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Journal: The American journal of clinical nutrition

Year: 2018 Jan 1

Issue: 107

Volume: 1

Pages: 3-11

DOI: 10.1093/ajcn/nqx006

TITLE PAGE

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

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Sources of support: This study is supported by the Swiss Cancer Research (KLS-3412-02-2014, and KLS-3644-02-2015) and the Foundation Force, CHUV, Lausanne, Switzerland. The work of the Swiss Childhood Cancer Registry is supported by the Swiss Pediatric Oncology Group (www.spog.ch), Schweizerische Konferenz der kantonalen Gesundheitsdirektorinnen und –direktoren (www.gdk-cds.ch), Swiss Cancer Research (www.krebsforschung.ch), Kinderkrebshilfe Schweiz (www.kinderkrebshilfe.ch), the Federal Office of Health (FOH), and the National Institute of Cancer Epidemiology and Registration (www.nicer.org). MG is supported by national funding from the Swiss National Science Foundation (SNF320030_173044).

Short running head: Overweight in Childhood Cancer Survivors

Abbreviations: ALL, acute lymphoblastic leukemia; BMI, body mass index; CCS, childhood cancer survivors; CI, confidence interval; CNS, central nervous system; CRT, cranial radiation therapy; Dx, diagnosis; Gy, gray; HSCT, hematopoietic stem cell transplantation; ICCC-3, International Classification of Childhood Cancer, 3rd edition; IQR, interquartile range; OR, odds ratio; SCCR, Swiss Childhood Cancer Registry; SCCSS, Swiss Childhood Cancer Survivor Study; SHS, Swiss Health Survey

ClinicalTrials.gov identifier: NCT03297034

ABSTRACT

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

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

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

Results: The study included 2,365 CCS, 819 siblings, and 9,591 SHS participants. At survey, on average 15 years after diagnosis, overweight prevalence in CCS overall (26%) and in leukemia survivors (26%) was similar to that of siblings (22%) and the general population (25%). Risk factors for being overweight in CCS were male sex (OR=1.8, 95%CI 1.5, 2.1), both young ($OR_{5\text{-}14yrs}$=1.6, 1.2, 2.3) and older age at study (range $OR_{25\text{-}29yrs}$=1.7, 1.2, 2.4; $OR_{40\text{-}45yrs}$=4.0, 2.5, 6.5), lower education (OR=1.4, 1.1, 1.8), migration background (OR=1.3, 1.1, 1.7), and no sports participation (OR=1.4, 1.1, 1.7). Risk factors for overweight were similar in peers. CCS treated with cranial radiotherapy (≥20 gray) were more likely to be overweight than their peers (OR=1.6, 1.2, 2.2).

Conclusion: Prevalence and risk factors for being overweight are similar in long-term CCS and their peers. This suggests that prevention methods can be the same as in the general population. An important exception is CCS treated with cranial radiotherapy ≥20 gray who may need extra attention during follow-up care.

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 (CCS) already have an elevated burden of chronic diseases due to cancer treatment, which rises with age (2, 3). It is thus important to avoid additional, preventable risk factors like obesity by identifying CCS at high risk and offering them targeted interventions.

Whether CCS are more overweight in the long term after treatment is not clear. Two meta-analyses suggested that obesity was more common in childhood acute lymphoblastic leukemia (ALL) survivors within five years of treatment (BMI z-score, 0.89), but obesity diminished 5–9 years post-treatment (BMI z-score, 0.64) compared to healthy peers (4, 5). Results are inconclusive for those ≥10 years 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 CCS most risk factors were the same as in the general population, but no study has considered birth weight. ALL and lymphoma survivors who have been overweight at diagnosis were substantially more likely to be overweight or obese 12 years after treatment (9). The same was true for cranial radiotherapy (CRT); ALL survivors treated with CRT were more likely to be overweight or obese than their siblings 21-25 years after diagnosis (10, 11).

