Title: Long-term pulmonary disease among Swiss childhood cancer survivors

Rahel Kasteler[1]; Annette Weiss[1]; Matthias Schindler[1]; Grit Sommer[1]; Philipp Latzin[2]; Nicolas X. von der Weid[3]; Roland A. Ammann[2]; Claudia E. Kuehni[1,2]; for the Swiss Pediatric Oncology Group (SPOG)[a].

[1] Swiss Childhood Cancer Registry, Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland.

[2] Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland.

[3] Department of Pediatrics, University Children`s Hospital Basel UKBB, University of Basel, Basel, Switzerland.

[a] Swiss Pediatric Oncology Group (SPOG) Scientific Committee: Prof. Dr. med. R. Ammann, Bern; Dr. med. R. Angst, Aarau; Prof. Dr. med. M. Ansari, Geneva; Prof. Dr. med. M. Beck Popovic, Lausanne; PD Dr. med. E. Bergstraesser, Zürich; Dr. med. P. Brazzola, Bellinzona; Dr. med. J. Greiner, St. Gallen; Prof. Dr. med. M. Grotzer, Zürich; Dr. med. H. Hengartner, St. Gallen; Prof. Dr. med. T. Kuehne, Basel; Prof. Dr. med. K. Leibundgut, Bern; Prof. Dr. med. F. Niggli, Zürich; PD Dr. med. J. Rischewski, Lucerne; Prof. Dr. med. N. von der Weid, Basel.

Corresponding author: Claudia E. Kuehni, Prof. MD MSc; Institute of Social and Preventive Medicine, University of Bern, Finkenhubelweg 11, 3012 Bern, Switzerland; E-mail: claudia.kuehni@ispm.unibe.ch; Telephone: +41 31 631 35 07; Facsimile: +41 31 631 35 20

Word count for abstract: 232

Word count for main text: 3111 (excludes title page, abstract, conflicts of Interest, acknowledgments, references, tables, figures, and legends)

Figures and Tables: Tables: 3, Figures: 3

Supplemental files: Supplementary text: 1, Tables: 5, Figures: 3

Running title: Lung disease in Swiss childhood cancer survivors

Key words: childhood cancer, late effects, pulmonary disease, lung injury, cancer treatment, pneumonia

Abbreviations:

BCNU	Carmustine
BMI	Body Mass Index
CCNU	Lomustine
CCS	Childhood cancer survivor
CCSS	US-Childhood Cancer Survivor Study
CNS	Central nervous system
CI	Confidence interval
Gy	Gray
HSCT	Hematopoietic stem cell transplantation

ICCC-3	International Classification of Childhood Cancer, Third edition
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
IQR	Interquartile range
LCH	Langerhans cell histiocytosis
N	Number
OR	Odds ratio
P	P-value
SCCR	Swiss Childhood Cancer Registry
SCCSS	Swiss Childhood Cancer Survivor Study

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Abstract

Background

Pulmonary diseases are potentially severe late complications of childhood cancer treatment that increase mortality risk among survivors. This nationwide study assesses the prevalence and incidence of pulmonary diseases in long-term childhood cancer survivors and their siblings, and quantifies treatment-related risks.

Methods

As part of the Swiss Childhood Cancer Survivor Study we studied childhood cancer survivors who were diagnosed between 1976-2005 and alive at least five years after diagnosis. We compared prevalence of self-reported pulmonary diseases (pneumonia, chest wall abnormalities, lung fibrosis, emphysema) between survivors and their siblings, calculated cumulative incidence of pulmonary diseases using the Kaplan-Meier method, and determined risk factors using multivariable logistic regression.

Results

Childhood cancer survivors reported more pneumonias (10% vs. 7%, P=0.020) and chest wall abnormalities (2% vs. 0.4%, P=0.003) than siblings. Treatment with busulfan was associated with prevalence of pneumonia (odds ratio [OR] 4.0, 95% confidence interval [CI] 1.1-14.9), and thoracic surgery was associated with chest wall abnormalities and lung fibrosis (OR 4.1, 95%CI 1.6-10.7 and OR 6.3, 95%CI 1.7-26.6). Cumulative incidence of any pulmonary disease after 35 years of follow-up was 21%. For pneumonia, the highest cumulative incidence was seen in childhood cancer survivors treated with both pulmotoxic chemotherapy and radiotherapy to the thorax (23%).

Conclusion

This nationwide study in childhood cancer survivors found an increased risk for pulmonary diseases, especially pneumonia, while still young, which indicates that childhood cancer survivors need long-term pulmonary follow-up.

Introduction

Pulmonary diseases are potentially severe late complications of childhood cancer treatments. Bleomycin, alkylating agents, radiotherapy to the thorax, and thoracic surgery can lead to restrictive lung disease.[1,2] Especially when followed by chronic graft versus host disease, allogeneic hematopoietic stem cell transplantation (HSCT) can cause obstructive lung disease such as bronchiolitis obliterans or restrictive lung disease like lung fibrosis.[2] Childhood cancer survivors (CCS) have a three-fold increased risk for hospitalization for pulmonary diseases and up to 14 times increased risk for late pulmonary death,[3-5] with pneumonia being particularly common.[6] Impaired lung function has been found in a large proportion of CCS (44–65%) depending on inclusion criteria and type of lung function tests.[7-10] The US Childhood Cancer Survivor Study (CCSS) included CCS diagnosed 1970-1986 and found more lung fibrosis, recurrent pneumonia, chronic cough, and chest wall abnormalities in CCS than in their siblings.[11,12] The incidence of pulmonary diseases remained elevated up to 25 years after cancer diagnosis.[13]

Data on pulmonary diseases in CCS are nevertheless scarce. Few studies have been conducted in Europe, where treatment protocols differ from those used in the US. Previous studies have come from selected high profile clinics, included only certain types of cancer, or CCS treated many years ago (1970-1986).[11-13] CCS treated with newer regimens need renewed study.

We employed a nationwide, population-based, prospective cohort study to examine pulmonary disease in Swiss CCS diagnosed between 1976 and 2005. We compared the long-term prevalence of self-reported pneumonia, chest wall abnormalities, lung

fibrosis, and emphysema between CCS and their siblings, calculated cumulative incidence of pulmonary disease, and quantified treatment-related risks.

Methods

Swiss Childhood Cancer Survivor Study

The Swiss Childhood Cancer Registry (SCCR) is a nationwide population-based cancer registry that includes all children and adolescents diagnosed with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis (LCH) before the age of 21.[14] The Swiss Childhood Cancer Survivor Study (SCCSS) is a long-term follow-up cohort study of all patients registered in the SCCR who have been diagnosed since 1976 and who survived five or more years after initial diagnosis of cancer.[15] For this study, we included all CCS, who were diagnosed 1976-2005 and aged ≥16 years at survey.

Between 2007 and 2013 we sent questionnaires to all eligible CCS. Nonresponders received a second copy of the questionnaire 4–6 weeks after the first and, if they still did not answer, were contacted by phone. We asked CCS for consent to contact their siblings as a comparison group. If CCS agreed, we sent the same questionnaire without cancer-related questions to their siblings. Siblings who did not respond to the first questionnaire received a second copy 4–6 weeks later, but we did not contact them by phone. Details of the study design have been published elsewhere.[15]

The Ethics Committee of the Canton of Bern granted approval to the SCCR and SCCSS (KEK-BE: 166/2014). In line with this approval, informed consent of registration

in the SCCR and corresponding studies, like the SCCSS, is collected at time of cancer diagnosis or later with the reply to the SCCSS survey.

