Title: Impact of Participation in Screening for Cardiovascular Disease and Secondary Breast Cancer on Severity at Diagnosis and Mortality in Childhood Cancer Survivors: A Childhood Cancer Survivor Study

Working Groups: Chronic Disease, Subsequent Malignancy, Cancer Control

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Background and Rationale

Approximately 15,000 pediatric patients receive a cancer diagnosis each year in the United States[1] and current 5-year survival rates are estimated to be 85%, with > 511,000 survivors of childhood cancer currently living in the US as of 2021[2, 3]. A recent analysis demonstrated an increase in average life expectancy for childhood cancer survivors from approximately 48 years in the 1970s to 57 years for those diagnosed in the 1990s[4]. With the significant increase in the number of survivors of childhood cancer, an enhanced understanding of the risks for chronic health conditions and subsequent malignancies is imperative for their long-term care. Compared to the general population, childhood cancer survivors experience 3 times the number of severe or life-threatening health conditions by the age of 50 years[5] and they have a greater than 5-fold increased risk for subsequent malignant neoplasms (SMNs) compared to the general population[6].

Cardiovascular disease (CVD) is among the most frequently observed chronic diseases among survivors, and includes heart failure, valvular disease, and stroke. Notably, a recent study found that less than 30% of patients who qualified for carotid ultrasound assessment based on risk factors completed this screening recommendation[7]. Similarly, one study demonstrated that 32.5% of female patients at their institution with previous diagnosis of Hodgkin lymphoma did not obtain the recommended echocardiogram screening for heart failure and valvular disease[8]. Another study demonstrated similar conclusions with screening rates for cardiovascular disease of only 41.4% among high-risk cancer survivors[9]. The low rates of

screening is especially concerning given the significant prevalence of CVD amongst cancer survivors with subsequent elevated mortality compared to that of the general population. One study described a prevalence of a cardiovascular event in cancer survivors up to 7%[10]. Of survivors who experienced systolic heart failure, coronary artery disease (CAD), and stroke, 10-year all-cause mortalities were 30%, 6%, and 29%, respectively, compared to 14%, 14%, and 4%, among sibling controls[10].

SMNs within the cancer survivor cohort are defined as histologically new, non-recurrent invasive cancers. Subsequent breast and colorectal cancers are among the few SMNs that have established screening guidelines based on childhood cancer treatment exposures[11, 12]. Alarmingly, one study demonstrated that among high-risk cancer survivors, only 12.6% were adherent to the aforementioned breast cancer screening guidelines[9]. Though interestingly, rates of breast cancer screening for average risk cancer survivors per the American Cancer Society screening guidelines was improved at 57.1%[9]. This suggests a low penetration of COG and other oncology guidelines in the primary care space. Similar to CVD, low rates of adherence to screening guidelines are disquieting given that cancer survivors are at higher risk compared to the general population for development of breast cancer. Specifically, female cancer survivors who received chest radiation have a cumulative risk for breast cancer at age 50 of 30%, comparable to those in the general population with a *BRCA 1/2* gene mutation[13]. One cohort study demonstrated cancer survivors with breast cancer have a nearly 3.5-fold greater mortality risk compared to a non-cancer survivor with breast cancer[13]. Notably, it appears that this increased mortality risk persists among childhood cancer survivors regardless of age at breast cancer diagnosis[14].

Survivors are considered high risk for these conditions due to clinical factors related to the primary cancer, including young age at diagnosis, chest-directed radiation, and exposure to anthracycline chemotherapy[5]. Given the high proportion of survivors exposed to these risk factors and the associated significant risk of mortality, appropriate screening for prevention and early detection of these complications remains of high importance in long term follow-up. Screening guidelines have been established through the Children's Oncology Group to help guide appropriate long-term follow-up care for survivors. Therefore, the goal of this study is to understand the impact of survivor participation in screening recommendations on late health outcomes, specifically severity at diagnosis and mortality of cardiovascular disease and secondary breast cancers.

Aims and Hypotheses

<u>Aims</u>

1. Among individuals diagnosed with CVD (specifically cardiomyopathy and valvular disease) or subsequent breast cancer, assess participation in screening (echocardiogram for targeted CVD outcomes and breast MRI and/or mammogram for breast cancer) prior to diagnosis.
2. For cardiovascular conditions (cardiomyopathy or valvular disease), we will examine the cumulative incidence and severity (CTCAE grade) of the condition when first detected and determine if participation (ever/no) and/or frequency of participation in screening is associated with grade/severity at diagnosis.

