STUDY TITLE

Exercise and Risk of Major Health Outcomes in Adults Treated for Childhood Cancer: A Report from the Childhood Cancer Survivor Study

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1.0 ANALYSIS CONCEPT PROPOSAL

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WORKING GROUP Primary: Cancer Control
Secondary: Psychology / Neuropsychology

BACKGROUND AND SIGNIFICANCE

It is established that adult survivors of childhood cancers are at substantial elevated risk of late-occurring treatment-related adverse health outcomes. Similar to the general population, adult survivors of childhood cancer are subject to the normal effects of aging, age-related and/or disease-related comorbid conditions that predispose to the pathogenesis of adverse healthy status and chronic morbidity. These normal consequences are, however, dramatically compounded by the direct as well as the indirect effects of cancer treatment.[7] Many therapies used in the treatment of childhood cancers such as chemotherapy and radiation cause damage to virtually all organ systems leading to major cardiovascular and endocrine and reproductive complications, second malignancies, and impairments in psychosocial outcomes. Together, the constellation of conditions leads to chronic morbidity, poor quality of life, and ultimately premature mortality. Preventive and/or treatment strategies with the ability to simultaneously lower the risk of chronic and long-term global adverse heath consequences across multiple conditions in childhood cancer are of paramount importance.

Regular exercise may be particularly indicated in this setting since it is one of the few interventions shown to confer pleiotropic benefit across multiple organ systems resulting in substantial reductions in the incidence and severity of the most common physical and psychosocial non-communicable conditions in both men and women. Whether exercise reduces the risk of physical and psychosocial non-communicable conditions in adult survivors of childhood cancers with an elevated risk phenotype due to cancer treatment exposure in children is not known.

Against this background, our group recently investigated, for the first time, the association between vigorous intensity exercise and risk of major cardiovascular events in 1,187 adult survivors of childhood Hodgkin lymphoma participating in the Childhood Cancer Survivor Study (CCSS). The primary end point was (the first) incidence of any major (grade 3 to 5) cardiovascular (CV) event. Poisson regression analyses were used to estimate the association between exercise exposure [metabolic equivalent-hrs·wk^{-1} (MET-hrs·wk^{-1})] and risk of major CV events after adjustment for clinical covariates and cancer treatment. Median follow-up was 11.9 (range 1.7 to 14.3) years. Cumulative incidence of any CV event was 12.2% at 10 years for survivors reporting 0 MET-hrs·wk^{-1}, compared to 5.2% for those reporting ≥9 MET-hrs·wk^{-1}. In multivariable analyses, the incidence of any CV event declined across increasing MET categories (P_{trend}=0.002). This paper was presented at the 50th Annual Meeting of American Society of Clinical Oncology (ASCO) and is currently under secondary review at the *Journal of Clinical Oncology*.

In this proposal, we seek approval to extend our prior work to investigate the association between vigorous-intensity exercise and risk of non-cardiac health conditions in the CCSS. To our knowledge, this will be the first study, in any clinical population, to simultaneously examine the modifying effect of exercise across multiple adverse health conditions in the same individual. We hypothesized that exercise would reduce the risk of subsequent major health conditions in a dose-dependent manner beyond adverse health conditions at baseline and treatment exposure.

SPECIFIC AIMS

Primary

To determine the association between exercise and the (first) incidence of any major (grade 3-5) physical health condition.

Secondary

- To determine the association between exercise and incidence of individual major (grade 3-5) physical health conditions, defined as follows:
    - Pulmonary (i.e., composite incidence of any major event including lung fibrosis, pleurisy, and emphysema);
    - Endocrine and reproductive (i.e., composite incidence of any major event including renal failure / dialysis, thyroid issues, and osteoporosis);
    - Cerebrovascular (i.e., composite incidence of any major event including stroke); and
    - Subsequent neoplasms/malignancies (i.e., new primaries).

- To determine the association between exercise and incidence of individual major (grade 1-5) physical health conditions, defined as follows:
    - Pulmonary (i.e., composite incidence of any major event including lung fibrosis, pleurisy, and emphysema);
    - Endocrine and reproductive (i.e., composite incidence of any major event including renal failure / dialysis, thyroid issues, and osteoporosis);
    - Cerebrovascular (i.e., composite incidence of any major event including stroke); and
    - Subsequent neoplasms/malignancies (i.e., new primaries as well as recurrence).

- To determine the association between exercise and any psychosocial conditions (see definitions below).

