Deficits in Physical Function Among Young Childhood Cancer Survivors

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ABSTRACT

Purpose

Childhood cancer survivors (CCSs) are at risk for physical disability. The aim of this investigation was to characterize and compare physical performance among CCSs and a group of siblings age < 18 years and determine if diagnosis, treatment, and physical activity levels were associated with lower performance scores.

Methods

CCSs ≥ 5 years from diagnosis and a sibling comparison group were recruited and evaluated for strength, mobility, and fitness. Physical performance measures were compared in regression models between survivors and siblings by diagnosis and among survivors by treatment exposures and physical activity levels.

Results

CCSs ($n = 183$; mean age $\pm$ standard deviation [SD], 13.5 ± 2.5 years; 53% male) scored lower than siblings ($n = 147$; mean age $\pm$ SD, 13.4 ± 2.4 years; 50% male) on lower-extremity strength testing, the timed up-and-go (TUG) test, and the 6-minute walk (6MW) test, despite reporting similar levels and types of habitual physical activity. The lowest scores were prevalent among survivors of CNS tumors and bone and soft tissue sarcomas on strength testing (score $\pm$ SD: CNS tumors, 76.5 ± 4.7 ; sarcoma 67.1 ± 7.2 v siblings, 87.3 ± 2.4 Newton-meters quadricep strength at 90° per second; $P = .04$ and $.01$, respectively) and among CNS tumor survivors on the TUG (score $\pm$ SD: 5.1 ± 0.1 v siblings, 4.4 ± 0.1 seconds; $P < .001$) and 6MW tests (score $\pm$ SD: 533.3 ± 15.6 v siblings, 594.1 ± 8.3 m; $P < .001$).

Conclusion

CCSs may have underlying physiologic deficits that interfere with function that cannot be completely overcome by participation in regular physical activity. These survivors may need referral for specialized exercise interventions in addition to usual counseling to remain physically active.

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INTRODUCTION

Advances in treatment for children with cancer have improved survival.^{1,2} However, two thirds of long-term survivors will develop $\geq$ one chronic conditions related to prior therapy.^{3,4} In addition, childhood cancer survivors (CCSs) are less physically active than siblings.⁵⁻⁸ Although recent evidence suggests that children and adolescents who have survived cancer are not more obese than siblings,⁹⁻¹¹ many have treatment-related neurologic or musculoskeletal issues¹² that interfere with development and participation in regular physical activity. Physical impairments after cancer therapy contribute to long-term health problems and functional decline.¹³

Rehabilitation, which may prevent ongoing decline and promote an active lifestyle, is available when physical performance deficits are identi-

fied.^{14,15} The aims of this investigation were to compare physical performance between CCSs and siblings age < 18 years and determine associations with cancer diagnosis and treatment to identify individuals most in need of rehabilitation services.

METHODS

Study Participants

Children and adolescents treated for cancer at the University of Minnesota Medical Center or Children's Hospitals and Clinics of Minnesota, at least 5 years from diagnosis and 9 to < 18 years of age, were identified from clinical databases and invited to participate in the Metabolic Syndrome in Childhood Cancer Survivors Study.¹¹ Siblings were recruited from among family members of survivors, frequency matched by age and sex. A subgroup of the population was assessed to determine physical function. Testing was completed between October 2007 and February 2010. Parental consent and participant assent

were obtained; approval for human subject research was granted from both institutions.

