

# Physical Inactivity in Adult Survivors of Childhood Acute Lymphoblastic Leukemia: A Report from the Childhood Cancer Survivor Study

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## Abstract

**Purpose:** To determine if adult survivors of childhood acute lymphoblastic leukemia (ALL) are less active (and more inactive) than the general population and to identify modifying factors.

**Patients and Methods:** Physical activity was assessed by self-report in 2,648 adult survivors of the Childhood Cancer Survivor Study. Participants in the Behavioral Risk Factor Surveillance System (BRFSS) survey administered through the Centers for Disease Control and Prevention (CDC) were used as a comparison group.

**Results:** Survivors had a mean age of 28.7 years (range, 18.0-44.0 years) and were a mean of 23.1 years from their cancer diagnosis (range, 16.0-33.8 years). In multivariate models, ALL survivors were more likely to not meet CDC recommendations for physical activity [odds ratio (OR), 1.44; 95% confidence interval (95% CI), 1.32-1.57] and more likely to

be inactive (OR, 1.74; 95% CI, 1.56-1.94) in comparison with the BRFSS general population. Survivors treated with >20-Gy cranial radiotherapy were at particular risk. Compared with BRFSS participants and adjusted for age, race, and ethnicity, survivors were more likely to not meet CDC recommendations (females: OR, 2.07, 95% CI, 1.67-2.56; males: OR, 1.43, 95% CI, 1.16-1.76) and more likely to be inactive (females: OR, 1.86; 95% CI, 1.50-2.31; males: OR, 1.84; 95% CI, 1.45-2.32).

**Conclusions:** Long-term survivors of childhood ALL are less likely to meet physical activity recommendations and more likely to report no leisure-time physical activity in the past month. This level of inactivity likely further increases their risk of cardiovascular disease, osteoporosis, and all-cause mortality. (Cancer Epidemiol Biomarkers Prev 2007;16(7):1356-63)

## Introduction

Childhood cancer survivors, once rare, now make up a significant segment of the U.S. population; an estimated 1 in 640 young adults aged 20 to 39 years are such survivors (1). Survivors of childhood acute lymphoblastic leukemia (ALL) account for 25% of all long-term survivors of childhood cancer, the result of achievements in combination chemotherapy and radiation therapy that have dramatically improved cure rates for ALL from 61% in the period from 1975 to 1984 to 83.6% in 1995 to 2001 (2, 3). Secondary to their treatment exposures, survivors of childhood ALL are at increased risk of cardiovascular disease (4-6), obesity (7, 8), osteoporosis (9, 10), and cardiovascular and all-cause mortality (11).

In the general population, regular moderate-intensity physical activity has been shown to be protective against osteoporosis (12), hypertension (13), non-insulin-dependent diabetes mellitus (14), cardiovascular disease (15, 16), and all-cause mortality (17-19). However, in 2001, only 45.4% of the general population reported meeting the Centers for Disease Control and Prevention (CDC) recommendation of  $\geq 30$  min of moderate-intensity physical activity on  $\geq 5$  days per week or  $\geq 20$  min of vigorous-intensity activity on  $\geq 3$  days per week (20). Given that ALL survivors are at higher risk than the general population for several modifiable health problems, the importance of participating in regular physical activity is even greater for this group. Six cross-sectional studies assessing 220 leukemia survivors in their childhood and adolescent years have reported a mild to moderate reduction in exercise capacity and habitual physical activity levels (21-26). How these changes extend into adulthood is not known.

The purpose of this study was to use the large and diverse population followed in the Childhood Cancer Survivor Study (CCSS) to determine the level of physical activity in adult survivors of childhood ALL and to identify modifying treatment and demographic factors. *A priori*, we hypothesized that adult survivors of childhood ALL would be less likely to meet the CDC-recommended levels of physical activity than adults in the general population, and self-reported activity levels would be independently associated with cancer treatment, age, and body mass index (BMI). Specifically, we hypothesized that subjects treated with cranial radiotherapy, especially at higher doses or with moderate to higher doses ( $\geq 300$  mg/m<sup>2</sup>) of an anthracycline would show decreased activity levels.

