiac dysfunction by global longitudinal strain (28%), American Society of Echocardiography–graded diastolic assessment (8.7%), or both. Abnormal global longitudinal strain was associated with chest-directed radiotherapy at 1 to 19.9 Gy (rate ratio [RR]: 1.38; 95% confidence interval [CI]: 1.14 to 1.66), 20 to 29.9 Gy (RR: 1.65; 95% CI: 1.31 to 2.08), and >30 Gy (RR: 2.39; 95% CI: 1.79 to 3.18) and anthracycline dose > 300 mg/m^2 (RR: 1.72; 95% CI: 1.31 to 2.26). Survivors with metabolic syndrome were twice as likely to have abnormal global longitudinal strain (RR: 1.94; 95% CI: 1.66 to 2.28) and abnormal diastolic function (RR: 1.68; 95% CI: 1.39 to 2.03) but not abnormal 3D LVEFs (RR: 1.07; 95% CI: 0.74 to 1.53).

CONCLUSIONS Abnormal global longitudinal strain and diastolic function are more prevalent than reduced 3D LVEF and are associated with treatment exposure. They may identify a subset of survivors at higher risk for poor clinical cardiac outcomes who may benefit from early medical intervention. (J Am Coll Cardiol 2015;65:2511–22) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional

ASE = American Society of Echocardiography

CI = confidence interval

LV = left ventricular

LVEF = left ventricular ejection fraction

RR = rate ratio

RT = radiotherapy

In the modern era, more than 80% of children and adolescents diagnosed with malignancies will become long-term cancer survivors (1,2). However, as these patients age, the therapies that cured their primary malignancies place them at increased, lifelong risk for adverse health conditions (3–5). Late onset cardiac dysfunction is common, and the attribution of major cardiac events to childhood exposure to chest-directed radiotherapy (RT) and anthracycline chemotherapy is now well established (6,7). The cumulative incidence of congestive heart failure by 30 years from diagnosis is 12% for those exposed to both chest-directed RT and anthracycline therapy, and treatment-related cardiac death is the most common noncancer cause of mortality in this population (7–9).

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This high risk for adult-onset cardiac dysfunction warrants early detection, when intervention is expected to be of greatest benefit (10). The Children's Oncology Group long-term follow-up guidelines recommend periodic evaluation by echocardiography (11). Left ventricular (LV) ejection fraction (LVEF) is the established parameter for the evaluation of LV systolic function. However, LVEF by echocardiography is only reliable to detect differences of 10% or more (12,13) and often overestimates the true LVEF in survivors as measured by cardiac magnetic resonance imaging, the reference standard for LVEF (14). In addition, at least 47% of heart failure in the general population is diastolic in nature, occurring with a preserved LVEF (15).

More sensitive screening modalities for LV dysfunction are needed. Reduction in LVEF likely occurs late in the natural history of treatment-related injury, as it may not be overt until a substantial amount of cardiac reserve has been exhausted (16). Global longitudinal strain is a well-validated, reproducible technique for measurement of LV deformation (17). In noncancer populations, reduced global longitudinal strain is a significant, independent predictor of cardiac mortality and major cardiac events, with prognostic value superior to that of LVEF (18–20). In populations of adults actively receiving cancer therapy, early reduction in global longitudinal strain predicts subsequent chemotherapy-related cardiac dysfunction (21–23). Despite these promising findings, myocardial strain for the early detection of cardiac dysfunction has not been systematically evaluated in a large population of aging adult survivors of childhood cancer.

Our objectives were to: 1) determine the prevalence of late onset cardiac dysfunction in a large population of adult, 10-year survivors of childhood malignancies using state-of-the-art comprehensive echocardiographic evaluation of cardiac function (3-dimensional [3D] LVEF, myocardial strain imaging, and comprehensive diastolic assessment); 2) identify whether abnormal myocardial strain was associated with anthracycline and chest-directed RT dose exposures; and 3) identify strain imaging abnormalities in survivors exposed to cardiotoxic therapy who subsequently developed traditional cardiovascular risk factors and/or metabolic syndrome, a population at very high risk for major cardiac events (8,24,25).

METHODS

PARTICIPANTS. Patients treated for childhood cancer at St. Jude Children's Research Hospital who were 18 years of age or older and 10 or more years from diagnosis were eligible for SJLIFE (St. Jude Lifetime Cohort Study). SJLIFE provides lifetime, risk-based longitudinal follow-up for adult survivors of childhood cancer. The current analysis was limited to participants exposed to anthracycline chemotherapy and/or chest-directed RT who underwent a SJLIFE medical assessment, including echocardiography, because of their prior exposure to cardiotoxic therapy and reports on the baseline assessment at entry into the SJLIFE cohort. Participants who completed the SJLIFE survey only (i.e., no campus visit for direct assessment) were excluded. Details of eligibility, recruitment methods, and study design have been previously published (26). Participation involved the completion of questionnaires and risk-based medical screening according to the *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent,*

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and Young Adult Cancers (11), developed by the Children's Oncology Group. The Institutional Review Board at St. Jude Children's Research Hospital approved the investigation.

