STUDY TITLE: Exercise and Chronic Health Conditions and Health Care Utilization in Adults Survivors of Childhood Cancer

Investigators:

Lead Investigators:
Lee W. Jones, PhD jonesl3@mskcc.org
Jessica M. Scott, PhD scottj1@mskcc.org

Co-Investigators:
Gregory T. Armstrong, MD Greg.Armstrong@stjude.org
Rebecca M. Howell, MD rhowell@mdanderson.org
Wendy M. Leisenring, ScD wleisenr@fhcrc.org
Paul C. Nathan, MD, MSc paul.nathan@sickkids.ca
Kirsten K. Ness, PhD kiri.ness@stjude.org
Joseph Neglia, MD jneglia@umn.edu
Kevin C. Oeffinger, MD kevin.oeffinger@duke.edu
Qi Liu, MSc ql3@ualberta.ca
Yutaka Yasui, PhD yutaka.yasui@stjude.org

1.0 ANALYSIS CONCEPT PROPOSAL

DRAFT DATE 10 June 2018

TITLE Exercise and Chronic Health Conditions and Health Care Utilization in Adults Survivors of Childhood Cancer

WORKING GROUP Primary: Chronic Disease
Secondary: Cancer Control; Second Malignancy

BACKGROUND AND SIGNIFICANCE

Improvements in multimodal cancer treatment together with more effective risk stratification have contributed to a significant decline in late mortality among 5-year survivors of childhood cancer.[1] Nevertheless, these individuals remain at substantially elevated risk of late mortality compared to the general population due to recurrence of primary disease as well as treatment (health)-related late effects (e.g., subsequent malignant neoplasms (SMN), cardiovascular disease (CVD)).[2-5] Specifically, as reported in the Childhood Cancer Survivor Study (CCSS), a retrospective cohort of 34,033 patients surviving at least 5 years after initial childhood cancer diagnosis,[6] all-cause mortality rates from 5 to 9, 10 to 19, 20 to 29, and 30 years from diagnosis were 13.57, 6.00, 6.52, and 14.22 deaths per 1,000 person-years, respectively, compared to expected (age-adjusted) rates of 0.66, 1.03, 1.44, and 2.07 deaths per 1,000 person-years for the general United States population.[1] The principal cause of excess mortality in the short term is recurrence or progression of the initial cancer. However, with increasing time from diagnosis, mortality attributable to SMN and CVD are the leading causes of death.[1,3] Compared to siblings, adult survivors of childhood cancer have approximately 15-fold and seven-fold increased risks for SMN and CVD death, respectively.[7,8] Strategies that complement advances in conventional cancer treatment, especially those that offset treatment-related late effects, are urgently required.[9]

Excess health-related mortality in adult survivors of childhood cancer is driven by the direct adverse effects of cancer treatment on virtually all major organs systems in conjunction with secondary lifestyle perturbations (e.g., physical inactivity, weight gain),[10-12] synergistically predisposing to multiple chronic conditions (e.g., cardiovascular, and endocrine dysfunction). In the general population, exercise is associated with substantial reductions in the risk of multiple risk factors as well as reductions in the risk of death from CVD and any cause.[13,14] Moreover, there is a growing body of observational as well as preclinical work from our group,[15-17] as well as others,[18-21] showing that exercise is associated with lower risk of incidence, relapse, and cancer-specific mortality. However, whether the protective impact of exercise extends to adult survivors of childhood cancers who have a higher risk for treatment-associated toxicities compared to adult cancer patients[22] is not known. Similarly, given stark differences in the pathogenesis of disease, it is not known whether exercise attenuates the risk of chronic health conditions to a comparable degree in childhood cancer survivors to that observed in the general population.

An important corollary to this line of investigation is an examination of whether or not exercise associated prevention of chronic health conditions is correlated with health care utilization. As neither cancer nor prior or current treatment with anticancer agents are a qualifying diagnosis for exercise rehabilitation in North America, evidence showing that exercise prevents chronic condition onset and also reduces health care utilization will be critical in building the evidence base to support inclusion of exercise as a standard aspect of cancer management.