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## Materials and Methods

**Subject Selection and Contact.** CCSS is a multi-institution retrospective cohort study of long-term survivors of childhood cancer who met the following eligibility criteria: (a) diagnosis of leukemia, brain tumor, Hodgkin's disease, non-Hodgkin's lymphoma, Wilms' tumor, neuroblastoma, sarcoma, or bone tumor; (b) diagnosis and initial treatment at one of 26 collaborating CCSS institutions; (c) diagnosis date between January 1, 1970 and December 31, 1986; (d) age younger than 21 years at diagnosis; and (e) survival at least 5 years from diagnosis. The CCSS protocol and contact documents were reviewed and approved by the Human Subjects Committee at each participating institution. A detailed description of the methodology and cohort characteristics has been reported previously (27).

Of the 20,720 childhood cancer survivors included in the cohort, 3,013 (14.6%) were lost to follow-up. Among the 17,703 subjects located, 14,372 (81.2%) completed baseline enrollment. Among 2,747 ALL survivors in the cohort, 2,648 were 18 years of age or older, provided information about their physical activity levels at the time of their most recent contact (2003), and are the population of interest for this analysis. To define the potential for introducing bias among the studied cohort,

we previously compared demographic and cancer-related characteristics among participants, non-participants, and those who were lost to follow-up. These three groups were found to be very similar with regard to gender, type of cancer, age at diagnosis, age when asked to participate in the study (or for those lost to follow-up, age when cohort was assembled), and type of cancer treatment (27, 28).

As a comparison group, participants in the 2003 Behavior Risk Factor Surveillance System (BRFSS), conducted through the CDC, were used. The BRFSS is a state-based system that collects data annually on many behaviors and conditions that place adults 18 years or older at risk for chronic disease. Details of the survey design and sampling procedures are described elsewhere (28). For the purposes of this study, data from 2003 BRFSS were used as a comparison group. BRFSS data were limited to those subjects between 18 and 45 years of age ( $N = 110,623$ ), as to make the ages of survivors and comparison subjects comparable. Demographics of survivors and the comparison group are provided in Table 1.

**Cancer Treatment Information.** Information on the characteristics of the original cancer diagnosis and treatment was obtained for eligible cases from the treating institution as previously described (27). Copies of the questionnaires and

**Table 1. Demographic characteristics of ALL survivors and participants in the 2003 BRFSS, 18-44 y old**

	ALL survivors ( $N = 2,648$ ), $n$ (%)	BRFSS ( $N = 110,623$ ), $n$ (%)	$P$
Age at interview, y			
18-24	788 (29.8)	18,359 (16.6)	<0.001
25-34	1,375 (51.9)	40,238 (36.4)	
35-44	485 (18.3)	52,026 (47.0)	
Sex			
Male	1,314 (49.6)	44,945 (40.6)	<0.001
Female	1,334 (50.4)	65,678 (59.4)	
Race/ethnicity			
White, NH	2,332 (88.4)	122,803 (72.5)	<0.001
Black, NH	81 (3.1)	14,582 (9.4)	
Other, NH	87 (3.3)	11,417 (7.6)	
Hispanic/Latino	138 (5.2)	14,807 (10.6)	
Household income (US\$)			
<20,000	321 (14.6)	17,832 (17.9)	<0.001
$\geq 20,000$	1,875 (85.4)	81,943 (82.1)	
Educational level			
Did not graduate HS	120 (4.6)	9,639 (8.7)	<0.001
Graduated from HS	442 (16.8)	31,939 (28.9)	
Some college or technical school	1,061 (40.4)	32,147 (29.1)	
Graduated from college or technical school	1,003 (38.2)	36,746 (33.3)	
Current smoker			
Yes	419 (15.9)	28,676 (26.0)	<0.001
No	2,219 (84.1)	81,773 (74.0)	
BMI categories			
Neither overweight nor obese (<25 kg/m <sup>2</sup> )	1,031 (40.6)	44,171 (45.7)	<0.001
Overweight (25 to <30 kg/m <sup>2</sup> )	814 (32.1)	34,875 (33.1)	
Obese ( $\geq 30$ kg/m <sup>2</sup> )	694 (27.3)	22,450 (21.3)	
Cancer therapy			
Chemotherapy (% yes)*			
Cytarabine	1,286 (53.0)	Not applicable	
Cyclophosphamide	1,232 (50.8)		
Daunorubicin	697 (28.7)		
Dexamethasone	295 (12.2)		
Doxorubicin	673 (27.8)		
Thioguanine	365 (15.1)		
Etoposide	198 (8.2)		
Anthracycline, any			
None	1,301 (55.0)	Not applicable	
<300 mg/m <sup>2</sup>	662 (28.0)		
$\geq 300$ mg/m <sup>2</sup>	404 (17.0)		
CRT (Gy)			
None	810 (35.5)	Not applicable	
10.0-19.9	695 (30.4)		
$\geq 20$	778 (34.1)		

