Childhood Cancer Survivor Study

Analysis Concept Proposal

February 2019

1. Project Title:

Predictors of Neurocognitive and Psychosocial Outcomes in Long-Term Survivors of Hodgkin Lymphoma: A Report from the Childhood Cancer Survivor Study.

2. Working group:

   Psychology/Neuropsychology (primary)

   Epidemiology/Biostatistics (secondary)

3. Investigators:


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## 4. Background:

Cancer survivors may experience sequelae related to their cancer diagnosis and/or treatment, including neurocognitive and psychosocial impairments. Neurocognitive impairment frequently involves problems with attention, memory, executive function, and processing speed, while psychosocial impairment can include anxiety and depression. Impairment in these domains has been associated with lower quality of life, unemployment, lower educational attainment, as well as decreased independence, social engagement, and productivity.[1]

While it is widely accepted that patients treated with central nervous system (CNS) directed therapies are at risk for brain abnormalities, emerging evidence indicates that treatments that impact cardiac, pulmonary and/or endocrine function may pose a significant risk to the CNS.[2] Hodgkin lymphoma (HL) patients are treated with thoracic radiation, placing them at increased risk of cardiopulmonary and endocrine morbidity, as well as chemotherapies that also increase risk for cardiac and pulmonary morbidity. The risk of CNS abnormalities in this population is not widely recognized, despite initial reports from the CCSS that demonstrate HL survivors are at increased risk for cerebrovascular accidents compared to sibling controls.[3, 4] Additionally, a pilot study of HL survivors in the St. Jude Lifetime cohort study (SJLIFE) found neurocognitive problems on objective assessments of memory and attention, and roughly 50% of survivors displayed leukoencephalopathy.[5] There has been no comprehensive report of neurocognitive function in a large geographically diverse sample of HL survivors.

Exposure to thoracic radiation in HL is associated with increased risk of cardiovascular morbidity including congestive heart failure, myocardial infarction, pericardial disease, and heart valve abnormalities.[3, 6, 7] Thoracic radiation exposure has also been associated with an increased risk of hyperthyroidism, hypothyroidism, and thyroid nodules in survivors of HL.[8-10] Further, up to 20% of Hodgkin lymphoma patients will experience late pulmonary toxicity.[11-14] In adult non-cancer populations, cardiovascular disease, impaired pulmonary function, and hypothyroidism are associated with neurocognitive and psychosocial problems. Hypothyroidism has been associated with impaired memory and processing speed and some large epidemiologic cohorts associate it with an increased risk of dementia and Alzheimer's disease.[15-17] Cardiopulmonary disease has been associated with impaired memory, verbal fluency,

and processing speed.[18-20] Additionally, cardiopulmonary morbidity and hypothyroidism are associated with depression in non-cancer populations.[18, 21]

Neurocognitive impairment has been associated with cardiopulmonary and endocrine morbidity among survivors of childhood cancer of heterogeneous diagnoses.[22] However, the role of specific chronic health conditions and treatment exposures in neurocognitive and psychosocial impairment among Hodgkin lymphoma survivors has not been described. This is of high importance as cardiopulmonary and endocrine morbidity typically develop over time, which may provide a window of opportunity for prevention of neurocognitive problems.

Few studies have comprehensively characterized the prevalence of neurocognitive and psychosocial impairment in HL. Further, little work has been done to examine how specific treatments or subsequent comorbidities may exacerbate these impairments. We aim to examine the prevalence and predictors of neurocognitive and psychosocial impairment in HL. We will examine demographic, treatment and chronic health conditions as predictors of neurocognitive and psychosocial outcomes. Based on the pattern of findings, we will explore mediation models of the pathway from treatment to chronic condition to neurocognitive/psychosocial outcomes. We will also examine the impact of neurocognitive and psychosocial outcomes on social attainment in adult survivors of HL. Findings from this study will help identify underlying pathways contributing to neurocognitive impairment and targeted interventions to prevent or alleviate adverse outcomes in survivors of HL.

## 5. Specific Aims:

**Aim 1.1: Describe the neurocognitive and psychosocial outcomes of survivors of childhood Hodgkin lymphoma in reference to sibling controls.**

Hypothesis 1.1: Survivors will report significantly worse neurocognitive outcomes (NCQ task efficiency, emotional regulation, organization and memory), emotional outcomes (BSI anxiety, depression and somatization) and health-related quality of life (SF-36) compared to sibling controls.

