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ORIGINAL REPORT

Risk Factors for Obesity in Adult Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

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ABSTRACT

Purpose
Many Childhood Cancer Survivor Study (CCSS) participants are at increased risk for obesity. The etiology of their obesity is likely multifactorial but not well understood.

Patients and Methods
We evaluated the potential contribution of demographic, lifestyle, treatment, and intrapersonal factors and self-reported pharmaceutical use to obesity (body mass index $\geq$ 30 kg/m^2) among 9,284 adult (> 18 years of age) CCSS participants. Independent predictors were identified using multivariable regression models. Interrelationships were determined using structural equation modeling (SEM).

Results
Independent risk factors for obesity included cancer diagnosed at 5 to 9 years of age (relative risk [RR], 1.12; 95% CI, 1.01 to 1.24; $P = .03$), abnormal Short Form–36 physical function (RR, 1.19; 95% CI, 1.06 to 1.33; $P < .001$), hypothalamic/pituitary radiation doses of 20 to 30 Gy (RR, 1.17; 95% CI, 1.05 to 1.30; $P = .01$), and paroxetine use (RR, 1.29; 95% CI, 1.08 to 1.54; $P = .01$). Meeting US Centers for Disease Control and Prevention guidelines for vigorous physical activity (RR, 0.90; 95% CI, 0.82 to 0.97; $P = .01$) and a medium amount of anxiety (RR, 0.86; 95% CI, 0.75 to 0.99; $P = .04$) reduced the risk of obesity. Results of SEM (N = 8,244; comparative fit index = 0.999; Tucker Lewis index = 0.999; root mean square error of approximation = 0.014; weighted root mean square residual = 0.749) described the hierarchical impact of the direct predictors, moderators, and mediators of obesity.

Conclusion
Treatment, lifestyle, and intrapersonal factors, as well as the use of specific antidepressants, may contribute to obesity among survivors. A multifaceted intervention, including alternative drug and other therapies for depression and anxiety, may be required to reduce risk.

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INTRODUCTION

Survivors of childhood cancer are at risk for treatment-related sequelae that place them at an increased risk for being obese. Compared with US normative data from the 1995 National Health Interview Survey, risk of obesity (body mass index [BMI] $\geq$ 30 kg/m^2) was increased 50% among adult female and 20% among adult male leukemia survivors in the Childhood Cancer Survivor Study (CCSS).[1] Among CCSS male survivors, Hispanic race/ethnicity and brain radiation were associated with an increased risk of obesity, whereas age at diagnosis of 5 to 9 years, black, non-Hispanic race/ethnicity, brain radiation, and treatment with an anthracycline and an alkylating agent increased the risk of obesity among CCSS female survivors.[2]

Survivors treated for acute lymphoblastic leukemia (ALL), Hodgkin's lymphoma (HL), and non-Hodgkin's lymphoma (NHL) were more likely to report symptomatic levels on the Brief Symptom Inventory−18 (BSI) depression subscale (ALL, 5.4%; HL, 5.5%; and NHL, 4.4%) than were siblings (3.4%). Female ALL and HL survivors were approximately twice as likely to report symptomatic levels for depression as compared with male survivors.[3] CCSS participants with solid tumors had significantly higher scores on the BSI depression, somatic distress, and anxiety subscales than did CCSS sibling participants.[4]

Table 1. Characteristics of CCSS Survivors

Variable	Adult Survivors (N = 9,284) No.	%
Sex		
Male	4,707	50.70
Female	4,577	49.30
Race/ethnicity		
Non-Hispanic white	8,262	89.33
Hispanic	332	3.59
Non-Hispanic black	394	4.26
Other	261	2.82
Missing	35	
Education level		
No high school or GED	430	4.68
High school or GED	2,111	22.98
Some college; no bachelor's degree	2,773	30.18
Bachelor's degree or higher	3,873	42.16
Missing	97	
Age at diagnosis, years		
0-4	3,769	41.38
5-9	2,071	22.74
10-14	1,866	20.49
15-20	1,403	15.40
Missing	175	
Age at questionnaire, years		
18-25	2,479	26.70
26-35	4,070	43.84
36-45	2,404	25.89
46-55	331	3.57
> 55		
Family income		
< $20,000/year	1,056	13.30
≥ $20,000 and < $40,000/year	1,870	23.55
≥ $40,000/year	5,015	63.15
Missing	1,343	
Health insurance		
Yes or Canadian	8,090	87.88
No	1,116	12.12
Missing	78	
Baseline frequency of aerobic exercise, days/wk		
0	2,786	31.13
1	1045	11.67
2	1,273	14.22
3	1,326	14.81
4	807	9.02
5	854	9.54
6	295	3.30
7	565	6.31
Missing	333	
Physical activity		
No	6,572	72.01
Yes	2,555	27.99
Missing	157	
Inactive lifestyle		
No	7,140	77.21
Yes	2,107	22.79
Missing	37	