OUTCOME MEASURES. Echocardiograms were obtained using a Vivid 7 machine (n = 1,750 [96%]; GE Medical Systems, Milwaukee, Wisconsin) or an iE33 (n = 70; Philips Medical Systems, Andover, Massachusetts). Complete systolic function by 3D echocardiography with Doppler was performed according to American Society of Echocardiography (ASE) guidelines (abnormal, LVEF < 50%) (27). For Vivid 7 studies, speckle tracking-based global longitudinal peak systolic strain and global circumferential strain were obtained using 3 apical views with standard, commercially available software (EchoPAC PC version 10.0; GE Medical Systems).

Abnormal strain was defined as >2 SDs below the mean using sex-specific, age-specific, and vendor-specific strain values identified in a normative population (28). The largest potential normative populations, based on a recent meta-analysis of U.S. data were extremely small (Marwick et al. [29], Cleveland Clinic: n = 97; Saleh et al. [30], Mayo Clinic: n = 82; and Narayanan et al. [31], University of Massachusetts: n = 52). Given the known associations of age and sex with strain outcomes, as recently discussed in "Expert Consensus for Multimodality Imaging Evaluation of Adult Patients During and After Cancer Therapy" (16), these small populations would clearly not allow us to stratify comparisons of these key variables between our study population and the normative population. In particular, our study population is generally younger than these U.S. cohorts. Thus, we determined that use of these small cohorts that do not contain age-specific, sex-specific, and vendor-specific normative data would be a particular risk to the validity of the study findings. Alternatively, the JUSTICE (Japanese Ultrasound Speckle Tracking of the Left Ventricle) study (28) evaluated a large population (n = 817) and provided age-specific and sex-specific normative values, which improve the ability to provide valid comparisons between our cases and the normative standard. Although this does raise the possibility that the Japanese and U.S. populations may have different strain values on the basis of race, we were reassured by recent evidence to the contrary from similar sex-specific and vendor-specific normative values in a European population (32).

Diastolic assessment included peak mitral flow velocity (E), mitral septal and lateral early diastolic velocity (e′), their ratios with E (E/e′ ratio), and left atrial volume (33). Diastolic function was graded per ASE recommendations for the evaluation of LV diastolic function, with any grade from 1 to 3 considered abnormal (33). A core echocardiography laboratory at the Cleveland Clinic centrally evaluated all echocardiograms.

To estimate the interobserver variability, the lead cardiologist for this study from the Cleveland Clinic echocardiography core lab (J.C.P., who read 625 of the 1,807 evaluable studies) reviewed a sample of echocardiograms read by each of the other cardiologists. We randomly selected 10 studies from each of the 6 additional reviewers (60 total studies). Selection was stratified on LVEF <50% versus ≥50% to ensure the inclusion of a sufficient number of both normal and abnormal echocardiograms in the review. Across our major echocardiographic outcomes, overall agreement (normal vs. abnormal) was as follows: for LVEF, 76% agreement; for global longitudinal strain, 76% agreement; for circumferential strain, 36% agreement; for left atrial volume, 95% agreement; and for lateral e′ 60% agreement.

DEMOGRAPHIC AND EXPOSURE VARIABLES. The cumulative anthracycline dose was abstracted from the medical record along with demographic characteristics. As described by Stovall et al. (34), the primary RT record and tissue-equivalent phantoms were used to estimate the mean radiation dose to the heart, regardless of primary tumor site or target volume. Additional covariates included metabolic syndrome and its components. Metabolic syndrome was defined using the third report of the National Cholesterol Education Program Adult Treatment Panel (35). Patients with 3 or more of the following were classified as having metabolic syndrome: 1) abdominal obesity (waist circumference >102 cm in men and >88 cm in women); 2) triglycerides ≥150 mg/dl or treatment for elevated triglycerides; 3) high-density lipoprotein cholesterol <40 mg/dl in men and <50 mg/dl in women; 4) hypertension (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg) or treatment for hypertension; and 5) fasting plasma glucose ≥100 mg/dl or medical therapy for diabetes.

Abdominal circumference at the narrowest point between the xiphoid process and the navel was determined with a Gullick tape measure (36), with the measurement repeated twice and recorded to the nearest 0.1 cm. The highest abdominal circumference measurement was used for analysis. Resting blood pressure was taken after a 5-min rest period, with the participant seated with both feet on the floor. Duplicate readings were taken to ensure accuracy; participants rested for 1 min between measurements. The lowest of 3 blood pressure measurements was used for analysis.

TABLE 1 Demographic and Treatment Characteristics of Adult Survivors of Childhood Cancer

