HHS Public Access

Author manuscript

JACC CardioOncol. Author manuscript; available in PMC 2021 March 01.

Published in final edited form as:

JACC CardioOncol. 2020 March ; 2(1): 26–37. doi:10.1016/j.jaccao.2020.02.016.

Longitudinal Changes in Echocardiographic Parameters of Cardiac Function in Pediatric Cancer Survivors

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Abstract

Background—Childhood cancer survivors undergo serial echocardiograms to screen for cardiotoxicity. It is not clear whether small longitudinal changes in functional or structural parameters over time have clinical significance.

Objectives—To assess the timing of changes in serial echocardiographic parameters in pediatric age childhood cancer survivors and to evaluate their associations with cardiomyopathy development.

Methods—We performed a multi-center retrospective case-control study of ≥1-year survivors following the end of cancer therapy. Cardiomyopathy cases (fractional shortening (FS) ≤28% or

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Disclosures

The authors do not have any relationships relevant to the content of this paper to disclose.

ejection fraction (EF) ≤50% on ≥2 occasions) were matched to controls (FS ≥30%, EF ≥55%, not on cardiac medications) by cumulative anthracycline and chest radiation dose, follow-up duration, and age at diagnosis. Digitally archived clinical surveillance echocardiograms were quantified in a central core lab, blinded to patient characteristics. Using mixed models with interaction terms between time and case status, we estimated the least square mean differences of 2D, M-mode, pulsed wave Doppler and tissue Doppler imaging derived parameters across time between cases and controls.

Results—We identified 50 matched case-control pairs from 5 centers. Analysis of 412 echocardiograms (cases, n=181; controls, n=231) determined that indices of LV systolic function (FS, biplane EF), diastolic function (mitral E/A ratio), and LV size (end diastolic dimension z-scores) were significantly different between cases and controls, even four years prior to the development of cardiomyopathy.

Conclusions—Longitudinal changes in cardiac functional parameters can occur relatively early in pediatric age childhood cancer survivors and are associated with the development of cardiomyopathy.

Condensed Abstract

This multi-center retrospective study examined whether small longitudinal changes in echocardiographic functional and structural parameters are associated with the development of cardiac dysfunction in pediatric age childhood cancer survivors. We observed a measurable decline in echocardiographic parameters of systolic function, diastolic function, and size prior to the development of overt cardiac dysfunction. These data indicate the potential role for an expanded analysis involving a larger cohort of cardiomyopathy cases, to facilitate development of predictive models incorporating functional and structural echocardiographic parameters to identify those at risk of developing subsequent cardiomyopathy.

Keywords

Echocardiography; Cancer Survivorship; Cardiomyopathy

Introduction

Survival rates in childhood cancer continue to improve with current 5-year overall survival rates at 80%, and over 430,000 childhood cancer survivors living in the United States (1). However, cardiovascular disease is one of the leading contributors to late morbidity and mortality in this population (2). More specifically, those treated with anthracycline chemotherapy and/or chest radiation are at an increased risk of developing heart failure and cardiomyopathy (3,4). Many of these patients will have detectable cardiac dysfunction prior to the development of overt clinical heart failure (5). As a result, national and international groups have developed recommendations regarding echocardiographic surveillance to detect cardiac dysfunction early (6,7).

The adult cardio-oncology community has published echocardiographic guidelines for the detailed evaluation of cardiac function in adults during and after cancer therapy, including non-EF based parameters such as global longitudinal strain (8). However, such specific

guidelines do not exist for pediatric patients, and there is a paucity of longitudinal data to facilitate comparable recommendations. With rare exceptions (9), most research studies examining echocardiographic changes in pediatric patients have been cross-sectional single-institution studies not enriched for cardiomyopathy cases, which makes it difficult to evaluate trajectories over time (10,11). The relative rarity at single centers of pediatric age patients developing cardiac dysfunction has hampered the ability to rigorously study echocardiographic parameters longitudinally. Greater insight into these trajectories could help identify the subpopulation of patients who will develop subsequent, true cardiac dysfunction, and potentially allow for earlier medical intervention.

We therefore undertook a retrospective multi-institutional study involving five pediatric cancer centers aimed at assessing the longitudinal trajectories of cardiac function and structure in childhood cancer survivors prior to the onset of cardiomyopathy and contrasting these with closely matched survivor controls. Specifically, we collected and centrally analyzed serial echocardiograms previously obtained as part of routine care prior to the onset of cardiomyopathy and over a similar time period for matched controls. Cases who developed cardiac dysfunction were matched to controls and detailed evaluation of echocardiographic indices of left ventricular (LV) systolic function, diastolic function, size and geometry were undertaken. By taking advantage of serial echocardiograms within a multi-institutional case-control study design we sought to address the question of which longitudinal changes in echocardiographic parameters are associated with the subsequent development of cardiac dysfunction in pediatric age childhood cancer survivors.