(continued in next column)

Table 1. Characteristics of CCSS Survivors (continued)

Variable	Adult Survivors (N = 9,284) No.	%
Hypothalamic/pituitary radiation dose		
None	2,916	35.00
< 20 Gy	3,547	42.58
≥ 20 to ≤ 30 Gy	1,111	13.34
> 30 Gy	757	9.09
Missing	953	
BSI-18 Depression Score*		
< 63	6,805	88.11
≥ 63	918	11.89
Missing	1,561	
BSI-18 Somatic Distress Score*		
< 63	6,644	86.06
≥ 63	1,076	13.94
Missing	1,564	
BSI-18 Anxiety Score*		
< 63	7,120	92.20
≥ 63	602	7.80
Missing	1,562	
Cancer-related anxiety		
No anxiety/fears	4,751	61.60
Small amount of anxiety/fears	2,089	27.08
Medium amount of anxiety/fears	607	7.87
A lot of anxiety/fears	199	2.58
Very many, extreme anxiety/fears	67	0.87
Missing	1,571	
Cancer-related pain		
No pain	5,928	77.06
Small amount of pain	962	12.50
Medium amount of pain	526	6.84
A lot of pain	204	2.65
Very bad, excruciating pain	73	0.95
Missing	1,591	
SF-36 Physical Function		
> 40	8,210	88.88
≤ 40	1,027	11.12
Missing	47	
Fluoxetine		
No	8,939	97.63
Yes	217	2.37
Missing	128	
Sertraline		
No	8,840	96.55
Yes	316	3.45
Missing	128	
Paroxetine		
No	8,899	97.19
Yes	257	2.81
Missing	128	
Citalopram		
No	8,975	98.02
Yes	181	1.98
Missing	128	
Escitalopram		
No	9,065	99.01
Yes	91	0.99
Missing	128	

(continued in next column)

Table 1. Characteristics of CCSS Survivors (continued)

Variable	Adult Survivors (N = 9,284) No.	%
Bupropion		
No	8,987	98.15
Yes	169	1.85
Missing	128	
Nefazodone		
No	9,135	99.77
Yes	21	0.23
Missing	128	
Venlafaxine		
No	8,991	98.20
Yes	165	1.80
Missing	128	
Amitriptyline		
No	9,125	99.66
Yes	31	0.34
Missing	128	
Imipramine		
No	9,155	99.99
Yes	1	0.01
Missing	128	
Desipramine		
No	9,153	99.97
Yes	3	0.03
Missing	128	
Nortriptyline		
No	9,149	99.92
Yes	7	0.08
Missing	128	
Olanzapine		
No	9,134	99.76
Yes	22	0.24
Missing	128	
Aripiprazole		
No	9,150	99.93
Yes	6	0.07
Missing	128	
Thioridazine		
No	9,155	99.99
Yes	1	0.01
Missing	128	
Quetiapine		
No	9,134	99.76
Yes	22	0.24
Missing	128	
Clozapine		
No	9,154	99.98
Yes	2	0.02
Missing	128	
Risperidone		
No	9,115	99.55
Yes	41	0.45
Missing	128	
Valproate		
No	9,061	98.96
Yes	95	1.04
Missing	128	

Abbreviations: BSI-18, Brief Symptom Inventory–18; CCSS, Childhood Cancer Survivor Study; GED, general education degree; SF-36, Short Form–36.
*A BSI-18 scale score of T ≥ 63 reflects a level of emotional symptoms reported by ≤ 10% of the most distressed subjects in the normative standardization sample.

Weight gain is a frequent adverse effect of the use of some antidepressants, including paroxetine (Paxil; GlaxoSmithKline, Research Triangle Park, NC)[5,6] and, in one study, sertraline (Zoloft; Pfizer Inc, New York, NY),[6] as well as antipsychotic drugs such as clozapine (Clozaril; Novartis Pharmaceuticals, East Hanover, NJ), olanzapine (Zyprexa; Eli Lilly, Indianapolis, IN), and risperidone (Risperdal; Janssen, Division of Ortho-Mcneil-Janssen Pharmaceuticals Inc, Titusville, NJ)[7-18]and some drugs used for seizure control and/or mood stabilization, such as sodium valproate (Depakote; Abbott Laboratories, Abbott Park, IL).[19-21]

In addition to treatment, lifestyle, and intrapersonal factors, this study sought to determine the contribution, if any, of the use of specific pharmaceuticals for depression, anxiety, or mood stabilization to the risk of obesity among adult survivors of childhood cancer. Additionally, we used structural equation modeling (SEM) to identify factors that directly predict, moderate, or mediate obesity to inform interventions for long-term health management.

