Published in final edited form as:

Ann Intern Med. 2016 January 19; 164(2): 93–101. doi:10.7326/M15-0424.

Cardiac Outcomes in Adult Survivors of Childhood Cancer Exposed to Cardiotoxic Therapy: A Cross-Sectional Study from the St. Jude Lifetime Cohort

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Abstract

Background—Studies of cardiac disease among adult survivors of childhood cancer have generally relied upon self-reported or registry-based data.

Objective—Systematically assess cardiac outcomes among childhood cancer survivors

Design—Cross-sectional

Setting—St. Jude Children's Research Hospital

Patients—1,853 adult survivors of childhood cancer, ≥18 years old, and ≥10 years from treatment with cardiotoxic therapy for childhood cancer.

Measurements—History/physical examination, fasting metabolic and lipid panels, echocardiogram, electrocardiogram (ECG), 6-minute walk test (6MWT) all collected at baseline evaluation.

Results—Half (52.3%) of the survivors were male, median age 8.0 years (range: 0-24) at cancer diagnosis, 31.0 years (18-60) at evaluation. Cardiomyopathy was present in 7.4% (newly identified at the time of evaluation in 4.7%), coronary artery disease (CAD) in 3.8% (newly identified in 2.2%), valvular regurgitation/stenosis in 28.0% (newly identified in 24.8%), and conduction/rhythm abnormalities in 4.6% (newly identified in 1.4%). Nearly all (99.7%) were asymptomatic. The prevalences of cardiac conditions increased with age at evaluation, ranging from 3-24% among those 30-39 years to 10-37% among those ≥40 years. On multivariable analysis, anthracycline exposure ≥250 mg/m^2 increased the odds of cardiomyopathy (odds ratio [OR] 2.7, 95% CI 1.1-6.9) compared to anthracycline unexposed survivors. Radiation to the heart increased the odds of cardiomyopathy (OR 1.9 95% CI 1.1-3.7) compared to radiation unexposed survivors. Radiation >1500 cGy with any anthracycline exposure conferred the greatest odds for valve findings.

Limitations—61% participation rate of survivors exposed to cardiotoxic therapies, which were limited to anthracyclines and cardiac-directed radiation. A comparison group and longitudinal assessments are not available.

Conclusions—Cardiovascular screening identified considerable subclinical disease among adult survivors of childhood cancer.

Funding—Cancer Center Support Grant (CA21765), U01 CA195547 1, American Lebanese Syrian Associated Charities

Introduction

Improvements in cancer therapies have led to an increasing number of survivors living many years following successful treatment. With overall 5-year survival rates in pediatric oncology exceeding 80%(1), the number of adult survivors of childhood or adolescent cancer, currently estimated to be 388,500 in the United States, is projected to surpass

500,000 by 2020.(2, 3) This success is tempered by recognition of adverse late effects of cancer therapy and elevated mortality years following treatment. An 8-fold increased risk of death has been reported among 5-year childhood cancer survivors compared to the age- and sex- matched general population.(4) Historically, the leading cause of death has been cancer recurrence. However, death from late-effects has become the leading cause of mortality 30 years from diagnosis, frequently attributed to premature cardiovascular disease.(5)

Given the rarity of childhood cancer and the challenges of following patients across the life spectrum, most studies have relied upon self-reported outcomes(6), registry(7) or death certificate data(8) to estimate the prevalence and incidence of adverse outcomes. Few have directly assessed survivors or performed detailed clinical evaluations.(9, 10) The aim of this study was to report clinically-evaluated cardiac outcomes among adults previously exposed to cardiotoxic therapies for the treatment of childhood cancer.

Methods

Participants

Cases for this analysis were participants who completed a baseline evaluation in the St. Jude Lifetime Cohort (SJLIFE), an ongoing study designed to facilitate longitudinal evaluation of health outcomes among adults previously treated for a pediatric malignancy. The study design and details have been previously published.(11) To be enrolled in the cohort participants must have been diagnosed and treated for a childhood cancer at St. Jude Children's Research Hospital, currently be ≥18 years old, and have survived ≥10 years from diagnosis. This cross-sectional analysis includes data collected during the baseline evaluation. Participants (recruited from 44 states and 28 countries) must have been treated with cardiotoxic therapy (anthracycline chemotherapy and/or cardiac-directed radiation therapy) and completed the initial on-campus SJLIFE comprehensive risk-based health evaluation as of April 30, 2013.

Survivors completed a detailed health questionnaire and underwent medical evaluation according to the Children's Oncology Group's Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.(12) Assessments included: a history and physical examination, fasting laboratory battery (blood counts, metabolic panel, insulin level, glycosylated hemoglobin, and lipid panel), echocardiogram, and electrocardiogram (ECG). Two-dimensional (2D) Doppler ultrasound echocardiography was performed using a VIVID-7 machine (GE Medical Systems) (n=1834) or an iE33 (Phillips Healthcare) (n=19) using Harmonic Imaging per American Society of Echocardiography guidelines with 3D imaging for left ventricular volumes.(13) All images were centrally reviewed by the echocardiography laboratory in the Department of Cardiovascular Medicine at the Cleveland Clinic. A total of 1,586 (86%) participants had an evaluable echocardiogram sufficient for adequate determination of ejection fraction and 1,742 (94%) sufficient for evaluation of cardiac valves. Twelve-lead ECG (GE MAC 1200 machine) was obtained and centrally reviewed and coded per the Minnesota classification system by the Epidemiological Cardiology Research Center at Wake Forest School of Medicine, Winston-Salem, NC (1,798 participants completed an ECG).

