Childhood Cancer Survivor Study
Analysis Concept Proposal

Study Title: Incidence of Cardiac Outcomes by Treatment Era and Temporal Trends in Treatment Exposure in Adult Survivors of Childhood Cancer

Working Group: Primary: Chronic Disease Working Group
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Background and Rationale

Improvements in pediatric cancer therapies have led to an increasing number of childhood cancer survivors living into adulthood. Current estimates suggest there are over 420,000 survivors of a pediatric malignancy alive in the United States, or nearly one in every 750 adults.[1] While this estimate is projected to surpass 500,000 by 2020, it may accelerate even faster given recent data suggesting improved survival among children treated on contemporary protocols.[2] However, the impact of therapy upon the long-term health of individuals treated for cancer is substantial. The majority experience medical conditions related to their prior therapy, many of which are severe or disabling.[3,4] Appropriate surveillance may help identify early health impairments and provide an opportunity to intervene and ameliorate this long-term morbidity. Understanding the trajectory of the health risks among childhood cancer survivors becomes increasingly important as these young adults transition from pediatric, cancer-focused treatment to adult primary care.

With consistently improving survival rates, contemporary treatment protocols have focused on advancing cure rates while attempting to minimize the long-term adverse effects of therapy. This has principally been accomplished by applying multi-modal therapies, developing response-based protocols, and using clinical, molecular, and/or genetic characteristics to risk-stratify patients. Modern trials have aimed to intensify therapy for children at high risk of relapse

while reducing the intensity for those at low-risk.[5,6] Despite these changes, many of the therapeutic exposures remain the same. Recent data have confirmed a reduction in late mortality, but the impact of this strategy on long-term health remains unknown. In fact, early data suggest, while survival has improved, late morbidity may remain or even increase. Hudson and colleagues examined the health status of CCSS survivors (diagnosed 1970-1986) over 15 years and identified an increased prevalence ratio, compared to siblings, for poor general health (2.4 95%CI 2.1-2.7), functional impairment (4.5 95%CI 3.9-5.2), and activity limitations (2.4 95%CI 2.1-2.7).[7] Using the expanded CCSS cohort, Ness et al. (abstract 10020, J Clin Oncol 33(15), 2015) reported survivors treated in 1980-1989 and 1990-1999 to be at higher risk of reporting poor general health compared to those treated between 1970-1979 (RR 1.1 95%CI 1.0-1.2 and 1.2 95%CI 1.1-1.3, respectively). Evaluation of temporal changes in chronic health conditions, particularly cardiac outcomes, has not been undertaken.

Considerable cardiovascular toxicity, clinical and sub-clinical, following childhood cancer therapy has been identified and remains an important concern.[8,9] The expanded CCSS cohort permits an opportunity to examine trends in chronic cardiac conditions and the impact of changes in therapeutic exposures on these outcomes over the past three decades. Cardiotoxic exposures have varied across the years but the impact of these changes on the long-term health of cancer survivors is unknown. The prevalence of survivors in the CCSS cohort exposed to chest radiation decreased from 33% to 23% to 19% from 1970-1979, 1980-1989, to 1990-1999. However, at the same time exposure to anthracycline chemotherapy increased from 27% to 48% to 58%, with no substantial change in the prevalence of those receiving doses ≥300 mg/m^2 (15%, 20%, and 13%, respectively).[2] The proposed analysis, for the first time, will provide an understanding of whether changes in treatment over time have altered the incidence or burden of specific long-term cardiac outcomes of children treated for cancer.

Aims/Objectives:

1. Determine the cumulative incidence and cumulative burden (mean cumulative count) of adverse cardiac outcomes in the CCSS cohort (original and expanded).

   Hypothesis: The cumulative incidence and burden of cardiac disease (overall and specifically congestive heart failure, coronary artery disease, pericardial disease, valvular heart disease, and arrhythmias) will be increased in childhood cancer survivors compared to a sibling comparison group.

2. Examine the cumulative incidence and burden of cardiac outcomes by treatment era and compare the cumulative incidence and burden between survivors of each era, as well as with a sibling cohort.

   Hypothesis: While elevated compared to a sibling comparison group, the cumulative incidence of cardiac disease (overall and specifically congestive heart failure, coronary artery disease, pericardial disease, valvular heart disease, and arrhythmias) in childhood cancer survivors will significantly decrease over time (1970s, 1980s, 1990s).

   Hypothesis: The incidence of cardiac disease will be lower across decades among survivors with historical reductions in cardiotoxic (anthracyclines and cardiac radiation doses) exposures, i.e. survivors of ALL, Hodgkin lymphoma, and Wilms tumor, etc.

3. Evaluate how temporal patterns in treatment (i.e. anthracycline and cardiac radiation exposures) have impacted cardiac outcomes.

Hypothesis: Reductions in the risk of cardiac outcomes across treatment eras will be at least partially attributed to changes in treatment exposure.