PATIENTS AND METHODS

A cohort of 20,720 previously untreated patients who were less than 21 years of age at diagnosis, survived for at least 5 years after the date of diagnosis, and were diagnosed with an eligible cancer between January 1, 1970, and December 31, 1986, was identified at the 26 participating institutions of the CCSS. This study was approved by the institutional review board at each participating institution. The study design, cohort characteristics, and baseline and follow-up data collection are presented in detail elsewhere.[22-24] Data from survivors who completed the baseline and follow-up 2003 questionnaires and who were older than 18 years at the time of the follow-up 2003 questionnaire were eligible for this analysis. A total of 1,842 of those who were sent the follow-up 2003 questionnaire received a shortened version of the questionnaire from which the four pages of psychological outcome measures had been deleted.

The current report is based on data from both the baseline (used to determine only baseline frequency of aerobic exercise, defined as the number of days [0 to 7] on which exercise sufficient to induce sweating or breathing hard, lasting ≥ 20 minutes, was performed[25]) and the 2003 follow-up questionnaire (used for ascertainment of all other data used in these analyses). Two previous CCSS reports on obesity used only data from the CCSS baseline questionnaire that were obtained between 1995 and 1996.[1,26] A more recent CCSS publication, restricted to CCSS participants diagnosed with acute lymphoblastic leukemia, used the follow-up 2003 data but evaluated only different categories of cranial irradiation and treatment that included chemotherapy as a dichotomous variable.[2]

Methods

The primary outcome of interest was BMI, which was calculated using the standard formula—weight (kg)/(height[m])^2—based on self-reported weight and height in the follow-up 2003 survey. Individuals were classified as obese if their BMI was ≥ 30 kg/m^2.[27] Self-reported body weight was adjusted for those with amputated extremities by the following percentages: amputation of foot, −1.5%; below-the-knee amputation, −3.7%; knee disarticulation, −5.7%; Van Ness rotationplasty, −7.2%; above-the-knee amputation, −11.0%; hip disarticulation or hemipelvectomy, −16.0%.[28]

Pharmaceutical use was assessed by the participant's response to the question, "Please indicate all medicines/drugs you took regularly during the two-year period between September 1, 2000 and September 1, 2002. We are only asking about medicines/drugs which you took consistently for more than one month, or for 30 days or more in a year " in several categories, including, "Antidepressants or other prescribed drugs for depression or other mood disorders such as Elavil, Prozac, Paxil, Zoloft, Navane, Ritalin or others," and "Other prescribed drugs." The specific pharmaceuticals evaluated included sertraline, paroxetine, fluoxetine (Prozac; Eli Lilly), citalopram (Celexa; Forest Laboratories, New York, NY), escitalopram (Lexapro; Forest Laboratories),

Table 2. Relative Risk of Obesity: Univariate Analyses

Variable	No. of Obese Participants	RR	95% CI
Sex			
Male	935	1.00	
Female	972	1.07	0.99 to 1.16
Race/ethnicity			
Non-Hispanic white	1,662	1.00	
Non-Hispanic black	86	*1.35*	*1.12 to 1.62*
Hispanic	105	*1.33*	*1.12 to 1.57*
Other	48	0.94	0.73 to 1.21
Age at questionnaire, years			
18-25	418	1.00	
26-35	884	*1.29*	*1.16 to 1.43*
36-45	533	*1.31*	*1.17 to 1.47*
46-55	72	*1.29*	*1.03 to 1.61*
Education level			
No high school or GED	98	1.00	
High school or GED	547	1.07	0.89 to 1.29
Some college no bachelor's degree	621	0.92	0.77 to 1.11
Bachelor's degree or higher	626	**0.61**	**0.51 to 0.74**
Age at diagnosis, years			
0-4	706	1.00	
5-9	473	1.09	0.97 to 1.22
10-14	404	0.97	0.85 to 1.10
15-20	278	0.85	0.72 to 1.01
Family income			
< $20,000/year	265	1.00	
≥ $20,000, < $40,000/year	450	0.93	0.82 to 1.06
≥ $40,000/year	910	**0.68**	**0.60 to 0.77**
Health insurance			
No	237	1.00	
Yes or Canadian	1,654	0.93	0.83 to 1.05
Baseline frequency of aerobic exercise*	1,754	**0.95**	**0.93 to 0.96**
Physical activity			
No	1,502	1.00	
Yes	377	**0.65**	**0.59 to 0.72**
Inactive lifestyle			
Yes	533	1.00	
No	1,371	**0.76**	**0.70 to 0.83**
Hypothalamic/pituitary radiation			
None	554	1.00	
< 20 Gy	652	0.94	0.84 to 1.04
20-30 Gy	318	*1.48*	*1.31 to 1.66*
> 30 Gy	181	*1.28*	*1.11 to 1.49*
BSI-18 Depression Score			
< 63	1,383	1.00	
≥ 63	206	1.13	0.99 to 1.28
BSI-18 Somatic Distress Score			
< 63	1,308	1.00	
≥ 63	279	1.30	1.16 to 1.45
BSI-18 Anxiety Score			
< 63	1,462	1.00	
≥ 63	126	1.02	0.87 to 1.20
Cancer-related anxiety			
1: None	1,023	1.00	
2: Small amount	**388**	**0.85**	**0.76 to 0.94**
3: Medium amount	123	0.91	0.77 to 1.08
4: A lot	41	0.94	0.71 to 1.23
5: Very many, extreme	14	0.97	0.61 to 1.54
Cancer-related pain			
1: None	1,173	1.00	
2: Small amount	202	1.03	0.90 to 1.17
3: Medium amount	118	1.11	0.94 to 1.31
4: A lot	58	*1.42*	*1.14 to 1.77*
5: Very bad, excruciating	25	*1.65*	*1.20 to 2.26*
SF-36 Physical Function			
> 40	8,210	1.00	
≤ 40	1,027	*1.53*	*1.38 to 1.70*
Fluoxetine			
No	1,824	1.00	
Yes	52	1.12	0.88 to 1.42
Sertraline			
No	1,794	1.00	
Yes	82	*1.26*	*1.04 to 1.52*
Paroxetine			
No	1,804	1.00	
Yes	72	*1.40*	*1.15 to 1.71*
Citalopram			
No	1,848	1.00	
Yes	28	0.76	0.54 to 1.07
Escitalopram			
No	1,857	1.00	
Yes	19	1.05	0.71 to 1.57
Bupropion			
No	1,832	1.00	
Yes	44	*1.29*	*1.00 to 1.66*
Venlafaxine			
No	1,836	1.00	
Yes	40	1.17	0.89 to 1.55
Amitriptyline			
No	1,870	1.00	
Yes	6	0.93	0.45 to 1.89
Risperidone			
No	1,860	1.00	
Yes	16	*1.98*	*1.36 to 2.89*
Valproate			
No	1,849	1.00	
Yes	27	*1.44*	*1.05 to 1.97*

