Title: Prevalence and Longitudinal Progression of Cardiovascular Risk Factors and Association with Serious Cardiovascular Outcomes in Childhood Cancer Survivors

Working Group: Primary: Chronic Disease Working Group
Secondary: Epidemiology/ Biostatistics

Investigators:

Wendy Bottinor, MD, MSCI	wendy.bottinor@vcuhealth.org
Scott C. Borinstein, MD, PhD	scott.c.borinstein@vumc.org
Jonathan H. Soslow, MD, MSCI	jonathan.h.soslow@vumc.org
Yutaka Yasui, PhD	yutaka.yasui@stjude.org
Debra L. Friedman, MD, MS	debra.l.friedman@vumc.org
Eric J. Chow, MD, MPH	ericchow@uw.edu
Kevin C. Oeffinger, MD	kevin.oeffinger@duke.edu
Emily Tonorezos, MD	emily.tonorezos@nih.gov
Nirupa Raghunathan, MD	raghunan@mskcc.org
Greg Armstrong, MD, MSCE	greg.armstrong@stjude.org
Wendy Leisenring, ScD	wleisenr@fredhutch.org
Saro Armenian, DO, MPH	sarmenian@coh.org

Background and Rationale:

Dramatic advances in the treatment of childhood cancer have resulted in five-year survival rates of greater than 80% [1]. Despite this accomplishment, childhood cancer survivors face unique long-term health challenges. Cardiovascular-related death is approximately seven-fold higher in survivors than in age-matched peers, and this risk increases with time [2, 3]. Other serious cardiovascular events including coronary artery disease, heart failure, valvular disease and stroke are approximately 10 times more frequent in survivors when compared with siblings [4, 5].

The increased prevalence of serious cardiovascular disease in survivors is likely multifactorial. Treatment related risk factors are well recognized and recent data have demonstrated that modifications to contemporary cancer protocols designed to minimize exposures to cardiotoxic treatments have reduced major cardiac events [6]. Additionally, modifiable cardiovascular risk factors are more prevalent in survivors compared with siblings [4, 7-9]. By age 50, the prevalence of hypertension and dyslipidemia among survivors is almost double that of siblings [4]. The risk for obesity is significantly higher among survivors treated for particular malignancies, such as acute lymphoblastic leukemia, and survivors are more likely to demonstrate lower levels of physical activity when compared with siblings and healthy controls[10-12].

The increased prevalence of modifiable cardiovascular risk factors in childhood cancer survivors potentiates in a near-multiplicative fashion serious cardiovascular outcomes. Compared with siblings who have similar cardiovascular risk profiles, survivors have a significantly higher incidence of serious cardiovascular events [4]. In comparison with survivors who do not have a history of cardiotoxic treatment exposure or cardiovascular risk factors, those with a history of chest radiation and hypertension are 56 times more likely to develop cardiomyopathy and the relative risks for coronary artery disease, arrhythmia, and valvular disease are 37, 19, and 107

respectively [4]. Elevated relative risks are also present for childhood cancer survivors with a history of cardiotoxic exposure and diabetes or hyperlipidemia [4]. These risks are more than additive, as demonstrated by significant relative excess risk due to interactions (RERI). For survivors treated with chest radiation who develop hypertension and at least one additional modifiable risk factor, RERIs for cardiomyopathy, coronary disease, valvular disease, and arrhythmia are 18, 28, 61, and 7, respectively [4].

Among childhood cancer survivors who have undergone hematopoietic cell transplantation, hypertension, dyslipidemia, and diabetes mellitus are independent risk factors for ischemic heart disease and cardiomyopathy [13]. Smoking, obesity, lower fruit/vegetable intake, and low physical activity are associated with these cardiovascular risk factors [13].

Recognition of the link between traditional modifiable risk factors and accentuated cardiovascular risk in survivors has led to recommendations for earlier and closer surveillance by the American Heart Association, American Academy of Pediatrics, and Children's Oncology Group. Suggested screening includes yearly blood pressure and cardiac exams, lipid, and blood glucose screening, electrocardiograms, and serial cardiovascular imaging studies performed every two to five years based on treatment and patient related risk factors [14, 15]. Despite this, a report from Hudson et al in 2013 showed traditional modifiable cardiovascular risk factors are under-diagnosed [16]. Gibson et al have also demonstrated under-treatment with over 20% of survivors diagnosed with hypertension having uncontrolled high blood pressure [17].