	Eligible (n = 3,029)		Nonparticipants (n = 1,209)		Participants (n = 1,820)		Anthracycline Alone (n = 1,050)		Chest-Directed RT Alone (n = 306)		Anthracycline + Chest-Directed RT (n = 464)	
	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*
Race/ethnicity												
Non-Hispanic white	2,517	83.8	965	81.2	1,552	85.5	905	86.4	260	85.0	387	83.8
Non-Hispanic black	415	13.8	193	16.2	222	12.2	116	11.1	40	13.1	66	14.3
Non-Hispanic other	41	1.4	18	1.5	23	1.3	12	1.2	6	2.0	5	1.1
Hispanic	31	1.0	13	1.1	18	1.0	14	1.3	0	0.0	4	0.9
Sex												
Male	1,684	55.6	738	61.0	946	52.0	548	52.2	164	53.6	234	50.4
Female	1,345	44.4	471	39.0	874	48.0	502	47.8	142	46.4	230	49.6
Age at diagnosis, yrs												
0–4	1,023	33.8	404	33.4	619	34.0	416	39.6	69	22.6	134	28.9
5–9	718	23.7	296	24.5	422	23.2	246	23.4	79	25.8	97	20.9
10–14	731	24.1	286	23.7	445	24.5	242	23.1	95	31.1	108	23.3
15–19	530	17.5	210	17.4	320	17.6	138	13.1	61	19.9	121	26.1
>19	27	0.9	13	1.1	14	0.8	8	0.8	2	0.7	4	0.9
Time since diagnosis, yrs												
10–20	1,027	34.1	366	30.3	661	36.3	392	37.5	80	26.3	189	41.3
21–30	1,228	40.7	498	41.2	730	40.1	468	44.8	87	28.6	175	38.2
31–40	643	21.3	280	23.2	363	19.9	179	17.1	101	33.2	83	18.1
41–50	118	3.9	65	5.4	53	2.9	6	0.6	36	11.8	11	2.4
Current age, yrs												
18–20	139	4.6	51	4.2	88	4.8	69	6.6	3	1.0	16	3.5
21–30	1,193	39.6	430	35.6	763	41.9	506	48.4	88	29.0	169	36.9
31–40	1,112	36.9	462	38.2	650	35.7	356	34.1	84	27.6	210	45.9
41–50	484	16.1	217	18.0	267	14.7	107	10.2	103	33.9	57	12.5
>50	88	2.9	49	4.1	39	2.1	7	0.7	26	8.6	6	1.3
Primary cancer diagnosis												
Leukemia	1,246	41.1	479	39.6	767	42.1	601	57.2	54	17.7	112	24.1
Acute lymphoblastic leukemia	1,053	34.8	384	31.8	669	36.8	550	52.4	31	10.1	88	19.0
Acute myeloid leukemia	146	4.8	72	6	74	4.1	51	4.9	1	0.3	22	4.7
Other leukemia	47	1.6	23	1.9	24	1.3	0	0.0	22	7.2	2	0.4
Lymphoma	799	26.4	332	27.5	467	25.7	136	13.0	121	39.5	210	45.3
Non-Hodgkin lymphoma	307	10.1	151	12.5	156	8.6	120	11.4	11	3.6	25	5.4
Hodgkin lymphoma	492	16.2	181	15	311	17.1	16	1.5	110	36.0	185	39.9
CNS tumor	140	4.6	62	5.1	78	4.3	2	0.2	76	24.8	0	0.0
Bone tumor	261	8.6	88	7.3	173	9.5	150	14.3	0	0.0	23	5.0
Ewing sarcoma	119	3.9	38	3.1	81	4.5	60	5.7	0	0.0	21	4.5
Osteosarcoma	142	4.7	50	4.1	92	5.1	90	8.6	0	0.0	2	0.4
Soft tissue sarcoma	143	4.7	59	4.9	84	4.6	60	5.7	5	1.6	19	4.1
Rhabdomyosarcoma	97	3.2	43	3.6	54	3	42	4.0	3	1.0	9	1.9
Nonrhabdo sarcoma	46	1.5	16	1.3	30	1.6	18	1.7	2	0.7	10	2.2
Other malignancies												
Germ cell tumor	20	0.7	11	0.9	9	0.5	0	0.0	9	2.9	0	0.0
Melanoma	3	0.1	2	0.2	1	0.1	0	0.0	1	0.3	0	0.0
Neuroblastoma	142	4.7	57	4.7	85	4.7	60	5.7	13	4.3	12	2.6
Retinoblastoma	16	0.5	11	0.9	5	0.3	5	0.5	0	0.0	0	0.0
Wilms tumor	230	7.6	97	8	133	7.3	26	2.5	20	6.5	87	18.8
Carcinoma	6	0.2	3	0.2	3	0.2	1	0.1	2	0.7	0	0.0
Other	23	0.8	8	0.7	15	0.8	9	0.9	5	1.6	1	0.2

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Blood samples were collected after an overnight fast. Triglycerides and high-density lipoprotein were measured using an enzymatic spectrophotometric assay (Roche Diagnostics, Indianapolis, Indiana). Glucose was measured using an enzymatic spectrophotometric assay using hexokinase coupled with glucose-6-phosphate dehydrogenase (Roche Diagnostics). All samples were analyzed using the

