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#04-10

Childhood Cancer Survivor Study Analysis Concept Proposal

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Title: Physical disability and limitations in physical function in long-term neuroblastoma survivors

Working Group and Investigators:

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1.0 Background and Rationale:

Current treatment options for neuroblastoma, based on risk classification and tumor dissemination, include conservative surgical resection, chemotherapy, immunotherapy, radiation, 13-cis retinoic acid, and hematopoietic stem cell transplantation. Local tumors in low risk children are typically managed with surgery only(1-3), whereas children with high risk or metastatic disease may require transplantation and intensive chemotherapy to achieve and maintain complete remission(1, 4).

Most long-term survivors of neuroblastoma are those who had low-risk disease and were treated in an earlier treatment era when treatment included radical surgery, aggressive chemotherapy, and orthovoltage (x-ray) radiation. Reported treatment complications include musculoskeletal impairments (scoliosis, kyphosis, hypoplasia and fibrosis of bone and soft tissue, and slipped capital femoral epiphysis)(5-7), and neurological problems (paresthesias, paresis, paraplegia and neurogenic bladder).(7, 8) Musculoskeletal damage is usually related to high doses of orthovoltage therapy, and neurological dysfunction to either damage from the tumor itself or the surgical procedure used to remove the tumor.(9-11) Both musculoskeletal and neurological problems have the potential to impact physical function and may result in significant physical disability.

Long-term complications of treatment in high-risk neuroblastoma survivors are not well described in the medical literature. However, in a recent study of 63 long term survivors treated at Memorial Sloan Kettering Cancer Center, Laverdiere et al. report hypothyroidism and pulmonary dysfunction in addition to musculoskeletal abnormalities, neurocognitive and neurosensory deficits.(12) Endocrine dysfunction has the potential to alter body composition(13) which may interfere with optimal physical function. Cardiac or pulmonary late effects may result in diminished aerobic capacity with diminished mobility and physical independence.

It is important to describe the long-term complications of treatment for neuroblastoma to develop and implement appropriate surveillance and follow up treatment interventions. It is also important to describe how late-effects influence the ability of survivors to participate in daily activities and to interact with their environment to design and provide rehabilitation for individuals who may benefit from remediation, compensatory education, or environmental adaptations. Structural and physiological impairments imposed on organs or organ systems may result in limitations in physical function (the inability to perform a physical action, task or activity in an efficient, typically expected, or competent manner) such that the individual may have difficulty interacting with their environment to perform activities as simple as bathing or dressing, or as difficult as working or attending school.

2.0 Specific Aims

To estimate the prevalence of functional limitations and the prevalence of disability among a cohort of 5-plus year survivors of childhood neuroblastoma, and compare the prevalence of functional limitations and the prevalence of disability in neuroblastoma survivors to a sibling comparison group. In addition, this analysis will evaluate the extent to which major medical late effects are associated with functional limitations among neuroblastoma survivors.

3.0 Hypotheses

- 3.1 The group of neuroblastoma survivors will have a higher prevalence of self-reported functional limitations and physical disability than the study's sibling comparison group.
- 3.2 The group of neuroblastoma survivors with musculoskeletal and/or neurological problems will have increased relative odds of reporting functional limitations and disability than those who do not report musculoskeletal or neurological problems.

4.0 Analysis Framework (baseline questionnaire items)

4.0 Direction: The analyses will be conducted by Ms. Ness at the University of Minnesota under the direct supervision of Dr. Gurney. Ms. Ness is a licensed physical therapist and research assistant in the Department of Pediatrics with a strong background in statistical methods of epidemiologic and clinical data. She also is a Ph.D. Candidate in the Division of Epidemiology. This analysis is part of a dissertation project that Ms. Ness will complete for her Ph.D. degree in epidemiology, scheduled for completion in December 2004. Dr. Melanie Wall, associate professor in the Division of Biostatistics at the University of Minnesota, is a member of Ms. Ness's Ph.D. dissertation committee and she will provide close consultation related to the analytic approach and conduct of this evaluation. Dr. Yasui from the Statistical Center at Fred Hutchison Cancer Research Center will also be relied upon for statistical consultation during the course of the analysis.

4.1 Subject Population

- 4.1.1. Cases: 802 Neuroblastoma survivors alive at baseline questionnaire
- 4.1.2. Comparison group: All CCSS Siblings

4.2 Outcomes: The primary outcome variables for this analysis are self-reported functional limitations and self-reported disability. Functional limitations will be scored by evaluating the answers to the series of six questions about the 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?"

4.3 Independent variables: Major medical late effects as risk factors of interest for these analyses and will be defined as dichotomous indicators based on self-report. Gender, age at interview, age at diagnosis, diagnosis era, total household income, and race/ethnicity will be considered for modifying or confounding effects in all models. Late effects will be grouped by body systems as follows:

1. Endocrine late effects
 - a. Hypothyroidism
 - b. Growth hormone deficiency
 - c. Medication needed to initiate puberty
2. Bone and joint health
 - a. Scoliosis surgery
 - b. Leg lengthening or shortening
 - c. Osteoporosis
3. Neurological problems
 - a. Paralysis
 - b. Seizures
 - c. Problems with balance
 - d. Tremor or movement problems
 - e. Weakness in arms
 - f. Weakness in legs
 - g. Decreased sense of touch, feeling in hands, fingers, arms or leg
 - h. Prolonged pain or abnormal sensation in arms, legs or back
4. Sensory Problems
 - a. Hearing loss
 - b. Deafness
 - c. Blindness
 - d. Cataracts
 - e. Dry eyes
5. Cardiopulmonary problems
 - a. Arrhythmia
 - b. Congestive heart failure
 - c. Hypertension
 - d. Exercise induced chest pain, shortness of breath, or irregular heart beat

- e. Chronic cough
- f. Lung fibrosis
- 6. Second malignant neoplasm
 - a. New malignancy
 - b. Recurrence
 - c. Breast lump removal/biopsy
 - d. Non-melanoma skin cancer

4.4 Statistical analyses: Descriptive statistics, including means and standard deviations, ranges, frequencies and percents will be calculated for demographic variables, medical late effects, functional limitations, and disability. The prevalence odds ratios of functional limitations among the survivors as a function of late effects will be evaluated using multiple logistic regressions, potentially adjusting for age at interview, age at diagnosis, diagnosis era, sex, total household income and race/ethnicity.