- To determine the association between exercise and individual psychosocial conditions, defined as follows:
    - Depression;
    - Anxiety;
    - Pain;
    - Cognitive function;
    - Quality of life
    - Sleep quality; and
    - Fatigue

HYPOTHESES

Primary

Vigorous-intensity exercise will reduce the composite incidence of any major (grade 3-5) physical health condition in a dose-dependent fashion.

Secondary

- Exercise will reduce the incidence of individual major (grade 3-5) physical health conditions in a dose-dependent fashion.

- Exercise will reduce the incidence of individual major (grade 1-5) physical health conditions in a dose-dependent fashion.

- Exercise will be associated with more favorable psychosocial health, in a dose-dependent fashion.

OUTCOMES OF INTEREST:

1. **Grade 3 to 5 non-cardiac physical health conditions**: pulmonary (i.e., composite incidence of any major event including lung fibrosis, pleurisy, and emphysema), endocrine and reproductive (i.e., composite incidence of any major event including renal failure / dialysis, thyroid issues, and osteoporosis), cerebrovascular (i.e., composite incidence of any major event including stroke), and second neoplastic malignancies (i.e., new primaries). All events will be graded according to the CTCAE (version 4.3) which grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), and life-threatening or disabling (grade 4).

2. **Psychosocial conditions**: Depression (FU questionnaire 2003, Section G; Q1 – 18; FU questionnaire 2007, Section L; L1 – L18), anxiety (FU questionnaire 2003, Section G; Q1 – 20; FU questionnaire 2007, Section L; L20), pain (FU questionnaire 2003, Section E; Q21 – 22; FU questionnaire 2007, Section L; L21 – L23), cognitive function (FU questionnaire 2003, Section J) and quality of life (FU questionnaire 2003, Section E & F), fatigue / vitality (FU questionnaire 2003, Section F), and sleep quality (FU sleep survey questionnaire).

INDEPENDENT VARIABLES

Exercise behavior: will be operationalized using the following outcome: Exercise behavior data will be obtained from the baseline questionnaire. Section Health Habits. Physical activity, page 15, question N.9.

a. **Total vigorous-intensity exercise:** the frequency of exercise sessions per week will be multiplied by the assumed duration (i.e., 20 mins), weighted by the estimate of the metabolic equivalent (MET; i.e., 9 METs) expressed as average MET-hours per week. Categories of total vigorous-intensity exercise will be defined as 0, 3 to 6, 9 to 12, and 15 to 21 MET-hrs.wk^{-1}.

b. **Meeting vigorous-intensity exercise guidelines:** the proportion of participants reporting <9 MET-hrs.wk^{-1} vs. ≥9 MET–hrs.wk^{-1} of exercise per week; 9 MET–hrs.wk^{-1} equates to approximately 75 mins of vigorous intensity exercise per week, which is the current national recommendations for adult cancer survivors.

COVARIATES

1. Sex (baseline questionnaire, question A.1),
2. Race or ethnic group (baseline questionnaire, question A.4),
3. Weight (2003 questionnaire; page 3; question 8; Fu2007, A.1-A.2)
4. Body mass index (2003 questionnaire, needs to be calculated from height and weight on page 3, questions 7 and 8, Fu2007, A.1 & A.2),
5. Cancer diagnosis (medical record abstraction)
6. Cancer treatment (e.g., anthracycline dose, chest irradiation) (medical record abstraction; doxorubicin equivalent doses will be used for anthracyclines; dose of radiation to the heart will be also be abstracted from medical records)
7. Education (baseline questionnaire, page 16; question O.1 – O.3 & 2003 questionnaire page 3; question 1, Fu2007 A.3),
8. Age at interview (2003 and 2007 questionnaire),
9. Cardiovascular risk profile (i.e., incidence of diabetes mellitus, hypertension, dyslipidemia, smoking) (diabetes medication, hypertension, cardiac medications, etc. = baseline questionnaire, page 4, question B.8, and drugs from any subsequent questionnaires; smoking = baseline questionnaire, page 14, question N.1 and 2003 questionnaire page 13; question L),
10. Time interval between diagnosis and assessment of exercise behavior.