Medical record abstraction was performed to capture cumulative anthracycline exposure in milligrams per body surface area in meters squared (mg/m^2), mean cardiac radiation dose, and medical events during and after therapy. Anthracycline doses were converted to doxorubicin isotoxic equivalents by summing doxorubicin, daunorubicin (x0.83), epirubicin (x0.67), idarubicin (x5), and mitoxantrone (x4) doses.(14) Mean radiation dose to the heart in centigray (cGy) was estimated using previously established methods by the radiation physicists at MD Anderson Cancer Center, Houston, TX.(15) Radiation treatment details included energy source, tumor dose, and field locations. Scatter dose to the heart was estimated for each case, regardless of radiation site and target volume. The SJLIFE protocol and study documents were approved by the Institutional Review Board, and survivors provided informed consent prior to participation.

Outcomes

Outcomes analyzed included cardiomyopathy, coronary artery disease (CAD), valve function, and conduction/rhythm defects. Medical records were obtained to validate established cardiac outcomes reported prior to the SJLIFE assessment. Cardiomyopathy was defined as a systolic ejection fraction <50% on echocardiogram. Coronary artery disease was defined as a history of myocardial infarction, evidence of wall motion defect on echocardiogram, and/or ischemia on ECG. Valves were assessed for function (regurgitation or stenosis) and structure (thickening and/or calcification) identified by echocardiogram. Only functional valve findings (graded as mild, moderate, or severe) were used in the analysis.(16, 17) Conduction/rhythm disorders included major conduction abnormalities or arrhythmias (Appendix Table 1) as assessed by the Minnesota ECG Code.(18)

Covariates

Physical activity was assessed by asking participants if they participated in “usual weekly vigorous activities for at least 10 minutes at a time such as: running, aerobics, wheelchair basketball, heavy yard work, or anything else that caused large increases in breathing or heart rate; or moderate activities for at least 10 minutes such as: brisk walking, bicycling, gardening, manual operation of a wheelchair, or anything else that caused small increases in breathing or heart rate” (http://www.cdc.gov/nchs/data/nhanes/nhanes_09_10/paq_f.pdf). The frequency of exercise sessions per week was multiplied by the duration of each session and weighted by the standardized classification of the energy expenditure in metabolic equivalents expressed as metabolic equivalent minutes/week (inactive ≤450). Physical fitness was assessed by the 6-minute walk test (6MWT)(19) and considered abnormal if the participant walked <490 meters.(20) Risky drinking was defined as alcohol consumption of ≥5 drinks on one occasion or ≥15 drinks per week for men, and ≥4 drinks on one occasion or ≥8 drinks per week for women (http://www.cdc.gov/alcohol/faqs.htm#heavyDrinking). Survivors who reported smoking within the last month were classified as current smokers, and those who smoked at least 100 cigarettes in their lifetime, but not within the last month, were considered past smokers. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥160 mg/dl, high-density lipoprotein cholesterol <40 mg/dl (men) or <50 mg/dl (women), triglycerides >150 mg/dl, or on treatment for a lipid abnormality. Diabetes was defined as a fasting blood glucose ≥126 mg/dl, glycosylated hemoglobin ≥6.5%, or on an oral hypoglycemic agent or insulin for diabetes. Duplicate blood pressure readings were

obtained in a seated position with both feet on the floor following a 5 minute rest with the lowest used for analysis. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or being on an anti-hypertensive agent.

Statistical analysis

Descriptive statistics were calculated for demographic, treatment, and cardiovascular risk factors (i.e. body mass index (BMI) at SJLIFE assessment, smoking, drinking, physical activity, hypertension, diabetes, and dyslipidemia). Chi-square tests were used to compare demographic and treatment characteristics between study participants and non-participants. Frequencies of cardiac conditions reported before or diagnosed during the on-campus evaluations were ascertained and prevalence by age at detection reported. Multivariable logistic models were used to evaluate associations between potential risk factors and cardiac conditions detected during the on-campus evaluations, excluding participants with cardiac outcomes detected prior to SJLIFE participation. Results are reported as odds ratios (OR) with 95% confidence intervals (CI). Covariates were selected due to their known and previously reported associations with cardiac outcomes in the general population and among adult survivors of childhood cancer. Proportions of participants with poor physical fitness (6MWT <490 meters) were calculated and associations with cardiac conditions evaluated by multivariable logistic regression with age, sex, and height as covariates. To account for any missing cardiac outcomes, radiation dose (N=26), and 30 missing 6MWT (not due to a musculoskeletal cause), we used multiple imputation (SAS proc MI and proc MIANALYZE). Markov Chain Monte Carlo (MCMC) methods were used for partial imputation of non-monotone missing records.(21) Monotone missing data were imputed using logistic regression. Pooled estimates of 20 multiply imputed datasets of the multivariable analyses for each outcome are reported as OR with 95% CI. SAS version 9.3 (Cary, NC) was used for all analyses. All statistical inference was based on two-sided tests.

