Research Article

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Obesity and Risk for Second Malignant Neoplasms in Childhood Cancer Survivors: A Case–Control Study Utilizing the California Cancer Registry

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Abstract

Background: Obesity is a known modifiable risk factor associated with adverse outcomes in children with cancer. We sought to determine whether obesity during childhood cancer treatment increases risk for second malignant neoplasms (SMN).

Methods: In this case–control study, cases (with SMN) and controls (with a single-primary cancer) were selected from the California Cancer Registry who had primary cancer diagnosed <21 years treated at Children's Hospital Los Angeles between 1988 and 2014. Controls were matched 3:1 to cases at the registry level by clinical factors. Medical records were abstracted for cancer treatment exposures, cancer predisposition syndrome, body mass index (BMI), BMI Z-score, and BMI category at diagnosis and end of therapy (EOT).

Results: A total of 59 cases and 130 controls were included. Median age at primary cancer diagnosis was 6 years, 64.5% were male, median time from primary cancer to SMN was 7.5 years, and 31.7% were obese or overweight. In matched multivariable analyses, there were elevated but nonsignificant associations between SMN and higher BMI Z-score at diagnosis [OR 1.27 (0.99–1.63)] and higher BMI categories at diagnosis [adjusted OR (aOR) overweight, 1.25 (0.55–2.52); aOR obese, 2.51 (1.00–6.29)]. There was a significantly increased risk for SMN among patients who were obese at both diagnosis and EOT [aOR, 4.44 (1.37–14.34)].

Conclusions: This study suggests that obesity during childhood cancer treatment may be associated with increased risk for SMNs, particularly among those obese throughout therapy.

Impact: Additional studies to confirm these findings and to develop interventions have the potential to impact SMN development in children with cancer.

Introduction

Because long-term cancer survival for children and adolescents now exceeds 80% (1), late effects of therapy have assumed great importance for this growing population. Among these, second malignant neoplasms (SMN) lead to more deaths among 25-year survivors of cancer than any other cause (2). Compared with development of first cancers among the general population, survivors of childhood cancer have a 6-fold higher risk of developing SMNs, with a 30-year cumulative incidence of 9.3% (3, 4). Known risk factors for SMN include younger age at primary cancer diagnosis, female sex, primary cancer type, genetic predisposition, longer follow-up time, and exposure to alkylators, anthracyclines, epipodophyllotoxins, and ionizing radiation (4–12).

Another potential contributor to SMNs is obesity, a condition associated with increased risk for cancer and adverse outcomes in patients with cancer. Among adults, obesity is associated with an increased risk for developing many cancer types (13, 14), including esophageal (15), liver (16), gallbladder (17), pancreas (18), breast (19, 20), gastric (15), uterine (21), ovarian (21, 22), endometrial (23), kidney (24), colorectal cancer (25, 26), and meningioma (27, 28). Obese adults with breast cancer demonstrate poorer survival (29), and obese children have demonstrated excess chemotherapy toxicity, higher rates of cancer relapse, and lower overall survival compared with patients with normal body mass index (BMI; refs. 29–33). Several mechanisms, such as hormonal changes, proinflammatory states, and chemotherapy sequestration have been proposed to explain how obesity may create a microenvironment that protects the tumor from chemotherapeutic agents and promotes cancer cell growth (34–39). These observations offer biologic plausibility for obesity influencing the development of SMNs, perhaps in combination with known oncogenic effects of cancer treatments. With obesity affecting up to 15%–30% of childhood cancer survivors (40–42), it is important to evaluate this as a candidate risk factor for developing SMNs, especially because it is potentially modifiable.

We undertook an exploratory study to evaluate the independent impact of obesity during cancer treatment on the development of SMN in pediatric cancer survivors. Our primary aim was to assess BMI at primary cancer diagnosis as a potential risk factor for SMN after controlling for known treatment and host factors. A secondary aim included evaluating BMI at end of therapy (EOT) to determine whether changes in BMI over time could also impact

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the risk of SMNs. Our general hypothesis was that obesity during cancer treatment is associated with increased risk for SMNs.

Materials and Methods

Case and control selection

This case–control study involving medical record review was approved by the Children's Hospital Los Angeles (CHLA) Institutional Review Board (Los Angeles, CA) and was in accordance with good research practices. To identify cases and controls, we utilized longitudinal data from the California Cancer Registry, a large, well-established Surveillance Epidemiology and End Results registry that collects demographic, clinical, treatment, and follow-up vital statistics data on all incident cancers (excluding skin basal and squamous carcinomas) among residents of California.