Studies of overweight conducted to date have been of somewhat limited relevance to childhood cancer survivors. Research on overweight prevalence has involved mostly ALL survivors (9-19), while study of risk factors has led to inconsistent conclusions (4). Studies conducted in the US reflect the lifestyles and eating habits of CSS in that country (10-13, 16,

17, 19-22), while the duration of follow-up in other studies has been only short to medium-term (4, 5), and many have had small (<250) 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 CCS overall and for specific, different diagnoses, 2) compare overweight prevalence in CCS to that of their siblings and the Swiss general population, and 3) identify sociodemographic and clinical risk factors for excessive weight.

METHODS

Study populations

The Swiss Childhood Cancer Survivor Study (SCCSS)

The SCCSS is a population-based, long-term follow-up study of all childhood cancer patients registered in the Swiss Childhood Cancer Registry (SCCR, www.childhoodcancerregistry.ch) who have been diagnosed with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis; survived ≥5 years after initial diagnosis of cancer; were under the age of 21; and 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).

As part of the SCCSS, we traced all addresses of CCS diagnosed between 1976 and 2005, and sent them a questionnaire between 2007 and 2013. Nonresponders received a second copy of the questionnaire four to six weeks later. If they again did not responded, 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 two comparison groups for this study: siblings of the CCS 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 CCS for consent to contact siblings and for their contact information. We have sent siblings the same questionnaire as CCS, omitting questions about cancer history. Siblings who did not responded received another copy of the questionnaire four to six weeks later, but were not contacted by phone (23). The second comparison group consisted of participants in the SHS survey 2012 (30). SHS is a representative national telephone survey repeated every five years. The SHS compiled a randomly selected representative sample of Swiss households with landline telephones, and attempted to contact one person per household. Sampling was stratified by region and conducted in a stepwise manner. Households were selected first, and then the survey was administered to anyone 15 or older who answered the phone.

Measurements

Body weight and BMI

We obtained information on participants' weight and height. For all CCS 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 CCS and anonymous birth statistics having no personal identifiers that was collected by the Swiss Federal Statistical Office. Information on gender, 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 kg/m^2), normal weight (≥ 18.5 to <25 kg/m^2), or overweight (≥ 25 kg/m^2) (1). As recommended for children ≤19 years, we calculated BMI z-scores 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 over 5 years, >2 for age 5 years or less) (32). Birth weight was classified into three categories: low (<2,500 g), normal (2,500-4,000 g), and high (>4,000 g) (33).

Risk factors for being overweight at time of survey

For all three study populations, we assessed gender, 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 at least one parent who was not a Swiss citizen were classified as having a migration background. We classified education using three categories: primary education (compulsory schooling only, ≤9 years), secondary education (vocational training, 10-13 years), 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 at least one hour per week, or no sports with less or no such participation.

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

Statistical Analyses

We included all participants in the SCCSS (CCS and their siblings) and the SHS (general population), who were aged ≤45 years at time of survey and who provided self-reported height and weight (**Supplemental Figure 1**). For better comparison between CCS and peers, we standardized comparison groups for gender, 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 CSS at survey and stratify diagnostic groups. We divided BMI into two categories: overweight (overweight and obesity) versus non-overweight (underweight and normal) as separate categories were small and logistic regression outcomes for the categories overweight and obesity were in the same direction and magnitude as for the category overweight or obesity combined. Then we compared the prevalence of overweight between CCS and comparison groups using chi-square tests. Finally, we determined risk factors for being overweight at survey within each group separately 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 CCS and comparison groups. We also included both CCS and comparison groups in multivariable logistic regression models to investigate whether the risk for being overweight was similar between groups stratified for CRT. We used Stata software (version 14, Stata Corporation, Austin, Texas) for all statistical analysis.

