04-11

CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

1. **STUDY TITLE:** Physical Activity in Adult Survivors of Childhood Acute Lymphoblastic Leukemia

2. **WORKING GROUP AND INVESTIGATORS:** The proposed analyses will be within the Chronic Disease Working Group. The proposed investigators (name/email/phone) will include:

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3. **BACKGROUND AND RATIONALE:**

Childhood cancer survivors, once rare, are now becoming a large, productive segment of our population, currently representing an estimated 1 in 640 young adults aged 20-39 in the United States.[1] Ever increasing numbers of children diagnosed with and treated for childhood acute lymphoblastic leukemia (ALL) are surviving into adulthood, currently representing over 25% of all long-term survivors of childhood cancer. As a result of developments in combination chemotherapy and radiation therapy, cure rates for ALL have increased dramatically from 61% in the period from 1975-84 to 77% in 1985-1994.[2] Over the last forty years, chemotherapy has included vincristine, methotrexate, prednisone, asparaginase, and anthracyclines. Cranial irradiation was a standard part of ALL therapy from the 1960s up until the 1980s, at which time intrathecal methotrexate became the modality of choice for central nervous system prophylaxis. The currently recognized late sequelae of these treatments include cardiovascular disease[3], obesity[4], and osteoporosis.[5] Because of the increased risk of these entities, and the significant morbidity and mortality that accompanies them, it is essential to identify areas where clinicians and survivors can work to improve opportunities to prevent or reduce the occurrence of these sequelae.

In the general population, regular moderate-intensity physical activity has been demonstrated to be protective against cardiovascular disease, including hypertension[6] and non-insulin-dependent diabetes mellitus[7], and osteoporosis.[8] The benefits derived from physical activity may be even more important in the growing population of ALL survivors whose risk for these health problems is increased above and beyond that of the general population. Despite these increased risks, several small studies have suggested that survivors of childhood malignancy have decreased levels of physical activity and energy expenditure when compared to subjects without history of malignancy. For example, in a sample of 88 children 7 to 18 years of age, Warner et al suggested that total daily energy expenditure and physical activity levels were significantly reduced in the 35 ALL survivors when compared to 21 survivors of other malignancies and 32 children without history of cancer.[9] In a different study using the same cohort, ALL survivors showed a reduced submaximal and maximal response to exercise, which was also associated with increasing body fat.[10] Reilly et al also demonstrated significantly reduced total energy expenditure in a group of 20 ALL survivors (mean age, 10.9 years) compared to healthy subjects, which was found to be due largely to reduced habitual physical activity in the survivor group.[11] Mayer et al specifically found that cranial irradiation in ALL survivors 10-20 years old was associated with a decreased

resting metabolic rate and lower levels of physical activity when compared to non-irradiated ALL survivors.[12] In 2001, only 45.4% of the general population report meeting CDC-recommended physical activity guidelines of 30 or more minutes of moderate-intensity physical activity on 5 or more days per week or 20 or more minutes of vigorous-intensity activity on 3 or more days per week.[13] The studies cited above suggest that it may be possible that this number is even lower for survivors of childhood cancer, making it vital for there to be a definitive study on physical activity levels in childhood cancer survivors.

The underlying mechanisms by which physical activity seems to be decreased in ALL survivors are unknown. One hypothesis is that craniospinal irradiation, anthracycline administration, and/or bone marrow transplantation can lead to toxicity that reduces lung function and thus exercise capacity. Jenney et al demonstrated that there was a significant reduction of FEV1, FVC, TLC, and DLCO in ALL survivors with a mean age of 14.6 years. In addition, 42% of survivors reported some degree of exercise intolerance.[14]Another possible mechanism is that the neuromuscular effects of vincristine therapy occur during a critical period in the acquisition of motor skills and coordination. Though the mixed motor-sensory peripheral neuropathy of vincristine is generally believed to reverse after cessation of therapy, several studies have demonstrated prolonged morbidity after completion of therapy. Harila-Saari et al reported that after ALL therapy 63% of subjects had gross motor difficulties and 31% had fine motor difficulties.[15] Other hypotheses for decreased activity levels are that ALL survivors are depressed, overprotected or have lower self-esteem when compared with their peers.