5.0 Proposed Tables

Table 1: Characteristics of neuroblastoma survivors

Characteristic	Survivors (n = 802)		Siblings (n=3846)	
Gender				
Male				
Female				
Vital status at baseline questionnaire				
Alive				
Dead				
Age at diagnosis (years)				
<1				
1-4				
5-9				
10-14				
15-20				
Age at interview (years)				
<10				
10-19				
20-29				
30-39				
40-49				
Year of diagnosis				
1970-1978				
1979-1984				
1985-1986				
Survival time (years)				
5-9				
10-14				
15-19				
20-24				
25+				

Table 2: Medical outcomes and functional limitations

	Cases		Siblings		OR	95% CI
	N	(%)	N	(%)		
Endocrine impairments						
Hypothyroidism						
Growth hormone deficiency						
Growth hormone injections						
Medication needed to initiate puberty						
Musculoskeletal impairments						
Scoliosis surgery						
Leg lengthening or shortening						
Osteoporosis						
Neurological impairments						
Paralysis						
Seizures						
Problems with balance						
Tremor or movement problems						
Weakness in arms						
Weakness in legs						
Decreased sense of touch						
Prolonged pain or abnormal sensation						
Sensory						
Hearing loss						
Deafness						
Blindness						
Cataract						
Dry eyes						
Cardiopulmonary impairments						
Arrhythmia						
Congestive heart failure						
Exercise induced chest pain, shortness of breath, or irregular heart beat						
Chronic cough						
Lung fibrosis						
Second Cancer						
New malignancy						
Recurrence						
Breast lump removal/biopsy						
Non melanoma skin cancer						
Limitations in physical function						
Limited in vigorous physical activity						
Limited in moderate physical activity						
Limited ability to climb steps						
Limited ability to bend or lift						
Limited ability to walk more than one block						
Disability status						
Needs help with personal care						
Needs help with routine activities						
Health prevents school or work attendance						

Table 3. Medical late effects as risk factors for any disability or limitation in physical function (comparison between cases with and without the medical late effect)

	OR	95% CI	p-value
Help with personal cares			
Endocrine impairment			
Musculoskeletal impairments			
Neurological impairments			
Sensory impairments			
Cardiopulmonary impairments			
Second Cancer			
Help with routine activities			
Endocrine impairment			
Musculoskeletal impairments			
Neurological impairments			
Sensory impairments			
Cardiopulmonary impairments			
Second Cancer			
Health prevents school or work attendance			
Endocrine impairment			
Musculoskeletal impairments			
Neurological impairments			
Sensory impairments			
Cardiopulmonary impairments			
Second Cancer			
Limited in vigorous physical activity			
Endocrine impairment			
Musculoskeletal impairments			
Neurological impairments			
Sensory impairments			
Cardiopulmonary impairments			
Second Cancer			
Limited in moderate physical activity			
Endocrine impairment			
Musculoskeletal impairments			
Neurological impairments			
Sensory impairments			
Cardiopulmonary impairments			
Second Cancer			
Limited ability to climb steps			
Endocrine impairment			
Musculoskeletal impairments			
Neurological impairments			
Sensory impairments			
Cardiopulmonary impairments			
Second Cancer			
Limited ability to bend or lift			
Endocrine impairment			
Musculoskeletal impairments			
Neurological impairments			
Sensory impairments			
Cardiopulmonary impairments			
Second Cancer			

Limited ability to walk more than one block			
Endocrine impairment			
Musculoskeletal impairments			
Neurological impairments			
Sensory impairments			
Cardiopulmonary impairments			
Second Cancer			

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July 1, 2004

Dear Dr. Meadows & members of the CCSS Publications Committee:

The proposal we are submitting, "Physical disability and limitations in physical function in long-term neuroblastoma survivors" was originally included in a larger proposal designed to address the late effects of cancer and its treatment among survivors of neuroblastoma. We have separated this portion of the proposal to more clearly indicate the aims of this analysis.

Changes have been made in the proposal to address the concerns of the committee:

1.2. Specific Aim 3 looks at functional limitations by occurrence of adverse events. However there is no discussion of the timing of these two: i.e. for an adverse event to have an effect on function, it must occur prior to the functional limitation.

Since this is a cross sectional analysis of an existing cohort, we acknowledge that we will not be able to definitively ascertain whether or not a medical late effect occurred before the onset of a limitation in function. Thus, the analysis will evaluate the extent to which medical late effects are associated with functional limitations among neuroblastoma survivors. We will be very cautious and thoughtful when writing the interpretation of possible causal effects from our findings.

1.8 Power may be limited for a rare outcome, given the size of neuroblastoma survivors in the CCSS.

We acknowledge that power may be limited for certain outcomes in these analyses, and in those cases, multiple variable regressions may not yield significant results. However, this is the largest cohort of neuroblastoma survivors ever assembled, and as such, we believe reporting the prevalence of medical late effects, limitations in physical function and disability among these survivors will be an important addition to the childhood cancer literature.

Thank you for considering our revised proposal.

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