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Association of Exercise With Mortality in Adult Survivors of Childhood Cancer

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IMPORTANCE Adult survivors of childhood cancer are at excess risk for mortality compared with the general population. Whether exercise attenuates this risk is not known.

OBJECTIVE To examine the association between vigorous exercise and change in exercise with mortality in adult survivors of childhood cancer.

DESIGN, SETTING, AND PARTICIPANTS Multicenter cohort analysis among 15 450 adult cancer survivors diagnosed before age 21 years from pediatric tertiary hospitals in the United States and Canada between 1970 and 1999 enrolled in the Childhood Cancer Survivor Study, with follow-up through December 31, 2013.

EXPOSURES Self-reported vigorous exercise in metabolic equivalent task (MET) hours per week. The association between vigorous exercise and change in vigorous exercise and cause-specific mortality was assessed using multivariable piecewise exponential regression analysis to estimate rate ratios.

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality. Secondary end points were cause-specific mortality (recurrence/progression of primary malignant neoplasm and health-related mortality). Outcomes were assessed via the National Death Index.

RESULTS The 15 450 survivors had a median age at interview of 25.9 years (interquartile range [IQR], 9.5 years) and were 52.8% male. During a median follow-up of 9.6 years (IQR, 15.5 years), 1063 deaths (811 health-related, 120 recurrence/progression of primary cancer, 132 external/unknown causes) were documented. At 15 years, the cumulative incidence of all-cause mortality was 11.7% (95% CI, 10.6%-12.8%) for those who exercised 0 MET-h/wk, 8.6% (95% CI, 7.4%-9.7%) for 3 to 6 MET-h/wk, 7.4% (95% CI, 6.2%-8.6%) for 9 to 12 MET-h/wk, and 8.0% (95% CI, 6.5%-9.5%) for 15 to 21 MET-h/wk ($P < .001$). There was a significant inverse association across quartiles of exercise and all-cause mortality after adjusting for chronic health conditions and treatment exposures ($P = .02$ for trend). Among a subset of 5689 survivors, increased exercise (mean [SD], 7.9 [4.4] MET-h/wk) over an 8-year period was associated with a 40% reduction in all-cause mortality rate compared with maintenance of low exercise (rate ratio, 0.60; 95% CI, 0.44-0.82; $P = .001$).

CONCLUSIONS AND RELEVANCE Vigorous exercise in early adulthood and increased exercise over 8 years was associated with lower risk of mortality in adult survivors of childhood cancer.

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Supplemental content

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Improvements in multimodal cancer treatment, together with more effective risk stratification, have contributed to a significant decline in mortality among long-term adult survivors of childhood cancer.[1] Despite such advances, these individuals remain at substantially elevated risk of mortality, with life expectancy shortened by a mean of 10 years compared with the general population.[2] Of importance, mortality attributable to recurrence or progression of primary disease decreases over time, indicating that treatment (health)-related effects (eg, subsequent malignant neoplasms [SMNs], cardiovascular disease [CVD]) primarily drive excess mortality.[3-5] Strategies that complement advances in conventional cancer treatment, especially those that offset treatment-related effects, are of major clinical importance in this at-risk population.[6]

In the general population, adherence to healthy lifestyle behaviors including regular exercise is associated with substantial reductions in CVD mortality[7] and mortality from any cause.[8,9] Exercise also reduces the primary incidence of several forms of cancer and the risk of recurrence following a diagnosis of certain adult-onset cancers (eg, breast, colon, prostate).[10] Whether these findings extend to adult survivors of childhood cancer with excess risk of mortality is not known. Accordingly, the aim of this study was to evaluate the association between vigorous exercise in early adulthood and change in vigorous exercise with mortality in long-term adult survivors of childhood cancer participating in the Childhood Cancer Survivorship Study (CCSS).[11] We hypothesized that vigorous exercise in early adulthood and increased exercise reduces the risk of mortality in a dose-dependent manner.