NOTE: Percentage is based upon available data for each variable.

Abbreviations: NH, non-Hispanic; HS, high school; CRT, cranial radiation therapy.

\*Over 90% of survivors received the following chemotherapy agents: L-asparaginase, 6-mercaptopurine, methotrexate, prednisone, and vincristine.

the treatment abstraction form are available for review online.<sup>10</sup>

**Physical Activity Measures.** As in the BRFSS survey, participants were asked, "During the past month, did you participate in any physical activities or exercises such as running, calisthenics, golf, gardening, bicycling, swimming, wheelchair basketball, or walking for exercise?" Participants were then asked a series of six questions to quantify the amount of time (number of days per week and number of minutes per day) spent in moderate or vigorous physical activity during a usual week. Vigorous activities were defined as any activity causing a large increase in breathing or heart rate. Examples provided include running, aerobics, wheelchair basketball, and heavy yard work. Moderate activities were defined as any activity causing small increases in breathing or heart rate, including brisk walking, bicycling, vacuuming, gardening, and manual wheelchair operation. Questions were identical in the CCSS and BRFSS surveys, with the exception of the addition of "wheelchair basketball" and "manual wheelchair operation" to the CCSS survey.

Two primary outcomes were used for this analysis. First, participants were considered to "not meet CDC recommendations" if they did not report moderate-intensity physical activities for at least 30 min on  $\geq 5$  days of the week or vigorous-intensity physical activity  $\geq 3$  days per week for  $\geq 20$  min per occasion (29). Second, participants were considered "inactive" if they reported no leisure-time physical activity in the month preceding completion of the survey.

**Independent Variables.** Demographic and socioeconomic variables considered in the analysis included age at time of interview, sex, race/ethnicity, annual household income, educational attainment, current smoking status, BMI, and state of residence. BMI was calculated from self-reported height and weight data. The current National Heart, Lung, and Blood Institute definitions of overweight and obese were used: overweight, BMI 25 to 29.9 kg/m<sup>2</sup>; obese, BMI  $\geq 30.0$  kg/m<sup>2</sup> (30).

Cancer-related variables included age at cancer diagnosis and interval from cancer diagnosis to interview. Treatment variables included 13 chemotherapy agents (yes/no; cytarabine, cyclophosphamide, dexamethasone, daunorubicin, doxorubicin, idarubicin, L-asparaginase, 6-mercaptopurine, methotrexate, prednisone, thioguanine, vincristine, etoposide), cumulative dose of anthracycline chemotherapy (doxorubicin, daunorubicin, idarubicin), and cranial radiation therapy (yes/no and total dose).

**Statistical Analysis.** Several variable transformations in both files (CCSS and BRFSS) were made to allow records for subjects in each of the two study groups to be merged and easily compared. Using self-reported days per week and minutes per day of moderate and vigorous-intensity physical activity, the prevalence of participants in both groups not meeting CDC recommendations and who were inactive was determined. In bivariate analyses of nominal data,  $\chi^2$  tests were used to determine the statistical significance of associations of independent variables investigated with meeting physical activity recommendations and with inactive behavior. Variables found to be statistically significant in bivariate analyses at  $P < 0.10$  were included in multivariate logistic regression analyses to determine the factors independently associated with meeting physical activity and inactive behavior. Odds ratios (OR) were adjusted for the effects of all predictor variables in the regression equations to directly compare activity levels of the CCSS and BRFSS study groups.