**Aim 1.2 (exploratory): In a subset of survivors, from the original cohort with complete surveys at FU2 and FU5, describe the frequency of impairment of self-reported neurocognitive and psychosocial outcomes.**

**Aim 2: Identify individual demographic and treatment factors and historical treatment regimens that are associated with poor neurocognitive and psychosocial outcomes.**

Hypothesis 2: Chest/neck radiation therapy, bleomycin exposure, anthracycline dose, smoking history, younger age at diagnosis, and female sex will be associated with significantly worse neurocognitive, emotional, and health-related quality of life outcomes. We will examine predictors both as continuous treatment exposures and as regimens as described in 6c below.

**Aim 3: Examine the impact of chronic health conditions (i.e., grade 2-4 cardiac, pulmonary, endocrine, neurologic) on neurocognitive and psychosocial outcomes in survivors of childhood Hodgkin lymphoma.**

Hypothesis 3a: The presence of Grade 2-4 cardiac, pulmonary and endocrine chronic health conditions will be associated with poor neurocognitive, emotional, and health-related quality of life outcomes.

Hypothesis 3b: Chronic health conditions will mediate the impact of treatment exposures on neurocognitive, emotional, and health-related quality of life outcomes.

**Aim 4: Examine associations between social attainment and neurocognitive and psychosocial factors in survivors of childhood Hodgkin lymphoma.**

Hypothesis 4.1 Survivors with neurocognitive problems will report significantly worse social attainment (as measured by education, employment, independent living, and income) compared to sibling controls.

Hypothesis 4.2: Younger age at diagnosis, female sex, neurocognitive impairment, emotional distress, and poor health-related quality of life will be associated with significantly worse social attainment.

**6. Analysis Framework:**

**a. Study Population:** Survivors of childhood Hodgkin lymphoma (N=3107) and siblings (N=5059) enrolled in the CCSS cohort who were ≥ 18 years attained age at the required follow-up survey. Participants from the original cohort must have

completed the CCSS-NCQ, BSI-18, or SF-36 at Follow-up 2 (FU2) and participants from the expansion cohort must have completed the CCSS-NCQ, BSI-18, or SF-36 at Follow up 5 (FU5). Aim 1.2 will utilize participants from the original cohort who completed the CCSS-NCQ, BSI-18, or SF-36 at both FU2 and FU5. Exclusion criteria include a diagnosis of a genetic disorder that would predispose the survivor to mental or physical impairments not related to disease or treatment. Examples would include Trisomy 21, Neurofibromatosis 1, Turner syndrome, or polycystic kidney disease. Hodgkin lymphoma survivors who did not complete the BSI on their own will be excluded from BSI-specific analyses.

**b. Outcome Variables:**

**i.** Neurocognitive Outcomes: Neurocognitive impairment will be assessed using the Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ; FU2: J1-J25, FU5: Q1-Q33). The CCSS-NCQ was developed and validated for use in cancer survivors and assesses four specific domains: task efficiency, emotional regulation, organization, and memory. Scores for each of the four domains will be operationalized as binary variables (impaired vs not) for each of the Aims (unless otherwise noted). Participants will be considered impaired if their score is ≥ the $90^{th}$ percentile based on values obtained in the sibling cohort.

ii. Emotional Outcomes: Emotional distress will be assessed using a self-reported Brief Symptom Inventory 18 (BSI-18; FU2: G1-G18, FU5: L1-L18) which has been validated to measure psychosocial distress in cancer patients. Three specific domains of the BSI-18 will be evaluated for each aim: anxiety, depression, and somatization. Scores for each of the three domains will be operationalized as binary variables (distressed or not). Participants will be considered distressed if their score is ≥ the $90^{th}$ percentile of published norms.

iii. Health-related quality of life outcomes: Health-related quality of life will be assessed using the Medical Outcomes Short Form (SF-36; FU2: E1-E22 and F1-F14, FU5: O1-O8 and P1-3). The SF-36 includes questions on general health and quality of life over the past four weeks. Eight specific domains of the SF-36 will be used in all aims: general health, physical function, physical role function, physical role limitation, pain, emotional role limitation, vitality, social functioning. Scores for each of the eight

domains will be operationalized as binary variables (impaired vs not). Participants will be considered impaired if their score falls below a T-score of 40 (1 standard deviation below the mean).