Key Points

Question Is vigorous exercise and change in exercise associated with a reduction in mortality in adult survivors of childhood cancer?

Findings In this cohort analysis using a questionnaire after a median follow-up of 10 years among 15 450 adult survivors of childhood cancer, there was a significant inverse association across quartiles of exercise and all-cause mortality after adjustment for chronic health conditions and treatment exposures. Increased exercise over 8 years was associated with a 40% reduction in all-cause mortality rate compared with maintenance of low exercise.

Meaning Vigorous exercise in early adulthood and increased exercise over 8 years is associated with lower risk of mortality in adult survivors of childhood cancer.

Methods

Study Population and Design

The CCSS is a retrospective cohort study, with longitudinal follow-up of childhood cancer survivors diagnosed and treated at 27 institutions in the US and Canada (https://ccss.stjude.org/) between January 1, 1970, and December 31, 1999. Details of the study design, methods, and cohort characteristics have been reported previously.[11] In brief, major eligibility criteria were (1) a diagnosis of cancer before age 21 years, (2) primary cancer treatment between January 1, 1970, and December 31, 1999, (3) survival of at least 5 years beyond initial diagnosis, and (4) age older than 18 years at baseline enrollment.[11] The CCSS protocol was approved by the human subjects committee at each participating institution, and written informed consent was obtained from each participant. The CCSS study population consists of 35 651 eligible survivors, with 24 357 completing the baseline questionnaire (1992-2013).[11]

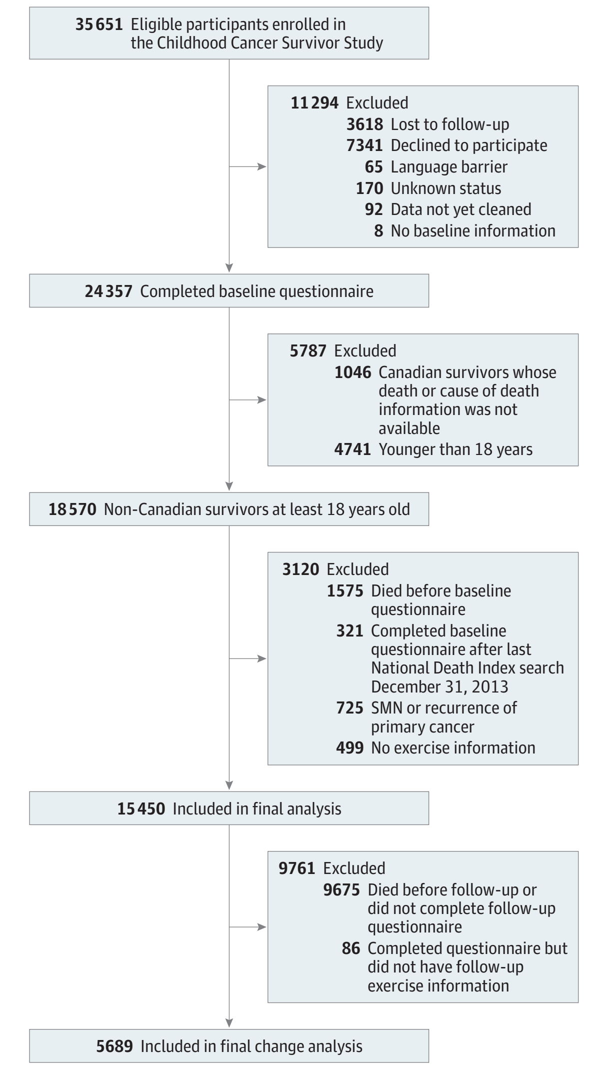
We excluded 1046 Canadian survivors for whom death or cause of death information was not available, 4741 nonadult survivors (age <18 years at baseline), 1575 who died before the baseline questionnaire (questionnaires were completed by a proxy), 499 who did not complete exercise exposure questions, 321 who completed the baseline questionnaire after the most recent National Death Index search (December 31, 2013), and 725 survivors with recurrence of primary cancer, or an SMN before study entry, for a final analytic cohort of 15 450 (**Figure 1**). After baseline enrollment, new-onset events were ascertained in periodic follow-up questionnaires, the most recent of which was administered between 2007 and 2009. Compared with excluded survivors (8907), those included in this analysis were more likely to be older, female, a current smoker, have a higher body mass index, and report CVD risk factors (eTable 1 in the Supplement).