Material and Methods

Patients

Eligibility for this retrospective case-control study was limited to individuals previously diagnosed with cancer at age <21 years and followed at one of 5 participating centers (City of Hope, Children's Healthcare of Atlanta/Emory University, Hospital for Sick Children, Seattle Children's Hospital, and Masonic Children's Hospital/University of Minnesota). All participants had to survive at least 1-year beyond the end of initial cancer therapy. Cardiomyopathy cases were defined by echocardiography as having either a fractional shortening (FS) ≤28% or ejection fraction (EF) ≤50%, on at least two occasions, with at least one of those measurements occurring after completion of cancer therapy. Cases where these FS or EF criteria were met only once were also accepted if the qualifying measurement occurred after the completion of cancer therapy and led to the initiation of medical treatment for cardiomyopathy. Controls were individually matched to cases based on the following criteria (in order of descending priority): 1) cumulative anthracycline dose and type (50 mg/m^2 increments for doxorubicin and daunorubicin; 25 mg/m^2 for idarubicin and mitoxantrone); 2) chest radiotherapy (none, <15 Gy, 15–34 Gy, ≥35 Gy); 3) follow-up duration (±1, ±2, and ±3 years to within 5, 5–9, and ≥10-years of cancer diagnosis, respectively); 4) age at cancer diagnosis (±5 years); and 5) sex. Furthermore, controls had to have, by their institutional echocardiographic reports, FS ≥30% and EF ≥55%, without known qualitative changes concerning for cardiomyopathy during the same follow-up time interval as their matched case. To avoid issues with misclassification, controls also could not

be treated with anti-hypertensive medications during the follow-up time interval. We also excluded patients with known congenital heart anomalies (except patent foramen ovale) or underlying genetic syndrome associated with abnormal cardiovascular development. The institutional review boards at all participating institutions approved the study procedures with waiver of consent.

Exposures

The medical records of cases and controls were reviewed. Information on patient demographics, the original cancer diagnosis, and any relapse, if applicable, was abstracted. Lifetime anthracycline and anthraquinone doses, by individual agent, were summed based on doxorubicin equivalency, as was any radiotherapy field potentially affecting the heart, using the Children's Oncology Group version 5 guideline definitions (12), with the exception that mitoxantrone was considered 10-times more cardiotoxic than doxorubicin. Age and vital status at last follow-up were also recorded.

Outcomes

All available archived echocardiographic images for selected cases and matched controls were de-identified and submitted in DICOM format to a central core laboratory at Emory University for off-line analysis, using a vendor-neutral software analysis package (TOMTEC Corporation USA, Chicago, IL). The submitted studies were obtained for routine clinical purposes from multiple institutions over a 13-year period (2004 to 2017). A single blinded reviewer (DEC) analyzed all studies. Study parameters included those related to LV size and geometry (posterior wall thickness, end-diastolic dimension [EDD], thickness-to-dimension ratio), LV systolic function (FS, EF derived by Biplane Simpson's method], mitral S', septal S'), LV diastolic function (mitral E/A ratio, mitral E', mitral E/E', septal E', and septal E/E'), and combined LV systolic/diastolic function (myocardial performance index [MPI], derived from both pulsed wave Doppler and tissue Doppler). Both two-dimensional (2D) and M-mode measurements were made, but unless otherwise specified, all reported values are based on 2D views. We attempted to derive indices of deformation such as global longitudinal strain (GLS). However only 10% of the submitted echocardiograms had adequate apical 2-, 3- and 4- chamber views for accurate quantitation. This was felt to be an inadequate sample, and thus GLS was not included in the analysis.

Statistical Analyses

Categorical patient characteristics and treatments are presented as frequencies (percents) and were compared between cases and controls using chi-squared tests. For continuous measures, normality was evaluated based on the Kolmogorov-Smirnov statistic, and measures are presented as mean (standard deviation [SD]) if normally distributed or median with interquartile 25^{th} and 75^{th} percentiles (IQR) if not, with p-values based on either t-tests or Wilcoxon tests, respectively. Because distributions of the echocardiographic parameters were normally distributed, mixed models were used to compare cases and controls over time prior to cardiomyopathy diagnosis or the same time for controls (case index time). Models included a random effect to account for matched pairs, and an autoregressive correlation structure was assumed for repeated measurements within individuals. Categorical time variables were created for echocardiogram timing prior to the index diagnosis, mapping

continuous times to integer year categories as follows: index, <1 year, 1 to <2 year, 2 to <3 year, 3 to <4 year, 4 to <5 year, 5 to <6year, 6 to <7 year, and ≥7 years prior to index time. Mixed models included indicator variables for all time categories, indicator of case status, and the interaction terms between time and case variables. Least square means (LSM) with 95% confidence intervals (CI) were estimated for each time category and displayed for cases and controls. Additional comparisons within specific time intervals (e.g. more than 2 years before the index time) were calculated using differences between LSMs, constructed from the relevant parameter and variance covariance estimates from the model.

During the time period more than 2 years prior to the index time, all endpoints were fit as a linear model as a function of time. To illustrate the trajectory of echocardiogram endpoints over this time for cases and controls, linear mixed models with continuous time, case status, and an interaction between time and case status were also fit for each endpoint; predicted means with 95% confidence bands were displayed.

Most echocardiograms were assessed post-therapy. However, an additional set of mixed models compared cases and controls with time categorized into three exclusive categories: 1) at the time of cancer diagnosis; 2) on cancer therapy; and 3) post-cancer therapy. These models all included an interaction term between case status and time, with results presented as LSMs (95% CIs) and p-values. Data were analyzed using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA), and a two-sided p-value <0.05 was considered statistically significant.

Results

By design, demographic and treatment characteristics among the 50 cases and 50 matched controls were similar (Table 1). Notably, 64% of cases were male (56% of controls; p=0.414) and approximately 40% of the sample was of a minority racial/ethnic background. Among cases, the mean time interval from cancer diagnosis to the cardiomyopathy index time point was 6.4 ±5.3 years. Most cases and controls received only one anthracycline or anthraquinone (76% or 78%, respectively); only 4% received three agents.

