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## Physical activity among adult survivors of childhood lower extremity sarcoma

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### Abstract

**INTRODUCTION**—Adult survivors of childhood lower-extremity sarcoma are largely physically inactive, a behavior which potentially compounds their health burden. Altering this behavior requires understanding those factors that contribute to their physical inactivity. Therefore, this investigation sought to identify factors associated with inactivity in this subpopulation of cancer survivors.

**METHODS**—Demographic, personal, treatment and physical activity information from adult survivors of childhood lower-extremity sarcomas was obtained from the Childhood Cancer Survivor Study (CCSS) cohort. Generalized linear models were used to identify variables that best identified those individuals who were physically inactive.

**RESULTS**—Only 41% of survivors met Center for Disease Control (CDC) activity guidelines. Survivors were 1.20 (95% CI 1.11–1.30) more likely compared to CCSS sibling cohort and 1.12 (95% CI 1.10–1.15) times more likely than the general population to fail to meet CDC guidelines. Significant predictors of physical inactivity included female sex, hemipelvectomy surgery, and platinum and vinca alkaloid chemotherapy.

**CONCLUSIONS**—The primary findings of this study are that survivors of childhood onset lower-extremity sarcoma are 1) highly likely to be physically inactive and 2) less likely than their siblings or the general population to regularly exercise. This study has identified treatment related

risk factors associated with inactivity that will help health and wellness practitioners develop successful exercise interventions to help these survivors achieve recommended levels of physical activity for health.

**IMPLICATIONS FOR CANCER SURVIVORS**—These results suggest that physical activity interventions for adult survivors of childhood lower-extremity sarcomas should be sex specific and responsive to unique physical late effects experienced by these survivors.

### Keywords

Childhood cancer; physical activity; exercise; late-effects; sedentary

## INTRODUCTION

Significant improvements in treatment interventions and medical care have increased 5 year survival rates among children with lower extremity sarcoma to over 65 percent [1–4]. Unfortunately, even after successful treatment, survivors face an increased risk for cardiovascular, orthopedic, neurologic, and functional abnormalities, many of which are the result of either the cancer or its treatment [3, 5–11]. Emerging evidence now suggests that substantial numbers of these survivors are also physically inactive. We recently reported that over 50% of adult survivors of childhood cancers did not meet the minimum physical activity guidelines established by the Centers for Disease Control (CDC) (30 minutes of moderate intensity physical activity on five or more days of the week or 20 minutes of vigorous intensity physical activity on three or more days of the week) [12].

The proportions of sarcoma survivors in this cohort who did not meet minimum activity guidelines were some of the highest from the Childhood Cancer Survivorship Study (CCSS); for example 56.8% of women with soft tissue sarcoma, 57.4% of men with osteosarcoma and 69.0% of women with Ewing sarcoma histories reported not meeting minimum activity guidelines. [12]. Although we identified amputation and anthracycline therapy as important treatment related risk factors for inactivity, the high correlation between cancer type and treatment did not allow us to specifically characterize a phenotype of the sarcoma survivor at greatest risk for a poor activity outcome in this cohort [12]. The ability to characterize the risk profile for inactivity among lower extremity sarcoma survivors by type of amputation, and or by chemotherapeutic agent will provide clinicians and researchers with important information for both early rehabilitation referral and targeted intervention study design.

A growing body of literature demonstrates that participation in exercise programs improves the physiological and psychological status of cancer survivors across the entire spectrum of cancer care including long-term survivorship [13]. Successful programs are often dependent on an understanding of barriers faced by survivors of cancer [14–16]. The constellation of potential barriers in adult survivors of childhood sarcomas has not been reported, despite the fact that these survivors have some of the highest rates of inactivity found in cancer survivors [12]. This information is necessary for the development of programs that can successfully alter the activity patterns of these survivors. Therefore, the purpose of this study was to identify specific treatment, demographic, and personal factors that are associated with suboptimal physical activity behaviors in adult survivors of childhood lower-extremity sarcoma.

