CCSS Analysis Concept Proposal
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STUDY TITLE: A longitudinal assessment of physical activity in the Childhood Cancer Survivor Study cohort

WORKING GROUP AND INVESTIGATORS

Working groups: Cancer Control, Chronic Disease

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1. BACKGROUND AND RATIONALE:

Advances in therapy for pediatric cancer over the past 40 years have resulted in substantial improvements in rates of sustained remission. Approximately 80% of individuals diagnosed with cancer during childhood are now expected to survive for at least five years after their initial diagnosis. Although increases in survival rates have been largely brought about by improvements in multi-modal therapy, increases in survival have not come without cost. Many survivors of childhood cancer are at risk of long-term adverse health conditions[1]. Between 60% and 70% of survivors of childhood cancer will develop at least one medical condition as a result of the therapy received in childhood. Late effects include, but are not limited to endocrine dysfunction, osteoporosis, obesity and cardiovascular disease[2,3].

In the general population, physical activity has been shown to be an important contributor to maintaining healthy weight, and has been associated with decreased risk of developing many weight-related conditions such as, obesity, cardiovascular disease[4,5], hypertension[6] and non-insulin dependent diabetes mellitus[7], as well other diseases including osteoporosis[8] and some cancers[9]. As physical activity is an important contributor to weight control and disease prevention in healthy populations, physical activity may be of particular significance to survivors of childhood cancer who represent a population at high risk of developing a variety of cardiovascular conditions, skeletal morbidities and endocrine dysfunction[10]. Previous studies that report physical activity levels among survivors have found that many survivors do not engage in regular exercise; [10-12] some studies report that less than 50% of cancer survivors meet recommended guidelines for physical activity[13-15]. Factors associated with inactivity include female sex[10,16], hispanic race[17], and prior therapy with cranial radiation[13]. In addition, psychosocial factors such as anxiety, fatigue, low stamina and cancer-related pain have also been associated with reduced likelihood to participate in exercise[18]. Although

there is some evidence to suggest that survivors who are older at follow-up may be less likely to engage in recommended levels of activity than their younger counterparts[10,19], reports are contradictory[11,20], and little longitudinal data exists examining how physical activity levels are likely to change over time as survivors age[21].

The aim of this study is to determine demographic, diagnosis and treatment related predictors of declining physical activity as a function of age in the Childhood Cancer Survivor Study cohort. Although previous reports from the CCSS have indicated that survivors of childhood cancer do not engage in the recommended levels of weekly physical activity[10,13,17], no analysis has examined physical activity as a function of age in this population. By evaluating potential associations between demographic and treatment related characteristics and age related declines in activity levels, we hope to identify those survivors who may benefit most from early intervention and educational programs promoting the importance of regular physical activity on health and well-being.

2. AIMS/HYPOTHESES:

Primary Aims:
1. To describe activity patterns as a function of current age in the CCSS cohort among both survivors and siblings.
2. To determine demographic, diagnosis and treatment related predictors of age related decline in physical activity in the CCSS cohort.

Hypotheses:
1. Survivors of childhood cancer will engage in less physical activity than siblings as they age and this will be less than that recommended by national guidelines (30 minutes of moderate intensity physical activity on five or more days of the week or 20 minutes of vigorous activity on three or more days of the week).
2. Greater age related declines in physical activity levels will be observed among survivors of childhood cancer when compared to their siblings.
3. Survivors of central nervous system malignancies and bone tumors will exhibit the largest declines in physical activity levels with age.
4. Treatment modalities associated with the sharpest age related declines in physical activity levels will include exposure to cranial irradiation amputation of a lower limb, or treatment with an anthracycline, platinum-based agent or vincristine.
5. Demographic factors associated with the age related decline in physical activity will include female sex, obesity, depression, cancer-related pain, non-white race, annual household income less than $20 000 per annum, and not having completed high school. (The variables obesity, depression cancer-related pain and annual household income will be treated as age varying covariates in analyses).
6. Survivors who report the presence of grade 3 (severe) or grade 4 (disabling or life threatening) conditions as defined by the Common Terminology Criteria for Adverse Events (CTCAE version 3) will report accelerated age related deterioration in physical activity when compared to those who do not have these conditions (This will be treated as an age varying co-variate).

3. ANALYSIS FRAMEWORK

Population:

CCSS participants who are alive and completed either the 2003 or 2007 questionnaires will be eligible for this study. A comparison group of siblings who completed both the 2003 or 2007 follow-up questionnaire will also be included.