Accordingly, we propose to extend our prior work[23,24] to investigate the association between vigorous exercise in early-adulthood as well as longitudinal change in exercise on preventable chronic health conditions in adult survivors of childhood cancer in CCSS. We will also leverage the unique design of CCSS to compare the relationship between exercise and risk of chronic health conditions in survivors versus the same relationship in age-

matched non-cancer siblings. A secondary objective is to examine the direct and indirect effects and health care utilization. We hypothesize that vigorous exercise in early adulthood as well as increased exercise would reduce the risk of all preventable chronic health conditions and associated health care utilization patterns in a dose-dependent manner.

OBJECTIVES

Primary

1) To determine the association between vigorous exercise and the incidence of modifiable cardiovascular risk factors (i.e., hypertension, obesity, dyslipidemia, and diabetes) among childhood cancer survivors.
Hypothesis: Vigorous exercise in early adulthood and increased exercise will be associated with a reduction in modifiable cardiovascular risk factors compared to inactivity.

2) To determine the association between vigorous exercise and the (first) composite incidence of major (grade 3-4) chronic health conditions (i.e., cardiovascular, secondary neoplasms, respiratory, renal, musculoskeletal, and neurological). Severity of conditions were graded according to the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE; version 4.03), defined as severe (grade 3), or life threatening or disabling (grade 4) among childhood cancer survivors.
Hypothesis: Vigorous exercise in early adulthood and increased exercise will be associated with a reduction in chronic health conditions compared to inactivity.

3) To determine the association between vigorous exercise on health care utilization (e.g., physician visits, emergency room visits, medical tests, prescription drug use and hospitalizations) among childhood cancer survivors.
Hypothesis: Vigorous exercise in early adulthood and increased exercise will be associated with a reduction in health care utilization compared to inactivity.

Secondary

- To determine the association between exercise and incidence of individual major (grade 3-4) preventable chronic health conditions, defined as follows:
    - Cardiovascular (i.e., composite incidence of any event including Heart Attack, Congestive Heart Failure, Arrhythmia, Hypertension, Stiff or Leaky Valves, Cerebrovascular, Pericardial Disease, Other Vascular, Blood Clot, Other Cardiac Conditions)
    - Subsequent neoplasms/malignancies (i.e., new primaries).
    - Other chronic health conditions [i.e., respiratory (emphysema, primary pulmonary hypertension); renal (dialysis); musculoskeletal (joint replacement); neurological (memory problems, balance).
- *Hypothesis:* Exercise will be associated with a reduction in independent chronic health conditions compared to inactivity.
- To compare the association between vigorous exercise as well as change in exercise and CVD risk factors and the (first) composite incidence of major (grade 3-4) preventable chronic health conditions and health care utilization in survivors versus the same association in siblings.
- *Hypothesis:* The association between exercise and chronic health conditions and health care utilization will be blunted in survivors compared to siblings.

OUTCOMES OF INTEREST:

1. **Modifiable cardiovascular risk factors after baseline:** Hypertension (CTCAE), dyslipidemia (CTCAE condition “Cholesterol”), diabetes requiring medication (CTCAE grade 2+); obesity defined as a BMI of 30 kg/m^2 or greater. We will use obesity from follow-up (FU) 2 for participants from the original cohort (OC) and FU 5 for participants from the expansion cohort (EC).

2. **Grade 3 to 4 chronic health conditions after baseline**: Grade 3 and 4 chronic health conditions according to the CTCAE (version 4.3) including: (1) cardiovascular (i.e., composite incidence of any event including Heart Attack, Congestive Heart Failure, Arrhythmia, Hypertension, Stiff or Leaky Valves, Cerebrovascular, Pericardial Disease, Other Vascular, Blood Clot, Other Cardiac Conditions), (2) second neoplastic malignancies (i.e., new primaries, excluding non-melanoma skin cancer), and (3) other ([i.e., respiratory (emphysema, primary pulmonary hypertension); renal (dialysis); musculoskeletal (joint replacement); neurological (memory problems, balance)]. (**Table A1)**.