## METHODS

### Study population

The current analysis was completed using data from survivors of lower-extremity sarcoma who were members of the Childhood Cancer Survivor Study (CCSS) cohort. The CCSS was designed to gain new knowledge about the long-term effects of childhood cancer and treatment. It is hoped that new knowledge will provide information to help design treatment protocols and intervention strategies to increase survival and minimize harmful health effects. The study design has been described previously [17]. Briefly, this cohort includes over 14,000 childhood cancer survivors who lived for five or more years after diagnosis, were diagnosed with one of eight different malignancies between 1970 and 1986 when younger than 21 years of age, and were treated at one of 25 participating institutions in the United States and one institution in Canada. This cohort has been followed since 1994 and has been contacted approximately every two years and asked questions about their health and well-being. For the current analyses, we only included individuals who had been diagnosed with a pelvic or lower extremity (International Classification of Disease – Oncology (ICD-O) site codes C40.2, C40.3, C41.4, C41.8, C49.2, C49.5) bone or soft tissue sarcoma who were alive and completed the 2003 physical activity follow-up questionnaire, and who consented to medical record abstraction (Figure 1) [18]. A random sample of siblings of all study participants was also contacted for enrollment into the CCSS sibling cohort. Siblings completed questionnaires similar to those completed by survivors at each time point. Approval for study documents and questionnaires was obtained from each participating institution's Institutional Review Board prior to contacting potentially eligible participants. Consent was obtained from study participants or their guardians at study entry and again at age of majority for participants who were younger than age 18 years at study enrollment.

### Outcomes

The primary outcome of interest for the current analysis was whether or not participants met the Centers for Disease Control and Prevention (CDC) Physical Activity Guidelines [19]. Participants were asked six questions from the Behavioral Risk Factor Surveillance System (BRFSS) Survey about the frequency and intensity of physical activity (Figure 2). For analysis, we calculated the average number of minutes per day and number of days per week of both moderate and vigorous intensity physical activity and constructed a binary variable to indicate whether or not individuals met CDC Physical Activity Guidelines. Those who did not report at least 30 minutes of moderate intensity physical activity on five or more days of the week, or at least 20 minutes of vigorous intensity physical activity on three or more days per week, were classified as not meeting the CDC Guidelines for Physical Activity (physical inactivity). As in our previous analysis [12], a three-to-one population-based sample was selected for comparison, frequency matched on age and gender, from individuals who answered the same six questions on the 2003 BRFSS survey [20].

### Diagnosis and treatment

Diagnosis and treatment information was obtained from the medical records at each of the treating institutions. For these analyses, the following variables were considered for possible association with the outcome: 1) age at diagnosis; 2) type of surgery used to the lower extremity sarcoma, classified as hemipelvectomy, above the knee amputation, below the knee amputation, limb salvage, or no bone surgery; 3) lung surgery; 4) chest or lung radiation; 5) local radiation; and 6) chemotherapy types (vinca-alkaloids, anthracyclines, bleomycin, platinum). Vinca alkaloid exposure was treated as a dichotomous variable. Anthracyclines, bleomycin and platinum were evaluated as both dose tertiles and as dichotomies.

## Demographic and personal variables

Demographic and personal variables were selected based on previous literature that documented physical activity correlates in both healthy populations [21,22], and in persons with mobility limitations [23], and were classified according to participants' answers to questions on both the initial baseline questionnaire and the 2003 follow-up questionnaire. Sex, race/ethnicity (white, black, Hispanic, other), obesity status in 2003 (body mass index (BMI)  $\geq 30$  kilograms per meter squared after accounting for the loss of all or a portion of a limb) [24], smoking status in 2003 (yes or no), and current age were evaluated along with treatment variables as predictors of physical inactivity. A history of depressive symptoms [25], measured at baseline (1995–1996), current pain and or anxiety as a result of the cancer, and annual household income were also considered as potential predictors inactivity. Participants with T-scores of 63 or higher on the Brief Symptom Inventory–18 (BSI-18) were classified as depressed [26]. Cancer pain and cancer anxiety were dichotomized as none/mild or moderate/more than moderate. Annual household income was dichotomized as less than \$40,000 per year or \$40,000 or more per year.