TABLE 1 Continued

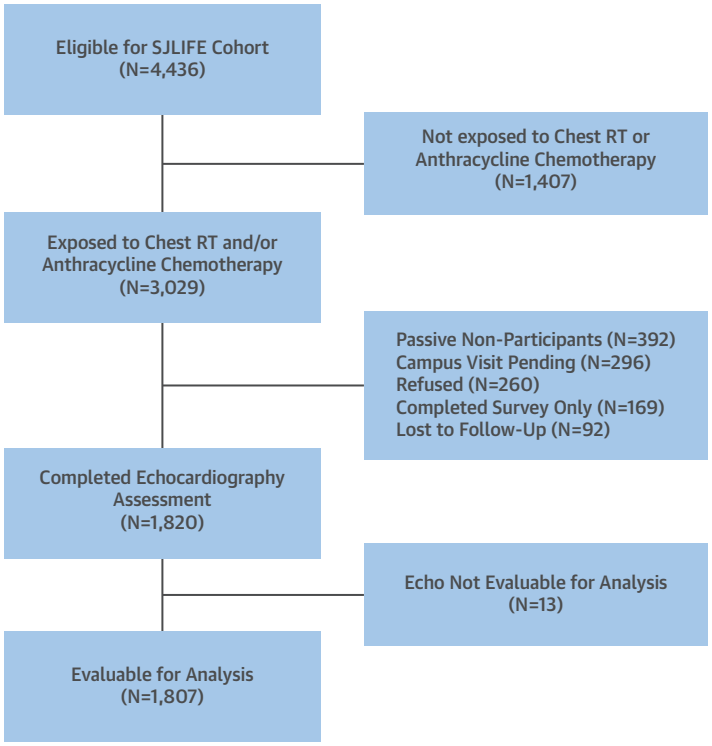
	Eligible (n = 3,029)		Nonparticipants (n = 1,209)		Participants (n = 1,820)		Anthracycline Alone (n = 1,050)		Chest-Directed RT Alone (n = 306)		Anthracycline + Chest-Directed RT (n = 464)	
	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*
Anthracycline cumulative dose, mg/m^2												
0	510	16.9	204	17.1	306	16.9	0	0.0	306	100.0	0	0.0
1–100	784	26.0	296	24.6	488	26.9	419	40.0	0	0.0	69	15.0
101–200	882	29.2	364	30.3	518	28.6	292	27.9	0	0.0	226	49.0
201–300	336	11.1	141	11.7	195	10.8	105	10.0	0	0.0	90	19.5
301–400	332	11.0	107	8.9	225	12.4	163	15.6	0	0.0	62	13.5
401–500	100	3.3	41	3.4	59	3.3	51	4.9	0	0.0	8	1.7
501–600	23	0.8	5	0.4	18	1.0	13	1.2	0	0.0	5	1.1
>600	48	1.6	43	3.6	5	0.3	4	0.4	0	0.0	1	0.2
Chest-directed RT, Gy												
0	1,765	60.5	715	62.1	1,050	59.4	1,050	100.0	0	0.0	0	0.0
1–19.9	653	22.4	250	21.7	403	22.8	0	0.0	131	45.0	272	63.7
20–29.9	330	11.3	121	10.5	209	11.8	0	0.0	72	24.7	137	32.1
≥30	172	5.9	66	5.7	106	6.0	0	0.0	88	30.2	18	4.2
Metabolic syndrome												
Yes	–	–	–	–	509	28.6	280	27.2	99	33.5	130	28.8
No	–	–	–	–	1,269	71.4	750	72.8	197	66.6	322	71.2
Components of metabolic syndrome												
Abdominal obesity												
Yes	–	–	–	–	538	30.4	355	34.5	69	23.7	114	25.4
No	–	–	–	–	1,232	69.6	675	65.5	222	76.3	335	74.6
Elevated triglycerides												
Yes	–	–	–	–	470	26.0	234	22.4	98	32.2	138	30.0
No	–	–	–	–	1,338	74.0	810	77.6	206	67.8	322	70.0
Low HDL cholesterol												
Yes	–	–	–	–	665	36.8	379	36.3	113	37.2	173	37.6
No	–	–	–	–	1,143	63.2	665	63.7	191	62.8	287	62.4
Hypertension												
Yes	–	–	–	–	816	45.2	436	41.8	160	53.2	220	47.8
No	–	–	–	–	989	54.8	608	58.2	141	46.8	240	52.2
Fasting glucose ≥100 mg/dl												
Yes	–	–	–	–	577	31.9	295	28.2	125	41.1	157	34.1
No	–	–	–	–	1,233	68.1	750	71.8	179	58.9	304	65.9
Previously diagnosed with cardiomyopathy	–	–	–	–	47	2.6	19	1.8	10	3.3	18	3.9
Previously diagnosed with cardiomyopathy and on medications at the time of evaluation	–	–	–	–	23	1.3	7	0.7	6	2.0	10	2.2

*Percents are provided for the total number of participants for whom data were available for a given characteristic.
CNS = central nervous system; HDL = high-density lipoprotein; RT = radiotherapy.

Roche Modular P chemistry analyzer. Exercise capacity was determined by a 6-min walk performed indoors, according to the American Thoracic Society guidelines (abnormal, <490 m) (37,38). Quality of life was measured using the physical and mental component summaries of the SF-36 (39).

STATISTICAL METHODS. Descriptive statistics were used to characterize the eligible population and study participants. The prevalence of cardiac abnormalities was estimated for the entire cohort of 10-year survivors and by treatment exposure (anthracycline only, chest-directed RT only, and anthracycline and chest-directed RT combined). Associations between treatment characteristics and cardiac abnormalities were investigated using Poisson regression models with robust error variances. A similar approach was used to determine whether metabolic syndrome and its components were associated with abnormal cardiac function. These models were adjusted for current

FIGURE 1 CONSORT Diagram of SJLIFE Population Eligible for Echocardiographic Evaluation



CONSORT = Consolidated Standards of Reporting Trials; RT = radiotherapy; SJLIFE = St. Jude Lifetime Cohort Study.

