

## Overall and cardiac-specific survival following serious cardiovascular events in childhood cancer survivors

Working groups: (1) Epi/Biostats, (2) Chronic Diseases

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### **BACKGROUND & RATIONALE**

Cardiovascular disease is the second leading cause of death among survivors of childhood cancer (1, 2). Data from the Childhood Cancer Survivor Study and other cohorts and studies have shown that long-term survivors of childhood cancer have an increased risk of premature cardiovascular disease (3-6). Whether an increased prevalence of risk factors, including anthracycline chemotherapy, radiation, age at exposure, genetic predisposition, and conventional cardiovascular risk factors alone can explain the profound impact of cardiovascular disease on mortality in survivors is unclear. Worse conditional survival after a diagnosis of serious cardiovascular disease may also contribute to the increased mortality of survivors of childhood cancer. However, survival after a diagnosis of a major cardiac event in childhood cancer survivors has not been previously investigated in a large survivor cohort.

There is increasing evidence to suggest that outcomes after incident myocardial ischemia may be worse among cancer survivors at large vs. the general population. In a retrospective study of adult-onset cancer survivors who underwent percutaneous coronary intervention (PCI), an increased risk of cardiovascular morbidity and death compared with cancer naïve patients was noted up to 6 years later (7). After acute myocardial infarction, an increase in 30-day and 1-year all-cause mortality and heart failure has also been observed (8). There is also evidence of higher all-cause mortality in patients with adult-onset cancer and radiation-associated coronary artery disease (9). However, an observation of increased mortality following a diagnosis of ischemic heart disease among cancer survivors has not been uniformly reported. In a study of patients undergoing PCI for ST elevation myocardial infarction (STEMI), cardiac mortality was higher for patients with an acute diagnosis of cancer, but not for those with a duration of 6 months or greater between cancer diagnosis and PCI (10).

In addition to outcomes disparities for survivors with coronary artery disease, cardiovascular morbidity and mortality may also be higher for some survivors with heart failure. Higher rates of early post-operative mortality after cardiac transplant have been observed for patients with radiation-induced cardiomyopathy (11, 12). In contrast, several studies have demonstrated no difference in mortality rates in patients who underwent transplant for anthracycline-related cardiomyopathy (13, 14). Oliveira et al. observed similar rates of survival but an increased need for right ventricular support prior to transplant (15). Patients receiving durable mechanical circulatory support (MCS), also appeared to have an

increased need for right ventricular support but otherwise experienced similar survival compared with other groups (16, 17). While these observations are informative, the populations studied are not exclusively cancer survivors and with very few survivors of childhood cancer at best.

Although most evidence suggests similar survival rates after advanced heart failure therapy (transplant or MCS) for cancer survivors with an anthracycline-related cardiomyopathy, data regarding survival rates for those who do not receive advanced therapies are still indeterminate. Araujo-Gutierrez et al. found higher survival rates while Felker et al. observed higher mortality rates in survivors with anthracycline-related cardiomyopathy who did not undergo advanced treatment (13, 17). Overall, much of the evidence base is derived from the experience of adult-onset breast cancer survivors, and research examining these outcomes specifically in childhood cancer survivors is lacking.

Valvular disease is also a known complication of some cancer therapies. In survivors with radiation-related valvular disease, surgical repair or replacement is associated with poor 5-year survival (18). In addition, durability of atrioventricular valve repairs may be limited due to the continuing progressive deleterious effects of radiation therapy (19). In patients with radiation-induced aortic valve disease, high mortality has been observed when surgical replacement was pursued (20). However, survival was similar to those with other valvular disease etiologies when a percutaneous transcatheter aortic valve replacement approach was used (21). The observation of increased short- and long-term mortality in patients undergoing surgical procedures for radiation-related cardiovascular disease extends beyond valve surgery to other cardiac surgeries as well (22). Therefore, it is possible that this difference in mortality may signify a higher overall surgical risk for individuals with previous radiation exposure and suggests that the optimal treatment strategy for cancer survivors with radiation-related valvular disease may be different than for other populations. Additionally, more recent evidence has suggested that anthracyclines may cause direct valvular toxicity as well as functional valvular disease (23-25). Outcomes related to anthracycline-related valvular disease are understudied, and whether disparities in outcomes exist when compared to other etiologies of valvular disease remains unknown.