Outcome: pulmonary diseases

The SCCSS questionnaire included a section on pulmonary health similar to US and British childhood cancer survivor studies.[16,17] We asked CCS and siblings whether they had ever been diagnosed with pneumonia, chest wall abnormalities, lung fibrosis, or emphysema (**Supplementary Fig. S1**). We created a summary variable *any pulmonary disease* which combined all four pulmonary disease outcomes. To assess whether a pulmonary disease had occurred before or after cancer diagnosis we asked participants for the year of first occurrence. Pneumonia is associated with a high morbidity and mortality in patients with comorbidities,[18] and CCS have a high burden of comorbidities due to cancer treatment.[9] We increased sensitivity of the questions on pneumonia by asking about both single and repeated events. Previous studies have only asked about recurrent pneumonia.[11,13]

Explanatory factors

Information on cancer and cancer treatment

We extracted these diagnosis- and treatment-related variables from the SCCR: age at cancer diagnosis, time since cancer diagnosis, cancer diagnosis, year of cancer diagnosis, chemotherapy, treatment protocol, radiotherapy, surgery, HSCT. We classified cancer diagnosis according to the International Classification of Childhood Cancer, third edition (ICCC-3) into twelve main groups and LCH.[19] We assessed whether CCS had been treated with busulfan, nitrosoureas (carmustine [BCNU] or

lomustine [CCNU]), or bleomycin from data on treatment protocols. Radiotherapy to the thorax included radiotherapy to the total body, mantle field, thorax, lungs, mediastinum, or thoracic spine. We categorized radiotherapy to the thorax into four categories according to radiation doses based on radiotherapy treatment records: no radiotherapy to the thorax, 1-19 Gray (Gy), 20-39 Gy, and ≥40 Gy.[20] We collected information on thoracic surgery (yes/no) and categorized the types of surgery (**Supplementary Table S1**). We assessed whether CCS had an autologous, allogeneic, or no HSCT.

Information on sociodemographic and lifestyle characteristics

From the SCCSS survey, we extracted information on sociodemographic data (gender, age at survey, Swiss language region, migration background) and lifestyle (body mass index [BMI], smoking status, performing sports). We calculated BMI from the survey's self-reported height and weight data. For participants younger than 19 at survey, we calculated BMI z-scores using the Swiss references.[21] BMI at survey was classified as underweight (>19yrs, <18kg/m2; ≤19yrs, <-2 z-scores), normal weight (>19yrs, ≥18 to <25kg/m2; ≤19yrs, ≥-2 to ≤1 z-score), overweight/obese (>19yrs, ≥25 kg/m2; ≤19yrs, >1 z-score).[22,23] We categorized smoking status as never smoker, ex-smoker, and current smoker. We defined performing sports as engagement in at least moderate gym or sports activity for more than one hour per week.

Statistical Analysis

We compared long-term prevalence of self-reported pulmonary diseases between CCS and siblings ever in life using chi-squared tests. For better comparison between CCS and siblings, we standardized siblings for gender, age at survey, Swiss language

region, and migration background as described previously.[24,25] Characteristics of siblings are shown in **Supplementary Table S2**.

To estimate the cumulative incidence of pulmonary disease, we used the Kaplan-Meier method. We assessed the first occurrence of any pulmonary disease separately and combined for each specific disease. For pneumonia, we also computed cumulative incidence curves for different cancer treatments. We used log-rank tests to test for equivalence of incidence curves. Start of follow-up time was age at cancer diagnosis for CCS, and for siblings mean age at cancer diagnosis of CCS. End of follow-up time was either the year of disease occurrence or time of survey completion if participants had no pulmonary disease. We imputed age at pulmonary disease if a participant reported a pulmonary disease but not the year of first occurrence using observed values (in CCS gender, age at survey, smoking status, age at cancer diagnosis, cancer diagnosis, radiotherapy to the thorax, and pulmotoxic chemotherapy; and in siblings, using gender, age at survey, smoking status, **Supplementary text**).[26] Controls were censored at time of survey if they had no pulmonary disease.

For CCS we quantified treatment-related risks by using uni- and multivariable logistic regressions. Explanatory factors were pulmotoxic chemotherapy (nitrosureas, busulfan, or bleomycin), radiotherapy to the thorax, thoracic surgery, and HSCT. We used likelihood ratio tests to assess whether explanatory variables were associated with pulmonary diseases. We adjusted for the following confounding factors mentioned in the literature: gender, age at diagnosis, smoking status, performing sport, and BMI at survey.[27-29]

We used R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) to calculate BMI z-scores and to impute missing values with the package missForest.[26] For all other analysis, we used Stata (Version 14, Stata Corporation, Austin, Texas).

Results

Characteristics of study population

Of 2,918 CCS and 1,280 siblings contacted and eligible for this analysis, 1,894 CCS (65%) and 731 siblings (57%) responded **(Supplementary Fig. S2)**. Responders were more often female, between 20-29 years old at survey, from the German-speaking region of Switzerland, and younger at diagnosis than nonresponders. They also differed by cancer diagnosis and treatment **(Supplementary Table S2)**.

Fifty-three percent of CCS were male, median (interquartile range [IQR]) age at survey was 27 years (20–32) **(Table 1)**. CCS performed less sport than siblings (60% vs. 67%, P=0.001) and were more often underweight (6% vs. 3%, P=0.004). Median (IQR) age at cancer diagnosis was 9 years (4–14); median time since diagnosis (IQR) was 18 years (13-23); common diagnoses were leukemia (32%), lymphoma (20%) and CNS tumors (14%). Eighty-two percent had been treated with chemotherapy and 8% had received pulmotoxic chemotherapy: 1% busulfan, 2% nitrosoureas, and 5% bleomycin. Fifteen percent of CCS had received radiotherapy to the thorax, the majority with doses between 20-39 Gy (8%). Four percent had had thoracic surgery, and 5% had received HSCT (3% autologous and 2% allogeneic) **(Table 1, Supplementary Table S2)**.

Prevalence of pulmonary diseases in CCS and siblings

Long-term prevalence of any pulmonary disease was higher in CCS than in siblings (12% vs. 7%, P=0.001) **(Table 2, Supplementary Fig. S3).** The difference in long-term prevalence of pneumonia ever in life was marked, 10% vs. 7% (P=0.020), and 3% of CCS compared to 1.5% of siblings had one pneumonia, and 0.8% vs. 0% had two or more pneumonias (overall, P=0.006) in the last two years **(Table 2)**. When stratified by pulmotoxic treatment, CCS treated with no pulmotoxic treatment, pulmotoxic chemotherapy alone and both pulmotoxic chemotherapy and radiotherapy to the thorax had a higher long-term prevalence of pneumonia than siblings (10% vs. 7% P=0.048, 15% P=0.042; and 14%, P=0.014, respectively) **(Supplementary Table S3)**. Further, CCS reported more chest wall abnormalities (2% vs. 0.4%, P=0.003) than siblings. Lung fibrosis and emphysema were rare in both groups (0.8% vs. 0.3%, P=0.137; and 0.2% vs. 0.2%, P=0.763) **(Table 2)**. When stratified by period of cancer diagnosis, CCS treated in 1976-1985 had a higher long-term prevalence of lung fibrosis (1.8%), than those treated in 1986-1995 (0.4%) and 1996-2005 (0.7%, P=0.026). Long-term revalence of all other pulmonary diseases did not differ between periods of cancer diagnosis **(Table 3)**.