Cases were defined as patients diagnosed at <21 years old who had a primary diagnosis of invasive cancer (cancer that has spread beyond the tissue in which it develops, i.e., not *in situ* cancers) at CHLA between January 1988 and December 2014 (date of registry data completion at time of study) and were later diagnosed at any time after primary cancer with a second invasive cancer (SMN) anywhere in California through December 2014. Controls were selected via the registry from the entire cohort of all pediatric cancer patients <21 years old diagnosed at CHLA between January 1988 and December 2014 who did not develop SMN. Controls were matched using registry variables by the following criteria to control optimally for other known potential risk factors for SMN: age at diagnosis of primary cancer (exact age if possible, but extended to <1, 1–9, and 10–20 years old if matching by exact age yielded insufficient number of matches), sex, cancer site, histology code, radiation exposure for upfront therapy (no/yes), stage (exact stage if possible, but extended to dichotomous localized/regional vs. distant if matching by exact stage yielded insufficient number of matches), year of diagnosis (if possible), and days of follow-up (matched controls had to be followed at least as long as the interval between the case's primary diagnosis and SMN to minimize survival bias). The goal was to match three controls per case with exact matching criteria. If fewer than three controls were available, some characteristics (age, stage, and year of diagnosis) were relaxed (as described above) to achieve the three controls. If there were more than three controls found to match per case, controls were selected with the closest year of diagnosis. Two cases did not have any good matches based on all strict matching criteria, however were included in the analysis and matched with controls that were mismatched on only one of the strict criteria (one mismatched on sex and one mismatched on upfront radiation exposure); we confirmed after chart review that these pairings had no impact on chemoradiotherapy treatment exposure.

Chart abstraction and definition of variables

Categorization of race/ethnicity (non-Latino white, Latino white, black, Asian/Pacific Islander, and other) was collected at the registry level. Race/ethnicity was reported to the registry by the hospitals and physician offices as documented in the patient's medical record.

Abstraction of medical records for the selected cases and controls was performed by two CHLA physicians (D.J. Moke and L. Chehab) for all treatment received at CHLA using predefined variables of interest and strict adherence to a detailed protocol. Information on treatment patients received elsewhere was not available. Medical record data were censored as of the date of SMN for cases or the corresponding follow-up time for controls matched to each case.

Obesity-related variables included BMI (calculated from height in centimeters and weight in kilograms), BMI Z-score, and BMI category at initial diagnosis and EOT. BMI as kg/m^2 and corresponding pediatric BMI Z-score (for patients up to 20 years old; ref. 43) were calculated for each patient at each timepoint. To include comparable BMI Z-scores for 12 measurements of 10 patients ≥20 years old (age range, 20.0–22.0 years), Z-score was estimated as if the collected height and weight were for a patient 19.99 years old. A BMI Z-score of 0.0 corresponded to the 50th percentile of BMI, 1.04 to the 85th percentile of BMI (overweight threshold), and 1.64 to the 95th percentile of BMI (obese threshold) for sex and height. For BMI category, BMI percentile for age and sex for patients ≥2 and <20 years old, and weight for length (WFL) for patients <2 years old were obtained and categorized using the U.S. Centers for Disease Control pediatric calculator and World Health Organization infant calculator, respectively (44, 45). Patients were categorized into BMI category as normal/underweight (BMI < 85% or WFL < 95% for age and sex), overweight (85% ≤ BMI < 95% or WFL ≥ 95% for age and sex), or obese (BMI ≥ 95% for age and sex; refs. 44, 46). For patients ≥20 years old, BMI category was categorized as normal or underweight BMI < 25 kg/m^2, overweight 25 ≤ BMI < 30 kg/m^2, and obese BMI ≥ 30 kg/m^2.

Genetic predisposition variables included documentation of suspected or diagnosed cancer predisposition syndrome (prespecified as Down syndrome, *BRCA1* or *2* mutation, Li-Fraumeni syndrome, neurofibromatosis type 1 or 2, tuberous sclerosis, Beckwith–Wiedemann syndrome, retinoblastoma, hemihypertrophy, von Hippel Lindau syndrome, or other). To minimize detection bias, cases that were not suspected to have an underlying genetic predisposition syndrome until after SMN diagnosis were categorized as not having an underlying syndrome, because the controls would not have had this additional scrutiny.

The selected matching criteria were selected to, as nearly as possible, approximate treatment exposures between cases and controls. To confirm cases and controls had similar treatment exposures, treatment data were obtained from one of the following sources: cumulative chemotherapy and radiation doses documented in CHLA survivorship clinic treatment summaries; chemotherapy and radiation doses indicated in individualized roadmaps; or total doses administered as documented in the patient's medical record. Treatment-related data included radiation dose and field from the radiation oncology treatment summary, cumulative doses of alkylating agents [in cyclophosphamide-equivalent dose (CED); ref. 47], anthracyclines (in doxorubicin-equivalent dose; ref. 48), epipodophyllotoxins, platinum-based chemotherapy (5), and EOT date. Chemoradiotherapy doses were censored at the follow-up time when the corresponding matched case developed SMN. Treatment factors were categorized as follows: upfront radiation exposure as this is collected at the registry level and was a matching criteria (no/yes), radiation for progressive/relapsed disease which is not collected at the registry level and was not a matching criteria (no/yes), cumulative CED (0 mg/m^2, 1–4,000 mg/m^2, >4,000 mg/m^2), cumulative anthracycline dose (0 mg/m^2, 1–169 mg/m^2, >169 mg/m^2), cumulative epipodophyllotoxin dose (0 mg/m^2, 1–1,800 mg/m^2, >1,800 mg/m^2), and platinum-based chemotherapy exposure (no/yes).

