Childhood Cancer Survivor Study - Concept Proposal
Date: September, 2014

Title: Impact of Endocrine disorders on Health-Related Quality of Life and Physical Activity in Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study (CCSS)

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Background and Rationale: Significant improvements in the diagnosis and treatment of childhood cancers have led to an overall survival of 80% at 5 years accounting for about 360,000 childhood cancer survivors (CCS) as of January 2011.(Howlader N 2013) The childhood cancer survivor study (CCSS) has shown that approximately 75% of CCS treated between 1970 and 1986 will develop a chronic health condition by 30 years following treatment (Oeffinger, et al. 2006) while the clinically assessed SJ.LIFE cohort found that 95.5% had a chronic condition by age 45. (Hudson, et al. 2013) The CCSS study has also shown that CCS have poorer health-related quality of life (HRQOL) in physical and social but not mental health domains compared with siblings.(Zeltzer, et al. 2008) Apart from demographic (female gender, unmarried status) and socio-economic variables (annual household income of less than 20,000, unemployed, lower educational attainment, and lack of medical insurance)

contributing towards this lower HRQOL, the treatment related variable that correlates most with lower HRQOL is cranial radiation. Although presence of a major medical condition also contributes towards a lower HRQOL, studies exploring the contributions of the various organ-specific chronic health conditions on HRQOL are plagued by small sample size. Evaluation of organ-specific contribution to HRQOL using the well characterized, large, and prospectively followed cohort of cancer survivors as in the CCSS would be helpful for early identification and treatment of at-risk survivors to improve HRQOL.

After neurologic disorders, endocrine disorders are the most common chronic health conditions in the CCSS cohort. (Oeffinger, et al. 2006) Endocrine disorders (grades 1 to 3) were reported by about 18% of CCS in the CCSS cohort with a relative risk of about 5.9 (95% CI 4.9-7.1) compared to siblings. The CCSS study also revealed that the cumulative incidence of endocrine disorders continues to increase over time, even 25 years following therapy, necessitating life-long surveillance.(Oeffinger, et al. 2006) Endocrine disorders such as thyroid diseases, inadequate growth, obesity, disrupted pubertal development, hypogonadism, impaired glucose homeostasis, and bone health can be caused by childhood cancer treatments.(Chow, et al. 2007; Chow, et al. 2013; Dalton, et al. 2003; Darzy and Shalet 2005; Gurney, et al. 2003; Loeffler, et al. 1988; Meacham, et al. 2010; Sklar, et al. 2000b) CCS with endocrine disorders have greater odds of limitations in physical performance that includes exercise, self-care, and activities of daily living as well as limitations in either work or school related physical activities compared to those survivors without endocrine disorders.(Ness, et al. 2009) The negative contribution of endocrine disorders on HRQOL and physical-activity and more specifically, the contribution of different sub-types of endocrine disorders, are unknown.

Neuro-endocrine dysfunction as a result of involvement of the hypothalamic-pituitary axis (HPA) within the radiation field, most commonly used for the treatment of brain-tumors and some hematological malignancies, is the most prevalent endocrine abnormality.(Appelman-Dijkstra, et al. 2011; Schmiegelow, et al. 2000) This dysfunction produces progressive and irreversible hormonal deficiencies that negatively impact growth, skeletal maturation, fertility, sexual health and function all of which can affect physical functioning.(Darzy 2013) Moreover, conventional radiotherapy doses and fields used for the treatment of childhood brain-tumors can impact multiple anterior pituitary hormones leading to multi-system endocrinopathy. In addition, these abnormalities can manifest at lower radiation doses in younger children compared to older. The impact of this progressive HPA dysfunction on HRQOL and physical-activity in CCS is unknown. Adult studies of pituitary disorders have shown increased psychological distress and lower HRQOL among adults with pituitary disorders compared to healthy controls.(Sonino, et al. 2007) (Li Voon Chong, et al. 2000; Lofdahl, et al. 2012)

Isolated growth hormone deficiency (Hussein, et al.) is the most common endocrine disorder among children treated with radiation that involves the HPA with the risk being dose dependent. (Merchant, et al. 2011) GHD in adults can lead to increased clustering of cardiovascular risk-factors, decreased lean body mass and exercise intolerance.(Molitch, et al. 2006) In addition, it can have long-standing impact on bone-mineral density (Kaufman, et al. 1992), exacerbate metabolic syndrome risk-factors(Vahl, et al. 2000) and cause neuro-psychological deficits that can all impede

HRQOL.(Carroll, et al. 1998) Studies of adults with adult-onset GHD and one additional pituitary hormone deficiency showed higher cardiovascular risk factors and poorer HRQOL compared to the general population.(Carroll, et al. 1998; Sanmarti, et al. 1999) Although, the impact of GHD on HRQOL among adult survivors of childhood cancer is not known, based on adult data, one could hypothesize poorer functional outcomes in this group.