age, age at diagnosis, race/ethnicity, chest RT and anthracycline exposure, and the rate ratios (RRs) and 95% confidence intervals (CIs). Frequencies and percents of all combinations of abnormal echocardiographic results were summarized, and 6-min walk distances were compared with the in the group with normal echocardiographic results using 2-sample Student *t* tests. Associations between cardiac dysfunction and impaired quality of life (defined as impaired physical and mental quality of life on the SF-36) were assessed by Poisson regression with robust error variance and adjusted for sex, education, marital status, annual household income, employment status, and treatment with cranial RT. All analyses were performed in SAS version 9.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Of the 4,436 survivors eligible for SJLIFE, 3,029 were exposed to cardiotoxic therapy and eligible for echocardiography (Figure 1). At the time of this analysis, 1,820 (60% of those eligible) had completed SJLFE medical assessments, including echocardiography. Thirteen echocardiographic studies were of insufficient quality for analysis. Demographic and treatment characteristics of survivors included in this analysis and potentially eligible nonparticipants are summarized in Table 1. Participants were more likely to be female but were similar on other demographic and treatment-related characteristics. The median time from primary cancer diagnosis was 22.6 years (range: 10.4 to 48.3 years); the median age at evaluation was 31 years (range: 18 to 65 years). Forty-seven survivors had been previously diagnosed with cardiomyopathy, 23 of whom were on medications for heart failure at the time of evaluation.

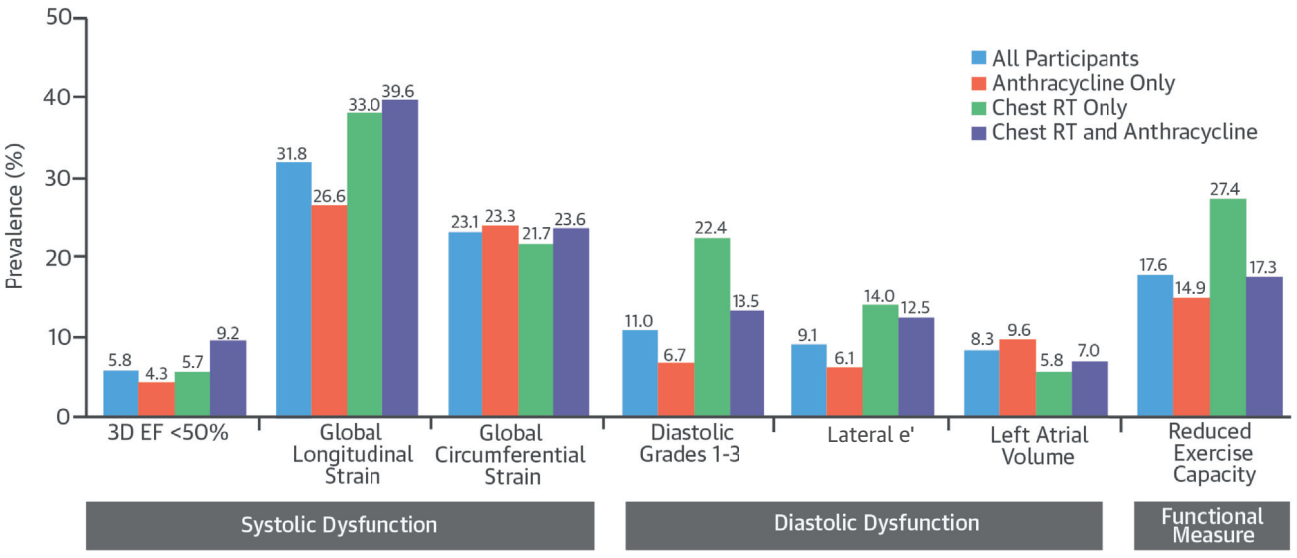
Only 5.8% of the population had 3D LVEFs <50%. However, systolic dysfunction detected by global longitudinal (31.8%) and global circumferential (23.1%) strain and by diastolic dysfunction (ASE grades 1 to 3; 11%) was more prevalent (**Central Illustration**, Online Table 1) than an abnormal LVEF. Among survivors with preserved 3D LVEFs (≥50%), comprehensive echocardiography identified significant systolic (28%; global longitudinal strain) and diastolic (8.7%; ASE grades 1 to 3) dysfunction. Thus, when both longitudinal strain and ASE grade 1 to 3 diastolic function were considered, one-third (32.1%) of survivors with normal 3D LVEFs had cardiac dysfunction. Notably, among survivors exposed to chest RT only, 22.4% had evidence of diastolic dysfunction.

Abnormal 3D LVEF was associated with chest-directed RT at 20 to 29.9 Gy (RR: 1.86; 95% CI: 1.00 to 3.45) and ≥30 Gy (RR: 7.99; 95% CI: 3.88 to 16.48) (Table 2) and cumulative anthracycline dose >100 mg/m^2. Global longitudinal strain was associated with any dose exposure to chest-directed RT at 1 to 19.9 Gy (rate ratio: 1.38; 95% CI: 1.14 to 1.66), 20 to 29.9 Gy (RR: 1.65; 95% CI: 1.31 to 2.08) and >30 Gy (RR: 2.39; 95% CI: 1.79 to 3.18) and anthracycline dose >300 mg/m^2. Diastolic dysfunction was associated with chest-directed RT but not with cumulative dose of anthracycline.

Survivors with metabolic syndrome were almost twice as likely to have abnormal global longitudinal strain (RR: 1.94; 95% CI: 1.66 to 2.28) and abnormal diastolic function (RR: 1.68; 95% CI: 1.39 to 2.03) but did not have a higher risk for abnormal 3D LVEF (RR: 1.07; 95% CI: 0.74 to 1.53). Each individual component of metabolic syndrome was associated with an increased risk for abnormal global longitudinal strain and diastolic dysfunction (Table 3).