iv. Social Attainment (Aim 4):
    1. Highest educational attainment (FU2 question 1; FU5 question A4; college graduate vs. below college graduate)
    2. Employment status (FU2 question 4; FU5 question A5; full-time employment vs. other)
    3. Independent living (yes vs. no, FU2 question 3; FU5 question M1). If a participant responded, “live with parent”, “Live with brothers and/or sisters”, “live with other relatives”, or specified they had nursing or caregiver support under “other” living arrangements will be considered as not living independently.
    4. Personal income (FU2 question S3; FU5 question A9). The distribution of personal income will be reviewed and if frequencies are sufficient for analyses this variable will be collapsed to compare those <$20,000 to ≥$20,000.

c. Predictors:
    i. Predictors for Aims 2 and 4:
        1. Treatment decades (1970-1979, 1980-1989, 1990-1999)
        2. Treatment combinations (will match classification used in Dr. Kevin Oeffinger’s paper on chronic health conditions in HL)
        3. Chest radiation, maximum tumor dose (max TD, per 10 Gy; additionally will explore direct cardiac dose(mean heart dose v5, v20), will explore direct lung dosing if it becomes available)
        4. Neck radiation, maxTD (per 10 Gy)
        5. Bleomycin exposure (yes/no)
        6. Cumulative anthracycline dose (per 100 mg/$m^2$)
        7. IV methotrexate (co-linear with relapse) (yes/no)
        8. Corticosteroids (yes/no)
        9. Relapse (none, 1 or more)
        10. Second malignancy (yes/no)
        11. Age at diagnosis (also for Aim 4)
        12. Sex (also for Aim 4)

13. Smoking (on FU2 survey for original cohort, FU5 survey for expansion cohort; never a smoker, >100 cig/lifetime but not currently smoking, >100 cigs/lifetime and current smoker)
14. Time since diagnosis (years, if not colinear with current age)

ii. Predictors for Aim 3: Chronic health conditions that pre-date the follow-up survey where neurocognitive and psychosocial outcomes were assessed. Presence of chronic health conditions will be operationalized as a categorical variable examining the presence of any CTCAE grade 3 or 4 condition, grade 2 condition, or grade 0-1 condition. We will also evaluate the presence of a grade 2+ chronic health condition vs. grade 0-1 within each of the following systems: cardiovascular, pulmonary, endocrine, and neurologic. If significant effects are noted within a system and if the sample size is large enough we will conduct exploratory analyses to identify individual chronic health conditions (e.g. stroke) that predict neurocognitive, emotional, or quality of life outcomes.

d. Covariates
   i. Age at follow up (years)
   ii. Race/ethnicity

7. Statistical Analysis
   a. Frequency distributions will be used to categorize relevant outcome variables, predictors and covariates according to reasonable groupings and consistent with previous CCSS manuscripts. Descriptive statistics including means, standard deviations, medians, ranges, frequencies, and percentages will be calculated for the outcomes and predictors of interest (Table 1). Additionally, HL participants who completed neurocognitive and psychosocial surveys at FU2 (original cohort) or FU5 (expansion cohort) will be compared to HL participants that did not on relevant demographic and treatment characteristics to assess any potential for selection bias (Table 2).
   b. Specific Aim 1.1: Describe the neurocognitive and psychosocial outcomes of survivors of childhood Hodgkin lymphoma in reference to sibling controls. Mean T-scores for the CCSS-NCQ, BSI-18, and SF-36 domains in survivors and controls will be reported and compared with a two-sample t-test (Table 3).

Frequencies of neurocognitive impairment, emotional distress, and impaired quality of life in survivors and sibling controls will be reported and compared using chi-square tests (Table 3). Survivors and siblings will also be compared using log-binomial regression adjusting for age, gender, and race. RR and 95% confidence intervals will be reported (Table 3).