## Statistical methods

Descriptive statistics were calculated for the diagnosis, treatment, demographic, and personal factors and are reported as medians and ranges and frequencies and percents. The distribution of each of these variables was normal; however medians and ranges were reported to give the reader a sense of the middle and extremes of these variables. The percentages of sarcoma survivors, siblings and population based comparison group members who were physically inactive were calculated and compared using generalized linear models with a binomial distribution and a log link to obtain age adjusted prevalence ratios (PR) and 95% confidence intervals (95% CI). Generalized estimating equations with robust variance estimates were used to account for intra-family correlation between siblings [27]. The percentage of sarcoma survivors who were physically inactive was compared by treatment, demographic and personal factors variables. Generalized linear models were used to evaluate predictors of physical inactivity. These models, with a binomial distribution with a log link, were used to estimate PRs and associated 95% CI [27]. A copy macro was employed to account for model restrictions on the parameter space [28]. Final models include variables whose univariate associations had p-values of  $< 0.25$ . However, the final model was adjusted for age, obesity, and smoking status, regardless of p-values. SAS version 9.1 (Cary, N.C.) was used for all analyses.

## RESULTS

### Study participants

Of the 956 CCSS survivor participants diagnosed with soft tissue sarcoma, osteosarcoma, Ewing sarcoma, or other bone tumor of the lower extremity or pelvis, 610 were eligible for the current analysis by completing both the 2003 questionnaire and questions about physical activity (Figure 1). Among the 956 members of the baseline cohort, 68.9% of females and 62.3% of males ( $p=0.03$ ) completed the 2003 questionnaire. The follow up questionnaire was also completed more frequently by those who reported race/ethnicity as white (68%) versus those who reported their race as non-white (50%) ( $p < 0.001$ ). The analysis cohort's median age at diagnosis was 14 years (range 0–20); and 37 years (range 19–53) when reporting physical activity. Their median time since diagnosis was 23 years (range 16–34), and just over half (50.3%) were male. Members of the sibling comparison group were a median age of 34 years (range 18–58) when reporting physical activity, and included 1,298 males (46.3%) and 1,507 (53.7%) females.

Additional characteristics of the study population are shown in Table 1. Most reported their race/ethnicity as white, and over half had a primary diagnosis of osteosarcoma. Over half of the members of this cohort were treated with amputation; a minority were treated with radiation, more than half had chemotherapy that included a vinca alkaloid, and over 70% were treated with an anthracycline. Less than 25% received bleomycin or platinum as part of their treatment regimen. Annual household income less than \$40,000 per year, cancer related pain, and obesity were prevalent among approximately one-fourth of participants. Of the cancer survivors 14.1% reported experiencing cancer related anxiety and 16.4% reported smoking. Of the 610 participants with complete physical activity data, 49 were missing exposure information in household income, persistent cancer pain, anxiety, depression, smoking status, or BMI (Table 1). Comparisons between participants included in the model, and participants with missing physical activity or exposure data revealed no differences by sex, race, age at diagnosis, age at evaluation, diagnosis group, radiation exposure, surgical intervention, anthracycline exposure or vincristine exposure. Platinum exposure was higher among those with missing data (38.8% vs. 20.4%,  $p < 0.001$ ).

### Participation in physical activity

The percentage of survivors, siblings, and population comparison group members who were physically inactive are shown in Figure 3. After adjusting for age, sex, and intrafamily correlation, sarcoma survivors were 1.20 (95% CI 1.11–1.30) times more likely than siblings and 1.12 (95% CI 1.10–1.15) times more likely than the general population to be physically inactive.