3. **Health care utilization after baseline:** We will use health care utilization from FU 2 for participants from the original cohort and FU 5 for participants from the expansion cohort. Defined as:

    a. Physician visits.
        i. **FU2: A.3, FU5: B2**. During this 2 year period, how many times did you see a physician? *Categorical*
        ii. **FU2: A.5, FU5: B3**. How many of the physician visits were related to previous cancer?
    b. Emergency Room Visits – Expansion Cohort Only
        i. **FU2: NA, FU5: B6**. During the past 12 months, how many times have you gone to a hospital emergency room about your own health?
    c. Hospitalizations – Expansion Cohort Only
        i. **FU2: NA; FU5: U1**. Have you been admitted to a hospital in the last 12 months
        ii. **FU 2: NA; FU5: U2**. How many times have you been admitted to a hospital in the last 12 months?
    d. Medical Screening Tests
        i. **FU2: B1-4** (females), **B1-3, 5** (males); **FU5: C1 a, d, f, m** (females), **a, d, f, n** (males): When was the last medical screening test?
    e. Prescription drug use
        i. **FU 2: Q1-9; FU5: C2.1-6, 9, 11**. We are interested in drugs you have taken consistently for more than one month or a total of 30 days in one year. Only list those prescribed by your doctor.

INDEPENDENT VARIABLES

Exercise: will be operationalized using the following outcome: Exercise data will be obtained from the baseline questionnaire. OC: Physical activity, question N.9; EC: O.15

a. Total vigorous 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. Change in vigorous exercise: Vigorous exercise as reassessed in follow-up questionnaires (FU 2 (OC) or FU 5 (EC)) among xxx adult survivors diagnosed between 1970 and 1999.[6] Change in vigorous exercise will be defined as: (1) decreased, (2) increased, (3) low maintenance (remaining in low exercise categories, i.e., 0 and 3-6 MET-h/wk), and (4) high maintenance (remaining in high exercise categories, i.e., 9-12 MET-h/wk or 15- 21 MET-h/wk).

COVARIATES

1. Sex (baseline: OC question A.1; EC, question A.1),
2. Race or ethnic group (baseline: OC A.4, EC, A.5),
3. Cancer diagnosis (medical record abstraction),
4. Cancer treatment (e.g., anthracycline dose, [doxorubicin equivalent doses will be used for anthracyclines]; chest radiation dose [maximum target dose (maxTD) to the chest (Gy)] and cranium radiation [y/n])
5. Education (baseline: OC: O.1 – O.4; EC R.1-R.4 & FU2: question 1; FU5: question A4),
6. Age at interview,
7. Time interval between diagnosis and baseline assessment of exercise.

SUBJECT POPULATION

Inclusion Criteria

1. >=5-year cancer survivors who were diagnosed between 1970 and 1999 at age <21 years at one of 28 institutions.
2. Histological confirmation of diagnosis with leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, central nervous system (CNS) malignancies, Wilms tumor, neuroblastoma, soft tissue sarcoma, or bone tumors.
3. Survivor participants who completed the baseline exercise item, and at least one of FU2 and FU5 survey
4. Baseline age > 18 years.
5. Participants without any major (Grade 3 to 4) chronic health conditions at baseline.
6. Siblings participating in the original and expansion cohort, who were >18 years at baseline, with at least one follow-up question in addition to the baseline, and without any major (grade 3-4) chronic health condition.

STATISTICAL ANALYSIS FRAMEWORK

Demographic, disease, and treatment characteristics will be assessed for their associations with the baseline quartiles of exercise exposure, using Chi-square tests for categorical outcomes and ANOVA for continuous variables. Analysis of incidence rate of chronic health conditions after baseline will be conducted for all listed outcomes of interest, censoring the at-risk time at the most recent follow-up survey. Piecewise exponential regression will be used to estimate the rate ratios and 95% confidence intervals for the association between exercise exposure/change in exercise categories and rates of CVD risk factors (hypertension, diabetes, dyslipidemia) and chronic health conditions using the logarithm of person-years as the offset. Log-binomial regression models will be used to assess the association between exercise/change in exercise and obesity/prescription drug use, and risk ratios will be reported. All models will be adjusted for all available potential confounding variables including attained age as cubic splines, age at diagnosis, sex, race, smoking, education, any anthracycline and equivalent dose,[25] cyclophosphamide and equivalent dose,[26] and radiation exposure.[27] Poisson regression models will be used to assess the association between exercise/change in exercise and health care utilization (physician visits, emergency room visits, and hospitalizations). Polytomous logistic regression will be used when the outcome is time of the last medical screening test (If there are clearly 2 groups, the outcome can be collapsed into binary and log-binomial regression will be used). Quartiles of exercise levels will be used for the assessment of the dose-response relationship. A multivariable-adjusted rate for modifiable risk factors and chronic conditions and each MET-hr/wk category (i.e., 0, 3, 6, 9, 12, 15, 18, 21) will be generated to identify the optimal exercise exposure. Vigorous exercise will be collapsed into two categories [no vigorous-intensity exercise exposure (0 MET-h/wk) versus the optimal exercise dose. Change in exercise will be calculated and its association on the outcomes after the exercise change will be assessed. Generalized estimating equations will be used to account for within-family association when survivors and siblings are compared.

