Overweight in childhood cancer survivors: the Swiss Childhood Cancer Survivor Study

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ABSTRACT

Background: An increased risk of becoming overweight has been reported for childhood cancer survivors (CCSs), in particular leukemia survivors, although the evidence is inconclusive.

Objective: We assessed the prevalence of overweight in CCSs, with a focus on leukemia survivors, compared it with their peers, and determined potential risk factors.

Design: As part of the Swiss Childhood Cancer Survivor Study, we sent a questionnaire between 2007 and 2013 to all Swiss resident CCSs aged <21 y at diagnosis who had survived ≥5 y. We calculated body mass index (BMI) from medical records at diagnosis and self-reported heights and weights at survey. We calculated BMI *z* scores by using Swiss references for children and compared overweight prevalence in CCSs, their siblings, and the general population with the use of the Swiss Health Survey (SHS) and assessed risk factors for being overweight by using multivariable logistic regression.

Results: The study included 2365 CCSs, 819 siblings, and 9591 SHS participants. At survey, at an average of 15 y after diagnosis, the prevalence of overweight in CCSs overall (26%) and in leukemia survivors (26%) was similar to that in siblings (22%) and the general population (25%). Risk factors for being overweight in CCSs were male sex (OR: 1.8; 95% CI: 1.5, 2.1), both young (OR for ages 5–14 y: 1.6; 95% CI: 1.2, 2.3) and older (range—OR for ages 25–29 y: 1.7; 95% CI: 1.2, 2.4; OR for ages 40–45 y: 4.0; 95% CI: 2.5, 6.5) age at study, lower education (OR: 1.4; 95% CI: 1.1, 1.8), migration background (OR: 1.3; 95% CI: 1.1, 1.7), and no sports participation (OR: 1.4; 95% CI: 1.1, 1.7). Risk factors for overweight were similar in peers. CCSs treated with cranial radiotherapy (≥20 Gy) were more likely to be overweight than their peers (OR: 1.6; 95% CI: 1.2, 2.2).

Conclusions: The prevalence of and risk factors for being overweight are similar in long-term CCSs and their peers. This suggests that prevention methods can be the same as in the general population. An important exception is CCSs treated with cranial radiotherapy ≥20 Gy who may need extra attention during follow-up care. This study was registered at clinicaltrials.gov as NCT03297034. *Am J Clin Nutr* 2018;107:3–11.

Keywords: overweight, obesity, late effects, childhood cancer survivors, leukemia, Swiss Childhood Cancer Registry, Europe

INTRODUCTION

Overweight and obesity are well-known risk factors for chronic diseases, such as diabetes, dyslipidemia, hypertension, and cardiovascular disease (1). Fortunately, these risk factors are modifiable: primary- and secondary-prevention methods can reduce morbidity and mortality. Childhood cancer survivors (CCSs) already have an elevated burden of chronic diseases due to cancer treatment, which increases with age (2, 3). It is thus important to avoid additional, preventable risk factors such as obesity by identifying CCSs at high risk and offering them targeted interventions.

Whether CCSs are more overweight in the long term after treatment is not clear. Two meta-analyses suggested that obesity

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Supplemental Figure 1 and Supplemental Tables 1–5 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: ALL, acute lymphoblastic leukemia; CCS, childhood cancer survivor; CNS, central nervous system; CRT, cranial radiation therapy; SCCR, Swiss Childhood Cancer Registry; SCCSS, Swiss Childhood Cancer Survivor Study; SHS, Swiss Health Survey.

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was more common in childhood acute lymphoblastic leukemia (ALL) survivors within 5 y of treatment (BMI *z* score: 0.89), but obesity diminished 5–9 y post-treatment (BMI *z* score: 0.64) compared with their healthy peers (4, 5). Results are inconclusive for those ≥10 y post-treatment, although overweight prevalence (34–46%) in these long-term ALL survivors seemed to be similar to that in noncancer comparison groups (4). Risk factors for overweight in the general population are sedentary lifestyle, low (≤2.5 kg) and high (>4 kg) birth weights (6, 7), and overweight during early childhood (8). In CCSs, most risk factors were the same as in the general population, but no study has considered birth weight. ALL and lymphoma survivors who were overweight at diagnosis were substantially more likely to be overweight or obese 12 y after treatment (9). The same was true for cranial radiation therapy (CRT); ALL survivors treated with CRT were more likely to be overweight or obese than their siblings 21–25 y after diagnosis (10, 11).