Role of the Funding Source

The funding sources had no role in the design, conduct, or analysis of the study or the decision to submit the manuscript for publication.

Results

Among 3,054 participants exposed to cardiotoxic therapies, 1,853 (61%) returned to St. Jude Children's Research Hospital for a risk-based medical evaluation. Reasons for non-participation are shown in Appendix Figure 1. Compared to non-participants, participating survivors were more likely to be female, white, and have a history of leukemia. Additionally, participants were on average 8 months older and received on average less (9 mg/m^2) total anthracycline exposure (Table 1). Just over half (52.3%) of participants were male with a median age at diagnosis of 8.0 years (range: 0-24) and 31.0 years (18-60) at time of study. Median time from diagnosis was 22.6 years (10-48); nearly two-thirds were more than 20 years from exposure. The majority of survivors had been treated for leukemia or lymphoma (67.2%). Other diagnostic categories included: sarcoma (14%), Wilms tumor (7.2%), neuroblastoma (4.5%), central nervous system (CNS) tumors (4.3%), and a variety of other tumors (2.8%).

Cardiotoxic exposures included anthracycline and radiation therapy. Over 82% were exposed to anthracyclines, with 20.8% receiving cumulative doses in excess of 250 mg/m^2. Less than half received radiation to the heart, but 22.2% had a cardiac dose >1500 cGy. (Appendix Table 2) Cardiovascular risk factors present at the time of SJLIFE assessment included being overweight or obese (61.3%), smoking (23.7% current, 11.7% past), physical inactivity (49.6%), hypertension (23.3%), diabetes (6.8%), and dyslipidemia (61.9%).

The prevalence of each outcome and the result of cardiovascular screening is shown in Table 2. Cardiomyopathy was identified in 7.4% of the population with more than half being detected during the SJLIFE assessment. Screening identified 4.7% with previously undiagnosed cardiomyopathy. Similarly, 3.8% and 4.6% of the population was found to have evidence of CAD or a conduction/rhythm disorder; 2.2% and 1.4%, respectively, newly identified by screening. Functional valve findings were frequent (28.0%) with most being identified during the SJLIFE assessment (24.8%). The prevalence and severity of regurgitation and stenosis in each valve is shown in Table 3. The majority were mild, with most being regurgitation of the tricuspid or pulmonary valves. Moderate or severe mitral regurgitation or stenosis was identified in 26 (1.5%) and 2 (0.1%) survivors, respectively. Sixty-four survivors (3.7%) had aortic regurgitation (16 were moderate, 3 severe) and 31 (1.8%) had aortic stenosis (4 moderate, 9 severe). Mitral valve thickening or annular calcifications were identified in 351 (20.2%) and 177 (10.2%), respectively, and 414 (23.8%) had aortic valve thickening and 107 (6.1%) aortic calcifications. One hundred sixty survivors (9.2%) had more than one valve involved.

The prevalence of each outcome increased with increasing age at evaluation and ranged from 10-37% among those more than 40 years old (Table 4). Nearly 5% of participants <30 years old had evidence of cardiomyopathy. However, most of the outcomes were identified in participants 30 years or older, with the exception of valvular regurgitation and/or stenosis, which was identified in over a quarter of survivors between 18-29 years.

Table 5 shows the associations between sex, age at diagnosis, age at evaluation, treatment factors, and traditional cardiovascular risk factors for cardiomyopathy and valvular disease. The odds of cardiomyopathy were significantly associated with male sex, anthracycline doses ≥250 mg/m2, cardiac radiation exposure in excess of 1500cGy, and hypertension. Younger age at diagnosis and higher radiation doses were associated with increased odds of functional valve findings. Associations between radiation and valvular disease varied according to the anthracycline exposure (interaction $p<0.001$), with the highest odds being among those exposed to the highest doses of radiation and any anthracycline exposure. A reduction in the odds ratio for valve disease was noted among obese survivors and those with dyslipidemia. There were not enough CAD and conduction/rhythm abnormalities to support a fully adjusted multivariable model, yet it appeared these outcomes were more common with older age (≥40 years) and among those with cardiac radiation doses >1500 cGy. (Appendix Table 3).

Although most findings were asymptomatic (4 survivors reported intermittent chest pain; 1 palpitations) and only identified on screening, physical performance was significantly

impaired. Survivors with cardiomyopathy and CAD had approximately twice the odds of having an abnormal 6MWT compared to those without these cardiac effects. (Table 6)

Discussion

Cardiovascular disease and cancer, the leading causes of death among U.S. adults, have both been the target of therapeutic advances and survival gains over the last five decades. However, among adults previously treated for a pediatric malignancy, cardiovascular disease can present at an earlier age with substantial morbidity for which screening methods, modalities, and frequencies remain unclear.(6) Systematically screening the largest prospective cohort of adults previously treated for a childhood cancer, we identified subclinical cardiovascular disease among individuals generally too young for typical cardiovascular risk-stratification. While most cardiovascular disease was asymptomatic, significant associations with limited physical performance were identified.

Studies of cardiotoxicity following cancer therapy have largely focused on cardiomyopathy while only a few have included a broader range of outcomes, such as CAD, valvular disease, and conduction/ rhythm abnormalities.(6, 22-26) Frequencies of these findings have varied widely due to differing screening methods, diagnostic groups studied, outcome definitions, and study methodologies. In a systematic review, Kremer et al. reported subclinical cardiomyopathy ranging from 0-57%.(27) However, many of the studies focused on a particular diagnosis and a variety of definitions for cardiomyopathy. Among studies that evaluated a cross-section of childhood cancer diagnoses and more closely defined cardiomyopathy, the prevalence was narrower, between 5-20%.