Table A1: Grade 3-4 Chronic Health Conditions Scored According to Common Terminology Criteria of Adverse Events (CTCAE) v4.03 with Adaptations.

Category	Chronic Condition	Grade 3 Definition	Grade 4 Definition
Second Malignant Neoplasm	Second Malignant Neoplasm	• Thyroid, benign meningiomas who had neurosurgery • Breast cancer in situ (LCIS)	• Other malignancies • Breast cancer in situ (DCIS/mixed)
Cardiovascular	Heart Attack	• Heart attack, angina, or coronary heart disease not requiring a cardiac catheterization but on anti-anginal medication	• Heart attack, requiring cardiac catheterization, or angioplasty or CABGl
	Congestive Heart Failure	• Congestive heart failure, requiring medication	• Heart transplant
	Arrhythmia	• Arrhythmia, requiring pacemaker	• Ventricular fibrillation/flutter
	Hypertension	• Unspecified hypertensive renal disease without renal failure • Unspecified hypertensive heart and renal disease without heart failure or renal failure	• Not applicable
	Stiff or Leaky Valves	• Not applicable	• Heart valve replacement
	Cerebrovascular	• Occlusion of cerebral arteries • Cerebral embolism	• Stroke/CVA
	Pericardial Disease	• Pericardial disease requires surgical intervention	• Not applicable
	Other Vascular	• Aorta-subclavian-carotid bypass • Other (peripheral) vascular shunt or bypass • Other repair of aneurysm • Repair of arteriovenous fistula	• Other excision of vessels, aorta, abdominal (aorta) • Thoracic aneurysm, ruptured
	Blood Clot	• Blood clot in head, lung, arm, leg, or pelvis	• Pulmonary embolism/infarction • Embolism and thrombosis of unspecified artery
	Other Cardiac Condition	• Acute myocarditis in diseases classified elsewhere • Thromboangiitis obliterans [Buerger's disease] • Other chronic pulmonary heart diseases • Hypotension, unspecified	• Not applicable
Respiratory	Emphysema	• Chronic obstructive asthma	• Not applicable
	Other Respiratory	•	• Primary pulmonary hyptertension
Renal	Dialysis	• Acute kidney failure	• Artificial kidney hemodiafiltration, peritoneal disease, stage V chronic kidney disease, end stage renal disease, renal failure unspecified
Musculoskeletal	Joint replacement	• Joint replacement	• Not applicable
Neurological	Memory problems	• Problems with learning or memory, severe	• Problems with learning or memory, disabling
	Balance	• Problems with balance or ability to manipulate objects, severe	• Problems with balance or ability to manipulate objects, severe

Table 1. Characteristics of Participants According to Exercise Exposure Quartile at Baseline.

		MET-h/wk				
Characteristic	**Total**	**0**	**3 to 6**	**9 to 12**	**15 to 21**	***P***
No. of participants, (%)						
No. of survivors, (%)						
No. of siblings, (%)						
Age at interview – years						
Median						
IQR						
Age at diagnosis – years						
Median						
IQR						
Interval between baseline and follow-up – years						
Median						
IQR						
Male – no. (%)						
Race – no. (%)						
Non-Hispanic white						
Other group						
BMI – kg/m^2 (SD)						
Mean						
Range						
Smoking – no. (%)						
Current						
Former						
Never						
Cancer treatment – no. (%)						
Chemotherapy						
Any chemotherapy						
Anthracycline						
Doxorubicin equivalent dose,mg/m^2						
None						
<250mg/m^2						
>=250mg/m^2						
Alkylating agent cyclophosphamide equivalent dose, mg/m^2						
None						
0 - <4000						
>=4000 - <8000						
>=8000						
Radiation therapy						
Any radiation therapy						
Chest						
Chest RT dose						
None						
<20Gy						
20-<30Gy						
30-<40Gy						
40-<50Gy						
50+Gy						
Abdominal or pelvic						

Abbreviations: BMI, body mass index; CV, cardiovascular

Table 2. Multivariable-Adjusted Rate Ratios of CVD Risk Factors According to 0 and optimal MET-h/wk in survivors.

