Childhood Cancer Survivorship Study
Analysis Concept Proposal

Study Title: Disparities in Cardiovascular Outcomes among Childhood Cancer Survivors

Working Groups: Chronic Disease, Cancer Control, Epidemiology/Biostatistics

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Background and Rationale:

Childhood cancer survivors represent a vulnerable population regarding adverse health effects related to their primary malignancy and late effects of treatment. Marked improvements in pediatric oncology care, particularly for acute lymphoblastic leukemia, over the past half century have focused on the reduction of cardiotoxic exposures.[1] Despite improvements in overall survival, significant health disparities persist in both morbidity and mortality.[2-4] Ethnic and socioeconomic disparities are well documented in cancer survivorship as well as baseline health disparities in cardiovascular risk factors among the general population.[5] Understanding whether childhood cancer modifies disparities in cardiovascular outcomes for survivors would further aid in risk stratification and inform strategies to reduce health inequity.

Cardiovascular disease is a significant cause of morbidity and mortality for childhood cancer survivors.[6,7] Chemotherapy, most notably anthracyclines, as well as chest radiation are cardiotoxic,[8] whereas other treatments are associated with the development or progression of cardiovascular risk factors such as hypertension, dyslipidemia, obesity and diabetes mellitus (DM). Socioeconomic factors influence overall cardiovascular health[9] and childhood cancer survivors report lower physical activity levels,[10] which could further exacerbated treatment-related effects. A previous study from CCSS showed an increased incidence of serious cardiac events among childhood cancer survivors compared to siblings.[7] Furthermore, cardiovascular disease represents a major cause of late mortality, second only to disease recurrence.[11] Therefore, early diagnosis and appropriate management of cardiovascular risk factors and prevention of major cardiac events represents a key target for interventions, such as preventive care and access to healthy lifestyle modifications, to reduce disparities in outcomes for childhood cancer survivors.

Clinical survivorship guidelines offer a framework for disease surveillance of late effects from cancer treatment. The Children's Oncology Group (COG) provides recommendations for screening of heart failure through periodic echocardiograms based on previous treatment exposures.[12] In addition, for survivors treated with total body irradiation (TBI), the COG recommends optimization of blood pressure, lipid management, and blood glucose for prevention of coronary artery disease. Other international guidelines[13] seek to harmonize current understanding of cardiac risk factors among cancer survivors and identify current gaps in knowledge. Indeed, novel targeted therapeutic approaches to pediatric cancers offer new challenges to quantify risk and stratify survivors to optimize long-term outcomes.[14,15] Previous work to understand the epidemiology and burden of cardiovascular outcomes for childhood cancer survivors lays the foundation for earlier detection of individuals at risk in addition to the opportunity to test the effectiveness of cardioprotective strategies, which are largely based on adult studies in the general population.[16] With the aim of prevention, at risk populations require particular attention.

There is a strong association between race/ethnicity, socioeconomic status, and cardiovascular risk factors, such as hypertension, diabetes, and obesity. In the general population, Native Americans, Hispanics, and African Americans tend to demonstrate a higher prevalence of the aforementioned risk factors.[17-19] Health disparities in the recent pediatric obesity epidemic also emphasize the importance of prevention and national efforts to curb current trends are vital to prevent long-term cardiovascular sequelae.[20,21] Baseline disparities are likely exacerbated by the cardiotoxicities of cancer treatment among childhood survivors; however, whether this excess risk is additive or a risk modifier is unclear. Patient characteristics, similar to risk stratification by cardiotoxic exposures, would inform strategies to improve late effects of cancer on childhood survivors.

Specific Aims:

Using data from the Childhood Cancer Survivorship Study (CCSS), a retrospective cohort of 24,214 survivors (including 7,542 childhood leukemia survivors), we will:

1) Determine the incidence of grade ≥2 cardiovascular risk factors (CVRF; obesity, hypertension, diabetes, dyslipidemia) among childhood cancer survivors and stratify by race/ethnicity and socioeconomic status (SES) to identify potential disparities and whether such disparities persist after controlling for additional demographic, lifestyle, and treatment exposures through multivariable Cox regression modeling, counting all occurrences of CVRF as "recurrent events" in each survivor.