### Risk factors for inactivity

The percentages of survivors who were physically inactive are shown in Table 2 by demographic, treatment status and personal variables. Treatments involving radiation, bleomycin, anthracycline, and lung surgery and self reported cancer related pain or anxiety were not predictors of physical activity nor did they improve the model fits and thus, were not included in the final models. Chemotherapy was not associated with level of physical activity in a dose-dependent manner, so platinum and vinca alkaloids were included as dichotomous variables. In adjusted models, female sex, having undergone a hemipelvectomy, treatment with platinum, and treatment with vinca-alkaloids increased the risk for inactivity. We found no associations between smoking status, obesity, depression or income and whether or not a survivor was physically inactive.

## DISCUSSION

While we have previously described that adult sarcoma survivors are less active than their siblings [12], our current analysis allowed us to 1) describe their activity patterns compared to the general population and 2) specifically characterize a phenotype of the sarcoma survivor at greatest risk for a poor activity outcome in this cohort. The prevalence of inactivity in our study (58.9%) is higher than the 50.1% among individuals with impaired mobility status and lower than the 75% among individuals with diabetes reported by investigators who used data from the National Health Interview Survey [29,30]. In our analysis, being female, having a hemipelvectomy, and having received platinum or vinca alkaloid chemotherapy were associated with increased risk for physical inactivity. Demographic and personal factors (smoking, obesity depression, cancer pain, anxiety, or low income) were not associated with inactivity in our analysis.

Some treatment factors were predictors of poor activity behaviors. An important finding in this study is that there is an association between two classes of chemotherapeutic agents, vinca alkaloids and platinum, and physical inactivity. Both vinca alkaloids and platinum

chemotherapeutic agents are known for their neurotoxic impact on the peripheral nervous system. The resulting chemotherapy-induced peripheral neuropathy (CIPN) has been reported in patients during and after treatment for many childhood cancers, including adolescents and young adults treated for sarcomas [8]. Peripheral neuropathies typically present during treatment, and although they may diminish over time, such deficits are likely to persist in many survivors [31–33]. In adolescents and young adults previously treated for sarcoma, evidence of persistent symptoms of neurotoxicity from cisplatin exposure have been reported, including decreased deep tendon reflexes and increased vibration sensation thresholds [8]. Persistent neuropathy in lower extremities may account for the balance deficits and decreased levels of activity that have been reported in survivors of childhood cancer [34–35].

The fact that besides female sex, we found no associations between demographic and personal factors and inactivity in our analysis is interesting and important. In this population, it appears that interventions targeted specifically at females and treatment related outcomes, like managing exercise with a missing or prosthetic limb, or when less than optimal sensation or motor function is available, may be more important for this population than other factors like lower household income, depression, and obesity. Sarcoma survivors may benefit from working with skilled providers who are knowledgeable and who have experience with prosthetics and movement retraining, such as physical therapists, to help them optimize physical activity levels among lower extremity sarcoma survivors before they can reintegrate into community wellness and exercise programs.

There are several limitations to this study. First, our analysis was limited to the data provided by the CCSS questionnaires and medical record abstractions. Differential participation in the 2003 questionnaire by sex and race were present. If females or those who were non-white were more likely to be inactive completed the questionnaire, our estimates of the prevalence of inactivity are inflated. Conversely, if those more likely to be inactive avoided completing the questionnaire, our estimates of the prevalence of inactivity are too low. Because our analyses were focused on discovery of personal and treatment related risks for inactivity, we did not evaluate comorbid conditions, for example, diabetes and cardiac disease, also likely to be associated with poor activity outcomes. In addition, there are potentially additional psychosocial predictors of inactivity, such as self efficacy, self motivation, or social support [22], that were not part of the data set. Also, the study relied on self-report of physical activity. While self-report methods have been criticized, Strath et al have reported an 80% agreement between objective and self-report measures of meeting moderate and vigorous activity guidelines [36]. Finally, these data describe individual characteristics of individuals who are at greater risk of physical inactivity but they do not provide information about perceived barriers to participation in physical activity. Such information would provide additional insights into the design of successful interventions for this population of survivors.