Cumulative incidence of pulmonary disease after cancer diagnosis

Over 35 years of follow-up, 21% (95% CI 15 – 28%) of CCS had developed at least one pulmonary disease **(Fig. 1)**. The cumulative incidence was highest for pneumonia (18%, 95% CI 13-24%), lower for chest wall abnormalities (4%, 95% CI 2-9%) and lung fibrosis (3%, 95% CI 1-14%), and lowest for emphysema (0.2%, 95% CI 0.1-0.6%).

Cumulative incidence of pneumonia by treatment group

Cumulative incidence of pneumonia in CCS within 25 years of follow-up differed by treatment group **(Fig. 2)**: CCS without pulmotoxic treatment and those with radiotherapy to the thorax only had a similar cumulative incidence of pneumonia as siblings (Panel A, 11%, 95% CI 9–14% vs. 9%, 95% CI 7–11%, P=0.074; Panel B, 12%, 95% CI 7–19% vs. 9%, 95% CI 7–11%, P=0.226). The graph suggests a trend, though it is not statistically significant, for increasing risk among those treated with radiotherapy to the thorax starting approximately 20 years after diagnosis. CCS treated with pulmotoxic chemotherapy had a higher cumulative incidence than siblings (Panel C, 18%, 95% CI 9-33% vs. 9%, 95% CI 7–11%, P=0.014), starting soon after treatment. CCS treated with both pulmotoxic chemotherapy and radiotherapy to the thorax had the highest cumulative incidence (Panel D, 23%, 95% CI 13–38% vs. 9%, 95% CI 7–11%, P=0.001) differing from siblings.

Risk factors for pulmonary disease

CCS treated with busulfan were more likely to develop pneumonia (OR 4.0, 95% CI 1.1 – 14.9). We found no significant effect of treatment with nitrosoureas and bleomycin.Thoracic surgery was associated with chest wall abnormalities (OR 4.1, 95% CI 1.6 – 10.7) and lung fibrosis (OR 6.3, 95% CI 1.7 – 26.6) **(Fig. 3, Supplementary Table S4)**. There was also a trend for more chest wall abnormalities (OR 1.7, 95% CI 0.7 – 4.3) and lung fibrosis (OR 2.0, 95% CI 0.6 – 6.3) in CCS treated with radiotherapy. HSCT was associated with any pulmonary disease (autologous, OR 1.7, 95% CI 0.8 – 3.8; allogeneic, OR 1.8, 95% CI 0.8-4.0) and pneumonia (autologous, OR 1.7, 95% CI 0.7 – 4.0; allogeneic: OR 1.9, 95% CI 0.8 – 4.4), but this was not statistically significant.

Of the assessed life style characteristics, only underweight was associated with lung fibrosis (OR 6.1, 95% CI 1.7 – 24.9).

Results from univariable regression (unadjusted) are in **Supplementary Table S5.**

Discussion

Pulmonary diseases, particularly pneumonia and chest wall abnormalities, were increased in this nationwide, population-based comparison of childhood cancer survivors with their siblings. Busulfan was associated with pneumonia, and thoracic surgery with chest wall abnormalities and lung fibrosis. Cumulative incidence of all pulmonary diseases after cancer diagnosis continued to increase throughout life without reaching a plateau 25 years after diagnosis. Cumulative incidence of pneumonia differed by cancer treatment, with the highest incidence in those treated with both pulmotoxic chemotherapy and radiotherapy to the chest.

The Childhood Cancer Survivor Study is a multicenter cohort study that also used patient-reported data and found a slightly increased cumulative incidence of pulmonary disease in CCS compared to siblings, 30% vs. 27% (P<0.001).[11,13] The lower long-term prevalence in our study, 12%, is explained by our exclusion of asthma and chronic cough, which are very common in the general population **(Supplementary text)**. The CCSS, which included patients diagnosed from 1970 to 1986 found fewer chest wall abnormalities (2.2% vs. 1.3%), and more lung fibrosis than we did (0.8% vs. 3.1%).[11] This might be because Swiss CCS were younger and the development of lung fibrosis can occur with a latency of up to 25 years,[13] or because the Swiss cohort was treated with treatment protocols of more recent years, including lower radiation doses and volumes, as for example in CCS of Hodgkins Lymphoma.[30] These assumptions are

supported by the observed lower long-term prevalence of lung fibrosis diagnosed in Swiss CCS in recent years. The proportion of CCS in our study who had repeated pneumonia within the previous two years is comparable to that in the CCSS.[11] Because pneumonia is associated with high morbidity and mortality in patients with comorbidities,[18] we also looked at all events of pneumonia and found that 10% of CCS had had pneumonia at some time, while the long-term prevalence was 7% in their siblings. The prevalence of pneumonia did not decrease in CCS diagnosed in recent years. The cumulative incidence of pneumonia increased over the 25-year follow-up without plateauing. Dietz et al. reported the same for recurrent pneumonia.[13] The CCSS identified different risk factors for pneumonia, radiotherapy to the thorax, and HSCT,[11,13] while in our study pneumonia risk was higher after busulfan treatment. We also observed that cumulative incidence of pneumonia differed by treatment groups and was highest in those treated with both pulmotoxic chemotherapy and radiotherapy to the thorax. HSCT with subsequent graft versus host disease and immunodeficiency could explain development of repeated infections such as pneumonia.[6,31] However, our multivariable analysis found no evidence that the association between pneumonia and busulfan was mediated via HSCT (the effect of busulfan was not reduced when we adjusted for HSCT). We found also no evidence for an independent effect of HSCT on risk of pneumonia. Therefore our results suggest that busulfan itself has a long-term effect on the immune system or lung tissues. We don’t know the underlying mechanisms, as the few experimental data from animal models and cell culture studies have focused on short-term effects. The risk for chest wall abnormalities and lung fibrosis was higher in CCS treated with radiotherapy to the thorax and thoracic surgery,

289 which also is similar to CCSS findings.[11-13] We found a higher proportion of pulmonary
290 disease in CCS treated with alkylating agents (busulfan) or surgery to the lungs as was
291 also reported by Record et al.[7] Lung fibrosis was associated with underweight at survey.
292 We think this might be a secondary effect, because CCS with lung fibrosis are more
293 likely to be sick and thus more often suffer from malnutrition and have elevated exertion
294 because of difficulties with breathing, as hypothesized in adult idiopathic lung fibrosis
295 patients.[32] Finally, up to 65% of CCS have been found to have impaired lung-function.[7-
296 10] This rate is higher than the cumulative, overall incidence of disease in our study
297 because lung function tests may indicate subclinical pathology possibly well in advance
298 of diagnosis of disease.
299 Strengths of our study are the population-based nature and the high response rate
300 that make our study population representative for the entire population of Swiss CCS.
301 Nonresponse bias seems to play a minor role in the SCCSS. We recently assessed the
302 difference in typical prevalence estimates (somatic health, medical care, mental health,
303 health behaviours) among early responders (40%), all responders (69%) and a
304 complete representative population constructed with inverse probability weighting
305 (100%).[33] We found similar results among those populations, suggesting that
306 prevalence estimates in participants are close to the true prevalence in the total
307 population.[33] Further, we have no evidence that CCS reported differently than their
308 siblings: asthma and chronic cough, common disorders not specifically caused by
309 cancer treatment,[34] were reported equally often (**Supplementary text**). Our study
310 covers all cancer diagnoses and treatment periods from 1976 to 2005, while previous
311 studies often focused only on specific diagnostic groups[12,35] and CCS diagnosed until

1986.[11,13] Last, the SCCSS assessed a large number of sociodemographic and life-style characteristics, which we could include in the analyses.