(continued in next column)

NOTE. Boldface indicates decreased risk of obesity. Italics indicates increased risk of obesity.

Abbreviations: BSI-18, Brief Symptom Inventory–18; GED, general education degree; RR, relative risk; SF-36, Short Form–36.

*Baseline frequency of aerobic exercise included as a continuous variable.

bupropion (Wellbutrin; GlaxoSmithKline), venlafaxine (Effexor; Pfizer Inc), amitriptyline (Elavil; AstraZeneca UK Limited, London, United Kingdom), risperidone, and sodium valproate. Drugs used by fewer than 30 patients including quetiapine (Seroquel; AstraZeneca Pharmaceuticals LP, Wilmington, DE), clozapine (Clozaril; Novartis Pharmaceuticals), desipramine (Norpramin; sanofi-aventis US LLC, Bridgewater, NJ), nortriptyline (Pamelor; Mallinckrodt Inc, St Louis, MO), ziprasidone (Geodon; Pfizer), thioridazine (Mellaril; Novartis Pharmaceuticals), aripiprazole (Abilify; Otsuka America Pharmaceutical Inc, Rockville, MD), olanzapine, doxepin (Sinequan; Pfizer), imipramine (Tofranil; Ciba-Geigy AG, Basel, Switzerland), and nefazodone (Serzone; Bristol-Myers Squibb, Princeton, NJ) were not included in the univariable or multivariable regression analyses or the SEM analysis.

Additional independent variables included demographics, treatment exposures, baseline frequency of aerobic exercise,[25] physical activity, physical

function, intrapersonal factors, cancer-related pain, and cancer-related anxiety/fears. Radiation dose to the hypothalamic/pituitary region was estimated for each patient[29,30] as previously described by Stovall et al.[31,32]

Patients were classified as physically active if they indicated that they satisfied the US Centers for Disease Control and Prevention (CDC) guidelines for physical activity (30 minutes of moderate-intensity physical activity on ≥ 5 days of the week or 20 minutes of vigorous intensity physical activity on ≥ 3 days of the week).[33] Patients were classified as inactive if they reported no participation in any leisure-time physical activity over the past month (1 = active; 0 = inactive). Physical function was categorized on the basis of participant scores on the physical function subscale of the Short Form–36 (SF-36), with a score ≤ 40 indicating abnormal physical function.[34,35]

Intrapersonal factors were quantified using the scores on the BSI subscales of depression, somatic distress, and anxiety. Cancer-related pain was quantified using a 5-point scale (1 = no pain; 5 = very bad, excruciating pain). Cancer-related anxiety/fears was quantified using a 5-point scale (1 = no anxiety/fears; 5 = very many, extreme anxiety/fears).