RESULTS

Response rate and characteristics of the study populations

Among 4,116 eligible CCS, we traced and contacted 3,577, of whom 2,527 returned a questionnaire. We excluded 119 questionnaires that did not report height and weight, and a further 43 from survivors who were over 45 years old. We thus included 2,365 CCS in this study, of whom 770 were leukemia survivors, 461 diagnosed between 1990 and 2005 (**Supplemental Figure 1**). We received consent to contact 1,530 siblings, of whom 866 returned the questionnaire; 27 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, 9,591 persons who were 45 years old or younger were included in the analysis.

Among CCS, the most common cancers were leukemia (predominantly ALL with 88%), lymphoma, and CNS and renal tumors (**Table 1**). Median age at diagnosis was 7 (IQR 3–12) years for CCS overall and 5 (IQR 3–9) years for leukemia. The median time from diagnosis to survey was 15 (IQR 10–21) years for CCS overall and 16 (IQR 11–22) years for leukemia survivors. Most leukemia survivors got chemotherapy. Among the subgroup of leukemia

survivors diagnosed between 1990 and 2005, 10% had a high birth weight and 6% were overweight at diagnosis (**Supplemental Table 1**).

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

Overweight prevalence among childhood cancer survivors and comparison groups

Overall, the prevalence of overweight among CCS was 26% (median $BMI_{>19yrs}$: 27, IQR 26-30; median BMI $Z\text{-score}_{\leq 19yrs}$: 1, IQR 1-2), which was similar to overweight prevalence in the comparison groups: 22% in siblings (p=0.07, median $BMI_{>19yrs}$: 27, IQR 26-29; median BMI $Z\text{-score}_{\leq 19yrs}$: 1, IQR 1-2), 25% in the general population (p=0.64, median $BMI_{>19yrs}$: 27, IQR 26-29; median BMI $Z\text{-score}_{\leq 19yrs}$: 1, IQR 1-2). However, CCS diagnostic groups differed: 31% of CNS neoplasm survivors were overweight, while only 13% of neuroblastoma and 18% soft tissue sarcoma survivors were overweight; the prevalence differences were statistically significant (p-values <0.001, <0.001, and 0.04, respectively; **Figure 1**). The prevalence of overweight in leukemia survivors (26%) was similar to the average of all CCS.

Risk factors for being overweight among childhood cancer survivors and comparison groups

In a multivariable regression, we found associations between all sociodemographic factors and being overweight. In all three study populations, males, those who were older at survey, and those who did not take part in sport activities were more likely to be overweight (**Table 3**). Also associated with being overweight were lower education (CCS, leukemia survivors), migration

background (CCS, the general population), and living in the German-speaking part of Switzerland (siblings, the general population). Results of univariable logistic regression can be found in **Supplemental Table 2**.

Interaction tests (**Supplemental Table 3**), showed that most effects of sociodemographic factors did not differ between CCS and the comparison groups (all interaction p-values ≥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 gender, which was weaker in CCS (OR 1.7, 95% CI 1.45, 2.14) compared to the general population (OR 2.42, 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 CCS who got ≥20 Gy CRT of whom 29% was diagnosed with leukemia and 45% with CNS neoplasms, were around 1.5 times more likely to be overweight in comparison to their peers, ($OR_{CCS\ vs\ siblings}$ 1.5, 1.1, 2.2; $OR_{CCS\ vs\ general\ population}$ 1.6, 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, 3.97, 24.51) (**Supplemental Table 4**). Results of univariable logistic regression can be found 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 15 years after cancer diagnosis, 26% of all childhood cancer survivors were overweight. This is a prevalence 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 CCS, their siblings, and the general population. Among clinical factors, we confirmed that ≥20 Gy CRT was associated with being overweight.