In summary, childhood lower-extremity sarcoma survivors are at risk for being physically inactive. This study has identified sex and treatment factors associated with these behaviors including being female, hemipelvectomy surgery, and treatment with platinum, or vinca-alkaloid chemotherapy. Interventions tailored to address these identified factors need to be developed and should consider the new CDC guidelines for children which are even more rigorous (60 minutes 7 days a week of moderate to vigorous activity - adults 30 minutes 5 times per week in addition to 2 days a week strengthening exercises) than the guidelines we used to identify outcomes in this analysis [37]. In addition, physical activity programs should address the unique needs of lower extremity sarcoma survivors such as poor balance, peripheral neuropathy, and prosthetic or missing limbs. We hypothesize that programs designed and implemented specifically for this population of cancer survivors will be more



likely to meet with success, less frustrating, and more successful in sustaining changes in physical activity levels. Such interventions will become increasingly more important as medical care for sarcoma continues to improve, resulting in more adult survivors.

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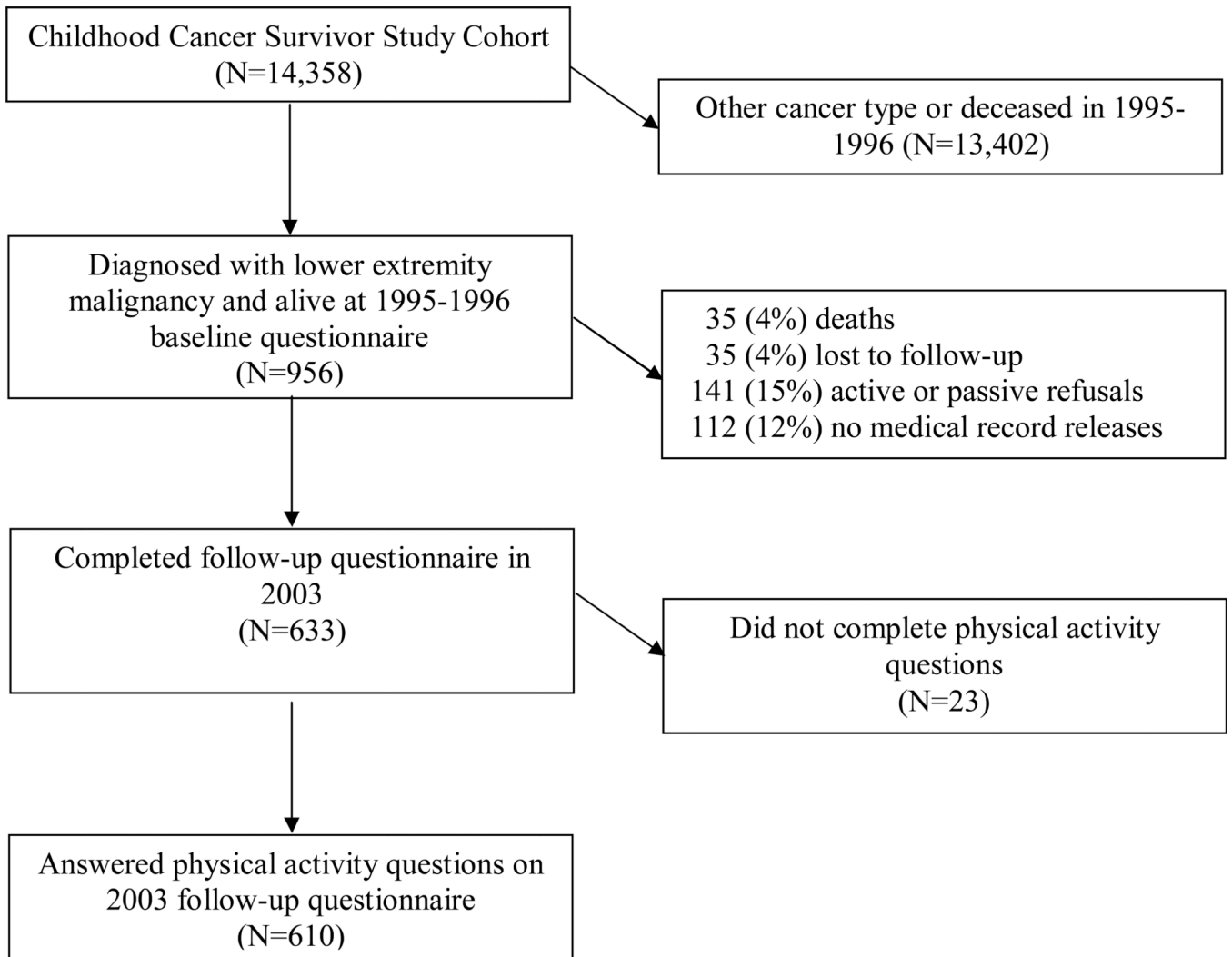
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**Figure 1.**  
A description of how CCSS cohort participants were chosen for this retrospective analysis.