In regression models, ORs were determined using the dichotomous dependent variable of not meeting CDC recommendations versus meeting such recommendations and the dichotomous dependent variable of having no physical activity versus having any physical activity. A multivariate logistic regression analysis stratified by sex, adjusted for age, race, and ethnicity and using the BRFSS sample as the reference group was done. Because of the significant independent influence of BMI on physical activity outcomes and because prior studies have shown female survivors to be at higher risk for obesity, BMI was included in all multivariate models. All analyses were done using SPSS version 13.0.

## Results

The mean age at interview for survivors was 28.7 years (range, 18-44 years). The mean age at cancer diagnosis was 5.6 years (range, 0.1-20.0 years), with a mean interval of 23.1 years (range, 16.0-33.8 years) between diagnosis and completion of questionnaire. Females comprised 50.4% of the survivor group, and 88.4% of survivors were White, non-Hispanic. Among survivors, 40.6% were of normal weight, 32.1% were overweight, and 27.3% were obese. Compared with the BRFSS comparison group, survivors were younger, less likely to be current smokers, and more likely to be male, White, non-Hispanic, with an annual income of US\$20,000 or more and a higher level of education. Survivors were also more likely to be obese (Table 1).

The percentage of survivors and BRFSS participants not meeting physical activity recommendations and those who reported no leisure-time physical activity (inactive) in the past month are shown in Table 2. Overall, a greater proportion of survivors did not meet CDC recommendations (52.8% versus 48.2%;  $P < 0.001$ ), and a greater number of survivors were inactive (23.0% versus 20.3%;  $P = 0.001$ ) compared with the general population. This difference was most evident in survivors who were previously treated with cranial radiotherapy  $> 20$  Gy: not meeting CDC recommendations, 58.9% versus 48.2% in BRFSS population ( $P < 0.001$ ); inactive, 27.8% versus 20.3% in BRFSS population ( $P < 0.001$ ).

In multivariate regression analyses adjusting for age, sex, race/ethnicity, income, education, and cigarette smoking status, survivors were more likely to not meet CDC recommendations [OR, 1.44; 95% confidence interval (95% CI), 1.32-1.57;  $P < 0.001$ ] compared with the BRFSS population (Table 3). Survivors were also significantly more likely to be inactive (OR, 1.74; 95% CI, 1.56-1.94;  $P < 0.001$ ). Odds of not meeting CDC recommendations for both CCSS and the BRFSS population were significantly higher for women compared with men; older age compared with younger age; ethnic or racial minority group compared with White, non-Hispanic; and overweight and obese participants compared with normal weight subjects.

Among ALL survivors who received chemotherapy without cranial radiotherapy, women were significantly more likely to not meet recommendations compared with female BRFSS subjects (OR, 1.31; 95% CI, 1.10-1.59;  $P = 0.006$ ; Table 4). However, this subgroup of female survivors was not more likely to be inactive than the female BRFSS population. Furthermore, male survivors who received chemotherapy without cranial radiotherapy were not significantly different from the male BRFSS population with respect to meeting the CDC guidelines or inactive behavior.

For both genders, cranial radiotherapy was associated with an increased likelihood of not meeting CDC recommendations and of inactive behavior. The odds of not meeting CDC recommendations in women who received cranial radiotherapy  $\geq 20$  Gy was 2.07 (95% CI, 1.67-2.56;  $P < 0.001$ ) compared with females in the BRFSS population, when adjusted for age,

<sup>10</sup> <http://www.stjude.org/ccss>

**Table 2. Percentage of participants meeting CDC physical activity recommendations and those reporting no leisure-time physical activity in the past month (inactive)**