The studies produced thus far exploring physical activity levels in childhood cancer survivors all have been limited by their small sample size. In a recent NIH R01 grant proposal, Oeffinger notes that "six European cross-sectional, generally well-designed studies assessing 220 leukemia survivors in their childhood and adolescent years have reported a mild to moderate reduction in exercise capacity and habitual physical activity levels."[16] The Childhood Cancer Survivor Study (CCSS) has data from 4,155 survivors of childhood ALL, which would, as far as we know, make this study the largest investigation of physical activity levels in childhood cancer survivors yet produced, analyzing data from almost 4,000 more ALL survivors than all six previous studies combined. In addition to its size, it also will be the first study of physical activity levels in survivors that is generalizable because it draws subjects from 26 institutions across the country, rather than a single center. All six of the previous studies have explored physical activity levels specifically in children and adolescents after their cancer experience. As the number of adult survivors increases, it becomes imperative to understand the health behaviors of this productive, yet vulnerable population. To our knowledge, there has been no study that explores whether these trends in physical inactivity extend into adulthood. Our study will therefore not only contain the largest number of subjects compared to prior studies, but it will also be the first analysis exploring *adult* survivors of childhood cancer and their physical activity levels. In addition, this sample size will allow us to explore the role of cranial irradiation, chemotherapeutic agents, smoking, body mass index, and general health status on physical activity levels. Furthermore, because the physical activity questions are identically worded to those utilized in the Behavioral Risk Factor Surveillance System (BRFSS) survey, we will be able to make the unprecedented comparison between physical activity levels in a large data set representing the general population and childhood cancer survivors. By exploring physical activity levels in a large group of adult survivors of childhood cancer and comparing them to the general population, we will be able to begin to understand patterns of behavior never before examined that could have a profound impact on the quality of life of this population. We hope that it will highlight the importance of finding effective means of increasing physical activity in a population vulnerable for cardiovascular disease, obesity, and osteoporosis.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES

This series of analyses is designed to investigate the physical activity levels of adult survivors of ALL and other pediatric malignancies, and to determine treatment variables that may be related to decreased physical activity. We have two objectives: (1) to describe the levels of physical activity in ALL and other childhood cancer survivors, including the number of subjects meeting CDC recommendations for physical activity, by demographic and clinical treatment characteristics, and (2) to compare the physical activity levels of this population of childhood cancer survivors with the general U.S. population (2003 Behavior Risk Factor Surveillance System [BRFSS]).

Hypotheses:

1. Adult survivors of childhood ALL will be even less likely to meet the CDC-recommended levels of physical activity compared to adults in the general population with no history of malignancy.

2. Self-reported diminished physical activity levels will be independently associated with cancer type and treatment, age at diagnosis, age at response to questionnaire, ethnicity, general health status, and body mass index (BMI). Specifically, we hypothesize that subjects treated with cranial or craniospinal irradiation or with moderate to higher doses (>200 mg/m^2) of anthracyclines (daunomycin, doxorubicin) will demonstrate decreased activity levels. In addition, subjects with an increased BMI or a general health status of "poor" or "fair" will be more likely to be physically inactive.