While an augmented relationship between modifiable risk factors and cardiovascular outcomes in survivors has been clearly demonstrated, opportunities to further define this relationship exist. The link between cardiovascular risk factors and outcomes have not been studied in survivors who have not reported being on medications [4, 13] or who have a blood pressure less than 140/90 [18]. Given the expansion of the CCSS cohort and further extension of long-term follow-up of the entire cohort over the past 5-10 years, our objective is to update and further detail the natural history of cardiovascular risk factors and outcomes in survivors, determine whether lifestyle factors augment attributable risk for cardiovascular risk factors, determine whether lifestyle factors and cardiovascular risk factors augment attributable risk for cardiovascular events and define the relationship between risk factor severity, cancer treatment history, and cardiovascular outcomes. This knowledge will help to shape the approach to cardiovascular risk factor management for childhood cancer survivors in the future.

Specific Aims

Aim 1: Investigate the baseline and longitudinal natural history of cardiovascular risk factors including hypertension, dyslipidemia, diabetes mellitus, obesity, smoking and sedentary behavior among childhood cancer survivors.

Hypothesis 1.1: The prevalence of all cardiovascular risk factors combined will be greater among survivors when compared with siblings across all ages, extending into the 6th decade of life.

Hypothesis 1.2: Among those with hypertension or diabetes mellitus, survivors will have more severe disease (higher CTCAE grade) when compared with hypertensive or diabetic siblings.

Hypothesis 1.3: Lifestyle characteristics will contribute a higher attributable risk for hypertension, dyslipidemia, and diabetes (when cumulative anthracycline and chest

radiation doses are accounted for) in survivors compared with attributable risks of the same lifestyle factors for siblings.

Aim 2: Among childhood cancer survivors exposed to cardiotoxic cancer treatments, determine if the risk for serious CV events is differentially modified by hypertension and diabetes severity and duration (determined by CTCAE grades 1-3 as applicable).

Hypothesis 2.1: There will be an incremental increase in the risk for serious cardiovascular events by anthracycline dose and risk factor severity, such that higher anthracycline dose (≥250 mg/m^2), more severe grades of hypertension (grade 2 vs grade 1) and diabetes (grades 2 and 3 vs grade 1), and longer duration since onset of hypertension or diabetes will be associated with a higher risk for serious cardiovascular events over time.

Hypothesis 2.2: There will be an incremental increase in the risk for serious cardiovascular events by chest radiation dose and risk factor severity, such that higher radiation dose (≥1500 cGy), more severe grades of hypertension (grade 2 vs grade 1) and diabetes (grades 2 and 3 vs grade 1), and longer duration since onset of hypertension or diabetes will be associated with a higher risk for serious cardiovascular events over time.

Analysis Plan

Study Population: Cancer survivor or a surrogate (parent, spouse, next of kin) who have completed a baseline questionnaire and sibling population (who will serve as a comparison group). Survivors who develop a second malignant neoplasm (SMN) or late recurrence (5 or more years from diagnosis) of primary cancer before the baseline questionnaire will be censored (i.e., SMN or late recurrence will be classified as a competing risk) as treatment information for these neoplasms was not uniformly obtained.

Outcomes of Interest:

- Cardiovascular events:
  - Congestive heart failure (CHF)
  - Myocardial infarction (MI)
  - Valvular heart disease
  - Arrhythmia
  - Cardiac death
- Cardiovascular risk factors:
  - Hypertension
  - Dyslipidemia
  - Diabetes mellitus
  - Obesity
  - Smoking
  - Sedentary behavior

Outcomes are based on CCSS' adaptation of the Common Terminology Criteria for Adverse Events and defined in Table A

Table A. Primary cardiovascular outcomes of interest

Grade	Heart Failure	Myocardial infarction	Valvular Disease	Arrhythmia

3	Cardiomyopathy requiring medication	MI, angina, or coronary heart disease not requiring cardiac catheterization but on anti-anginal medication	None	Arrythmia requiring pacemaker
4	Cardiac transplantation	MI requiring cardiac catheterization/ angioplasty or CABG	Heart valve replacement	Ventricular fibrillation
5	Death from cardiomyopathy	Death from MI, ischemic heart disease, or atherosclerosis	Death from valvular heart disease	Death from dysrhythmia

Covariates of Interest:

Demographic

- Race/Ethnicity
- Age at cancer diagnosis
- Year of cancer diagnosis
- Sex
- Cancer diagnosis

Cancer Treatment

- Anthracycline / anthraquinone (Y/N, dose)
- Alkylators (Y/N, dose)

Radiotherapy

- Brain (Y/N)
- Heart exposure (Y/N, dose)

Modifiable Cardiovascular Risk Factors

- Diabetes mellitus (CTCAE definitions below, Table B)
- Hypertension (CTCAE definitions below, Table B)
- Dyslipidemia (CTCAE definitions below, Table B)
- Smoking status over time
- Obesity defined by BMI (determined at each survey prior to the onset of an outcome of interest or end of follow-up)
- Sedentary lifestyle defined as 0 days of physical activity in last 7 days (determined at each survey prior to the onset of an outcome of interest or end of follow-up)

Table B. Risk factor grading of potentially modifiable cardiovascular risk factors based on CCSS' adaptation of the Common Terminology Criteria for Adverse Events

Grade*	Hypertension	Dyslipidemia	Diabetes
1	Not requiring medication	(Not applicable)	Not requiring medication
2	Requiring medication	Requiring medication	Oral agents only

3	(Not applicable)	(Not applicable)	Requiring insulin

* Grades 4/5 not applicable for these conditions

Methods:

Survivors who have completed the baseline questionnaire will be considered eligible. Demographic, disease, and treatment characteristics will be tabulated (Example Table 1).

For **Aim 1 (Hypotheses 1.1 and 1.2)**, given the cross-sectional nature of lifestyle variables (i.e. obesity, physical activity) [4] the prevalence and grade (as applicable) of hypertension, dyslipidemia, diabetes, obesity, smoking, and sedentary behavior among childhood cancer survivors and siblings across all ages will be tabulated by using reported data from each completed questionnaire while accounting for age at time of questionnaire completion. This data will be used to describe the age-specific prevalence and grade of hypertension, dyslipidemia, and diabetes among survivors with a history of cardiotoxic treatment exposure, survivors without a history of cardiotoxic treatment exposure, and siblings. The prevalence of hypertension, dyslipidemia, diabetes, obesity, smoking, and sedentary behavior will be modelled as a function of age and survivor groups (with and without cardiotoxic treatment exposures) vs. siblings, adjusted for race and sex using generalized linear models with log-link function and Poisson errors. Based on these models, age-specific comparisons of prevalence between survivor groups and siblings will be calculated and illustrated using Prevalence Ratios (PR) and 95% Confidence intervals (CI). Interactions between age and survivor/sibling group will be evaluated to determine whether the PRs vary across age. Similar models/comparisons will be evaluated for each of the different grade levels of the cardiovascular risk factors where relevant. (i.e., grades 1-2 hypertension, grade 2 hypertension, grades 1-3 diabetes, grades 2-3 diabetes, grade 3 diabetes) (Example Tables 2 and 3).

For **Aim 1 (Hypothesis 1.3)** at each survey prior to the onset of one of the cardiovascular risk factor outcomes or prior to end of follow-up, obesity, smoking history (defined as any history of smoking), and current sedentary behavior will be generated. At each survey prior to the onset of one of the cardiovascular events or prior to end of follow-up, obesity, smoking history (defined as any history of smoking), current sedentary behavior, and cardiovascular risk factors will be generated. Analyses using data from all relevant surveys will pair the information about these factors with subsequent age of onset of hypertension (CTCAE grades 1 and 2), dyslipidemia (CTCAE grade 2), and diabetes (CTCAE grades 1, 2 and 3) so that at each survey time point a survivor contributes information about history of behaviors and current status of their outcome variable. Timing/age of first report of adverse behavior variables will be explored in relation to onset of the condition in these models. Multivariable loglinear regression models will be fit to determine the association of history of behavioral factors with the development of hypertension, dyslipidemia, and diabetes, with the ultimate goal of determining the attributable risk (AR) for the development of each of these cardiovascular risk factors due to obesity, smoking history, and sedentary behavior after accounting for cumulative anthracycline and chest radiation doses (Example Figure 1) [19]. These attributable risks in survivors will be compared with those generated for siblings based on similar methods (without adjustment for cancer treatment).

