

CHILDHOOD CANCER SURVIVOR STUDY Analysis Concept Proposal

- TITLE:** Physical performance and health related quality of life in adult survivors of childhood cancer
- WORKING GROUP INVESTIGATORS:** This proposed study will be within the Neuropsychological working group. Proposed investigators include:

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3. BACKGROUND AND RATIONALE:

This concept proposal is in response to the study group chair and principle investigator's requests for the investigators to use the proposed model to examine the whole cohort prior to examining the brain cancer survivor cohort within CCSS. The proposals are submitted simultaneously and have nearly identical analyses plans.

3.1 Introduction: Progress in the treatment of childhood cancers over the past few decades has led to an increase in the population of survivors and to an increasing interest in the long term consequences of cancer and its treatment modalities. Estimates from the National Cancer Institute (NCI) indicate that there are 1/300 adults alive today who have had a diagnosis of a cancer during childhood.¹ Treatment today is focused both on survival and on reducing morbidity in children who survive. Despite these efforts, surgery, radiation and chemotherapy continue to be necessary to save lives. These medical procedures may have a detrimental effect on the developing child.

Structural or physiological impairments of the body's organ systems as a consequence of either the cancer or treatment intervention may alter normal organ system functioning. Survivors of childhood cancer may have limitations in cognitive, emotional, and physical performance. Less than optimal function within these domains may interfere with activities of daily living and affect the survivor's health related quality of life (HRQOL) and their life satisfaction. We are particularly interested in the type and extent of limitations in physical performance among survivors of childhood malignancies, in the impact of these limitations on HRQOL and life satisfaction, and in treatment related risk factors that may predict limitations in physical performance and adverse QOL outcomes.

3.2 Functional limitations in childhood cancer survivors: There is evidence to suggest that a certain proportion of individuals who survive childhood cancer may be left with long-term neurological or musculoskeletal deficits that limit physical performance. The evidence suggests that adults who have survived childhood brain cancer, bone tumors, neuroblastoma, or Hodgkin's disease are at greatest risk for the development of physical performance limitations. Radiation or chemotherapy and neurological, musculoskeletal, or cardiopulmonary late effects were also risk factors for poor physical performance outcomes.²

3.3 QOL and life satisfaction in childhood CANCER survivors: The association between persistent limitations in physical performance, and HRQOL or life satisfaction once survivors of childhood malignancies reach adult status are not clear. The literature rarely addresses this association, making it difficult to determine the impact of physical limitations on daily life and participation in social roles. Many QOL instruments include a component or subscale that measures physical functioning, indicating that intact physical functioning is necessary for quality in and satisfaction one's life. There have been several studies that have examined HRQOL in childhood cancer survivors who were still children. Foreman et al.³ examined health status in 52 teenage long-term survivors of childhood brain tumors and reported increased morbidity among brain tumor survivors when compared to other cancer survivors. The interview included questions about mobility; however, specific limitations in physical performance and their association with health status or life satisfaction were not evaluated. Another study⁴ evaluated HRQOL in 41 childhood brain tumor survivors and found that global health status was lowest for children who received radiation therapy. The authors did not evaluate the association between limitations in physical performance and either HRQOL or life satisfaction. In one study of adult survivors of a variety of childhood solid tumors,⁵ 220 survivors completed a telephone interview and cancer specific questionnaires to evaluate HRQOL. Health status was found to be a predictor of HRQOL. Again, the associations between limitations in physical performance and HRQOL or life satisfaction were not evaluated.

Recent evaluations of HRQOL in adult survivors of childhood cancer have demonstrated an association between fatigue and HRQOL, suggesting the possibility that deficits in muscle performance may also contribute to HRQOL deficits. Meeske et al. reported an inverse association between fatigue and HRQOL in 196 young adult survivors of childhood leukemia,⁶. In their study, fatigue was also associated with poor exercise tolerance. Fatigue is inversely associated with HRQOL in the CCSS cohort (Mulrooney – manuscript in process).