Physical Function Assessment

An isokinetic dynamometer (System 4; Biodex, Shirley, NY) was used to determine lower-extremity strength. Knee extension was tested while sitting with the hip in 90° of flexion. The trunk, waist, and thigh of the tested leg were secured with straps, with the resistance pad on the leg attachment positioned 3 cm superior to the lateral malleolus. Three submaximal practice repetitions were followed by 20 repetitions of knee extension and flexion in concentric mode at 90°, 120°, and 180° per second. Participants rested 45 seconds between velocities. Mean peak torques in Newton meters (Nm) for both lower extremities were used for analysis.¹⁶

A handheld dynamometer, adjusted for hand size, was used to determine grip strength (Grip-D; Creative Health Products, Ann Arbor, MI). Participants were tested while standing with the shoulder in 0° of flexion and slightly abducted, with the elbow extended.¹⁷ Participants were instructed to squeeze hard for 3 seconds. Three trials were performed on each hand, separated by 30 seconds rest. The mean of the trials was calculated for each hand, and the mean of both hands was used for analysis. Results are in kilograms.

The 6-minute walk (6MW) test was used to evaluate cardiopulmonary fitness.¹⁸ Participants were instructed to walk as fast as possible, without running, up and down a 100-ft corridor for 6 minutes. Those who required an assistive device were allowed to use it during testing. Rest was permitted, but the clock continued. Participants were encouraged to resume walking as soon as possible. Distance was recorded in meters.

Mobility was evaluated with the timed up-and-go (TUG) test.¹⁹ Participants stood from a 46-cm high armed chair, walked 3 m, turned, returned to the chair, and sat down. The examiner demonstrated one attempt. Once participants confirmed understanding, they completed a practice attempt, rested, and then completed the test attempt. Time in seconds was used for analysis.

Independent Variables

Demographic and treatment data were obtained from medical records by trained abstractors. Case status and diagnosis and treatment modalities were considered as predictors of functional outcome in separate models. Diagnoses were grouped as follows: one, leukemia or lymphoma; two, CNS tumor; three, bone or soft tissue sarcoma; four, neuroblastoma or renal tumor; and five, other solid tumor. Treatment factors included age at diagnosis, time

since diagnosis, and exposure to corticosteroids,²⁰ anthracyclines,²¹⁻²³ intrathecal methotrexate, platinum compounds, vincristine, craniospinal irradiation, and surgery (eg, brain tumor resection, thoracotomy, laparotomy, lower-extremity bone surgery).

Sex, anthropomorphics, and weekly minutes of physical activity were considered as confounders of associations between case status, diagnosis, treatment modalities, and each functional outcome. Height (cm) and weight (kg) were measured with a digital scale (Model 5002; Scale-Tronix, Wheaton, IL) and stadiometer. Weight divided by height in square meters was converted to body mass index (BMI) percentile using data from the 2000 Centers for Disease Control and Prevention growth charts.²⁴ Weekly minutes of physical activity were calculated from the Past-Year Leisure-Time Physical Activity section of the Modifiable Activity Questionnaire,²⁵ an instrument validated in healthy populations²⁶ and among children with chronic disease.²⁷⁻²⁹

Data Analysis

Descriptive statistics were calculated for demographic and treatment variables and compared between those who did and did not complete assessments with two-sample *t* tests and χ^2 statistics. Distributions of scores on function measures were evaluated for normality before analysis. Comparisons between survivors and siblings for each measure were completed in separate general linear mixed models including sex, height, BMI percentile, and weekly minutes of physical activity as independent variables. To account for correlation between children in the same families, we included a variance component for family membership.³⁰ Treatment-related predictors of physical function were examined in general linear models.³¹ Initial modeling indicated significance only for surgical procedures. Associations between surgical procedure and physical function were evaluated in multivariable models, adjusted for age and sex. Analyses were conducted with SAS version 9.2 (SAS Institute, Cary, N.C.).

