Childhood Cancer Survivor Study
Analysis Concept Proposal

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Title: Health Status Outcomes in Long-term Survivors of Childhood Hodgkin Lymphoma: A Report from the Childhood Cancer Survivor Study (CCSS).

Working Group: Cancer Control

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1 Background and Rationale

1.1 Background

Hodgkin lymphoma is one of the most treatable pediatric cancers with current five-year event-free survival rates of 70-90% for high-risk patients and >90% for those with localized disease.[1-6, 7-9] Unfortunately, past survivors have a high rate of secondary malignancies, cardiovascular disease, cerebrovascular events, pulmonary disease, and endocrine dysfunction. In a study by Castellino et al., 70% of 1927 pediatric Hodgkin survivors surveyed had at least one serious chronic medical condition.[10] While the organ system dysfunction associated with pediatric Hodgkin treatment has been well described,[10-19] few studies have focused on the health status outcomes (long-term physical and psychosocial functioning) of these patients.

The majority of studies evaluating health status outcomes of Hodgkin survivors have concentrated on survivors of adult lymphoma. These studies have shown mixed results in general health, physical function, and social function quality of life scores.[20-28] A cross-sectional study assessing quality of life reported that vitality, social functioning, and emotional health were significantly better in patients 10-15 years after diagnosis compared

to those 5-9 years after diagnosis. However, patients with subsequent or recurrent primary malignancies were excluded from the analysis. [29] No studies have investigated longitudinal changes in health status outcomes.

Previous cross-sectional CCSS investigations evaluating health status, physical performance limitations, and psychological outcomes have included Hodgkin survivors among the cohort.[30-32] Hudson et al. reported that 40.2% of Hodgkin survivors had an adverse health status outcome (poor general health, mental health, functional status, activity limitation, anxiety, or pain) at the baseline CCSS evaluation and their odds of having a moderate to extreme adverse health status outcome across all domains were significantly higher compared to sibling controls.[30] Additionally, Ness et al. showed Hodgkin lymphoma survivors had significant physical performance limitations with only survivors of brain and bone tumors reporting more limitations.[31] Another study observed that Hodgkin survivors experienced more somatic distress than sibling controls, leukemia survivors, or non-Hodgkin lymphoma survivors.[32]

1.2 Rationale: Advantage of Longitudinal Evaluation

No previous analyses of the CCSS data have evaluated health status outcomes in Hodgkin survivors in a longitudinal manner or examined the effect of chronic medical conditions on these outcomes. The current proposal aims to compare longitudinal changes in health status of Hodgkin survivors to that of sibling controls and to examine the influence of serious chronic medical conditions on these outcomes. With multiple time points, we will be able to determine if survivor health status outcomes worsen over time at an accelerated rate compared to sibling controls. Additionally, by examining the influence of serious chronic medical conditions, we will evaluate whether the decline in health status outcomes is due solely to medical conditions.

2 Study population

The study population will consist of Hodgkin lymphoma survivors and sibling controls from the original CCSS cohort, who were 18 years of age or older at baseline questionnaire. Hodgkin survivors will be limited to those who consented for medical record abstraction, were alive, and completed at least one of the baseline, 2003, or 2007 questionnaires. Sibling controls will include all those who were alive and completed at least one of the baseline, 2003 with psychosocial, or 2007 questionnaires. Only responses from living participants will be included at each questionnaire. The number of proxy responses will be closely evaluated.

The most recent data freeze includes completed questionnaires from 1473 survivors alive at baseline, 966 alive at the follow-up 2003 with psychosocial section, and 963 alive at the follow-up 2007 questionnaires. There are 3206 sibling controls from the baseline, 394 alive at the follow-up 2003 with psychosocial section, and 2370 alive at the follow-up 2007 questionnaires.

3 Methods

This proposal addresses health status outcomes among pediatric Hodgkin lymphoma survivors compared to sibling controls and will be divided into two sections, each with specific aims, hypotheses, and statistical approaches. Karen Effinger along with her mentor Alice Whittemore, Professor of Epidemiology and Biostatistics at Stanford University, will be performing the statistical analysis with final statistical programs and results reviewed by CCSS statisticians.

3.1 Analysis 1: Longitudinal evaluation of health status outcomes among Hodgkin lymphoma survivors to identify treatment variables associated with poor outcomes. This analysis will compare how the trajectories of poor health status change with age among Hodgkin lymphoma survivors divided into four strata: no chronic conditions, 1 chronic condition, 2 chronic conditions, and 3+ chronic conditions. We will evaluate the association of therapy exposures with longitudinal changes in health status outcomes.