3.4 Summary: Reports of neuromotor, musculoskeletal or cardiopulmonary dysfunction in childhood malignancies suggest that some survivors are likely to have limitations in physical function that may affect HRQOL and life satisfaction. Previous studies indicate that type of cancer, radiation, chemotherapy may be important predictors of physical performance limitations. The association between physical performance limitations, the impact of these limitations on HRQOL, and the specific treatment variables (e.g. radiation dose and tumor location) that place the survivor at the greatest risk for developing physical performance limitations are not available.

A description of HRQOL and life satisfaction in this large cohort of childhood cancer survivors and an analysis of the association between baseline physical performance and HRQOL measured 6-8 years later during the second follow-up survey will add to the literature. It will describe HRQOL outcomes in the largest cohort of childhood cancer survivors, and provide an evaluation of the impact of reported physical performance at one point in time on HRQOL and life satisfaction several years in the future. It is important for researchers and clinicians to understand the impact of physical performance limitations are on HRQOL and life satisfaction over time, so that they design interventions to restore function, teach compensatory strategies for losses in function, or recommend environmental adaptations to optimize function. If limitations in function result in poor HRQOL or less than optimal life satisfaction, early interventions designed to remediate functional losses may prevent or reduce disability and improve quality of life in childhood cancer survivors. It is important to understand if these limitations vary among cancer survivors who have had different treatment interventions (for example radiation treatment), so that persons at greatest risk for the development of functional limitations can be targeted for close surveillance and early intervention.

We will evaluate HRQOL with the SF-36 and life satisfaction with the Ladder of Life. The SF-36 widely used and well-validated measure of HRQOL. It is scored with two component summary scales and 8 individual subscales that represent different aspects of well-being.⁷ The component scales are the physical component summary (PCS) and the mental component summary (MCS). The subscales include physical functioning, role function-physical (assessing role limitations caused by physical factors), bodily pain, social functioning, mental health, role function-emotional (assessing role limitations caused by emotional factors), vitality, and general health. General population norms are available for the SF-36.⁸ The data for the summary scales and the subscales are presented as T-scores, with a normal healthy population mean score of 50 and a standard deviation (SD) of 10. Higher scores indicate "better" HRQOL. The Ladder of Life assesses respondents' life satisfaction with three self-report items that provide a subjective rating of life satisfaction in the past, at the present time, and anticipated for the future. Ratings are made on a 10-point scale ranging from "Best Possible Life" to "Worst Possible Life."⁹ This scale provides a global rating of life satisfaction and is widely used in epidemiologic and population studies as well as in clinical samples of cancer survivors.¹⁰

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

The purpose of this manuscript will be to describe quality of life and life satisfaction, and to evaluate the association between physical performance and both HRQOL and life satisfaction in adult survivors of childhood cancer. We will also describe those survivors at greatest risk for physical performance limitations, poor HRQOL or poor life satisfaction. To accomplish this, we will examine the relationship between physical performance variables, cognitive and emotional performance variables, sociodemographic variables, disease and treatment variables, and HRQOL and life satisfaction outcomes.

- 4.1 Aim 1:** To describe HRQOL and life satisfaction among adult survivors of childhood cancer. *We hypothesize that adult survivors of childhood cancer will report lower mean scores on the SF-36 and Ladder of Life Scales when compared to both sibling and population normative values.*
- 4.2 Aim 2:** To evaluate the association between physical, cognitive and emotional performance, and both HRQOL and life satisfaction among childhood cancer survivors. *We hypothesize that survivors who report lower physical performance, after accounting for cognitive and emotional performance will have lower mean scores on the SF-36 and Ladder of Life Scales.*
- 4.3 Aim 3:** To evaluate the associations between treatment and disease related variables and adverse performance, HRQOL and life satisfaction outcomes. *We hypothesize that the disease variables related to adverse outcomes include younger age at treatment and the type of the primary cancer. We hypothesize that treatment the primary treatment variable related to adverse outcomes will be radiation therapy (particularly higher dose, cranial radiation, field involving the frontal lobes or cerebellum). We hypothesize that the impact of both disease and treatment variables will be partially mediated by physical, cognitive and emotional performance limitations.*
- 4.4 Aim 4:** To evaluate the associations between sociodemographic variables and adverse HRQOL and life satisfaction outcomes. *We hypothesize that sociodemographic variables related to adverse outcomes include female gender, failure to complete high school and lower household annual income*

5. ANALYSIS FRAMEWORK:

This analysis will be done by Kirsten Ness at the University of Minnesota with guidance from Melanie Wall, a Structural Equation Model expert, and oversight provided by Wendy Leisenring at the Statistical Coordinating Center.