Exercise Assessment

At baseline enrollment and follow-up questionnaires, vigorous exercise was assessed 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 (eg, jogging, basketball, etc)?" This item has acceptable test-retest reliability for assessment of total minutes of vigorous exercise.[12] In brief, total vigorous exercise was estimated as the self-reported number of exercise sessions (frequency) per week multiplied by session duration (ie, 20 minutes [specified in the questionnaire]), weighted by the standardized classification of energy expenditure for vigorous exercise (ie, 9 metabolic equivalent tasks [METs][13]) in METs expressed as average MET-h/wk.[13] Thus, exercise exposure ranged from a minimum of 0 MET-h/wk to a maximum of 21 MET-h/wk, categorized as 0, 3 to 6, 9 to 12, and 15 to 21 MET-h/wk.[14] These categories correspond to the equivalent of approximately less than 20, 20 to less than 40, 60 to less than 80, and 100 to less than 140 minutes per week of vigorous exercise.

Vigorous exercise was reassessed in a follow-up questionnaire (2002-2005) among 8150 survivors diagnosed between 1970 and 1986.[11] Change in vigorous exercise data were available in 5689 (70%) survivors (Figure 1) and defined as (1) decreased, (2) increased, (3) low maintenance (remaining in low exercise categories, ie, 0 or 3-6 MET-h/wk), and (4) high maintenance (remaining in high exercise categories, ie, 9-12 or 15-21 MET-h/wk). In the follow-up questionnaire, patients were asked, "How many days per week do you do these vigorous activities for at least 10 minutes at a time such as running, aerobics, heavy yard work, or anything else that causes large increases in breathing or heart rate?" and "On days when you do

Figure 1. Cohort Composition Diagram of Eligible and Enrolled Childhood Cancer Survivors



SMN indicates subsequent malignant neoplasm.

vigorous activities for at least 10 minutes at a time, how much total time per day do you spend doing these activities?" To permit comparison between surveys, reported exercise greater than 20 minutes was truncated at 20 minutes, whereas reported exercise less than 20 minutes was scored as 0.

Ascertainment of Deaths

The primary end point was all-cause mortality. Secondary end points were cause-specific mortality defined as (1) recurrence/progression of primary malignant neoplasm and (2) health-related mortality (ie, SMN, CVD, pulmonary, and other health-related causes, collectively and individually). Initiating causes of death were provided by the National Death Index,[5] and deaths were grouped into categories using the *International Classification of Diseases, Ninth Revision (ICD-9)* and *Tenth Revision (ICD-10)* coding: (1) recurrence/progression of the primary childhood malignant neoplasm; (2) health-related causes: SMN (*ICD-9:* 140-239, *ICD-10*: C00- C97, D10-D36), cardiac (*ICD-9:* 390-398, 402, 404, 410-429, *ICD-10:* I00-I02, I05-I09, I11, I13, I14, I20-I28, I30-I52), pulmonary (*ICD-9:* 460-519, *ICD-10:* J00-J99), and all other health-related causes.

Covariates

All analyses were adjusted for confounding variables including attained age as cubic splines (knots at 22, 25, 30, 35, and 40 years), age at diagnosis, sex, race, smoking, education, CVD risk factor profile (ie, diabetes, hypertension, dyslipidemia, obesity) as time-dependent variables, any anthracycline and equivalent dose, cyclophosphamide and equivalent dose, chest radiation exposure, and any baseline grade 3 to 4 chronic conditions (eTable 2 in the Supplement).[15] Type of cancer diagnosis correlates with treatment and therefore was not included as a covariate.