3.1.1 Aim: Evaluate the change in general health, mental health, activity limitations, functional impairments, cancer-related anxiety, and cancer-related pain of Hodgkin survivors grouped by number of chronic conditions, adjusting for treatment factors including chemotherapy and radiation received.

3.1.2 Hypothesis: Treatment factors and the number of chronic conditions will impact the trajectory of health status decline in Hodgkin survivors.

3.1.3 Statistical Approach:

Using observations from all time points, a correlation matrix will be evaluated to determine if significant correlations exist between outcomes. If strong correlations exist, measures will be employed to reduce the dimensionality of the data. Generalized estimating equations with a binomial distribution and a log link will be used to evaluate the impact of treatment factors on the odds of six poor health status outcomes in Hodgkin survivors as they age. Survivors will be grouped into four strata based upon the number of serious chronic conditions present at questionnaire completion. Models will include a repeated statement and exchangeable correlation matrix to account for within participant correlation, utilizing robust variance estimates for inference. Models will be adjusted for race, gender, chemotherapy received, and radiation received. Univariate analyses will be performed to determine if adjustment will be made for treatment era, age at diagnosis, and time from diagnosis to questionnaire completion. Model diagnostics will be used to evaluate the appropriate functional form required for the time 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 change in predicted prevalence over time for each group.

3.2 Analysis 2: Longitudinal evaluation of health status outcomes among Hodgkin lymphoma survivors compared to sibling controls. This analysis will evaluate the health status outcomes as pediatric Hodgkin lymphoma survivors age to determine if the trajectory varies compared to sibling controls. In addition, it will examine the role of chronic conditions in the trajectories.

3.2.1 Aim: Compare changes with aging in the general health, mental health, activity limitations, and functional impairments between sibling controls and Hodgkin survivors.

3.2.2 Hypothesis: As Hodgkin survivors age, they will have greater deterioration in health status outcomes compared to sibling controls, which will worsen with increasing number of chronic health conditions.

3.2.3 Statistical Approach:

A correlation matrix will be examined to determine if significant correlation exists between any of the four health status outcomes. If strong correlations exist, measures will be employed to reduce the dimensionality of the data. Generalized estimating equations will be used to evaluate the difference between Hodgkin survivors and sibling controls in the odds of poor health status with aging. A binomial distribution with a log link will be assumed in order to directly estimate odds ratios. Models will include repeated statements to account for within participant and possible within family correlation. Initial models will include data from all three time points and will evaluate whether the impact of age is different in Hodgkin survivors compared to sibling controls. Models will be adjusted for gender, race, and number of serious chronic conditions present at the time of each questionnaire. Model diagnostics will be used to evaluate the appropriate functional form required for the time 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 change in predicted prevalence over time for each group. If time permits, we will evaluate the chronic conditions by organ systems to determine which have the largest influence on health status.

4 Outcome Variables

This study will evaluate the odds of survivors and siblings having adverse outcomes in each of four domains of health status. Mental status will be further subdivided into depression, anxiety, and somatization. Additionally cancer-related anxiety and pain will be evaluated in survivors only.

4.1 Domains of Health Status

4.1.1 General Health (BL N15; FU2003 E1; FU2007 L19)

4.1.2 Mental Health (BL J16-24, J26, J27, J29-35; FU2003 G1-18; FU2007 L1-18)

4.1.2.1 Depression (BL J19,21-23, 30, 35; FU2003 G4, 6-8, 13, 18; FU2007 L4, 6-8, 13, 18)

4.1.2.2 Anxiety (BL J16, 20, 24, 32-34; FU2003 G1, 5, 9, 15-17; FU2007 L1, 5, 9, 15-17)

4.1.2.3 Somatization (BL J17-18, 26-27, 29, 31; FU2003 G2-3, 10-12, 14; FU2007 L2-3, 10-12, 14)

4.1.3 Functional Impairment (BL N10-N12; FU2003 E12, E15, E16; FU2007 N22-N24)

4.1.4 Activity Limitations (BL N14 b,c,e; FU2003 E4-E6, E11; FU2007 N26 b,c,e)

4.1.5 Anxiety (Survivors Only: BL J37; FU2003 G20; FU2007 L20)

4.1.6 Pain (Survivors Only: BL J36 ;FU2003 G19; FU2007 L21)

4.2 Definition of Outcomes

Outcomes will be dichotomized to define "adversely" affected individuals as follows:

4.2.1 General health: Answer of fair or poor vs. good, very good or excellent

4.2.2 Mental health: T-score of 63 or higher vs. score of less than 63 on the any of subscales of the brief symptom inventory (BSI)-18. Answers will then be subdivided into scores of 63 or higher vs. score of less than 63 in each of the subscales: depression, anxiety, and somatization.