SUBJECT POPULATION

Inclusion Criteria

1. >5-year cancer survivors who were diagnosed between 1970 and 1986 at age <21 years at one of 26 institutions

2. Histological confirmation of diagnosis with leukemia, Hodgkin disease, non-Hodgkin lymphoma, central nervous system (CNS) malignancies, Wilms tumor, neuroblastoma, soft tissue sarcoma, or bone tumors
3. Survivor participants who completed the baseline physical activity item, and at least one of Fu2003 and Fu2007 survey.
4. Baseline age > 18 years, and
5. Participants without any major (Grade 3 to 5) non-cardiac physical health conditions at baseline

STATISTICAL ANALYSIS FRAMEWORK

Demographic , disease, and treatment characteristics will be reported by exercise (MET-hrs·wk^{-1}) categories and compared using Chi-square tests for categorical measures and ANOVA for continuous measures.

In the analysis of physical l health conditions, survivors will be censored at either the completion date of the latest questionnaire or the most recent National Death Index (NDI) search (December 31, 2007), whichever occurred first. Cumulative incidence of major chronic physical health conditions will be estimated and compared across exercise (MET-hrs·wk^{-1}) categories or meeting national guidelines using Gray's K-sample test[27] using death as a competing risk event. Poisson regression will be used to estimate adjusted associations between exercise exposure categories or meeting national guidelines and incidence of major chronic physical health conditions using the logarithm of person-years as the offset. Results will be reported as rate ratios (RRs) with 95% confidence intervals (CIs).

In the analysis of psychosocial conditions, log-binomial regression will used to estimate the prevalence ratio, corresponding p-values, and 95% confidence intervals (CI) of comparing the exercise exposure categories in reference to the 0 MET-hrs.wk^{-1} or those who meet national guidelines in opposite to those who don't.

All regression models will be adjusted for attained age, age at diagnosis, sex, race, smoking, education, cardiovascular risk factors (hypertension, diabetes, dyslipidemia, obesity) as time dependent covariates, and anthracycline and chest radiation exposures as potential confounders. Treatment exposures within the first five years of the original diagnosis were considered. Statistical analyses will be conducted using SAS Version 9.3 (SAS Institute, Inc., Cary, NC) and R Version 2.14.2. All statistical inferences will be two-sided.

EXAMPLE TABLE SHELLS & FIGURES

See below

Table 1. Demographic and Treatment Characteristics of the Participants

Characteristic	All Subjects	MET·hrs·wk^{-1}				*P*
		0	3 to 6	9 to 12	15 to 21	
No. of participants, (%)						
Age at latest follow-up – years						
Mean						
Range						
Age at diagnosis – years						
Mean						
Range						
Interval between diagnosis and study entry - years						
Mean						
Range						
Male – no. (%)						
Race – no. (%)						
Non-Hispanic white						
Other group						
BMI – kg/m^2						
Mean						
Range						
Smoking – no. (%)						
Current						
Former						
Never						
Cancer treatment – no. (%)						
Chemotherapy						
Any chemotherapy						
Alkylating agent						
Anthracycline						
Radiation therapy						
Any radiation therapy						
Chest						
Abdominal or pelvic						
CV risk factors – no. (%)						
Diabetes mellitus						
Hypertension						
Dyslipidemia						
Obesity						
Any of the above 4 factors						

Abbreviations: BMI, body mass index; CV, cardiovascular.

Table 2. Rate Ratios (RR) of Major (Grade 3 to 5) Physical Health Conditions According to Quartile of Total Exercise (Total MET-hrs·wk^{-1})[a]

	MET·hrs·wk^{-1}							
Major Chronic Condition	0	3 to 6		9 to 12		15 to 21		P_{trend}
No. at risk	xx	xx		xx		xx		
Any major chronic condition, no.	xx	xx		xx		xx		
RR (95% CI)	Referent	xx	(xx to xx)	xx	(xx to xx)	xx	(xx - xx)	xx
Pulmonary, no.	xx	xx		xx		xx		
RR (95% CI)	Referent	xx	(xx to xx	xx	(xx to xx)	xx	(xx - xx)	xx
Endocrine and Reproductive, no.	xx	xx		xx		xx		
RR (95% CI)	Referent	xx	(xx to xx)	xx	(xx to xx)	xx	(xx - xx)	xx
Cerebrovascular, no.	xx	xx		xx		xx		
RR (95% CI)	Referent	xx	(xx to xx)	xx	(xx to xx)	xx	(xx to xx)	xx
Second neoplasm malignancies, no.	xx	xx		xx		xx		
RR (95% CI)	Referent	xx	(xx to xx)	xx	(xx to xx)	xx	(xx to xx)	xx

[a]Adjusted for attained age, age at diagnosis, sex, race, smoking status, education, and cardiovascular disease risk factor profile as time dependent variables, anthracycline exposure, and chest radiation exposure.