Categorization cutoffs were determined on the basis of sample distribution quartiles.

Statistical analysis

Conditional logistic regression was performed on the basis of a variable number of controls matched to each case (ranging from one to three). Risk factors for development of SMN were assessed by univariate followed by multivariable analyses for all included matched case–control sets and separately for matched case–control sets that had sufficient EOT data. The final multivariable model for each subset included all factors with $P < 0.10$ in univariate analysis. Interaction of sex, follow-up time, and BMI category with each candidate predictor variable was assessed. All analyses were performed using pHReg in SAS version 9.4. For all analyses, significance was two-sided and set at $P < 0.05$.

Results

Cases and controls

A total of 71 pediatric cases with SMN were identified by the registry. After exclusion criteria were applied, a total of 64 case–control sets underwent chart review (Fig. 1).

After chart review, five additional case–control sets were excluded (three sets for cases having incomplete data, one set for all controls having incomplete data, and one set because the case was later determined to be a testicular relapse misclassified as SMN). Thus, the final sample included 59 cases matched to 130 controls. Three controls were matched per case for 30 cases, two controls per case for 11 cases, and one control per case for 18 cases (Fig. 1). The sample of case–control sets with EOT BMI data included 50 cases matched to 108 controls. For the EOT sample, three controls were matched per case for 22 cases, two controls per case for 14 cases, and one control per case for 14 cases.

Demographic and treatment characteristics

In aggregate unmatched analysis, our sample of cases and controls was 64.5% male with a median age of 6.0 years at primary cancer diagnosis (Table 1). The most common primary cancer diagnosis was acute lymphocytic leukemia (ALL; 36.5%), followed by Ewing sarcoma/primitive neuroectodermal tumor (PNET; 11.6%), and brain glioma (World Health Organization grades I–III; 11.6%; Table 1). A total of 56% had distant stage disease at diagnosis (Table 1). Although 34 (18%) patients did not complete therapy at CHLA, and therefore only partial treatment information was able to be extracted, these were equally distributed between cases and controls. As a result of the matching criteria, cases and controls had similar distribution by sex, age at diagnosis, year of diagnosis, radiation exposure as upfront therapy, cancer diagnosis, and stage of