	0 MET-h/wk (0 days/wk)		optimal MET-h/wk (xdays/wk)	
	Survivors (n=)	***P***	**Survivors (n=)**	***P***
Median MET-hr/wk				
≥ 2 Cardiovascular risk factors				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			
Hypertension				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			
Dyslipidemia				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			
Diabetes				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			
Obesity				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			

Abbreviations: MET, metabolic equivalent task; RR, rate ratio; CI, confidence interval

*Adjusted for attained age, sex, race/ethnicity, smoking status, education, and non-cardiac grade 3 to 4 chronic health conditions in both siblings and survivors; additional adjustment in survivors for: age at cancer diagnosis, cumulative doxorubicin dose, cumulative cyclophosphamide-equivalent dose, radiation.

Cardiovascular risk factors include hypertension, dyslipidemia, diabetes, and obesity.

Table 3. Multivariable-Adjusted Rate Ratios of CVD Risk Factors According to 0 and optimal MET-h/wk in siblings.

	0 MET-h/wk (0 days/wk)		optimal MET-h/wk (xdays/wk)	
	Siblings (n=)	***P***	**Siblings (n=)**	***P***
Median MET-hr/wk				
≥ 2 Cardiovascular risk factors				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			
Hypertension				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			
Dyslipidemia				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			
Diabetes				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			
Obesity				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			

Abbreviations: MET, metabolic equivalent task; RR, rate ratio; CI, confidence interval

*Adjusted for attained age, sex, race/ethnicity, smoking status, education, and non-cardiac grade 3 to 4 chronic health conditions in both siblings and survivors; additional adjustment in survivors for: age at cancer diagnosis, cumulative doxorubicin dose, cumulative cyclophosphamide-equivalent dose, radiation.

Cardiovascular risk factors include hypertension, dyslipidemia, diabetes, and obesity.

Table 4. Multivariable-Adjusted Rate Ratios of Major (Grade 3-4) Chronic Health Conditions According to 0 and optimal MET-h/wk in survivors.

	0 MET-h/wk (0 days/wk)		**optimal MET-h/wk (optimal days/wk)**	
	Survivors (n=)	***P***	**Survivors (n=)**	***P***
Median MET-hr/wk				
Composite Chronic Health Conditions				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			
Cardiovascular				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			
SMN				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			
Other Chronic Health Conditions				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			

Abbreviations: MET, metabolic equivalent task; RR, rate ratio; CI, confidence interval

in both siblings and survivors; additional adjustment in survivors for: age at cancer diagnosis, cumulative doxorubicin dose, cumulative cyclophosphamide-equivalent dose, radiation.

Chronic Health Conditions is a composite of cardiovascular, subsequent neoplasms and other ([i.e., respiratory (emphysema, primary pulmonary hypertension); renal (dialysis); musculoskeletal (joint replacement); neurological (memory problems, balance).

Table 5. Multivariable-Adjusted Rate Ratios of Major (Grade 3-4) Chronic Health Conditions According to 0 and optimal MET-h/wk in siblings.

	0 MET-h/wk (0 days/wk)		optimal MET-h/wk (optimal days/wk)	
	Siblings (n=)	***P***	**Siblings (n=)**	***P***
Median MET-hr/wk				
Composite Chronic Health Conditions				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			
Cardiovascular				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			
SMN				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			
Other Chronic Health Conditions				
No. of events				
Age-adjusted RR (95% CI)	Ref			
Multivariable-adjusted RR (95% CI)*	Ref			

Abbreviations: MET, metabolic equivalent task; RR, rate ratio; CI, confidence interval

in both siblings and survivors; additional adjustment in survivors for: age at cancer diagnosis, cumulative doxorubicin dose, cumulative cyclophosphamide-equivalent dose, radiation.

Chronic Health Conditions is a composite of cardiovascular, subsequent neoplasms and other ([i.e., respiratory (emphysema, primary pulmonary hypertension); renal (dialysis); musculoskeletal (joint replacement); neurological (memory problems, balance).

Table 6. Age-Adjusted and Multivariable-Adjusted Rate Ratios of CVD Risk Factors According to Change in Exercise Exposure in Survivors.