Strengths and limitations

Height and weight at survey were self-reported; both under- and over-reporting could have occurred. However, since height and weight were self-reported in all study populations we expected the degree of nondifferential errors of BMI assessment to be similar across CCS 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). Prevalence of overweight might be underestimated as having a higher BMI at diagnosis is associated with a poorer survival. This could have resulted in more exclusion of overweight CCS due to our exclusion criteria of ≥5 years survival after initial diagnosis of cancer (39). Furthermore, our results could have been biased by reverse causation, e.g. a lack of sport 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 one but two comparison groups: siblings of CCS (who share environmental factors with CCS), 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 CCS 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 to reference populations (4, 5), and potentially increased among late adolescent and adult long-term ALL survivors ≥15 years at survey (40). In our study, prevalence of overweight among CCS overall and leukemia survivors was similar to that of 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, 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 those studies' lack of detailed treatment information on CRT and dose-dependent associations with overweight. Our findings do agree with those of a recent US-based study of 14,290 CCS (median 24 [5-39] years after diagnosis) and 4,031 siblings in which self-reported obesity in CCS and siblings was similar to our result, and the 4,100 survivors treated with ≥18 Gy of CRT were more likely to be obese (20). By way of contrast, a study of 7,195 survivors of a variety of cancer types ≥5 years after diagnosis reported underweight in CCS treated for different cancers, including neuroblastoma and soft tissue sarcoma, when compared to 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 put CCS at risk for neuroendocrine abnormalities such as obesity (13). However, previous studies of overweight in CCS 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, CCS 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 CCS 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 level, survivors in these studies were diagnosed between 1970-1986 (22) and 1966-1996 (44) and the majority might have received high-dose CRT.

Female gender 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 CCS published in 2014 and 2015 report no conclusive effect due to gender (4, 5). This suggests that gender 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 CCS: type II 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. Also, children may receive high steroid doses, which increases 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 multiprofession teams including physicians, dieticians, nurses, and physiotherapists might be a promising approach.

Conclusion

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

CONFLICT OF INTEREST

None of the authors report any conflict of interest related to the study.

AUTHORS' CONTRIBUTIONS

FB conducted the statistical analyses and wrote the article; CK contributed to the concept and the design of the study; and AW, MS, and CK gave support in the statistical analyses. All authors have revised earlier drafts and approved the final article.

ACKNOWLEDGEMENTS

The authors express their gratitude to all childhood cancer survivors and their siblings in Switzerland for filling in the questionnaire and supporting this study. Additionally, we thank the Swiss Federal Statistical Office for providing data for the Swiss Health Survey 2012. We thank the study team of the Swiss Childhood Cancer Survivor Study (Rahel Kuonen, Erika Brantschen Berclaz, Rahel Kasteler, Laura Wengenroth, Corina Rueegg, and Cornelia Rebholz), the data managers of the Swiss Paediatric Oncology Group (Claudia Anderegg, Pamela Balestra, Nadine Beusch, Rosa-Emma Garcia, Franziska Hochreutener, Friedgard Julmy, Nadia Lanz, Rodolfo Lo Piccolo, Heike Markiewicz, Annette Reinberg, Renate Siegenthaler, and Verena Stahel), and the team of the Swiss Childhood Cancer Registry (Verena Pfeiffer, Katherina Flandera, Shelagh Redmond, Meltem Altun, Parvinder Singh, Vera Mitter, Elisabeth Kiraly, Marlen Spring, Christina Krenger, and Priska Wölfli). Finally, we would like to thank Ben Spycher for the linkage between the national birth registry and SCCSS, and Christopher Ritter for editorial assistance.

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TABLE 1. Clinical characteristics of childhood cancer survivors (CCS) and childhood leukemia survivors