   Hypotheses: Hispanic and non-Hispanic (NH) black childhood cancer survivors will have an increased incidence rate of grade ≥2 CVRF compared to white, NH survivors.

   Survivors with a lower SES (household income <$40,000) will have an increased incidence rate of grade ≥2 CVRF.

2) Using CVRFs as ordinal covariates (0, 1, 2, 3 or 4 CVRFs), utilize multivariable Cox regression modeling of grade 3-5 cardiac events to determine the CVRF effects on cardiac-event risk and their effect modification by race/ethnicity and SES.

   Hypotheses: Hispanic and NH black childhood cancer survivors will have a higher hazard ratio of cardiac events associated with the CVRF count, compared to white NH survivors.

Survivors with a lower SES will have a higher hazard ratio of cardiac events associated with the CVRF count, compared to survivors with higher SES.

3) (Exploratory) Among childhood cancer survivors with sibling pairs, attempt to control for potential unmeasured confounders (i.e., environment) and assess the survivor-sibling differences in the incidence of CVRFs and the effects of CVRF on cardiac-event risk by race/ethnicity, using the multivariable Cox regression with GEE inference.

Analysis Framework:

Study Population:

The Childhood Cancer Survivorship Study (CCSS) is a multi-institutional collaboration, which emerged due to the significant improvement in survival rates of pediatric cancer over the latter half of the twentieth century and the need to understand the long-term outcomes among survivors.[25] This retrospective cohort includes 24,214 childhood cancer survivors diagnosed between 1970 and 1999 with longitudinal follow-up and a survival of at least five years.[3,26] A series of questionnaires were administered and extensive exposure data from their cancer treatment was obtained. We will use data from all available CCSS questionnaires. Additionally, matched siblings also completed questionnaires. Corresponding sibling questionnaires will be analyzed. A total of 5,050 survivors in the original and expansion cohorts have a matched sibling to be used as controls (Table 1). For the purposes of the third aim for this study, we will include all survivors with a matched sibling (n = 5050 for all cancer diagnoses). We will use the Chronic Disease Matrix, based upon the Common Terminology Criteria for Adverse Events (CTCAE, v4.03).

Outcomes of Interest:

1) Cardiovascular Risk Factors (Grade ≥2)
   - Hypertension
   - Dyslipidemia
   - Diabetes
   - Obesity
   - NOTES: We will focus on grade 2 conditions for hypertension and dyslipidemia (on a medication). For diabetes, we will include grade 2 and grade 3/4 (diabetes with end-organ failure). Obesity will NOT be graded according to CTCAE v4.03 since class III obesity (i.e., BMI >= 30) is considered a grade 4 condition - the severity of this outcome is not consistent with our other grade 4 outcomes. Thus, we will consider obesity to be a grade ≥2. Of note, we will still evaluate different categories of obesity in the subanalysis.

2) Cardiovascular Disease (Grade 3-5) as defined by Common Terminology Criteria for Adverse Events
   - Coronary Artery Disease
   - Heart Failure
   - Arrhythmia

Explanatory Variables:

1) Age at Diagnosis

- 0 to 5-years-old
- 6 to 10-years-old
- 11 to 14-years-old
- 15 to 20-years-old

2) Race/Ethnicity
   - White, non-Hispanic
   - Hispanic
   - Black, non-Hispanic
   - Other, non-Hispanic
3) Sex
4) Socioeconomic Status
   - Educational attainment
   - Income
   - Employment Status
   - Insurance Status
   - NOTES: For analysis, we will use income to dichotomize into household income <$40,000 as low SES and household income ≥$40,000 as high SES
5) Health Behaviors
   - Smoking (Never, Former, Current)
   - Exercise
6) Treatment Exposures
   - Cumulative doxorubicin equivalent dose
   - Cumulative dose of alkylating agents
   - Glucocorticoids exposure
   - Cranial radiation therapy (none, 1-19 Gy, >= 20 Gy)