		Change in Exercise Exposure‡			
	Total (n=)	**Low Maintenance (n=)**	**Decreased Exposure (n=)**	**Increased Exposure (n=)**	**High Maintenance (n=)**
> 2 Cardiovascular risk factors			P	P	P
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Hypertension					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Dyslipidemia					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Diabetes					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Obesity					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			

‡ Low maintenance (referent group): survivors remaining in 0 or 3-6 MET categories; Decreased exposure: a decline in exercise exposure from baseline to follow-up in MET classification (e.g., 3 to 6 to 0); increased exposure: an improvement in exercise exposure from baseline to follow-up in MET classification (e.g., 3 to 6 to 9 to 12); High maintenance: survivors remaining in 9-12 MET or 15-21 MET category. *Adjusted for attained age, sex, race/ethnicity, smoking status, education, and non-cardiac grade 3 to 4 chronic health condition, age at cancer diagnosis, cumulative doxorubicin dose, cumulative cyclophosphamide-equivalent dose, radiation.

Table 7. Age-Adjusted and Multivariable-Adjusted Rate Ratios of CVD Risk Factors According to Change in Exercise Exposure in Siblings.

		Change in Exercise Exposure‡			
	Total (n=)	**Low Maintenance (n=)**	**Decreased Exposure (n=)**	**Increased Exposure (n=)**	**High Maintenance (n=)**
> 2 Cardiovascular risk factors			P	P	P
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Hypertension					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Dyslipidemia					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Diabetes					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Obesity					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			

‡ Low maintenance (referent group): remaining in 0 or 3-6 MET categories; Decreased exposure: a decline in exercise exposure from baseline to follow-up in MET classification (e.g., 3 to 6 to 0); increased exposure: an improvement in exercise exposure from baseline to follow-up in MET classification (e.g., 3 to 6 to 9 to 12); High maintenance: remaining in 9-12 MET or 15-21 MET category. *Adjusted for attained age, sex, race/ethnicity, smoking status, education, and non-cardiac grade 3 to 4 chronic health condition.

Table 8. Age-Adjusted and Multivariable-Adjusted Rate Ratios of Chronic Health Conditions According to Change in Exercise Exposure in Survivors.

		Change in Exercise Exposure‡			
	Total (n=)	**Low Maintenance (n=)**	**Decreased Exposure (n=)**	**Increased Exposure (n=)**	**High Maintenance (n=)**
Composite Chronic Health Conditions§			P	P	P
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Cardiovascular					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Subsequent neoplasms					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Other Chronic Health Conditions					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			

‡ Low maintenance (referent group): survivors remaining in 0 or 3-6 MET categories; Decreased exposure: a decline in exercise exposure from baseline to follow-up in MET classification (e.g., 3 to 6 to 0); increased exposure: an improvement in exercise exposure from baseline to follow-up in MET classification (e.g., 3 to 6 to 9 to 12); High maintenance: survivors remaining in 9-12 MET or 15-21 MET category.

§ Composite Chronic Health Conditions includes: cardiovascular, subsequent neoplasms and other ([i.e., respiratory (emphysema, primary pulmonary hypertension); renal (dialysis); musculoskeletal (joint replacement); neurological (memory problems, balance).

Table 9. Age-Adjusted and Multivariable-Adjusted Rate Ratios of Chronic Health Conditions According to Change in Exercise Exposure in Siblings.

		Change in Exercise Exposure‡			
	Total (n=)	**Low Maintenance (n=)**	**Decreased Exposure (n=)**	**Increased Exposure (n=)**	**High Maintenance (n=)**
Composite Chronic Health Conditions§			P	P	P
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Cardiovascular					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Subsequent neoplasms					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Other Chronic Health Conditions					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			

‡ Low maintenance (referent group): survivors remaining in 0 or 3-6 MET categories; Decreased exposure: a decline in exercise exposure from baseline to follow-up in MET classification (e.g., 3 to 6 to 0); increased exposure: an improvement in exercise exposure from baseline to follow-up in MET classification (e.g., 3 to 6 to 9 to 12); High maintenance: survivors remaining in 9-12 MET or 15-21 MET category.

§ Chronic Health Conditions is a composite of cardiovascular, subsequent neoplasms and other ([i.e., respiratory (emphysema, primary pulmonary hypertension); renal (dialysis); musculoskeletal (joint replacement); neurological (memory problems, balance).