Statistical Analysis

Univariate log-binomial regression analysis was applied to evaluate the effect of demographic, treatment, lifestyle, intrapersonal, and pharmaceutical usage variables on the relative risk of obesity.[36,37] Covariates with $P < .1$ in the univariate analysis were selected for the multivariable model and were further reduced on the basis of the likelihood ratio statistics for type III contrasts.[38] Age at questionnaire, sex, and race/ethnicity were forced into both univariate and multivariable models. The data analysis was performed on SAS 9.1 (SAS Institute, Cary, NC).

SEM Measures

Observed and latent variables were modeled in SEM. Factorial validity of the latent variables was established through exploratory and confirmatory factor analyses. The latent variables in the SEM included depression (defined by four of six items from the BSI[39,40]: lonely, blue, no interest, hopeless) and physical function (defined by five of 10 items from the physical function subscale of the SF-36[41,42]: climb several stairs, climb one flight of stairs, walk several miles, walk several blocks, walk one block). The conceptually sound, best-fitting model was based on established SEM fit criteria (a root mean square error of approximation [RMSEA] ≤ 0.05,[43,44] comparative fit index [CFI] and Tucker Lewis index [TLI] ≥ 0.90,[45] and a weighted root mean square residual [WRMR] less than 0.90[46] when the outcome variable was binary).

SEM was analyzed using Mplus 6.1 software.[47] To model the mediators and moderators in SEM, a sub-program, INDIRECT, was used. The significance of the mediator or moderator was determined by the strength of the estimate, divided by the SE.

RESULTS

Study Population

Nine thousand two hundred eighty-four survivors who were ≥ 18 years of age at the time of completion of the follow-up 2003 questionnaire were included in these analyses (Table 1). Slightly more than half of the study population was male, and participants were predominantly white. Most had at least a high school diploma or equivalent. More than 60% were diagnosed when younger than age 10 years, and nearly 30% were older than age 35 years at the time of evaluation. Approximately 13% of survivors had annual household incomes of less than $25,000 per year. Almost 90% had health insurance or were Canadian residents. Radiation to the hypothalamic-pituitary axis was part of treatment for more than 60% of survivors.

Antidepressant use was reported by 13.8% of survivors overall. Of those who used an antidepressant, 77.4% reported the use of only a single antidepressant during the 2-year period. Fluoxetine, sertraline, and paroxetine were the most commonly used of this class of drugs.

Table 3. Relative Risk of Obesity: Multivariate Analyses

Variable	RR	95% CI
Sex		
Male	1.00	
Female	1.02	0.95 to 1.09
Race/ethnicity		
Non-Hispanic white	1.00	
Non-Hispanic black	1.10	0.88 to 1.36
Hispanic	1.12	0.93 to 1.33
Other	0.84	0.65 to 1.10
Age at questionnaire, years		
18-25	1.00	
26-35	*1.11*	*1.00 to 1.24*
36-45	1.13	0.98 to 1.30
46-55	1.19	0.95 to 1.51
Education level		
No high school or GED	1.00	
High school or GED	1.03	0.85 to 1.26
Some college no bachelor's degree	1.00	0.82 to 1.21
Bachelor's degree or higher	0.85	0.70 to 1.03
Age at diagnosis, years		
0-4	1.00	
5-9	*1.12*	*1.01 to 1.24*
10-14	1.06	0.94 to 1.19
15-20	1.04	0.90 to 1.20
Family income		
< $20,000/year	1.00	
≥ $20,000, < $40,000/year	1.08	0.96 to 1.22
≥ $40,000/year	0.95	0.85 to 1.07
Baseline frequency of aerobic exercise*	0.99	0.97 to 1.00
Physical activity		
No	1.00	
Yes	**0.90**	**0.82 to 0.97**
Hypothalamic/pituitary radiation		
None	1.00	
< 20 Gy	0.94	0.86 to 1.02
20-30 Gy	*1.17*	*1.05 to 1.30*
> 30 Gy	1.00	0.87 to 1.15
BSI-18 Somatic Distress Score		
< 63	1.00	
≥ 63	1.04	0.94 to 1.16
Cancer-related anxiety		
None	1.00	
Small amount	0.94	0.87 to 1.02
Medium amount	**0.86**	**0.75 to 0.99**
A lot	0.85	0.67 to 1.08
Very many, extreme	0.76	0.50 to 1.17
SF-36 Physical Function		
> 40	1.00	
≤ 40	*1.19*	*1.06 to 1.33*
Paroxetine		
No	1.00	
Yes	*1.29*	*1.08 to 1.54*
Bupropion		
No	1.00	
Yes	1.15	0.91 to 1.47
Risperidone		
No	1.00	
Yes	1.32	0.88 to 1.98
Sertraline		
No	1.00	
Yes	1.08	0.91 to 1.30

NOTE. Boldface indicates decreased risk of obesity. Italics indicates increased risk of obesity.

Abbreviations: BSI-18, Brief Symptom Inventory–18; GED, general education degree; RR, relative risk; SF-36, Short Form–36.

