**STUDY TITLE**

**Association Between Exercise Behavior and Incidence of Major Cardiac Events in Adult Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study**

Investigators:

| | |
|---|---|
| Lee W. Jones, PhD | jones442@mc.duke.edu |
| Kirsten K. Ness, PhD | kiri.ness@stjude.org |
| Kathryn Devine, PhD | Katie_devine@urmc.rochester.edu |
| Pamela S. Douglas, MD | Pamela.douglas@duke.edu |
| Graeme J. Koelwyn, MS | Graeme.koelwyn@ubc.ca |
| Michel G. Khouri, MD | Michel.khouri@duke.edu |
| Susan G. Lakoski, MD | Susan.Lakoski@uvm.edu |
| Yutaka Yasui, PhD | yutaka.yasui@ualberta.ca |
| Yan Chen, MM | ychen9@ualberta.ca |
| Emily Tonorezos, MD, MPH | tonoreze@mskcc.org |
| Jessica M. Scott, PhD | Jessica.m.scott@nasa.gov |
| Greg T. Armstrong, MD | Greg.Armstrong@stjude.org |
| Charles A. Sklar, MD | sklarc@mskcc.org |
| Leslie L. Robison, PhD | Les.Robison@STJUDE.ORG |
| Kevin C. Oeffinger, MD | oeffingk@mskcc.org |

## 1.0 ANALYSIS CONCEPT PROPOSAL

**DRAFT DATE** 12 February 2013

**TITLE** Association Between Exercise Behavior and Major Cardiac Events in Adult Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study

**WORKING GROUP** Primary: Cancer Control
Secondary: Chronic Disease

## BACKGROUND AND SIGNIFICANCE

The Childhood Cancer Survivor Study (CCSS), a prospective cohort of over 20,000 adult survivors of childhood cancer diagnosed between 1970 and 1986, has provided remarkable insights into the long-term adverse effects of cancer and associated cytotoxic therapy. The CCSS has demonstrated that significant improvements in cancer-specific survival come at the cost of marked increases in the risk of competing (non-cancer) causes of morbidity and mortality. As such, identification of effective strategies to prevent and/or mitigate therapy-associated late-effects in adult childhood cancer survivors is a high priority.

Over the past decade, exercise has gained acceptance as a potential adjunct therapy following a cancer diagnosis. To date, approximately, 80 studies have been conducted investigating the effects of structured exercise training in patients following a diagnosis of cancer. Meta-analyses and systematic reviews report that structured exercise training is a safe and well-tolerated therapeutic strategy associated with significant improvements in a broad range of cancer-related toxicities including fatigue, exercise capacity, and physical quality of life. Based on the extant literature, several national and international organizations have published exercise guidelines for cancer patients both during and following the completion of adjuvant therapy.

A major question of considerable interest in the field of exercise-oncology research is whether the benefits of exercise extend beyond symptom control to improved survival following a cancer diagnosis. In a recent systematic review by our group, we identified a total of 20 epidemiological studies that have investigated the association between self-reported exercise behavior and prognosis following a diagnosis of cancer in adults. In brief, the majority of studies were conducted in women with early breast cancer (50%), with fewer conducted in patients with gastrointestinal malignancies (25%) and prostate cancer (10%). One study each was performed in patients with ovarian, non-small cell lung cancer, and primary malignant glioma.

Overall, 15 studies (75%) found a significant inverse relationship between exercise and prognosis (cancer-specific or all-cause mortality) with a range of risk reduction between 15 to 67% and 18 to 67% for cancer-specific mortality and all-cause mortality, respectively. A dose-response was reported in 11 (55%); five studies found no significant association between exercise and cancer-specific mortality. Finally, the dose of exercise required for mortality reduction was not uniform either within or between cancer populations ranging from ≥9 metabolic equivalent time (MET)-hours per week of exercise (MET-hrs·wk$^{-1}$) of moderate intensity exercise (equivalent to approximately 150 mins·wk$^{-1}$ of moderate intensity exercise) to ≥27 MET-hrs·wk$^{-1}$ (equivalent to ≥500 mins·wk$^{-1}$ of moderate intensity exercise).

Overall, the current literature base provides initial (promising) evidence that regular exercise may reduce the risk of death following a cancer diagnosis in adult survivors. It is currently unknown whether the observations extend to adult survivors of childhood cancers. Furthermore, the vast majority of prior studies have focused primarily on the relationship between exercise and cancer-specific survival with less emphasis or interest in the risk of competing causes of morbidity or mortality, although such conditions are rapidly becoming the primary cause of mortality in long-term adult cancer survivors.