Systematic screening identified a substantial number of survivors with asymptomatic cardiomyopathy at high risk for progression to symptomatic heart failure. At a median age of 31 years, we identified 7.5% of survivors with evidence of decreased systolic function; an estimate expected in a much older population. In a randomly selected healthy population, Redfield and colleagues found an EF ≤50% in 3% of those 45-54 years old and 4.8% and 7.1% among those 55-64 and 65-74 years, respectively.(28) The risk of progression to heart failure among persons with untreated systolic dysfunction is significant (29) and has been reported to be as high as 9% per year with a 3-year mortality of 16%.(30) In fact, according to the American College of Cardiology and American Heart Association classification system, these cancer survivors have already progressed from stage A (high risk for developing congestive heart failure) to stage B (asymptomatic) heart failure.(31)

The prevalence of CAD, valve findings, and conduction/rhythm defects has been less frequently described and commonly only within smaller disease-focused studies. Coronary artery disease, typically associated with cardiac directed radiation, has mostly been studied among survivors of Hodgkin lymphoma or breast cancer.(32, 33) However, the Childhood Cancer Survivor Study (CCSS) reported myocardial infarction in 0.7% of 14,358 childhood cancer survivors at a median age of 27 years.(6) In the SJLIFE cohort the prevalence of ischemic disease was higher (3.8%), likely due to the inclusion of subclinical findings, but also potentially influenced by the slightly older age of the cohort and longer follow-up time. Studies among Hodgkin lymphoma survivors have suggested a high fatality rate for

radiation-induced CAD and a higher risk for patients treated under age 21 years.(34) CAD in this population is often proximal in the coronary tree, resulting in considerable myocardial loss following infarction. In fact, using CT angiography screening in a pilot study of Hodgkin lymphoma survivors from the SJLIFE cohort, we found obstructive and non-obstructive coronary disease, with 67% of the lesions located in the proximal coronary circulation.(35)

Valvular disease has also been mostly studied among survivors of Hodgkin lymphoma, due to the common use of mediastinal radiation therapy to treat this disease.(36) Based upon self-report, the prevalence of valve abnormalities in the CCSS cohort was 1.6% across a variety of diagnostic groups and was associated with radiation and anthracycline exposure ($\geq$250 mg/m^2).(6) The prevalence of valve findings was much higher as a result of systematic screening. In our initial report (26), we identified an abnormality in 29% of the SJLIFE cohort and 56.7% of those treated with radiation to the heart. In a recent study, van der Pal and colleagues(37) identified mild, moderate, and severe valve abnormalities in 169 of 545 (31%) childhood cancer survivors. In our analysis, 28% had a functional valve finding. Six survivors had a bicuspid aortic valve and none a known history of rheumatic fever. In a population-based study, Nkomo et al. estimated the prevalence of mild or greater left-sided valve disease in the general population to be 0.3% (0.2-0.3%) among 18-44 year olds and 11.7 % (11.0-12.5%) among those $\geq$75 years.(38) Notably, the risk of death among those with valve disease was 1.36 (95% CI 1.15-1.62) compared to those without. While most of the findings in our study were right-sided, 13.7% had a left-sided lesion (8.2% mitral, 5.5% aortic).

Like the CCSS, we also identified an association between valvular disease and anthracycline exposure. It is not entirely clear why anthracycline therapy might be associated with valvular disease but could result from anthracycline-induced cardiomyopathy with secondary annular dilatation leading to valvular incompetence or toxicity to the valvular endothelium. An inverse relationship was noted with BMI. However, this association has been described in the general population(39, 40) and may be due to reduced image quality in obese patients or hemodynamic changes related to body habitus. Follow-up and focused study of valvular disease in this population is warranted.

Conduction and rhythm abnormalities following cancer therapy can be of varied clinical significance and more difficult to characterize. Reports have frequently focused on particular diagnostic groups and been associated with radiation and/or anthracycline exposures.(7, 32, 41) Myocardial fibrosis can induce an arrhythmogenic focus or interrupt the normal electrical impulse. ECG abnormalities were identified in 4.6% of our cohort and significantly associated with radiation exposure. This prevalence is lower than our previous report that also included non-cardiotoxic therapies(26), suggesting that these disorders may occur more frequently than expected but may not be exclusively associated with particular cardiotoxic exposures. The estimated prevalence of a conduction/rhythm disorder beyond age 40 years was 10.3% in this study, higher than that reported in the CCSS.(42) The CCSS did not have the benefit of validated ECG screening of all survivors, thus could not report on subclinical abnormalities and may be an underestimate. CCSS also reported only Common Terminology Criteria for Adverse Events grade 3-5 abnormalities, thus, the lower

prevalence might suggest that severe rhythm and conduction defects wane with time from diagnosis. A dedicated investigation and classification of ECG findings in cancer survivors following cardiotoxic and non-cardiotoxic therapies is needed.