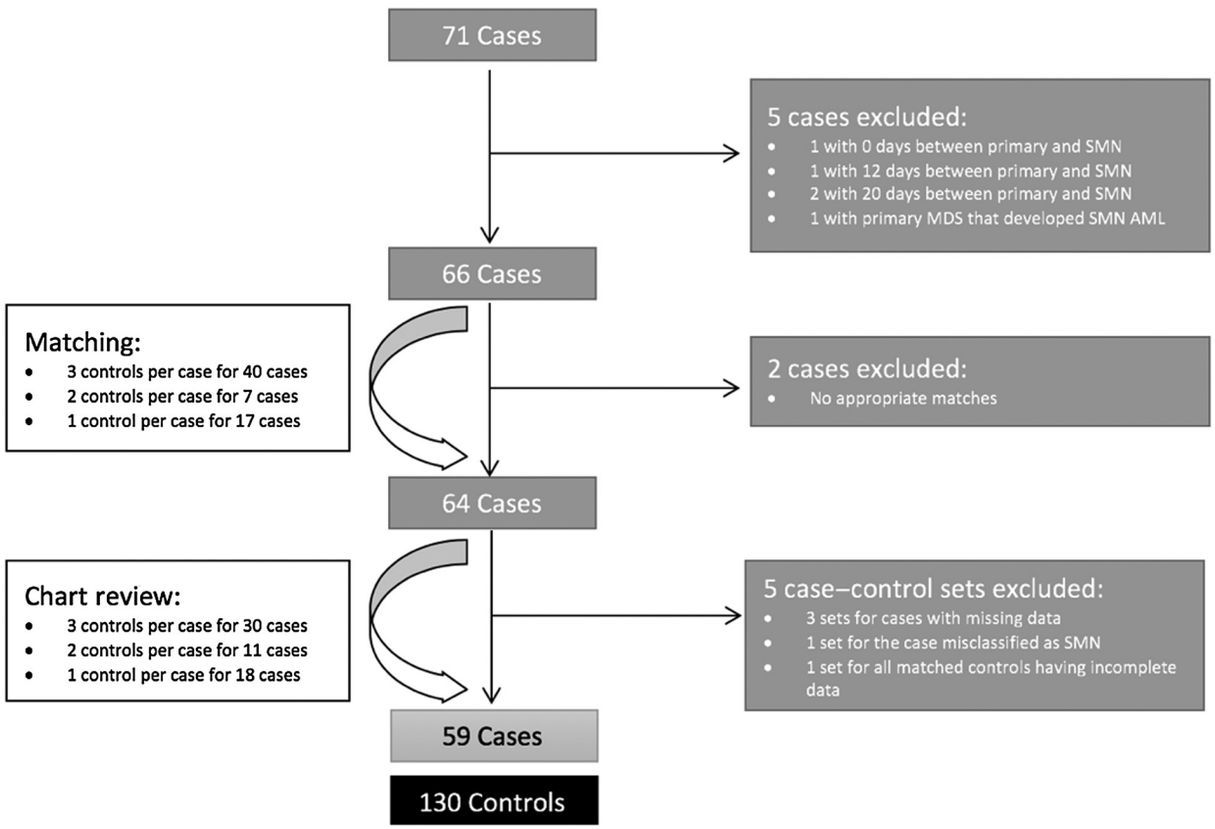

Figure 1.

Consort diagram. Cases were patients with primary cancer diagnosed at <21 years old who developed SMN. Controls were patients with primary cancer diagnosed at <21 years old who did not develop SMN. MDS, myelodysplastic syndrome.

Table 1. Demographics, cancer features, treatment factors, and BMI data for cases and controls included in 59 matched sets

	Cases	Controls	*P*
Number of individuals	**59**	**130**	
Male	35 (59.3%)	85 (65.4%)	0.42
Median age at diagnosis in years	5.0	7.0	0.54
SD (range)	5.7 (0–20)	5.3 (0–20)	
Age group at diagnosis (in years)			0.64
<1 year old	4 (6.8%)	11 (8.5%)	
1–9 years old	37 (62.7%)	72 (55.4%)	
10–20 years old	18 (30.5%)	47 (36.2%)	
Race/Ethnicity			0.21[a]
Non-Latino white	21 (35.6%)	40 (30.8%)	
Latino white	29 (49.2%)	67 (51.5%)	
Black	0 (0.0%)	8 (6.2%)	
Asian/Pacific Islander	9 (15.2%)	13 (10.0%)	
Unknown	0 (0.0%)	2 (1.5%)	
Suspected/confirmed syndrome at primary cancer			0.26
No	52 (88.1%)	121 (93.1%)	
Yes	7 (11.9%)	9 (6.9%)	
Year of diagnosis			0.37
1988–1997	31 (52.5%)	54 (41.5%)	
1998–2007	22 (37.3%)	60 (46.2%)	
2008–2013	6 (10.2%)	16 (12.3%)	
Diagnosis			0.99[a]
ALL	18 (30.5%)	51 (39.2%)	
AML	1 (1.7%)	3 (2.3%)	
Acute leukemia	1 (1.7%)	1 (0.8%)	
Hodgkin lymphoma	3 (5.1%)	9 (6.9%)	
Non-Hodgkin lymphoma	2 (3.4%)	3 (2.3%)	
Ewing sarcoma/PNET	8 (13.6%)	14 (10.8%)	
Osteosarcoma/malignant fibrous histiosarcoma	4 (6.8%)	9 (6.9%)	
Soft tissue sarcoma/rhabdomyosarcoma	3 (5.1%)	4 (3.1%)	
Neuroblastoma	4 (6.8%)	9 (6.9%)	
Ovarian germ cell tumor	1 (1.7%)	1 (0.8%)	
Retinoblastoma	1 (1.7%)	3 (2.3%)	
Wilm tumor/nephroblastoma	2 (3.4%)	5 (3.8%)	
Brain glioma	7 (11.9%)	13 (10.0%)	
Brain ependymoma	1(1.7%)	1 (0.8%)	
Medulloblastoma/PNET	3 (5.1%)	4 (3.1%)	
Stage			0.057
Localized/regional	23 (39.0%)	56 (43.1%)	
Distant	32 (54.2%)	73 (56.2%)	
Unknown	4 (6.8%)	1 (0.8%)	
Radiation exposure (upfront therapy)			0.41
No	33 (55.9%)	81 (62.3%)	
Yes	26 (44.1%)	49 (37.7%)	
Radiation exposure (progression/relapse)			0.20
No	51 (86.4%)	120 (92.3%)	
Yes	8 (13.6%)	10 (7.7%)	
Cumulative CED			0.13
0	13 (22.0%)	21 (16.2%)	
1–4,000	14 (23.7%)	50 (38.5%)	
4,001+	32 (54.2%)	59 (45.4%)	
Cumulative anthracycline dose			0.68
0	14 (23.7%)	27 (20.8%)	
1–169	15 (25.4%)	41 (31.5%)	
170+	30 (50.8%)	62 (47.7%)	
Cumulative epipodophyllotoxin dose			0.063
0	30 (50.8%)	89 (68.5%)	
1–1,800	11 (18.6%)	14 (10.8%)	
1,801+	18 (30.5%)	27 (20.8%)	
Platinum-based chemotherapy exposure			0.39
No	41 (69.5%)	98 (75.4%)	
Yes	18 (30.5%)	32 (24.6%)	