RESULTS

Participants included 183 survivors (57%) and 147 siblings (71%) from 319 survivors and 206 siblings who completed the parent study. Characteristics of those who did and did not complete physical performance assessments are listed in Tables 1 and 2. Survivors who

Table 1. Characteristics of the Study Population

Characteristic	Participant Survivors (n = 183)*		Survivors With No Physical Performance Assessment (n = 136)		P	Participant Siblings* (n = 147)		Siblings With No Physical Performance Assessment (n = 59)		P
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Current age, years	13.5	2.5	15.9	1.9	< .001	13.4	2.4	13.9	2.3	.17
Age at diagnosis, years	4.2	3.0	4.8	3.1	.07					
Time since diagnosis, years	9.3	3.0	11.1	3.0	< .001					
Height, cm	158.1	12.8	164.9	12.3	< .001	159.5	13.6	161.4	14.5	.37
Weight, kg	55.9	18.4	63.8	19.5	< .001	55.0	17.4	57.9	18.5	.28
BMI percentile	65.9	27.4	62.5	29.5	.29	62.8	27.6	65.9	26.9	.47
Weekly minutes of physical activity	89.0	89.2	79.0	59.6	.26	94.0	63.9	100.0	75.3	.59
Sex					.80					.10
Female										
No.	86		62			73		22		
%	47.0		54.4			50.0		37.3		
Male										
No.	97		74			74		37		
%	53.0		45.6			50.0		62.7		

Abbreviations: BMI, body mass index; SD, standard deviation.

*Participant survivors did not differ from participant siblings by sex, age, height, weight, BMI percentile, or weekly minutes of physical activity.

Table 2. Diagnosis and Treatment-Related Characteristics of Survivors

Characteristic	Participant Survivors (n = 183)		Nonparticipant Survivors (n = 136)		P
	No.	%	No.	%	
Diagnosis					< .001
Leukemia or lymphoma	59	32.8	75	55.1	
CNS tumor	32	17.8	31	22.8	
Bone or soft tissue sarcoma	13	7.2	20	14.7	
Neuroblastoma or Wilms tumor	49	27.2	4	2.9	
Other solid tumor	30	16.4	6	4.4	
Chemotherapy					
Steroids	51	27.9	79	58.1	< .001
Intrathecal methotrexate	47	25.7	70	51.5	< .001
Platinum	32	17.5	11	8.1	.02
Anthracyclines	83	45.4	87	64.0	.001
Vincristine	104	56.8	93	68.4	< .001
Irradiation					
Brain	14	7.7	19	14.0	.07
Spine	10	5.5	6	4.4	.67
Other	38	15.3	13	9.6	.12
Surgery					
Partial or complete brain tumor resection	26	14.2	24	17.7	.40
Thoracotomy	14	7.7	3	2.2	.03
Laparotomy	44	24.0	13	9.6	< .001
Lower extremity bone surgery	4	1.6	3	2.2	.71

completed were younger, were shorter in stature, and had lower body weight than those who did not complete assessments. Compared with those who did not, participants who completed assessments were less likely to be leukemia or lymphoma survivors and more likely to be survivors of neuroblastoma or Wilms tumor. They had less steroid, anthracycline, intrathecal methotrexate, and vincristine exposure. BMI percentiles were similar. Participating siblings did not differ from nonparticipating siblings. Survivors and siblings who completed assessments were similar in age, height, weight, BMI percentile, and weekly minutes of physical activity.

Table 3 lists means of physical function measures for siblings and survivors. After adjusting for sex, height, BMI percentile, and weekly minutes of physical activity, survivors performed lower than siblings on every measure, except grip strength. Impaired performance on 6MW and TUG tests was driven by CNS tumor survivors, who walked, on average, 61 m fewer and took 0.7 seconds longer to complete the TUG test than siblings. Quadricep strength was low in CNS survivors but more pronounced among survivors of bone and soft tissue sarcomas. Mean peak torques were 20.2, 20.3, and 16.5 Nm lower among sarcoma survivors and 10.8, 12.4, and 6.6 Nm lower among survivors of CNS tumors than siblings at 90°, 120°, and 180° per second of knee extension. Survivors of leukemia or lymphoma had lower peak strength values than siblings at 120° (8.9 Nm) and 180° (6.2 Nm) per second of knee extension.