Detailed, core lab quantified measurements were performed on 412 echocardiograms (cases, n=181 studies; controls, n=231 studies), with a median number of 5 echocardiograms for cases and 4 echocardiograms for controls, and a mean follow-up time since cancer diagnosis of 5.4±5.0 years for cases and 6.2±4.4 years for controls. We then examined differences in LV systolic function, diastolic function, MPI, size, and geometry across categorical time periods. We observed significant differences between cases versus controls for FS, EF, mitral E/A ratio, and LVEDD across multiple time periods, while significant differences in MPI and LV thickness-dimension ratio were only seen at the index time point (Table 2; Figure 1). For example, even 2 to 3.9 years prior to the index point, significant differences in FS, EF, mitral E/A ratio, and LVEDD were observed, while the difference in MPI, derived by pulsed wave Doppler, was of borderline significance (p=0.055). Combining estimates from all time periods other than the two years within the index time point, differences in FS, EF, mitral E/A ratio, and LVEDD remained significant. Results for LV FS and EDD by M-mode were similar to 2D results (data not shown).

Given our interest in the trajectory of change prior to cardiomyopathy diagnosis, we also assessed differential model shapes and slopes over time, excluding data within two years of the index time point. In these models, which included an interaction of case status with time, significant non-linearity was not detected, and therefore linear models were used (Central Illustration). The slope of biplane EF (as well as septal E' and septal E/E'; data not shown) was significantly different between cases versus controls over this time period, but FS, mitral E/A ratio, pulsed wave Doppler MPI, LVEDD and thickness-dimension ratio did not have differing trajectories.

Finally, we evaluated differences in central, core lab quantified echocardiographic parameters between cases and controls during three clinically-defined time periods: at time of cancer diagnosis; while on cancer therapy and; after therapy up to and including the time of the index case echocardiogram (Table 3). Notably, significant differences between cases and controls were seen during the "on therapy" period.

Discussion

This retrospective multi-institutional case-control study of pediatric age childhood cancer survivors demonstrated that there was a measurable decline in echocardiographic parameters of cardiac function and remodeling prior to developing overt cardiac dysfunction. This held true for indices of systolic function, diastolic function, and cardiac size. Even as far back as four years prior to the development of overt cardiac dysfunction, cases exhibited a decline in LV systolic function (both FS and EF) and diastolic function (mitral E/A) compared with matched controls. This trajectory has been difficult to demonstrate in the past, given the relative paucity of pediatric age cancer survivors with cardiac dysfunction in individual centers.

Echocardiographic Screening for Cardiac Dysfunction

Increased survival in childhood cancer survivors has led to an associated increase in long-term cardiovascular complications such as cardiac dysfunction and heart failure (13,14). Select chemotherapy agents (e.g., anthracyclines) and chest radiotherapy are associated with this increased risk. Early detection of cardiac dysfunction would potentially provide the opportunity to intervene to impact pathological remodeling of the heart prior to the development of sustained abnormalities. This has led to the development of consensus-based guidelines that attempt to standardize the frequency and modality to best surveil for the development of cardiac dysfunction (7,12). Given the safety, convenience and ubiquity of echocardiography, this modality has formed the backbone of this screening effort. However, many of the echocardiographic indices of cardiac function (such as EF and FS) have been considered binary variables (normal/not normal) in the past, making it difficult to be able to intervene before the abnormal finding is reported. This has started to change in more recent guidelines in adult cancer patients with an effort to account for trajectory of change in these indices (8).

Traditional Echocardiographic Measures of LV Systolic Function and Remodeling

Early studies showed progressive cardiac dysfunction in childhood cancer survivors primarily by documenting the development of abnormalities in systolic function as measured by fractional shortening and geometric changes such as reduced LV mass and wall thinning (9). Similar changes have been demonstrated even in pediatric patients exposed to low doses of anthracycline (≤100mg/m^2), manifesting as decreased posterior wall thickness and decreased FS compared to controls (15). Interestingly, our study did not show significant differences in posterior wall thickness z-score between cases and controls, and only the LVEDD z-score was significantly greater in cases across multiple time intervals.

Left ventricular EF has surpassed FS as a more reliable measure of LV systolic function (16). However, the detection of abnormal FS or EF is felt to be a relatively late finding, occurring after injury and pathological remodeling have already occurred (17). This has led investigators to search for other more sensitive early markers of cardiac dysfunction. However, this has perhaps ignored the value of studying the rate of change in these more traditional indices over time, prior to crossing the threshold into dysfunction. This has also been difficult to document, given the relative lack of longitudinal data available in pediatric age cancer survivors. Lipshultz et al., have previously published their experience among high-risk leukemia survivors, but among these participants, only 18 developed clinical cardiomyopathy (9). By evaluating serial echocardiograms in a larger group of cardiomyopathy cases prior to the onset of LV dysfunction, we were able to examine this trajectory of change and identify significant changes in FS and EF relative to controls up to four years prior. This trajectory of change raises the potential possibility of deriving a predictive equation to calculate risk of developing cardiac dysfunction in individual patients. However, our study was not sufficiently powered to be able to do this.

Echocardiographic Measures of Diastolic Function

Diastolic dysfunction can occur in the setting of preserved systolic function and hence echocardiographic guidelines have recommended incorporating measures of diastolic function into standard practice (8,18). Adult studies have shown a high prevalence of diastolic abnormalities in anthracycline-exposed cancer survivors (19). However, the picture has been far more mixed in pediatric age cancer survivors with some studies showing normal diastolic function (20) and others showing impaired relaxation and/or filling (21–23). Standard methods have included evaluating LV inflow by PW Doppler and reporting the E/A ratio as a measure of relaxation. In addition, tissue Doppler imaging (TDI) has been used to measure tissue velocities of the mitral annulus (free wall and septum), and report E' velocities as a measure of relaxation. When combined with the mitral PW Doppler as the E/E' ratio, this has been felt to reflect LV compliance and be a marker of restrictive physiology. In our study, when evaluated across multiple time points, only the mitral PW E/A ratio showed significant differences between cases and controls, even years before cardiomyopathy diagnosis.