Studies of overweight conducted to date have been of somewhat limited relevance to CCSs. Research on overweight prevalence has involved mostly ALL survivors (9–19), whereas study of risk factors has led to inconsistent conclusions (4). Studies conducted in the United States reflect the lifestyles and eating habits of CSSs in that country (10–13, 16, 17, 19–22), whereas the duration of follow-up in other studies has been only short to medium term (4, 5), and many have had small (<250 participants) sample sizes (4, 11, 13–15, 17–19). With this background of research in mind, we analyzed data from the Swiss Childhood Cancer Survivor Study (SCCSS) to *1*) assess overweight prevalence in CCSs overall and for specific, different diagnoses; *2*) compare overweight prevalence in CCSs with that in their siblings and the Swiss general population; and *3*) identify sociodemographic and clinical risk factors for excessive weight.

METHODS

Study populations

The SCCSS

The SCCSS is a population-based, long-term follow-up study in all childhood cancer patients registered in the Swiss Childhood Cancer Registry (SCCR; available from: www.childhoodcancerregistry.ch) who have been diagnosed with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis; who survived ≥5 y after initial diagnosis of cancer; who were under the age of 21 y; and who were alive at the time of the study (23–25). Ethical approval of the SCCR and the SCCSS was granted by the Ethics Committee of the Canton of Bern (KEK-BE: 166/2014). This study was registered at clinicaltrials.gov as NCT03297034.

As part of the SCCSS, we traced all addresses of CCSs diagnosed between 1976 and 2005 and sent them a questionnaire between 2007 and 2013. Nonresponders received a second copy of the questionnaire 4–6 wk later. If they again did not respond, we contacted them by phone. Our questionnaire included core questions from the US and UK CCS studies (26, 27), with added questions about health behaviors and sociodemographic measures from the Swiss Health Survey (SHS) (28) and the Swiss Census (29). The main domains covered by the questionnaire were quality of life, somatic health, fertility, current medication and health services use, psychological distress, health behaviors, and socioeconomic status. Detailed information on our study design was published previously (23).

Comparison groups

We used 2 comparison groups for this study: siblings of the CCSs and a random sample of the general Swiss population represented by data from the SHS. The sibling survey was conducted from 2009 to 2012. We asked CCSs for consent to contact siblings and for their contact information. We sent siblings the same questionnaire as CCSs, omitting questions about cancer history. Siblings who did not respond received another copy of the questionnaire 4–6 wk later, but were not contacted by phone (23). The second comparison group consisted of participants in the 2012 SHS (30). The SHS is a representative national telephone survey repeated every 5 y. The SHS compiled a randomly selected representative sample of Swiss households with landline telephones and attempted to contact 1 person/household. Sampling was stratified by region and conducted in a stepwise manner. Households were selected first, and then the survey was administered to anyone aged ≥15 y who answered the phone.

Measurements

Body weight and BMI

We obtained information on participants' weight and height. For all CCSs and both comparison groups, we had information on weight and height at time of survey from the self-administered questionnaires. Study participants were instructed to record height without shoes and weight without clothes. For leukemia survivors diagnosed between 1990 and 2005 and treated in a specialized pediatric cancer clinic, we also had information on weight and height at diagnosis and at birth. Weight and height at diagnosis were obtained via a retrospective medical record audit. We obtained 98% of birth weights by using a probabilistic linkage procedure (G-LINK 2.3; Statistics Canada) to link CCSs and anonymous birth statistics with no personal identifiers, which was collected by the Swiss Federal Statistical Office. Information on sex, date of birth, first name, nationality, municipality of residence at birth, and parental birth dates was used for linking. The remaining birth weights (2%) were obtained from medical records. We calculated BMI by dividing weight in kilograms by height in meters squared (kg/m^2). BMI in adults was classified as underweight (<18.5), normal weight (≥18.5 to <25), or overweight (≥25) (1). As recommended for children aged ≤19 y, we calculated BMI *z* scores by using the latest available Swiss growth curves (31). BMI *z* scores were classified as underweight (<–2), normal weight (–2 to 1), or overweight (>1 for age >5 y, >2 for age ≤5 y) (32). Birth weight was classified into 3 categories: low (<2500 g), normal (2500–4000 g), and high (>4000 g) (33).

Risk factors for being overweight at time of survey

For all 3 study populations, we assessed sex, age at survey, educational level, migration background, language region in Switzerland, and participation in sports at time of survey as potential sociodemographic risk factors for being overweight. Participants who were not Swiss citizens at birth, not born in Switzerland, or had ≥1 parent who was not a Swiss citizen were classified

as having a migration background. We classified education into 3 categories: primary education (compulsory schooling only; ≤9 y), secondary education (vocational training; 10–13 y), and tertiary education (higher vocational training, college, or university degree). Sports participation was classified as sports if respondents reported engaging in a specific gym or sports activity for ≥1/wk, or no sports with less or no such participation.

