CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal
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1. STUDY TITLE: Longitudinal Changes in Health Status of the Childhood Cancer Survivor Cohort

2. WORKING GROUP AND INVESTIGATORS: This proposed publication will be within the Cancer Control Committee. Proposed Investigators will include:

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3. BACKGROUND AND RATIONALE:

Treatment for cancer during childhood and adolescence predisposes long-term survivors to a variety of adverse effects can substantially impact their health status. The etiology of the resulting cancer-related morbidity is multi-factorial. In most cases, late treatment sequelae can be anticipated based on therapeutic exposures, but their risk and manifestation in an individual patient is influenced by a myriad of cancer- and host-related factors.[1] Cancer patients may present with pre-morbid health conditions that affect their tolerance to therapy and enhance treatment toxicity.[2-4] Genetic or familial characteristics may confer additional risks for adverse outcomes.[5-8] Treatment modalities and intensity are determined by cancer-related factors including tumor location, histology, and biology. Complications experienced during and after cancer therapy may add further morbidity. Cancer-related effects on psychosocial factors including educational achievement, employment status, and household income influence access to health insurance, health care and remedial services.[9-11] Survivors with cancer-related subclinical organ dysfunction may experience an earlier onset or accelerated progression of adverse health conditions commonly associated with aging. Finally, lifestyle issues such as tobacco and alcohol use, sun exposure, dietary practices, and physical activity may augment the risk of specific health problems predisposed by cancer treatment. Identification of sociodemographic, treatment, and behavioral characteristics associated with increased risk of physical morbidity and psychological maladjustment after childhood cancer is critical for the development of health screening and health promoting interventions aiming to optimize health status in long-term childhood cancer survivors.

We previously evaluated the baseline health status of adults participating in the CCSS cohort in the context of six domains that assessed general health, mental health, functional impairment, activity limitations, cancer-related pain and anxiety/fears.[9] Our results demonstrated that despite frequent long-term adverse effects in specific aspects of health, the overall general health as perceived by adults surviving childhood cancer was very good. Fair or poor health was self-reported in 10.9% of survivors (mean age at interview, 26.8 years) compared with 4.9% of siblings (mean age, 29.2 years). Sociodemographic factors associated with impaired health status were similar to those identified in the

general population and included being female, not completing high school, and having a household income below $20,000. Survivors of CNS tumors, bone tumors, and sarcomas predictably demonstrated greater risk of functional impairment and/or activity limitations. Persistent cancer-related anxiety and fears were more common among long-term survivors of Hodgkin lymphoma, sarcomas, and bone tumors relative to other cancer types.

Further in-depth studies of special populations, such as minority survivors and those diagnosed in their pre-adolescent and adolescent period, provided insights into the associations of race, ethnicity, and age at diagnosis with health status and health care outcomes. Survivors with racial and ethnic minority status enrolled in the CCSS do not appear to have an increased risk of mortality, second cancers, or adverse health status relative to their white counterparts.[12] When adjusting for socio-economic status, the health care utilization patterns are similar regardless of race or ethnicity. While age at cancer diagnosis does not appear to be associated with a different likelihood of adverse health status or health care utilization, pre-adolescence appears to be a vulnerable time for developing risky health behaviors.

Our previous studies of health status provided only a brief snapshot of survivorship in the adult years. However, significant knowledge deficits remain regarding important areas of long-term health, despite the wealth of information published about childhood cancer outcomes. In particular, we are limited in our understanding about how cancer-related morbidity is affected by the natural course of organ senescence during adulthood and its ultimate impact on long-term health status. A follow-up comprehensive assessment of the cohort's health status using the original six health domains (general health, mental health, functional impairment, activity limitations, cancer-related pain and anxiety/fears) will provide important information about the impact of aging on cancer-related morbidity and facilitate identification of sociodemographic, treatment, and behavioral factors associated with changing health status. This analysis will be based on survivor responses from the baseline survey, the 2003 survey and the 2007 survey, which should provide more than 10 years of follow-up for the majority of survivors.

4. Specific Aims:

A. To evaluate health status as a function of current age, and to compare the trajectory of change in health status of survivors to that of siblings.

B. To identify cancer - host- and treatment- related factors associated with age related worsening health status.

5. Hypotheses:

A. Health status among childhood cancer survivors will decline with age and will decline at a greater rate among survivors than among siblings. That is, the age related trajectory of decline in health status will be steeper among survivors compared to the slope of decline in health status among siblings.