Variable	Categories	Baseline Questionnaire
Age at Diagnosis	0 to 5-years-old	
	6 to 10-years-old	
	11 to 14-years-old	
	15 to 20-years-old	
Sex	Male	A.2
	Female	
Ethnicity	Other, non-Hispanic	A.4 (A.5 for expansion cohort)
	White, non-Hispanic	
	Black, non-Hispanic	
	Hispanic	
Educational Attainment	Less than high school	O.1
	High school diploma	
	Some college or vocational	
	College graduate	
Marital Status	Married	L.1; L.2
	Living as married	
	Married formerly but not currently	
	Never married	
Employment	Employed	O.5
	Unemployed	

Household income	<$20,000	Q.8 (T.1 for expansion cohort)
	$20,000-<$40,000	
	$40,000-<$60,000	
	$60,000+	
	Unknown	
Personal income	<$20,000	Q.9 (T.3 for expansion cohort)
	$20,000-<$40,000	
	$40,000-<$60,000	
	$60,000+	
	Age <18	
	Unknown	
Insurance Status	Insured	Q.2
	Uninsured	
Smoking	Current Smoker	N.1a-f (O1-3 for expansion cohort)
	Former Smoker	
	Never Smoker	
Exercise (Days/week)	None (0)	N.9 (O15 for expansion cohort)
	Some (1-3 days/week)	
	Frequent (>3 days/week)	
Cumulative Doxorubicin Equivalent Dose	None	Medical Record Abstract Form
	1-99mg/m2	
	100-199mg/m2	
	200-299mg/m2	
	≥300mg/m2	
Alkylating Agents (CPM equivalents mg/m^2)	None	Medical Record Abstract Form
	0 to <4,000	
	≥4000-<8000	
	≥8000-12,000	
	≥12,000-<16,000	
	≥16,000-<20,000	
	≥20,000	
Mean Cardiac Radiotherapy Dose	None	Medical Record Abstract Form
	>0-9.9 Gy	
	10-19.9 Gy	
	20-29.9 Gy	
	≥30 Gy	
Glucocorticoids	Dexamethasone Yes/No	Medical Record Abstract Form
Hypertension	Grade ≥2	Refer to chronic disease matrix
Obesity	Normal (BMI 18.5 – 24.9 kg/m^2)	Refer to chronic disease matrix

	Overweight (BMI 25.0 – 29.9 kg/m^2)	
	Class 1 (BMI 30 – 34.9 kg/m^2)	
	Class 2 (BMI 35 – 39.9 kg/m^2)	
	Class 3 (≥ 40 kg/m^2)	
Dyslipidemia	Grade ≥2	
Diabetes	Grade 2, 3 or 4	Refer to chronic disease matrix
Heart Failure	Grade 3 or 5	Refer to chronic disease matrix
Coronary Artery Disease	Grade 3 or 5	Refer to chronic disease matrix
Arrhythmia	Grade 3 or 5	Refer to chronic disease matrix

Statistical Analysis:

Aim 1: Determine the incidence of grade ≥2 cardiovascular risk factors (CVRF; obesity, hypertension, diabetes, dyslipidemia) among childhood cancer survivors and stratify by race/ethnicity and socioeconomic status (SES) to identify potential disparities and whether such disparities persist after controlling for additional demographic, lifestyle, and treatment exposures through multivariable Cox regression modeling, counting all occurrences of CVRF as "recurrent events" in each survivor.