	CCS (*n*= 2,365)	**Leukemia (*n*= 770)**
Characteristics	*n* (%)	*n* (%)
ICCC3 diagnosis		
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 & XII: Other tumor	54 (2)	-
Langerhans cell histiocytosis	83 (4)	-
Age at diagnosis, year		
<5	1,413 (60)	389 (51)
≥5	952 (40)	381 (49)
Year of diagnosis		
Before 1990	762 (32)	291 (38)
1990-2000	977 (41)	299 (39)
After 2000	626 (26)	180 (23)
Time since diagnosis, median (IQR)	15.0 (10.0-20.9)	15.6 (10.7-22.0)
Chemotherapy[1]		
No	509 (22)	-
Yes	1,856 (78)	767 (100)
Cranial radiation therapy (CRT)		
No CRT	1,950 (82)	599 (78)
<20 Gy	157 (7)	95 (12)
≥20 Gy	258 (11)	76 (10)
Hematopoietic stem cell transplantation (HSCT)		
No	2,248 (95)	709 (92)
Yes	117 (5)	61 (8)
History of relapse		
No	2,081 (88)	670 (87)
Yes	284 (12)	100 (13)

Abbreviations: CNS, central nervous system; ICCC3, International Classification of Childhood Cancer, 3rd edition; Gy, Gray; HSCT, hematopoietic stem cell transplantation

[1] *n*=3 missing (<1%)

TABLE 2. General characteristics of childhood cancer survivors (CCS) and comparison groups

	Childhood cancer survivors		**Siblings**[1] **(*n* =819)**		**General population**[1] **(*n* =9,591)**	
	CCS (*n* =2,365)	**Leukemia (*n* =770)**				
Characteristics	*n* (%)	*n* (%)	*n* (%$_{std}$)	***p-value***[2]	*n* (%$_{std}$)	***p-value***[2]
Gender						
Female	1,086 (46)	367 (48)	473 (45)		4,946 (46)	
Male	1,279 (54)	403 (52)	346 (55)	***n.a.***	4,645 (54)	***n.a.***
Age at survey, year						
5-14	329 (14)	121 (16)	94 (18)		-	
15-19	541 (23)	184 (24)	142 (20)		1,518 (33)	
20-24	530 (22)	167 (22)	162 (19)		1,440 (23)	
25-29	401 (17)	136 (18)	168 (19)		1,174 (13)	
30-34	277 (12)	87 (11)	115 (12)		1,424 (11)	
35-39	185 (8)	47 (6)	84 (8)		1,601 (9)	
40-45	102 (4)	28 (4)	54 (5)	***n.a.***	2,434 (10)	***n.a.***
Parents' education (highest degree)[3]						
Primary schooling	62 (7)	26 (9)	8 (3)		n.a.	
Secondary education	469 (54)	165 (54)	115 (47)			
Tertiary education	339 (39)	114 (37)	113 (50)	***0.007***		
Personal education[4]						
Primary schooling	117 (8)	36 (8)	24 (4)		691 (8)	
Secondary education	1,010 (68)	337 (72)	359 (61)		4,549 (62)	
Tertiary education	368 (25)	92 (20)	200 (35)	***<0.001***	2,833 (30)	***<0.001***
Migration						
No migration background	1,762 (75)	573 (74)	657 (75)		6,137 (77)	
Migration background	603 (26)	197 (26)	162 (25)	***n.a.***	3,454 (23)	***n.a.***
Language region of Switzerland						
German speaking	1,658 (70)	571 (74)	650 (70)		6,300 (70)	
French speaking	630 (27)	172 (22)	143 (27)		2,620 (27)	
Italian speaking	77 (3)	27 (4)	26 (3)	***n.a.***	671 (3)	***n.a.***
Sports						
Yes	1,623 (69)	544 (71)	593 (75)		5,598 (64)	
No	742 (31)	226 (29)	226 (25)	***0.002***	3,993 (36)	***<0.001***
BMI at survey[5]						
Underweight	127 (5)	43 (6)	20 (2)		349 (3)	
Normal	1,632 (69)	525 (68)	602 (76)		6,354 (72)	
Overweight	606 (26)	202 (26)	197 (22)	***<0.001***	2,888 (25)	***<0.001***

Abbreviations: BMI, body mass index; Dx, diagnosis; n.a., not applicable

[1] Standardized on gender, age at survey, migration background and language region according to CCS

[2] p-value calculated from Chi-Square statistics comparing comparison group to CCS (2-sided test)