c. Specific Aim 1.2: Specific Aim 1.2: In a subset of survivors, from the original cohort with complete surveys at FU2 and FU5, describe the trajectory over time of self-reported neurocognitive and psychosocial outcomes. Analyses for specific aim 1.2 will be conducted on survivors and siblings who were recruited as part of the original cohort and have complete outcome data from FU2 and FU5. Prevalence of impairment in CCSS-NCQ, BSI-18, and SF-36 domains will be plotted over time for survivors and siblings (Figure 1). Analyses will be weighted with the inverse probability of being included in this subsample. The inverse probability will be generated by examining what demographic and treatment variables predict inclusion (e.g. logistic regression).
d. Specific Aim 2: Identify individual demographic and treatment factors and historical treatment regimens that are associated with poor neurocognitive and psychosocial outcomes. Within the Hodgkin lymphoma survivors only, we will use log-binomial regression to identify demographic and treatment factors (noted above) associated with each outcome. These models will be adjusted for age, sex, and race. Adjusted RR and 95% confidence intervals will be reported (Table 4). Univariate analyses will be run for each predictor, then multivariable models will be generated that account for all marginally significant predictors ($p<0.20$). Additionally, in exploratory analyses, we will examine the Pearson correlations between neurocognitive, emotional and quality of life outcomes, and the frequency to which impairment overlaps across constructs.
e. Specific Aim 3: Examine the impact of chronic health conditions (i.e., grade 2-4 cardiac, pulmonary, endocrine, neurologic) on neurocognitive and psychosocial outcomes in survivors of childhood Hodgkin lymphoma. Within the Hodgkin lymphoma survivors, we will develop a multivariable model to investigate associations between chronic health conditions and primary outcomes using log-binomial regression adjusted for age, sex, and race. RR and 95% confidence intervals will be reported. First, we will examine the risk of neurocognitive, emotional, and health-related quality of life impairment associated with any grade

2 or grade 3 or 4 health condition (relative to grade 0 or 1). Then we will examine the risk associated within each system (cardiac, pulmonary, etc.) (Table 5). If a particularly strong association is noted and there is sufficient sample size we will examine individual conditions (e.g. stroke).

We will also perform mediation analyses of the effect of treatment on functional outcomes as mediated by relevant chronic condition using the Baron and Kenny approach[23] (see Figure 2). Potential mediation will be explored for any significant associations between treatment and functional outcomes identified in Aim 2. We will then use regression models to determine if these treatments predict chronic health conditions. For any significant treatment-chronic health condition and treatment-functional outcome relationships, we will run a third model that includes the chronic health conditions as well as treatments as predictors of the functional outcome. If the effect of the chronic health condition and treatment remains significant and the effect size of treatment attenuates we can conclude there is partial mediation.

f. Specific Aim 4: Examine associations between social attainment and neurocognitive and psychosocial factors in survivors of childhood Hodgkin lymphoma. Frequencies of educational attainment and employment in survivors and sibling controls will be compared using chi-square tests (Table 6). Survivors and siblings will also be compared using either log-binomial regression adjusting for age, gender, and race. RR and 95% confidence intervals will be reported (Table 6). Within the Hodgkin lymphoma survivors only, we will use log-binomial regression to identify demographic, neurocognitive, emotional, and psychosocial factors associated with each outcome. These models will be adjusted for age, sex, and race. Adjusted RR and 95% confidence intervals will be reported (Table 7).

8. Special Considerations: None

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Table 1: Characteristics of Study Population

| | Survivors | Siblings | p-value |
|---|---|---|---|
| | N (%) | N (%) | |
| **Sex** | | | |
| Male | | | |
| Female | | | |
| **Race** | | | |
| White | | | |
| Other | | | |
| **Age at Diagnosis (Years)** | | | |
| Mean (sd) | | | |
| Median (range) | | | |
| **Age at Follow Up (Years)** | | | |
| Mean (sd) | | | |
| Median (range) | | | |
| **Time Since Diagnosis (Years)** | | | |
| Mean (sd) | | | |
| Median (range) | | | |
| **Smoking Status** | N (%) | N (%) | |
| Never | | | |
| Former (>100 cigs and no current smoking) | | | |
| Current (>100 cigs and current smoking) | | | |
| **Anthracycline dose (n=)** | | - | - |
| Mean (sd) | | - | - |
| Median (range) | | - | - |
| **Treatment Decade** | N (%) | - | - |
| 1970-1979 | | - | - |
| 1980-1989 | | - | - |
| 1990-1999 | | - | - |
| **Treatment Combinations** | | - | - |
| (to be determine from Oeffinger paper) | | - | - |
| **IV Methotrexate** | | - | - |
| Yes | | - | - |
| No | | - | - |
| **Bleomycin** | | - | - |
| Yes | | - | - |
| No | | - | - |
| **Corticosteroids** | | - | - |
| Yes | | - | - |
| None | | - | - |
| **Chest Radiation (n=)** | | - | - |
| <10 Gy | | - | - |
| 10 to <20 Gy | | - | - |
| 20 to <30 Gy | | - | - |
| 30 to <40 Gy | | - | - |