Damage to the gonadotrophic axis leading to sex hormone deficiency is the second most common impact of radiation on the HPA.(Darzy 2013) This can lead to adverse health outcomes both in males and females that can affect HRQOL.(Zebrack, et al. 2010) (Green, et al. 2009) In both males and females, HPA radiation can also lead to precocious puberty (PP) .The occurrence of PP in the setting of GHD can exacerbate short-stature. If strategies to prevent PP are used in this setting with growth hormone replacement therapy then it can exacerbate skeletal disproportion among those with impaired spinal growth due to spinal radiation.(Adan, et al. 2000; Gleeson, et al. 2003) Both these conditions can affect HRQOL adversely. However, other factors not related to HPA can lead to gonadal dysfunction in CCS. Hypoandrogenism due to testicular failure can cause low testosterone in males. The biggest impact of low testosterone is a negative impact on sexual health and function such as reduced libido and spontaneous erections that can cause significant psychological distress. Low testosterone can lead to decreased muscle mass, gynecomastia, loss of body hair and smaller testicular volume.(Kenney, et al. 2012; Romerius, et al. 2009) that can affect HRQOL. In addition, it can also be affected through hot flashes/sweating, fatigue, reduced bone mineral density (Howell, et al. 2000a; Howell, et al. 2000b) and lean muscle mass. Finally with reduced fertility, increased psychosocial stress can contribute towards lower HRQOL. In females, premature ovarian failure due to direct ovarian damage from chemotherapy and / or radiation leading to premature menopause prior to the age of 40 years (Sklar, et al. 2006) can cause adverse health outcomes such as reduced bone mineral density and clustering of risk-factors for metabolic syndrome, which can adversely affect HRQOL.(Green, et al. 2009)

ACTH deficiency as a result of HPA suppression, either by radiation or chemotherapy, is uncommon in CCS except in survivors of craniopharyngioma, medulloblastoma, and suprasellar tumors.(Rose, et al. 2005)

Thyroid disorders that include central hypothyroidism due to HPA suppression, primary hypothyroidism and thyroid neoplasms are all common in CCS. (Sklar, et al.2000b) Primary hypothyroidism is most commonly due to direct damage of the thyroid gland following radiotherapy. Thyroid disorders have a long latency period and can occur 25+ years after cancer diagnosis and treatment. Although there are no data on the impact of thyroid disorders on HRQOL and physical-activity in CCS, based on adult studies there is reason to believe that these can be negatively impacted .(Bianchi, et al. 2004) Adult studies have shown that patients on thyroid replacement medications with a normal TSH (euthyroid state) experience significant general health impairment compared to healthy, age and sex matched controls.(Bianchi, et al. 2004; Quinque, et al. 2013; Samuels, et al. 2007; Saravanan, et al. 2002)

CCS can have reduced BMD and are at increased risk for osteopenia, osteoporosis, and fractures.(Wasilewski-Masker, et al. 2008) This is due to a combination of exposure to medications like glucocorticoids, methotrexate, and hormonal deficiencies (mainly growth hormone and sex hormones) due to cancer and its treatment. Although fractures were shown to occur in up to 39% of children during treatment for acute lymphoblastic leukemia (Halton, et al. 1996), the CCSS study has shown reduced fracture rate for CCS compared to siblings.(Wilson, et al. 2012a) CCS with impairment of the musculoskeletal system had higher odds of poor physical functioning (Ness, et al. 2009) than those without. In a small study of childhood brain-tumor survivors, osteopenia was found to be associated with cranial radiotherapy and affected ambulation and physical-activity. (Odame, et al. 2006) The impact of bone health on HRQOL and physical-activity within the CCSS has not been investigated, although it is clear that they are affected in other populations irrespective of presence or absence of vertebral fractures, particularly in the domain of role-physical.(Wilson, et al. 2012b)