One potential explanation for these seemingly discordant findings may be the heterogeneity of previously studied populations. Most previously studied populations have included all individuals with a history of cancer (most likely predominantly adult-onset cancers) or radiation-mediated cardiac disease. Type of cancer, age at diagnosis, and treatments received after the development of cardiovascular disease likely all affect outcomes and are not well described in these cohorts. Recent work by Potts et al. demonstrating increased in-hospital mortality for lung cancer survivors undergoing PCI, but not for survivors of breast, colon, or prostate cancer supports this concept (26). Differences in clinical management strategies between cancer survivors and cancer naïve patients may also contribute. For example, some studies have found that cancer survivors undergoing PCI were more likely to be treated with bare metal stents and less likely to receive cardioprotective medications after an acute myocardial infarction (7, 8).

Research focused on mortality conditioned on the onset of serious cardiovascular disease specifically among survivors of childhood cancer relative to the general population has not been published to our knowledge. Therefore, this study will help provide the critical foundation necessary for further exploration into secondary prevention strategies to improve outcomes in survivors of childhood cancer after a diagnosis of cardiovascular disease.

## **SPECIFIC AIMS**

Aim 1: Among childhood cancer survivors (CCS) who self-report cardiomyopathy/heart failure (CHF), coronary artery disease (CAD), stroke, and valve disease, assess the long-term survival following the respective diagnosis of each one of these cardiovascular conditions compared with siblings and/or available general population sample(s) (e.g., NHANES, CARDIA) with similar conditions.

*Hypothesis 1.1: Overall survival in CCS following the development of one of these serious cardiovascular (CV) conditions will be lower compared with siblings or the general population affected by the same condition.*

*Hypothesis 1.2: Even after accounting for competing causes of death, cardiac-specific survival in CCS following the development of one of these serious CV conditions will remain lower in CCS vs. siblings or the general population affected by the same condition.*

Aim 2: Among CCS affected by one of the serious CV conditions, overall survival and cardiac-specific survival will be differentially influenced by prior cancer treatment exposures.

*Hypothesis 2.1: Compared with CCS without a history of radiation (to head, neck, or chest) or anthracycline chemotherapy, those exposed will have lower overall survival and cardiac-specific survival.*

*Hypothesis 2.2: Compared with siblings or the general population, CCS without a history of radiation (to head, neck, or chest) or anthracycline chemotherapy will also have lower cardiac-specific survival, but survival will be better compared with CCS with a history of cardiotoxic therapies.*

Exploratory Aim: Based on the chronic condition CTCAE grading system, compare the latency and timing of CHF (grades 2->5), CAD (grades 3->5), stroke (grades 4->5), and valve disease (grades 1->5) progression from lower to higher grades among CCS and siblings.

## **ANALYSIS PLAN**

Population: Entire CCSS (original and expanded cohorts) and sibling population (who will serve as a comparison group). As the number of siblings with serious CV events of interest may be low (in our prior analyses with ~4000 siblings, approximately 15-30 siblings reported each of these conditions by age 50), we will also use data from the following publicly available datasets that represent a general population experience:

- NHANES linked with the National Death Index (NDI; available from NHANES 1999-2014 survey years, linked through year 2015 NDI data). From this dataset, we will construct an age-, sex-, and race/ethnicity-matched sample with similar (to longer) follow-up duration as the CCSS sample (<https://www.cdc.gov/nchs/data-linkage/mortality-public.htm>)
- CARDIA (Coronary Artery Risk Development in Young Adults; <https://www.cardia.dopm.uab.edu/>). This cohort enrolled ~5000 18-30 year-old Black and White young adults between 1985-1986, and features approximately 30 years of periodic in-person follow-up, and thus is fairly comparable to the CCSS experience in terms of age, follow-up duration, and era. Given the sample size, we would expect approximately similar numbers of serious CV events in this group as we will observe in CCSS siblings.

- Other cardiovascular-focused cohorts with publicly available datasets (e.g., Framingham, ARIC, MESA, CHS) typically feature individuals who were enrolled in middle age (and thus represent an older life trajectory/experience), and/or began in a more historic era so that outcomes are less comparable due to changes in medical/surgical management of CV diseases over time.