| | | | |
|---|---|---|---|
| 40 to <50 Gy | | - | - |
| ≥50 Gy | | - | - |
| **Neck Radiation (n=)** | | - | - |
| <10 Gy | | - | - |
| 10 to <20 Gy | | - | - |
| 20 to <30 Gy | | - | - |
| 30 to <40 Gy | | - | - |
| 40 to <50 Gy | | - | - |
| ≥50 Gy | | - | - |
| **Relapsed** | | - | - |
| None | | - | - |
| ≥1 | | - | - |
| **Diagnosed with 2$^{nd}$ Malignancy** | | - | - |
| Yes | | - | - |
| No | | - | - |

Table 2: Characteristics of Study Population

| | HL Survivors With Complete Survey Data | HL Survivors without complete survey data | p-value |
|---|---|---|---|
| | N (%) | N (%) | |
| **Sex** | | | |
| Male | | | |
| Female | | | |
| **Race** | | | |
| White | | | |
| Other | | | |
| **Age at Diagnosis (Years)** | | | |
| Mean (sd) | | | |
| Median (range) | | | |
| **Age at Follow Up (Years)** | | | |
| Mean (sd) | | | |
| Median (range) | | | |
| **Time Since Diagnosis (Years)** | | | |
| Mean (sd) | | | |
| Median (range) | | | |
| **Anthracycline dose (n=)** | | | |
| Mean (sd) | | | |
| Median (range) | | | |
| **Treatment Decade** | N (%) | N (%) | |
| 1970-1979 | | | |
| 1980-1989 | | | |
| 1990-1999 | | | |
| **Treatment Combinations** | | | |
| (to be determine from Oeffinger paper) | | | |
| **IV Methotrexate** | | | |
| Yes | | | |
| No | | | |
| **Bleomycin** | | | |
| Yes | | | |
| No | | | |
| **Corticosteroids** | | | |
| Yes | | | |
| None | | | |
| **Chest Radiation (n=)** | | | |
| <10 Gy | | | |
| 10 to <20 Gy | | | |
| 20 to <30 Gy | | | |
| 30 to <40 Gy | | | |
| 40 to <50 Gy | | | |

| | | | |
|---|---|---|---|
| ≥50 Gy | | | |
| **Neck Radiation (n=)** | | | |
| <10 Gy | | | |
| 10 to <20 Gy | | | |
| 20 to <30 Gy | | | |
| 30 to <40 Gy | | | |
| 40 to <50 Gy | | | |
| ≥50 Gy | | | |
| **Relapsed** | | | |
| None | | | |
| ≥1 | | | |
| **Diagnosed with 2nd Malignancy** | | | |
| Yes | | | |
| No | | | |

Table 3: Survey Outcomes of Childhood HL Survivors.

| | HL Survivors (N=XYZ) | | Sibling Controls (N=XYZ) | | | | |
|---|---|---|---|---|---|---|---|
| Outcome | Mean (SD) | % Impaired | Mean (SD) | % Impaired | P * | P ** | RR (95%CI)*** |
| **CCSS-NCQ** | | | | | 0.000 | 0.000 | 1.00 (1.00, 1.00) |
| Task Efficiency | | | | | | | |
| Emotional Regulation | | | | | | | |
| Organization | | | | | | | |
| Memory | | | | | | | |
| **BSI-18** | | | | | | | |
| Anxiety | | | | | | | |
| Depression | | | | | | | |
| Somatization | | | | | | | |
| **SF-36** | | | | | | | |
| General Health | | | | | | | |
| Physical function | | | | | | | |
| Physical Role Limitation | | | | | | | |
| Pain | | | | | | | |
| Emotional Role Limitation | | | | | | | |
| Vitality | | | | | | | |
| Social Functioning | | | | | | | |

* P-value for two-sample t-test comparing mean values, **p-value for chi-square tests comparing the frequency of impaired,
*** relative risk from log-binomial regression adjusted for age, sex, and race.

Figure 1: Prevalence of impairment at FU2 and FU5 on CCSS-NCQ domains in survivors and siblings.