Reduced exercise capacity (<490 m, 6-min walk) was identified in 17.6% of participants

CENTRAL ILLUSTRATION **Prevalence of Cardiac Dysfunction and Reduced Exercise Capacity in Adult, 10-Year Survivors of Childhood Cancer**



Armstrong, G.T. et al. J Am Coll Cardiol. 2015; 65(23):2511–22.

EF = ejection fraction; RT = radiotherapy; 3D = 3-dimensional.

(Central Illustration). Survivors with global longitudinal strain as the only abnormal finding on echocardiography had a lower mean 6-min walk distance compared with survivors with normal echocardiographic results (560 vs. 590 m; p = 0.0002; Online Table 2). However, on multivariate analyses adjusting for pulmonary function, muscle strength, height, and weight, no independent association between echocardiographic outcomes and reduced exercise capacity was identified.

Abnormal longitudinal strain (RR: 1.71; 95% CI: 1.33 to 2.19), LVEF (RR: 1.92; 95% CI: 1.33 to 2.76), and diastolic function (grades 1 to 3; RR: 1.83; 95% CI: 1.36 to 2.45) were associated with reduced quality of life on the physical component summary scale, but only abnormal LVEF (RR: 1.53; 95% CI: 1.02 to 2.29) and abnormal atrial volume (RR: 1.37; 95% CI: 1.01 to 1.86) were associated with the mental component summary scale of the SF-36 (Online Table 3).

DISCUSSION

Systematic, protocol-driven echocardiographic assessment of a large population of adult survivors of childhood cancer has been difficult to achieve as this population has transitioned from academic pediatric centers to adult care, largely provided in a community setting (40). However, with more than 1,800 participants, we provide the largest study to date using modern echocardiographic techniques (3D LVEF [14]; myocardial strain; and uniform, ASE guideline-driven grading of diastolic function) for the comprehensive assessment of cardiac function in aging adult survivors of childhood cancer exposed to cardiotoxic therapy (41–43). Only 5.8% had 3D LVEFs <50%. However, by applying comprehensive echocardiographic assessment, we identified evidence of underlying systolic and/or diastolic cardiac dysfunction in one-third of survivors with normal 3D LVEFs.

DIASTOLIC FUNCTION. It is known that chest-directed RT results in microvascular damage with subsequent myocardial interstitial fibrosis, leading to a noncompliant ventricle with resulting diastolic dysfunction, often with preserved LVEF (44). Traditionally, diastolic dysfunction has been difficult to quantify in survivors of childhood cancer (45,46), with more accurate assessment occurring in adults diagnosed with Hodgkin lymphoma (47). Given the large size of our population, evaluation of the independent effect of chest-directed RT, without the confounding influence of anthracyclines was possible. Our use of the ASE consensus-based

TABLE 2 Multivariate Associations Between Treatment Characteristics and Systolic and Diastolic Dysfunction in Adult Survivors of Childhood Cancer

	3D LVEF < 50%		Abnormal Global Longitudinal Strain		Abnormal Global Circumferential Strain		Diastolic Grade 1-3		Abnormal Lateral e′		Abnormal Left Atrial Volume	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Race/ethnicity												
Other	1.53	0.93–2.52	**1.22**	**1.03–1.46**	0.84	0.64–1.09	1.24	0.86–1.78	1.32	0.89–1.96	**2.03**	**1.41–2.93**
Non-Hispanic white	1.00		1.00		1.00		1.00		1.00			
Sex												
Female	**0.54**	**0.36–0.83**	**1.55**	**1.34–1.79**	1.01	0.84–1.21	1.15	0.88–1.51	0.98	0.73–1.32	0.60	0.43–0.83
Male	1.00		1.00		1.00		1.00		1.00		1.00	
Age at diagnosis, yrs												
0–4	0.66	0.35–1.27	1.02	0.82–1.27	1.24	0.92–1.67	0.85	0.56–1.29	0.91	0.58–1.44	1.26	0.79–2.01
5–9	0.67	0.36–1.25	0.92	0.74–1.15	1.01	0.74–1.38	0.81	0.53–1.22	0.80	0.50–1.26	1.23	0.74–2.05
10–14	1.02	0.59–1.76	1.02	0.83–1.24	1.11	0.84–1.48	0.87	0.61–1.23	0.77	0.50–1.17	1.18	0.74–1.86
≥15	1.00		1.00		1.00		1.00		1.00		1.00	
Current age, yrs												
31–40	1.38	0.81–2.35	**1.25**	**1.05–1.48**	0.85	0.69–1.06	**2.43**	**1.59–3.71**	**1.96**	**1.31–2.93**	**2.40**	**1.67–3.45**
>40	0.98	0.52–1.84	**1.49**	**1.20–1.85**	0.98	0.73–1.33	**4.74**	**2.90–7.75**	1.52	0.90–2.54	**3.59**	**2.25–5.73**
18–30	1.00		1.00		1.00		1.00		1.00		1.00	
Anthracycline cumulative dose, mg/m^2												
1–100	1.74	0.66–4.61	**1.38**	**1.05–1.82**	0.99	0.66–1.48	0.75	0.43–1.30	0.62	0.29–1.32	2.07	0.95–4.51
101–200	**2.80**	**1.24–6.31**	1.16	0.89–1.50	1.24	0.86–1.79	0.80	0.51–1.25	1.13	0.65–1.97	1.82	0.85–3.91
201–300	**3.80**	**1.59–9.10**	1.06	0.78–1.45	1.36	0.90–2.04	0.76	0.42–1.37	1.77	0.99–3.15	1.34	0.55–3.25
301–400	**4.76**	**2.16–10.50**	**1.72**	**1.31–2.26**	**1.61**	**1.08–2.40**	1.00	0.59–1.69	1.53	0.84 2.81	1.72	0.73–4.05
>400	**7.71**	**3.04–19.57**	**1.73**	**1.19–2.50**	1.34	0.78–2.31	1.33	0.72–2.45	2.05	0.99–4.24	0.95	0.30–2.99
None	1.00		1.00		1.00		1.00		1.00		1.00	
Chest RT cumulative dose (Gy)												
1–19.9	1.24	0.70–2.22	**1.38**	**1.14–1.66**	0.86	0.66–1.11	1.47	0.99–2.20	1.09	0.69–1.72	0.47	0.29–0.78
20–29.9	**1.86**	**1.00–3.45**	**1.65**	**1.31–2.08**	1.14	0.83–1.57	**2.03**	**1.30–3.17**	**2.01**	**1.27–3.21**	1.10	0.65–1.87
≥30	**7.99**	**3.88–16.48**	**2.39**	**1.79–3.18**	**1.64**	**1.05–2.56**	**2.44**	**1.44–4.14**	**4.03**	**2.22–7.32**	0.63	0.21–1.89
None	1.00		1.00		1.00		1.00		1.00		1.00	