The cumulative incidence of cardiovascular risk factors (Grade 2) by age will be estimated based on the earliest recorded occurrence. The at-risk time will start at 5 years since childhood cancer diagnosis (i.e., the time of cohort entry) and end at the earliest of the time of the event of interest, death, or last questionnaire completed. Cox proportional hazards models with age as the time axis will be used to compare outcomes of interest, CVRFs individually and as "recurrent events", across ethnicity and SES among all childhood cancer survivors, adjusting for treatment exposures and lifestyle (i.e., smoking, exercise).

Aim 2: Using CVRFs as ordinal covariates (0, 1, 2, 3 or 4 CVRFs), utilize multivariable Cox regression modeling of grade 3-5 cardiac events to determine the CVRF effects on cardiac-event risk and their effect modification by race/ethnicity and SES.

The cumulative incidence of cardiac events (Grades 3-5) by age will be estimated based on the earliest recorded occurrence. The at-risk time will start at 5 years since childhood cancer diagnosis (i.e., the time of cohort entry) and end at the earliest of the time of the event of interest, death, or last questionnaire completed. Multivariable Cox regression models with age as the time axis will be used to compare cardiac events across ethnicity and SES among all childhood cancer survivors, adjusting for treatment exposures and lifestyle (i.e., smoking, exercise), and using CVRFs as time-dependent ordinal covariates. Effect modification will then be assessed by race/ethnicity and SES.

Aim 3: (Exploratory) Among childhood cancer survivors with sibling pairs, attempt to control for potential unmeasured confounders (i.e., environment) and assess the survivor-sibling differences in the incidence of CVRFs and the effects of CVRF on cardiac-event risk by race/ethnicity, using the multivariable Cox regression with Generalized Estimating Equation (GEE) inference.

The cumulative incidence of cardiovascular risk factors (Grade 2) or cardiac events (Grade 3-5) by age will be estimated based on the earliest recorded occurrence for childhood cancer survivors and their siblings. The at-risk time will start at 5 years since childhood cancer diagnosis (i.e., the time of cohort entry) and end at the earliest of the time of the event of interest, death, or last questionnaire completed. Sibling-survivor differences will be calculated and compared across race/ethnicity, using multivariable Cox regression models with GEE inference (Wei-Lin-Weissfeld model) will be constructed to determine the effects of CVRF on cardiac-event risk by race/ethnicity.

Tables and Figures:

Table 1. Demographic and Exposure Characteristics

	Race/Ethnicity			
	White, non-Hispanic	**Black, non-Hispanic**	**Hispanic**	**Other**
Age at Diagnosis				
0 to 5-years-old				
6 to 12-years-old				
13 to 20-years-old				
Sex				
Male				
Female				
Educational Attainment				
Less than high school				
High school diploma				
Some college or vocational				
College graduate				
Marital Status				
Married				
Married formerly but not currently				
Never married				
Employment				
Employed				
Unemployed				
Household Income				
<$20,000				
$20,000-<$40,000				

$40,000-<$60,000				
$60,000+				
Insurance Status				
Insured				
Uninsured				
Smoking				
Yes				
No				
Heavy Alcohol Intake				
Yes				
No				
Cumulative Doxorubicin Equivalent Dose				
None				
1-99mg/m2				
100-199mg/m2				
200-299mg/m2				
≥300mg/m2				
Alkylating Agents (CPM equivalents mg/m^2)				
None				
0 to <4,000				
≥4000-<8000				
≥8000-12,000				
≥12,000-<16,000				
Mean Cardiac Radiotherapy Dose				
None				
>0-9.9 Gy				
10-19.9 Gy				
20-29.9 Gy				
≥30 Gy				

Table 2. Cardiovascular Risk Factors by Race/Ethnicity

Race/Ethnicity	Hypertension	Dyslipidemia	Diabetes	Obesity	Recurrent Events
	Hazards Ratio (95% CI; P-value)	Hazards Ratio (95% CI; P-value)	Hazards Ratio (95% CI; P-value)	Hazards Ratio (95% CI; P-value)	Hazards Ratio (95% CI; P-value)