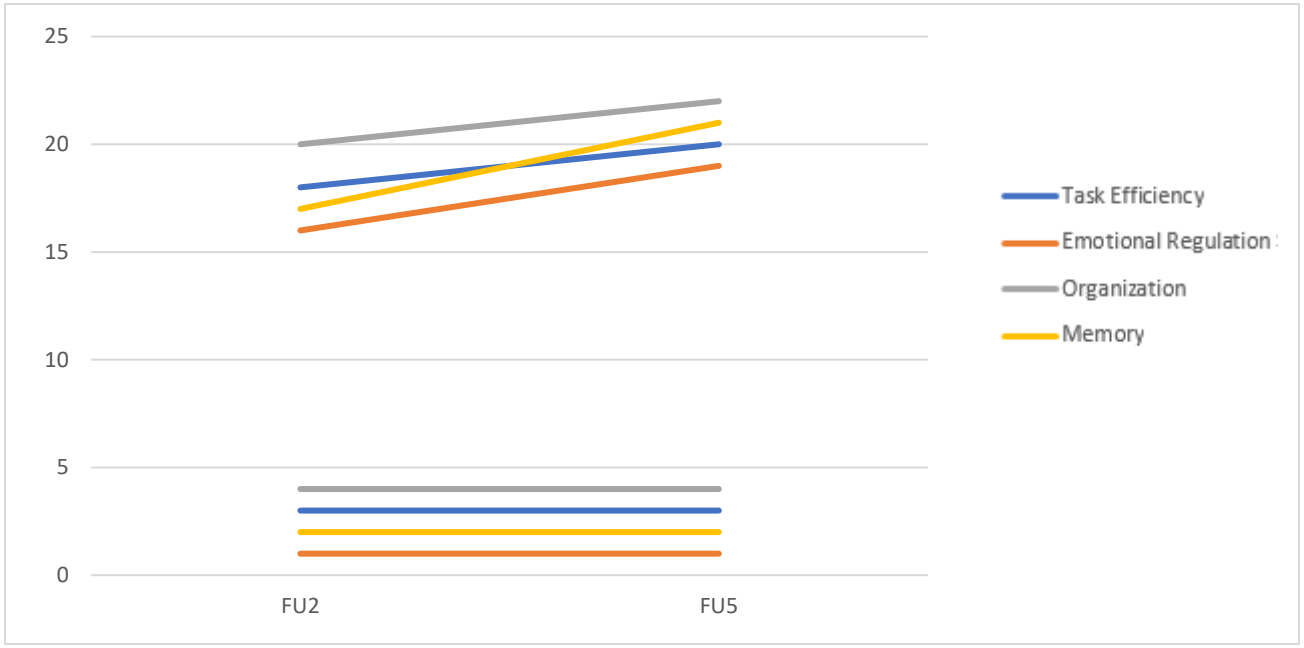


Table 4: Associations of neurocognitive and psychosocial outcomes with demographic and clinical variables.

| | CCSS-NCQ | | | | BSI | | |
|---|---|---|---|---|---|---|---|
| | Task Efficiency | Emotional Regulation | Organization | Memory | Anxiety | Depression | Somatization |
| | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) |
| **Sex** | | | | | | | |
| Female | | | | | | | |
| Male | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) |
| **Race** | | | | | | | |
| Other | | | | | | | |
| White | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) |
| **Age at Diagnosis (Years)** | | | | | | | |
| **Age at Follow Up (Years)** | | | | | | | |
| **Time Since Diagnosis (Years)** | | | | | | | |
| **Smoking Status** | | | | | | | |
| Current (>100 cigs and current smoking) | | | | | | | |
| Former (>100 cigs and no current smoking) | | | | | | | |
| Never | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) |
| **Treatment Era** | | | | | | | |
| 1970-1979 | | | | | | | |
| 1980-1989 | | | | | | | |
| 1990-1999 | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) |
| **Treatment Combinations** | | | | | | | |
| (to be determined) | | | | | | | |
| **Anthracycline dose (per 100 mg/m$^2$)** | | | | | | | |
| **IV Methotrexate** | | | | | | | |
| Yes | | | | | | | |
| No | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Bleomycin** | | | | | | | |
| Yes | | | | | | | |
| No | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) |
| **Corticosteroids** | | | | | | | |
| Yes | | | | | | | |
| None | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) |
| **Chest Radiation (per 10 Gy)** | | | | | | | |
| **Neck Radiation (per 10 Gy)** | | | | | | | |
| **Relapsed** | | | | | | | |
| ≥1 | | | | | | | |
| None | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) |
| **Diagnosed with 2nd Malignancy** | | | | | | | |
| Yes | | | | | | | |
| No | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) |
| | | | | | | | |

Table 4 continued: Associations of neurocognitive and psychosocial outcomes with demographic and clinical variables.