Statistical Analysis

Demographic, disease, and treatment characteristics were stratified by the baseline quartiles of exercise exposure, and compared using χ^2 tests for categorical outcomes and analysis of variance for continuous variables. Analysis of mortality after baseline was conducted in all-cause and cause-specific death, censoring the at-risk time at the most recent National Death Index search. Cumulative incidence at 15 years from baseline was stratified by quartiles of exercise exposure at baseline and compared using permutation tests. When cumulative incidence for a specific cause was estimated, all other causes of death were treated as competing risk events. For assessment of the association between change in vigorous exercise and mortality, the follow-up period started at the completion of the second follow-up questionnaire. Piecewise exponential regression was used to estimate the rate ratios (RRs) and 95% confidence intervals for the association between exercise exposure/change in exercise categories and mortality rates using the logarithm of person-years as the offset. All 15 450 survivors were used in cumulative incidence rate estimate and age-adjusted RR estimate. Survivors with missing treatment were excluded in the multivariate analysis. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute), and R, version 3.2.4. All statistical inferences were 2 sided, with $P < .05$ considered statistically significant.

Results

At baseline, exercising survivors (ie, >0 MET-h/wk) were younger at cancer diagnosis, more likely to be nonsmokers, and had a lower prevalence of CVD risk factors and grade 3 to 4 chronic conditions (eTable 3 in the Supplement). The median interval between initial cancer diagnosis and completion of the baseline questionnaire was 17.8 years (interquartile range, [IQR] 6.3 years). Median interval between baseline and follow-up was 9.6 years (IQR, 15.5 years). During this period, 1063 deaths were documented (n = 811 due to health-related events, n = 120 due to recurrence or progression of primary disease, and n = 132 external or unknown causes, respectively).