White, non-Hispanic (Ref)					
Black, non-Hispanic					
Hispanic					
Other					

Table 3. Cardiovascular Disease by Race/Ethnicity

Race/Ethnicity	Coronary Artery Disease		Heart Failure		Arrhythmia	
	Relative Risk (95% CI)	P-Value	Relative Risk (95% CI)	P-Value	Relative Risk (95% CI)	P-Value
White, non-Hispanic (Ref)						
Black, non-Hispanic						
Hispanic						
Other						

Table 4. Multivariable Cox Regression Modeling for Cardiovascular Risk Factors and Disease, controlling for treatment exposures

	Hypertension HR (95% CI), p-value	Coronary Artery Disease HR (95% CI), p-value	Heart Failure HR (95% CI), p-value
Age at Diagnosis			
0 to 5-years-old (Ref)			
6 to 10-years-old			
11 to 14-years-old			
15 to 20-years-old			
Sex			
Male (Ref)			
Female			
Ethnicity			
White, non-Hispanic (Ref)			
Black, non-Hispanic			
Hispanic			
Other			
Educational Attainment			
Less than high school			
High school diploma			
Some college or vocational			

College graduate (Ref)			
Marital Status			
Married (Ref)			
Married formerly but not currently			
Never married			
Employment			
Employed (Ref)			
Unemployed			
Insurance Status			
Insured (Ref)			
Uninsured			
Smoking			
Current Smoker			
Former Smoker			
Never Smoker (Ref)			

Table 5. Cardiovascular Risk Factors among Childhood Cancer Survivors and Sibling Pair by Race/Ethnicity

Race/Ethnicity	Hypertension			Dyslipidemia			Diabetes			Obesity		
	Survivor (%)	Sibling (%)	P-Value	Survivor (%)	Sibling (%)	P-Value	Survivor (%)	Sibling (%)	P-Value	Survivor (%)	Sibling (%)	P-Value
White, non-Hispanic												
Black, non-Hispanic												
Hispanic												
Other												

Table 6. Cardiovascular Disease Factors among Childhood Cancer Survivors and Sibling Pair by Race/Ethnicity

Race/Ethnicity	Coronary Artery Disease			Heart Failure			Arrhythmia		
	Survivor (%)	Sibling (%)	RR (CI)	Survivor (%)	Sibling (%)	RR (CI)	Survivor (%)	Sibling (%)	RR (CI)
White, non-Hispanic									
Black, non-Hispanic									
Hispanic									
Other									

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Appendix:

Table 1. CCSS Matched Siblings by Primary Malignancy

DXGROUP	Expanded cohort N=1028	Original cohort N=4022	All N=5050
Acute lymphoblastic leukemia	201 (40.8%)	1234 (30.7%)	1435 (33.3%)
Acute myeloid leukemia	61 (4.4%)	101 (2.5%)	162 (3.0%)
Other leukemia	17 (1.2%)	40 (1.0%)	57 (1.1%)
Astrocytomas	132 (9.4%)	311 (7.7%)	443 (8.2%)
Medulloblastoma, PNET	69 (4.9%)	110 (2.7%)	179 (3.3%)
Other CNS tumors	44 (3.1%)	88 (2.2%)	132 (2.4%)
Hodgkins disease	97 (6.9%)	533 (13.3%)	630 (11.6%)
Non-Hodgkins lymphoma	90 (6.4%)	308 (7.7%)	398 (7.3%)
Kidney tumors	73 (5.2%)	383 (9.5%)	456 (8.4%)
Neuroblastoma	122 (8.7%)	263 (6.5%)	385 (7.1%)
Soft tissue sarcoma	49 (3.5%)	351 (8.7%)	400 (7.4%)
Ewings sarcoma	37 (2.6%)	105 (2.6%)	142 (2.6%)
Osteosarcoma	32 (2.3%)	181 (4.5%)	213 (3.9%)
Other bone tumors	4 (0.3%)	14 (0.3%)	18 (0.3%)