Values in **bold** are statistically significant.

CI = confidence interval; LVEF = left ventricular ejection fraction; RR = rate ratio; RT = radiotherapy; 3D = 3-dimensional.

diastolic assessment found that 22% of survivors exposed to RT alone had evidence of diastolic dysfunction. These findings are driven by the large number of survivors of Hodgkin lymphoma treated with high doses of chest-directed RT before the era in which combined-modality therapy with anthracyclines and low-dose, involved-field chest RT was introduced. Many of these survivors, who have a well-documented increased risk for major cardiac events, are now entering the fifth decade of life (6,8). Thus, our findings underscore that screening evaluations of these survivors cannot be limited to traditional assessment of LV systolic function but should also include comprehensive diastolic assessment.

SYSTOLIC FUNCTION. Strain imaging has emerged as a powerful tool to quantify myocardial mechanics, including both longitudinal shortening and circumferential torsion (17). Although LVEF is the most widely used measure of systolic dysfunction, it has a number of limitations, including the use of geometric assumptions (2-dimensional LVEF) of ventricular shape, load dependency, and poor reproducibility and interobserver variability (20). Myocardial strain is a semiautomated tool to assess multidimensional myocardial deformation that is more reproducible and not reliant on geometric assumptions (17). In the general population, the association of LVEF with poor outcome is strongest in moderately to severely impaired ventricles (48). Thus, LVEF may not be ideal for screening asymptomatic survivors. Furthermore, in a recent meta-analysis that included almost 6,000 patients with a diverse array of underlying cardiac insults (congestive heart failure, acute myocardial infarction, valvular disease), global longitudinal strain had superior prognostic value compared with LVEF for predicting both overall mortality and major cardiac events (20). In that meta-analysis, a 1-SD change in global longitudinal strain was associated with a 1.62-fold (95% CI: 1.13 to 2.33) greater reduction in mortality than a comparable change in LVEF. Given that evidence from the general non-cancer population indicates that abnormal global

TABLE 3 Association Between Metabolic Syndrome and Systolic and Diastolic Echocardiographic Abnormalities in Adult Survivors of Childhood Cancer*

	3D LVEF < 50%		Abnormal Global Longitudinal Strain		Abnormal Global Circumferential Strain		Diastolic Grade 1–3		Abnormal Lateral e′		Abnormal Left Atrial Volume	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Metabolic syndrome												
Yes	1.07	0.74–1.53	**1.94**	**1.66–2.28**	1.02	0.84–1.24	**1.68**	**1.39–2.03**	**1.65**	**1.35–2.02**	**1.41**	**1.14–1.74**
No	1.00		1.00		1.00		1.00		1.00		1.00	
Abdominal obesity												
Yes	1.34	0.99–1.82	**1.73**	**1.48–2.01**	1.10	0.92–1.32	**1.69**	**1.39–2.06**	**1.49**	**1.23–1.82**	**1.83**	**1.53–2.19**
No	1.00		1.00		1.00		1.00		1.00		1.00	
Triglycerides ≥ 150 mg/dl												
Yes	1.01	0.70–1.44	**1.65**	**1.40–1.95**	1.01	0.82–1.23	**1.44**	**1.17–1.78**	**1.35**	**1.07–1.70**	1.03	0.79–1.33
No	1.00		1.00		1.00		1.00		1.00		1.00	
Low HDL cholesterol												
Yes	1.01	0.74–1.38	**1.40**	**1.23–1.59**	0.92	0.78–1.08	**1.36**	**1.14–1.62**	1.20	0.97–1.47	1.20	0.98–1.47
No	1.00		1.00		1.00		1.00		1.00		1.00	
Hypertension												
Yes	**1.44**	**1.22–1.70**	**1.48**	**1.33–1.65**	1.04	0.92–1.18	**1.39**	**1.22–1.58**	**1.34**	**1.17–1.55**	**1.30**	**1.13–1.49**
No	1.00		1.00		1		1.00		1.00		1.00	
Fasting glucose ≥100 mg/dl												
Yes	1.02	0.75–1.39	**1.37**	**1.19–1.59**	1.06	0.89–1.25	**1.42**	**1.18–1.70**	**1.47**	**1.22–1.77**	1.00	0.81–1.25
No	1.00		1.00		1.00		1.00		1.00		1.00	