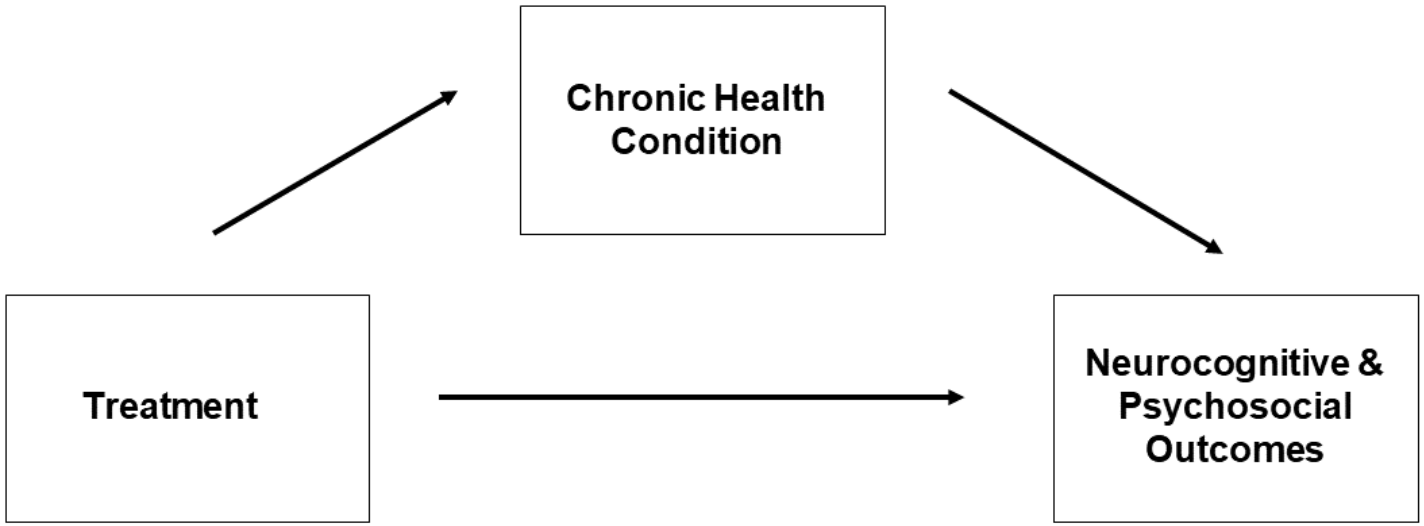
| | SF-36 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | General health | Physical Function | Physical Role Limitation | Pain | Emotional Role Limitation | Vitality | Social Functioning | Mental health |
| | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) |
| **Sex** | | | | | | | | |
| Female | | | | | | | | |
| Male | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | |
| **Race** | | | | | | | | |
| Other | | | | | | | | |
| White | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | |
| **Age at Diagnosis (Years)** | | | | | | | | |
| **Age at Follow Up (Years)** | | | | | | | | |
| **Time Since Diagnosis (Years)** | | | | | | | | |
| **Smoking Status** | | | | | | | | |
| Current (>100 cigs and current smoking) | | | | | | | | |
| Former (>100 cigs and no current smoking) | | | | | | | | |
| Never | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | |
| **Treatment Era** | | | | | | | | |
| 1970-1979 | | | | | | | | |
| 1980-1989 | | | | | | | | |
| 1990-1999 | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | |
| **Treatment Combinations** | | | | | | | | |
| To be determined | | | | | | | | |
| **Anthracycline dose (per 100 mg/m$^2$)** | | | | | | | | |
| **IV Methotrexate** | | | | | | | | |
| Yes | | | | | | | | |
| No | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Bleomycin** | | | | | | | | |
| Yes | | | | | | | | |
| No | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | |
| **Corticosteroids** | | | | | | | | |
| Yes | | | | | | | | |
| None | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | |
| **Chest Radiation (per 10 Gy)** | | | | | | | | |
| **Neck Radiation (per 10 Gy)** | | | | | | | | |
| **Relapsed** | | | | | | | | |
| ≥1 | | | | | | | | |
| None | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | |
| **Diagnosed with 2nd Malignancy** | | | | | | | | |
| Yes | | | | | | | | |
| No | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | 1.0 (ref.) | |