The limited sensitivity and specificity of self-reported disease could have biased our results. However, one study's comparison of self-reports of pulmonary diseases including pneumonia, lung fibrosis, and emphysema to information from medical records of childhood cancer survivors of HSCT has shown good validity (96% sensitivity, 91% specificity).[36] We could not determine if the effects of drugs or radiotherapy to the thorax were dose-dependent, as we did not have exact cumulative doses of chemotherapeutic drugs and numbers of patients with pulmonary outcomes were too low to stratify them into more categories. Due to survival bias, our results might underestimate the true prevalence. The absolute numbers of CCS with pulmonary disease was small, because our study population was young, and incidence of pulmonary disease increases over the life of CCS.[5,13]

Childhood cancer survivors are at increased risk of pneumonia, which is the most common pulmonary cause of death among CCS.[6] The underlying causes of this are poorly understood. The long-term prevalence of pneumonia remained increased among CCS diagnosed in recent years and treated with newer treatment protocols. Future research should investigate pathophysiological mechanisms leading to pneumonia in CCS. Lung fibrosis and emphysema are rare; to evaluate associations with cancer-treatment, international data must be pooled. The increased incidence of pulmonary disease, particularly pneumonia, continues throughout the life of a CCS, and the risk depends on the type of cancer treatment. We therefore must consider preventive measures for pneumonia such as vaccination for influenza or pneumococcal pneumonia

in susceptible CCS. Lifelong clinical monitoring of pulmonary health of former childhood cancer patients at risk for pulmonary disease is necessary.

Acknowledgements

We thank all childhood cancer survivors and families for participating in our survey. We thank the study team of the SCCSS (Rahel Kuonen, Erika Brantschen-Berclaz, Annette Schneeberger, Laura Wengenroth, Corina Rueegg, Cornelia Rebholz), the data managers of the SPOG (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 SCCR (Verena Pfeiffer, Katharina Flandera, Shelagh Redmond, Meltem Altun, Parvinder Singh, Vera Mitter, Elisabeth Kiraly, Marlen Spring, Christina Krenger, Priska Wölfli). Finally, we thank Christopher Ritter for his editorial assistance.

Conflict of Interest Statement

The commercial funders of the Swiss Childhood Cancer Registry support the daily running of the registry and have not had and will not have any role in the design, conduct, interpretation, or publication of the Swiss Childhood Cancer Registry itself as well as the related research projects.

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Legends

TABLE 1 Characteristics of childhood cancer survivors and siblings

TABLE 2 Long-term prevalence of self-reported pulmonary diseases and number of pneumonias occurring in the last two years in childhood cancer survivors and siblings

TABLE 3 Prevalence of pulmonary diseases in childhood cancer survivors by period of cancer diagnosis

FIGURE 1 Cumulative incidence of self-reported pulmonary diseases in survivors during follow-up.

Imputation was used for missing year of onset of pulmonary disease. Time of onset of pulmonary disease was reported as years of follow-up. Start of follow-up time was individual age at cancer diagnosis for survivors and for siblings we used mean age at cancer diagnosis of survivors. Any pulmonary disease refers to the first occurrence of the disease. If a survivor reported more than one pulmonary disease, only the first occurrence was counted.

FIGURE 2 Cumulative incidence of self-reported pneumonia in years of follow-up in survivors by treatment group and siblings

Start of follow-up time was individual age at cancer diagnosis for survivors and for siblings we used mean age at cancer diagnosis of survivors.

CT, Chemotherapy; RT, Radiotherapy

FIGURE 3 Associations between cancer treatments and self-reported pulmonary diseases occurring after cancer diagnosis.

Multivariable logistic regression adjusted for all treatment factors shown and gender, age at diagnosis, smoking status, BMI at survey, and performing sports.

n.a., not applicable

Supplemental:

Supplementary text Additional Methods

TABLE S1 Surgical details for survivors who had thoracic surgery

TABLE S2 Characteristics of responding and nonresponding survivors and siblings before and after weighting for survivor's gender, age at survey, Swiss language region and migration background

TABLE S3 Prevalence of pneumonia in childhood cancer survivors and siblings by cancer treatment

TABLE S4 Associations between sociodemographic and treatment characteristics and self-reported pulmonary diseases. Results from multivariable logistic regression, adjusted for all factors in the table.

TABLE S5 Associations between sociodemographic and treatment characteristics and self-reported pulmonary diseases. Results from univariable logistic regression.

FIGURE S1 English translation of original questions for adults on pulmonary health in the SCCSS questionnaire

FIGURE S2 Response rates in the Swiss Childhood Cancer Survivor Study for both, childhood cancer survivors and siblings, ≥16 years old at survey

FIGURE S3 Long-term prevalence of self-reported pulmonary diseases in childhood cancer survivors and siblings

TABLE 1 Characteristics of childhood cancer survivors and siblings

	Survivors N = 1,894		Siblings N = 731		
	n	(%) [a]	n	(%) [a]	P [b]
Sociodemographic characteristics					
Gender					<0.001
Female	898	(47)	428	(59)	
Male	996	(53)	303	(41)	
Age at survey (years)					<0.001
16-19	419	(22)	116	(16)	
20-29	892	(47)	333	(45)	
≥30	583	(31)	282	(39)	
Lifestyle characteristics					
Smoking status					0.104
Never smoker	1,218	(64)	457	(62)	
Ex-smoker	222	(12)	108	(15)	
Current smoker	454	(24)	166	(23)	
Performing sports					0.001
No	757	(40)	242	(33)	
Yes	1,137	(60)	489	(67)	
BMI at survey					0.004
Underweight	108	(6)	19	(3)	
Healthy	1,271	(67)	513	(70)	
Overweight/obese	515	(27)	199	(27)	
Clinical characteristics					
Age at diagnosis (years)					
0-5	695	(37)			
>5-10	446	(23)			
>10	753	(40)			
Period of cancer diagnosis					
1976 - 1985	463	(24)			
1986 - 1995	839	(44)			
1996 - 2005	592	(31)			
Diagnosis (ICCC-3)					
I Leukemia	601	(32)			
II Lymphoma	391	(20)			
III CNS tumor	262	(14)			
IV Neuroblastoma	73	(4)			
V Retinoblastoma	39	(2)			
VI Renal tumor	107	(6)			
VII Hepatic tumor	11	(1)			
VIII Bone tumor	86	(4)			
IX Soft tissue sarcoma	116	(6)			
X Germ cell tumor	94	(5)			
XI & XII Other rare tumors [c]	114	(6)			

Treatments		
Chemotherapy		
No chemotherapy	347	(18)
Any chemotherapy	1,547	(82)
Pulmotoxic chemotherapy		
Busulfan	13	(1)
Nitrosureas (BCNU/CCNU)	30	(2)
Bleomycin	102	(5)
Radiotherapy [d]		
No radiotherapy	1,155	(63)
Any radiotherapy	739	(37)
Radiotherapy to the thorax	284	(15)
Dose 0-19 Gy	82	(4)
Dose 20-39 Gy	143	(8)
Dose >=40 Gy	50	(3)
Dose unknown	9	(0.5)
Surgery [e]		
No surgery	836	(44)
Any surgery	1,058	(56)
Thoracic surgery	80	(4)
Hematopoietic stem cell transplantation (HSCT)		
No HSCT	1,802	(95)
Any HSCT	93	(5)
Autologous	48	(3)
Allogenic	45	(2)

[a] Column percentages are given.