Analysis Framework:

A) Outcomes of interest – per CTCAE (v4.03) criteria, Grades 3 (severe) – 5 (death)

a. Congestive heart failure
b. Coronary artery disease
c. Valvular heart disease
d. Pericardial disease
e. Arrhythmia

Cardiac conditions per CTCAE Grade

Grade	CHF	CAD	Valvular heart disease	Pericardial disease	Arrhythmia
3 (severe)	Cardiomyopathy or CHF requiring medication	MI, angina, coronary heart disease not requiring heart catheterization but on antianginal medication	None	Pericardial disease requires surgical intervention	Arrhythmia requiring pacemaker
4 (life-threatening)	Cardiac transplantation	MI requiring catheterization/PTCA, or CABG	Valve replacement	N/A	Ventricular fibrillation/ flutter
5 (death)	Death from heart failure	Death from MI, ischemic heart disease, or atherosclerosis	Death from valvular heart disease	Death from pericardial disease	Death from arrhythmia

Common Terminology Criteria for Adverse Events v4.03

Research Population:

Inclusion Criteria:

1. All CCSS survivors (diagnosed 1970-1999) and siblings (baseline, Follow-Up 2003, Follow-Up 2007, or on the Expanded cohort baseline).

Exclusion Criteria:

1. Cases and/or siblings reporting a cardiac event prior to cohort entry at five years from primary diagnosis

Explanatory Variables:

The cohort will be divided into three 10-year as well as six 5-year treatment eras across each decade (1970s, 1980s, and 1990s) based upon the date of diagnosis.

1. Age at follow up
2. Gender
3. Age at diagnosis
4. Primary cancer diagnosis
5. Year of diagnosis
6. Race/ethnicity
7. Obesity (body mass index)

a. Underweight BMI <18.5 kg/m^2
b. Normal weight BMI=18.5-24.9 kg/m^2
c. Overweight BMI=25-29.9 kg/m^2
d. Obese BMI ≥ 30 kg/m^2

8. Household income
9. Education level
10. Tobacco use
11. Hypertension (requiring medication and above)
    a. per CTCAE (v4.03) criteria, Grades 2 – 4 (requiring medication) – 5 (death)
12. Dyslipidemia (requiring medication and above)
    a. per CTCAE (v4.03) criteria, Grades 2 – 4
13. Diabetes (requiring medication and above)
    a. per CTCAE (v4.03) criteria, Grades 2 – 4
14. Cumulative anthracycline exposure
    a. <250 mg/m^2, 250 mg/m^2 to <350 mg/m^2, 350 mg/m^2 to <450 mg/m^2, 450 mg/m to <550 mg/m^2, and ≥550 mg/m^2
15. Cardiac radiation exposure
    a. None, <500 cGy, 500 to <1500 cGy, 1500 to <3500 cGy, and ≥3500 cGy
16. Family history of cardiac disease

Statistical Plan:

1. Descriptive statistics:
   a. Characteristics of survivors (demographic and treatment) and siblings (demographic) will be described, means (SD) and medians (range).

   b. Frequency of cardiac late effects will be described across 3 strata:
      i. 1970-1979
      ii. 1980-1989
      iii. 1990-1999

2. Cumulative incidence and burden (mean cumulative count) will be calculated for each cardiac late effect overall as well as stratified by treatment decade. Imputed datasets will be created to account for missing reports of age at first occurrence among subjects who did report a cardiac condition but without age of onset. Comparisons will be made across treatment era among survivors and between survivors and sibling controls (sibling controls assigned to the decade of their respective case sibling) in each treatment era.

3. Piecewise exponential models will be used to estimate rate ratios of cardiac conditions among survivors relative to the sibling comparison group in each treatment decade. Models will be adjusted for variables likely to affect cardiac outcomes such as gender, current age, tobacco, etc. Models with and without the covariates of diabetes, dyslipidemia, and hypertension will be considered and compared, as these covariates may be on the causal pathway. Potential intra-family correlation will be accounted for using Generalized Estimating Equations.

4. Piecewise exponential models will be used to estimate rates of cardiac conditions among survivors by treatment decade with and without adjusting for cardiotoxic

treatments (chemotherapy, radiation therapy, chemotherapy and radiation therapy combined). Models will be adjusted for variables likely to affect cardiac outcomes such as gender, current age, tobacco, diabetes, dyslipidemia, and hypertension, etc.

5. Changes in cardiotoxic treatment exposures (radiation to the heart and anthracyclines) will be described across 3 strata:

    i. 1970-1979
    ii. 1980-1989
    iii. 1990-1999

    This will be used in conjunction with the regression results of #4 to examine whether the strength of the association between treatment decade and cardiac conditions is attenuated by including treatment variables in the models, which would indicate the reduction of cardiovascular events over treatment era is likely attributable to changes in the cardiotoxic treatment exposures over the same time period.