Given the lack of randomized controlled trials to test screening practices, the current guidelines for the care of childhood cancer survivors were developed by incorporating best available evidence and expert clinical consensus. Only a few studies have investigated the effectiveness of adherence to these screening guidelines. In a clinic-based study of 370 childhood cancer survivors, median age at evaluation 23.9 years (5.3-57.2), Landier et al. classified screening practices, based upon the prevalence of late effects observed in the literature, as high (≥10%), intermediate (1 to <10%), and negligible (<1%) yield. Cardiomyopathy screening was determined to be of intermediate yield (6%) while yield of cardiac conduction screening was low (0.08%). Ischemic disease and cardiac valves were not evaluated. Two recent analyses assessed cost-effectiveness of echocardiographic screening of survivors for cardiomyopathy. Both concluded that the current guideline suggestions of imaging every 1-5 years is cost effective, though these benefits might be retained even if imaging was performed less frequently and/or with other modalities, such as cardiac magnetic resonance imaging.(43, 44) Our study provides important additional clinical parameters not available in these studies that relied upon self-reported cardiac outcomes. Future longitudinal studies, as can be conducted in the SJLIFE cohort, are needed to better clarify the progression of cardiomyopathy, the effects of treatment, and the implications for clinical practice guidelines related to cardiovascular health surveillance as this population ages. Furthermore, our study assessed additional cardiac outcomes and, to date, cost effectiveness studies have not been performed for those. The proportion of individuals with newly identified cardiac disease in our study was higher for all outcomes assessed than previously reported, albeit lowest for conduction/rhythm disorders.

A number of limitations should be considered when interpreting our results. Given the 61% participation, selection bias could potentially influence our findings. However, significant differences between participants and the SJLIFE source population have not been identified. (45) An on-campus evaluation was required, thus excluding survivors who may not have been able to travel due to commitments, illness, or death, potentially affecting our estimates of disease. Additionally, medical records were not routinely obtained for individuals who did not report a cardiac event, thus, potentially biasing our estimates. Comparisons were not made to a non-cancer control population and, while survivors will be invited to return for a repeat evaluation, longitudinal assessments are currently lacking. Only survivors with a history of cardiotoxic therapies were studied, limiting the ability to generalize these findings and potentially missing cardiac disease in survivors with other exposure histories. Finally, among those who did participate, 267 echocardiograms were missing (101 participants failed to complete scheduled cardiac evaluations and 166 for technical reasons – suboptimal recording, poor electrical transmission, etc.). All reasons were reviewed and treated as missing completely at random.

We identified considerable cardiovascular disease in this large cohort of adults cured of childhood cancer. The prevalence is inconsistent with the chronological age of the population and suggests a substantial future health care burden. Clinically, these data may

guide risk factor stratification, screening practices, health counseling, and potential therapeutic measures aimed at changing the disease trajectory in this young adult population.

Acknowledgments

The authors with to thank Ms. Taryn Donley for technical support with manuscript preparation.

Grant Support: Supported by Cancer Center Support (CORE) Grant (CA21765) to St. Jude Children's Research Hospital, U01 CA195547 1 (PI: Dr. Melissa M. Hudson), and the American Lebanese Syrian Associate Charities (ALSAC), Memphis, TN.

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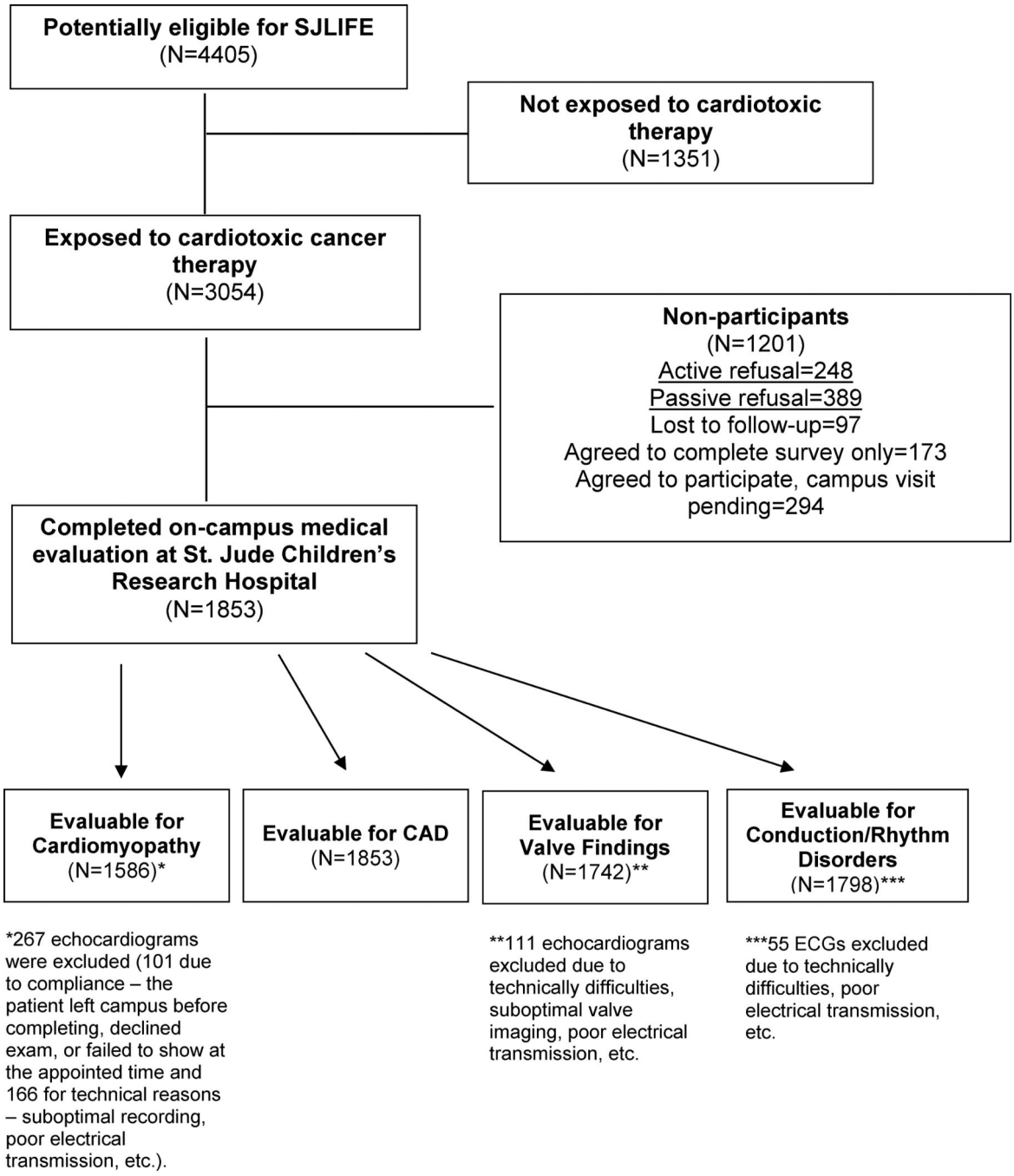