[b] P-values calculated from chi-squared tests comparing survivors and siblings.

[c] Including Langerhans cell histiocytosis; other malignant epithelial neoplasms, malignant melanomas, and other or unspecified malignant neoplasms.

[d] Including radiotherapy to the total body, mantle-field, thorax, lungs, mediastinum or thoracic spine.

[e] Including thoracotomy, sternotomy, chest wall surgery, rib resection, thoracoscopy.

TABLE 2 Long-term prevalence of self-reported pulmonary diseases and number of pneumonias occurring in the last two years in childhood cancer survivors and siblings

	Survivors (N=1,894)						Siblings [a] (N=731)		
	No	Yes, ever in life	Prevalence [b]		Yes, after diagnosis [c]		Prevalence		
	n	n	%	(95%CI)	n	(%)	%	(95%CI)	P [d]
Any pulmonary disease [e]	1,668	226	11.9	(10.5 - 13.5)	215	(11.4)	7. 3	(5.6 - 9.5)	0.001
Chest wall abnormalities	1,852	42	2.2	(1.6 - 3.0)	38	(2.0)	0.4	(0.1 - 1.4)	0.003
Lung fibrosis	1,878	16	0.8	(0.5 - 1.4)	15	(0.7)	0.3	(0.1 - 1.2)	0.137
Emphysema	2,183	3	0.2	(0.1 - 0.5)	3	(0.1)	0.2	(0.0 - 0.9)	0.763
Pneumonia	1,704	190	10.0	(8.8 - 11.5)	182	(9.6)	7.0	(5.3 - 9.2)	0.020

Number of pneumonias in the last two years

	Survivors (N=1,894)		Siblings [a] (N=731)	
	n	% [f]	% [f]	P [g]
0	82	4.3	3.5	0.006
1	56	3.0	1.5	
>= 2	15	0.8	0	
missing	37	1.9	2.0	

[a] Siblings are weighted for gender, age at survey, Swiss language region, and migration background according to survivors.

[b] Long-term prevalence of pulmonary diseases of survivors is calculated for survivors who stated “Yes, ever in life”.

[c] “Yes, after diagnosis” column contains persons who affirmed having developed the condition after cancer diagnosis.

[d] P-values calculated from chi-squared tests comparing long-term prevalence of survivors reporting pulmonary disease “Yes, ever in life” and long-term prevalence of pulmonary disease in siblings.

[e] All pulmonary diseases, e.g., pneumonia, chest wall abnormalities, lung fibrosis and/or emphysema.

[f] Column percentages are given.

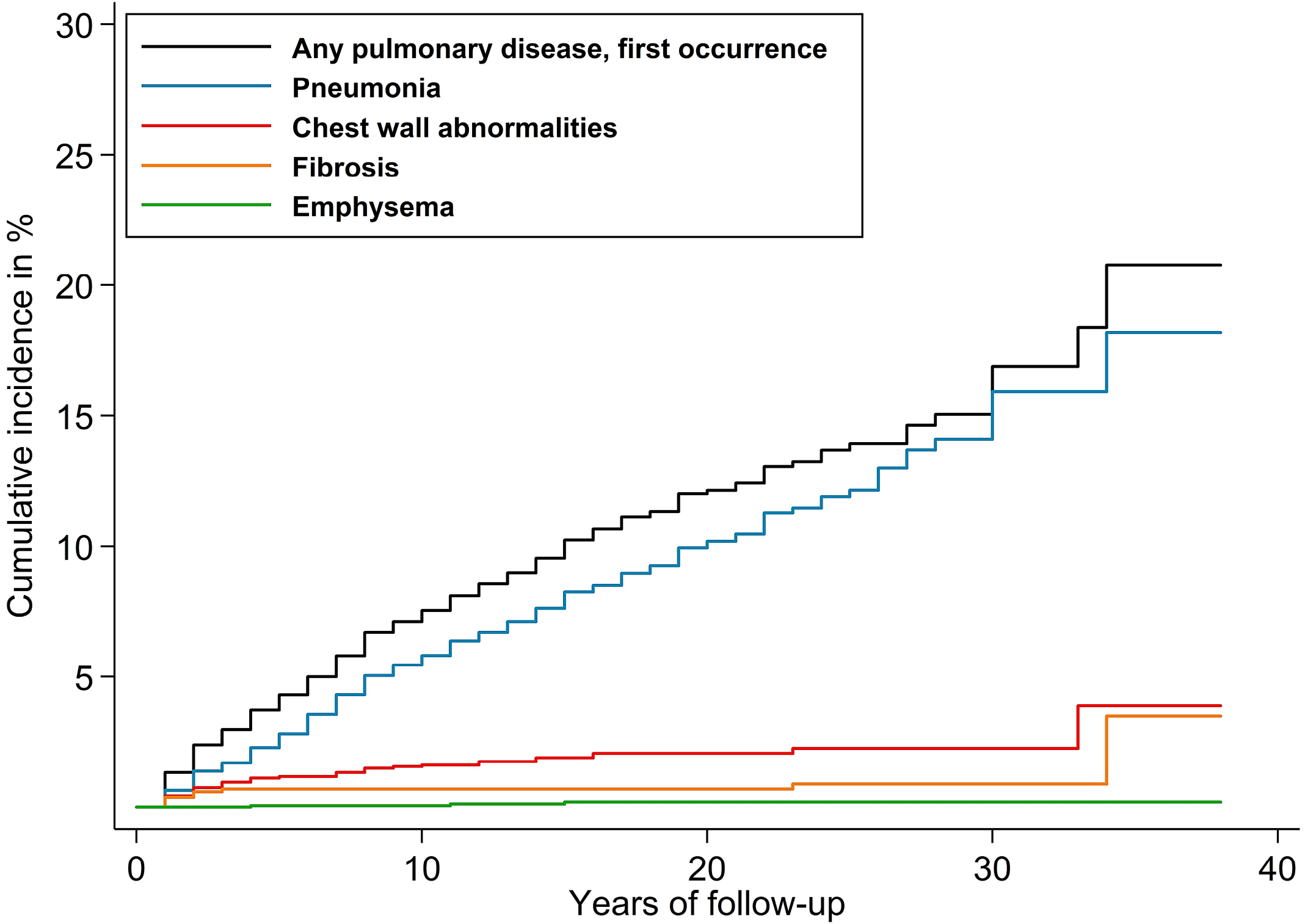
[g] P-values calculated from chi-squared tests comparing numbers of pneumonias in survivors and siblings.