5.1 Sample: Adults (≥ 18 years at time of response to 2nd follow-up questionnaire) who are survivors of childhood cancer and siblings.

5.2 Outcomes:

5.2a. Health related Quality of Life: SF-36; summary measures (physical health, mental health); scales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health) (E and F questions on 2nd follow up questionnaire).

5.2b. Life satisfaction: Ladder of life (1 questions on 2nd follow up questionnaire)

5.3 Independent (exploratory variables)

5.3.a. Physical performance: will be scored by adding the answers to N.14 a-f from the baseline questionnaire where survivors indicate performance of particular physical activities over the past two years. Scores of 1 to 3 will be assigned to each of the six questions: 1=limited in the particular activity for more than three months, 2=limited in the particular activity for 3 months or less, and 3=not limited at all. A lower score indicates more difficulty with physical performance. Disability will be defined as a yes answer to either of the following two questions: 1) "Because of any impairment or health problem, do you need the help of other persons with personal care needs, such as eating, bathing, dressing, or getting around the home?" and 2) "Because of any impairment or health problem, do you need the help of other persons in handling routine needs, such as everyday household chores, doing necessary business, shopping or getting around for other purposes?" This variable will be evaluated both as a continuous and a dichotomous variable. It has previously been compared between survivors and siblings as both a continuous and a dichotomous indicator, so a "cutoff" score for the lowest 10th percentile of siblings is available to classify participants.

5.3.b. Cognitive performance: will be evaluated by scoring the Behavioral Rating Inventory of Executive Function – Adult Version (BRIEF-A), questions J.1-J.25 from the second follow-up survey. "The BRIEF-A is a standardized measure that captures views of an adult's executive functions or self-regulation in his or her everyday environment."¹¹

5.3.c. Emotional health: will be evaluated by scoring the Brief Symptom Inventory-18 (BSI-18), questions G.1-18 from the second follow-up survey. The BSI-18 is a measure of global mental health and of depression, somatization, and anxiety. The BSI-18 has been validated in cancer survivors and population controls.¹² It is highly correlated with the Symptom Checklist-90-Revised ($r = 0.93$) and the Minnesota Multiphasic Personality Inventory (MMPI) ($r=0.60$). Participants with scores on the global status index ≥ 63 are classified as having poor emotional health.

5.3.b. Disease variables:

- i. Age at diagnosis
- ii. Time at risk (from diagnosis to interview)
- iii. Specific Diagnosis ICD-0 codes)

5.3.c. Treatment variables:

- i. Chemotherapy vs. surgery vs. radiation vs. combination
- ii. If radiation → field, dose
- iii. If surgery → specific surgical procedure abstracted from ICD-9 procedure codes:

5.3.d. Sociodemographic variables:

- i. Age at interview
- ii. Gender
- iii. Race/ethnicity
- iv. Household income
- v. Health insurance
- vi. Education
- vii. Marital status
- viii. Employment status

5.4 Statistical analysis

5.4.a. Aim 1: To describe HRQOL and life satisfaction among adult survivors of childhood cancer we will calculate norm-based means and standard deviations, reporting them in either table or graphic format for the SF-36 component summary scales and the subscales. We will compare the norm-based scores to same age and sex population normative values and the sibling comparison group with one sample t-tests and report the results as mean differences with standard errors and p-values.

5.4.b. Aim 2: To describe the association between physical performance, and both HRQOL and life satisfaction among childhood cancer survivors we will use general linear regression models with the physical performance variable first as a continuous variable and then as a dichotomous variable. We will consider cognition, emotion, age at interview, sex and race/ethnicity as possible confounders or modifiers of this association in multiple variable models.