For the CCS population, we extracted additional clinical information from the SCCR. This included information on cancer diagnosis and age at diagnosis. Diagnosis was classified according to the *International Classification of Childhood Cancer, 3rd Edition* (34). Radiotherapy was classified as CRT if the survivor had received direct radiation to the brain, skull, or both. The cumulative dosage of CRT was obtained from medical records and categorized as either <20 Gy or ≥20 Gy. We also retrieved records on hematopoietic stem cell transplantation, chemotherapy, and relapse during follow-up time.

Statistical analyses

We included all participants in the SCCSS (CCSs and their siblings) and the SHS (general population) who were aged ≤45 y at time of survey and who provided self-reported height and weight (**Supplemental Figure 1**). For better comparison between CCSs and peers, we standardized comparison groups for sex, age at survey, migration background, and language region, as previously described (35–37). The first step in our analyses was to assess the overall prevalence of overweight in CSSs at survey and stratify diagnostic groups. We divided BMI into 2 categories: overweight (overweight and obesity) and nonoverweight (underweight and normal weight) as separate categories were small and logistic regression outcomes for the categories of overweight and obesity were in the same direction and magnitude as for the category of overweight or obesity combined. We then compared the prevalence of overweight between CCSs and comparison groups by using chi-square tests. Finally, we determined risk factors for being overweight at survey within each group separately by using multivariable logistic regression. We identified potential sociodemographic, lifestyle, and clinical risk factors and included them in uni- and multivariable logistic regressions. To test for statistical significance, we used likelihood ratio tests for unstandardized groups and Wald tests for standardized groups. We investigated whether birth weight and BMI at diagnosis were additional risk factors for overweight at survey in a subgroup of leukemia survivors who had been diagnosed between 1990 and 2005. Interaction terms were used to formally test differences in effects of risk factors between CCSs and comparison groups. We also included both CCSs and comparison groups in multivariable logistic regression models to investigate whether the risk of being overweight was similar between groups stratified for CRT. We used Stata software (version 14; StataCorp) for all statistical analysis.

RESULTS

Response rate and characteristics of the study populations

Among 4116 eligible CCSs, we traced and contacted 3577, of whom 2527 returned a questionnaire. We excluded 119 questionnaires that did not report height and weight, and a further 43 from survivors who were >45 y old. We thus included 2365 CCSs in this study, of whom 770 were leukemia survivors and 461 of whom were diagnosed between 1990 and 2005 (Supplemental Figure 1). We received consent to contact 1530 siblings, of whom 866 returned the questionnaire. Twenty-seven were outside the age range and 20 did not report height and weight; thus, 819 siblings were finally included in the analyses. Of 41,008 households surveyed in the general population (SHS), 21,597 households replied to the survey. In those responding households, 9591 persons who were ≤45 y old were included in the analysis.

Among CCSs, the most common cancers were leukemia (predominantly ALL; 88%), lymphoma, and CNS and renal tumors (**Table 1**). The median age at diagnosis was 7 y (IQR: 3–12 y) for CCSs overall and 5 y (IQR: 3–9 y) for leukemia. The median time from diagnosis to survey was 15 y (IQR: 10–21 y) for CCSs overall and 16 y (IQR: 11–22 y) for leukemia survivors. Most leukemia survivors received chemotherapy. Among the subgroup of leukemia survivors diagnosed between 1990 and 2005, 10%

TABLE 1
Clinical characteristics of CCSs and childhood leukemia survivors[1]

	CCSs ($n = 2365$)	Leukemia survivors ($n = 770$)
Characteristics		
ICCC3 diagnosis, *n* (%)		
I: Leukemia	770 (33)	770 (100)
II: Lymphoma	424 (18)	—
III: CNS neoplasm	341 (14)	—
IV: Neuroblastoma	118 (5)	—
V: Retinoblastoma	72 (3)	—
VI: Renal tumor	144 (6)	—
VII: Hepatic tumor	20 (1)	—
VIII: Malignant bone tumor	96 (4)	—
IX: Soft tissue sarcoma	137 (6)	—
X: Germ cell tumor	106 (4)	—
XI and XII: Other tumor	54 (2)	—
Langerhans cell histiocytosis	83 (4)	—
Age at diagnosis, *n* (%)		
<5 y	1413 (60)	389 (51)
≥5 y	952 (40)	381 (49)
Year of diagnosis, *n* (%)		
Before 1990	762 (32)	291 (38)
1990–2000	977 (41)	299 (39)
After 2000	626 (26)	180 (23)
Time since diagnosis,[2] y	15.0 (10.0–20.9)	15.6 (10.7–22.0)
Chemotherapy,[3] *n* (%)		
No	509 (22)	—
Yes	1856 (78)	767 (100)
CRT, *n* (%)		
None	1950 (82)	599 (78)
<20 Gy	157 (7)	95 (12)
≥20 Gy	258 (11)	76 (10)
HSCT, *n* (%)		
No	2248 (95)	709 (92)
Yes	117 (5)	61 (8)
History of relapse, *n* (%)		
No	2081 (88)	670 (87)
Yes	284 (12)	100 (13)

[1]CCS, childhood cancer survivor; CNS, central nervous system; CRT, cranial radiation therapy; HSCT, hematopoietic stem cell transplantation; ICCC3, *International Classification of Childhood Cancer, 3rd edition*.
[2]Values are medians (IQRs).
[3]$n = 3$ missing (<1%).