Against this background, the purpose of this study is to examine the association between self-reported exercise behavior and incidence of major cardiac events in the CCSS cohort. We hypothesized that higher levels of exercise behavior will be associated with lower incidence of major cardiac events in a dose-dependent manner.

## SPECIFIC AIMS

**Primary**

To determine the association between exercise behavior and subsequent incidence of major (grade 3-4) cardiac events (i.e., ischemic coronary artery disease, congestive heart failure, heart valve replacement and serious arrhythmia) as well as risk of death.

**Secondary**

- To determine the association between exercise behavior and subsequent incidence of condition-specific major (grade 3-4) cardiac events (i.e., ischemic coronary artery disease vs. congestive heart failure vs. heart valve replacement vs. serious arrhythmia).
- Association between exercise behavior and subsequent incidence of major (grade 3-4) cardiac events and condition-specific events as a function of cancer diagnosis.
- Association between exercise behavior and subsequent incidence of major (grade 3-4) cardiac events and condition-specific events as a function of cancer therapy (i.e., treatment with anthracyclines or chest-directed radiotherapy).

## HYPOTHESES

**Primary**

Higher levels of self-reported exercise behavior will be associated with a subsequently lower incidence of major cardiac events and cardiac-related mortality.

**Secondary**

- Higher levels of self-reported exercise behavior will be associated with a subsequently lower condition-specific incidence of major cardiac events.
- Higher levels of self-reported exercise behavior will be associated with a subsequently lower incidence of major cardiac events, and that of condition-specific events across all cancer diagnoses.
- Higher levels of self-reported exercise behavior will be associated with lower incidence of major cardiac events, and that of condition-specific events across all treatment types.

## OUTCOMES OF INTEREST:

1. **Incidence of major cardiac events**: defined as incidence of cardiac conditions occurring after the baseline questionnaire in four categories (ischemic coronary artery disease, congestive heart failure, heart valve replacement and serious arrhythmia) as defined by Armstrong et al. *submitted*. 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), life-threatening or disabling (grade 4), and fatal (grade 5).

2. **Condition-specific events:** defined as the individual incidence of major cardiac events as defined above. All events will be graded by CTCAE.

## INDEPENDENT VARIABLES

**Exercise behavior:** will be operationalized using the following major outcomes:
Primary exercise behavior data will be obtained from the Baseline survey, Health Habits. Physical activity, page 15, question N.7.

Secondary exercise behavior data will be obtained from the 2003 Follow-up survey, Section D. Physical activity, page 7, questions 1 – 7.

1. **Exercise Behavior Data from Baseline Survey**

   a. **Total vigorous exercise behavior:** the frequency of vigorous exercise in days per week (0 – 7 days) for at least 20 mins per session. This will enable analysis of whether frequency of exercise behavior is associated with clinical events (i.e., 0 – 7 days per weeks) or total minutes of exercise behavior is associated with clinical events (calculated as days per week x 20 mins per session). From this, we could also calculate MET-hrs-wk. The frequency of vigorous exercise sessions per week is multiplied by the average reported duration (i.e., 20 mins), weighted by an estimate of the metabolic equivalent (MET), summed across both intensities, and expressed as average MET-hours per week. The standard MET weightings for vigorous exercise is 9 METs, (e.g., running, vigorous swimming). From this calculation, categories of MET-hrs per week can be defined to examine a potential dose-response relationship.
   b. **Meeting exercise Guidelines:** the proportion of participants reporting at least 3 exercise sessions per week vs. those not achieving this level – this is equivalent to 60mins of vigorous intensity exercise per week, which are the current national recommendations for adult cancer survivors.