Table 10. Multivariable-Adjusted Risk Ratios of Health Care Utilization According to 0 and Optimal MET-h/wk.

	Siblings			Survivors		
	0 MET-h/wk (0 days/wk) (n=)	**xx MET-h/wk (optimal days/wk) (n=)**	***P***	**0 MET-h/wk (0 days/wk) (n=)**	**xx MET-h/wk (optimal days/wk) (n=)**	***P***
Median MET-hr/wk						
Composite Utilization						
No. of events						
Age-adjusted RR (95% CI)	Ref					
Multivariable-adjusted RR (95% CI)*	Ref					
Physician Visits						
No. of events						
Age-adjusted RR (95% CI)	Ref					
Multivariable-adjusted RR (95% CI)*	Ref					
Emergency Room Visits						
No. of events						
Age-adjusted RR (95% CI)	Ref					
Multivariable-adjusted RR (95% CI)*	Ref					
Medical Tests						
No. of events						
Age-adjusted RR (95% CI)	Ref					
Multivariable-adjusted RR (95% CI)*	Ref					
Prescription Drug Use						
No. of events						
Age-adjusted RR (95% CI)	Ref					
Multivariable-adjusted RR (95% CI)*	Ref					
Hospitalization						
No. of events						
Age-adjusted RR (95% CI)	Ref					
Multivariable-adjusted RR (95% CI)*	Ref					

Abbreviations: MET, metabolic equivalent task; RR, rate ratio; CI, confidence interval

*Adjusted for attained age, sex, race/ethnicity, smoking status, education, and any baseline grade 3 to 4 chronic health conditions in both siblings and survivors; additional adjustment in survivors for: age at cancer diagnosis, cumulative doxorubicin dose, cumulative cyclophosphamide-equivalent dose, radiation.

Table 11. Age-Adjusted and Multivariable-Adjusted Risk Ratios of Health Care Utilization According to Change in Exercise Exposure in Survivors.

		Change in Exercise Exposure‡			
	Total (n=)	**Low Maintenance (n=)**	**Decreased Exposure (n=)**	**Increased Exposure (n=)**	**High Maintenance (n=)**
Composite Utilization			P	P	P
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Physician Visits					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Emergency Room Visits					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Medical Tests					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Prescription Drug Use					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Hospitalization					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			

‡ Low maintenance (referent group): survivors remaining in 0 or 3-6 MET categories; Decreased exposure: a decline in exercise exposure from baseline to follow-up in MET classification (e.g., 3 to 6 to 0); increased exposure: an improvement in exercise exposure from baseline to follow-up in MET classification (e.g., 3 to 6 to 9 to 12); High maintenance: survivors remaining in 9-12 MET or 15-21 MET category.

* Adjusted for attained age, sex, race/ethnicity, smoking status, education, and any baseline grade 3 to 4 chronic health conditions, age at cancer diagnosis, cumulative doxorubicin dose, cumulative cyclophosphamide-equivalent dose, radiation.

Table 12. Age-Adjusted and Multivariable-Adjusted Risk Ratios of Health Care Utilization According to Change in Exercise Exposure in Siblings.

		Change in Exercise Exposure‡			
	Total (n=)	**Low Maintenance (n=)**	**Decreased Exposure (n=)**	**Increased Exposure (n=)**	**High Maintenance (n=)**
Composite Utilization			P	P	P
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Physician Visits					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Emergency Room Visits					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Medical Tests					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Prescription Drug Use					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			
Hospitalization					
No. of events					
Age-adjusted RR (95% CI)		Ref			
Multivariable-adjusted RR (95% CI)*		Ref			

‡ Low maintenance (referent group): remaining in 0 or 3-6 MET categories; Decreased exposure: a decline in exercise exposure from baseline to follow-up in MET classification (e.g., 3 to 6 to 0); increased exposure: an improvement in exercise exposure from baseline to follow-up in MET classification (e.g., 3 to 6 to 9 to 12); High maintenance: remaining in 9-12 MET or 15-21 MET category.

* Adjusted for attained age, sex, race/ethnicity, smoking status, education, and any baseline grade 3 to 4 chronic health conditions.