5. ANALYSIS FRAMEWORK

(a) Outcome of Interest:

1. Leisure-time physical activity levels as defined below. (Questions D1-7 in CCSS LTFU 2, Questions 3.1, 18.2-18.7 in BRFSS 2003)
    a. Inactive: No leisure-time physical activities in the past month (Question D1 LTFU, 3.1 BRFSS).
    b. Moderate: Physical activity for at least 10 minutes at a time that causes a small increase in breathing or heart rate (Question D5 LTFU, 18.5 BRFSS).
    c. Vigorous: Physical activity for at least 10 minutes at a time that causes a large increase in breathing or heart rate (Question D2 LTFU, 18.2 BRFSS).
    d. CDC-recommended Physical Activity Levels: Moderate intensity physical activities for ≥30 minutes per day on ≥5 days per week or vigorous intensity physical activities for ≥20 minutes per day on ≥3 days per week. (Calculated from Questions D3-4 and D6-7 in LTFU, 18.3-4 and 18.6-7 in BRFSS)

(b) Subject Population:

Subjects will be drawn from the CCSS population ≥18 years of age who have participated in the Long-Term Follow-Up (LTFU) Study 2 in 2002 to 2003. We will exclude all brain tumor survivors and patients with a history of lower extremity amputations or limb-salvage procedures. Our primary target population will be survivors of ALL, as this population is the most numerous and has demonstrated increased risk for obesity, osteoporosis, and cardiovascular complications, all of which have been shown to decrease with adequate physical activity in the general population. We would like to also compare this target population to the remaining CCSS cohort as a secondary target population. Exploring the cancer survivors with diagnoses other than ALL will allow us to examine the role of cranial irradiation and vincristine therapy in physical activity outcomes. Our comparison group, the general population, will be drawn from the 2003 cohort of the Behavioral Risk Factor Surveillance System (BRFSS) survey, a survey with significant precedents in representing the

general population in scientific studies.[17] The wording of the physical activity questions in the LTFU 2 Survey are identical to the corresponding questions in the BRFSS 2003 Survey, with the exception of the addition of "wheelchair basketball" to the CCSS survey.

(c) Independent Variables:

1. Sex
2. Age at response to CCSS questionnaire
3. Annual Household Income
4. Educational Attainment
5. Ethnicity
6. Cancer Type
7. Age at cancer diagnosis
8. Interval from cancer diagnosis
9. Type of treatment (surgery, radiation, chemotherapy)
10. Type and cumulative doses of chemotherapy drugs, including vincristine and anthracyclines (daunomycin, doxorubicin)
11. Dose of cranial or craniospinal irradiation
12. Body mass index (BMI, calculated by converting height and weight from inches and pounds to centimeters and kilograms to achieve kg/m^2)
13. Self-reported general health status
14. Current tobacco use

Analysis Plan:

The descriptive data will be reported as means with standard deviations and/or medians with ranges. The primary outcome variable will be expressed in percentages with 95% confidence intervals. We will first perform bivariate analysis. Multivariate analyses will be performed to determine the factors independently associated with differences in physical activity between the ALL population and the general population, and to determine the factors that modify outcomes solely in the ALL population. In the following tables, income and age groups are arbitrary and may change based on the available data.

Ed Fryer and Peggy Auinger at the American Academy of Pediatrics' Center for Child Health Research in Rochester, New York will carry out the analyses. We anticipate having data available by early October. We will merge the data from the CCSS and BRFSS and proceed with the bivariate and multivariate analyses during the month of October and early November. An abstract will be prepared for submission prior to the end of November, so that a final abstract can be submitted by December 6, 2004 to the Pediatric Academic Societies' for presentation at their annual meeting in May 2005. The text of the paper will be written between December 2004 and March 2005, and submitted for publication by the end of April 2005.

(d) Examples of Specific Tables and Figures:

Table 1: Demographic Characteristics of CCSS and BRFSS Populations

Variable	CCSS ALL Survivors (n =)	CCSS Other Cancer Survivors (n =)	BRFSS General Population Cohort (n =)
Age at Interview			
18-29			
30-39			
≥40			
Sex, % female			
Ethnicity, %			
White, NH			
Black, NH			
Hispanic/Latino			
Other			
Income, %			
<$20,000			
≥$20,000			
Educational Attainment			
High School Graduate or less			
High School Graduate and some college			
Age at Cancer Diagnosis, years			
Mean			
SD			
Median			
Range			
Interval from diagnosis, years			
Mean			
SD			
Median			
Range			
Treatment			
Chemotherapy			
Dexamethasone			
Prednisone			
Antracyclines >300 mg/m^2			
Vincristine			
Chemotherapy, no CRT			
Chemotherapy, with CRT			
10.0-19.9 Gy			
≥20 Gy			