3. For subsequent breast cancer, we will examine the cumulative incidence and severity (stage, if available, or in situ vs. invasive disease) of the condition when first detected and determine if participation (ever/no) and/or frequency of participation in screening is associated with grade/severity at diagnosis.
4. Assess conditional mortality associated with each condition of interest (all cause and cause-specific mortality) and its association with participation (ever/no) and/or frequency of participation in screening.
5. In exploratory analyses, we will also examine the impact of a) attendance in a survivorship/long-term follow-up clinic, b) having a survivorship care plan, and c) routine check-up attendance on the severity of the target CVD conditions and secondary breast cancer, and all-cause and cause-specific (cardiovascular disease or breast cancer-associated) mortality when present on survey responses before the diagnosis of interest.

Hypotheses

1. In those with cardiovascular disease (cardiomyopathy or valvular disease) or subsequent breast cancer, the grade/severity at diagnosis will be lower in those that have participated in screening compared those that have not.
    a. In those that have participated in screening, those with more frequent screening will be diagnosed with the aforementioned chronic conditions at a lower grade/severity compared to those with less participation in screening
2. In those with cardiovascular disease (cardiomyopathy or valvular disease) or subsequent breast cancer, mortality will be lower in those that have participated in screening compared those that have not.
    a. In those that have participated in screening, those with more frequent screening will have lower cause specific and all-cause mortality compared to those with less participation in screening

Analysis Framework

A. Case based analysis: This analysis will include survivors enrolled in the CCSS cohort with all included cancer diagnoses from 1970-1999 who developed a cardiovascular condition (cardiomyopathy or valvular disease) or subsequent breast cancer after the CCSS baseline survey.
    a. Descriptive characteristics of the cohort including age at diagnosis, sex, race, ethnicity, childhood malignancy, attained age, time from initial diagnosis, decade of diagnosis (1970s, 80s, 90s)
    b. Environmental/lifestyle exposures (time-varying or most recent values prior to CVD/breast cancer onset): smoking status (ever smoked more than 100 cigarettes, yes/no)[15], alcohol use (yes/no/average drinks per week), physical activity (maximum metabolic equivalent of task hours/week [MET-h/wk]), BMI (time-varying prior to outcomes of interest), lifestyle score (0-4)[15]
    c. Baseline sociodemographic characteristics:
        i. Individual level (time-varying or most recent values prior to CVD/breast cancer onset): Educational attainment, household income, health insurance status

B. Outcomes of interest post-baseline questionnaire: Disease severity based on common terminology criteria for adverse events (CTCAE) grade for cardiovascular disease, histology (in situ vs invasive) and stage for subsequent breast cancer (if available), and mortality (secondary to cardiovascular disease, breast cancer, and all-cause).
C. Primary predictor of interest: participation in screening
    a. Cardiovascular disease: echocardiogram, MUGA scan, cardiac MRI
        i. For cardiovascular disease, high screening engagement is defined as within 5 years, and low screening engagement is defined occurring as greater than 5 years ago
    b. Breast Cancer: mammogram, breast MRI
        i. For breast cancer, high screening engagement is defined as within 2 years, and low screening engagement is defined as occurring greater than 2 years ago.
D. Therapeutic exposures within five years of childhood cancer diagnosis: treatments for these patients may include chemotherapy, HCT, and/or radiation therapy.
    a. Specific chemotherapy of interest is anthracyclines due to risk of cardiovascular side effects[16]. Chemotherapy will be considered both as yes/no and cumulative dose variables.
    b. Radiation information includes TBI (yes/no), cranial irradiation (yes/no), neck irradiation (yes/no), axillary irradiation (yes/no), chest radiation (yes/no), heart dose, and maximum dose to exposed body region
    c. HCT (yes/no)
E. Other predictors of interest post-completion of baseline questionnaire and on a survey completed prior to the diagnosis CVD or secondary breast cancer: survivorship clinic attendance, routine check-up attendance, presence of any non-cardiac grade 3+ chronic health conditions in addition to the total number/burden of chronic conditions, or secondary malignancy prior to baseline survey, timing of clinic visits (never, <1 year ago, 1-2 years ago, >2 to <5 years ago, ≥5 years ago, had one but do not know when, do not know if ever had one).