Echocardiographic Measures of Combined Systolic-Diastolic Function

Myocardial performance index (MPI) is a measure which incorporates both isovolumic contraction and isovolumic relaxation and hence has been used as a measure of combined

systolic and diastolic function. It can be measured using both PW Doppler and TDI techniques. Studies in adult cancer survivors have shown the usefulness of MPI in detecting early cardiotoxicity (24). These findings have been replicated in pediatric age cancer survivors (25–27). In our series, differences in PW Doppler MPI and TDI MPI between cases and controls were noted at the time of cardiomyopathy diagnosis, but we only saw borderline differences in Doppler MPI in the years prior to cardiomyopathy diagnosis.

Advanced Echocardiographic Measures of Deformation

Given the potential for regional myocardial abnormalities in childhood cancer survivors and the limitations around the geometric and uniform contractility assumptions made by FS and EF, global longitudinal strain (GLS) has been recognized as a new method for early cardiotoxicity detection (28,29). In adult breast cancer patients, screening that includes EF and GLS has nearly twice the predictive power for future symptomatic disease compared to EF alone (30). The St. Jude Lifetime Cohort Study has provided some of the strongest data supporting a comprehensive approach utilizing EF, indices of diastolic function and GLS. In a cohort of 1,820 adult cancer survivors, 5.8% had abnormal 3D LVEF, but in those with normal EF, 28% had abnormal GLS, and 8.7% had diastolic dysfunction (31). In the present study, we attempted to perform post hoc measurements of GLS at the core echo laboratory. However, this requires excellent quality apical 2, 3 and 4 chamber views to allow for accurate calculation of GLS. Due to the retrospective nature of our study, many of the images our study had access to (90%), especially in the earlier eras, did not have the required views or were not of an acceptable quality, and thus we had to abandon this component of the study.

Study Limitations

The study required that echocardiograms were stored in DICOM format and could be uploaded to the central core lab for post hoc review and analysis. This meant that certain cases or controls could not be included in the study and may have biased us towards more of a contemporary cohort. In addition, this included less than complete echocardiographic data at earlier time points, such as time of cancer diagnosis, which limited our ability to determine the significance of any differences during those time periods. We also monitored for the issue of left truncated data (i.e., patients only having echocardiographic data starting after the time point at which their institution began archiving digitally). We attempted to minimize any bias that this could introduce among cases and controls by matching on echocardiogram follow-up duration and by institution.

Due to the retrospective nature of this study, we relied on the post hoc analysis of clinically obtained echocardiograms for routine surveillance from multiple institutions. We found significant variability in quality and completeness of the echocardiograms since they were not obtained with a specific research protocol in mind. Thus, not every echocardiographic measure could be obtained in each patient.

Conclusion

This multi-institutional study of 50 case-control pairs of pediatric age childhood cancer survivors demonstrated that there is a measurable longitudinal decline in many standard echocardiographic parameters of cardiac function prior to crossing the traditionally defined threshold of LV dysfunction (FS ≤28% or EF ≤50%). Cases and controls exhibited differences in indices of systolic function, diastolic function, and cardiac geometry. While power limitations of the present sample size preclude development of cardiomyopathy risk prediction algorithms, these data indicate the potential role for an expanded analysis involving a larger cohort of cardiomyopathy cases, to facilitate development of predictive models incorporating more sensitive echocardiographic indices to identify those at risk of cardiomyopathy.

Acknowledgements

We would like to thank the following research coordinators for their considerable work on this study: Cardiovascular Imaging Research Core at Emory/Children's Healthcare of Atlanta (Heather Friedman, Nicole Krupa, Kelsey Zinck, and Cortlin Yancey); Children's Healthcare of Atlanta Aflac Cancer Center (Rebecca Lewis); City of Hope Medical Center (Lanie Lindenfeld); Fred Hutchinson Cancer Research Center (Nancy Blythe); The Hospital for Sick Children (Emily Lam); University of Minnesota Masonic Children's Hospital (Susan C. Anderson). This work was supported by a generous grant from The Rally Foundation, Atlanta, Georgia, and the National Institutes of Health (R01 CA211996).

Funding: This work was supported by a generous grant from The Rally Foundation, Atlanta, Georgia, and the National Institutes of Health (R01 CA211996).

Abbreviations

TTE	Transthoracic Echocardiography
FS	Fractional Shortening
EF	Ejection Fraction
PW	Pulsed Wave
TDI	Tissue Doppler Imaging

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Perspectives

Competencies in Medical Knowledge

This study demonstrates that there is a measurable decline in echocardiographic parameters of cardiac systolic function, diastolic function, and size in pediatric age childhood cancer survivors prior to the development of overt cardiac dysfunction. Even four years prior to overt dysfunction, cases exhibited a decline in LV systolic function (both FS and EF), diastolic function (mitral E/A), and size (LVEDD) compared with matched controls.

Translational Outlook

Future studies should consider an expanded analysis involving a larger cohort of pediatric cancer survivors with cardiomyopathy to facilitate the development of predictive models, incorporating echocardiographic indices, to allow for accurate identification of those at risk prior to the development of overt cardiac dysfunction.