Outcome of interest:

The primary outcome of interest for these analyses are physical activity levels of survivors and their siblings as reported in the 2003 or 2007 follow-up questionnaires (D1-7 FU2003, N15-22 FU2007). Based on participants answers to questions regarding activity levels, the outcome will be considered in two ways, firstly, as a binary variable classifying the participant as either meeting the Centers for Disease Control and Prevention (CDC) guidelines for physical activity (30 minutes of moderate intensity physical activity on 5 or more days of the week or 20 minutes of vigorous activity 3 or more days a week) and secondly as a binary variable classifying whether survivors participated in any physical activity in their leisure time in the month before completing the questionnaire.

Independent variables:

1. Date of birth
2. Date of questionnaire completion (for both follow-up questionnaires)
3. Sex
4. Cancer diagnosis
5. Date of cancer diagnosis
6. Race/ethnicity (Race 5 code)
7. Highest level of educational attainment (< high school, high school graduate, college graduate – A1 FU2003 and A3 FU2007)
8. Employment status (working/caring for home or family, student, unemployed, unable to work – A4 FU2003 and A4 FU2007)
9. Annual household income (<$20000, ≥$20000 – S1 FU2003 and A6 FU2007)
10. BMI (calculated from 7-8 FU2003 and A1-2 FU2007)
11. Smoking status (current/ever/never - L1-6 FU2003 and N7-N14 FU2007)
12. Depression status (yes/no - G1-18 FU2003, L1-18 FU2007)
13. Radiation therapy (cranial/chest/other/none)
14. Chemotherapy (yes/no)
15. Anthracycline agents (yes/no, cumulative dose)
16. Platinum agents (yes/no, cumulative dose)
17. Vincristine (yes/no)
18. Hematopoeitic stem cell transplant (allogenic/autologous/no)
19. Surgery (amputation of lower limb/other surgery/none)
20. History of or surgery for a bone-related condition (yes/no – E10, I1-6 BL and F10-11, J1-J6 FU2007)
21. Blindness in one or both eyes (yes/no - C8 BL and D8 - 9 FU2007)
22. Chronic disease variables based on the scoring rubric (CTCAE) used by Oeffinger[3] will be used to grade the severity of the following chronic conditions among study participants. (Participants reporting

Grade 3 (severe) or grade 4 (disabling or life-threatening) conditions will be compared to survivors reporting grade1 (mild) or grade 2 (moderate) conditions.
   a. Cardiac
   b. Respiratory
   c. Neurologic
23. Pain (E20-22 and G19 FU2003, L19-23 FU2007)
24. Attendance at a long-term follow-up clinic (yes/no - B1-2 FU2007)

Statistics:
Aim 1: Generalized estimating equations will be used to evaluate 1) the impact of age on prevalence of physical activity levels among survivors, and 2) differences between cancer survivors and their siblings in changes in the prevalence of physical activity levels with age. In these analyses, physical activity will be expressed as a dichotomous variable (meets or does not meet recommended physical activity guidelines). A binomial distribution with a log link will be assumed in order to directly estimate relative risks, or prevalence ratios. For models with both survivors and siblings included, we will include repeated statements to account for within participant and intrafamily correlations via robust variance estimates. Initial models will include data from both time points and will evaluate whether the impact of age on the physical activity outcomes is different for cancer survivors and their siblings using interaction terms for age by case status. Models will be adjusted for gender, race, education and employment status. Model diagnostics will be used to evaluate the appropriate functional form required for the age variable in the model (i.e. linear, categorical or spline).   If interactions exist, separate relative risk estimates will be presented within relevant age categories.

Aim 2; Among survivors, generalized estimating equations will also be used to evaluate the influence of treatment modality, patient/disease characteristics and health status on changes in the prevalence of physical activity levels among cancer survivors with age. As described above, a log-link binomial distribution will be assumed in order to estimate relative risks, and all models will include repeated statements to account for within participant and intrafamily correlations. Initial models will assess the main effect of these factors on physical activity, and subsequent models, similar to analyses for Aim 1 will evaluate the impact of those factors on age effects via interactions between age and treatment/patient characteristic factors.   If significant interactions exist, then separate relative risk estimates for the impact of a specific risk factor across different age categories will be presented.

Adjusted models will be used to create figures depicting the change in predicted prevalence (or relative risk) across increasing age for each analysis.

Finally, it is possible that bias may be introduced into the proposed study if cancer survivors who complete both follow-up questionnaires are more or less physically active than those cancer survivors who only complete the 2003 follow-up questionnaire. We will evaluate possible bias by comparing characteristics, such as physical activity levels, between those cancer survivors who only completed the 2003 questionnaire against those survivors who completed both questionnaires.