Statistical Approach

We will first assess which patients have reported the subsequent conditions of interest, cardiovascular disease (cardiomyopathy or valvular disease) or subsequent breast cancer on any survey that was completed after the baseline questionnaire through the Follow Up 7 survey. The rationale for excluding conditions of interest from the baseline questionnaire is due to requiring that the presence of the conditions of interest occurred after screening and other covariates to avoid reverse causation bias. Then these patients will be classified as having undergone screening (Yes/No) for that condition prior to the diagnosis. For analyses considering screening frequency, survivors with the chronic health conditions of interest and who completed 2 or more surveys where screening information was queried will be evaluated. The CCSS questionnaires have assessed if and when the survivor underwent various screening studies, including a) an echocardiogram, b) MUGA scan, c) cardiac MRI, d) mammogram, e) breast MRI. See Table B summarizing which screening studies were assessed on each CCSS questionnaire. In those that have participated in screening, we will quantify their frequency of

participation in screening on responded surveys that were completed prior to the survey at which the target condition (CVD or secondary breast cancer) was reported on. This will allow for better assessment of the pattern of screening over time among those who filled out >1 survey.

Study Limitations

There are several limitations to this study and the data set that are important to note. One such limitation regarding the available data is the inability to distinguish between studies (echo or mammogram, for example) ordered for screening compared to diagnostic due to development of symptoms which will be addressed in the final manuscript of this project. We will also attempt to avoid double counting screening participation based on observing the dates at which the follow up surveys were completed and reported screening occurred. Our plan is to also limit obtaining data for participants with pre-existing conditions, who had a particular condition diagnosed prior to the baseline survey.

Table A. CCSS Questionnaires by Year of Initial Distribution

Questionnaire	**Year**
Baseline	1992
Follow Up 1	2000
Follow Up 2	2003
Follow Up 3	2005
Follow Up 4	2007
Follow Up 5	2014
Follow Up 6	2017
Follow Up 7	2019
Follow Up 8*	2023

*Unclear if FU8 SMN data will be frozen and available at the time of data analysis

Table B. Summary of screening questions and if they are included across CCSS questionnaires.

Screening Test	**Baseline**	**FU1**	**FU2**	**FU3**	**FU4**	**FU5**	**FU6**	**FU7***
Echocardiogram	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Mammogram	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Breast MRI	No	No	No	No	Yes	Yes	Yes	Yes
Attendance at primary care	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Received a care plan	No	No	Yes	No	No	Yes	Yes	Yes
Survivorship Clinic Attendance	No	No	Yes	No	Yes	Yes	Yes	Yes

*Will include FU7 for screening behaviors if FU8 SMN data is frozen in time for analysis

Table C. Summary of definition of positive screening responses across CCSS questionnaires.

Screening Test	Baseline	FU2	FU4	FU5	FU6	FU7*
Echocardiogram	"Never/lower/higher/engagement	"Never/lower/higher/engagement	"Never/lower/higher/engagement	"Never/lower/higher/engagement	"Never/lower/higher/engagement	"Never/lower/higher/engagement
Mammogram	"Yes (Age?)/No"	"Never/lower/higher/engagement	"Never/lower/higher/engagement	"Never/lower/higher/engagement	"Never/lower/higher/engagement	"Never/lower/higher/engagement
Breast MRI	N/A	N/A	"Never/lower/higher/engagement	"Never/lower/higher/engagement	"Never/lower/higher/engagement	"Never/lower/higher/engagement
Attendance at primary care	Yes	"Yes/No"	"Yes/No"	"Yes/No"	"Yes/No"	Frequency response
Received a care plan	N/A	"Yes/No/Don't Know"	N/A	"Yes/No/Not Sure"	"Yes/No/Not Sure"	"Yes/No/Not Sure"
Survivorship Clinic Attendance	N/A	"Yes/No"	"Yes/No"	Time varying response	Time varying response	Time varying response

*Will include FU7 for screening behaviors if FU8 SMN data is frozen in time for analysis
**Across the table, for cardiovascular disease, high screening engagement is defined as within 5 years and low screening engagement is defined as greater than 5 years. For breast cancer, high screening engagement is defined as within 2 years and low screening engagement as defined as greater than 2 years.

Aim 1: In those with cardiovascular disease and subsequent breast cancer, assess participation in screening. The chronic health conditions of interest are cardiomyopathy, valvular disease and breast cancer. Among those with these conditions, descriptive statistics will be used to summarize how many participated in relevant screening prior to diagnosis of the conditions.

