**CCSS Analysis Concept Proposal**

## 1. Study Title.

Exercise and Late Mortality in 5-Year Survivors of Childhood Cancer: a Report from the Childhood Cancer Survivor Study.

## 2. Working Group and Investigators.

Cancer Control (Primary); Epidemiology/Biostatistics (Secondary); Chronic Disease (Secondary).

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## 3. Background and Rationale.

Improvements in therapies for childhood cancer have resulted in significant reductions in primary cancer-specific mortality; the 5-year overall relative survival rate is now over 83%.[1] As a result, there are currently over 420,000 survivors of childhood cancer in the United States, and by the year 2020 this number is expected to surpass 500,000.[2] Despite continual improvements in cancer outcomes, childhood cancer survivors remain at high risk of excess late mortality (death > 5 years from diagnosis), with the primary causes being recurrence of disease and other health-related causes from late-effects of treatment.[3,4] For example, an assessment of late mortality in 34,033 5-year survivors of childhood cancer (diagnosed <21 years of age, median follow-up 21 years, range 5-38) in CCSS found that of the 3,958 deaths, 2002 (51%) were attributable to recurrence or progression of primary cancer whereas 1618 (41%) were attributable to non-primary cancer related causes, including 746 (19%) subsequent neoplasm, 241 (6%) cardiac, and 137 (3%) pulmonary deaths.[5] To improve overall survival in adult survivors of childhood malignancies, preventive and/or treatment strategies are urgently needed to off-set both cancer-specific and non-cancer causes of mortality.[6]

Exercise may be one strategy to reduce the both the risk of cancer-specific[7] as well as other health-related causes of mortality after a cancer diagnosis.[8,9] In terms of the former, among adults with cancer, a recent systematic review of 26 observational studies of breast, colorectal, and prostate cancer patients, found that "high" exercise was associated with a pooled 37% reduction in the risk of cancer-specific mortality compared to inactivity (pooled relative risk = 0.63; 95% confidence interval: 0.54-0.73).[7] For other health-related causes of mortality, in 1,187 Hodgkin lymphoma survivors participating in CCSS, cumulative incidence of any cardiovascular (CV) event was 12.2% at 10 years for survivors reporting 0 MET-hrs.wk$^{-1}$, compared with 5.2% for those reporting ≥ 9 MET-hrs.wk$^{-1}$.[8] In multivariable analyses, the incidence of any CV event decreased across increasing MET categories (Ptrend = .002).[8] In further work, Jones et al. found that regular exercise (i.e., ≥ 9 MET-hrs.wk$^{-1}$) was associated with an adjusted 23% reduction in the risk of CV events in comparison with not meeting the guidelines (< 9 MET hours/week; P < .001) in 2,973 women with non-metastatic breast cancer.[9] The association with exercise did not differ according to age, CV risk factors, menopausal status, or anticancer treatment. Finally, in initial work from the CCSS, Cox et al. found that compared to 3 or more days of exercise per week, engaging in no exercise was associated with a 1.4-fold and 1.8-fold increased risk of mortality from secondary malignancy and cardiovascular or pulmonary causes, respectively.[10] This study, however, had several important limitations. Of these, the most important was the use of a case-control design that only included participants that died within the follow-up period (n=445 cancer survivors). With the expansion of the CCSS cohort to now include over 10,000 additional participants diagnosed 1987-1999, and the use of the most recent NDI data that identifies deaths through 2013, the proposed study will allow a more powerful and more detailed assessment of the impact of exercise on late-mortality in adult survivors of childhood malignancies. Additional limitations were lack of quantification of exercise dose and analysis of a dose-response relationship.[10] Finally, the authors also only analyzed the relationship between exercise behavior at study entry – whether change in exercise behavior is associated with clinical outcomes was not evaluated. Thus, we propose a more comprehensive evaluation of the association between exercise and late mortality in CCSS.

**4. Objectives.**

*Primary Objective:* To determine the association between exercise exposure and late all-cause mortality.
*Hypothesis*: Exercise will be associated with a reduction in all-cause mortality compared to inactivity in a dose-dependent manner.
*Secondary Objectives:*

1) To determine the association between exercise exposure and cause-specific mortality.
   *Hypothesis*: Exercise will be associated with a reduced risk of recurrence and health-related causes mortality in a dose-dependent manner.

2) To determine the association between meeting national exercise guidelines and all-cause mortality and cause-specific mortality.
   *Hypothesis*: Meeting national guidelines ($\geq$9 MET-hrs.wk$^{-1}$) will reduce the risk of late all-cause mortality and cause-specific mortality compared to not meeting guidelines.

3) To determine whether change in exercise exposure is associated with late mortality.
   *Hypotheses*: A decrease in exercise exposure from baseline to follow-up will be associated with a greater risk of late mortality whereas increases in exercise exposure will reduce the risk of late mortality.

**5. Analysis Framework.**

*Study Population and Eligibility*
The study population will include the ~24,463 CCSS participants. Eligible participants will include the >5-year cancer survivors who were diagnosed between 1970 and 1999 at age <21 years at 1 of 31 institutions. Eligible diagnoses include leukemia, Hodgkin disease, non-Hodgkin lymphoma, central nervous system (CNS) malignancies, Wilms tumor, neuroblastoma, soft tissue sarcoma, and bone tumors.