B. The trajectory of decline in health status will be associated with the original cancer diagnosis with brain tumor, bone tumor and Hodgkin lymphoma survivors having the steepest trajectories of decline

C. Host factors associated with worsening health status over time will be:
   a. younger age at cancer treatment
   b. older attained age
   c. female gender

D. Treatment factors associated with a steeper trajectory of decline in health status will be:
   a. Chemotherapy
      i. anthracycline exposure or
      ii. alkylating agent exposure or
      iii. both anthracyclines and alkylators
   b. Radiation exposure (maximum dose) to brain, heart, lungs, kidneys, and gonads,
   c. Surgical resection (partial or complete, excluding biopsy) of lesions in brain, lungs, kidney, bladder, upper extremities or lower extremities (AKA, BKA, limb-sparing)

6. METHODS

A. **Target population:** All survivors who were $\geq$ 18 years of age at any questionnaire completion (Baseline, FU 2003 or FU 2007). Because health status was completed by a proxy for those who were < 18 years of age at the time of questionnaire completion, these data will not be included. We will include data from all three time points for 18+ year old survivors if it is available. We will compare the baseline health status of participants who responded to the 2003 and/or 2007 questionnaires to those who did not respond to the 2003 and/or 2007 questionnaires to assess the extent to which our results might be biased due to selective attrition (or death).

B. **Primary outcomes/dependent variables:** As in the original analysis, six domains of health status will be used for the survivors (general health, mental health, functional impairment, limitations of activity, pain following cancer, anxiety/fears following cancer) plus a composite (any adverse health status domain). For siblings, four domains will be used (omitting pain and anxiety/fears following cancer).

C. **Analytic approach:**
   a. Aim 1: Compare changes in the general health, mental health, activity limitations, and functional impairments, between childhood cancer survivors and siblings over time.
      (1) **Hypothesis 1:** Childhood cancer survivors will have more deterioration in health status over time than will siblings.
      (2) **Outcomes of interest**
         (a) Domains of Health Status
            i. General Health (J35 BL, E1 FU2003, L19 FU2007)
            ii. Mental Health (J16-J35 BL, G1-G18 FU2003, L1-L18 FU2007)
            iii. Functional Impairment (N10-N12 BL, E12, E15, E16 FU2003, N22-N24 FU2007)
            iv. Activity Limitations (N14 b,c,e BL, E4-E6, E11 FU2003, N26 b,c,e FU2007)
            v. Cumulative health status score (0-4)
      (3) **Exploratory Variables**
         (a) Survivor vs. sibling status
         (b) Age (evaluated as both continuous and categorical variables18-29, 30-39, 40+ years
         (c) Health behaviors
            i. BMI
            ii. Smoking status
            iii. Physical activity
            iv. Alcohol intake
         (d) Chronic disease status
      (4) **Potential Confounders and effect modifiers**
         (a) Gender
         (b) Race/Ethnicity
      (5) **Statistical Approach:**

(a) Outcomes will be dichotomized to define "adversely" affected individuals as follows:
   i. Poor general health - answers fair or poor vs. good, very good or excellent
   ii. Poor mental health – score of 63 or higher on the brief symptom inventory on any of the three subscales vs. no score of 63 or higher on any of the three subscales of the Brief symptom Inventory
   iii. Functional impairment – answers yes to any of the three questions vs. answers no to all three questions listed above
   iv. Activity limitation – answers limited for more than three months over the past two years to any of the three questions vs. does not answer limited for more than three months over the past two years to any of the three questions listed above

(b) Generalized estimating equations (GEE) will be used to evaluate the difference between childhood cancer survivors and siblings in the change in the prevalence of poor health status and participation outcomes over time. A binomial distribution with a log link will be assumed in order to directly estimate relative risks, or prevalence ratios. Models will include repeated statements to account for within participant and within family correlations. Initial models will include data from all three time points and will evaluate whether the impact on the outcome is different for survivors when compared to siblings. Models will be adjusted for attained age, gender, and race. Model diagnostics will be used to evaluate the appropriate functional form required for the age variable in the model (i.e. linear, or more flexible spline or simply categorical factors). Adjusted models will be used to create figures depicting the age related change in predicted prevalence over time for each group. We will test the group (survivor vs. sibling) by age interaction to determine if there is a difference in the age related trajectory of the change between survivors and siblings.