4.2.3 Functional impairment: Answer of yes vs. no to any of the three questions listed in 4.1.3 above

4.2.4 Activity limitation: Answer of limited for more than three months over the past two years or limited a lot (in 2003 survey) vs. limited for 3 months or less/not limited at all or limited a little/not limited at all (in 2003 survey) to any of the questions listed in 4.1.4 above

4.2.5 Anxiety: Answer of a lot/very many, extreme anxiety/fears vs. other answers

4.2.6 Pain: Answer of very bad/a lot of pain or severe/very severe vs. other answers

4.3 Risk Factor of Interest/Time Variable

4.3.1 Age at Questionnaire

4.4 Potential Confounders

4.4.1 Both Analyses

4.4.1.1 Gender

4.4.1.2 Race/Ethnicity

4.4.2 Analysis 1 Specific Confounders

4.4.2.1 Age at diagnosis

4.4.2.2 Time from diagnosis to questionnaire completion

4.4.2.3 Treatment decade (1970-79 vs 1980-86)

4.4.2.4 Chemotherapy for primary disease

4.4.2.4.1 Anthracycline (yes/no)

4.4.2.4.2 Alkylating agent (yes/no)

4.4.2.5 Radiation for primary disease

4.4.2.5.1 Location (Supradiaphragmatic, Infradiaphragmatic, Both)

4.4.2.5.2 Dose (</= 30Gy, >30Gy)

4.5 Chronic Conditions

Serious chronic conditions will be defined as Grade 3-4 conditions based on the Common Terminology Criteria for Adverse Events 4.0 as previously described.[33] Strata will be assigned according to conditions present at time of questionnaire completion. Individuals will be divided into four strata based on the presence of serious chronic conditions, as follows: Group 1- no chronic conditions, Group 2- 1 chronic condition, Group 3- 2 chronic conditions, Group 4- 3+ chronic conditions.

4.5.1 Malignancy (Grade 3-4: secondary malignant neoplasm other than basal cell carcinoma, recurrent Hodgkin lymphoma)

4.5.2 Cardiovascular Disorders (Grade 3-4: coronary artery disease- on medication, congestive heart failure- on medication, atrial fibrillation/flutter, supraventricular dysrhythmia, hypotension, myocardial infarction, heart transplant for cardiomyopathy, cerebrovascular accident, endocarditis, cardiac arrest, arterial embolism)

4.5.3 Pulmonary Disorders (Grade 3-4: emphysema- on medication, thromboembolic disease- leg or arm, pulmonary fibrosis- on oxygen, pulmonary embolism and infarct, respiratory arrest)

4.5.4 Endocrine Disorders (Grade 3-4: hyperthyroidism, thyroid nodules requiring thyroidectomy, diabetes- on insulin, ovarian failure- on estrogen replacement, testicular failure- on testosterone replacement, panhypopituitarism, diabetes insipidus, corticoadrenal insufficiency

4.5.5 Gastrointestinal Disorders (Grade 3-4: cirrhosis, rectal stricture, surgery for intestinal obstruction)

4.5.6 Renal Disorders (Grade 3-4: urethral stricture, urinary incontinence, dialysis or kidney transplant)

4.5.7 Musculoskeletal Disorders (Grade 3-4: removal of ball/socket of femur, hip disarticulation, modified hemipelvectomy, reattachment of lower leg, major joint replacement or amputation of: arm above elbow, upper arm, arm at shoulder [disarticulation], forequarter [shoulder], arm, below knee, or above knee)

4.5.8 Neurological Disorders (Grade 3-4: facial/cranial nerve paralysis, paralysis of vocal cords, neurogenic bowel, severe cognitive deficit, intracranial abscess, symptomatic torsion dystonia, monoplegia of lower limb, diplegia of upper limbs, hemiplegia, paraplegia, quadriplegia, other specified paralytic syndromes, paralysis [unspecified], Guillain-Barre syndrome)

4.5.9 Other Disorders (Grade 3-4: legally blind or loss of an eye, deafness or deafness not corrected by hearing aid)

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Table 1. Overall Characteristics of the Study Population