Outcomes of interest:

- Overall survival (inverse of all-cause mortality)
- CV condition-specific survival (and CV condition-specific mortality, and non-CV condition-specific mortality)

Serious CV conditions of interest: to be based on CCSS’ chronic disease CTCAE definitions (see Table 1 below; gray shaded grade level represents the minimum grade that will be considered for analysis). For each of these CV outcomes, if limited to those occurring  $\geq 5$ -years from cancer diagnosis, there are approximately 600-1000 events among the CCSS cohort (per Yan Chen, 7/18/2020 email).

**TABLE 1.**

Condition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cardiomyopathy / heart failure (CHF)	N/A*	Not on medications	Requiring medications	Heart transplant	Death
Coronary artery disease (CAD)	N/A	N/A	Anti-anginal medications only	Requiring procedure (catheterization, angioplasty, bypass graft)	Death
Stroke	N/A*	N/A*	N/A*	Stroke	Death
Valve disease	History of stiff/leaky valves only	N/A*	N/A	Valve replacement	Death

N/A = not applicable, as not defined by CCSS chronic disease matrix

\*While CCSS has assigned ICD codes for this grade, we will not include it in our analysis

- NHANES: similar to CCSS in that it features self-reported medical conditions, including specific questions regarding congestive heart failure (MCQ160b), coronary heart disease (MCQ160c), angina (MCQ160d), heart attack (MCQ160e), and stroke (MCQ160f). Age at first onset is also ascertained. NB: Valve disease is not ascertained by NHANES. More detailed “grading” of heart failure will not be possible given the available NHANES questions. The degree of detail available in relation to mortality will be limited in the public use dataset, as it will only feature broad death categories (e.g., heart disease, stroke, cancer, chronic respiratory disease, and several other common causes of death). A more detailed restricted-use dataset is available (for a fee of ~\$7000 for 15-years of follow-up; and requires a separate application and approval process) and includes underlying and contributing causes of death as supplied by the NDI.
- CARDIA: Clinical in-person assessments supplemented with participant self-report. Primary cardiovascular outcomes of interest are then adjudicated by the study (<https://www.cardia.dopm.uab.edu/study-information/endpoints/endpoints-forms>). As such the outcomes grading available to CARDIA will be more refined than the CCSS CTCAE grades. We will attempt to map them as closely as possible to the CCSS definitions to facilitate comparisons.

#### Other covariates of interest:

- Demographic
  - Age at cancer diagnosis
  - Year of cancer diagnosis
  - Sex
  - Race/ethnicity
  - Insurance status [this variable is cross-sectional, so may be more difficult to incorporate into a time-to-event analysis]
- Cancer treatment [we will explore dose but depending on the complexity of the analyses, may not be able to incorporate dose information into all models]
  - Chemotherapy
    - Anthracycline / anthraquinone (Y/N, dose)
    - Alkylator (Y/N, dose [CED])
    - Platinum (Y/N, dose)
    - Vinca alkaloid (Y/N)
  - Radiotherapy
    - Brain (Y/N, dose)
    - Neck (Y/N, dose)
    - Heart (Y/N, dose, including heart substructure dose data as available)
- CV risk factors [will explore modeling these as time-dependent variables, although if these are already present at time of the specific CV outcome of interest, then they would be classified as a “baseline” variable]
  - Hypertension requiring medications, age at onset
  - Dyslipidemia requiring medications, age at onset
  - Diabetes requiring medications, age at onset
  - Smoking, age at onset, years total smoked if no longer current smoker
  - Second cancer (SMN), age at onset
  - Some other variables like physical activity and medical screening practices are available in the CCSS dataset and may influence subsequent cardiovascular risk, but are cross-sectional. Therefore, while we will consider them, they may be difficult to model in a time-dependent fashion.