Table 1: Proportion of survivors and siblings not meeting nationally recommended guidelines for physical activity or reporting no leisure time physical activity over the past month (Inactive lifestyle) by selected characteristics

	Did not meet physical activity guidelines						Inactive lifestyle					
	Survivors			Siblings			Survivors			Siblings		
	Age at follow-up			Age at follow-up			Age at follow-up			Age at follow-up		
	18-29	20-39	40+	18-29	20-39	40+	18-29	20-39	40+	18-29	20-39	40+
Gender												
Male												
Female												
Race/Ethnicity												
Black												
Hispanic												
White												
Other												
Educational attainment												
< High school												
High school graduate												
College graduate												
Not indicated												
Employment												
Working/caring for home												
Student												
Unemployed												
Unable to work												
Annual household income												
<$20000												
≥$20000												
Body Mass Index												
Underweight												
Normal weight												
Overweight												
Obese												
Smoking Status												
Current												
Former												
Never												
Depression at time of survey												
No												
Yes												

Table 2: Diagnosis and treatment-related characteristics of the cancer survivor population

	Number	%
Diagnosis		
ALL		
AML		
Other leukemia		
Astrocytoma		
Medulloblastoma/PNET		
Other CNS		
Hodgkins lymphoma		
Non-hodgkins lymphoma		
Wilms tumor		
Neuroblastoma		
Ewing sarcoma		
Osteosarcoma/other bone tumor		
Ewings sarcoma		
Soft tissue sarcoma		
Age at diagnosis (years)		
0-4		
5-9		
10-14		
15-20		
Radiation[†]		
None		
Cranial		
Chest		
Other		
Chemotherapy[†]		
Anthracycline		
Alkylating agent		
Platinum agent		
Platinum agent		
Surgery		
Amputation of lower limb		
Other surgery		
None		
BMT[†]		
Allogenic		
Autologous		

† Categories are not mutually exclusive

Table 3: Relative risk of not meeting nationally recommended guidelines for physical activity or reporting no leisure time physical activity over the past month in survivors compared to siblings

	Did not meet physical activity guidelines			Inactive lifestyle		
	RR*	95% CI	p-value	RR*	95% CI	p-value
Siblings						
Survivors						
Gender						
Male						
Female						
Race/Ethnicity						
Black						
Hispanic						
White						
Other						
Educational attainment						
< High school						
High school graduate						
College graduate						
Not indicated						

Table 3 continued from previous page

	Did not meet physical activity guidelines			Inactive lifestyle		
	RR*	95% CI	p-value	RR*	95% CI	p-value
Employment						
Working/caring for home or						
Student						
Unemployed/looking for work						
Unable to work						
Annual household income						
<$20000						
≥$20000						
Body Mass Index						
Underweight						
Normal weight						
Overweight						
Obese						
Smoking Status						
Current						
Former						
Never						
Depression at time of survey						
No						
Yes						

*Adjusted for within person correlation

Table 4: Relative risk describing associations between treatment and not meeting nationally recommended guidelines for physical activity or reporting no leisure time physical activity over the past month (Inactive lifestyle) in survivors

	Did not meet physical activity guidelines			Inactive lifestyle		
	RR*	95% CI	p-value	RR*	95% CI	p-value
Radiotherapy						
None						
Cranial						
Chest						
Other						
Anthracycline						
No						
Yes						
Alkylating agent						
No						
Yes						
Platinum agent						
No						
Yes						
Vincristine						
No						
Yes						
Surgery						
None						
Amputation of lower limb						
Other surgery						

Table 5: Relative risk describing associations between health status and not meeting nationally recommended guidelines for physical activity or reporting no leisure time physical activity over the past month (Inactive lifestyle) in survivors

	Did not meet physical activity guidelines			Inactive lifestyle		
	RR*	95% CI	p-value	RR*	95% CI	p-value
History of a cardiac condition (Grade 3 or 4)						
No						
Yes						
History of a respiratory condition (Grade 3 or 4)						
No						
Yes						
History of a bone related illness (Grade 3 or 4)						
No						
Yes						
Condition affecting balance or equilibrium (Grade 3 or 4)						
No						
Yes						
Blindness in one or both eyes						
No						
Yes						
Cancer-related pain						
No						
Yes						
Attendance at long-term follow-up clinic						
No						
Yes						

*Adjusted for within person correlation

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