Aims 2-3: For all examined conditions, we will explore the grade/severity at diagnosis and determine its association with screening participation and subsequent frequency of participation in screening.
Cardiovascular disease will be graded using CTCAE version 4.03. Breast cancer stage is available for a subset of breast cancer cases (from Turcotte K08 ancillary study, concept 23-01). Logistic regression will be used, adjusting for treatment variables and relevant demographic characteristics, to assess whether screening participation (yes/no) and/or frequency (across 2+ surveys) is associated with lower (CTCAE grade < 3 or cancer stage 0/I/II) vs. higher (CTCAE grade ≥ 3 or cancer stage III/IV) severity disease.

Aim 4: For all examined conditions, we will explore the conditional mortality associated with each condition of interest (all cause and cause-specific mortality) to assess if participation and frequency of participation in screening results in decreased mortality.

Among survivors who develop the conditions above, we will compare both condition-specific mortality and all cause mortality where the time at risk will begin at diagnosis of the condition, with censoring at last follow-up for those without events. For patients who develop any of the chronic health conditions, the cumulative incidence of all cause mortality will be estimated with the Kaplan-Meier method and compared with the log-rank test between those participating in screening vs those that have not. Cause-specific mortality probabilities will be estimated considering other causes of death as competing risks and screening-defined groups will be compared with Gray's test. The Cox proportional hazards model can be fitted to test the association between participating in screening and all cause and cause-specific mortality risk. Cox models will be adjusted for age, sex (for cardiovascular disease), race, ethnicity, treatment exposures (anthracycline dose, radiation (dose and body specific region), smoking exposure, and alcohol exposure, physical activity, BMI, lifestyle score, and social demographic factors (educational attainment, household income, health insurance status).

Exploratory Aim 1: Examine the impact of a) attendance in a survivorship/long-term follow-up clinic, b) having a survivorship care plan, and c) routine check-up attendance on the severity of the target CVD conditions and secondary breast cancer, and all-cause and cause-specific (cardiovascular disease or breast cancer-associated) mortality when present on survey responses prior to the diagnosis of interest. Using the methods described above, the cumulative incidence of i) all-cause and cause-specific mortality and ii) by grade/stage of disease, stratified by exposures a-c which are attendance in a survivorship/long-term follow-up clinic, having a survivorship care plan, and routine check-up attendance. Separate Cox proportional hazards models can be fitted to test the association between exposures a-c and all cause and cause-specific mortality risk, as well as risks for developing grade ≥ 3 cardiovascular disease or stroke or stage III/IV breast cancer.

Proposed Tables and Figures

Table 1. Cohort Characteristics

Variable	Total Cohort (N=)	Survivors with cardiovascular disease (cardiomyopathy and valvular disease) (N=)	Survivors with breast cancer (N=)
Age at diagnosis (mean, SD)			
Age at last follow-up			
<10			
10-19			
20-29			
30-39			
40-49			
≥50			
Sex (%)			

Female			
Male			
Decade of diagnosis			
1970-79			
1980-89			
1990-99			
Race/Ethnicity (%)			
Black, NH			
White, NH			
Asian, NH			
Hispanic			
Other			
Primary Cancer			
ALL			
AML			
Other leukemia			
Astrocytoma			
Medulloblastoma, PNET			
Other CNS			
Hodgkin lymphoma			
NHL			
Wilms tumor			
Neuroblastoma			
STS			
Ewing sarcoma			
Osteosarcoma			
Other bone			
Radiation therapy			
None			
Any site			
Chest			
Brain or spine			
Abdomen			
Pelvis			
CED; mg/m^2			
None			
Any			
1-<4,000			
4,000-<8,000			
8,000-<12,000			
12,000-<16,000			
16,000-<20,000			
≥20,000			
Anthracycline; mg/m^2			

None			
Any			
1-<100			
100-<250			
250-<400			
≥400			
Smoking			
Never			
Ever			
Current			
Risky Drinking*			
Yes			
No			
Heavy Drinking*			
Yes			
No			
Physical activity (mean MET-hours/week)			
Vital status			
Alive			
Dead			

*Risky drinking defined as > 6 per day for men and > 5 per day for women at least once per month in the last year. Heavy drinking defined as > 4 drinks per day or 14 per week for men, > 3 per day, or 7 per week for women

Table 2. Cohort characteristics for those who participated in screening compared to those that did not.