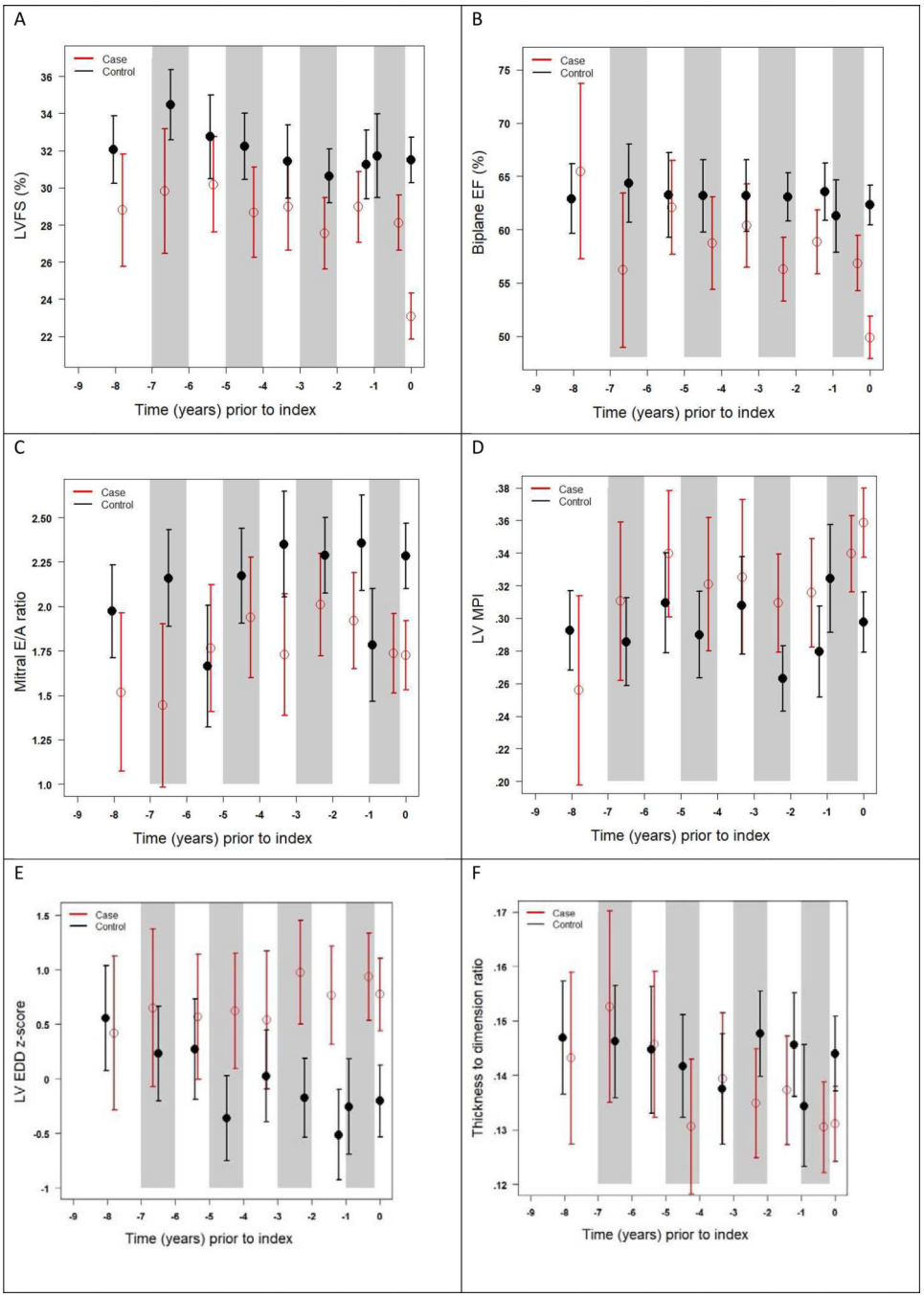
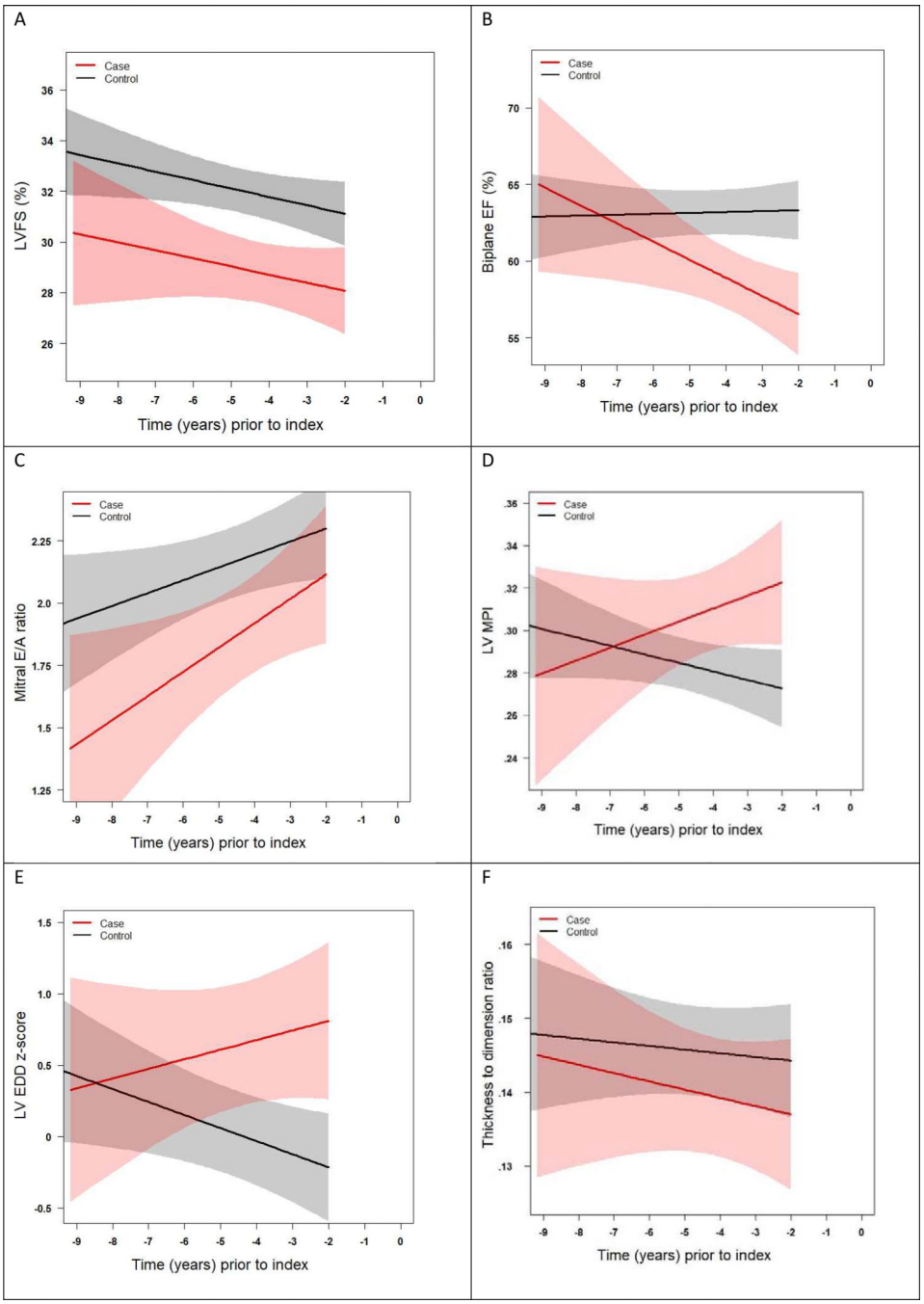