*Primary and Secondary End Points*
The primary end point is all-cause mortality.
Secondary end points are cause-specific mortality: (1) recurrence/progression of primary childhood malignancy, (2) composite health-related (secondary malignant neoplasm (SMN), cardiovascular, pulmonary, and other health-related causes), and (3) individual cause-specific mortality.

Patients eligible for participation were included in a search for matching death records using the National Death Index through 2013. Underlying and multiple causes of death for deceased subjects using the International Classification of Disease – 9th and 10th Revision were provided by the National Death Index and identified the initiating cause of death using standardized rules useful for classification of deaths. For deaths that predated the National Death Index (i.e., those in 1975-1978, N=139), death certificates from states where deaths occurred were requested.

Cause of death for this analysis will be categorized as:

1. All-cause
2. Recurrence/progression of primary childhood malignancy
3. Health-related cause (attributable to chronic health conditions)
    a. SMN
    b. Cardiac
    c. Pulmonary
    d. Other health-related

*Exercise Exposure*
Exercise exposure is assessed as described in our previous CCSS publication.[8] Briefly, exposure to vigorous intensity exercise was ascertained in the baseline questionnaire using the following single item from the Youth

Risk Behavior Surveillance Survey "On how many of the past 7 days did you exercise or do sports for at least 20 minutes that made you sweat or breathe hard (e.g., dancing, jogging, basketball, and so on)." To calculate the primary exposure of total vigorous intensity exercise, the frequency of reported sessions per week was multiplied by the session duration (i.e., 20 minutes), weighted by the standardized classification of the energy expenditure associated with vigorous intensity exercise in metabolic equivalents METs expressed as average MET-hrs.wk$^{-1}$.[11] The standard MET weighting for vigorous intensity exercise is 9 METs. Using this approach, the range of self-reported exercise behavior ranged from 0 MET-hrs.wk$^{-1}$ to a maximum of 21 MET-hrs.wk$^{-1}$. Categories of total vigorous intensity exercise were defined as 0, 3 to 6, 9 to 12, and 15 to 21 MET-hrs.wk$^{-1}$. We also calculated the proportion of participants meeting the national guidelines for vigorous intensity exercise for individuals with cancer (i.e., $\geq$ 3 sessions of vigorous intensity exercise/week of $\geq$ 20 minutes in duration), the equivalent to $\geq$ 9 MET-hrs.wk$^{-1}$.[12] Follow-up exercise exposure will be obtained from the 2007 follow-up questionnaire. In this survey, patients were asked to report the frequency and duration of vigorous (i.e., activities that cause large increases in breathing or heart rate) or moderate (i.e., activities that cause small increases in breathing or heart rate) activities performed in a usual week. For continuity, only vigorous intensity exercise was calculated. Specifically, the frequency of reported sessions per week was multiplied by the session duration, weighted by 9 METs. Change in exercise exposure from baseline to follow-up will be defined in the following three categories: (1) decreased exposure: a decline in exercise exposure from baseline to follow-up in MET classification (e.g., 3 to 6 to 0), and (2) increased exposure: an improvement in exercise exposure from baseline to follow-up in MET classification (e.g., 0 to 3 to 6), and (3) maintenance: no change in exercise exposure from baseline to follow-up.

*Statistical Analysis*

Demographic, disease, and treatment characteristics will be reported by quartiles of exercise exposure, and compared using Chi-square tests for categorical outcomes and ANOVA for continuous variables. Analysis of mortality after the baseline questionnaire completion will be conducted, treating death, late recurrence, and other causes of death when analyzing cause-specific mortality, as competing risks and censoring at either the completion date of the latest questionnaire or the most recent National Death Index search (December 31, 2013), whichever occurred first. Cox proportional hazards regression models will be used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for the association between exercise exposure categories and incidence of mortality, adjusted for covariates. The analysis will be conducted for overall and cause-specific mortality (primary and secondary outcomes).

*Exploratory Variables*

Models will be adjusted for attained age, age at diagnosis, sex, race, smoking, education, CV risk factors, baseline grade 3 to 4 (non-CV) chronic conditions, and anthracycline and chest radiation exposures. Time since baseline (time since exercise survey) will be considered as a potential modifier of the exercise effects on mortality.