For **Aim 2 (Hypotheses 2.1 and 2.2)**, the cumulative incidence of our outcomes of interest including CHF, MI, valvular heart disease, arrhythmia, and cardiac death as defined in Table A, will be calculated into the 6th decade of life (Example Figure 2). Death, secondary cancers, and late recurrence will be considered competing risk events (the latter two due to the potential for unknown additional treatments likely received). We will carry out sensitivity analyses regarding

the impact of treating secondary cancers and recurrences as competing risks. Multivariable Poisson models with piecewise time since diagnosis (or attained age) variables will be used to calculate the Relative Risks and 95% CI of cardiovascular events according to the grade of the cardiovascular risk factors present, adjusted for cumulative anthracycline dose, and chest radiation, age at cancer diagnosis or current age, sex, race, and behavioral factors. We will carry out sensitivity analyses regarding the impact of duration of documented cardiovascular risk factors on cardiac events. Since the impact of behavioral factors could be mediated through cardiovascular risk factors, we will also carry out sensitivity analyses examining these factors together and in separate models for cardiac events. Time at risk for cardiac events will begin at 5 years after cancer diagnosis will end at the first cardiac outcome of interest, death, development of a secondary cancer, late recurrence, or completion of the last questionnaire. Only the first occurrence of a cardiac outcome of interest will contribute to the analysis. Interactions between cardiovascular risk factors and treatment variables will be evaluated. If important, RRs for cardiovascular risk factors will be presented separately for relevant treatment histories. Relative excess risk due to interactions (RERI) will be calculated to identify associations that are more than additive. Similar to Aim 1, estimates of AR will be calculated for cardiovascular risk factors and behavioral risk factors for cardiac events.

Limitations:

Some childhood cancer survivors may inaccurately report medication use for hypertension, dyslipidemia, or diabetes and therefore CTCAE grading may be incorrectly assigned. It will not be possible to account for survivors who experience a down-grading based on CTCAE definitions of their cardiovascular risk factors over time. Some covariates of interest, for example the development of obesity, may be first reported on the same survey that hypertension, dyslipidemia, and diabetes are first reported. This will limit analyses of the attributable risk for these covariates. Additionally, the available duration of follow up data may limit our ability to characterize cardiovascular risk factors and outcomes in younger survivors.

Example Tables

Table 1: Basic Demographic Data and Characteristics

Characteristic	Survivor	Sibling
Race/Ethnicity		
Age at cancer diagnosis		
Sex		
Cancer diagnosis		N/A
Anthracycline / anthraquinone (Y/N, dose)		N/A
Brain (Y/N, dose)		N/A
Neck (Y/N, dose)		N/A
Chest (Y/N, dose)		N/A
Diabetes		
Hypertension		
Dyslipidemia		
Smoking status		
BMI		
Sedentary lifestyle		

Table 2: Prevalence ratio of hypertension, dyslipidemia, and diabetes among survivors (stratified by cardiotoxic treatment history) compared with a sibling reference group

	Survivor +cardiotoxic tx Prevalence ratio (CI 95%)	Survivor -cardiotoxic tx Prevalence ratio (CI 95%)
Hypertension		
Current Age: <20		
20-29		
30-39		
40-49		
50-59		
≥ 60		
Dyslipidemia		
Current Age: <20		
20-29		
30-39		
40-49		
50-59		
≥ 60		
Diabetes		
Current Age: <20		
20-29		
30-39		
40-49		
50-59		
≥ 60		
Obesity		
Current Age: <20		
20-29		
30-39		
40-49		
50-59		
≥ 60		
Smoking		
Current Age: <20		
20-29		
30-39		
40-49		
50-59		
≥ 60		
Sedentary Behavior		
Current Age: <20		
20-29		
30-39		
40-49		
50-59		

≥ 60		

Table 3: Prevalence ratios and 95% confidence intervals for hypertension (grade 1 and 2) and diabetes (grades 1-3) for Survivors vs. siblings