Figure 1. Least Square Means for Echocardiographic Functional Parameters Across Time Periods Prior to Cardiomyopathy

Mean estimates (cases: red open circles; controls: black closed circles) with 95% confidence intervals (cases: red bars; controls: black bars) for categorical time periods prior to cardiomyopathy diagnosis (or index time for controls; denoted as time “0”) of (A) left ventricular fractional shortening [FS], (B) biplane Simpson’s derived ejection fraction [EF], (C) pulsed wave Doppler mitral E/A ratio, (D) pulsed wave Doppler derived myocardial performance index [MPI], (E) left ventricular end-diastolic dimension [LVEDD], and (F) left ventricular wall thickness to dimension ratio. Shaded areas represent the same time period

included in each category, with estimates and bars placed on the x-axis at the median time within the given period.



Central Illustration. Longitudinal Changes in Echocardiographic Functional Parameters Excluding Data from the 2 Years Prior to Cardiomyopathy.

Fitted line plots up to two years prior to cardiomyopathy, with 95% confidence intervals of (A) left ventricular fractional shortening [LVFS], (B) biplane Simpson's derived ejection fraction [EF], (C) pulsed wave Doppler mitral E/A ratio, (D) pulsed wave Doppler derived myocardial performance index [MPI], (E) left ventricular end-diastolic dimension [LVEDD], and (F) left ventricular wall thickness to dimension ratio. Cardiomyopathy cases denoted by

red line and controls denoted by black line, both based on a linear model. Time “0” denotes time point when cardiomyopathy was diagnosed

Table 1.

Demographic and treatment characteristics of matched cardiomyopathy cases and controls

Characteristics	Cases	Controls	P-value[2]
	N=50	N=50	
Female, n (%)	18 (36)	22 (44)	0.414
Race/ethnicity, n (%)			
White, non-Hispanic	26 (56)	27 (63)	0.547[3]
Black	7 (15)	4 (9)	
Asian	7 (15)	7 (16)	
Hispanic	4 (9)	5 (12)	
Multiracial	2 (4)	0	
Unknown	4 (8)	7 914)	
Mean age at cancer diagnosis, years (SD)	8.0 (5.5)	7.2 (4.6)	0.431
Year of cancer diagnosis, n (%)			0.773
1991–1999	8 (16)	7 (14)	
2000–2005	17 (34)	15 (30)	
2006–2009	17 (34)	22 (44)	
2010–2015	8 (16)	6 (12)	
Cancer diagnosis, n (%)			0.127
Leukemia	14 (28)	14 (28)	
Lymphoma	11 (22)	15 (30)	
Sarcoma	14 (28)	18 (36)	
Other solid tumor	11 (22)	3 (6)	
Doxorubicin exposure, n (%)	41 (82)	42 (84)	0.790
Median dose, mg/m^2 (IQR)	260 (225–375)	300 (200–375)	0.934
Daunorubicin exposure, n (%)	17 (34)	14 (28)	0.516
Median dose, mg/m^2 (IQR)	120 (95–300)	100 (100–300)	0.732
Mitoxantrone exposure, n (%)	5 (10)	5 (10)	1.000
Median dose, mg/m^2 (IQR)	48 (48–50)	48 (48–48)	n-e
Idarubicin exposure, n (%)	1 (2)	2 (4)	0.557
Cumulative anthracycline dose, mg/m^2 (IQR)[1]	280 (200–450)	300 (200–450)	0.994
Radiotherapy affecting the heart, n (%)	22 (44)	21 (42)	0.839
Years of follow-up (cancer diagnosis to last follow-up), n (%)			0.588
<10 yrs	23 (46)	29 (58)	
10+	27 (54)	21 (42)	
Years of follow-up from cancer diagnosis to 1st abnormal echo, n (%)			n/a
<2	17 (34)	n/a	
2–9	17 (34)	n/a	