(c) A proportional odds model will also be fit with the GEE method to evaluate the impact of survivor status and age on the ordered ordinal response health status score variable. A multinomial distribution with a cumulative logit link will be assumed. This model will also include a repeated statement to account for within participant and within family correlation. Models will again be adjusted for gender and race. Model diagnostics will be used to evaluate the functional form required for age.

b. **Aim 2:** To identify cancer - host- and treatment- related factors associated with worsening health status.

(1) **Hypothesis 2:** Deterioration in health status over time than will differ as a function of original cancer diagnosis, host factors and treatment exposures

(2) **Outcomes of interest**

(a) Domains of Health Status
   i. General Health (J35 BL, E1 FU2003, L19 FU2007)
   ii. Mental Health (J16-J35 BL, G1-G18 FU2003, L1-L18 FU2007)
   iii. Functional Impairment (N10-N12 BL, E12, E15, E16 FU2003, N22-N24 FU2007)
   iv. Activity Limitations (N14 b,c,e BL, E4-E6, E11 FU2003, N26 b,c,e FU2007)
   v. Pain (J36 BL, G19 FU2003, L21 FU2007)
   vi. Anxiety (J37 BL, G20 FU2003, L20 FU2007)

(3) **Exploratory Variables**

(a) Cancer type

(b) Host factors
   i. Gender
   ii. Race/Ethnicity
   iii. Age at diagnosis

iv. Current age
v. Time from diagnosis to questionnaire completion (only 2 of the 3 time variables will be included)

(c) Treatment factors
i. Chemotherapy
1. Anthracycline
2. Alkylating agent
3. Both anthracyclines and alkylators
ii. Radiation exposure (maximum dose) to brain, heart, lungs, kidneys, and gonads,
iii. Surgical resection (partial or complete, excluding biopsy) of lesions in brain, lungs, kidney, bladder, upper extremities or lower extremities (AKA, BKA, limb-sparing)

(4) **Statistical approach**

(a) Outcomes will be dichotomized to define "adversely" affected individuals as follows:
i. Poor general health - answers fair or poor vs. good, very good or excellent
ii. Poor mental health – score of 63 or higher on the brief symptom inventory on any of the three subscales vs. no score of 63 or higher on any of the three subscales of the Brief symptom Inventory
iii. Functional impairment – answers yes to any of the three questions vs. answers no to all three questions listed above
iv. Activity limitation – answers limited for more than three months over the past two years to any of the three questions vs. does not answer limited for more than three months over the past two years to any of the three questions listed above
v. Pain – answers a lot of or very bad excruciating pain vs. no, small amount or medium amount of pain
vi. Anxiety – answers a lot or very many/extreme anxiety/fears vs. no, small or medium amount of anxiety/fears

(b) Using observations from all time points, generalized estimating equations with a binomial distribution and a log link will be used to compare prevalence rates of poor health status by cancer type and treatment exposure in separate models. Host related factors will be included in both models. Models will include a repeated statement and utilize robust variance estimates with independence correlation matrix to account for within participant correlation. Model diagnostics will be used to evaluate the appropriate functional form required for the age variable in the model (i.e. linear, or more flexible spline or simply categorical factors). Interactions between the age variable and treatment/diagnosis variables will be evaluated to determine whether specific factors are associated with greater decline. Adjusted models will be used to create figures depicting the change in predicted prevalence over time for each group.

References

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Tables

Characteristics of Adult Survivors of Childhood Cancer and Siblings

Variables	Age 18-29 years		Age 30-39 years		Age 40+ years	
	Survivors (No., %)	Siblings (No., %)	Survivors (No., %)	Siblings (No., %)	Survivors (No., %)	Siblings (No., %)
Sex						
Female						
Male						
Race/Ethnicity						
White, non-Hispanic						
Black, non-Hispanic						
Hispanic						
Other						
Education						
High school or less						
High school + some college						
Annul Household Income						
<$20,000						
$20,000						
Health Insurance						
No						
Yes or Canadian						
Cancer Diagnosis						
Leukemia						
Central nervous system						
Hodgkin disease						
Non-Hodgkin lymphoma						
Wilms tumor						
Neuroblastoma						
Sarcoma						
Bone						
Cancer Treatment						
Chemotherapy						
Anthracycline exposure						
Alkylating agent exposure						
Anthracyclines and alkylators						
Radiation (maximum dose)						
Brain						
Heart						
Lungs						
Kidneys						
Gonads						
Surgical resection						
Brain						
Lungs						
Kidney						
Bladder						
Upper extremity						
Lower extremity						
Age at cancer diagnosis, years						
Mean (Standard deviation)						
Range						
Interval from cancer diagnosis, years						
Mean (Standard deviation)						
Range						