CCS are at increased risks for metabolic dysfunction secondary to obesity and diabetes mellitus.(Meacham, et al. 2009; Sklar, et al. 2000a) The etiology of these conditions is multi-factorial, with both cancer treatment-related and underlying genetic predispositions. (Ross, et al. 2004)Risk-factors for obesity include cranial radiotherapy (> 20 Gray) particularly in young, white females (less than 4 yrs. of age) with ALL. (Oeffinger, et al. 2003)Brain-tumors developing near the sellar region and their treatment with surgery and radiotherapy can disrupt the HPA and induce morbid obesity.(Lustig, et al. 2003) The main risk factors associated with the development of diabetes mellitus were use of total body irradiation, abdominal radiation, and alkylating agents.(Meacham, et al. 2009) CCS who received a stem-cell transplant following a conditioning regimen that included TBI also developed disorders of glucose homeostasis primarily due to increased insulin resistance. (Chemaitilly, et al. 2009) In the CCS population, the impact of metabolic dysfunction on HRQOL and physical-activity is not known.

Thus, CCS can develop a wide array of treatment-related endocrine disorders that can include more than one endocrine system. Often, one disorder can predispose to dysfunctions in other endocrine systems such as GHD and obesity or sex-hormone deficiency and low bone mineral density. Therefore those CCS with more than one endocrine dysfunction may suffer a cumulative negative impact on HRQOL. In addition to the number of disorders, the relationship between HRQOL and type and duration of disorders -particularly diabetes, bone-disorders, and obesity- that can cause progressive morbidity needs to be explored. Therefore, understanding the impact of the various endocrine disorders on HRQOL would help in timely and appropriate treatment of at-risk survivors that can alleviate any limitation.

The overall aim of this study is to investigate the independent effects of endocrine disorders on HRQOL and physical-activity among CCS enrolled within the CCSS.

The aims for this study are as follows:

Specific-aim-1: To compare HRQOL and physical activity among CCS with and without an endocrine disorder.
Hypothesis-1: After adjusting for covariates (as listed below), CCS with any endocrine disorder will have inferior HRQOL and physical activity compared to those without an endocrine disorder.

Specific-aim-2: To evaluate the independent effects of the characteristics of endocrine disorders that include number, type, and, duration on HRQOL and physical activity among CCS diagnosed with an endocrine condition.
Hypothesis-2a: Among CCS with an endocrine disorder**,** after adjusting for covariates, HRQOL and physical activity decrease as the number of existing endocrine disorders increases.
Hypothesis-2b: Among CCS with an endocrine disorder**,** after adjusting for covariates, HRQOL and physical activity will vary based on the type of endocrine disorder.
Hypothesis-2c: Among CCS with an endocrine disorder**,** after adjusting for covariates, HRQOL and physical activity will vary based on the duration of endocrine disorder.

Study-Population

The study population will include individuals in the original CCSS survivor cohort with and without a reported endocrinopathy who have completed the baseline, 2003 and 2007 follow-up surveys. Inclusion of the data from the 2007 survey is only for the purposes of identifying endocrine disorders that are reported on the 2007 survey, but had onset prior to 2003 survey. Outcomes of HRQOL and physical activity will be obtained from the 2003 survey as they are not fully captured in the 2007 survey.

Outcomes (Dependent variables: Mental and Physical-Component of SF-36 and Physical-activity) obtained from 2003 survey.

a. **Physical and Mental Health Component of SF-36.**

   -The "T-scores" for physical component summary score and mental function summary score

   -The "T-scores" of 8 individual subscales.

   - A dichotomized "T-score" indicating poor HRQOL or not, if they were at least 1SD below the population mean (≤ 40) will be used in multivariable regression models.

b. <u>Health Behaviors: Physical Activity. (D-1 to D-7) from 2003 survey.</u>

-The Physical activity outcome will be categorized as a binary indicator of Yes/No for question D-1

-From questions D-2 to D-7 based on Center for Disease Control (CDC) criteria of moderate physical activity 5 times a week or vigorous physical activity 3 times a week, a binary outcome of Yes/No of meeting CDC criteria or not will be computed.

<u>Independent variable:</u> Endocrine disorders data (grades 1-4) with age of onset prior to 2003 survey using earliest age of report from baseline or other follow up surveys. BMI will be as calculated per the self-reported height and weight from the 2003 follow-up survey.