(Continued on the following column)

Table 1. Demographics, cancer features, treatment factors, and BMI data for cases and controls included in 59 matched sets (Cont'd)

	Cases	Controls	*P*
N	**59**	**130**	
Completed therapy at CHLA			0.80
No	10 (16.9%)	24 (18.5%)	
Yes	49 (83.0%)	106 (81.5%)	
Records available at CHLA until censored			**0.027**
No	27 (45.8%)	38 (29.2%)	
Yes	32 (54.2%)	92 (70.8%)	
Mean BMI Z-score diagnosis (SD)	0.60 (1.34)	0.17 (1.34)	**0.043**
BMI category at diagnosis			0.16
Underweight	3 (5.1%)	12 (9.2%)	
Normal	33 (55.9%)	81 (62.3%)	
Overweight	11 (18.6%)	25 (19.2%)	
Obese	12 (20.3%)	12 (9.2%)	
N	**50**	**108**	
Mean BMI Z-score EOT (SD)	0.39 (1.67)	0.38 (1.50)	0.95
BMI category at EOT			**0.041**
Underweight	5 (10.0%)	8 (7.4%)	
Normal	26 (52.0%)	60 (55.6%)	
Overweight	4 (8.0%)	24 (22.2%)	
Obese	15 (30.0%)	16 (14.4%)	
BMI category change diagnosis to EOT			0.066
Not obese to not obese	33 (66.0%)	89 (82.4%)	
Not obese to obese	6 (12.0%)	10 (9.2%)	
Obese to not obese	2 (4.0%)	3 (2.8%)	
Obese to obese	9 (18.0%)	6 (5.6%)	

NOTE: *P* values for categorical variables were calculated using Pearson χ^2, *P* values for continuous variables derived from Wilcoxon rank sum. Bolded values indicate $P < 0.05$.

[a]Fisher exact test.

disease. Radiotherapy for relapse/progressive disease, chemotherapy exposures, and underlying cancer predisposition syndrome distributions were also similar between cases and controls (Table 1).

Characteristics of SMNs

The median time from primary cancer diagnosis to SMN was 7.5 years (SD 5.6 years, range 0.5–25.3 years). The most common primary cancer was ALL, while the most common SMN was acute myeloid leukemia (AML; Table 2). Whereas thyroid cancer was the second most common SMN, there were no thyroid cancers as first primaries (Table 2).

BMI status

In aggregate unmatched analysis, 19% of all cases and controls combined were overweight, and 12.7% were obese at diagnosis (Table 1). For cases compared with controls, a higher proportion of cases were obese at diagnosis (20.3% vs. 9.2%). The mean BMI Z-score was higher for cases than for controls at the time of diagnosis (0.60 vs. 0.17); however, the groups had similar mean Z-scores at EOT (Table 1). Similarly, compared with controls, a higher proportion of cases were obese at EOT (30.0% vs. 14.4%), and at both diagnosis and EOT (18.0% vs. 5.6%; Table 1).

Relationship of BMI and obesity with development of SMN

Using conditional logistic regression for matched groups, on univariate analysis we found statistically significant associations between SMN and higher pediatric BMI Z-score at diagnosis (OR 1.30; 95% CI, 1.02–1.66; $P = 0.038$), BMI category at diagnosis (OR 2.58 for obese; 95% CI, 1.06–6.38; $P = 0.039$, compared with normal/underweight), and moderate epipodophyllotoxin exposure (OR 2.95; 95% CI, 1.00–8.76; $P = 0.051$

Table 2. Distribution of primary and secondary cancer site/histology for 59 cases by cancer sequence