Vigorous Exercise and Mortality

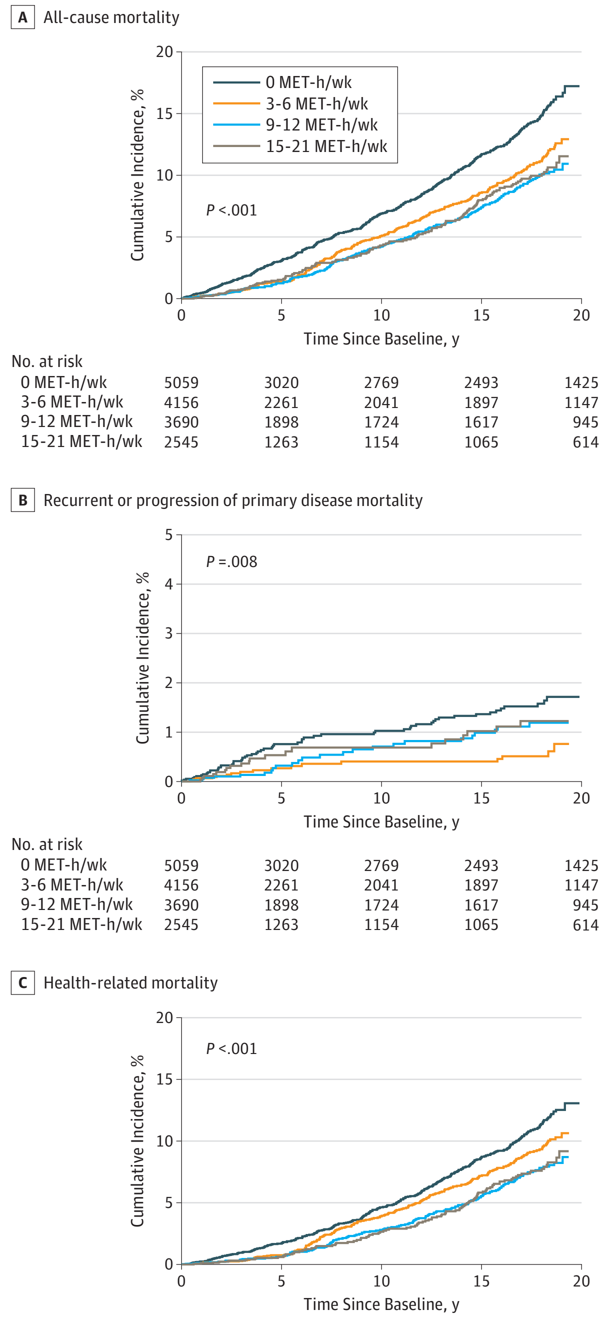
Exercise exposure greater than the referent group (0 MET-h/wk) was associated with a significant reduction in the cumulative incidence of all-cause, relapse, and health-related mortality at 15 years (**Figure 2**). At 15 years, the cumulative incidence of all-cause mortality was 11.7% (95% CI, 10.6%-12.8%) for 0 MET-h/wk, 8.6% (95% CI, 7.4%-9.7%) for 3 to 6 MET-h/wk, 7.4% (95% CI, 6.2%-8.6%) for 9 to 12 MET-h/wk, and 8.0% (95% CI, 6.5%-9.5%) for 15 to 21 MET-h/wk ($P < .001$). There was a statistically significant, nonlinear inverse association between exercise and all-cause mortality ($P = .02$ for trend) (eTable 4 in the Supplement). Compared with 0 MET-h/wk, the adjusted RR was 0.81 (95% CI, 0.68-0.97) for 3 to 6 MET-h/wk, 0.82 (95% CI, 0.68-1.00) for 9 to 12 MET-h/wk, and 0.79 (95% CI, 0.62-1.00) for 15 to 21 MET-h/wk. Similar nonlinear relationships were observed for recurrence/progression and health-related mortality (eTable 4 in the Supplement).

Given limited evidence for a dose-response relationship, a multivariable-adjusted rate for all-cause mortality and each MET-h/wk category (ie, 0, 3, 6, 9, 12, 15, 18, 21) was generated to identify the optimal exercise exposure. The adjusted rate indicated that the optimal exercise exposure was 15 to 18 MET-h/wk (eFigure and eTable 5 in the Supplement). On this basis, exercise was collapsed into 2 categories (0 MET-h/wk [n = 5059] vs 15-18 MET-h/wk [n = 1669]) for subsequent analyses. Using this dichotomy, cumulative incidence of all-cause, recurrence/progression, and health-related mortality was 11.7%, 1.4%, and 8.7% for 0 MET-h/wk compared with 5.7% ($P < .001$), 1.0% ($P = .10$), and 4.1% ($P < .001$) for 15 to 18 MET-h/wk, respectively. Compared with 0 MET-h/wk, the adjusted RR for all-cause, recurrent/progressive, and health-related mortality was 0.58 (95% CI, 0.42-0.80), 0.80 (95% CI, 0.37-1.71), and 0.63 (95% CI, 0.43-0.92) for 15 to 18 MET-h/wk, respectively (eTable 6 in the Supplement).

Change in Vigorous Exercise and Mortality

Survivors reporting increased exercise were more likely to be nonsmokers and had a lower prevalence of any preexisting comorbid conditions compared with those maintaining low exercise (eTable 7 in the Supplement). Longitudinally, 29% (n = 1677) maintained low exercise, 40% (n = 2279) decreased exercise (mean [SD], −8.2 [4.9] MET-h/wk), 20% (n = 1174) increased exercise (mean [SD], 7.9 [4.4] MET-h/wk), and 10% (n = 559) maintained high exercise. Increased exercise exposure over 8 years was associated with an adjusted 40% reduction in the rate of death from any cause, compared with maintenance of low exercise (RR, 0.60; 95% CI, 0.44-0.82) (**Figure 3** and eTable 8 in the Supplement). Using continuous values of exercise change, a 6-MET-h/wk increase in vigorous exercise was associated with a 13% reduction in the rate of death from any cause.