Table 2: Physical Activity in ALL Survivors Compared to the General Population

	ALL Survivors (n =)					BRFSS Population (n =)				
Variable	**Inactive, % (95% CI)**	**Moderate Activity, % (95% CI)**	**Vigorous Activity, % (95% CI)**	**Both, % (95% CI)**	**Recommended Activity, % (95% CI)**	**Inactive, % (95% CI)**	**Moderate Activity, % (95% CI)**	**Vigorous Activity, % (95% CI)**	**Both, % (95% CI)**	**Recommended Activity, % (95% CI)**
TOTAL										
Sex										
Male										
Female										
Age Group										
18-29										
30-39										
≥40										
Annual Income										
<$20,000										
≥$20,000										
Ethnicity										
White, NH										
Black, NH										
Hispanic/Latino										
Other										
Educational Attainment										
High School Graduate or Less										
High School Graduate and Some College										

Variable	Inactive, % (95% CI)	Moderate Activity, % (95% CI)	Vigorous Activity, % (95% CI)	Both, % (95% CI)	Recommended Activity, % (95% CI)	Inactive, % (95% CI)	Moderate Activity, % (95% CI)	Vigorous Activity, % (95% CI)	Both, % (95% CI)	Recommended Activity, % (95% CI)
Interval from diagnosis, years										
Treatment										
Chemo Only										
Chemo + 1-19 Gy CRT										
Chemo + ≥20 Gy CRT										
Age at Diagnosis										
0-4 years										
5-9 years										
10-14 years										
15-21 years										
BMI (kg/m^2)										
<25										
25-29.9										
≥30										
General Health Status (Question E.1.)										
Poor										
Fair										
Good										
Very Good										
Excellent										
Current Smoker										

Table 3: Multivariate Analysis of Physical Activity Patterns, General Characteristics

Covariates*	Mod Activity, OR (vs. none)	Vigorous Activity, OR (vs. none)	Both, OR (vs. none)	Recommended Activity, OR (vs. less than recommended)
Group				
ALL Survivors				
BRFSS Controls				
Sex				
Male				
Female				
Age Group				
18-29				
30-39				
≥40				
Annual Income				
<$20,000				
≥$20,000				
Educational Attainment				
High School Graduate or Less				
High School Graduate and Some College				
Ethnicity				
White, NH				
Black, NH				
Hispanic/Latino				
Other				
BMI (kg/m^2)				
<25				
25-29.9				
≥30				
General Health Status (Question E.1.)				
Poor				
Fair				
Good				
Very Good				
Excellent				
Current Smoker				

*Variables will be evaluated only if significant at $p<0.10$ in bivariate analysis.

Table 4: Multivariate Analysis of Physical Activity Patterns in ALL Survivors, Cancer-Related Factors

Covariates*	Mod Activity, OR (vs. none)	Vigorous Activity, OR (vs. none)	Both, OR (vs. none)	Recommended Activity, OR (vs. less than recommended)
Treatment				
Chemo Only				
Anthracyclines >300 mg/m^2				
Vincristine				
Prednisone/Dexamethasone				
Chemo + 1-19 Gy CRT				
Chemo + ≥20 Gy CRT				
Age at Diagnosis				
0-4 years				
5-9 years				
10-14 years				
15-21 years				

*Variables will be evaluated only if significant at $p<0.10$ in bivariate analysis.

6. SPECIAL CONSIDERATION:

Resources are available to handle the dataset and analyze the data at the Center for Child Health Research of the American Academy of Pediatrics and the University of Rochester.

7. REFERENCES:

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