Cancer site/histology	Primary cancer, *n* (%)	SMN, *n* (%)
ALL	18 (30.5)	3.3 (2)
AML	1 (1.7)	15 (25.4)
Acute leukemia, mixed phenotypic	1 (1.7)	0 (0.0)
Hodgkin lymphoma	3 (5.1)	0 (0.0)
Non-Hodgkin lymphoma	2 (3.3)	1 (1.7)
Brain glioma	7 (11.9)	9 (15.2)
Brain ependymoma	1 (1.7)	0 (0.0)
Medulloblastoma/PNET	3 (5.1)	0 (0.0)
Neuroblastoma	4 (5.6)	0 (0.0)
Ewing sarcoma/PNET	8 (13.6)	4 (6.8)
Osteosarcoma/malignant fibrous histiosarcoma	4 (6.8)	6 (10.1)
Soft tissue sarcoma/rhabdomyosarcoma	3 (5.1)	4 (6.8)
Wilm tumor/nephroblastoma	2 (3.3)	0 (0.0)
Renal cell carcinoma	0 (0.0)	1 (1.7)
Renal papillary adenocarcinoma	0 (0.0)	1 (1.7)
Ovarian germ cell tumor	1 (1.7)	0 (0.0)
Testicular germ cell tumor	0 (0.0)	1 (1.7)
Retinoblastoma	1 (1.7)	0 (0.0)
Thyroid	0 (0.0)	10 (16.9)
Salivary gland carcinoma	0 (0.0)	2 (3.3)
Melanoma	0 (0.0)	1 (1.7)
Rectal adenocarcinoma	0 (0.0)	1 (1.7)
Breast carcinoma	0 (0.0)	1 (1.7)

Table 3. ORs associated with development of SMN based on univariate analysis of matched sets

	N Matched sets	Univariate analysis	
		OR (95% CI)	*P*
BMI Z-score at diagnosis	59	1.30 (1.02–1.66)	**0.038**
BMI category at diagnosis	59		
Normal/underweight		1.00 (Ref)	—
Overweight		1.24 (0.56–2.74)	0.60
Obese		2.58 (1.05–6.38)	**0.039**
Global null hypothesis test		—	*0.12*
BMI Z-score EOT	50	1.06 (0.82–1.36)	0.68
BMI category at EOT	50		
Normal/underweight		1.00 (Ref)	—
Overweight		0.40 (0.10–1.46)	0.16
Obese		2.37 (0.93–6.06)	0.071
Global null hypothesis test		—	***0.033***
BMI category change diagnosis to EOT	50		
Not obese to not obese		1.00 (Ref)	—
Not obese to obese		1.98 (0.60–6.56)	0.26
Obese to not obese		1.34 (0.20–8.90)	0.76
Obese to obese		4.24 (1.35–13.34)	**0.014**
Global null hypothesis test		—	*0.09*
Suspected/confirmed syndrome at primary cancer	59		
No		1.00 (Ref)	—
Yes		2.86 (0.75–10.98)	0.12
Race/ethnicity	59		
Non-Latino white		1.00 (Ref)	—
Black, Latino white, Asian/Pacific Islander, or other		0.68 (0.30–1.54)	0.36
Radiation exposure (progression/relapse)	59		
No		1.00 (Ref)	—
Yes		1.61 (0.53–4.89)	0.40
Cumulative CED	59		
0		1.00 (Ref)	—
1–4,000 mg/m^2		0.31 (0.07–1.33)	0.12
4,001+ mg/m^2		0.58 (0.19–1.78)	0.34
Global null hypothesis test		—	*0.29*
Cumulative anthracycline dose	59		
0		1.00 (Ref)	—
1–169 mg/m^2		1.78 (0.28–11.43)	0.54
170+ mg/m^2		2.16 (0.31–15.16)	0.44
Global null hypothesis test		—	*0.73*
Cumulative epipodophyllotoxin dose	59		
0		1.00 (Ref)	—
1–1,800 mg/m^2		2.95 (1.00–8.76)	0.051
1,801+ mg/m^2		1.99 (0.68–5.83)	0.21
Global null hypothesis test		—	*0.13*
Platinum-based chemotherapy exposure	59		
No		1.00 (Ref)	—
Yes		1.23 (0.38–4.01)	0.73

NOTE: No significant interactions between sex and BMI Z-score at diagnosis, sex and each predictor, BMI category and each predictor, and follow-up time and BMI Z-score at diagnosis. Italicized values indicate *P* values for global null hypothesis testing. Bolded values indicate $P < 0.05$.

for 1–1,800 mg/m^2 compared with 0 mg/m^2; Table 3). There were no associations between race/ethnicity, cumulative CED, cumulative anthracycline dose, or platinum-based chemotherapy exposure and SMN. For the subset of 50 matched groups who had EOT BMI data, there was also an association between BMI category over time and SMN. For patients who were obese at both diagnosis and EOT compared with those who were not obese at both timepoints, the OR for SMN was 4.24 (95% CI, 1.35–13.34; $P = 0.014$; Table 3).

On multivariable analysis, after controlling for epipodophyllotoxin dose (the only treatment factor with association on univariate analysis $P < 0.10$), there were elevated but nonsignificant associations of higher BMI Z-score at diagnosis and higher BMI categories with SMN, but they did not reach statistical significance (Table 4). However, in a multivariable model that included the 50 case–control matched sets with EOT BMI data available, after controlling for epipodophyllotoxin dose, there was a significantly increased risk of SMN for patients who were obese at both diagnosis and EOT compared with those who were not obese at both timepoints [adjusted OR (aOR) 4.44; 95% CI, 1.37–14.34; $P = 0.013$; Table 5]. Those who were not obese at diagnosis and then became obese at EOT had an elevated risk of SMN, although this did not reach statistical significance. Conversely, patients who were obese at diagnosis but not EOT did not display an increased risk of SMN, but the numbers were small (Table 5).