Chemotherapy and radiation exposures were not associated with physical function in bivariate analyses or in models that considered chemotherapy or radiation dose. In analysis that included survivors of all tumor types, those treated with brain tumor resection (n = 26) had shorter mean ($\pm$ standard deviation [SD]) distances on the 6MW test (532.4 ± 89.9 v 576.7 ± 99.2 m; $P = .03$) and took longer (mean time $\pm$ SD) to complete the TUG test (5.2 ± 0.9 v 4.6 ± 0.8 seconds; $P < .001$) than those who did not undergo brain surgery (n = 157). Four participants who underwent a limb-sparing procedure or below-knee amputation had lower quadricep strength in the unaffected leg than 179 participants who did not undergo a lower limb surgical procedure (differences of 21.5, 16, and 13.8 Nm at 90°, 120°, and 180° per second).

Weekly minutes of physical activity did not differ between survivors and siblings but was associated with physical performance measures. Figure 1 shows sex-, height-, and BMI percentile-adjusted values for each performance measure as a function of weekly minutes of physical activity. Interestingly, survivors and siblings with similar activity levels did not perform equally. For each performance measure, at any value of weekly minutes of physical activity, survivors performed worse than siblings. Although there seemed to be interactions between survivor status and weekly minutes of physical activity for strength measures, none were statistically significant. This observation

Table 3. Adjusted Mean Values for Physical Function Outcomes Among Siblings and Survivors, Overall and by Diagnosis*

Variable	6-Minute Walk Test (m)†			Timed Up-and-Go Test (seconds)			Grip Strength (kg)‡			Isokinetic Quadricep Strength (Nm)§								
										90° (per second)			120° (per second)			180° (per second)		
	Mean	SE	P	Mean	SE	P	Mean	SE	P	Mean	SE	P	Mean	SE	P	Mean	SE	P
Siblings	594.1	8.3	Referent	4.4	0.1	Referent	18.7	0.5	Referent	87.3	2.4	Referent	80.5	2.3	Referent	68.7	2.0	Referent
All survivors	567.8	7.0	.003	4.7	0.1	.002	19.1	0.7	.49	80.7	2.0	.02	73.1	1.9	.01	63.5	1.6	.05
Leukemia or lymphoma¶	572.2	11.9	.12	4.6	0.1	.12	18.6	0.7	.56	81.3	3.7	.17	71.6	3.5	.03	62.5	3.0	.08
CNS tumor¶	533.3	15.6	< .001	5.1	0.1	< .001	18.0	0.9	.48	76.5	4.7	.04	68.1	4.6	.01	62.1	3.9	.01
Bone or soft tissue sarcoma¶	558.5	23.2	.15	4.7	0.2	.17	22.9	1.3	.003	67.1	7.2	.008	60.2	6.9	.006	52.2	6.0	.008
Neuroblastoma or Wilms tumor¶	568.5	13.1	.09	4.6	0.1	.17	18.6	0.7	.88	85.4	3.9	.69	79.2	3.8	.78	67.5	3.3	.77
Other solid tumor¶	600.5	16.6	.67	4.5	0.1	.68	19.9	0.9	.25	83.0	5.0	.44	77.3	4.9	.54	65.6	4.2	.52

*Adjusted for sex, height, body mass index percentile, and weekly minutes of physical activity.

†Two participants used an assistive device (one walker, one white cane) during the 6-minute walk test.

‡Mean of the right plus left hand.

§Mean of the right and left leg or, in the case of the one survivor who underwent amputation and the three who underwent limb-sparing surgery, the value from the unaffected lower extremity.

||Survivors were compared with siblings on each measure overall in the first general linear mixed model.

¶A second general linear mixed model compared survivors with siblings by diagnosis; diagnosis group was included as an independent categorical variable.