1. Thyroid disorders:
   A. hypothyroidism
   B. hyperthyroidism
   C. thyroid cancer
   D. thyroid nodules
2. Growth disorders:
   A. Short- stature (final height less than 10% percentile among those survivors without amputation)
   B. Growth hormone deficiency/ has taken growth hormone injections.
3. Gonadal dysfunction (females); Ovarian failure (using hormone replacement medications)
4. Gonadal dysfunction (males); Leydig cell dysfunction (using testosterone)
5. Osteoporosis or osteopenia (low bone mineral density)
6. Diabetes Mellitus: has taken oral pills, insulin-shots
7. Overweight or obese (self-reported BMI ≥ 25 kg/m^2)

Covariates (at time of 2003 survey)

1. Age: age at treatment and at time of survey.
2. Gender
3. Race
4. Socio-economic: Household income; medical insurance; employment; education
5. Cancer diagnosis
6. Cancer treatment: Cranial radiotherapy (yes/no); Total Body Irradiation (yes/no); Cranio Spinal Irradiation (yes/no); alkylators (yes/no); anthracyclines (yes/no).
7. Non-endocrine medical conditions. (Any serious Grade-3-4 non-endocrine medical condition)
8. Emotional health: per BSI-18 (dichotomized score with impairment based on T-score>=63) to be used as a covariate for outcome of physical activity only.
9. NCQ: Neuro-cognitive questionnaire from 2003 with impaired task efficiency scores to be used as a covariate for the outcome of physical activity only.

Statistical Analysis

HRQOL in this study will be assessed by the Mental and Physical-Component sub-scales of the SF-36 while the physical-activity outcomes are based on separate questions. The Mental and Physical-Component sub-scales of the SF-36 and physical activity will be assessed both as continuous measures and dichotomized to reflect impairment.

For the continuous outcomes, multivariable linear models will be used to assess differences in adjusted mean values between groups, defined to be consistent with each hypothesis, after adjusting for covariates including age, gender, race, socio-economic variables, and other non-endocrine medical and emotional health conditions. Type of cancer and treatment received will be assessed as potential modifiers, but we will

be cautious about inclusion of these factors in models due to the possibility that they are part of an initiating step of the causal pathways to the outcome via endocrine dysfunction.

For the dichotomized measures, assuming ”impairment” is prevalent (>10%), relative risks (RR) will be calculated from multivariable generalized linear models with a log link function, a Poisson distribution and robust error variances to assess comparisons of rates of impairment between groups defined consistently with each hypothesis. Adjustment will be carried out as for the linear models. Covariates significant at the .05 level, or those which modify the effect of the risk factor of interest (incurring >10% change) will be retained in the final models.

Table-1: Types of Endocrine Disorders prior to follow-up survey 2003 as reported by Adult Survivors of Childhood Cancer at the 2007 follow-up survey.

TYPE OF ENDOCRINE DISORDER	N (%) OF CCSS
THYROID DISORDERS	
A. HYPOTHYROIDISM	
B. HYPERTHYROIDISM	
C. THYROID CANCER	
D. THYROID NODULES	
GROWTH DISORDERS	
A. SHORT STATURE	
B. GROWTH HORMONE DEFICIENCY	
GONADAL DYSFUNCTION (FEMALES); OVARIAN FAILURE	
GONADAL DYSFUNCTION (MALES); LEYDIG CELL DYSFUNCTION	
OSTEOPOROSIS OR OSTEOPENIA (LOW BONE MINERAL DENSITY)	
DIABETES MELLITUS	
OVERWEIGHT/OBESITY	

Table-2: Characteristics of Adult Survivors of Childhood Cancer with and without Endocrine Disorders as of the 2003 follow-up survey

Characteristics	Survivors with endocrine disorders, n (%)	Survivors without endocrine disorders, n (%)	p value
Gender- n (%) Female Male			
Race- n (%) White Black Hispanic Other			
Age at diagnosis- years Mean ± SD			
Age at survey- years Mean ± SD			
Educational attainment <High school High school graduate College graduate			
Marital Status Single Married/living as married Divorced/separated Not known			
Annual household income < $20,000 $20,000+			
Health insurance Yes No			
Major medical condition (other than endocrine)			