Figure 2. Cumulative Incidence of All-Cause, Relapse, and Health-Related Mortality According to Quartiles of Vigorous Exercise at Study Entry



A. No. at risk

	0	5	10	15	20
0 MET-h/wk	5059	3020	2769	2493	1425
3-6 MET-h/wk	4156	2261	2041	1897	1147
9-12 MET-h/wk	3690	1898	1724	1617	945
15-21 MET-h/wk	2545	1263	1154	1065	614

B. No. at risk

	0	5	10	15	20
0 MET-h/wk	5059	3020	2769	2493	1425
3-6 MET-h/wk	4156	2261	2041	1897	1147
9-12 MET-h/wk	3690	1898	1724	1617	945
15-21 MET-h/wk	2545	1263	1154	1065	614

C. No. at risk

	0	5	10	15	20
0 MET-h/wk	5059	3020	2769	2493	1425
3-6 MET-h/wk	4156	2261	2041	1897	1147
9-12 MET-h/wk	3690	1898	1724	1617	945
15-21 MET-h/wk	2545	1263	1154	1065	614

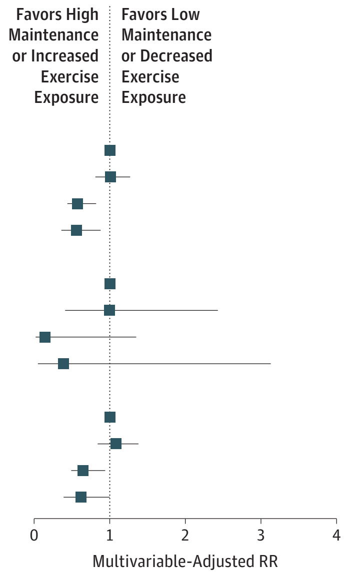
MET indicates metabolic equivalent task.

Discussion

This analysis of a large cohort of adult survivors of childhood cancer after a median of 10 years' follow-up indicates that vigorous exercise in early adulthood was associated with substantial reductions in the risk of mortality after controlling for important clinical covariates including key treatment exposures and chronic health conditions. Furthermore, increased vigorous exercise over 8 years was associated with a 40% reduction in risk of death from any cause.

Figure 3. Association Between Longitudinal Change in Vigorous Exercise and Mortality

Change in Exercise Exposure	RR (95% CI)	*P* Value
All-cause mortality		
Low maintenance	1 [Reference]	
Decreased exposure	1.01 (0.81-1.27)	.91
Increased exposure	0.60 (0.44-0.82)	<.01
High maintenance	0.56 (0.36-0.88)	.01
Recurrent or progressive primary cancer mortality		
Low maintenance	1 [Reference]	
Decreased exposure	1.00 (0.41-2.43)	>.99
Increased exposure	0.17 (0.02-1.35)	.09
High maintenance	0.39 (0.05-3.13)	.37
Health-related mortality		
Low maintenance	1 [Reference]	
Decreased exposure	1.08 (0.84-1.38)	.55
Increased exposure	0.67 (0.49-0.94)	.02
High maintenance	0.62 (0.39-1.00)	.05



Change in exercise exposure data was defined as (1) low maintenance (reference, remaining in low exercise categories, ie, 0 and 3-6 metabolic equivalent task [MET]-h/wk), (2) decreased category, (3) increased category, and (4) high maintenance (remaining in high exercise categories, ie, 9-12 or 15-21 MET-h/wk). Symbols represent rate ratios (RRs) and 95% confidence intervals adjusted for attained age, age at cancer diagnosis, sex, race/ethnicity, smoking status, education, and cardiovascular disease risk factor profile as time-dependent variables, cumulative doxorubicin-equivalent dose, cumulative cyclophosphamide-equivalent dose, chest radiation exposure, and any baseline grade 3 to 4 chronic health conditions. Health-related causes include subsequent neoplasms, cardiovascular, pulmonary, and other health-related causes of death.