5.4.c. Aim 3: To evaluate the associations between treatment and disease related variables and adverse physical performance, HRQOL and life satisfaction outcomes, we will construct structural equation models to determine the direct effects of each disease and treatment variable on the HRQOL/life satisfaction outcomes and the indirect effects of each disease and treatment variable on the HRQOL/life satisfaction outcome based on its' effect on cognitive, emotional and physical performance. We will also report associations between variables with shared antecedents and assumed prior correlations. Models will be evaluated with exploratory and confirmatory factor analysis and Chi-squared fit indices. Results will be reported as covariances/correlations and regression coefficients.

5.4.d. Aim 4: To evaluate the associations between sociodemographic variables and adverse HRQOL and life satisfaction outcomes we will use multiple variable linear regression, reporting results as mean differences with standard errors and p-values.

6. TABLES/FIGURES

Table 1: Sociodemographic characteristics of the study population

	Number	Percent
Gender		
Male		
Female		
Age at second follow-up		
18-24 years		
25-34 years		
35+ years		
Race/Ethnicity		
White		
American Indian		
Asian		
Black		
Hispanic		
Other		
Educational attainment		
< High school		
High school graduate		
College graduate		
Marital status		
Married or living as married		
Single		
Divorced or separated		
Employment		
Employed or caring for home		
Student		
Looking for work/unable to work		
Annual household income		
< \$20,000		
\$20,000 +		
Health insurance		
Yes		
No		

Table 2: Diagnosis and treatment characteristics of the study population

	Number	Percent
Age at diagnosis		
0-3 years		
4-9 years		
10-14 years		
15-20 years		
Diagnosis		
Radiation field		
Radiation dose		
Chemotherapy		

Table 3. Physical performance, quality of life and life satisfaction means, standard errors

	Survivors		Population norm		
	Mean	SE	Mean	SE	
Physical performance			****		
SF36 Physical summary scale					
SF36 Mental summary scale					
Role physical					
Physical function					
Bodily pain					
General health					
Vitality					
Role emotional					
Social function					
Mental health					
Ladder of life now					
Ladder of life 5 years ago					
Ladder of life 5 years in the future					

****CCSS Sibling norm

REFERENCES

1. National Cancer Institute. Seer Cancer Query System. 2005. Available at: <http://canques.seer.cancer.gov> (Accessed: August 10, 2005).
2. Ness KK, Mertens AC, Hudson MM, et al. Limitations on physical performance and daily activities among long-term survivors of childhood cancer. *Ann Intern Med* 2005;143:639-47.
3. Foreman NK, Faestel PM, Pearson J, et al. Health status in 52 long-term survivors of pediatric brain tumors. *J Neurooncol* 1999;41:47-53.
4. Barr RD, Simpson T, Whitton A, Rush B, Furlong W, Feeny DH. Health-related quality of life in survivors of tumours of the central nervous system in childhood--a preference-based approach to measurement in a cross-sectional study. *Eur J Cancer* 1999;35:248-55.
5. Crom DB, Chathaway DK, Tolley EA, Mulhern RK, Hudson MM. Health status and health-related quality of life in long-term adult survivors of pediatric solid tumors. *Int J Cancer Suppl* 1999;12:25-31.
6. Meeske KA, Siegel SE, Globe DR, Mack WJ, Bernstein L. Prevalence and correlates of fatigue in long-term survivors of childhood leukemia. *J Clin Oncol* 2005;23:5501-10.
7. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
8. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993;31:247-63.
9. Cantril H. The pattern of human concerns. New Brunswick, NJ: : Rutgers University Press, 1965.
10. Ganz PA, Desmond KA, Leedham B, Rowland JH, Meyerowitz BE, Belin TR. Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. *J Natl Cancer Inst* 2002;94:39-49.
11. Psychological Assessment Resources. Available at: <http://www3.parinc.com/products/product.aspx?Productid=BRIEF-A> (Accessed: November 11, 2005).
12. Derogotis L. Brief Symptom Inventory (BSI) administration, scoring, and procedures manual. 3rd ed. Minneapolis: NCS Pearson, Inc., 2000.