Variable	Not meeting		P	No leisure-time physical activity		P
	CDC recommendations			Inactive		
	CCSS, % (N = 2,648)	BRFSS, % (N = 110,623)		CCSS, % (N = 2,648)	BRFSS, % (N = 110,623)	
Total	52.8	48.2	<0.001	23.0	20.3	0.001
Age						
18-24	44.2	42.7	0.41	17.7	18.0	0.80
25-34	55.8	48.0	<0.001	23.5	20.0	0.002
35-44	58.7	51.4	<0.001	30.4	21.3	<0.001
Sex						
Male	47.7	45.8	0.16	20.9	17.6	0.002
Female	57.9	49.9	<0.001	25.1	22.1	0.011
Race/ethnicity						
White, NH	52.0	45.6	<0.001	22.5	16.8	<0.001
Black, NH	70.7	47.6	0.02	31.3	29.5	0.719
Other, NH	56.0	49.3	0.22	21.8	21.8	0.990
Hispanic	56.1	57.2	0.80	29.0	34.7	0.179
Income (US\$)						
<20,000	55.7	54.6	0.69	27.9	33.6	0.037
≥20,000	51.0	46.2	<0.001	20.4	16.7	<0.001
Education						
Some HS	60.6	58.0	0.59	39.8	41.5	0.778
Graduated HS	60.2	51.0	<0.001	35.1	27.1	<0.001
Some college*	52.1	47.1	0.002	21.7	17.6	0.001
College graduate †	49.3	44.3	0.002	16.4	11.1	<0.001
Current smoker						
Yes	54.3	49.1	0.04	29.3	26.6	0.219
No	52.5	47.9	<0.001	21.8	18.1	<0.001
BMI						
Normal (<25)	46.4	44.7	0.16	19.7	17.7	0.097
Overweight (25<30)	51.4	47.4	0.03	22.0	18.6	0.015
Obese (≥30)	63.4	56.1	<0.001	27.5	26.1	0.405
Age at cancer, y						
0-4	51.2	NA		21.6	NA	
5-9	53.6			23.4		
10-14	60.6			26.4		
15-20	57.0			27.5		
Interval, y †						
16-20	47.4	NA		19.2	NA	
21-25	55.0			22.6		
26-34	58.2			28.9		
Anthracyclines						
None	51.8	NA		23.1	NA	
<300 mg/m <sup>2</sup>	53.9			22.2		
≥300 mg/m <sup>2</sup>	51.3			20.1		
CRT (Gy)						
None	46.5	NA		17.7	NA	
<20	51.7			22.5		
≥20	58.9			27.8		

NOTE: Participants were considered to meet CDC recommendations if they reported moderate-intensity physical activities for at least 30 min on ≥5 d of the week or vigorous-intensity physical activity ≥3 d per week for ≥20 min per occasion (28).

\*Some college or vocational school.

†Graduated from college or completed vocational school.

‡Interval from cancer diagnosis to time of study.

race and ethnicity, and BMI (Table 4). In comparison with the BRFSS population, men who received cranial radiotherapy ≥ 20 Gy were 1.43 more likely to not meet CDC recommendations (95% CI, 1.16-1.76;  $P = 0.004$ ). Lower dose cranial radiotherapy (< 20 Gy) was also associated with an increased likelihood of not meeting CDC recommendations in both females (OR, 1.44; 95% CI, 1.15-1.80;  $P = 0.001$ ) and males (OR, 1.37; 95% CI, 1.11-1.69;  $P = 0.004$ ). Dose of cranial radiotherapy modified the effect only in females, where those who were treated with ≥ 20 Gy were more likely to not meet the CDC recommendations than those who were treated with < 20 Gy (45.3% versus 34.8%;  $P = 0.005$ ).

In the general population, there is a strong inverse relationship between BMI and level of physical activity, such that obese individuals are less likely to be physically active. Previously, we have reported that cranial radiotherapy, particularly doses > 20 Gy, is associated with obesity (7, 8).

To determine if ALL survivors were less physically active simply because of their obesity, ORs were also calculated in each of the above multivariate models with BMI added as an adjusting variable. There were no significant differences in any of the outcomes, whether or not BMI was included in the models (data not shown).