**D. PHYSICAL ACTIVITY**

The rest of the questions on this page are about exercise, recreation, or physical activities other than your regular job duties.

1. 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?

No     Yes

We are interested in two types of physical activity: vigorous and moderate. Vigorous activities cause large increases in breathing or heart rate while moderate activities cause small increases in breathing or heart rate.

2. Now thinking about the vigorous physical activities you do in a usual week, do you do vigorous activities for at least 10 minutes at a time, such as running, aerobics, wheelchair basketball, heavy yard work, or anything else that causes large increases in breathing or heart rate?

No → Go to Question 5.

Yes ↓

3. How many days per week do you do these vigorous activities for at least 10 minutes at a time?

Days per week

4. On days when you do vigorous activities for at least 10 minutes at a time, how much total time per day do you spend doing these activities?

Minutes per day

5. Now, thinking about the moderate physical activities you do in a usual week, do you do moderate activities for at least 10 minutes at a time, such as brisk walking, bicycling, vacuuming, gardening, manual operation of a wheelchair, or anything else that causes small increases in breathing or heart rate?

No → Go to next page.

Yes ↓

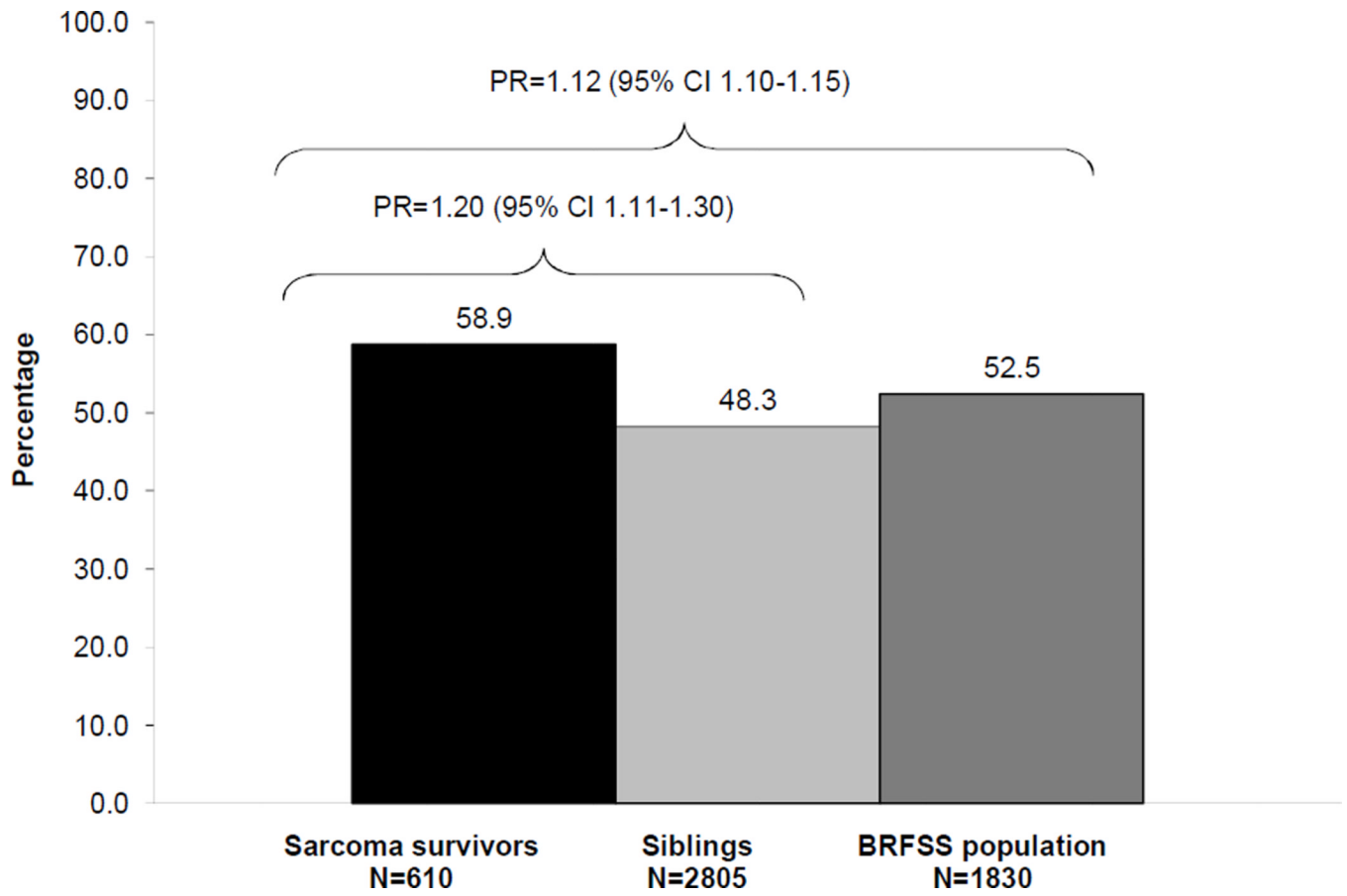
6. How many days per week do you do these moderate activities for at least 10 minutes at a time?

Days per week