Our findings are consistent with the wealth of data in the general population showing that regular exercise is associated with substantial reductions in all-cause and cause-specific mortality.[7-9] Comparably fewer studies have examined the impact of exercise performed in the period after diagnosis on long-term mortality in patients with adult-onset cancers. In a meta-analysis of prospective studies published through 2013, a total of 10 studies examined the association between postdiagnosis exercise and all-cause mortality in patients with early-stage colorectal (6 studies; 7523 total patients) or breast cancer (4 studies; 21 733 total patients).[16] Comparing the highest vs lowest levels of exercise, the overall relative risk of total mortality was 0.58 (95% CI, 0.48-0.70) and 0.52 (95% CI, 0.42-0.64) for colorectal and breast cancer, respectively. Thus, the magnitude of risk reduction is higher than that observed in the present study. However, studies included in this meta-analysis had small sample sizes (mean, n = 2925; range, 573-11 315), assessment of exercise within a short period following initial diagnosis (all ≤4 years), limited follow-up duration (mean, 7.2 years; range, 3.3-11.9 years), small number of all-cause mortality events (mean, 444; range, 82-1468), and inconsistent findings (25%-67% reduction in all-cause mortality).[16] In addition, due to the timing of exercise assessment and short duration of follow-up, observed reductions in total mortality are likely driven primarily by a reduction in death from recurrence. Thus, whether exercise reduces mortality due to competing (noncancer) causes, a major cause of death in 5-year survivors of cancer, remains to be resolved.[17] To this end, our findings with a median of 10 years' follow-up, a high number of events (>1000), and assessment of exercise approximately 18 years following initial diagnosis significantly extends the current evidence base and arguably provides the best available epidemiological evidence to support the endorsement of exercise for cancer survivors.

However, such a conclusion must be interpreted with caution given that observational studies are susceptible to reverse-causation bias. In the present study, we conducted several additional analytical procedures to directly address and minimize this issue including excluding participants with recurrence or SMN at baseline, and adjusting all analyses for available important clinical covariates that may alter the exercise-clinical outcomes relationship. Given these measures, and consistency of our findings across multiple outcomes, we contend that our findings, in conjunction with prior work,[18] support the general conclusion that exercise confers significant health benefit for cancer survivors. Nevertheless, the contribution of confounding cannot be disregarded and only data from randomized clinical trials can definitively prove causality.

In contrast to some,[19,20] but not all studies,[21,22] we did not observe a dose-dependent association between exercise and mortality. Rather, exercise exposure of 15 to 18 MET-h/wk (eg, brisk walking approximately 60 minutes/d, 5 d/wk)[21] seemed to be the optimal dose with benefit attenuated beyond this dose level, suggesting an upper threshold, at least in this unique cohort of adult survivors of childhood cancer. From a clinical perspective, these findings, together with data from randomized clinical trials demonstrating the efficacy of structured exercise training to improve symptom burden in diverse cancer populations,[23] support the recommendation of exercise consistent with the national guidelines for adult cancer

survivors (≥9 MET-h/wk).[24] However, similar to the interpretation of exercise efficacy, use of epidemiological data for the selection of the optimal dose of exercise for further testing in clinical trials, or clinical recommendation, is likely to be imprecise owing to methodological limitations concerning accurate assessment and quantification of dose, schedule, and length of exercise exposure.[25] Moreover, despite the widespread appeal of identifying 1 uniform optimal dose of exercise for a particular cancer population (ie, 1 size fits all), such efforts fail to consider the large degree of heterogeneity observed in response to exercise. Clinical studies, wherein exercise dose can be accurately implemented and quantified, are required to elucidate the exercise dose/exposure–clinical outcomes relationship and identify predictors of response to facilitate a personalized medicine approach.[26]