TABLE 2
General characteristics of CCSs and comparison groups[1]

Characteristics	CCSs, *n* (%)		Siblings[2] (*n* = 819)		General population[2] (*n* = 9591)	
	CCSs (*n* = 2365)	Leukemia (*n* = 770)	*n* (%std)	*P*[3]	*n* (%std)	*P*[3]
Sex, *n* (%)				NA		NA
Female	1086 (46)	367 (48)	473 (45)		4946 (46)	
Male	1279 (54)	403 (52)	346 (55)		4645 (54)	
Age at survey, *n* (%)				NA		NA
5–14 y	329 (14)	121 (16)	94 (18)		—	
15–19 y	541 (23)	184 (24)	142 (20)		1518 (33)	
20–24 y	530 (22)	167 (22)	162 (19)		1440 (23)	
25–29 y	401 (17)	136 (18)	168 (19)		1174 (13)	
30–34 y	277 (12)	87 (11)	115 (12)		1424 (11)	
35–39 y	185 (8)	47 (6)	84 (8)		1601 (9)	
40–45 y	102 (4)	28 (4)	54 (5)		2434 (10)	
Parents' education (highest degree),[4] *n* (%)				0.007	NA	NA
Primary schooling	62 (7)	26 (9)	8 (3)			
Secondary education	469 (54)	165 (54)	115 (47)			
Tertiary education	339 (39)	114 (37)	113 (50)			
Personal education,[5] *n* (%)				<0.001		<0.001
Primary schooling	117 (8)	36 (8)	24 (4)		691 (8)	
Secondary education	1010 (68)	337 (72)	359 (61)		4549 (62)	
Tertiary education	368 (25)	92 (20)	200 (35)		2833 (30)	
Migration, *n* (%)				NA		NA
No migration background	1762 (75)	573 (74)	657 (75)		6137 (77)	
Migration background	603 (26)	197 (26)	162 (25)		3454 (23)	
Language region of Switzerland, *n* (%)				NA		NA
German-speaking	1658 (70)	571 (74)	650 (70)		6300 (70)	
French-speaking	630 (27)	172 (22)	143 (27)		2620 (27)	
Italian-speaking	77 (3)	27 (4)	26 (3)		671 (3)	
Sports participation, *n* (%)				0.002		<0.001
Yes	1623 (69)	544 (71)	593 (75)		5598 (64)	
No	742 (31)	226 (29)	226 (25)		3993 (36)	
BMI at survey,[6] *n* (%)				<0.001		<0.001
Underweight	127 (5)	43 (6)	20 (2)		349 (3)	
Normal	1632 (69)	525 (68)	602 (76)		6354 (72)	
Overweight	606 (26)	202 (26)	197 (22)		2888 (25)	

[1]CCS, childhood cancer survivor; NA, not applicable; std, standardized.
[2]Standardized on sex, age at survey, migration background, and language region according to CCSs.
[3]*P* values were calculated from chi-square statistics comparing comparison groups to CCSs (2-sided test).
[4]Highest parental educational level of CCSs and siblings aged <20 y at time of survey.
[5]Highest personal educational level of CCSs, siblings, and the general population aged ≥20 y at time of survey.
[6]BMI *z* scores were calculated for CCSs, siblings, and the general population aged ≤19 y; BMI scores (kg/m^2) were calculated for adults (aged >19 y).

had a high birth weight and 6% were overweight at diagnosis (**Supplemental Table 1**).

Sociodemographic characteristics were mostly identical across CCSs and the comparison groups. Fewer CCSs than siblings had parents who completed tertiary education, however, and the educational level of CCSs was slightly lower than that of their peers (**Table 2**). CCSs engaged in fewer sports than their siblings but more than the general population.