Table 5. Risk of neurocognitive and psychosocial impairment associated with chronic health conditions.

| | **CCSS-NCQ** | | | | **BSI** | | | |
|---|---|---|---|---|---|---|---|---|
| | Task Efficiency | Emotional Regulation | Organization | Memory | Anxiety | Depression | Somatization | |
| | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | |
| Any Grade 3/4 | | | | | | | | |
| Any Grade 2 | | | | | | | | |
| Any Grade 0-1 | Ref (1.0) | Ref (1.0) | Ref (1.0) | Ref (1.0) | Ref (1.0) | Ref (1.0) | Ref (1.0) | |
| | | | | | | | | |
| Grade 2+ Cardiac CHC (vs. grade 0-1) | | | | | | | | |
| Grade 2+ Pulmonary CHC (vs. grade 0-1) | | | | | | | | |
| Grade 2+ Endocrine CHC (vs. grade 0-1) | | | | | | | | |
| Grade 2+ Neurologic CHC (vs. grade 0-1) | | | | | | | | |
| | **SF-36** | | | | | | | |
| | General health | Physical Function | Physical Role Limitation | Pain | Emotional Role Limitation | Vitality | Social Functioning | Mental health |
| | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) | RR (95%CI) |
| Any Grade 3/4 | | | | | | | | |
| Any Grade 2 | | | | | | | | |
| Any Grade 0-1 | Ref (1.0) | Ref (1.0) | Ref (1.0) | Ref (1.0) | Ref (1.0) | Ref (1.0) | Ref (1.0) | Ref (1.0) |
| | | | | | | | | |
| Grade 2+ Cardiac CHC (vs. grade 0-1) | | | | | | | | |
| Grade 2+ Pulmonary CHC (vs. grade 0-1) | | | | | | | | |
| Grade 2+ Endocrine CHC (vs. grade 0-1) | | | | | | | | |
| Grade 2+ Neurologic CHC (vs. grade 0-1) | | | | | | | | |
| | | | | | | | | |
| Models adjusted for age, sex, and race. Any Grade 3/4, grade 2, vs. grade 0-1 and specific Grade 2+ vs 0-1 will be analyzed in separate multivariable models. | | | | | | | | |

Figure 2: Mediation Model




*Treatment, chronic health conditions, and neurocognitive outcomes utilized will depend on results from Aim 2 and 3.

Table 6: Social attainment of HL survivors and sibling controls.

| | HL Survivors (N=XYZ) | Sibling Controls (N=XYZ) | | |
|---|---|---|---|---|
| Outcome | N(%) | N(%) | P * | RR (95%CI)*** |
| **Education** | | | 0.000 | 1.00 (1.00, 1.00) |
| < College graduate | | | | |
| ≥College graduate | | | | |
| **Employment** | | | | |
| Other (unemployed or part-time) | | | | |
| Full-time employed | | | | |
| **Independent Living** | | | | |
| Yes | | | | |
| No | | | | |
| **Personal Income** | | | | |
| <$20,000 | | | | |
| ≥$20,000 | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

*p-value for chi-square tests comparing the frequency of impaired, *** relative risk from log-binomial regression adjusted for age, sex, and race

Table 7: Associations between social attainment and demographic, neurocognitive, and psychosocial outcomes.

| | **College Graduate (vs < College Graduate)** | **Full Time Employment (vs. Other)** | **Independently Living (vs. Dependent)** | **Income <$20,000 (vs. ≥20,000)** |
|---|---|---|---|---|
| | RR 95%CI | RR 95%CI | RR 95%CI | RR 95%CI |
| Age at Diagnosis | | | | |
| Female Sex vs. Male | | | | |
| | | | | |
| **CCSS-NCQ (impaired vs. not)** | | | | |
| Task Efficiency | | | | |
| Emotional Regulation | | | | |
| Organization | | | | |
| Memory | | | | |
| **BSI (impaired vs. not)** | | | | |
| Anxiety | | | | |
| Depression | | | | |
| Somatization | | | | |
| **SF-36 (impaired vs. not)** | | | | |
| General Health | | | | |
| Physical Function | | | | |
| Physical Role Limitation | | | | |
| Pain | | | | |
| Emotional Role Limitation | | | | |
| Vitality | | | | |
| Social Functioning | | | | |
| Mental Health | | | | |
| | | | | |