2. **Exercise Behavior Data from the 2003 Follow-Up Survey**

   a. **Total exercise behavior:** the frequency of exercise sessions per week within each intensity category (i.e., moderate or vigorous) was multiplied by the average reported duration (in minutes), weighted by an estimate of the metabolic equivalent (MET), summed across both intensities, and expressed as average MET-hours per week. The standard MET weightings and examples for each level of exercise intensity are as follows: moderate (5 METs, e.g., brisk walking, tennis), and vigorous (9 METs, e.g., running, vigorous swimming). From this calculation, categories of MET-hrs per week can be defined to examine a potential dose-response relationship. For example, a participant reporting 1 mild intensity exercise session for 60 minutes and 3 moderate intensity exercise sessions for an average duration of 30 minutes per week would receive a score of 10.5 MET-hrs/wk [i.e., (1 x 60 x 3 x 30 x 5)/ 60]. Separate scores were also calculated for total exercise frequency (MET-times/wk), mild, moderate, and strenuous intensity exercise minutes and frequency.

   b. **Meeting 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 150mins of moderate to vigorous intensity exercise per week, which are 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 (baseline questionnaire, question A.11; 2003 questionnaire; page 3; question 8)
4. Body mass index (baseline questionnaire, needs to be calculated from questions A.10 and A.11; 2003 questionnaire, needs to be calculated from height and weight on page 3, questions 7 and 8),
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),
8. Age at interview (baseline questionnaire, A.1; 2003 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; smoking = baseline questionnaire, page 14, question N.1 and 2003 questionnaire page 13; question L),

## SUBJECT POPULATION

### Inclusion Criteria

1. >5-year cancer survivors who were diagnosed between 1970 and 1986 at age <21 years at 1 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 survey and at least one of the follow-up surveys, and
4. Age > 18 years at baseline.

## STATISTICAL ANALYSIS FRAMEWORK

*Primary Analyses*: Descriptive statistics will be reported for demographic and medical characteristics and study outcomes. The Cox proportional hazards model will be used to examine the association between exercise behavior and incidence of major cardiac events.
**Baseline Questionnaire:** Exercise behavior will be categorized via an unbiased quintile split as defined by total exercise frequency, total exercise minutes / week, MET-hrs.wk (e.g., < 3, 3 to 8.9, 9 to 14.9, 15 to 23.9, and ≥24 MET-hrs.wk$^{-1}$), and percentage meeting national exercise guidelines for vigorous activity (i.e., ≥60 mins / wk)
**2003 Follow-Up Questionnaire:** Exercise behavior will be categorized via an unbiased quintile split as defined by total exercise frequency, total exercise minutes / week, MET-hrs.wk (e.g., < 3, 3 to 8.9, 9 to 14.9, 15 to 23.9, and ≥24 MET-hrs.wk$^{-1}$),, and percentage meeting national exercise guidelines for moderate + vigorous activity (i.e., ≥150 mins / wk)

Follow-up time will start from the time of assessment of exercise behavior. Death, Second Malignant Neoplasm, and late recurrence (unable to characterize the treatment of these) will be treated as a competing event; patients who remain alive and event free will be censored at the time of last follow-up. A two-sided significance level of 0.05 will be used for all statistical tests. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

*Secondary Analyses:* A likelihood ratio (LR) test will be used in the context of the Cox model to assess the contribution of exercise behavior in predicting major cardiac events beyond that provided by demographic and medical parameters.

*Co-Variates*: The following covariates will be extracted from the medical record: sex, race or ethnic group, baseline weight, body mass index, cancer diagnosis, cancer treatment (e.g., anthracycline dose, chest irradiation), education, age at baseline interview, cardiovascular risk profile (i.e., incidence of diabetes mellitus, hypertension, dyslipidemia, obesity) time interval between diagnosis and assessment of exercise behavior.

## EXAMPLE TABLE SHELLS & FIGURES

See below

**Table 1. Characteristics of Participants According to Self-Reported Exercise Behavior Level**

| | MET-hrs.wk$^{-1}$ | | | | |
|---|---|---|---|---|---|
| **Characteristic** | **< 3** | **3 – 8.9** | **9 – 14.9** | **15 – 23.9** | **≥ 24** |
| Age at interview – yr | | | | | |
| Mean | | | | | |
| Range | | | | | |
| Sex – no. (%) | | | | | |
| Female | | | | | |
| Male | | | | | |
| Race or ethnic group – no. (%) | | | | | |
| Non-Hispanic white | | | | | |
| Other group | | | | | |
| Weight – kg | | | | | |
| Mean | | | | | |
| Range | | | | | |
| Body mass index – kg/m$^2$ | | | | | |
| Mean | | | | | |
| Range | | | | | |
| Cancer diagnosis – no. (%) | | | | | |
| Leukemia | | | | | |
| Central nervous system tumor | | | | | |
| Hodgkin's disease | | | | | |
| Non-Hodgkin's lymphoma | | | | | |
| Wilms' tumor | | | | | |
| Neuroblastoma | | | | | |
| Sarcoma | | | | | |
| Bone tumor | | | | | |
| Cancer treatment – no. (%) | | | | | |
| No chemotherapy or radiation | | | | | |
| Chemotherapy | | | | | |
| Any chemotherapy | | | | | |
| Alkylating agent | | | | | |
| Anthracycline | | | | | |
| Other chemotherapy | | | | | |
| Radiation therapy | | | | | |
| Any radiation therapy | | | | | |
| Brain irradiation | | | | | |
| Chest irradiation | | | | | |
| Abdominal or pelvic irradiation | | | | | |
| Cardiovascular risk factors – no. (%) | | | | | |
| Diabetes mellitus | | | | | |
| Hypertension | | | | | |