Overweight prevalence among CCSs and comparison groups

Overall, the prevalence of overweight among CCSs was 26% (median BMI in those aged >19 y: 27; IQR: 26–30; median BMI *z* score in those aged ≤19 y: 1; IQR: 1–2), which was similar to overweight prevalence in the comparison groups: 22% in siblings ($P = 0.07$; median BMI in those aged >19 y: 27; IQR: 26–29; median BMI *z* score in those aged ≤19 y: 1; IQR: 1–2), 25% in the general population ($P = 0.64$; median BMI in those aged >19 y: 27; IQR: 26–29; median BMI *z* score in those aged ≤19 y: 1; IQR: 1–2). However, CCS diagnostic groups differed: 31% of CNS neoplasm survivors were overweight, whereas only 13% of neuroblastoma and 18% of soft tissue sarcoma survivors were overweight; the prevalence differences were significant ($P < 0.001$, $P < 0.001$, and $P = 0.04$, respectively; **Figure 1**). The prevalence of overweight in leukemia survivors (26%) was similar to the average of all CCSs.

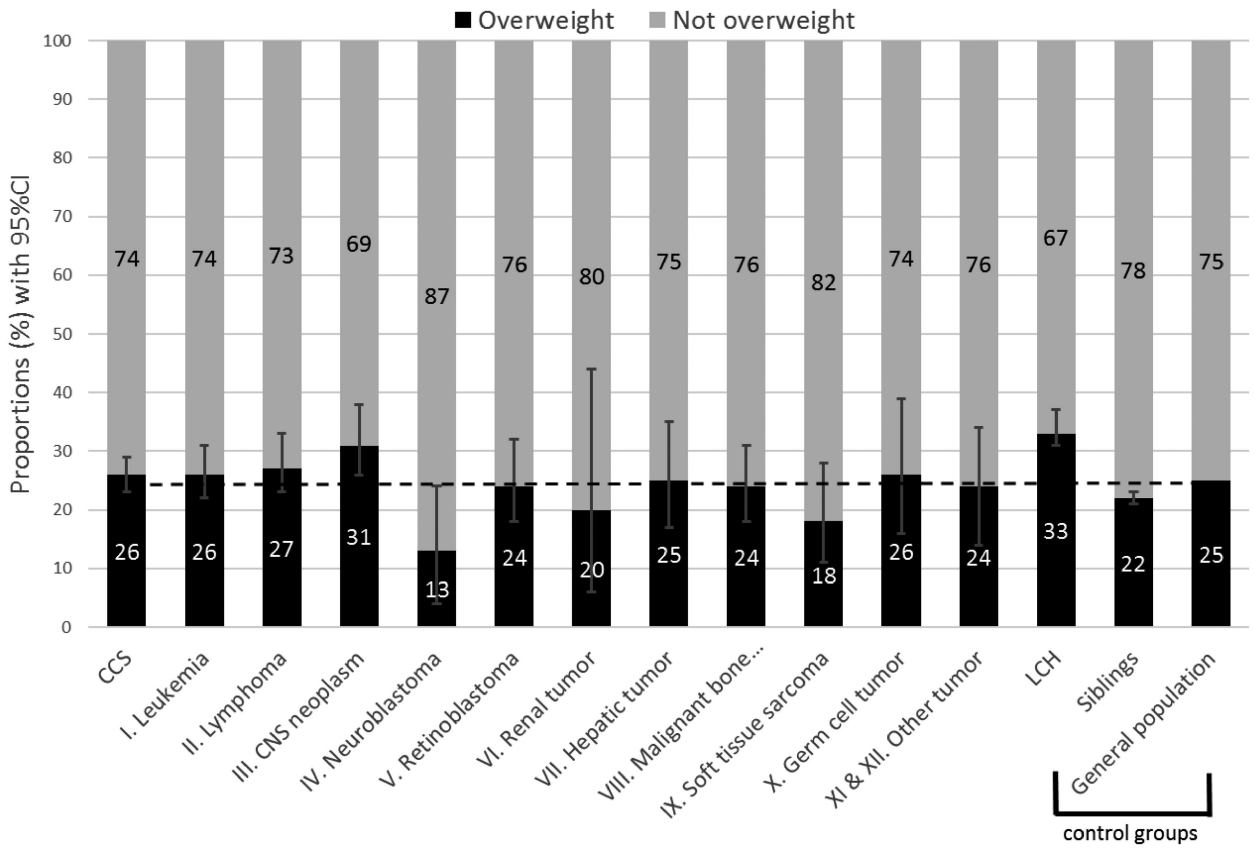

FIGURE 1 Overweight in childhood cancer survivors and comparison groups. The BMI distribution of comparison groups is standardized on sex, age at survey, migration background, and language region according to childhood cancer survivors. The dotted line reflects the overweight prevalence of the general population. CCS, childhood cancer survivors; CNS, central nervous system; LCH, Langerhans cell histiocytosis; Malignant bone..., malignant bone tumor.