*Baseline frequency of aerobic exercise included as a continuous variable.

Table 4. SEM Results: Impact of Survivor, Treatment, and Lifestyle Factors on Obesity in Childhood Cancer Survivors

Factor	Estimate	SE	Estimate/SE	*P*
Obesity				
Physical function*	–0.098	0.013	–7.407	< .001
Cancer-related anxiety	–0.127	0.027	–4.748	< .001
Education level	–0.068	0.020	–3.336	.001
Physical activity	–0.067	0.024	–2.842	.004
Age at questionnaire	0.007	0.002	2.791	.005
Hypothalamic/pituitary radiation	0.049	0.018	2.707	.007
Family income	–0.055	0.022	–2.490	.013
Paroxetine	0.081	0.041	1.972	.049
Physical function*				
Cancer-related pain	–0.964	0.063	–15.253	< .001
Gender	–0.711	0.073	–9.683	< .001
Inactive lifestyle	0.925	0.096	9.613	< .001
Education level	0.376	0.041	9.246	< .001
Age at questionnaire	-0.037	0.005	–8.001	< .001
Hypothalamic/pituitary radiation	–0.171	0.035	–4.878	< .001
Cancer-related anxiety	–0.136	0.042	–3.227	.001
Cancer-related anxiety				
Sex	0.238	0.029	8.164	< .001
Age at questionnaire	0.008	0.002	4.198	< .001
Cancer-related pain				
Cancer-related anxiety	0.465	0.021	22.629	< .001
Age at questionnaire	0.021	0.002	8.911	< .001
Education level	–0.144	0.021	–6.993	< .001
Physical activity	–0.083	0.023	–3.607	< .001
Baseline frequency of aerobic exercise	–0.062	0.020	–3.115	.002
Baseline frequency of aerobic exercise				
Age at questionnaire	–0.031	0.002	–20.136	< .001
Sex	–0.287	0.023	–12.218	< .001
Hypothalamic/pituitary radiation	–0.089	0.013	–6.850	< .001
Education level	0.065	0.013	4.946	< .001
Inactive lifestyle				
Education level	0.070	0.008	9.145	< .001
Baseline frequency of aerobic exercise	0.148	0.021	6.950	< .001
Hypothalamic/pituitary radiation	–0.013	0.005	–2.513	.012
Physical activity				
Baseline frequency of aerobic exercise	0.288	0.017	17.206	<0.001
Education level	0.138	0.018	7.704	< .001
Sex	0.223	0.031	7.283	< .001
Hypothalamic/pituitary radiation	–0.092	0.018	–5.125	< .001
Age at questionnaire	–0.005	0.002	–2.579	.010
Family income				
Education level	0.285	0.017	16.632	< .001
Age at questionnaire	0.026	0.002	12.521	< .001
Hypothalamic/pituitary radiation	–0.146	0.016	–9.110	< .001
Cancer-related pain	–0.124	0.019	–6.509	< .001
Sex	–0.125	0.030	–4.113	< .001
Inactive lifestyle	0.161	0.042	3.782	< .001
Physical activity	0.067	0.023	2.957	.003
Paroxetine				
Cancer-related anxiety	0.303	0.036	8.440	< .001
Sex	0.253	0.062	4.105	< .001
Education level	–0.128	0.032	–3.955	< .001

NOTE. Boldface variables represent the multiple outcome measures in the model. The unbolded variables reflect the predictors or antecedents of that outcome. The first column is the unstandardized estimate (EST), followed by the SE of that estimate, followed by the estimate divided by the SE (EST/SE). The final column represents the *P* value associated with the strength of the path from the predictor/antecedent to the outcome variable.

Abbreviation: SEM, structural equation modeling.

*Physical Function in the SEM is the five items retained from the SF-36 Physical Function scale by the analytical method (see Methods).

Poor physical function was present in 11.12% of survivors. Only 27.99% met the CDC guidelines for physical activity; 22.79% reported no physical activity over the past month. Using the BSI outcome, nearly 12% of survivors were depressed, 13.94% had somatic distress, and 7.80% had anxiety. More than 38% of the survivors reported some degree of cancer-related anxiety, and almost 23% reported some cancer-related pain.

Univariate and Multivariable Analyses

The results of univariate analyses to identify factors associated with obesity are shown in Table 2. Factors associated with an increased risk of obesity (BMI $>$ 30 kg/m^2) included Hispanic or non-Hispanic; black race/ethnicity; age at questionnaire of older than 25 years; hypothalamic/pituitary radiation dose exceeding 20 Gy; BSI-18 somatic distress score $\geq$ 63; a lot of or very bad, excruciating cancer-related pain; poor physical function based on the SF-36 score $\leq$ 40; and treatment with sertraline, paroxetine, risperidone, or valproate. Factors that decreased the risk of obesity included a bachelor's degree or higher educational attainment, family income $\geq$ $ 40,000/year, baseline frequency of aerobic exercise, meeting the CDC guidelines for physical activity, participation in any leisure-time physical activity over the past month, and a small amount of cancer-related anxiety/fears.