[3] Highest parental education level of CCS and siblings <20 years at time of survey

[4] Highest personal education level of CCS, siblings, and the general population ≥20 years at time of survey

[5] BMI Z-scores were calculated for CCS, siblings, and the general population ≤19 yrs, BMI scores (kg/m2) were calculated for adults (>19 yrs)

TABLE 3. Overweight prevalence and risk factors associated with overweight in childhood cancer survivors (CCS) or comparison groups (from multivariable logistic regression)

	Childhood cancer survivors				**Siblings**[1] **(*n* =819)**		**General population**[1] **(*n* =9,591)**	
	CCS (*n* =2,365)		**Leukemia (*n* =770)**					
	%ow[2] OR (95% CI)	***p-value***[3]	*%ow*[2] *OR (95% CI)*	***p-value***[3]	*%ow*[2] OR (95% CI)	***p-value***[4]	*%ow*[2] OR (95% CI)	***p-value***[4]
Sociodemographic characteristics								
Gender								
Female	(20) 1.00 (ref)	***<0.001***	(20) 1.00 (ref)	***<0.001***	(17) 1.00 (ref)	***<0.001***	(17) 1.00 (ref)	***<0.001***
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, year								
5-14	(25) 1.64 (1.16, 2.32)	***<0.001***	(29) 2.05 (1.16, 3.64)	***<0.001***	(12) 1.48 (0.65, 3.36)	***<0.001***	-	***<0.001***
15-19	(17) 1.00 (ref)		(16) 1.00 (ref)		(11) 1.00 (ref)		(16) 1.00 (ref)	
20-24	(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	(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	(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	(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	(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, year								
≥5	(26) 1.00 (ref)	***0.107***	(26) 1.00 (ref)	***0.161***	*n.a*		*n.a*	
<5	(25) 1.20 (0.96, 1.49)		(27) 1.29 (0.90, 1.86)					
Education[5]								
Primary schooling	(28) 1.45 (0.98, 2.15)	***0.008***	(31) 2.06 (1.03, 4.12)	***0.010***	(31) 1.75 (0.65, 4.72)	***0.268***	*n.a.*	
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								
No migration background	(25) 1.00 (ref)	***0.011***	(26) 1.00 (ref)	***0.368***	(22) 1.00 (ref)	***0.189***	(23) 1.00 (ref)	***<0.001***
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								
German speaking	(26) 1.00 (ref)	***0.287***	(27) 1.00 (ref)	***0.638***	(25) 1.00 (ref)	***0.017***	(26) 1.00 (ref)	***0.019***
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								
Yes	(23) 1.00 (ref)	***0.004***	(24) 1.00 (ref)	***0.427***	(19) 1.00 (ref)	***0.002***	(23) 1.00 (ref)	***<0.001***
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] Standardized on gender, age at survey, migration background, and language region according to CCS; multivariable logistic regressions are separately for each study population

[2] Column overweight percentages are given

[3] p-value calculated from likelihood ratio test

[4] Global p-value 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 (<20 years at time at survey) or personal education (≥20 years at time of survey)

FIGURE LEGENDS

Figure 1: Overweight in childhood cancer survivors and comparison groups Abbreviations: CNS, central nervous system; LCH, Langerhans cell histiocytosis

BMI distribution of comparison groups is standardized on gender, age at survey, migration background, and language region according to childhood cancer survivors.

The dotted line reflects the overweight prevalence of the general population.

Figure 2: Cranial radiation therapy-specific OR and 95%CI for overweight in childhood cancer survivors versus comparison groups (from multivariable logistic regression[1, 2]) Squares, OR for overweight; whiskers, the respective 95% CI

Abbreviations: CI, confidence interval; CRT, cranial radiation therapy; Gy, gray

[1] Both comparison groups are standardized on gender, age at survey, migration background, and language region according to CCS

[2] Adjusted for gender, age, education, migration background, language region of Switzerland, and sports