Fig 1. Physical performance outcomes among survivors and siblings as a function of weekly minutes of physical activity: (A) 6-minute walk test; (B) timed up-and-go test; (C) grip strength; (D) quadricep strength (90°); (E) quadricep strength (120°); (F) quadricep strength (180°).

persisted even when survivors of CNS or bone tumor were excluded. Further evaluation of type of physical activity reported by participants indicated that survivors were as likely as siblings to report participation in vigorous activities, like swimming, running, and dance (15.0% survivors, 13.6% siblings; $P = .78$), and contact sports, like football, soccer, and basketball (20.7% survivors, 23.0% siblings; $P = .69$).

DISCUSSION

The intensified treatment modalities for childhood cancer, although increasingly successful, have significant long-term complications. Therapy-induced physical performance limitations can contribute to sedentary lifestyles and reduced cardiopulmonary and musculoskeletal function. Using a series of validated physical function tests, we assessed CCSs in the pediatric age range and identified strength, mobility, and cardiopulmonary deficits. Lower-extremity strength was reduced among the survivors, particularly those treated for CNS tumor or bone or soft tissue sarcoma. CNS tumor survivors had compromised mobility and cardiopulmonary fitness.

Prior investigations have relied on self-reporting³² or clinician-based observations³³ to capture such deficits, focused on adult survivors of childhood cancer,^{34,35} or been limited to survivors of childhood acute lymphoblastic leukemia.³⁶⁻³⁹ Our study uniquely, to

our knowledge, objectified physical performance deficits among young survivors of varying diagnoses and identified that even when as physically active as siblings, survivors scored lower on measures of physical performance, suggesting that participation in regular physical activity is not sufficient to overcome underlying physiologic changes imposed by intensified therapies and prolonged hospitalizations. These deficits will likely worsen with longer follow-up unless early rehabilitation designed to specifically address these deficits is initiated.

Our findings of muscle weakness and diminished mobility and fitness among CNS tumor survivors are consistent with those of previous investigations in older cohorts. Helseth et al³³ evaluated 28 5-year survivors of posterior fossa tumors and described locomotion difficulties in 61%. Among 78 adult (mean age, 22 years) survivors of childhood brain tumors, we reported lower estimates of peak oxygen uptake and knee-extension strength compared with controls.³⁵ The magnitude of difference ranged from 19% lower peak oxygen uptake among women to 35% lower knee-extension strength among men. In the current study, the magnitude of difference was smaller: 10% shorter distance on the 6MW test and 15% lower knee extension strength. These findings suggest that physical performance deficits progress with time, particularly among persons treated for a childhood brain tumor. Although a longitudinal study is needed to definitively assess strength changes among survivors over time, these

findings are important for current survivors because physical performance limitations are associated with lower income, educational attainment, and quality of life.³⁵

Lower scores on physical performance measures were associated with invasive CNS surgery in this study. Previous reports have implicated radiation as the major risk factor for poor physical performance outcomes,⁴⁰ which we did not find. However, the association between surgery and motor deficits is consistent with reports suggesting that surgical disruption of motor centers or connections among the spinal cord, brainstem, cerebellum, and cerebral hemispheres are persistent and associated with poor motor performance.⁴¹⁻⁴³ Subtle problems have been reported in seemingly asymptomatic survivors of childhood CNS tumors.⁴⁴ Difficulty performing motor tasks because of inadequate, incorrect, or disrupted signaling to muscle may promote a sedentary lifestyle, further contributing to muscle atrophy, poor mobility, and suboptimal fitness.

Lower-extremity strength deficits were apparent among sarcoma survivors. These data are consistent with studies of older sarcoma survivors indicating musculoskeletal problems.^{45,46} Lopez-Guerra et al⁴⁶ reported weakness and impaired joint range of motion in 23% of Ewing sarcoma survivors (ages 11 to 27 years), and Gerber et al⁴⁵ reported limited range of motion and strength in 69% and 19% of sarcoma survivors, respectively (mean age, 35.4 years). Thirteen of 30 survivors in the Gerber et al study had slow gait velocity, a finding not evident in our younger cohort. In our cohort, muscle strength deficits were lower across isokinetic speeds, perhaps portending future deficits in moving from sit to stand, walking, and running. We previously reported that adult survivors of extremity sarcomas are less likely to be physically active than peers⁸; early loss in muscle strength may contribute to long-term inactivity.

