Title: Physical Functioning and Chronic Health Conditions in Pediatric Acute Lymphoblastic Leukemia and Non-Hodgkin Lymphoma Survivors Treated with Contemporary Therapy

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Background and Rationale:

Impairment in physical functioning compromises quality of life in childhood cancer survivors. In an analysis of the original 1970-1986 Childhood Cancer Survivor Study (CCSS) cohort, Ness et al. reported physical performance limitations in 19.6% of survivors at a median age of 23 years.[1] While survivors were more likely to report late effects of any organ system, including endocrine, musculoskeletal, neurologic, sensory, cardiac or pulmonary, after adjustment for demographic factors, both musculoskeletal and neurologic impairments were shown to increase risk for performance limitations.[1] Limitations included the inability to lift objects, carry groceries, climb a few flights of stairs, walk one block, bathe or use the toilet. A substantial proportion of survivors reported that their impairments restricted their ability to attend work (20.0%) or school (11.2%). Outcomes in acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL) survivors are of particular interest because these patients represent about 26% of incident cases of childhood cancer in the United States and have current five-year survival rates of 90.8% and 83.7%, respectively.[2]

The existing literature of physical functioning outcomes in ALL and NHL is largely based on patients treated with older treatment strategies that are now infrequently used. Many important innovations have occurred that may affect the risk of physical functioning outcomes necessitating the reevaluation of their late effects. Some treatment changes would be hypothesized to worsen later physical functioning, while others could lead to better outcomes. Table A below represents a summary of therapeutic changes for ALL and NHL.

Table A. General summary of therapy changes in recent decades in patients with ALL and NHL

Diagnosis:	CCSS Cases (n):	Therapeutic Changes:
ALL	Diagnosed 1970-1999: N=6115	• Greater use of dexamethasone vs prednisone • Higher doses of systemic methotrexate • Cranial irradiation only used for high risk patients • More stem cell transplants in high-risk patients: preparative regimens often with total body irradiation

NHL	Diagnosed 1970-1999: N=1959	• Cranial irradiation no longer used • Reduced utilization of radiation to the chest/heart • Greater use of dexamethasone vs prednisone • Higher doses of systemic methotrexate • Reduced cumulative dosage of anthracyclines • Intensification of CNS focused therapy (intrathecal, HDMTX, Ara-C) • More stem cell transplants for recurrent disease

Glucocorticoids are a key component of ALL and NHL therapy, usually in the form of prednisone and/or dexamethasone. With a longer half-life and better CNS penetration, dexamethasone resulted in a significantly reduced rate of CNS relapse compared to prednisone in both the U.S.[3] and the United Kingdom[4] in randomized control trials. Dexamethasone is now incorporated in most ALL and NHL trials. However, dexamethasone has a side effect profile that may confer greater risk of myopathy,[3] osteopenia, stress fractures, weight gain,[4] and osteonecrosis,[5] all impairments that are likely to influence physical functioning.

CNS prophylaxis in ALL and NHL was previously accomplished with cranial radiation. Starting in the early 1980's, other alternatives were sought to avoid the considerable morbidity associated with radiation including hormone deficiencies[6] leading to obesity[7] and impaired growth.[8] Sullivan et al. showed that cranial radiotherapy could be substituted for intrathecal chemotherapy when using effective systemic chemotherapy regimens.[9] Currently, intrathecal chemotherapy, dexamethasone, and higher dose methotrexate are used with great success.[10] Cranial radiation is used rarely and is reserved only for the highest risk patients. With the elimination of cranial irradiation, patients are expected to have lower rates of hormone deficiencies leading to improvement in overall physical functioning.

With improvement in risk-stratification of ALL, more patients with high-risk disease are receiving bone marrow transplantation if they have a suitable donor.[11] Unfortunately, while bone marrow transplantation gives these patients the best chance for long- term remission and potential cure, these patients are given toxic preparative regimens and often suffer long-term side effects of their transplantation. The most common transplant preparative regimens involve total body irradiation (TBI), high doses of cyclophosphamide, and busulfan. Unfortunately, children who receive TBI are at risk for late toxicities including impaired growth and cardiac dysfunction including cardiomyopathy and arrhythmias.[12,13] Transplant complications can include chronic graft versus host disease and the impact of prolonged steroid containing immunosuppression, both of which can impair function.[14]

CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) is one of the standard chemotherapy regimens for NHL. With refinement of risk-based histology/immunophenotype directed protocol therapy, the cumulative dosage doxorubicin has been reduced in favorable risk patients. Reduction in doxorubicin can lead to decreased cardiotoxicity[15] leading to improvement in different aspects of physical functioning.