Appendix Figure 1. Flow Diagram

Table 1

Demographic, Diagnostic, Treatment, and Lifestyle Characteristics of Study Participants and Non-participants

	Participant Survivors		Non-participants		
	N=1853	(%)	N=1201	(%)	p-value
Sex					
Female	884	(47.7)	464	(38.6)	<0.001
Male	969	(52.3)	737	(61.4)	
Race					
White	1589	(85.8)	977	(81.3)	
Black	232	(12.5)	200	(16.7)	0.005
Other	32	(1.7)	24	(2.0)	
Diagnosis Group					
Leukemia	763	(41.2)	473	(39.4)	
Hodgkin Lymphoma	313	(16.9)	181	(15.1)	
Non-Hodgkin Lymphoma	169	(9.1)	154	(12.8)	
Sarcomas	260	(14.0)	148	(12.3)	
Wilms Tumor	133	(7.2)	94	(7.8)	
Neuroblastoma	84	(4.5)	57	(4.8)	0.012
Central Nervous System (CNS)	79	(4.3)	52	(4.3)	
Germ Cell Tumors	11	(0.6)	11	(0.9)	
Liver Malignancies	7	(0.4)	3	(0.3)	
Retinoblastoma	6	(0.3)	13	(1.1)	
Carcinoma	19	(1.0)	9	(0.8)	
Other	9	(0.5)	6	(0.5)	
Age at Diagnosis (years)					
0 – 4	626	(33.8)	405	(33.7)	
5 – 9	429	(23.2)	288	(24.0)	0.81
10 – 14	461	(24.9)	282	(23.5)	
≥ 15	337	(18.2)	226	(18.8)	
Age at SJLIFE Evaluation (years)					
18 - 29	791	(42.7)	404	(33.6)	0.002

	Participant Survivors		Non-participants		
	N=1853	(%)	N=1201	(%)	p-value
30 – 39	701	(37.8)	477	(39.7)	
≥ 40	361	(19.5)	320	(26.6)	
Time Since Diagnosis (years)					
10 – 20	671	(36.2)	350	(29.1)	
20 – 30	753	(40.6)	495	(41.2)	0.118
> 30	429	(23.2)	356	(29.6)	
Cardiac Radiation (cGy)*					
None	1050	(56.7)	747	(62.2)	
≤ 1500	366	(19.8)	217	(18.1)	0.088
> 1500	411	(22.2)	237	(19.7)	
Unknown	26	(1.4)	0	(0.0)	
Anthracyclines (mg/m^2)					
None	332	(17.9)	203	(16.9)	
< 100	488	(26.3)	287	(23.9)	<0.001
100 – 249	647	(34.9)	513	(42.7)	
≥ 250	386	(20.8)	198	(16.5)	
All variables below obtained at the time of the SJLIFE assessment					
BMI (kg/m^2)					
Normal/underweight (< 25)	717	(38.7)			
Overweight (25 – 29)	525	(28.3)			
Obese (≥ 30)	611	(33.0)			
Smoker					
Past	217	(11.7)			
Current	439	(23.7)			
Never	1197	(64.6)			
Physical Activity					
Active (>450 metabolic equivalent minutes/week)	934	(50.4)			
Inactive (≤450 metabolic equivalent minutes/week)	919	(49.6)			
Risky drinking					
No	1132	(61.1)			