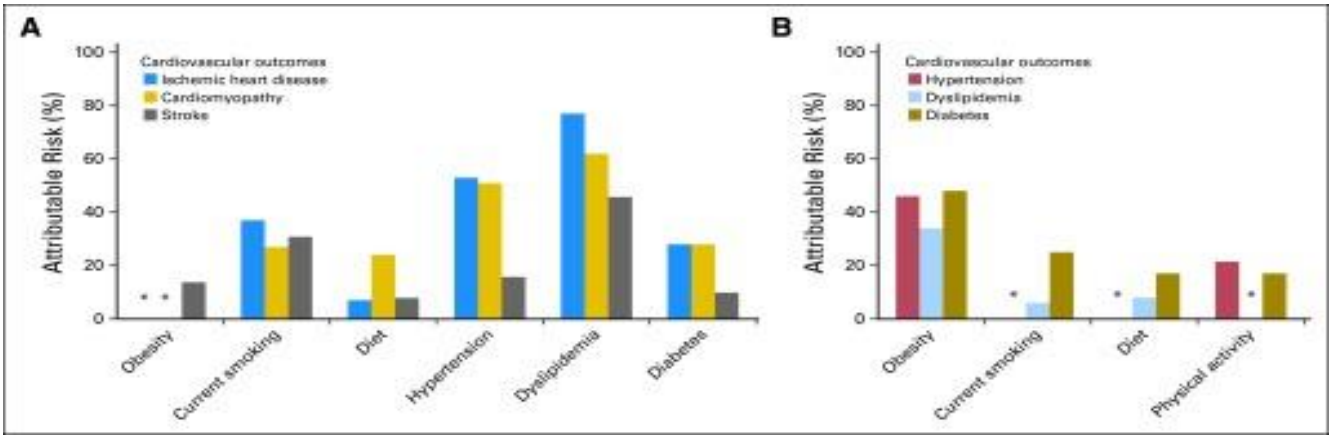
	HTN Grade 1 OR	HTN Grade 1 95% CI	HTN Grade 2 OR	HTN Grade 2 95% CI	DM Grade 1 OR	DM Grade 1 95% CI	DM Grade 2 OR	DM Grade 2 95% CI	DM Grade 3 OR	DM Grade 3 95% CI
PR										

Table 4: Relative Risk and Relative Excess Risk for Serious Cardiovascular Events Based on Treatment Exposure and Cardiovascular Risk Factors
*Note this table may be simplified if cumulative dose of anthracycline and cumulative dose of radiation do not show evidence of interactions with cardiovascular risk factors, or if limited cell sizes require pooling some exposure strata

Cardiovascular risk factor	Survivor Treatment history	CHF	Coronary disease	Valvular disease	Arrhythmia	Death
HTN grade 1 vs. no HTN	Anthracycline <250 mg/m^2 Anthracycline ≥ 250 mg/m^2 Chest radiation < 1500 cGy Chest radiation ≥ 1500 cGy					
HTN grade 2 vs. no HTN	Anthracycline <250 mg/m^2 Anthracycline ≥ 250 mg/m^2 Chest radiation < 1500 cGy Chest radiation ≥ 1500 cGy					
Diabetes grade 1 Vs. no Diabetes	Anthracycline <250 mg/m^2 Anthracycline ≥ 250 mg/m^2 Chest radiation < 1500 cGy Chest radiation ≥ 1500 cGy					
Diabetes grade 2 Vs. no Diabetes	Anthracycline <250 mg/m^2 Anthracycline ≥ 250 mg/m^2 Chest radiation < 1500 cGy					

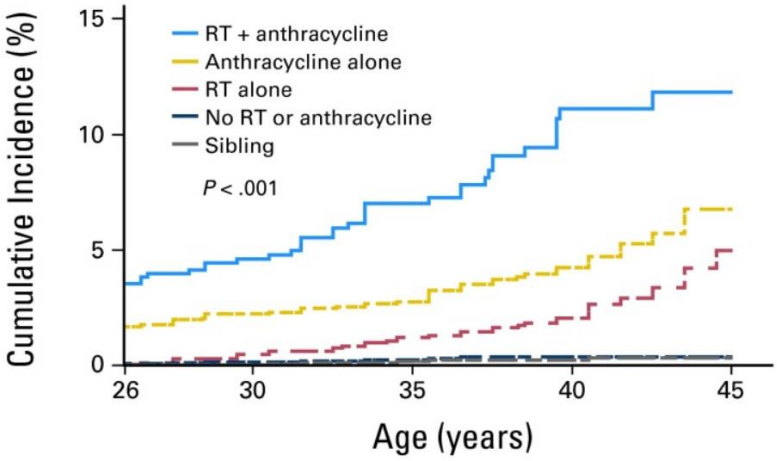
	Chest radiation ≥ 1500 cGy					
Diabetes grade 3 Vs. no diabetes	Anthracycline <250 mg/m^2 Anthracycline ≥ 250 mg/m^2 Chest radiation < 1500 cGy Chest radiation ≥ 1500 cGy					