7. On days when you do moderate activities for at least 10 minutes at a time, how much total time per day do you spend doing these activities?

Minutes per day

**Figure 2.** Behavioral Risk Factor Surveillance Survey questions answered by study participants in the Childhood Cancer Survivor Study 2003 Questionnaire.



**Figure 3.** Percentage of sarcoma survivors, siblings and members of the general population who completed the 2003 Behavioral Risk Factor Surveillance System (BRFSS) survey who did not meet the Centers for Disease Control and Prevention physical activity guidelines. Prevalence ratios (PR) and 95% confidence intervals (CI) were adjusted for age, sex, and in the sibling comparison adjusted for intrafamily correlation.

**Table 1**

## Characteristics of the survivor population

	N	%
<b>Sex</b>		
Female	303	49.7
Male	307	50.3
<b>Race/ethnicity</b>		
White	543	89.0
Black	22	3.6
Hispanic	24	3.9
Other/unknown	21	3.4
<b>Diagnosis</b>		
Soft tissue sarcoma	145	23.8
Ewing sarcoma	103	16.9
Osteosarcoma	346	56.7
Other bone tumors	16	2.6
<b>Lower extremity surgery</b>		
Hemipelvectomy	15	2.5
Transfemoral amputation	264	43.3
Transtibial amputation	36	5.9
Limb sparing surgery	214	35.1
No bone surgery	81	13.3
<b>Lung surgery (excluding biopsy)</b>		
No	519	85.1
Yes	91	14.9
<b>Chest or lung radiation</b>		
No	574	94.1
Yes	36	5.9
<b>Local radiation</b>		
No	455	74.6
Yes	155	25.4
<b>Vinca alkaloid</b>		
No	257	42.1
Yes	353	57.9
<b>Anthracycline</b>		
No	174	28.5
Yes	436	71.5
<b>Bleomycin</b>		
No	474	77.7
Yes	136	22.3
<b>Platinum</b>		
No	477	78.2