Percentage of survivors and siblings who reported moderate to extreme adverse health status by health status score at different ages

	Age 18-29		Age 30-39		Age 40+	
	Survivors (%)	Siblings (%)	Survivors (%)	Siblings (%)	Survivors (%)	Siblings (%)
General health						
Mental health						
Functional Impairment						
Activity limitations						
Pain						
Anxiety						
Any domain						
Health Status Score						
None						
One domain						
Two domains						
Three Domains						
Four domains						

Relative risk of moderate to extreme health status outcomes in adult survivors of childhood cancer and siblings by demographic (Will stratify by survivor status if there is an age by survivor interaction)

Variables	General Health	Mental Health	Functional Impairment	Activity limitations
	PR (95% CI)	PR (95% CI)	PR (95% CI)	PR (95% CI)
Survivor status				
Sibling				
Survivor				
Time point				
Age 18-29 years				
Age 30-39 years				
Age 40+ years				
Sex				
Female				
Male				
Race/Ethnicity				
White, non-Hispanic				
Minorities				

Percentage of cancer survivors with moderate to extreme adverse health status over time as a function of original cancer diagnosis

	General Health			Mental Health			Functional Impairment			Activity limitations		
	Age 18-29	Age 30-39	Age 40 +	Age 18-29	Age 30-39	Age 40 +	Age 18-29	Age 30-39	Age 40 +	Age 18-29	Age 30-39	Age 40 +
Siblings												
Leukemia												
Central nervous system												
Hodgkin disease												
Non-Hodgkin lymphoma												
Wilms tumor												
Neuroblastoma												
Sarcoma												
Bone												

Relative risk of moderate to extreme health status outcomes in adult survivors of childhood cancer and siblings by demographic (Will stratify by survivor status if there is a time by survivor interaction).

Variables	General Health	Mental Health	Functional Impairment	Activity limitations
	PR (95% CI)	PR (95% CI)	PR (95% CI)	PR (95% CI)
Survivor status				
Sibling				
Leukemia				
Central nervous system				
Hodgkin disease				
Non-Hodgkin lymphoma				
Wilms tumor				
Neuroblastoma				
Sarcoma				
Bone				
Leukemia				
Time point				
Age 18-29 years				
Age 30-39 years				
Age 40+ years				
Sex				
Female				
Male				
Race/Ethnicity				
White, non-Hispanic				
Minorities				

Percentage of cancer survivors with moderate to extreme health status by age group as a function of host and treatment factors (perhaps show graphically)

Variables	General Health			Mental Health			Functional Impairment			Activity Limitation			Pain			Anxiety			Any Domain		
	Age 18-29	Age 30-39	Age 40+	Age 18-29	Age 30-39	Age 40+	Age 18-29	Age 30-39	Age 40+	Age 18-29	Age 30-39	Age 40+	Age 18-29	Age 30-39	Age 40+	Age 18-29	Age 30-39	Age 40+	Age 18-29	Age 30-39	Age 40+
Sex																					
Female																					
Male																					
Race/Ethnicity																					
White, non-Hispanic																					
Minorities																					
Age at diagnosis, years																					
0-4																					
5-9																					
10-14																					
15-21																					
Chemotherapy																					
Anthracycline exposure																					
Alkylating agent exposure																					
Anthracyclines & alkylators																					
Radiation (maximum dose)																					
Brain																					
Heart																					
Lungs																					
Kidneys																					
Gonads																					
Surgical resection																					
Brain																					
Lungs																					
Kidney																					
Bladder																					
Upper extremities																					
Lower extremities																					

Multiple regression results of cancer related risk factors for adverse health status

Variables	General Health	Mental Health	Functional Impairment	Activity Limitation	Pain	Anxiety	Any Domain
	PR (95% CI)	PR (95% CI)	PR (95% CI)	PR (95% CI)	OR (95% CI)	PR (95% CI)	PR (95% CI)
Sex							
Female							
Male							
Race/Ethnicity							
White, non-Hispanic							
Minorities							
Age at interview, years							
18-29							
30-39							
40-49							
50+							
Age at diagnosis, years							
0-4							
5-9							
10-14							
15-21							
Chemotherapy							
Anthracycline exposure							
Alkylating agent exposure							
Both anthracyclines & alkylators							
Radiation exposure							
Brain							
Heart							
Lungs							
Kidneys							
Gonads							
Surgical resection							
Brain							
Lungs							
Kidney							
Bladder							
Upper extremity							
Lower extremity							