A subgroup ( $n = 57$ ; 45 males, 12 females) of the ALL participants had growth hormone (GH) replacement for GH deficiency during childhood, verified by medical records. Outcomes were compared between this subgroup of GH-deficient ALL survivors with ALL survivors who were treated with chemotherapy alone (no cranial radiotherapy) and thus at low risk for GH deficiency. Adjusted for age, sex, race and ethnicity, and BMI, the GH-deficient ALL survivors were more likely to not meet CDC recommendations (OR, 2.31; 95% CI, 1.27-4.23;  $P = 0.006$ ) and more likely to be inactive (OR, 2.66; 95% CI 1.40-4.9;  $P = 0.003$ ) than ALL survivors treated with

**Table 3. OR with 95% CI for not meeting CDC physical activity recommendations or for being inactive in adult survivors of childhood ALL compared with general population (BRFSS), adjusted for age at time of study**

Variable	Not meeting CDC recommendations		Inactive	
	OR (95% CI)	P	OR (95% CI)	P
Total				
BRFSS (reference)	1.00		1.00	
ALL	1.44 (1.32-1.57)	<0.001	1.74 (1.56-1.94)	<0.001
Sex				
Female	1.16 (1.13-1.19)	<0.001	1.33 (1.29-1.38)	<0.001
Male (reference)	1.00		1.00	
Race				
White, NH (reference)	1.00		1.00	
Black, NH	1.52 (1.46-1.60)	<0.001	1.73 (1.64-1.82)	<0.001
Other, NH	1.15 (1.10-1.20)	<0.001	1.32 (1.24-1.40)	<0.001
Hispanic	1.41 (1.35-1.47)	<0.001	1.91 (1.81-2.00)	<0.001
Income (US\$)				
<20,000	1.24 (1.20-1.29)	<0.001	1.66 (1.59-1.72)	<0.001
≥20,000 (reference)	1.00		1.00	
Education				
Some HS	1.49 (1.41-1.57)	<0.001	3.78 (3.55-4.01)	<0.001
Graduated HS	1.26 (1.22-1.31)	<0.001	2.52 (2.41-2.63)	<0.001
Some college*	1.11 (1.07-1.15)	<0.001	1.54 (1.47-1.62)	<0.001
College graduate <sup>†</sup> (reference)	1.00		1.00	
Current smoker?				
Yes	1.00 (0.98-1.04)	0.54	1.37 (1.32-1.42)	<0.001
No (reference)	1.00		1.00	

NOTE: Participants were considered to meet CDC recommendations if they reported moderate-intensity physical activities for at least 30 min on ≥5 d of the week or vigorous-intensity physical activity ≥3 d per week for ≥20 min per occasion (28).

\*Some college or vocational school.

<sup>†</sup>Graduated from college or completed vocational school.

chemotherapy alone. Exposure to an anthracycline or a corticosteroid was not associated with the two outcomes. Similarly, higher-dose anthracycline exposure (>300 mg/m<sup>2</sup>) was not associated with activity level. Age at cancer diagnosis did not modify outcomes.

Lastly, because of the potential influence of the state of residence of participants and the level of physical activity, we estimated the relationship of state as a covariate in the univariate and multivariate models. In the univariate models, state was not significantly associated with the two outcomes for the survivors. In the multivariate models, with state included as a covariate, the findings were not changed. Therefore, state of residence was not included in the models.

## Discussion

This study of 2,648 adult survivors of childhood ALL shows that they are almost 44% more likely to not meet CDC recommendations for physical activity and over 74% more

likely to be inactive (no leisure-time physical activity in the past month) when compared with the general U.S. population. Furthermore, these analyses indicate that treatment with cranial radiotherapy (18 or 24 Gy) is associated with an increased likelihood of not meeting CDC recommendations, with women who received cranial radiotherapy ≥ 20 Gy being over twice as likely to not meet these recommendations. These results are concerning considering the protective effects of physical activity on cardiovascular disease, osteoporosis, and obesity, all entities for which ALL survivors are at increased risk.