| | |
|---|---|
| Dyslipidemia | |
| Obesity | |
| Interval between cancer diagnosis and study entry - yr | |
| Mean | |
| Range | |

**Table 2. Unadjusted and Multivariate-Adjusted Relative Risks of Major Cardiac Events According to Self-Reported Exercise Behavior Level***

| | | MET-hrs.wk$^{-1}$ | | | | |
|---|---|---|---|---|---|---|
| | **Total (n=XX)** | **< 3 (n=xx)** | **3 – 8.9 (n=xx)** | **9 – 14.9 (n=xx)** | **15 – 23.9 (n=xx)** | **≥ 24 (n=xx)** |
| Any major cardiac events | | | | | | |
| Unadjusted RR (95% CI) | | 1.0 | | | | |
| Multivariate-adjusted RR (95% CI) | | 1.0 | | | | |
| Coronary artery disease | | | | | | |
| Unadjusted RR (95% CI) | | 1.0 | | | | |
| Multivariate-adjusted RR (95% CI) | | 1.0 | | | | |
| Congestive heart failure | | | | | | |
| Unadjusted RR (95% CI) | | 1.0 | | | | |
| Multivariate-adjusted RR (95% CI) | | 1.0 | | | | |
| Valve abnormality | | | | | | |
| Unadjusted RR (95% CI) | | 1.0 | | | | |
| Multivariate-adjusted RR (95% CI) | | 1.0 | | | | |
| Arrhythmia | | | | | | |
| Unadjusted RR (95% CI) | | 1.0 | | | | |
| Multivariate-adjusted RR (95% CI) | | 1.0 | | | | |

*Adjusted for age, age at diagnosis, sex, race, body mass index, anthracycline exposure, radiation exposure, cardiovascular disease risk factor profile.

**Table 3. Unadjusted and Multivariate-Adjusted Relative Risks of Major Cardiac Events According to Self-Reported Exercise Behavior Level Across Type of Cancer**

| | | MET-hrs.wk$^{-1}$ | | | | |
|---|---|---|---|---|---|---|
| | **Total (n=XX)** | **< 3 (n=xx)** | **3 – 8.9 (n=xx)** | **9 – 14.9 (n=xx)** | **15 – 23.9 (n=xx)** | **≥ 24 (n=xx)** |
| Bone tumors | | | | | | |
| Any major cardiac events | | | | | | |
| Unadjusted RR (95% CI) | | 1.0 | | | | |
| Multivariate-adjusted RR (95% CI) | | 1.0 | | | | |
| Central nervous system | | | | | | |
| Any major cardiac events | | | | | | |
| Unadjusted RR (95% CI) | | 1.0 | | | | |
| Multivariate-adjusted RR (95% CI) | | 1.0 | | | | |
| Hodgkin's disease | | | | | | |
| Any major cardiac events | | | | | | |
| Unadjusted RR (95% CI) | | 1.0 | | | | |
| Multivariate-adjusted RR (95% CI) | | 1.0 | | | | |
| Sarcoma | | | | | | |
| Any major cardiac events | | | | | | |
| Unadjusted RR (95% CI) | | 1.0 | | | | |
| Multivariate-adjusted RR (95% CI) | | 1.0 | | | | |
| Non-Hodgkin's lymphoma | | | | | | |
| Any major cardiac events | | | | | | |
| Unadjusted RR (95% CI) | | 1.0 | | | | |
| Multivariate-adjusted RR (95% CI) | | 1.0 | | | | |
| Neuroblastoma | | | | | | |
| Any major cardiac events | | | | | | |
| Unadjusted RR (95% CI) | | 1.0 | | | | |
| Multivariate-adjusted RR (95% CI) | | 1.0 | | | | |
| Leukemia | | | | | | |
| Any major cardiac events | | | | | | |
| Unadjusted RR (95% CI) | | 1.0 | | | | |
| Multivariate-adjusted RR (95% CI) | | 1.0 | | | | |
| Wilm's tumor | | | | | | |
| Any major cardiac events | | | | | | |
| Unadjusted RR (95% CI) | | 1.0 | | | | |
| Multivariate-adjusted RR (95% CI) | | 1.0 | | | | |