Risk factors for being overweight among CCSs and comparison groups

In a multivariable regression, we found associations between all sociodemographic factors and being overweight. In all 3 study populations, male participants, those who were older at survey, and those who did not take part in sports activities were more likely to be overweight (**Table 3**). Also associated with being overweight were lower education (CCSs, leukemia survivors), migration background (CCSs, the general population), and living in the German-speaking part of Switzerland (siblings, the general population). Results of univariable logistic regression are shown in **Supplemental Table 2**.

Interaction tests (**Supplemental Table 3**) showed that most effects of sociodemographic factors did not differ between CCSs and the comparison groups (all P-interaction ≥ 0.05), suggesting that the direction and strength of the associations between these risk factors and overweight were similar. The only difference was the effect of sex, which was weaker in CCSs (OR: 1.7; 95% CI: 1.45, 2.14) than in the general population (OR: 2.42; 95% CI: 2.16, 2.71; Table 3, Supplemental Table 3). Among clinical factors, only ≥20 Gy CRT was associated with overweight. After combining all diagnostic groups, we saw that CCSs who received ≥20 Gy CRT, of whom 29% were diagnosed with leukemia and 45% with CNS neoplasms, were around 1.5 times more likely to be overweight in comparison to their peers (OR for CCSs compared with siblings: 1.5; 95% CI: 1.1, 2.2; OR for CCSs compared with the general population: 1.6; 95% CI: 1.2, 2.2; **Figure 2**).

We found no association between being overweight at survey and birth weight ($P = 0.523$) in a subgroup of 461 leukemia survivors diagnosed between 1990 and 2005. However, being overweight at diagnosis was associated with being overweight at survey (OR: 9.86; 95% CI: 3.97, 24.51) (**Supplemental Table 4**). Results of univariable logistic regression are shown in **Supplemental Table 5**. Of 27 leukemia survivors who were overweight at diagnosis, 18 (67%) remained overweight at survey.

DISCUSSION

Principal findings

At a median of 15 y after cancer diagnosis, 26% of all CCSs were overweight. This prevalence is comparable to that of their healthy peers, but there were differences between diagnostic groups. Survivors of CNS neoplasms were most likely to be overweight, whereas survivors of neuroblastoma and soft tissue sarcoma were least likely to be overweight. Sociodemographic factors for being overweight were similar in CCSs, their siblings, and the general population. Among clinical factors, we confirmed that receiving ≥20 Gy CRT was associated with being overweight.

Strengths and limitations

Height and weight at survey were self-reported; both under- and overreporting could have occurred. However, because height

TABLE 3
Overweight prevalence and risk factors associated with overweight in CCSs or comparison groups (from multivariable logistic regression)[1]

	CCSs											
	CCSs ($n = 2365$)			Leukemia ($n = 770$)			Siblings[2] ($n = 819$)			General population[2] ($n = 9591$)		
Sociodemographic characteristics	Overweight, %	OR (95% CI)	P[3]	Overweight, %	OR (95% CI)	P[3]	Overweight, %	OR (95% CI)	P[4]	Overweight, %	OR (95% CI)	P[4]
Sex			<0.001			<0.001			<0.001			<0.001
Female	20	1.00 (ref)		20	1.00 (ref)		17	1.00 (ref)		17	1.00 (ref)	
Male	30	1.76 (1.45, 2.14)		32	1.95 (1.38, 2.76)		27	2.20 (1.51, 3.18)		32	2.42 (2.16, 2.71)	
Age at survey			<0.001			<0.001			<0.001			<0.001
5–14 y	25	1.64 (1.16, 2.32)		29	2.05 (1.16, 3.64)		12	1.48 (0.65, 3.36)		—	—	
15–19 y	17	1.00 (ref)		16	1.00 (ref)		11	1.00 (ref)		16	1.00 (ref)	
20–24 y	21	1.30 (0.94, 1.78)		21	1.25 (0.71, 2.20)		20	2.17 (1.07, 4.40)		23	1.58 (1.30, 1.92)	
25–29 y	25	1.71 (1.24, 2.38)		23	1.62 (0.90, 2.90)		25	2.87 (1.49, 5.54)		28	2.07 (1.70, 2.52)	
30–34 y	34	2.76 (1.94, 3.91)		40	3.64 (1.97, 6.70)		34	4.64 (2.33, 9.25)		31	2.39 (1.98, 2.88)	
35–39 y	43	3.80 (2.58, 5.60)		53	6.13 (2.94, 12.78)		43	7.04 (3.40, 14.58)		37	3.00 (2.50, 3.60)	
40–45 y	41	4.03 (2.50, 6.48)		39	3.81 (1.54, 9.42)		46	8.53 (3.65, 19.94)		41	3.73 (3.15, 4.42)	
Age at diagnosis			0.107			0.161	NA	NA		NA	NA	
≥5 y	26	1.00 (ref)		26	1.00 (ref)							
<5 y	25	1.20 (0.96, 1.49)		27	1.29 (0.90, 1.86)							
Education[5]			0.008			0.010			0.268	NA	NA	
Primary schooling	28	1.45 (0.98, 2.15)		31	2.06 (1.03, 4.12)		31	1.75 (0.65, 4.72)				
Secondary education	27	1.42 (1.13, 1.78)		29	1.88 (1.22, 2.89)		24	1.36 (0.90, 2.05)				
Tertiary education	22	1.00 (ref)		18	1.00 (ref)		19	1.00 (ref)				
Migration			0.011			0.368			0.189			<0.001
No migration background	25	1.00 (ref)		26	1.00 (ref)		22	1.00 (ref)		23	1.00 (ref)	
Migration background	29	1.34 (1.07, 1.68)		27	1.21 (0.80, 1.81)		23	1.37 (0.86, 2.18)		31	1.34 (1.19, 1.50)	
Language region of Switzerland			0.287			0.638			0.017			0.019
German-speaking	26	1.00 (ref)		27	1.00 (ref)		25	1.00 (ref)		26	1.00 (ref)	
French-speaking	24	0.84 (0.67, 1.05)		25	0.95 (0.63, 1.44)		16	0.46 (0.27, 0.79)		23	0.85 (0.74, 0.96)	
Italian-speaking	25	0.94 (0.55, 1.63)		19	0.62 (0.22, 1.74)		18	0.69 (0.19, 2.46)		24	0.84 (0.67, 1.04)	
Sports participation			0.004			0.427			0.002			<0.001
Yes	23	1.00 (ref)		24	1.00 (ref)		19	1.00 (ref)		23	1.00 (ref)	
No	31	1.35 (1.10, 1.66)		31	1.17 (0.80, 1.70)		34	1.90 (1.27, 2.85)		30	1.42 (1.27, 1.60)	