Given the major changes in therapy for pediatric ALL and NHL, physical functioning outcomes in long-term survivors must be readdressed. The expansion CCSS cohort with patients treated from 1987-1999 offers a unique opportunity to examine how specific changes in therapy have altered the risk of physical functioning outcomes. The proposed analysis will inform survivorship care and strategies for prevention and intervention for patients recently treated for ALL and NHL.

Specific Aims:

Aim 1: To describe changes in the prevalence of physical functioning outcomes (Physical Performance and Participation Restriction (defined in greater detail in the Analysis Framework section)) by treatment era in CCSS patients with a history of ALL and NHL and determine if changes in therapeutic exposures mediate this association.

Hypothesis: As changes in therapy over time led to decreases in cranial radiation, chest radiation involving the heart and reduced doses of anthracyclines, the prevalence of physical performance limitations and participation restrictions will decrease.

Aim 2: Evaluate associations between chronic health conditions influenced by ALL and NHL therapy (endocrinopathy, musculoskeletal impairment, neurological impairment, pulmonary disease and cardiac disease) and physical functioning outcomes.

Hypothesis: The presence of chronic health conditions including endocrinopathies, musculoskeletal impairment, neurological impairment, pulmonary disease and cardiac disease will be associated with an increased risk of physical function impairment or participation restriction.

Analysis Framework:

Subject population:
The study population will consist of all CCSS cases with a history of ALL or NHL from the overall CCSS cohort (diagnosed 1970-1999) who were alive and completed the CCSS Baseline survey as well as the sibling comparison group.

Outcomes of Interest:
We plan to analyze the outcomes using two strategies. For Aim 1, we will analyze overall physical functioning in terms of (1) Physical Performance and (2) Participation Restriction scales, consistent with the methods by Ness et al. (Ann Intern Med. 2005). For Aim 2, we will examine specific chronic health conditions and their effect on physical function (e.g., endocrine impairment).

1. Overall Physical Functioning:
   - Physical Performance: scored by adding the answers to a series of 6 questions about participant's performance of particular physical activities during the past 2 years (Baseline <18 N10 a-f & Baseline N14 a-f; expanded baseline O20 a-f & Baseline <18 O6 a-f). Scores of 1 to 3 are assigned to each of the 6 questions. A lower score indicates a greater degree of limitation.[15] This outcome will be calculated as a continuous score. In addition, patients will be categorized as impaired in Physical Performance if their cutoff score is below the 10th percentile of the distribution of the sibling group.[16]
   - Participation Restriction: categorized as yes/no. A participation restriction will be considered present if participants have a positive response for any of the corresponding questions (Baseline <18 N6-N8 & Baseline N10-N12; expanded Baseline <18 O16-18 & baseline O2-4)[16] regarding limited personal care skills, limited routine activities, or poor health preventing school or work attendance.

2. Predictor Variables
   - Era: Prevalence will initially be reported by era in five and ten-year increments.
   - Treatment: If there is a difference in physical functioning outcomes by era, treatment variables (listed in the table below) will be added to the initial model to see if the addition attenuates the projected effect of era.

Chronic health conditions: We will examine the association of chronic health conditions (Table B), and their impact on physical function. We will evaluate those using CTCAE criteria, looking at any grade 1-4, any grade 2-4, as well as any grade 3-4.