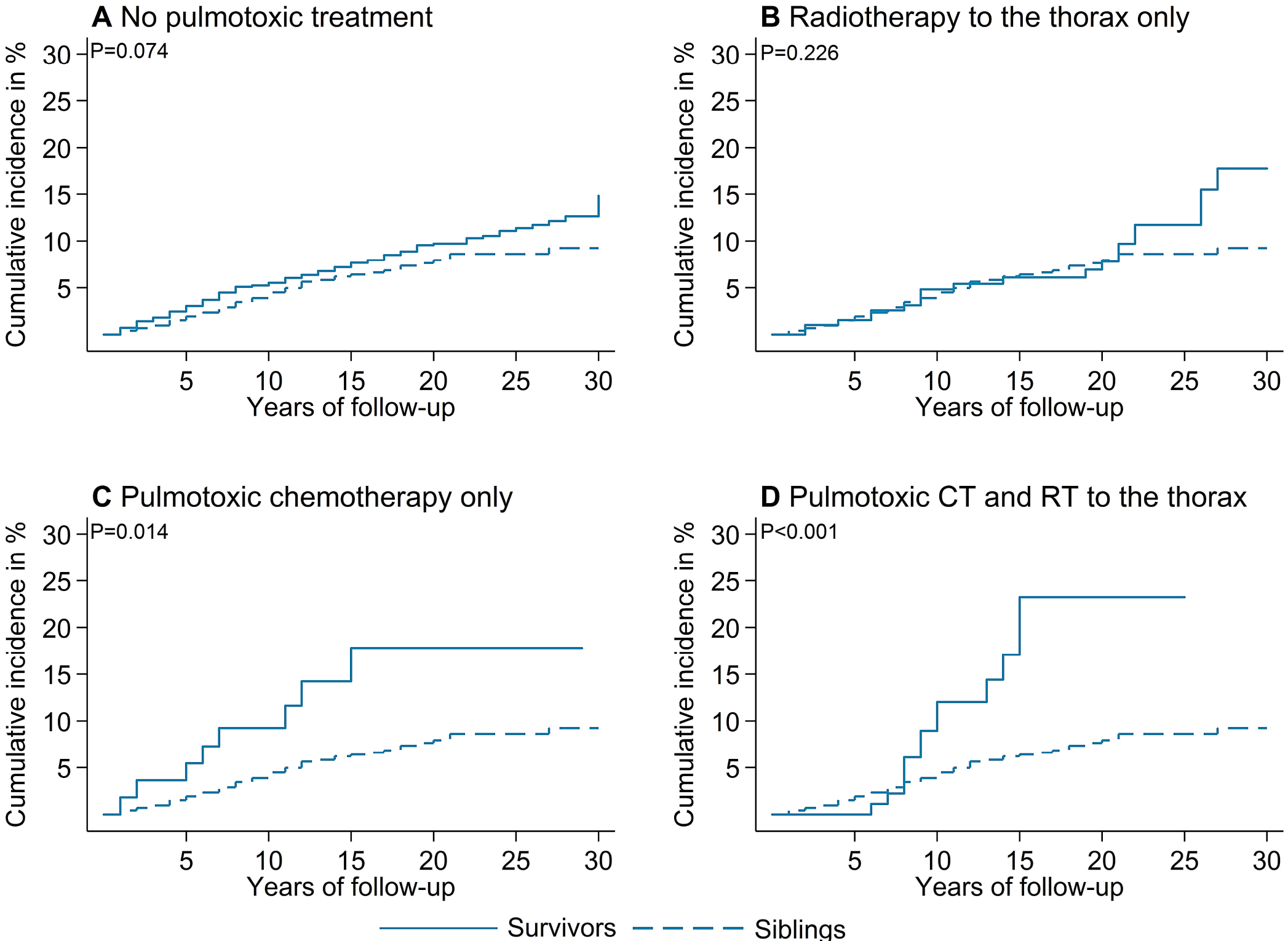
TABLE 3 Prevalence of pulmonary diseases in childhood cancer survivors by period of cancer diagnosis

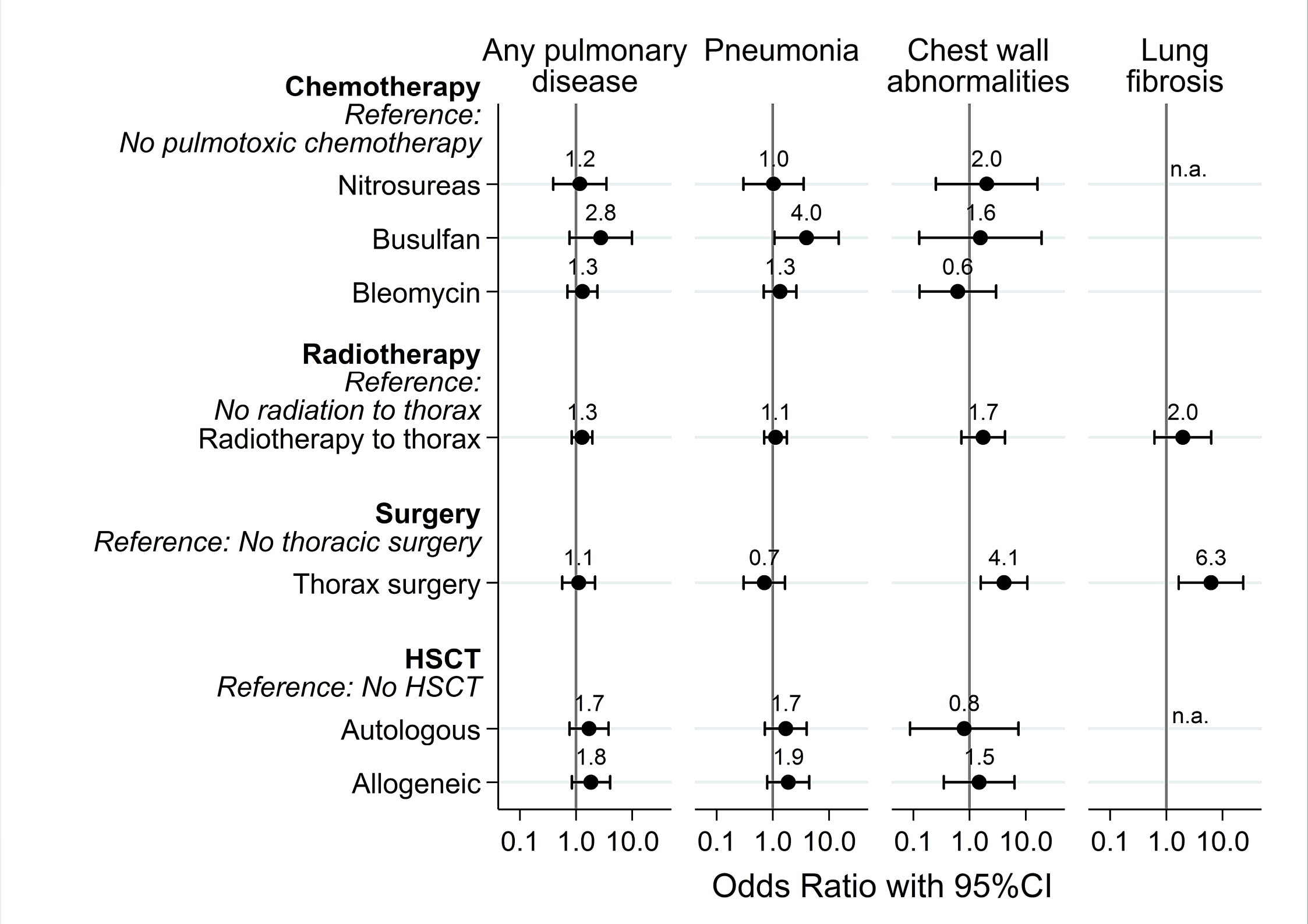
	Total Survivors	Any pulmonary disease			Pneumonia			Chest wall abnormalities			Lung fibrosis			Emphysema		
	(N=1894)	(N=215)			(N=182)			(N=38)			(N=15)			(N=3)		
	n	n	%[a]	P [b]	n	%[a]	P [b]	n	%[a]	P [b]	n	%[a]	P [b]	n	%[a]	P [b]
Period of cancer diagnosis				0.690			0.421			0.952			0.026			0.913
1976-1985	463	51	11		41	9		10	2		8	1.8		1	0.2	
1986-1995	839	101	12		89	11		16	2		3	0.4		1	0.1	
1996-2005	592	63	10		52	9		12	2		4	0.7		1	0.2	

[a] Row percentages are given.