Given the high proportion of AML as SMN in this cohort, we performed subanalyses on case–control sets with SMN limited to AML diagnosis ($n = 15$) and those with SMN excluding AML ($n = 44$) after controlling for epipodophyllotoxin dose. We found similar associations between higher BMI category SMN whether the SMN was AML (BMI Z-score at diagnosis OR 1.24, 95% CI 0.75–2.05, $P = 0.41$; OR for obese 6.00, 95% CI 0.67–53.87, $P = 0.11$ compared with normal/underweight) or excluded AML (BMI Z-score at diagnosis aOR 1.27, 95% CI 0.94–1.73, $P = 0.12$; aOR for obese 2.00, 95% CI 0.60–6.60, $P = 0.26$ compared with normal/underweight).

Discussion

In this case–control study of childhood cancer survivors, we found evidence suggesting that obesity at diagnosis and

Table 4. aORs associated with development of SMN based on multivariable analysis: all matched sets, $n = 59$

	Multivariable model 1		Multivariable model 2	
	aOR (95% CI)	***P***	**aOR (95% CI)**	***P***
BMI Z-score at diagnosis	1.27 (0.99–1.63)	0.06		
BMI category at diagnosis				
Normal/underweight			1.00 (Ref)	—
Overweight			1.25 (0.55–2.82)	0.60
Obese			2.51 (1.00–6.29)	0.05
Global null hypothesis test			—	*0.15*
Cumulative epipodophyllotoxin dose				
0	1.00 (Ref)	—	1.00 (Ref)	—
1–1,800 mg/m^2	2.59 (0.85–7.92)	0.09	2.80 (0.92–8.48)	0.07
1,801+ mg/m^2	2.00 (0.67–5.97)	0.21	2.06 (0.69–6.12)	0.20
Global null hypothesis test	—	*0.21*	—	*0.16*

NOTE: Factors with $P < 0.10$ in univariate analysis included in multivariable model. Italicized values indicate P values for global null hypothesis testing.

EOT might be associated with an increased risk for SMN. After controlling for other patient and treatment factors, the risk for developing SMN was elevated for patients who had been obese or overweight at start of treatment, with indications of greater risk for those who were obese, indicating a potential dose–response relationship with BMI category. Most strikingly, for patients with BMI data available from both diagnosis and EOT, those who had been obese at both timepoints exhibited a significant >4-fold higher risk of SMN compared with those who were not. We observed some indication that among those patients who were obese at diagnosis but not EOT, the degree of risk of SMN was reduced, but the sample size was small. These findings provide a preliminary signal that obesity at diagnosis and EOT might be associated with a predisposition for SMN development among childhood cancer survivors. Even though the underlying mechanism linking obesity during chemoradiotherapy exposure to SMNs has yet to be elucidated, the burgeoning work done examining the relationship between obesity and cancer provide several biological pathways that explain why obese patients may harbor a microenvironment that promotes genetic alterations and cancer cell growth during chemoradiotherapy exposure, including obesity-induced hormonal derangements, heightened inflammation, and altered pharmacodynamics of chemotherapy (34–39). The findings of this study are clinically significant because SMNs are an important source of substantial added morbidity and mortality, and also because obesity is potentially modifiable through targeted interventions.

Our findings add to the growing list of known concerns for obese children treated for cancer, which include poorer disease response, inferior survival, and increased treatment-related toxicity. In a cohort of pediatric leukemia patients, those with higher BMI had increased risk of residual leukemia after induction chemotherapy than their counterparts with normal BMI (32). Similar to the increased risk of residual disease in obese patients, being overweight or obese has also been associated with increased relapse rates in children after treatment for leukemia (32, 33). Obesity and overweight status has also been associated with increased treatment-related toxicity and decreased survival in children with ALL when compared with patients with normal BMI (30, 31, 33, 49).