The primary therapeutic exposure associated with a decrease in activity level is cranial radiotherapy. The use of cranial radiotherapy has changed over the past four decades. To interpret the findings of our study, with respect to both survivors treated in the past as well as those who are treated on contemporary regimens, it is important to understand the evolution of the use of cranial radiotherapy. Before the mid-1960s, few children survived acute lymphoblastic leukemia. The introduction of 24 Gy radiotherapy to the whole brain

**Table 4. Multivariate analysis, cancer-related variables, stratified by gender, adjusted for age, race, and BMI**

Variable	N	Not meeting CDC recommendations		Inactive	
		OR (95% CI)	P	OR (95% CI)	P
Females					
BRFSS	58,765	1.00		1.00	
ALL survivors					
Chemo only	424	1.31 (1.10-1.59)	0.006	1.06 (0.84-1.35)	0.62
Chemo + CRT < 20 Gy	293	1.44 (1.15-1.80)	0.001	1.37 (1.06-1.78)	0.10
Chemo + CRT ≥ 20 Gy	347	2.07 (1.67-2.56)	<0.001	1.86 (1.50-2.31)	<0.001
Males					
BRFSS	42,078	1.00		1.00	
ALL survivors					
Chemo only	349	0.96 (0.77-1.19)	0.69	1.10 (0.83-1.46)	0.52
Chemo + CRT < 20 Gy	339	1.37 (1.11-1.69)	0.004	1.68 (1.30-2.16)	<0.001
Chemo + CRT ≥ 20 Gy	352	1.43 (1.16-1.76)	0.002	1.84 (1.45-2.32)	<0.001

Abbreviation: Chemo, chemotherapy.

(cranial) and the spine in the mid-1960s proved to be the first effective therapy to prevent relapse in the central nervous system, thereby increasing long-term survival rates. However, it was soon recognized that spinal radiotherapy was associated with excessive myelosuppression and retardation of spinal growth. Thus, the spinal component was omitted, and 24 Gy cranial radiotherapy plus intrathecal methotrexate became the standard form of central nervous system preventive therapy from the early 1970s to the early 1980s. Then, with the recognition of the significant cognitive deficits associated with 24 Gy cranial radiotherapy in the early 1980s, efforts were made to reduce the dose and use of cranial radiotherapy. For the past two decades, most protocols have reserved 18 Gy cranial radiotherapy for children with high-risk features, such as T-cell ALL, overt central nervous system disease, or high-risk cytogenetics. Currently, between 5% and 25% of children with ALL are classified as high risk and receive 18 Gy cranial radiotherapy (31). Pui et al. at St. Jude Children's Research Hospital are currently testing the feasibility of omitting cranial radiotherapy in all children with ALL and reserving it only for those who have a relapse (32). Based on the incidence of ALL over the past 40 years and the transition in cranial radiotherapy therapy, ~25 to 30,000 long-term survivors of childhood ALL were exposed to cranial radiotherapy. This represents ~8% to 10% of all pediatric cancer survivors.

Previously reported, cranial radiotherapy  $\geq 20$  Gy is associated with becoming obese in adulthood, particularly in females (7, 8). Obesity is strongly associated with physical inactivity (33). However, when controlling for BMI, survivors treated with cranial radiotherapy were less likely to be physically active. Additional mechanisms by which cranial radiotherapy may affect levels of physical activity include decreased muscle mass and strength and impairment of balance and postural control.

Cranial radiotherapy in doses above 20 Gy frequently causes GH insufficiency or overt deficiency through damage to the hypothalamus. Children with GH deficiency (from cancer and non-cancer etiologies) may be less physically active than healthy controls, a problem that has been reported to resolve with GH replacement (34). Similarly, adults with GH deficiency increase their leisure-time physical activity with growth hormone replacement (35). GH deficiency in adults is associated with diminished strength and a reduction in muscle force, secondary to both a reduction in muscle mass and a reduction in the contractile properties of muscle fibers and neural recruitment of fibers (36, 37). Twelve months after withdrawal of GH therapy in young adults who were GH deficient, Rutherford et al. reported a reduction in muscle strength, size, and fiber area (38). GH replacement, in GH-deficient adults, leads to an increase in muscle mass and muscle strength of the limb and girdle muscles (39, 40). Supporting a possible role in the development of physical inactivity in ALL survivors treated with cranial radiotherapy, our data showed that ALL survivors with a verified history of previous GH therapy were 2.7 times more likely to be inactive than ALL survivors who were at low risk for GH deficiency.