Prior observational studies in cancer survivors have typically examined the impact of exercise (on clinical outcomes) assessed at 1 time point shortly after initial diagnosis and treatment.[16,18] These data do not address the essential clinical question of whether increases in exercise over time improve clinical outcomes. Our findings corroborate those in the general population[8,27] showing that a relatively small increase in vigorous exercise (approximately 40 min/wk) and maintenance of high vigorous exercise confers significant benefit. Of importance, in addition to all-cause and health-related mortality, the reductions in relapse mortality were noteworthy (albeit nonsignificant). Clearly, this finding could be explained by reverse causation (those survivors experiencing relapse reduce exercise). However, if this were the explanation then decreased exercise exposure would be associated with worse prognosis, but this was not observed. In addition, a similar pattern was observed for health-related mortality. Overall, while it is not possible to completely rule out reverse causation, these findings support the notion that increasing or maintaining high exercise may lower the risk of relapse mortality. This finding is consistent with prior epidemiological studies showing an inverse relationship between exercise (at 1 time point) and risk of recurrence in patients with adult-onset solid tumors. For instance, in a systematic review of 8 studies, Friedenreich et al[18] reported that postdiagnosis exercise exposure was associated with a pooled 35% reduction in risk of recurrence in patients with breast, colorectal, or prostate cancer, when comparing the most vs the least active patients. In support, exercise has antitumor activity in several mouse models of adult-onset solid tumors both as a single modality and in combination with conventional antitumor therapy.[28] It is currently unclear whether the inhibitory effects of exercise extend to pediatric tumors; however, the postulated mechanistic underpinnings of exercise antitumor activity are likely highly relevant to pediatric malignant neoplasms.[29] Collectively, these data support counseling all survivors, whenever appropriate, to increase participation in vigorous exercise at least once a week for 40 minutes. Such increases may be realistic and achievable for a significant proportion of patients.[30]

Limitations

There are important limitations that deserve consideration. Generalizability may be limited because analyses were restricted to survivors alive at the time of baseline enrollment and follow-up questionnaires. Relatedly, less than half of survivors eligible for CCSS were included, which may introduce selection bias. However, survivors included in this analysis were arguably unhealthier (eg, more likely to be older, a current smoker), which may have underestimated the protective impact of exercise. Exercise was assessed by a self-reported single item only evaluating vigorous exercise; as such, misclassification is expected because patients may have reclassified lower-intensity exercise to vigorous exercise. However, assessment of self-reported vigorous exercise is reproducible,[31] and strongly correlates with assessment of vigorous exercise by objective methods (eg, accelerometers).[32] Finally, higher levels of exercise also may be associated with better adherence to other health behaviors (eg, diet, alcohol consumption) or lower disease burden.[33] However, our findings are broadly consistent with those from other adult populations consistently showing an inverse relationship between exercise and risk of death from CVD,[34] cancer,[16,20,21] and any cause.[8,35]

Conclusions

Our findings indicate that regular vigorous exercise, as well as an increase in exercise, is associated with significant reductions in the risk of mortality in adult survivors of childhood cancer. These findings may be of importance for the large and rapidly growing global population of adult survivors of childhood cancer at substantially higher risk of mortality due to multiple competing risks.

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Study concept and design: Scott, Nathan, Gibson, Nilsen, Oeffinger, Ness, Armstrong, Jones.
Acquisition, analysis, or interpretation of data: Scott, Li, Liu, Yasui, Leisenring, Gibson, Amenian, Oeffinger, Ness, Adams, Robison, Armstrong, Jones.
Drafting of the manuscript: Scott, Li, Liu, Adams, Armstrong, Jones.
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