Table B. Proposed Analyses Treatment Factors and Chronic Health Conditions

Treatment Variables:	**Chronic Health Conditions:**
• Treatment with radiation (CRT or TBI) (yes/no; cumulative dose) • Treatment with dexamethasone vs prednisone • Cumulative dose of anthracyclines • Treatment with busulfan • Cumulative alkylating agent dose (CED) • Treatment with vincristine (yes/no; cumulative dosage [if available]) • Treatment with high dose methotrexate (yes/no; cumulative dosage) • Treatment with systemic methotrexate (yes/no; cumulative dosage (None, >0 and <4.3 g/m^2, ≥4.3 mg/m^2)) • Treatment with IT methotrexate (yes/no; cumulative dosage (None, >0 and <230 mg/m^2, ≥230 mg/m^2))	Endocrinopathy • Elevated BMI (>85%tile for age & sex) • See matrix for GH deficiency, hypothyroidism and diabetes Musculoskeletal impairment • Elevated BMI (>85%tile for age & sex) • See matrix for osteoporosis (under endocrine in matrix) and joint replacement Neurological impairment • See matrix for paralysis, problems with balance, weakness in arms and leg, sensory neuropathy Cardiovascular Disease • See matrix for arrhythmia, congestive heart failure, hypertension, stroke Pulmonary Disease • See matrix for chronic cough, emphysema and lung fibrosis

3. Other Predictor Variables

These variables will be evaluated for all analyses (i.e., for both aims)

<u>Individual characteristics:</u>

- Sex (A2 baseline, no option for non-binary)
- Age at diagnosis (continuous; 0-4, 5-9, 10-14, 15-20)
- Elapsed time since cancer diagnosis in years (continuous)

<u>Potential Cofounders</u>

- Smoking habits (Baseline N1-2) (Never smoker, Ever smoker: current, former)
- Drinking habits (Baseline N3-7) (Current: use in past year; Risky drinking: >4 drinks per day or 14 per week for men, >3 per day or 7 per week for women; Heavy drinking: >6 per day for men and >5 per day for women at least once per month in the last year)
- Educational level (Baseline<18 & Baseline O1-2; Exp &Exp<18 R1-R2 (descriptive only)
- Employment (Baseline O5-7, Baseline<18 O6-7; Exp & Exp<18 S1-S2) (descriptive only)
- Annual household income (Baseline & Baseline<18 Q8; Exp & Exp <18 T1) (descriptive only)

<u>Interactions to be tested:</u>

Based on original analysis from Ness et al. (Ann Intern Med. 2005), will check for interactions with age at diagnosis and sex.

Statistical Analysis

For Aim 1. The prevalence of performance limitations and participation restrictions among ALL and NHL survivors, overall and by diagnosis, stratified by era, will be compared with that among the participating siblings using generalized estimating equations (GEE) with the binomial error distribution and the log link, accounting for potential within-family correlation, and will be reported as prevalence ratios. If they appreciably alter the estimates of performance limitations, the patient's age at diagnosis, sex, and age at interview will also be included in the final models. A separate analysis will be done for survivors >25 years of age where smoking and drinking habits (confounders) will be included in the final model. We will also test for the interactions listed above. To address the effect of changes in therapy, year of diagnosis (treatment era) will be used as an explanatory variable and a mediation analysis will be conducted adjusting and un-adjusting for the treatment variables, assessing the change in the regression coefficient of the year of diagnosis: the statistical significance of the change will be assessed by bootstrap.

For Aim 2: The association between chronic health conditions (analyzed in separate models as grade 1-4, 2-4 and 3-4) and physical functioning measures will be analyzed in association with person characteristics, comparing survivors with siblings using GEE with the Poisson error distribution and the log link, estimating rate ratios. If they appreciably alter the regression coefficients, the patient's age at diagnosis, sex, age at interview, and potential confounding health behaviors will also be included in the final models. We will also test for interactions of age at diagnosis with sex on chronic health conditions.

We request that the proposed analysis be completed at the St. Jude Coordinating Center (the analyst will be determined by Dr. Ness).

Summary/Significance

There have been marked treatment changes in recent decades for patients with acute lymphoblastic leukemia and non-Hodgkin lymphoma leading to better overall survival rates. However, these therapeutic changes carry new side effect profiles that may affect the risk of late effects in physical functioning and chronic health conditions. This proposal will address the burden of these therapies on physical functioning and will provide critical data to identify current treatment strategies for the survivorship care of these patients.