Cranial radiotherapy also affects balance and postural control in ALL survivors, which may in turn affect the acquisition and maintenance of physically active lifestyles (41, 42). Lastly, cranial radiotherapy may damage hypothalamic structures involved in exercise regulation, thus decreasing exercise capacity. In animal studies, the caudal hypothalamus has been shown to be a potential site for the integration of pathways essential for regulating the cardiorespiratory drive during exercise (43).

Another mechanism that has been suggested as an etiology of physical inactivity in ALL survivors is the development of vincristine-related gait abnormalities. Vincristine causes a dose-related mixed motor-sensory peripheral neuropathy (44, 45). Most patients have minor neurologic symptoms,

including loss of ankle reflexes and numbness and tingling of the fingers and toes. Occasionally, children will have distal muscle weakness, motor clumsiness, and gait disturbances, characterized by a slapping, broad-based gait. The neuropathy has generally been considered to be reversible with cessation of therapy and have minimal long-term consequences. A longitudinal follow-up of a small cohort of ALL survivors, however, suggests that a third of survivors still have measurable and clinically relevant gross motor difficulties 5 years after therapy (46). In our analysis, survivors treated with only chemotherapy were not more likely to be inactive. However, females treated with only chemotherapy were less likely to meet CDC-guidelines; males were not. Because virtually all of the ALL survivors were treated with vincristine, we could not assess whether exposure to vincristine moderated the cranial radiotherapy effect. Thus, there may be additional factors that preferentially affect females.

There did not seem to be any evidence of subclinical cardiotoxicity leading to lower levels of physical activity or more inactive behavior. This is encouraging, recognizing that moderate to high doses of an anthracycline is associated with secondary cardiomyopathy and congestive heart failure in survivors of pediatric cancer (47). It should be noted, however, that ALL is generally not treated with the higher cumulative doses used in the treatment of sarcomas.

Limitations of this study should be considered when interpreting the findings. First, physical activity levels were assessed using self-reported data, which is subject to bias and imprecision. Many studies have addressed the reliability and validity of self-report of physical activity status. Only a single study, however, has specifically addressed the recent BRFSS physical activity questions (48). This study, comparing the BRFSS physical activity questions with an established objective measure of physical activity (heart-rate motion sensor technique), showed that underreporting and overreporting were only apparent for moderate-intensity activities, and the phenomenon of underreporting and overreporting cancelled each other out such that there were no mean differences between the BRFSS and the objective physical activity groups. Sensitivity for meeting recommendations was 91% with a specificity of 71%. Second, because ALL survivors who were treated with cranial radiotherapy may have cognitive deficits, it is possible that problems associated with question comprehension could have resulted in differential reporting. Third, our findings reflect therapy in the 1970s and 1980s. Contemporary therapy includes cranial radiotherapy, at a lower dose, only in specific high-risk groups or those with central nervous system relapse. Finally, because the BRFSS is a population-based study, and because the CCSS is a sample of subjects from 26 institutions, national inferences are difficult to make with the current data. Nevertheless, the CCSS is the largest, most comprehensive and diverse cohort of cancer survivors in North America.

In summary, adult survivors of childhood ALL are more likely to be physically inactive and inactive than the general population, with survivors who received cranial radiotherapy  $\geq 20$  Gy being at highest risk. These findings are also clinically relevant to survivors of a pediatric brain tumor, the second most common cancer of childhood and the most common solid tumor (3). Children with a brain tumor are generally also treated with cranial radiotherapy, but in higher doses. It is likely that long-term survivors of a pediatric brain tumor who were treated with cranial radiotherapy also have reduced levels of physical activity. These two populations, representing a sizable percent of pediatric cancer survivors, require closer clinical attention. Future studies are needed to further assess the factors that contribute to diminished physical activity, to investigate the mechanisms by which various treatment and psychosocial factors decrease physical activity, and to assess the effectiveness of lifestyle interventions on promoting

healthy habits in survivors of childhood cancer. Considering the profound morbidity and mortality caused by obesity and cardiovascular disease that could be modified by physical activity, these findings may have significant implications on the future health of survivors of childhood ALL and brain tumors.

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