	N	%
Yes	133	21.8
<b>Annual household income at follow-up</b>		
<\$40,000	145	23.8
\$40,000+	439	72.0
Not indicated	26	4.3
<b>Persistent cancer related pain at follow-up</b>		
None or mild	452	74.1
Moderate or greater	156	25.6
Not indicated	2	0.3
<b>Anxiety as a result of cancer at follow-up</b>		
None or mild	521	85.4
Moderate or greater	86	14.1
Not indicated	3	0.5
<b>Depression at baseline</b>		
T-score < 63 on Brief Symptom Inventory	558	91.5
T-score 63+ on Brief Symptom Inventory	46	7.5
Not indicated	6	1.0
<b>Current smoker at follow-up</b>		
Yes	100	16.4
No	508	83.3
Not indicated	2	0.3
<b>Body mass index at follow-up</b>		
< 30 kilograms per meter squared	457	74.9
30+ kilograms per meter squared	135	22.1
Not indicated	18	3.0

**Table 2**

Number of sarcoma survivors who were physically inactive by demographic, treatment, and personal variables adjusted for age, with prevalence ratios and 95 percent confidence intervals.

	No.	N	Row %	PR*	95% CI
<b>Did not meet CDC Guidelines for Physical Activity (Physically inactive) (N=359)</b>					
<b>Sex</b>					
Female	303	191	63.0	<b>1.15</b>	<b>1.01–1.32</b>
Male (referent)	307	168	54.7	1.00	
<b>Surgery for primary disease</b>					
Hemipelvectomy	15	13	86.7	<b>1.43</b>	<b>1.05–1.84</b>
Above Knee Amputation	264	168	63.6	1.04	0.86–1.31
Below Knee Amputation	36	21	58.3	1.04	0.70–1.44
Limb Sparing Surgery	214	110	51.4	0.90	0.72–1.15
No Bone Surgery (referent)	81	47	58.0	1.00	
<b>Platinum included in chemotherapy</b>					
Yes	133	88	66.2	<b>1.27</b>	<b>1.07–1.48</b>
No (referent)	477	271	56.8	1.00	
<b>Vinca-alkaloid included in chemotherapy</b>					
Yes	353	218	61.8	1.14	0.99–1.31
No (referent)	257	141	54.9	1.00	
<b>Current Smoker</b>					
Yes	100	64	64.0	1.10	0.91–1.27
No (referent)	508	294	57.9	1.00	
Not indicated#	2	1	50.0	NE	
<b>BMI 30+ kg/m<sup>2</sup></b>					
Yes	135	87	64.4	1.13	0.98–1.31
No (referent)	457	272	57.3	1.00	
Not indicated#	18	9	50.0	NE	
<b>Depression</b>					

Did not meet CDC Guidelines for Physical Activity (Physically inactive) (N=359)				
	No.	N	Row %	PR* 95% CI
Yes	46	30	65.2	1.07 0.82-1.28
No (referent)	558	326	58.4	1.00
Not indicated#	6	3	50.0	NE
<b>Household income</b>				
<\$40,000 per year	145	89	61.4	1.0 0.87-1.17
\$40,000+ per year (referent)	439	255	58.1	1.0
Not indicated#	26	15	57.7	NE

\* Adjusted for age,

# Not included in estimate

CDC=Centers for Disease control and Prevention, N=number, No.=total number, %=percent, PR=prevalence ratio, 95% CI=95 percent confidence interval, NE=not estimated, BMI=body mass index, kg/m<sup>2</sup>=kilograms per meter squared