References

1. Armstrong GT, Liu Q, Yasui Y, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2009;27(14):2328-2338.
2. Fidler MM, Reulen RC, Winter DL, et al. Long term cause specific mortality among 34 489 five year survivors of childhood cancer in Great Britain: population based cohort study. *BMJ.* 2016;354:i4351.
3. Reulen RC, Winter DL, Frobisher C, et al. Long-term cause-specific mortality among survivors of childhood cancer. *JAMA.* 2010;304(2):172-179.
4. Yeh JM, Nekhlyudov L, Goldie SJ, Mertens AC, Diller L. A model-based estimate of cumulative excess mortality in survivors of childhood cancer. *Ann Intern Med.* 2010;152(7):409-417, W131-408.
5. Armstrong GT, Chen Y, Yasui Y, et al. Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer. *N Engl J Med.* 2016;374(9):833-842.
6. Robison LL, Armstrong GT, Boice JD, et al. The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. *J Clin Oncol.* 2009;27(14):2308-2318.
7. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *Journal of the National Cancer Institute.* 2008;100(19):1368-1379.
8. Tukenova M, Guibout C, Oberlin O, et al. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. *J Clin Oncol.* 2010;28(8):1308-1315.
9. Scott JM, Koelwyn GJ, Hornsby WE, et al. Exercise therapy as treatment for cardiovascular and oncologic disease after a diagnosis of early-stage cancer. *Semin Oncol.* 2013;40(2):218-228.
10. Garmey EG, Liu Q, Sklar CA, et al. Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2008;26(28):4639-4645.
11. Hoffman MC, Mulrooney DA, Steinberger J, Lee J, Baker KS, Ness KK. Deficits in physical function among young childhood cancer survivors. *J Clin Oncol.* 2013;31(22):2799-2805.
12. Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. *J Clin Oncol.* 2004;22(15):3139-3148.
13. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med.* 2002;346(11):793-801.
14. Paffenbarger RS, Jr., Hyde RT, Wing AL, Lee IM, Jung DL, Kampert JB. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *N Engl J Med.* 1993;328(8):538-545.
15. Jones LW, Kwan ML, Weltzien E, et al. Exercise and Prognosis on the Basis of Clinicopathologic and Molecular Features in Early-Stage Breast Cancer: The LACE and Pathways Studies. *Cancer Res.* 2016;76(18):5415-5422.
16. Jones LW, Viglianti BL, Tashjian JA, et al. Effect of aerobic exercise on tumor physiology in an animal model of human breast cancer. *J Appl Physiol (1985).* 2010;108(2):343-348.
17. Jones LW, Antonelli J, Masko EM, et al. Exercise modulation of the host-tumor interaction in an orthotopic model of murine prostate cancer. *J Appl Physiol (1985).* 2012;113(2):263-272.
18. Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. *Ann Oncol.* 2014;25(7):1293-1311.
19. Meyerhardt JA, Giovannucci EL, Ogino S, et al. Physical activity and male colorectal cancer survival. *Arch Intern Med.* 2009;169(22):2102-2108.
20. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA.* 2005;293(20):2479-2486.
21. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med.* 1995;122(5):327-334.
22. Sarosiek KA, Fraser C, Muthalagu N, et al. Developmental Regulation of Mitochondrial Apoptosis by c-Myc Governs Age- and Tissue-Specific Sensitivity to Cancer Therapeutics. *Cancer Cell.* 2017;31(1):142-156.
23. Scott JM, Li N, Liu Q, et al. Association of Exercise With Mortality in Adult Survivors of Childhood Cancer. *JAMA Oncol.* 2018.

24. Jones LW, Liu Q, Armstrong GT, et al. Exercise and risk of major cardiovascular events in adult survivors of childhood hodgkin lymphoma: a report from the childhood cancer survivor study. *J Clin Oncol.* 2014;32(32):3643-3650.
25. Feijen EA, Leisenring WM, Stratton KL, et al. Equivalence Ratio for Daunorubicin to Doxorubicin in Relation to Late Heart Failure in Survivors of Childhood Cancer. *J Clin Oncol.* 2015;33(32):3774-3780.
26. Green DM, Nolan VG, Goodman PJ, et al. The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer.* 2014;61(1):53-67.
27. Ness KK, Hudson MM, Jones KE, et al. Effect of Temporal Changes in Therapeutic Exposure on Self-reported Health Status in Childhood Cancer Survivors. *Ann Intern Med.* 2017;166(2):89-98.