Excess weight is an important health factor affecting a large proportion of pediatric cancer patients and survivors (25, 27, 37). In our study, which included all invasive cancer diagnoses, 39% of cases and 28% of controls were overweight or obese at the time of diagnosis. Because higher BMI is known to increase the risk for multiple serious late effects and life-limiting comorbidities, such as heart disease, metabolic syndrome, and diabetes (41, 50, 51), our study suggests that SMN should also be

Table 5. aORs associated with development of SMN based on multivariable analysis: all matched sets with data on BMI at EOT, $n = 50$

	Multivariable model 3		Multivariable model 4	
	aOR (95% CI)	***P***	**aOR (95% CI)**	***P***
BMI category at EOT				
Normal/underweight	1.00 (Ref)	—		
Overweight	0.46 (0.12–1.74)	0.25		
Obese	2.65 (0.99–7.09)	0.051		
Global null hypothesis test	—	***0.03***		
BMI category change diagnosis to EOT				
Not obese to not obese			1.00 (Ref)	—
Not obese to obese			2.23 (0.63–7.89)	0.21
Obese to not obese			1.05 (0.15–7.53)	0.96
Obese to obese			4.44 (1.37–14.34)	**0.013**
Global null hypothesis test			—	*0.079*
Cumulative epipodophyllotoxin dose				
0	1.00 (Ref)	—	1.00 (Ref)	—
1–1,800 mg/m^2	2.90 (0.92–9.14)	0.07	3.03 (0.96–9.61)	0.059
1,801+ mg/m^2	1.89 (0.59–6.04)	0.28	2.10 (0.65–6.77)	0.21
Global null hypothesis test	—	*0.19*	—	*0.15*

NOTE: Factors with $P < 0.10$ in univariate analysis included in multivariable model. Bolded values indicate $P < 0.05$. Italicized values indicate P values for global null hypothesis testing.

regarded as another potential obesity-related late-effect among survivors.

In this study, the most common SMN diagnosed was AML, followed by thyroid cancer, and brain glioma. This is in contrast to the Childhood Cancer Survivor Study, the British Childhood Cancer Survivor Study, and the Dutch Childhood Oncology Group Late Effect Registry cohorts of 5-year cancer survivors, which observed that the most frequent SMNs were breast, thyroid, and central nervous system tumors (4, 52, 53). Our study differs from these cohorts in that it included SMN at any time after first cancer diagnosis rather than only after 5 years. In our sample, 22 of the 59 SMNs were diagnosed <5 years from primary cancer diagnosis. For the 37 SMNs diagnosed >5 years from diagnosis, the most common were differentiated thyroid cancer ($n = 9$), brain glioma/astrocytoma ($n = 6$), and AML ($n = 5$); we had no breast cancer cases. This study's shorter duration of median follow-up time and more recent treatment era with reduced chest irradiation may explain the different distributions of SMN cancer types among these different study groups.

Because matching criteria controlled for confounders upfront (including host- and cancer-related factors, which functioned as surrogates for chemotherapy and radiotherapy exposures), the only treatment-related variable that was found to be predictive of SMN in this sample was moderate epipodophyllotoxin dose. Somewhat surprisingly, we did not find that an underlying cancer predisposition syndrome at the time of the first cancer diagnosis was associated with SMN (see Supplementary Table S1 for distribution of underlying predisposition syndrome diagnoses of cases and controls). The overall prevalence of genetic predisposition syndromes has been reported to be 8.5% of pediatric cancer patients (54). This is the same percentage that we found at the time of diagnosis of the primary cancer based on the combination of cases and controls. We identified an additional four cases whose underlying syndrome was not identified until the time of the SMN (and did not code them as having a syndrome at diagnosis to avoid detection bias). However, even when these four cases were included in the multivariable model as having an underlying syndrome, the independent effect of obesity and SMN was unchanged.

Our study has several strengths, including the ability to ascertain comparably matched cases and controls at the registry level, the ability to match to one to three controls to each case on multiple factors to control efficiently for potential confounding factors with a small sample size, all cases and controls receiving treatment at one facility and standardized medical records available from one facility, incorporation of accurate chemotherapy and radiation data into the analysis, absence of recall bias given chart abstraction of an objective exposure variable, minimization of detection bias by following a strict protocol of chart review, and evaluation of BMI category over time. Limitations include a heterogeneous group of primary cancers and SMNs, inability to obtain sufficient BMI data at time of SMN or corresponding censor date, a relatively small sample, and inability to abstract non-CHLA treatment data for patients not followed at CHLA until censor date. Despite the small sample size, we found a consistent association between obesity and SMN that was particularly significant in patients who were obese both at diagnosis and EOT. From this observational study, it appears that obesity at diagnosis and EOT are likely highly correlated. Without interventions in place, patients who are obese at the start of therapy are most likely to be obese at EOT, and likely throughout their lifetimes. While we were unable to control for all potential external environmental and genetic factors that contribute to a patient's BMI category, this study provides support for continuing to study obesity and the effects of weight reduction in survivors of childhood cancer. If these findings are replicated, this would provide important justification for developing strategies to reduce obesity after diagnosis and prevent obesity during cancer treatment. These efforts may be helpful for preventing a variety of obesity-related sequelae in cancer survivors, including SMN.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The ideas and opinions expressed herein are those of the author(s) and do not necessarily reflect the opinions of the State of California, Department of Public Health, the NCI, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors.

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