	Participant Survivors		Non-participants		
	N=1853	(%)	N=1201	(%)	p-value
Yes	721	(38.9)			
Hypertension					
No	1421	(76.7)			
Yes	432	(23.3)			
Diabetes					
No	1727	(93.2)			
Yes	126	(6.8)			
Dyslipidemia					
No	706	(38.1)			
Yes	1147	(61.9)			
Six Minute Walk Test					
Normal (≥490 meters)	1387	(74.9)			
Impaired (<490 meters)	427	(23.0)			
Unknown	39	(2.1)			

* Radiation dosimetry was not performed for non-participants and was, therefore, estimated from institutional records. SJLIFE = St. Jude Lifetime Cohort, cGy = centigray BMI = body mass index

Table 2

Prevalence of cardiac outcomes in the SJLIFE cohort and outcomes newly identified by cardiovascular screening

Cardiac outcome	Number evaluated (N)	Detected prior to SJLIFE Assessment		Detected at SJLIFE Assessment		Total Prevalence		Percent Identified by Cardiovascular Screening*
Cardiomyopathy	1586ł	46	(2.9)	72	(4.5)	118	(7.4)	4.7%
Coronary artery disease	1853	29	(1.6)	40	(2.2)	69	(3.8)	2.2%
Valvular disease	1742ł	74	(4.2)	414	(23.8)	488	(28.0)	24.8%
Conduction/rhythm disorders	1798ł	53	(3.0)	25	(1.4)	78	(4.6)	1.4%

*Percent identified by cardiovascular screening = number of outcomes diagnosed during SJLIFE assessment ÷ the number evaluated minus outcomes diagnosed prior to SJLIFE assessment.

łOnly imaging that was successfully completed by the participants and of sufficient quality for interpretation was included, i.e. 1,586 completed the echocardiograms with images adequate for assessment of left ventricular function, 1,742 images were adequate for complete evaluation of valve function, and 1,798 participants completed the electrocardiogram. SJLIFE = St. Jude Lifetime Cohort

Table 3

Prevalence and severity of functional heart valve findings among 1742 survivors

	Mitral Valve				Aortic Valve				Tricuspid Valve				Pulmonic Valve			
	Regurgitation		Stenosis		Regurgitation		Stenosis		Regurgitation		Stenosis		Regurgitation		Stenosis	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Mild	101	(5.8)	14	(0.8)	45	(2.58)	18	(1.0)	241	(13.8)	1	(0.06)	173	(9.93)	0	0
Moderate	19	(1.1)	1	(0.06)	16	(0.92)	4	(0.23)	40	(2.3)	0	0	12	(0.69)	1	(0.69)
Severe	7	(0.4)	1	(0.06)	3	(0.17)	9	(0.52)	2	(0.11)	0	0	0	0	0	0

* Includes survivors with more than one functional valve finding.

Table 4

Prevalence of Cardiac Outcomes by Age at Detection

Cardiac outcome	Number evaluated	Age at detection (years)	Number evaluable	N	(%)
Cardiomyopathy	1586[ł]	18-29	(n=706)	33	(4.7)
		30-39	(n=610)	56	(9.2)
		≥ 40	(n=270)	29	(10.7)
Coronary artery disease	1853	18-29	(n=791)	7	(0.9)
		30-39	(n=701)	24	(3.4)
		≥ 40	(n=361)	38	(10.5)
Valvular disease	1742[ł]	18-29	(n=761)	214	(28.1)
		30-39	(n=660)	156	(23.6)
		≥ 40	(n=321)	118	(36.8)
Conduction/rhythm disorders	1798[ł]	18-29	(n=770)	21	(2.7)
		30-39	(n=677)	21	(3.1)
		≥ 40	(n=350)	36	(10.3)

[ł]Only imaging that was successfully completed by the participants and of sufficient quality for interpretation was included, i.e. 1,586 completed the echocardiograms with images adequate for assessment of left ventricular function, 1,742 images were adequate for complete evaluation of valve function, and 1,798 participants completed the electrocardiogram.

Table 5

Cardiomyopathy and Valvular Disease by Cardiac Risk Factors[*] [†]

	Cardiomyopathy		Valvular disease	
	OR[*]	95% CI	OR[*]	95% CI
Sex				
Female	1.0		1.0	
Male	1.9	(1.1-3.3)	0.8	(0.6-1.0)
Age at Diagnosis (years)				
0-4	0.5	(0.3-1.1)	1.5	(1.1-2.2)
5-9	0.6	(0.3-1.2)	1.3	(0.9-1.9)
10-14	0.9	(0.5-1.7)	1.0	(0.7-1.5)
≥ 15	1.0		1.0	
Age at SJLIFE Evaluation (years)				
18-29	1.0		1.0	
30-39	1.3	(0.7-2.3)	0.8	(0.6-1.1)
≥ 40	0.4	(0.2-1.0)	1.2	(0.8-1.7)
BMI at SJLIFE assessment (kg/m^2)				
Normal/underweight	1.0		1.0	
Overweight (BMI=25.0 to <30)	1.0	(0.5-1.9)	0.8	(0.6-1.1)
Obese (BMI ≥ 30)	1.2	(0.6-2.3)	0.4	(0.3-0.6)
Anthracycline (mg/m^2)				
None	1.0		-	--
< 250	1.2	(0.5-2.8)	-	--
≥ 250	2.7	(1.1-6.9)	-	--
Average Cardiac Radiation dose (cGy)				
None	1.0		-	--
≤ 1500	1.1	(0.5-2.2)	-	--
> 1500	1.9	(1.1-3.7)	-	--
Interaction Cardiac Radiation * Anthracycline				
≤ 1500 cGy * No anthracycline			1.0	
> 1500 cGy * ≥ 250 mg/m^2 anthracycline		N/A	4.5	(1.9-10.7)
≤ 1500 cGy * ≥ 250 anthracycline			0.9	(0.3-2.3)
No radiation * ≥ 250 anthracycline			1.1	(0.6-2.2)
> 1500 cGy * < 250 mg/m^2 anthracycline			3.1	(1.5-6.2)
≤ 1500 cGy * < 250 mg/m^2 anthracycline			1.9	(1.0-3.8)
No radiation * < 250 mg/m^2 anthracycline			1.1	(0.6-2.0)
> 1500 cGy * no anthracycline			4.1	(2.1-8.0)
Smoker (ever)				
No	1.0		1.0	
Yes	0.9	(0.5-1.5)	0.8	(0.6-1.0)