Characteristics	Cases	Controls	P-value[2]
10+	16 (32)	n/a	
Age at 1st abnormal echo in years, n (%)			
0–9	7 (14)	n/a	
10–14	17 (34)	n/a	
15–19	20 (40)	n/a	
20–24	4 (8)	n/a	
25–35	2 (4)	n/a	
Treated for cardiomyopathy, n (%)	27 (54)	n/a	
History of heart transplant, n (%)	1 (2)	n/a	
Mean age at last follow-up, years (SD)	18.3 (5.2)	17.2 (4.4)	0.224

Abbreviations: n/a, not applicable; n-e, not estimable

[1] Based on the following conversion for doxorubicin equivalence (daunorubicin 0.5, epirubicin 0.67, idarubicin 3.0, and mitoxantrone 10.0)

[2] Comparison of cases and controls based on chi-square test for categorical values; t-test or Wilcoxon for continuous values

[3] White non-Hispanic vs. other

Table 2.

Differences, derived by least square mean (LSM) (95% confidence intervals), of centrally quantified echocardiographic parameters between cases and controls as a function of time prior to the index time point (i.e., cardiomyopathy diagnosis)*

	≥6 years prior to index	4 to <6 years Prior to index	2 to <4 years prior to index	<2 years prior to index	Index timepoint	All times prior to index	>2 years prior to index
LV Systolic Function							
2D derived FS, %	4.0 (1.2, 6.7) p=0.005	3.1 (0.7, 5.5) p=0.013	2.8 (0.7, 4.8) p=0.008	3.0 (1.0, 4.8) p=0.003	8.4 (6.7, 10.1) p<0.001	3.2 (1.9, 4.5) p<0.001	3.3 (1.7, 4.8) p<0.001
Biplane EF, %	2.8 (−3.2, 8.8) p=0.364	2.8 (−1.4, 7.0) p=0.194	4.8 (1.5, 8.1) p=0.006	4.6 (1.6, 7.6) p=0.004	12.4 (9.8, 15.0) p<0.001	3.7 (1.3, 6.1) p=0.003	3.5 (0.5, 6.4) p=0.023
Mitral S' TDI, m/sec	−0.005 (−0.025, 0.015) p=0.602	0.003 (−0.013, 0.019) p=0.700	0.007 (−0.007, 0.021) p=0.316	0.007 (−0.004, 0.018) p=0.193	0.027 (0.017, 0.038) p<0.001	0.003 (−0.005, 0.011) p=0.469	0.002 (−0.009, 0.012) p=0.745
Septal S' TDI, m/sec	−0.005 (−0.014, 0.003) p=0.234	0.003 (−0.004, 0.010) p=0.406	0.003 (−0.004, 0.009) p=0.421	−0.003 (−0.008, 0.003) p=0.366	0.012 (0.007, 0.017) p<0.001	−0.001 (−0.004, 0.003) p=0.778	0.000 (−0.004, 0.005) p=0.952
LV Diastolic Function							
Mitral PW E/A ratio	0.59 (0.21, 0.96) p=0.002	0.07 (−0.27, 0.40) p=0.699	0.45 (0.16, 0.74) p=0.002	0.24 (−0.02, 0.50) p=0.069	0.56 (0.32, 0.80) p<0.001	0.34 (0.16, 0.51) p<0.001	0.37 (0.16, 0.58) p<0.001
Mitral E' (m/sec)	0.014 (−0.018, 0.046); p=0.405	0.004 (−0.022, 0.029) p=0.784	0.013 (−0.010, 0.036) p=0.268	−0.001 (−0.017, 0.016) p=0.930	0.045 (0.029, 0.061) p<0.001	0.007 (−0.007, 0.021) p=0.307	0.010 (−0.007, 0.027) p=0.257
Mitral E/E' ratio	0.10 (−1.62, 1.81) p=0.913	−0.38 (−1.69, 0.93) p=0.567	0.06 (−1.23, 1.35) p=0.927	−0.26 (−1.15, 0.62) p=0.560	−0.77 (−1.63, 0.08) p=0.078	−0.12 (−0.92, 0.67) p=0.762	−0.08 (−1.04, 0.89) p=0.878
Septal E' TDI, m/sec	−0.018 (−0.035, −0.002) p=0.032	0.010 (−0.004, 0.023) p=0.150	0.008 (−0.004, 0.021) p=0.192	−0.002 (−0.013−0.009) p=0.751	0.018 (0.009, 0.028) p<0.001	0.000 (−0.008, 0.007) p=0.918	0.000 (−0.009, 0.009) p=0.991
Septal E/E' ratio	1.74 (0.33, 3.16) p=0.016	−0.46 (−1.61, 0.69) p=0.431	−0.26 (−1.35, 0.83) p=0.639	−0.16 (−1.09, 0.76) p=0.729	−0.07 (−0.90, 0.76) p=0.867	0.21 (−0.46, 0.89) p=0.533	0.34 (−0.47, 1.15) p=0.413
LV Combined Systolic/ Diastolic Function							
PW Doppler −derived MPI	0.006 (−0.036, 0.048) p=0.788	−0.030 (−0.065, 0.004) p=0.088	−0.032 (−0.064, 0.001) p=0.055	−0.026 (−0.055, 0.003) p=0.084	−0.061 (−0.088, −0.034) p<0.001	−0.021 (−0.039, −0.003) p=0.026	−0.019 (−0.041, 0.003) p=0.093
	>6 years prior to index	4 to <6 years Prior to index	2 to <4 years prior to index	<2 years prior to index	Index timepoint	All times prior to index	>2 years prior to index
TDI−derived MPI	0.020 (−0.043, 0.084) p=0.536	−0.042 (−0.091, 0.008) p=0.100	−0.032 (−0.075, 0.011) p=0.144	0.001 (−0.041, 0.043) p=0.962	−0.063 (−0.101, −0.026) p=0.001	−0.013 (−0.042, 0.016) p=0.374	−0.018 (−0.053, 0.017) p=0.314