Values in **bold** are statistically significant. *Adjusted for current age, age at diagnosis, race/ethnicity, sex, chest RT, and anthracycline exposure.
Abbreviations as in Tables 1 and 2.

longitudinal strain is a valid predictor of poor outcome, our finding that 28% of survivors with normal 3D LVEFs have abnormal global longitudinal strain may identify a subset of survivors at high risk for clinical heart failure. It will be essential that future studies provide longitudinal follow-up of survivors evaluated with comprehensive echocardiographic imaging to determine whether (as in the general population) global longitudinal strain improves the prediction of major cardiac events.

The present study takes important steps in validating global longitudinal strain as a clinically relevant measure in survivors. First, we established that global longitudinal strain, like LVEF, measures treatment-related injury in this population. On the strength of detailed abstraction of cumulative dose exposure of anthracyclines and tissue-specific radiation dosimetry, we demonstrated that abnormal global longitudinal strain, but not global circumferential stain, was associated with increasing doses of both anthracyclines and chest-directed RT. Dose-response relationships between exposure and major cardiac events are well established in this population (6,10); thus, if strain is to be a meaningful early measure of cardiac injury, demonstrating a dose-response relationship is essential. Furthermore, studies in adult cancer populations have demonstrated changes in global longitudinal strain during the administration of anthracyclines (49). In these trials, early changes in global longitudinal strain precede and predict eventual reduction in LVEF and subsequent clinical heart failure (22). These findings have resulted in an expert consensus statement from the ASE that recommends strain in the assessment of adult patients during and after cancer therapy (16). In the present study, abnormal global circumferential strain, though prevalent, showed inconsistent associations with increased anthracycline or chest-directed RT exposure. This may be because the subendocardial region, which governs longitudinal LV mechanics, is generally the region most sensitive to myocardial injury (50). These findings should direct clinicians toward the preferential use of global longitudinal strain over circumferential strain in screening of this population.

It is now established that among aging survivors who received cardiotoxic therapies, the acquisition of traditional cardiovascular risk factors and metabolic syndrome potentiates risk for major cardiac events (8,24). More sensitive echocardiographic measures of cardiac injury would be expected to demonstrate higher rates of abnormal function in a population with metabolic syndrome. We identified higher rates of abnormal global longitudinal strain, but not 3D LVEF, in a subset of the population with metabolic syndrome. This strong association between

therapeutic dose exposure and increased rates of abnormal findings in a high-risk subset of the population with metabolic syndrome suggests that global longitudinal strain may be a valid measure for detecting myocardial injury in adult survivors of childhood cancer. However, baseline assessment before treatment and serial, longitudinal evaluation with strain in a large population of aging survivors are needed before this can be concluded.

STUDY LIMITATIONS. Eight previous studies have reported strain evaluation among a total of 366 long-term survivors of childhood cancer (largest study population, n = 111) (49,51) and identified between 6% and 30% of the population to have abnormal longitudinal strain. We present the most systematic assessment to date, including a study population of sufficient size for a robust multivariate analysis to evaluate confounding variables contributing to cardiac outcomes. Nonetheless, limitations should be considered. The cross-sectional nature of this analysis precludes definitive assessment of the predictive nature of global longitudinal strain, or any echocardiographic parameter, for major cardiac events, including congestive heart failure, cardiac hospitalization, and cardiac mortality. However, longitudinal follow-up of the SJLIFE cohort will allow future assessments as survivors age. Although the quality of echocardiography is inherently operator dependent, this protocol-driven systematic assessment should limit the imprecision inherent in previous studies that have reported on echocardiography by retrospective review. Furthermore, our use of 3D LVEF eliminates assumptions regarding ventricular size inherent in 2-dimensional LVEF estimates, providing the most valid assessment of LVEF to date (14). It is important to note that independent associations between echocardiographic abnormalities and reduced functional performance on the 6-min walk test were not identified on multivariate analysis. This may be a result of 6-min walk distance's being a poor surrogate for performance in this population. Thus, future studies will include maximal treadmill testing to assess functional performance. Additionally, calculation of mean RT dose to the heart, although providing organ-specific dosimetry, may not fully describe the differential dose received across the heart. Finally, current circumferential strain estimations may be unreliable, and future efforts should focus on improvement in reliability and validity.

CONCLUSIONS

These findings suggest that traditional echocardiographic evaluation of cardiac function in adult survivors of childhood cancer that focuses on LVEF as the primary measure of function may be inadequate. Evaluations that incorporate global longitudinal strain and ASE grading of diastolic function demonstrate evidence of cardiac dysfunction in 1 in 3 survivors with normal LVEFs. Long-term follow-up is needed to determine the predictive nature of these echocardiographic findings for major cardiac events.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Survivors of chest-directed RT and anthracycline chemotherapy for cancer in childhood are at risk for cardiac morbidity and mortality as adults.

TRANSITIONAL OUTLOOK: Additional work is needed to characterize the temporal evolution of structural and functional cardiac abnormalities during adulthood that arise as a consequence of therapy for cancer during childhood and predict adverse cardiac events.

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APPENDIX For supplemental tables, please see the online version of this article.