	Cardiomyopathy		Valvular disease	
	OR*	95% CI	OR*	95% CI
Physical Activity				
Inactive	1.0		1.0	
Active	1.2	(0.7-2.0)	1.0	(0.8-1.3)
Excessive alcohol				
No	1.0		1.0	
Yes	0.9	(0.5-1.5)	1.0	(0.8-1.3)
Hypertension				
No	1.0		1.0	
Yes	3.0	(1.7-5.2)	1.2	(0.9-1.7)
Diabetes				
No	1.0		1.0	
Yes	2.0	(0.9-4.2)	0.7	(0.4-1.3)
Dyslipidemia				
No	1.0		1.0	
Yes	1.0	(0.6-1.7)	0.7	(0.6-0.9)

*Estimates adjusted for all variables in the table.

†Analysis limited to only those outcomes detected at baseline SJLIFE visit. SJLIFE = St. Jude Lifetime Cohort, BMI = body mass index, cGy = centigray

Table 6

Impaired Physical Function* and Cardiac Outcomes†

	Odds Ratio	95% CI
Cardiomyopathy	1.9	(1.2-2.9)
Coronary Artery Disease	2.2	(1.3-3.8)
Valvular Disease	0.7	(0.6-1.0)
Conduction/rhythm Disorders	1.4	(0.8-2.4)

*Impaired physical function was defined as a 6MWT of <490 meters

†Adjusted for current age, sex, height, and all cardiac conditions

Appendix Table 1

Conduction/rhythm disorders per the Minnesota ECG Code*

- Ventricular conduction defects
  - Complete left/right bundle branch block
  - Non-specific major intra-ventricular block
  - Bi-fasicular block
- Major atrial-ventricular (AV) conduction abnormalities
  - Advanced AV block (second degree or complete block)
  - Wolf Parkinson White Syndrome
- Major QT prolongation
- Pacemaker
- Atrial fibrillation/flutter

* Prineas RJ, Crow RS, Blackburn H**.** *The Minnesota Code manual of electrocardiographic findings*. Littleton, MA: John Wright-PSG; 1982. ECG = electrocardiogram, AV = atrio-ventricular, QT = Q wave T wave

Ann Intern Med. Author manuscript; available in PMC 2016 July 19.

Appendix Table 2

Distribution of cardiac radiation and anthracycline exposures

	Anthracycline dose (mg/m^2)							
	None		< 250 mg/m^2		≥ 250 mg/m^2		Total	
Cardiac Radiation	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
None	0	(0)	799	(70.4)	280	(72.6)	1079	(58.2)
≤ 1500 cGy	127	(38.3)	183	(16.1)	53	(13.7)	363	(19.6)
> 1500 cGy	205	(61.7)	153	(13.5)	53	(13.7)	411	(22.2)
Total	332	(100)	1135	(100)	386	(100)	1853	(100)

Appendix Table 3

Coronary Artery Disease and Conduction/rhythm disorders by Cardiac Risk Factors*

	Coronary artery disease		Conduction/ rhythm disorders	
	OR*	95% CI	OR*	95% CI
Sex				
Female	1.0		1.0	
Male	1.7	(0.9-3.2)	1.1	(0.5-2.4)
Age at Diagnosis (years)				
0-4	0.5	(0.2-1.3)	1.1	(0.3-3.9)
5-9	0.8	(0.3-1.9)	1.8	(0.6-5.4)
10-14	0.4	(0.2-1.1)	1.0	(0.3-3.2)
≥ 15	1.0		1.0	
Age at SJLIFE Evaluation (years)				
18-29	1.0		1.0	
30-39	1.8	(0.7-4.7)	2.4	(0.7-8.1)
≥ 40	3.1	(1.2-8.2)	4.1	(1.2-14.1)
Anthracycline (mg/m^2)				
None	1.0		1.0	
< 250	2.0	(0.9-4.6)	0.5	(0.2-1.7)
≥ 250	2.0	(0.7-5.4)	1.5	(0.5-4.8)
Average Cardiac Radiation dose (cGy)				
None	1.0		1.0	
≤ 1500	2.2	(0.7-7.1)	1.3	(0.3-4.9)
> 1500	10.5	(4.2-26.3)	3.5	(1.1-10.7)

*Estimates adjusted for all variables in the table. SJLIFE = St. Jude Lifetime Cohort, cGy = centigray