#### Methods:

- Overall survival can be estimated using Kaplan-Meier method, censoring at time of last follow-up. Comparisons between survivors and siblings can be done via Cox proportional hazard models. Depending on the outcome and given the suspected small number of events among siblings and the general population samples, we will consider pooling sibling and general population data to improve the precision of estimates. The decision to directly pool datasets vs. analyze in a more segregated fashion (i.e., akin to a meta-analysis) will be made after general population datasets are made available and a detailed comparison can be made as to their comparability in data structure and coding to CCSS data. Overall, any final comparisons with survivors can be patterned after the figures used by Moskowitz et al, in their work describing conditional survival after breast cancer (27); example enclosed below.
- CV-specific survival following the development of each condition (CHF, CAD, stroke, and valve disease) can be depicted via cumulative incidence curves showing CV-specific mortality rates over time. The relative hazards of experiencing CV-specific mortality between survivors and siblings will also be estimated using Cox proportional hazard models. We recognize that these

rates and risks may provide different and important perspective on our outcomes of interest given that competing risks present among CCS may result in a lower CV mortality risk even if the CV mortality rate is similar.

- There are rarely some CCS who may have >1 serious CV condition (e.g., CHF following CAD or vice versa).(28) For this analysis, we will only focus on the first event for analysis (i.e., if CAD occurs prior to CHF, that individual will be used for the CAD-specific analysis but not the CHF-specific analysis). For the rare individual with synchronous (concurrent) presentation of multiple serious CV conditions, those individuals can contribute as cases to the analyses of multiple conditions, but we will evaluate the sensitivity of our estimates by excluding them in sensitivity analyses.
- Cox models will use time since onset of the CV condition as the index time point, and adjust for sex, age at index, race/ethnicity, index year, and insurance status at time of index (or before; if possible). Models will also examine the influence of baseline chemotherapy and radiotherapy exposures (listed above), and other CV risk factors (hypertension, dyslipidemia, diabetes, smoking, and SMN).
- We can also plot the survival probabilities after each CV event, showing the probability of survival and death due to CV causes or other causes, modeled after the work by Moskowitz et al (27); see Figure example below.

Limitations:

- Some individuals in the CCSS cohort will present with Grade 5 CV outcomes only, without a prior history of lower-grade outcome. We will still report those events as excluding them would bias our estimates of conditional survival. As such, our survival curves may start at <100% due to these individuals already being deceased prior to “baseline”.

**TABLE 2.** Frequency of <INSERT CV condition\*>

	No. cases (%)†	No. deaths overall (%)	No. deaths due to condition (%)	No. deaths due to other conditions (%)
Siblings				
General population sample(s)				
CCSS overall				
No cardiotoxic exposures				
With cardiotoxic exposures				

\*We will generate these frequencies for each of the 4 serious CV conditions of interest (CHF, CAD, stroke, and valve disease)

†These will be limited to the 1<sup>st</sup> serious CV condition as discussed above (e.g., if CHF follows CAD, then only CAD will be counted). We will note the number of individuals with multiple (synchronous) CV conditions as well. Finally, either as an expanded part of this table or as a sub-table, we also will examine the frequency of cases by the initial CTCAE grade at presentation (per Table 1 above)

**TABLE 3.** Overall and cause-specific survival for <INSERT CV condition\*>

	Overall survival HR (95% CI)	CV-specific survival† HR (95% CI)
CCS – no cardiotoxic exposures‡	Ref	Ref
Sibling		

CCS – anthracycline only		
CCS – radiotherapy only§		
CCS – anthracycline & radiotherapy§		

\*Separate models will be created for each of the target outcomes: CHF, CAD, stroke, and valve disease. While the table being shown features stratified groups, we will also explore presenting results where these risk factors are presented, adjusted for each other.

†We can consider CHF, CAD, stroke, and valve disease specific survival, however, given the close association between these conditions, it may be difficult to distinguish between them in terms of causes of death (e.g., myocardial infarction is more common after HF and vice versa).