References

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Table 1 Demographics and treatment characteristics by decade

Characteristics		Survivors				Siblings
Gender		**Total N=**	**1970-1979 N=**	**1980-1989 N=**	**1990-1999 N=**	**N=**
	Female					
	Male					
Current age (years)						
	Mean (SD)					
	Median (Range)					
	<20					
	20-29					
	30-39					
	40-49					
	≥50					
Age at diagnosis (years)						
	Mean (SD)					N/A
	Median (Range)					N/A
	0-4					N/A
	5-9					N/A
	10-14					N/A
	15-20					N/A
Time from cohort entry (years)						
	Mean (SD)					
	Median (Range)					
	0-4					
	5-15					
	15-24					
	25-34					
	≥ 35					
Race/ethnicity						
	Non-Hispanic White					
	Non-Hispanic Black					
	Hispanic					
	Asian					
	Other/Unknown					

Characteristics		Survivors				Siblings
Diagnosis						
	Leukemia					N/A
	Brain cancer					N/A
	Hodgkin lymphoma					N/A
	Non-Hodgkin lymphoma					N/A
	Kidney tumor					N/A
	Neuroblastoma					N/A
	Soft tissue sarcoma					N/A
	Bone cancer					N/A
Therapy						
	Surgery					N/A
	Radiation					N/A
	Chemotherapy					N/A
	Chemotherapy + radiation					N/A
	Chemotherapy + radiation + surgery					N/A
	Radiation + surgery					N/A
	Chemotherapy + surgery					N/A
Anthracycline*						
	None					N/A
	< 250 mg/m^2					N/A
	≥ 250 mg/m^2					N/A
Cardiac radiation dose						
	No cardiac radiation					N/A
	< 500 cGy					N/A
	500 to < 1500 cGy					N/A
	1500 to < 3500 cGy					N/A
	≥ 3500 cGy					N/A
Education						
	Some high school					
	High school graduate					
	Some college					
	College graduate					
	Post graduate					
Body mass index						
	< 18.5 kg/m2					
	18.5-24.9 kg/m2					
	25-29.9 kg/m2					
	≥ 30 kg/m2					

Characteristics		Survivors				Siblings
Smoking						
	Never					
	Former					
	Current					

*doxorubicin equivalents

Table 2. Rate ratios and 95% CI of cardiac outcomes compared to siblings, by treatment decade

Diagnosis	Decade	Congestive Heart Failure		Myocardial Infarction		Valvular Heart Disease		Pericardial Disease		Arrhythmia	
		Rate Ratio	(95% CI)	Rate Ratio	(95% CI)	Rate Ratio	(95% CI)	Rate Ratio	(95% CI)	Rate Ratio	(95% CI)
Siblings	1970-1979										
	1980-1989										
	1990-1999										
Leukemia	1970-1979										
	1980-1989										
	1990-1999										
CNS tumors	1970-1979										
	1980-1989										
	1990-1999										
Hodgkin Lymphoma	1970-1979										
	1980-1989										
	1990-1999										
Non-Hodgkin Lymphoma	1970-1979										
	1980-1989										
	1990-1999										
Kidney	1970-1979										
	1980-1989										
	1990-1999										
Neuroblastoma (etc.)											

*Estimates adjusted for all variables in the table as well as race, household income, education, tobacco use

Table 3. Multivariable analysis of Cardiac Conditions by Treatment and Risk Factors[*]

	Congestive Heart Failure			Myocardial Infarction			Valvular Heart Disease			Pericardial Disease			Arrhythmia		
	RR	**95% CI**	**(p)**	**RR**	**95% CI**	**(p)**	**RR**	**95% CI**	**(p)**	**RR**	**95% CI**	**(p)**	**RR**	**95% CI**	**(p)**
Gender															
Male	1.0**			1.0**			1.0**			1.0**			1.0**		
Female															
Age at diagnosis															
0-4															
5-9															
10-14															
15-20	1.0**			1.0**			1.0**			1.0**			1.0**		
Treatment Era															
1970-1979	1.0**			1.0**			1.0**			1.0**			1.0**		
1980-1989															
1990-1999															
Average Cardiac Radiation Dose[†] (cGy)															
No cardiac radiation	1.0**			1.0**			1.0**			1.0**			1.0**		
1-500															
500-1500															
1501-3499															
≥ 3500															
Chemotherapy															
Anthracycline vs. none[‡]															
< 250 mg/m^2															
≥ 250 mg/m^2															
Diabetes															
Dyslipidemia															
Hypertension															

[*]Estimates adjusted for all variables in the table as well as race, household income, education, tobacco use

** referent group

Table 4. Relative Rates of Cardiac Conditions by Treatment and Treatment Era*

	Congestive Heart Failure			Myocardial Infarction			Valvular Heart Disease			Pericardial Disease			Arrhythmia		
Treatment Era (continuous variable)	**RR**	**95% CI**	**(p)**	**RR**	**95% CI**	**(p)**	**RR**	**95% CI**	**(p)**	**RR**	**95% CI**	**(p)**	**RR**	**95% CI**	**(p)**
No adjustment for cardiotoxic therapy															
Adjustment for cardiotoxic therapy															

*Estimates adjusted for gender, age at diagnosis, attained age, race, household income, education, tobacco use

Figure 1. Consort diagram

Figure 2. Cumulative Incidence of cardiac conditions among childhood cancer survivors by treatment decade (**EXAMPLE**)

Figure 1. Cumulative Incidence and 95% CI of Cardiac Conditions Among Childhood Cancer Survivors