Factors that remained significant in the multivariable model are shown in Table 3. The risk of obesity was increased among those 5 to 9 years of age at diagnosis (RR = 1.12; 95% CI, 1.01 to 1.24; P = .03), those who received 20 to 30 Gy of hypothalamic/pituitary radiation dose (RR = 1.17; 95% CI, 1.05 to 1.30; P = .01), and those with abnormal SF-36 physical function (RR = 1.19; 95% CI, 1.06 to 1.33; $P <$ .001). The risk of obesity was decreased among those who met the CDC guidelines for physical activity (RR = 0.90; 95% CI, 0.82 to 0. 97; P = .01) and among those with a medium amount of cancer-related anxiety (RR = 0.86; 95% CI, 0.75 to 0.99; P = .04). Of the pharmaceuticals evaluated, only paroxetine was independently associated with an increased risk for obesity (RR = 1.29; 95% CI, 1.08 to 1.54; P = .01).

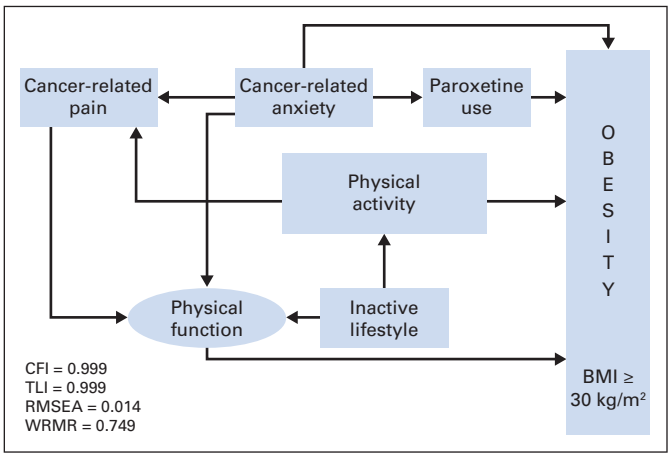

Fig 1. Direct and mediating influences on survivor obesity. Latent variables are illustrated as ellipses, and directly observed variables are illustrated as rectangles. BMI, body mass index; CFI, comparative fit index; TLI, Tucker Lewis index; RMSEA, root mean square error of approximation; WRMR, weighted root mean square residual.

SEM Analysis

All of the significant variables and their contributions to the model are shown in Table 4. A simplified graphic version of the complete SEM results is shown in Figure 1. A well-fitting model (N = 8,244; CFI = 0.999; TLI = 0.999; RMSEA = 0.014; WRMR = 0.749) identified the complex interrelationships among the directly observed and latent variables that influence obesity in adult survivors of childhood cancer.

Poor physical function was the strongest direct predictor of obesity, followed by lower self-reported cancer-related anxiety, less education, not meeting CDC guidelines for physical activity, older age at questionnaire, hypothalamic/pituitary radiation exposure, lower family income, and paroxetine use (Table 4). Analysis of potential moderators and mediators of obesity demonstrated significance for cancer-related pain through physical function (EST/SE = 7.714, $P \leq$ .001), cancer-related anxiety through physical function (EST/SE = 2.986, P = .003), and cancer-related anxiety through cancer-related pain and physical function (EST/SE = 7.279, $P \leq$ .001). Not meeting CDC guidelines for recommended physical activity mediated obesity through cancer-related pain and physical function (EST/SE = $-$3.411, P = .001).

DISCUSSION

In the general population, obesity is associated with increased morbidity and mortality.[48] The adverse health implications of obesity may be greater among childhood cancer survivors whose exposures place them at an increased risk for severe and life-threatening chronic health conditions.[49] Understanding the factors that contribute to obesity in childhood cancer survivors, either directly or as mediators and moderators, can facilitate clinical management. Greater insight into the predictors of obesity will facilitate design and evaluation of innovative intervention/prevention strategies targeting childhood cancer survivors.

Using two different, but complementary, analytic approaches, this study evaluated the risk factors associated with obesity among adult survivors of childhood cancer who participated in the CCSS. The results of the multivariable model demonstrated that impaired physical function, hypothalamic-pituitary radiation, use of paroxetine, and younger age at cancer diagnosis were statistically significant independent predictors for a BMI $\geq$ 30 kg/m^2. Meeting CDC guidelines for physical activity and a moderate amount of anxiety decreased the risk for a BMI $\geq$ 30 kg/m^2.