Example Figure **1** from Chow et. al. Influence of Conventional Cardiovascular Risk Factors and Lifestyle Characteristics on Cardiovascular Disease After Hematopoietic Cell Transplantation**[13]**



Attributable risk percent (AR%) associated with risk factors (*x*-axis) for (A) serious cardiovascular outcomes and (B) related conditions among exposed hematopoietic cell transplantation survivors. AR% assumes risk factor has causal relationship with outcome. Estimates adjusted for sex, nonwhite race/ethnicity, current age, obesity, current smoking, diet, recreational physical activity time, and, if applicable, hypertension, dyslipidemia, and diabetes status. (*) AR% < 1%.

Example Figure 2 from Armstrong et al Modifiable Risk Factors and Major Cardiac Events Among Adult Survivors of Childhood Cancer [4]



Age-specific cumulative incidence of the four major cardiac events

References

1. Ries LAG, S.M., Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds), *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995*, in *National Cancer Institute, SEER Program*. 1999, NIH Pub. No. 99-4649: Bethesda, MD.
2. Mertens, A.C., et al., *Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study.* J Natl Cancer Inst, 2008. **100**(19): p. 1368-79.
3. Armstrong, G.T., et al., *Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study.* J Clin Oncol, 2009. **27**(14): p. 2328-38.
4. Armstrong, G.T., et al., *Modifiable risk factors and major cardiac events among adult survivors of childhood cancer.* J Clin Oncol, 2013. **31**(29): p. 3673-80.
5. Oeffinger, K.C., et al., *Chronic health conditions in adult survivors of childhood cancer.* N Engl J Med, 2006. **355**(15): p. 1572-82.
6. Mulrooney, D.A., et al., *Major cardiac events for adult survivors of childhood cancer diagnosed between 1970 and 1999: report from the Childhood Cancer Survivor Study cohort.* Bmj, 2020. **368**: p. l6794.
7. Chen, Y., et al., *Traditional Cardiovascular Risk Factors and Individual Prediction of Cardiovascular Events in Childhood Cancer Survivors.* J Natl Cancer Inst, 2020. **112**(3): p. 256-265.
8. Meacham, L.R., et al., *Cardiovascular risk factors in adult survivors of pediatric cancer--a report from the childhood cancer survivor study.* Cancer Epidemiol Biomarkers Prev, 2010. **19**(1): p. 170-81.
9. Oeffinger, K.C., et al., *Insulin resistance and risk factors for cardiovascular disease in young adult survivors of childhood acute lymphoblastic leukemia.* J Clin Oncol, 2009. **27**(22): p. 3698-704.
10. Hocking, M.C., et al., *Prospectively examining physical activity in young adult survivors of childhood cancer and healthy controls.* Pediatr Blood Cancer, 2013. **60**(2): p. 309-15.
11. Ness, K.K., et al., *Predictors of inactive lifestyle among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study.* Cancer, 2009. **115**(9): p. 1984-94.
12. Chow, E.J., et al., *Obesity and hypertension among children after treatment for acute lymphoblastic leukemia.* Cancer, 2007. **110**(10): p. 2313-20.
13. Chow, E.J., et al., *Influence of conventional cardiovascular risk factors and lifestyle characteristics on cardiovascular disease after hematopoietic cell transplantation.* J Clin Oncol, 2014. **32**(3): p. 191-8.
14. Kavey, R.E., et al., *Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics.* Circulation, 2006. **114**(24): p. 2710-38.
15. *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers Version 5.0*. 2018, Children's Oncology Group.
16. Hudson, M.M., et al., *Clinical ascertainment of health outcomes among adults treated for childhood cancer.* Jama, 2013. **309**(22): p. 2371-2381.

17. Gibson, T.M., et al., *Blood Pressure Status in Adult Survivors of Childhood Cancer: A Report from the St. Jude Lifetime Cohort Study.* Cancer Epidemiol Biomarkers Prev, 2017. **26**(12): p. 1705-1713.
18. Mulrooney, D.A., et al., *Cardiac Outcomes in Adult Survivors of Childhood Cancer Exposed to Cardiotoxic Therapy: A Cross-sectional Study.* Ann Intern Med, 2016. **164**(2): p. 93-101.
19. Cox, C., *Model-based estimation of the attributable risk in case-control and cohort studies.* Stat Methods Med Res, 2006. **15**(6): p. 611-25.