[1]CCS, childhood cancer survivor; NA, not applicable; ref, reference.
[2]Standardized on sex, age at survey, migration background, and language region according to CCSs; multivariable logistic regressions are shown separately for each study population.
[3]P values were calculated from likelihood ratio tests.
[4]Global P values for an association between prevalence of overweight/obesity and the variables as a whole (Wald test comparing models with and without the variable).
[5]Highest parental (aged <20 y at time at survey) or personal (aged ≥20 y at time of survey) education.

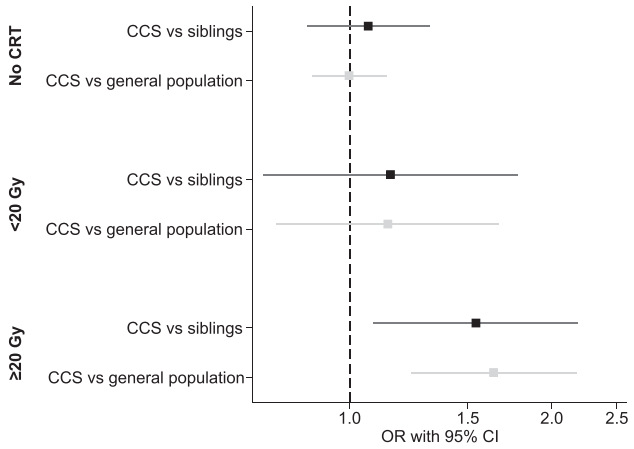

FIGURE 2 CRT-specific ORs (95% CIs) for overweight in childhood cancer survivors and comparison groups (from multivariable logistic regression). Both comparison groups were standardized on sex, age at survey, migration background, and language region according to childhood cancer survivors. Values were adjusted for sex, age, education, migration background, language region of Switzerland, and sports participation. CCS, childhood cancer survivors; CRT, cranial radiation therapy; Gy, Gray.

and weight were self-reported in all study populations we expected the degree of nondifferential error of BMI assessment to be similar across CCSs and comparison groups. BMI calculations are practical and inexpensive measures of overweight and are therefore widely used in population-based studies, and BMI values derived from self-reported height and weight can be as reliable as measured values in the estimation of health risks (38). The prevalence of overweight might be underestimated because having a higher BMI at diagnosis is associated with poorer survival. This could have resulted in excluding more overweight CCSs due to our exclusion criteria of ≥5 y of survival after initial diagnosis of cancer (39). Furthermore, our results could have been biased by reverse causation (e.g., a lack of sports participation could have been due to overweight).

Long-term follow-up is a strength of this study, as are the national coverage of the SCCSS and our high CCS response rate, which makes this the largest such study in Europe to date. We also had access to high-quality clinical information extracted from the SCCR, including extended information about clinical factors, birth weight, and height and weight at diagnosis for a large subgroup of leukemia patients. The questionnaire also allowed us to assess a wide variety of sociodemographic factors. Finally, we included not 1 but 2 comparison groups: siblings of CCSs (who share environmental factors with CCSs) and the general population with data derived from a population-based study performed simultaneously in Switzerland.