**6. Special Consideration.**

N/A

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**Table 1.** Demographic and Treatment Characteristics of Participants According to Exercise Exposure Quartile at Baseline.

| Characteristic | Total (n=) | MET·hrs·wk$^{-1}$ (n=) | (n=) | (n=) | (n=) | *P* |
|---|---|---|---|---|---|---|
| No. of participants, (%) | | | | | | |
| Age at interview – 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 | | | | | | |
| Anthracycline dose (mg/m²) | | | | | | |
| None | | | | | | |
| <250mg/m$^2$ | | | | | | |
| >=250mg/m$^2$ | | | | | | |
| Radiation therapy | | | | | | |
| Any radiation therapy | | | | | | |
| Chest | | | | | | |
| Chest RT dose | | | | | | |
| None | | | | | | |
| <20Gy | | | | | | |

| | |
|---|---|
| 20-<30Gy | |
| 30-<40Gy | |
| 40-<50Gy | |
| 50+Gy | |
| 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.** Age-Adjusted and Multivariable-Adjusted Hazard Ratios of All-Cause and Cause-Specific Mortality According to Quartile of Exercise Exposure (MET-hrs.wk$^{-1}$).

| | | **MET-hrs·wk$^{-1}$** | | | | |
|---|---|---|---|---|---|---|
| | **Total (N =)** | **(n =)** | **(n =)** | **(n =)** | **(n=)** | ***P*** |
| Median MET-mins·wk$^{-1}$ | | | | | | |
| All-cause mortality | | | | | | |
| No. of events | | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | | |
| Recurrent/progressive disease of primary disease | | | | | | |
| No. of events | | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | | |
| Health-related | | | | | | |
| No. of events | | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | | |
| Subsequent neoplasms | | | | | | |
| No. of events | | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | | |
| Cardiovascular | | | | | | |
| No. of events | | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | | |
| Pulmonary | | | | | | |
| No. of events | | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | | |
| Other health-related | | | | | | |
| No. of events | | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | | |

**Abbreviations:** MET, metabolic equivalent task; HR, hazard ratio; CI, confidence interval
*Adjusted for attained age, age at diagnosis, sex, race, smoking status, education, and CV disease risk factor profile as time dependent variables, anthracycline exposure, chest radiation exposure, and CVD.

**Table 3.** Multivariable-Adjusted Hazard Ratios of Overall and Cause-Specific Mortality According to Meeting the National Exercise Guidelines for Cancer Patients (i.e., < 9 versus ≥ 9 MET-hrs·wk$^{-1}$).

| | **MET-hrs·wk$^{-1}$** | | |
|---|---|---|---|
| | **< 9 MET-hrs·wk$^{-1}$ (n=)** | **≥ 9 MET-hrs·wk$^{-1}$ (n=)** | *P* |
| Median MET-hrs·wk$^{-1}$ | | | |
| All-cause mortality | | | |
| No. of events | | | |
| Age-adjusted HR (95% CI) | Ref | | |
| Multivariable-adjusted HR (95% CI)* | Ref | | |
| Recurrent/progressive disease of primary disease | | | |
| No. of events | | | |
| Age-adjusted HR (95% CI) | Ref | | |
| Multivariable-adjusted HR (95% CI)* | Ref | | |
| Health-related | | | |
| No. of events | | | |
| Age-adjusted HR (95% CI) | Ref | | |
| Multivariable-adjusted HR (95% CI)* | Ref | | |
| Subsequent neoplasms | | | |
| No. of events | | | |
| Age-adjusted HR (95% CI) | Ref | | |
| Multivariable-adjusted HR (95% CI)* | Ref | | |
| Cardiovascular | | | |
| No. of events | | | |
| Age-adjusted HR (95% CI) | Ref | | |
| Multivariable-adjusted HR (95% CI)* | Ref | | |
| Pulmonary | | | |
| No. of events | | | |
| Age-adjusted HR (95% CI) | Ref | | |
| Multivariable-adjusted HR (95% CI)* | Ref | | |
| Other health related | | | |
| No. of events | | | |
| Age-adjusted HR (95% CI) | Ref | | |
| Multivariable-adjusted HR (95% CI)* | Ref | | |

**Abbreviations:** MET, metabolic equivalent task; HR, hazard ratio; CI, confidence interval

*Adjusted for attained age, age at diagnosis, sex, race, smoking status, education, and CV disease risk factor profile as time dependent variables, anthracycline exposure, chest radiation exposure, and CVD.

**Table 4.** Association between Change in Exercise Exposure from Baseline to Follow-up and Mortality

| | | Change in Exercise Exposure | | | |
|---|---|---|---|---|---|
| | **Total (N =)** | **Decreased Exposure (n=)** | **Increased Exposure (n =)** | **Maintenance (n =)** | ***P*** |
| Median MET-mins·wk$^{-1}$ | | | | | |
| Overall | | | | | |
| No. of events | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | |
| All cancer | | | | | |
| No. of events | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | |
| All non-cancer | | | | | |
| No. of events | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | |
| Recurrent/progressive disease | | | | | |
| No. of events | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | |
| Subsequent neoplasms | | | | | |
| No. of events | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | |
| Cardiovascular | | | | | |
| No. of events | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | |
| Pulmonary | | | | | |
| No. of events | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | |
| Other health-related | | | | | |
| No. of events | | | | | |
| Age-adjusted HR (95% CI) | | Ref | | | |
| Multivariable-adjusted HR (95% CI)* | | Ref | | | |

**Abbreviations:** 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., 0 to 3 to 6); exercise maintenance: no change in exercise exposure from baseline to follow-up.

*Adjusted for attained age, age at diagnosis, sex, race, smoking status, education, and CV disease risk factor profile as time dependent variables, anthracycline exposure, chest radiation exposure, and CVD.