Variable	Total Cohort (N=)	Survivors who participated in screening activities(N=)	Survivors who did not participate in screening activities (N=)
Age at diagnosis (mean, SD)			
Age at last follow-up			
<10			
10-19			
20-29			
30-39			
40-49			
≥50			
Sex (%)			
Female			
Male			
Decade of diagnosis			
1970-79			

1980-89			
1990-99			
Race/Ethnicity (%)			
Black, NH			
White, NH			
Asian, NH			
Hispanic			
Other			
Primary Cancer			
ALL			
AML			
Other leukemia			
Astrocytoma			
Medulloblastoma, PNET			
Other CNS			
Hodgkin lymphoma			
NHL			
Wilms tumor			
Neuroblastoma			
STS			
Ewing sarcoma			
Osteosarcoma			
Other bone			
Radiation therapy			
None			
Any site			
Chest			
Brain or spine			
Abdomen			
Pelvis			
CED; mg/m^2			
None			
Any			
1-<4,000			
4,000-<8,000			
8,000-<12,000			
12,000-<16,000			
16,000-<20,000			
≥20,000			
Anthracycline; mg/m^2			
None			
Any			

1-<100			
100-<250			
250-<400			
≥400			
Smoking			
Never			
Ever			
Current			
Risky Drinking			
Yes			
No			
Heavy Drinking			
Yes			
No			
Physical activity (mean MET-hours/week)			
Vital status			
Alive			
Dead			

*Risky drinking defined as > 6 per day for men and > 5 per day for women at least once per month in the last year. Heavy drinking defined as > 4 drinks per day or 14 per week for men, > 3 per day, or 7 per week for women

Table 3. Outcomes by frequency of screening participation

Condition	N (total)	Screening on 1 Prior Survey	Screening on 2+ Prior Surveys	p-value
Cardiovascular				
High Screening Engagement				
Low Screening Engagement				
Breast cancer				
High Screening Engagement				
Low Screening Engagement				

For cardiovascular disease, high screening engagement is defined as within 5 years and low screening engagement is defined as greater than 5 years. For breast cancer, high screening engagement is defined as within 2 years and low screening engagement as defined as greater than 2 years.

Table 4. Mean age at condition diagnosis, by screening participation

Condition	Mean Age (IQR) at diagnosis for no participation in screening	Mean Age(IQR) at diagnosis for participation in screening	P-value
Cardiomyopathy			
Valvular disease			
Breast cancer			

Table 5. Risk for mortality by screening participation, all cause and stratified by condition

Outcome	HR (Previous Screening vs. No Previous Screening)	95% CI	P-value
All-cause mortality			
Cardiovascular death			
Breast cancer death			

Table 6. Odds of presenting with a severe condition, based on screening participation

Outcome	OR (Previous Screening vs. No Previous Screening)	95% CI	P-value
Heart failure or valve disease (≥G3)			
Breast cancer (stage III/IV)			

Table 7. Disease severity, by survivorship clinic attendance, survivor care plan, and routine check-up attendance

	Attendance at Survivorship Clinic, N (%)	Provided with a survivorship care plan, N (%)	Routine check-up attendance, N (%)
Overall cohort			
Cardiovascular disease			
Grade < 3			
Grade ≥ 3			
Breast cancer			
Stage 0,I,II			
Stage III, IV			
Any above condition			

Lower severity			
Higher severity			

Table 8. Cumulative incidence of all-cause & cause specific mortality, by participation in screening, attendance at survivorship clinic, receipt of survivor care plan, and routine check-up attendance

	At risk	**15-year cumulative incidence**	**95% CI**
All cause ● No participation in screening recommendations ● Participation in screening recommendations ● Attendance at survivorship clinic ● No attendance at survivorship clinic ● Receipt of survivor care plan ● No receipt of survivor care plan ● Routine check-up attendance ● No routine check-up attendance			
Death from cardiovascular disease ● No participation in screening recommendations ● Participation in screening recommendations ● Attendance at survivorship clinic ● No attendance at survivorship clinic ● Receipt of survivor care plan			

● No receipt of survivor care plan ● Routine check-up attendance ● No routine check-up attendance			
Death from breast cancer ● No participation in screening recommendations ● Participation in screening recommendations ● Attendance at survivorship clinic ● No attendance at survivorship clinic ● Receipt of survivor care plan ● No receipt of survivor care plan ● Routine check-up attendance ● No routine check-up attendance			

Figures. Cumulative incidence curves by a) participation in screening, b) attendance at survivorship clinic, c) receipt of survivor care plan, and d) routine check-up attendance. Separate plots for:

- Cardiovascular disease, by grade
- Breast cancer, by stage
- Mortality (all-cause and cause-specific)

Figures. Forest plot of adjusted hazard ratios by participation in screening, for all cause and cause-specific mortality

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