[b] P-values calculated from chi squared tests comparing prevalence of pulmonary diseases in periods of cancer diagnosis.


Any pulmonary disease, first occurrence
Pneumonia
Chest wall abnormalities
Fibrosis
Emphysema
Cumulative incidence in %
30
25
20
15
10
5
0
10
20
30
40
Years of follow-up


A No pulmotoxic treatment
P=0.074
B Radiotherapy to the thorax only
P=0.226
C Pulmotoxic chemotherapy only
P=0.014
D Pulmotoxic CT and RT to the thorax
P<0.001
Cumulative incidence in %
Years of follow-up
Survivors
Siblings


Any pulmonary disease
Pneumonia
Chest wall abnormalities
Lung fibrosis
Chemotherapy
Reference: No pulmotoxic chemotherapy
Nitrosureas
1.2
1.0
2.0
n.a.
Busulfan
2.8
4.0
1.6
Bleomycin
1.3
1.3
0.6
Radiotherapy
Reference: No radiation to thorax
Radiotherapy to thorax
1.3
1.1
1.7
2.0
Surgery
Reference: No thoracic surgery
Thorax surgery
1.1
0.7
4.1
6.3
HSCT
Reference: No HSCT
Autologous
1.7
1.7
0.8
n.a.
Allogeneic
1.8
1.9
1.5
0.1 1.0 10.0
Odds Ratio with 95%CI

Supplemental

Supplementary text

Additional Methods

Reporting of pulmonary diseases in the SCCSS

We also looked at asthma and chronic cough in survivors and their siblings. Both are common in the general population. Asthma was reported by 208 (11%) of 1894 survivors and 76 (10%) of 731 siblings, and chronic cough lasting more than 3 months by 78 (4%) of 1894 survivors and 29 (4%) of 731 siblings. The prevalence of asthma and chronic cough did not differ between survivors and siblings (P=0.979), regardless of whether siblings' figures were weighted for survivor's sociodemographic characteristics (gender, age at survey, Swiss language region, and migration background) or not. This suggests that survivors did not over-report pulmonary diseases in the SCCSS questionnaire compared to their siblings.

Handling of missing data

Few participants had missing outcome data: pneumonia (66 survivors [3%], 13 siblings [2%]), chest wall abnormalities (51 survivors [3%], 8 siblings [1%]), lung fibrosis (55 survivors [3%], 10 siblings [1%]), emphysema (55 survivors [3%], 12 siblings [2%]). The date of first occurrence of pulmonary diseases was missing in some CCS: pneumonia (68 of 190 survivors [36%], 16 of 58 siblings [28%]), chest wall abnormalities (12 of 42 survivor [29%]), lung fibrosis (0 of 16 survivors [0%]), emphysema (0 of 3 survivors [0%]). We performed non-parametric missing value imputation for mixed type data (continuous and categorical) to obtain estimates for these dates using the missForest package in R.[26]

TABLE S1 Surgical details for survivors who had thoracic surgery

	Survivors with thoracic surgery [a] n = 80	
	n	(%) [b]
Thoracotomy	57	(71)
Tumor biopsy	12	(15)
Tumor resection	39	(49)
with no further specification	23	(29)
for pulmonary metastasectomy	8	(10)
for pulmonary wedge resection	2	(3)
for pulmonary lobectomy	6	(7)
Further specification	6	(7)
Chest wall surgery [c]	11	(14)
Rib resection	7	(9)
Thoracoscopy	5	(6)
Tumor biopsy	1	(1)
Tumor resection	4	(5)
with no further specification	1	(1)
for pulmonary metastasectomy	1	(1)
for pulmonary wedge resection	2	(2)

[a] Survivors were only classified to a single category. If multiple surgeries were performed, we classified survivors by the most severe intervention in the following sequence (severe to less severe): lobectomy > wedge resection > metastasectomy > no further specification > biopsy.
[b] Column percentages are given.
[C] Including surgery to clavicle, scapulae and ribs, tumor excision from soft tissue on thorax, muscles on thorax, spine of thorax.

TABLE S2 Characteristics of responding and nonresponding survivors and siblings before and after weighting for survivor's gender, age at survey, Swiss language region, and migration background

	Survivors					Siblings				
	Responders		Nonresponders			Unweighted			Weighted	
	N = 1,894		N = 1,024			N = 731				
	n	(%)[a]	n	(%)[a]	P [b]	n	(%)[a]	P [b]	(%)[c]	P [b]
Sociodemographic characteristics										
Gender					**<0.001**			**<0.001**		0.871
Female	898	(47)	389	(38)		428	(59)		(48)	
Male	996	(53)	635	(62)		303	(41)		(52)	
Age at survey (years)					**<0.001**			**<0.001**		0.980
16-19	419	(22)	250	(25)		116	(16)		(22)	
20-29	892	(47)	403	(39)		333	(45)		(47)	
≥30	583	(31)	371	(36)		282	(39)		(31)	
Swiss language region					**<0.001**			**<0.001**		0.982
German	1,320	(70)	655	(64)		592	(81)		(70)	
French	515	(27)	350	(34)		117	(16)		(27)	
Italian	59	(3)	19	(2)		22	(3)		(3)	
Migration background								**<0.001**		0.896
No	1,436	(76)				618	(85)		(76)	
Yes	458	(24)				113	(15)		(24)	
Lifestyle characteristics										
Smoking status								0.104		0.666
Never smoker	1,218	(64)				457	(62)		(63)	
Ex-smoker	222	(12)				108	(15)		(13)	
Current smoker	454	(24)				166	(23)		(24)	

Performing sports							**0.001**	**0.003**
No	757	(40)			242	(33)	(33)	
Yes	1,137	(60)			489	(67)	(67)	
BMI at survey							**0.004**	**0.003**
Underweight	108	(6)			19	(3)	(2)	
Healthy	1,271	(67)			513	(70)	(72)	
Overweight / Obese	515	(27)			199	(27)	(26)	

Clinical characteristics					
Age at diagnosis (years)					**<0.001**
0-5	695	(37)	300	(29)	
>5-10	446	(23)	199	(20)	
>10	753	(40)	525	(51)	
Period of cancer diagnosis					**<0.001**
before 1986	463	(24)	207	(20)	
1986-1995	839	(44)	393	(38)	
after 1995	592	(31)	424	(42)	
Diagnosis (ICCC-3)					**<0.001**
I Leukemia	601	(32)	223	(22)	
II Lymphoma	391	(20)	241	(24)	
III CNS tumor	262	(14)	179	(17)	
IV Neuroblastoma	73	(4)	28	(3)	
V Retinoblastoma	39	(2)	18	(2)	
VI Renal tumor	107	(6)	27	(3)	
VII Hepatic tumor	11	(1)	3	(0.3)	
VIII Bone tumor	86	(4)	57	(5)	
IX Soft tissue sarcoma	116	(6)	68	(6)	
X Germ cell tumor	94	(5)	99	(10)	
XI&XII Other rare tumors [d]	114	(6)	81	(8)	