	≥6 years prior to index	4 to <6 years Prior to index	2 to <4 years prior to index	<2 years prior to index	Index timepoint	All times prior to index	>2 years prior to index
LV Size and Geometry							
Posterior wall thickness, z-score	−0.26 (−0.81, 0.30) p=0.364	−0.11 (−0.58, 0.35) p=0.628	−0.16 (−0.57, 0.25) p=0.437	−0.03 (−0.39, 0.33) p=0.867	0.10 (−0.21,0.41) p=0.532	−0.14 (−0.42, 0.14) p=0.330	−0.18 (−0.52, 0.16) p=0.305
End diastolic dimension, z-score	−0.28 (−1.04, 0.47) p=0.462	−0.87 (−1.49, −0.25) p=0.006	−1.09 (−1.64, −0.55) p<0.001	−0.81 (−1.31, −0.32) p=0.001	−1.18 (−1.62, −0.74) p<0.001	−0.77 (−1.19, −0.34) p<0.001	−0.75 (−1.24, −0.26) p=0.003
Thickness to dimension ratio	−0.001 (−0.016, 0.014) p=0.864	0.005 (−0.008, 0.018) p=0.439	0.005 (−0.005, 0.016) p=0.321	0.006 (−0.004, 0.016) p=0.231	0.013 (0.004, 0.022) p=0.004	0.004 (−0.004, 0.011) p=0.323	0.003 (−0.006, 0.012) p=0.507

Abbreviations: 2D, two dimensional; EF, ejection fraction; FS, fractional shortening; LV, left ventricular; MPI, myocardial performance index; PW, pulsed wave Doppler derived; TDI, tissue Doppler imaging

*Differences were based on comparisons of LSMs from longitudinal mixed models for each measure, including an interaction between case status and time period, using an autoregressive correlation structure between echocardiograms for the same patient. For example, at the index time point, the estimated FS is 8.5% greater in controls, as compared to cases; at the <2 year time point, the estimated FS is 3.0% greater in controls as compared to cases.

Table 3.

Estimates, derived by least square means (LSM), of centrally quantified echocardiographic parameters for cases and controls during three time periods: at time of cancer diagnosis; while on cancer therapy and; after therapy up to and including the time of the index case echocardiogram*

Parameter	Case			Control			P-value
	No.	No. echo time points	LSM Estimate (95% CI)	No.	No. echo time points	LSM Estimate (95% CI)	
2D derived FS, %							
At cancer diagnosis	15	15	31 (29, 33)	11	11	35 (33, 38)	0.010
On therapy	22	44	27 (26, 29)	14	3	34 (32, 35)	≤0.001
Post-therapy	37	121	26 (25, 27)	50	181	31 (30, 32)	<0.001
Biplane EF, %							
At cancer diagnosis	6	6	62 (57, 66)	3	3	64 (58, 70)	0.523
On therapy	10	13	55 (52, 59)	7	15	64 (61, 68)	<0.001
Post-therapy	28	67	55 (53, 56)	41	99	63 (61, 64)	<0.001
Mitral PW E/A ratio							
At cancer diagnosis	13	13	1.61 (1.28, 1.94)	9	9	2.14 (1.75, 2.53)	0.035
On therapy	18	34	1.65 (1.42, 1.88)	13	33	1.78 (1.53, 2.02)	0.419
Post-therapy	37	114	1.84 (1.69, 1.99)	50	170	2.24 (2.12, 2.37)	<0.001
PW Doppler-derived MPI							
At cancer diagnosis	9	9	0.32 (0.28, 0.36)	9	9	0.29 (0.25, 0.33)	0.247
On therapy	14	26	0.33 (0.31–0.36)	13	32	0.29 (0.26, 0.31)	0.006
Post-therapy	32	82	0.34 (0.32–0.35)	50	159	0.29 (0.28, 0.30)	<0.001
LV end diastolic dimension, z-score							
At cancer diagnosis	10	10	1.10 (0.54–1.67)	6	6	0.34 (−0.32, 1.00)	0.088
On therapy	17	33	0.95 (0.53–1.38)	14	31	0.10 (−0.33, 0.53)	0.006
Post-therapy	36	100	0.66 (0.34–0.97)	47	157	−0.11 (−0.39, 0.17)	<0.001
LV thickness-dimension ratio							
At cancer diagnosis	15	15	0.14 (0.13–0.15)	11	11	0.15 (0.14, 0.16)	0.088
On therapy	22	44	0.13 (0.12–0.14)	14	35	0.15 (0.14, 0.16)	0.003
Post-therapy	37	121	0.13 (0.13–0.14)	50	182	0.14 (0.14, 0.15)	0.027

Abbreviations: 2D, two dimensional; EF, ejection fraction; FS, fractional shortening; LV, left ventricular; MPI, myocardial performance index; PW, pulsed wave Doppler derived

*LSM, 95% CIs and p-values for case-control comparisons were from longitudinal mixed models for each measure, including an interaction between case status and time period, and using an autoregressive correlation structure between echocardiograms for the same patient. For example, the estimated FS is 31% in cases at cancer diagnosis.