SEM provided similar findings, while indicating that the impact of physical function on obesity was mediated by cancer-related anxiety, cancer-related pain, and an inactive lifestyle. The primary differences in findings between the two approaches relate to education level, age at questionnaire, and family income, where SEM identified a direct association with obesity, but no statistically significant associations were evident in the multivariable model. It is not immediately apparent why these differences exist. Possible explanations include the formulation of some variables in the SEM as continuous variables (eg, age at questionnaire) that were analyzed as categorical variables in the multivariable model. In addition, latent variables derived in the SEM (eg, physical function),

though based on the SF-36, are not the same variable as the dichotomized variable used in the multivariable analysis that was based on the entire SF-36 Physical Function score.

The association between obesity, the use of specific pharmaceuticals, and their relationship with cancer-related anxiety, cancer-related pain, physical activity, and physical function are novel findings. The use of antidepressants has increased dramatically in the 18- to 44-year age group during the period 1992 to 2002, along with a significant shift from prescribing tricyclic antidepressants to selective serotonin reuptake inhibitors.[50] Weight gain is a frequent adverse effect of the use of some antidepressant and antipsychotic drugs.[5-18] Among the drugs used for seizure control, weight gain is increased among patients treated with sodium valproate compared with carbamazepine (Tegretol; Novartis Pharmaceuticals).[19-21]

We identified the use of a specific antidepressant, paroxetine (Paxil), as a risk factor associated with obesity in adult survivors of childhood cancer in the multivariable model and as a direct predictor of obesity in the SEM. We lack longitudinal data, particularly BMI data, before the initiation of antidepressant therapy. Therefore, we cannot determine whether obesity, possibly caused by prior treatment, such as cranial irradiation, resulted in depression that was then treated with an antidepressant or whether depression in a nonobese CCSS participant treated with an antidepressant resulted in the development of obesity. A longitudinal study is needed to address these questions. In addition, we lack data on calorie intake and therefore cannot evaluate the relationship of this important determinant of energy balance to the risk of obesity in our population.

An additional unique finding of this analysis was poor physical function as a direct predictor of obesity. Poor physical function was predicted by female sex, older current age, having less education, having been exposed to hypothalamic/pituitary radiation, increased cancer-related pain and anxiety, and leisure-time physical inactivity. Increased physical performance limitations and decreased ability to do routine activities have been documented in adult childhood cancer survivors,[51] but their link to obesity has not been established. Diminished functional performance and disability have been linked to obesity, however, in the general population.[52-54]

Increased cancer-related anxiety/fears predicted nonobesity in the present study; previous studies have documented that underweight survivors were more likely to report adverse health and major medical conditions.[1] Correspondingly, those who are most worried about their cancer are those who also report more late effects and related symptoms.[25] Cancer-related anxiety was also antecedent to paroxetine use; paroxetine is commonly prescribed for the treatment of anxiety.

Although the single item addressing cancer-related fears/anxiety was significant in the SEM, the BSI anxiety subscale was not. The BSI anxiety subscale assesses symptoms present over the past 7 days and likely reflects generalized acute or "state" anxiety; it does not measure nonpathologic specific anxiety/worry as does the single-item cancer-related anxiety measure. Indeed, specific anxiety contributes to greater generalized anxiety,[55] and we have illustrated this relationship in previous reports.[25] Cancer-specific anxiety may well exacerbate state anxiety symptoms, but is conceptually and, in this case analytically, distinct from the BSI.

Cranial radiation is a well-established risk factor for obesity among adult survivors of ALL.[2,26] Cranial radiation $\geq$ 10 Gy was associated with a statistically significant mean BMI increase of 0.41 kg/m^2/year among female survivors and 0.29 kg/m^2/year among male survivors, in comparison with siblings.[2] In addition to the direct effect of hypothalamic/pituitary radiation exposure on obesity, the SEM identified radiation of hypothalamic/pituitary axis as a moderator of obesity through its negative impact on physical function, baseline exercise frequency, and leisure time physical activity.

Meeting CDC guidelines for regular physical activity was associated with a lower risk of obesity in both the multivariable analysis and in the SEM. Previous data from the CCSS indicated that male and female survivors with all diagnoses were more likely to lead an inactive lifestyle compared with CCSS sibling participants. Only male survivors with the diagnoses of other CNS tumor or HL and female survivors with the diagnoses of acute myeloid leukemia, other or unspecified leukemia, HL, kidney tumor, or Ewing sarcoma met the CDC physical activity guidelines.[56]

In conclusion, this study identified previously unreported factors that are associated with obesity in adult survivors of childhood cancer. The use of specific pharmaceuticals to address anxiety and depression and their relationship with cancer-related pain, decreased physical activity, and physical function have not been reported previously. Important mediators and moderators of obesity help to identify more accurately those who are at risk for obesity and potentially suggest novel strategies (eg, distance-delivered interventions that specifically target anxiety, motivation, and strategies for behavior change) that may be investigated in patients during and after pediatric cancer therapy to diminish their risk for post-therapy obesity.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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