	Hodgkin Survivors (N=)		Sibling Control (N=)	
	N	%	N	%
Gender				
Male				
Female				
Race/Ethnicity				
Non-Hispanic White				
Non-Hispanic Black				
Hispanic				
Asian				
Other				
Missing				
Age at baseline questionnaire (years)				
<20				
20-29				
30-39				
40-49				
Age at 2003 questionnaire (years)				
<20				
20-29				
30-39				
40-49				
50+				
Age at 2007 questionnaire (years)				
<20				
20-29				
30-39				
40-49				
50+				
Serious Chronic Medical Conditions (Grade 3 or 4) at baseline				
Malignancy[#]				
Cardiovascular Disease				
Pulmonary Disease				
Endocrine Conditions				
Gastrointestinal Conditions				
Renal Disease				
Musculoskeletal Conditions				
Neurological Conditions				
Other Serious Chronic Conditions				
Number of Chronic Medical Conditions (Grade 3 or 4) at baseline				
0				
1				
2				
3+				

[#] Recurrent or subsequent malignancies for Hodgkin survivors

Table 2. Characteristics of the Hodgkin Survivors by Chronic Medical Condition Strata (exploratory table)

	0 Chronic Conditions (N=)		1 Chronic Condition (N=)		2 Chronic Conditions (N=)		3+ Chronic Conditions (N=)	
	N	%	N	%	N	%	N	%
Gender								
Male								
Female								
Race/Ethnicity								
Non-Hispanic White								
Non-Hispanic Black								
Hispanic								
Asian								
Other								
Missing								
Age at diagnosis (years)								
0-4								
5-9								
10-14								
15-20								
Age at baseline questionnaire (years)								
<20								
20-29								
30-39								
40-49								
Age at 2003 questionnaire (years)								
<20								
20-29								
30-39								
40-49								
50+								
Age at 2007 questionnaire (years)								
<20								
20-29								
30-39								
40-49								
50+								

Treatment Era								
1970-79								
1980-86								
Chemotherapy								
Radiation Only								
Anthracycline (received)								
No anthracycline								
Unknown								
Alkylating agent (received)								
No alkylating agent								
Unknown								
Radiation Therapy								
Chemotherapy only								
Supradiaphragmatic <30Gy								
Supradiaphragmatic >/=30Gy								
Infradiaphragmatic <30Gy								
Infradiaphragmatic >/=30Gy								
Supra- and Infradiaphragmatic <30Gy								
Supra- and Infradiaphragmatic >/=30Gy								
Missing								

Table 3. Odds Ratios for Poor Functional Outcomes Among Survivors, including Treatment Factors

	General Health	Mental Health	Functional Impairment	Activity Limitation	Pain	Anxiety
	OR	OR	OR	OR	OR	OR
Survivors 0 Chronic Cond	Ref	Ref	Ref	Ref	Ref	Ref
Survivors 1 Chronic Cond						
Survivors 2 Chronic Cond						
Survivors 3+ Chronic Cond						
Male gender						
White race						
Black race						
Age at Diagnosis (<15yrs)						
Treatment Era (1970-1980)						
Received Chemotherapy						
Anthracycline (received)						
Alkylating agent (received)						
Received Radiation Therapy						
Supradiaphragmatic <30Gy						
Supradiaphragmatic >/=30Gy						
Infradiaphragmatic <30Gy						
Infradiaphragmatic >/=30Gy						
Supra- and Infradiaphragmatic <30Gy						
Supra- and Infradiaphragmatic >/=30Gy						

Table 4. Odds Ratios for Poor Functional Outcomes Comparing Survivors to Sibling Controls

	General Health	Mental Health	Functional Impairment	Activity Limitation	Pain	Anxiety
	OR	OR	OR	OR	OR	OR
Sibling Controls	Ref	Ref	Ref	Ref	Ref	Ref
All Survivors						
Survivors 0 Chronic Cond						
Survivors 1 Chronic Cond						
Survivors 2 Chronic Cond						
Survivors 3+ Chronic Cond						

Figures: Change in Functional Outcomes as Survivors and Siblings Age
There will be six panels for health status in survivors and four panels for health status in survivors compared to siblings.
Proportion of those with poor health status will be charted by age, with odds ratios noted for trend. These models will be adjusted for potential confounders. A potential alternative figure may be developed from the multivariate models. Similar figures will be constructed for the analysis of survivors adjusted for treatment factors.