References:

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Table 1. Participant Characteristics

Characteristic	Survivors n	Survivors %	Siblings n	Siblings %	p
Age at survey completion					
<20					
20-29					
30-39					
>40					
Age at diagnosis					
0-4					
5-9					
10-14					
15-20					
Survival time					
Sex					
Male					
Female					
Education					
Employment					
Annual Household Income					
Smoking habits (>25 yo)					
Never					
Ever					
Current					
Former					
Drinking habits (>25 yo)					
Current					
Risky					
Heavy					
Diagnosis					
Leukemia					
Non-Hodgkin lymphoma					
Treatment Era					
1970-1979					
1980-1989					
1990-1999					
Treatment					

Treatment with dexamethasone vs. prednisone
Treatment with systemic methotrexate
Treatment with IT methotrexate
Treatment with radiation (CRT or TBI)
Cumulative dose of anthracyclines
Treatment with alkylating agents (CED)
Treatment with busulfan
Medical record not available
Chronic Health Conditions
Endocrinopathy
Musculoskeletal
Neurological
Cardiovascular
Pulmonary

Table 2. Performance limitations and Participation restrictions among siblings and survivors of childhood cancer, combined and by cancer type and treatment era (reported in prevalence ratios) for all survivors and secondary analysis for those greater than 25 years of age.

Cancer Type and Treatment Era	Participants, n	Performance Limitation			Restricted Personal Care Skills			Restricted Routine Activities			Health Prevents School or Work Attendance		
		Participants, n(%)	PR (95% CI)	PR (95% CI) adj for tx**	Participants, n(%)	PR (95% CI)	PR (95% CI) adj for tx**	Participants, n(%)	PR (95% CI)	PR (95% CI) adj for tx**	Participants, n(%)	PR (95% CI)	PR (95% CI) adj for tx**
Siblings (no cancer)			Reference			Reference			Reference			Reference	
All cancer survivors													
1970-1979													
1980-1989													
1990-1999													

*PRs standardized for age, sex and intra-family correlation
**Adjusted additionally for treatment variables (Table B) nominally associated ($p<0.10$) with physical performance and role limitation outcomes in bivariate models

Cancer Type and Treatment Era	Participants, n	Performance Limitation			Restricted Personal Care Skills			Restricted Routine Activities			Health Prevents School or Work Attendance		
		Participants, n(%)	PR (95% CI)	PR (95% CI) adj for tx**	Participants, n(%)	PR (95% CI)	PR (95% CI) adj for tx**	Participants, n(%)	PR (95% CI)	PR (95% CI) adj for tx**	Participants, n(%)	PR (95% CI)	PR (95% CI) adj for tx**
Siblings (no cancer) >25 yo			Reference			Reference			Reference			Reference	
All cancer survivors >25 yo													
1970-1979													
1980-1989													
1990-1999													

*PRs standardized for age, sex and intra-family correlation with drinking and smoking habits included in final model
**Adjusted additionally for treatment variables (Table B) nominally associated ($p<0.10$) with physical performance and role limitation outcomes in bivariate models

Table 6: Risk ratio of physical functioning outcomes by chronic health condition* of patients diagnosed in 1970-1986 and 1987-1999

	1970-1979				1980-1989				1990-1999			
Chronic Health Condition	Performance Limitation	Restricted Personal Care Skills	Restricted Routine Activities	Health Prevents School or Work Attendance	Performance Limitation	Restricted Personal Care Skills	Restricted Routine Activities	Health Prevents School or Work Attendance	Performance Limitation	Restricted Personal Care Skills	Restricted Routine Activities	Health Prevents School or Work Attendance
Endocrine impairment	N, RR and 95% CI	N, RR and 95% CI	N, RR and 95% CI	N, RR and 95% CI	N, RR and 95% CI	N, RR and 95% CI	N, RR and 95% CI	N, RR and 95% CI	N, RR and 95% CI	N, RR and 95% CI	N, RR and 95% CI	N, RR and 95% CI
Musculoskeletal impairment												
Neurological impairment												
Cardiovascular impairment												
Pulmonary impairment												

*Will assess with any grade 1-4, grade 2-4 and grade 3-4 chronic health conditions