The most compelling finding in this study was that for any level of physical activity, survivors performed worse than siblings on every measure of physical function. Because types of activities reported by survivors were similar to those reported by siblings, this difference cannot be explained by the idea that survivors selected less vigorous activities than siblings, although it is possible that survivors engaged in the same activities with less intensity. Nor can this difference be explained by surgical disability, because removing survivors with CNS and bone tumor histories from analysis did not affect this finding. These data may indicate that CCSs have underlying physiologic changes related to cancer or therapy that have an impact on physical function and that even when they adopt a healthy lifestyle that should reduce risk for physical performance limitations, they cannot completely overcome early physiologic changes. These results are supported by a previous report of improvement in fitness, but not return to normal function, after a 12-week twice-per-week aerobic training program among 10 survivors (mean age $\pm$ SD, 19 $\pm$ 3 years) previously treated with anthracycline chemotherapy.⁴⁷ Even though these survivors showed improvement, capacity remained below that of normal subjects suggesting that a traditional training approach is not sufficient to overcome deficits.

Despite functional deficits, physical activity levels among young survivors in this study were similar to those of siblings. This is in contrast to previous investigations that have shown adult childhood cancer survivors to be less physically active than siblings,^{6,8,48} but similar to studies that report that young childhood cancer survivors have activity levels similar to population controls.⁴⁹⁻⁵² There are potential reasons for this discrepancy. First, adult survivors of childhood

cancer are further from treatment, when increasing numbers of medical late effects may interfere with their abilities to participate in sports.^{4,32} They may be working full time or taking care of a family. Survivors with diminished physical capacity may not have stamina to add physical activity to daily routines.⁵³ Additionally, our study included children and adolescents living with parents/guardians and our comparison group was comprised of siblings. Young survivors may be physically active because of family support and influences.⁵⁴⁻⁵⁶ This may change as they become adults and select independent leisure activities. Research to evaluate the impact of transition to independent living among childhood cancer survivors should include an evaluation of the impact of loss of family support on physical health and participation in activities that promote a healthy lifestyle.

This study has limitations that should be taken into account. Performance measurements were added to the study during year 2 of 5 after receipt of foundation funding for equipment; only 57% of survivors and 71% of eligible siblings were tested. Survivors who did not were older than survivors who did complete assessments. Previous literature indicates that physical performance outcomes are worse in older survivors; thus, our results may underestimate severity of physical performance limitations. Despite adequate power to detect differences in measures of physical performance, the population included heterogeneous diagnoses and treatments, making it difficult to examine specific treatment modalities. Our comparison group included siblings of survivors instead of population-based controls. Although this adds strength to internal validity, it is possible that siblings might limit activities because of an ill or disabled brother or sister and may have fewer opportunities than others to participate in sport, limiting the magnitude of observed differences. Finally, we do not know if any of the children in our study were receiving rehabilitation services that may have contributed to positive performance outcomes among those without deficits.

This study reports clinically measured rather than self-reported physical performance in a large cohort of CCSs and provides preliminary evidence that deficits underlying poor function may result from underlying physiologic impairments rather than sedentary lifestyles. Even though tested exercise interventions among young CCSs are scarce,¹⁴ they seem to be safe⁵⁷⁻⁵⁹ and are effective in healthy children and those with chronic diseases.^{60,61} Rather than simply encouraging physical activity, clinicians who care for young survivors may need to refer them for interventions specifically designed to target physiologic deficits not typical among children who are unfit.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Julia Steinberger, K. Scott Baker, Kirsten K. Ness

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Administrative support: Julia Steinberger, Kirsten K. Ness

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