Table 3. Rate Ratios (RR) of Major (Grade 3 to 5) Physical Health Conditions According to Meeting National Guidelines for Vigorous-Intensity Exercise (i.e., < 9 versus ≥ 9 MET-hrs·wk^{-1})[a]

	MET-hrs·wk^{-1}		
Cardiovascular event	< 9 MET-hrs·wk^{-1} (n=xx)	≥ 9 MET-hrs·wk^{-1} (n=xx)	*P*
Any major chronic condition, no.	xx	xx	
RR (95% CI)	Referent	xx (xx to xx)	xx
Cardiovascular, no.	XX	xx	
RR (95% CI)	Referent	xx (xx to xx)	
Pulmonary, no.	XX	xx	xx
RR (95% CI)	Referent	xx (xx to xx)	
Endocrine and Reproductive, no.	xx	xx	
RR (95% CI)	Referent	xx (xx to xx)	xx
Cerebrovascular, no.	xx	xx	
RR (95% CI)	Referent	xx (xx to xx)	xx
Second neoplasm malignancies, no.	xx	xx	
RR (95% CI)	Referent	xx (xx to xx)	xx

[a]Adjusted for attained age, age at diagnosis, sex, race, smoking status, education, and cardiovascular disease risk factor profile as time dependent variables, anthracycline exposure, chest radiation exposure.

Table 4. Prevalence Ratios (PR) of Psychosocial Conditions According to Quartile of Total Exercise (Total MET-hrs·wk^{-1})[a]

	MET·hrs·wk^{-1}							
Psychosocial Condition	0	3 to 6		9 to 12		15 to 21		P_{trend}
No. at risk	xx	xx		xx		xx		
Depression, no.	xx	xx		xx		xx		
PR (95% CI)	Referent	xx	(xx to xx)	xx	(xx to xx)	xx	(xx - xx)	xx
Anxiety, no.	xx	xx		xx		xx		
PR (95% CI)	Referent	xx	(xx to xx	xx	(xx to xx)	xx	(xx - xx)	xx
Pain, no.	xx	xx		xx		xx		
PR (95% CI)	Referent	xx	(xx to xx)	xx	(xx to xx)	xx	(xx - xx)	xx
Quality of life, no.	xx	xx		xx		xx		
PR (95% CI)	Referent	xx	(xx to xx	xx	(xx to xx	xx	(xx to xx	xx
Cognitive function, no.	xx	xx		xx		xx		
PR (95% CI)	Referent	xx	(xx to xx	xx	(xx to xx	xx	(xx to xx	xx
Sleep quality[b], no.	xx	xx		xx		xx		
PR (95% CI)	Referent	xx	(xx to xx	xx	(xx to xx	xx	(xx to xx	xx
Fatigue, no.	xx	xx		xx		xx		
PR (95% CI)	Referent	xx	(xx to xx)	xx	(xx to xx)	xx	(xx to xx)	xx

[a]Adjusted for attained age, age at diagnosis, sex, race, smoking status, education, and cardiovascular disease risk factor profile as time dependent variables, anthracycline exposure, chest radiation exposure.

[b]Data only available on XX participants

Table 5. Prevalence Ratios (PR) of Psychosocial Conditions According to Meeting National Guidelines for Vigorous-Intensity Exercise (i.e., < 9 versus ≥ 9 MET-hrs·wk^{-1})[a]

	MET-hrs·wk^{-1}		
Cardiovascular event	< 9 MET-hrs·wk^{-1} (n=xx)	≥ 9 MET-hrs·wk^{-1} (n=xx)	*P*
Depression, no.	xx	xx	
PR (95% CI)	Referent	xx (xx to xx)	xx
Anxiety, no.	XX	xx	
PR (95% CI)	Referent	xx (xx to xx)	
Pain, no.	XX	xx	xx
PR (95% CI)	Referent	xx (xx to xx)	
Quality of life, no.	xx	xx	
PR (95% CI)	Referent	xx (xx to xx)	xx
Cognitive function, no.	xx	xx	
PR (95% CI)	Referent	xx (xx to xx)	xx
Sleep quality[b], no.	xx	xx	
PR (95% CI)	Referent	xx (xx to xx)	xx
Fatigue, no.	xx	xx	
PR (95% CI)	Referent	xx (xx to xx)	xx

[a]Adjusted for attained age, age at diagnosis, sex, race, smoking status, education, and cardiovascular disease risk factor profile as time dependent variables, anthracycline exposure, chest radiation exposure

[b]Data only available on XX participants