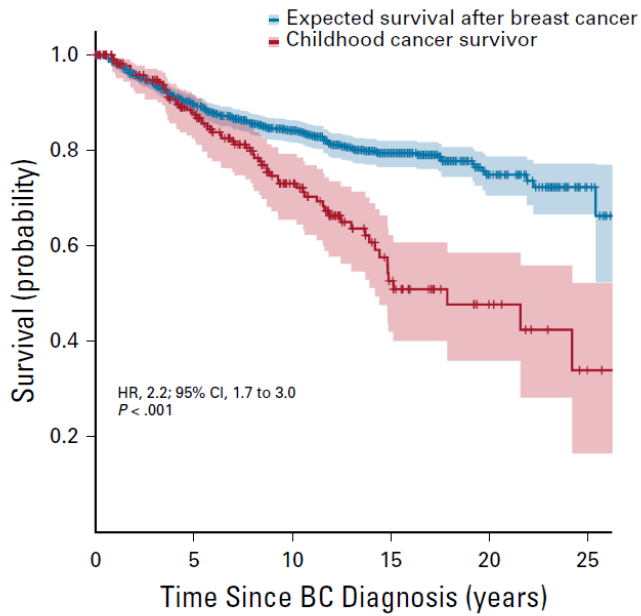
‡In our prior analyses based on the original CCSS cohort, we observed approximately 70 cases of CAD and stroke among CCS by age 50 without prior cardiotoxic cancer treatment exposures (out of n~7000-8000); there was only approximately 20 cases of CHF in this no cardiotoxic exposure group (n~5000).(29) These numbers should be larger once the CCSS expansion cohort is included and we would be reasonably confident that the sample sizes should be sufficient in order to allow us to compare differences between CCS with and without cardiotoxic exposures.

§Chest/heart radiotherapy exposure for CHF, CAD, and valve disease; neck and brain radiotherapy exposure will also be considered for stroke

**We propose to generate the additional FIGURES as part of this analysis:**

- Figure 1: Survival of CCS vs. siblings with CHF, overall, and CV-specific survival
- Figure 1A: Survival of CCS vs. siblings with CHF, overall, and CV-specific survival, limited to Grades 3-4
- Figure 1B: Survival of CCS vs. siblings with CHF, overall, and CV-specific survival, limited to Grade 4
- Figure 2: Survival of CCS vs. siblings with CAD, overall, and CV-specific survival
- Figure 2A: Survival of CCS vs. siblings with CAD, overall, and CV-specific survival, limited to Grade 4
- Figure 3: Survival of CCS vs. siblings with stroke, overall, and CV-specific survival
- Figure 4: Survival of CCS vs. siblings with valve disease, overall, and CV-specific survival
- Figure 4A: Survival of CCS vs. siblings with valve disease, overall, and CV-specific survival, limited to Grade 4

Examples of figures from Moskowitz et al's analysis of conditional survival after breast cancer (27):



No. at risk	0	5	10	15	20	25
Controls	1,095	895	633	297	87	15
Childhood cancer survivors	228	157	84	31	11	2

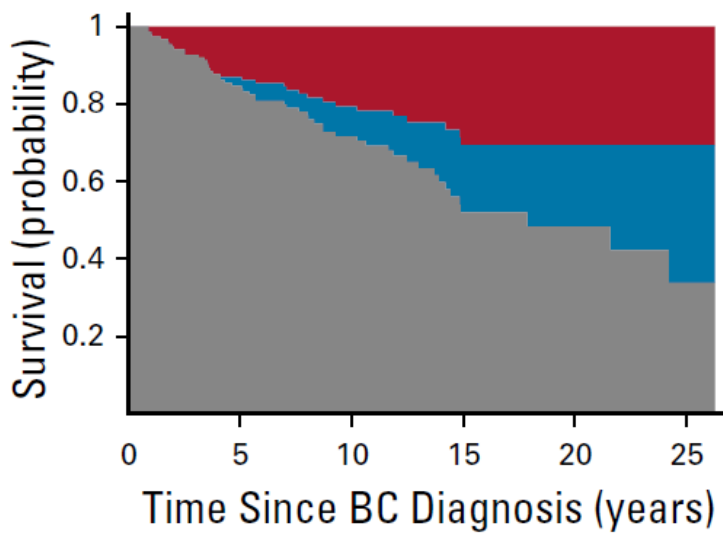
**Controls**

5-year estimate (95% CI) 90% (88% to 91%)  
 10-year estimate (95% CI) 84% (82% to 86%)

**Childhood cancer survivors**

5-year estimate (95% CI) 88% (82% to 92%)  
 10-year estimate (95% CI) 73% (65% to 80%)

**Childhood cancer survivors**





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