**Table 4. Unadjusted and Multivariate-Adjusted Relative Risks of Major Cardiac Events According to Whether Participants Meet National Exercise Guidelines**

| Characteristic | MET-hrs.wk$^{-1}$ | | Likelihood Ratio P |
|---|---|---|---|
| | < 9 MET-hrs.wk$^{-1}$ | ≥ 9 MET-hrs.wk$^{-1}$ | |
| Any major cardiac events | | | |
| Unadjusted RR (95% CI) | 1.0 | | |
| Multivariate-adjusted RR (95% CI) | 1.0 | | |
| Coronary artery disease | | | |
| Unadjusted RR (95% CI) | 1.0 | | |
| Multivariate-adjusted RR (95% CI) | 1.0 | | |
| Congestive heart failure | | | |
| Unadjusted RR (95% CI) | 1.0 | | |
| Multivariate-adjusted RR (95% CI) | 1.0 | | |
| Valve abnormality | | | |
| Unadjusted RR (95% CI) | 1.0 | | |
| Multivariate-adjusted RR (95% CI) | 1.0 | | |
| Arrhythmia | | | |
| Unadjusted RR (95% CI) | 1.0 | | |
| Multivariate-adjusted RR (95% CI) | 1.0 | | |

**Table 5. Unadjusted and Multivariate-Adjusted Relative Risks of Major Cardiac Events According to Whether Participants Meet National Exercise Guidelines Across Type of Cancer**

| Characteristic | MET-hrs.wk$^{-1}$ < 9 MET-hrs.wk$^{-1}$ | MET-hrs.wk$^{-1}$ ≥ 9 MET-hrs.wk$^{-1}$ | Likelihood Ratio P |
|---|---|---|---|
| Bone tumors | | | |
| Any major cardiac events | | | |
| Unadjusted RR (95% CI) | 1.0 | | |
| Multivariate-adjusted RR (95% CI) | 1.0 | | |
| Central nervous system | | | |
| Any major cardiac events | | | |
| Unadjusted RR (95% CI) | 1.0 | | |
| Multivariate-adjusted RR (95% CI) | 1.0 | | |
| Hodgkin's disease | | | |
| Any major cardiac events | | | |
| Unadjusted RR (95% CI) | 1.0 | | |
| Multivariate-adjusted RR (95% CI) | 1.0 | | |
| Sarcoma | | | |
| Any major cardiac events | | | |
| Unadjusted RR (95% CI) | 1.0 | | |
| Multivariate-adjusted RR (95% CI) | 1.0 | | |
| Non-Hodgkin's lymphoma | | | |
| Any major cardiac events | | | |
| Unadjusted RR (95% CI) | 1.0 | | |
| Multivariate-adjusted RR (95% CI) | 1.0 | | |
| Neuroblastoma | | | |
| Total cumulative incidence of major cardiac events | | | |
| Unadjusted RR (95% CI) | 1.0 | | |
| Multivariate-adjusted RR (95% CI) | 1.0 | | |
| Leukemia | | | |
| Total cumulative incidence of major cardiac events | | | |
| Unadjusted RR (95% CI) | 1.0 | | |
| Multivariate-adjusted RR (95% CI) | 1.0 | | |
| Wilm's tumor | | | |
| Any major cardiac events | | | |
| Unadjusted RR (95% CI) | 1.0 | | |
| Multivariate-adjusted RR (95% CI) | 1.0 | | |

**Figure Captions**

**Figure 1.** Risk of any major cardiac events according to self-reported exercise behavior (essentially figure representation of Table 2)

**Figure 2.** Risk of condition-specific major cardiac events according to self-reported exercise behavior (essentially figure representation of Table 3)

**Figure 3.** Risk of any major cardiac events according to whether participants meet national exercise guidelines (essentially figure representation of Table 4)