Yes No			
Major emotional health condition Yes No			
Neuro-cognitive status per 2003-NCQ			
Diagnosis Acute lymphoblastic leukemia Acute myeloid leukemia Other unspecified leukemias Astrocytomas Medulloblastoma, PNET Other CNS tumors Hodgkin's disease NHL Wilm's tumor Neuroblastoma Soft tissue sarcoma Ewing's sarcoma Osteosarcoma Other			
Cancer treatment-n (%) No chemotherapy or radiation Chemotherapy Any chemotherapy Alkylating agents Steroids HCT conditioning Radiation therapy (RT)			

Any Brain Chest Abdominal or pelvic Total body irradiation (TBI) Combined chemotherapy and RT Alkylator + TBI Alkylator + pelvic RT HCT conditioning + pelvic RT			
Interval between cancer diagnosis and 2003 survey Mean ± SD			

Table-3A: Adjusted Means and SEs on SF-36 for survivors with and without endocrine disorders

	Physical function Mean (95% CI)	Role Physical Mean (95% CI)	Bodily pain Mean (95% CI)	General health Mean (95% CI)	Vitality Mean (95% CI)	Role emotional Mean (95% CI)	Social function Mean (95% CI)	Mental health Mean (95% CI)	Physical component summary Mean (95% CI)	Mental component summary Mean (95% CI)
Survivors with endocrine disorders										
Survivors without endocrine disorders										

Table-3B: Adjusted Physical Activity for survivors with and without endocrine disorder.

	Recent participation in any organized physical activities. N (%)	Meets CDC guidelines for Physical activity. N (%)
Survivors with endocrine disorders		
Survivors without endocrine disorders		

Table-4A: Adjusted Mean and SEs on SF-36 based on type of endocrine disorder.

Type of disorder	Physical function Mean (95% CI)	Role Physical Mean (95% CI)	Bodily pain Mean (95% CI)	General health Mean (95% CI)	Vitality Mean (95% CI)	Role emotional Mean (95% CI)	Social function Mean (95% CI)	Mental health Mean (95% CI)	Physical component summary Mean (95% CI)	Mental component summary Mean (95% CI)
Survivors without endocrine disorders										
Thyroid disorders										
Growth disorders										
Gonadal dysfunction (females); Ovarian failure										
Gonadal dysfunction (males); Leydig cell dysfunction										
Osteoporosis or osteopenia or Low bone mineral density										
Diabetes mellitus										
Overweight/Obesity										

Table-4B: Adjusted Mean and SEs on SF-36 based on duration and number of endocrine disorder.

Endocrine disorder	Physical function Mean (95% CI)	Role Physical Mean (95% CI)	Bodily pain Mean (95% CI)	General health Mean (95% CI)	Vitality Mean (95% CI)	Role emotional Mean (95% CI)	Social function Mean (95% CI)	Mental health Mean (95% CI)	Physical component summary Mean (95% CI)	Mental component summary Mean (95% CI)
Survivors without endocrine disorders										
Duration (years) ≥ 10 but < 20 ≥ 20 but < 30 ≥ 30										
Number 1 2 >2										

Table-4C: Adjusted Physical Activity for Survivors based on type of Endocrine Disorder.

Type of disorder	Recent participation in any organized physical activities. N (%)	Meets CDC guidelines for Physical activity. N (%)
Survivors without endocrine disorders		
Thyroid disorders		
Growth disorders		
Gonadal dysfunction (females); Ovarian failure		
Gonadal dysfunction (males); Leydig cell dysfunction		
Osteoporosis or osteopenia or Low bone mineral density		
Diabetes mellitus		
Overweight/Obesity		

Table-4D: Physical Activity among Survivors Based on Duration and Number of Endocrine Disorders.

Endocrine disorder	Recent participation in any organized physical activities. N (%)	Meets CDC guidelines for Physical activity. N (%)
Survivors without endocrine disorders		
Duration (years) ≥ 10 but < 20 ≥ 20 but < 30 ≥ 30		
Number 1 2 >2		

Table-5: Frequencies and percent of adult survivors with endocrine disorders with poor outcomes on SF-36 (OR and 95% CI of poor outcomes by characteristics of endocrine disorder) (Results of regression analysis for each component of the SF-36)

Table-6: Multivariable regression model of meeting CDC physical activity guideline among adult survivors of childhood cancer by characteristics of endocrine disorder. (Results of the regression analysis)

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