Overweight prevalence: results in relation to other studies

Studies investigating overweight or obesity among CCSs other than ALL survivors are scarce. Meta-analyses have suggested that overweight or obesity is common among short-term ALL survivors who are still in childhood or early adolescence compared with reference populations (4, 5), and potentially increased among late-adolescent and adult long-term ALL survivors aged ≥15 y at survey (40). In our study, the prevalence of overweight among CCSs overall and leukemia survivors was similar to that in the general population but increased for CNS neoplasms. CNS neoplasm survivors are exposed to several risk factors (e.g., CRT, hypothalamic tumors, and surgical damage) that might lead to hypothalamic obesity, and more research on adequate management is needed (41, 42).

A contributor to differences in overweight prevalence between our results and those of pertinent studies across the literature included in meta-analyses may be the lack of detailed treatment information on CRT and dose-dependent associations with overweight in those studies. Our findings do agree with those of a recent US-based study in 14,290 CCSs [median of 24 y (5–39 y) after diagnosis] and 4031 siblings in which self-reported obesity in CCSs and siblings was similar to our results, and the 4100 survivors treated with ≥18 Gy of CRT were more likely to be obese (20). In contrast, a study in 7195 survivors of a variety of cancer types ≥5 y after diagnosis reported underweight in CCSs treated for different cancers, including neuroblastoma and soft tissue sarcoma, when compared with the general population (22), and an increased likelihood of obesity was observed in both male and female ALL survivors who received CRT ≥20 Gy (12, 22).

Potential mechanisms and risk factors: results in relation to other studies

CRT affects the hypothalamic-pituitary axis, which may lead to growth hormone deficiency and leptin insensitivity, which could, in turn, place CCSs at risk of neuroendocrine abnormalities such as obesity (13). However, previous studies of overweight in CCSs and CRT have shown mixed results that vary from weak to strong associations (4). Older studies usually showed a clear association between overweight and CRT (9, 10, 12, 14), whereas those with children treated more recently with no or lower-dose CRT have shown a smaller effect (15–17, 43). We found an association only between ≥20 Gy CRT and overweight. Overall, CCSs and leukemia survivors treated with ≥20 Gy CRT were more likely to be overweight, which suggests that ≥20 Gy CRT is a risk factor for obesity in all CCSs irrespective of the diagnosis. The positive association between CRT and obesity has also been seen in adult survivors of a variety of different childhood cancer types (22, 44). Although CRT was not stratified by dose amount, survivors in these studies were diagnosed between 1970–1986 (22) and 1966–1996 (44), and the majority might have received high-dose CRT.

Female sex also has been reported as a risk factor for obesity in ALL adult survivors (10, 12, 22). We could not confirm this. On the contrary, we found that men were more likely to be overweight or obese. This was the same in our comparison groups. Two systematic reviews on overweight in CCSs published in 2014 and 2015 reported no conclusive effect due to sex (4, 5). This suggests that sex differences mainly reflect social and cultural differences. We also found that leukemia survivors who are overweight at diagnosis have a substantially higher risk of being overweight later in life. This is in line with previous observations of survivors of leukemia (11, 17–19) and other childhood cancers (44) and the general population, in all of whom overweight tends to track strongly throughout life (45). As in our study, others have found that more than two-thirds of ALL survivors who were overweight at diagnosis remained overweight at the end of, or after, treatment (18, 19).

Implications and recommendations

Overweight and obesity are associated with chronic diseases that are frequently seen among CCSs, such as type 2 diabetes and cardiovascular disease (46, 47). Poor diet and a sedentary lifestyle could further increase these already elevated risks. Personal counseling should be offered to childhood cancer patients and their parents throughout treatment and beyond, and special attention should be given to patients with an increased BMI (48). However, counseling during this period, when patients and families face the crisis of a life-threatening illness and nutritional status is not a first priority, is challenging. In addition, children may receive high steroid doses, which increase appetite and fatty tissue, and they may experience fatigue or be immobilized for some time, which reduces their physical activity. During clinical follow-up, special attention should focus on CNS tumor and leukemia survivors treated with ≥20 Gy CRT, who have the highest risk of becoming overweight. Follow-up services with multi-profession teams, including physicians, dieticians, nurses, and physiotherapists, might be a promising approach.

Conclusions

This national survey in Switzerland found that the prevalence of and risk factors for overweight were similar in CCSs overall and in healthy peers, suggesting that prevention methods and interventions can be the same as in the general population. Important exceptions are CCSs treated with ≥20 Gy CRT who may need extra attention during follow-up care.

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