Treatments					
Chemotherapy					**<0.001**
No chemotherapy	347	(18)	361	(35)	
Any chemotherapy	1,547	(82)	663	(65)	
Radiotherapy					**0.027**
No radiotherapy	1,155	(63)	667	(65)	
Any radiotherapy	739	(37)	357	(35)	
Surgery					**<0.001**
No surgery	836	(44)	300	(29)	
Any surgery	1,058	(56)	724	(71)	
Hematopoietic stem cell transplantation (HSCT)					0.321
No HSCT	1,802	(95)	983	(96)	
Any HSCT	93	(5)	41	(4)	

[a] Column percentages are given.
[b] P-values calculated from chi-squared tests comparing respective group to responders.
[c] Column percentages given are weighted for gender, age at survey, Swiss language region, and migration background of survivors.
[d] Including Langerhans Cell Histiocytosis, other malignant epithelial neoplasms, malignant melanomas, and other or unspecified malignant neoplasms.

Table S3 Prevalence of pneumonia in childhood cancer survivors and siblings by cancer treatment

	Prevalence of Pneumonia [a]		
	%	**(95%CI)**	**P [b]**
Siblings (n=731)	7.0	(5.3 - 9.2)	
Survivors not treated with pulmotoxic chemotherapy or radiotherapy to the thorax (n=1,545)	9.6	(8.2 - 11.1)	**0.048**
Survivors treated with pulmotoxic chemotherapy (n=65)	14.5	(7.3 – 27.0)	**0.042**
Survivors treated with radiotherapy to the thorax (n=193)	10.4	(6.7 - 15.5)	0.129
Survivors treated with pulmotoxic chemotherapy and radiotherapy to the thorax (n=91)	14.4	(8.4 - 23.5)	**0.014**

[a] Prevalence of siblings is weighted for gender, age at survey, Swiss language region, and migration background of survivors. Prevalence of survivors is calculated with variable “Yes, ever in life.”
[b] P-values calculated from chi-squared tests comparing prevalence of survivors reporting pulmonary diseases and prevalence of pulmonary disease in siblings.

TABLE S4 Associations between sociodemographic and treatment characteristics and self-reported pulmonary diseases. Results from multivariable logistic regression, adjusted for all factors in the table.

	Any pulmonary disease (n=215)			**Pneumonia (n=182)**			**Chest wall abnormalities (n=38)**			**Lung fibrosis (n=15)**		
Total N=1'894	OR	(95% CI)	P [a]	OR	(95% CI)	P [a]	OR	(95% CI)	P [a]	OR	(95% CI)	P [a]
Socio-demographic characteristics												
Gender			0.164			**0.023**			0.120			0.933
Female	Ref.			Ref.			Ref.			Ref.		
Male	0.8	(0.6 - 1.1)		0.7	(0.5 – 1.0)		1.7	(0.9 - 3.5)		1.0	(0.3 - 3.2)	
Age at diagnosis			0.883			0.963			0.150			**0.046**
0-5 years	Ref.			Ref.			Ref.			Ref.		
>5-10 years	0.9	(0.6 - 1.4)		1.1	(0.7 - 1.6)		0.4	(0.1 - 1.2)		6.3	(0.7 - 59.6)	
>10 years	1.0	(0.7 - 1.5)		1.0	(0.7 - 1.5)		0.9	(0.4 - 1.9)		8.0	(1.0 - 65.8)	
Lifestyle characteristics												
Smoking status			0.214			0.816			0.409			0.107
Never smoked	Ref.			Ref.			Ref.			Ref.		
Ex-smoker	1.4	(1.0 - 2.2)		1.2	(0.7 - 1.9)		1.8	(0.7 - 4.7)		3.3	(1.0 - 10.9)	
Current smoker	1.0	(0.7 - 1.5)		1.0	(0.7 - 1.5)		1.4	(0.7 - 3.0)		0.7	(0.1 - 3.3)	
Performing sports			0.724			0.214			0.104			0.499
No	Ref.			Ref.			Ref.			Ref.		
Yes	1.1	(0.8 - 1.4)		1.2	(0.6 – 2.1)		0.6	(0.3 - 1.1)		0.7	(0.2 - 2.0)	
BMI at survey			0.697			0.717			0.289			**0.037**
Underweight	1.3	(0.7 - 2.3)		1.1	(0.6 - 2.1)		1.9	(0.6 - 5.9)		6.6	(1.7 - 24.9)	
Healthy	Ref.			Ref.			Ref.			Ref.		
Overweight /Obese	1.0	(0.7 - 1.4)		1.2	(0.8 - 1.6)		0.7	(0.3 - 1.5)		0.9	(0.2 - 3.6)	

Therapy												
Chemotherapy												
No pulmotoxic drug	Ref.		0.405	Ref.		0.202	Ref.		0.813	n.a.[b]		
BCNU/CCNU	1.2	(0.4 - 3.5)		1.0	(0.3 - 3.6)		2.0	(0.2 - 16.2)				
Busulfan	2.8	(0.8 - 9.9)		4.0	(1.1 – 14.9)		1.6	(0.1 – 19.2)				
Bleomycin	1.3	(0.7 - 2.4)		1.3	(0.7 – 2.6)		0.6	(0.1 – 3.0)				
Radiotherapy to the thorax			0.266			0.637			0.234			0.266
No RT to the thorax	Ref.			Ref.			Ref.			Ref.		
RT to the thorax	1.3	(0.8 - 1.9)		1.1	(0.7- 1.8)		1.7	(0.7 - 4.3)		2.0	(0.6 - 6.3)	
Surgery			0.799			0.400			**0.009**			**0.015**
No thoracic surgery	Ref.			Ref.			Ref.			Ref.		
Thoracic surgery	1.1	(0.6 - 2.2)		0.7	(0.3 - 1.6)		4.1	(1.6 - 10.7)		6.3	(1.7 - 26.6)	
Hematopoetic stem cell tansplantation			0.204			0.255			0.837	n.a.[b]		
No HSCT	Ref.			Ref.			Ref.					
Autologous	1.7	(0.8 - 3.8)		1.7	(0.7 - 4.0)		0.8	(0.1 - 7.4)				
Allogeneic	1.8	(0.8 - 4.0)		1.9	(0.8 - 4.4)		1.5	(0.3 - 6.3)				

n.a.: Not applicable; Ref.: Reference; RT: Radiotherapy
[a] P-value was calculated with likelihood ratio-tests.
[b] Treatment factor was not included in multivariable logistic regression, as there were no events in the groups for nitrosoureas treatment and autologous HSCT.

TABLE S5 Associations between sociodemographic and treatment characteristics and self-reported pulmonary diseases. Results from univariable logistic regression.

	Any pulmonary disease (n=215)				Pneumonia (n=182)				Chest wall abnormalities (n=38)				Lung fibrosis (n=15)				Emphysema[d] (n=3)	
				P [c]				P [c]				P [c]				P [c]		
Total N=1'894	n[a]	(%)[b]	OR	(95% CI)	n[a]	(%)[b]	OR	(95% CI)	n[a]	(%)[b]	OR	(95% CI)	n[a]	(%)[b]	OR	(95% CI)	n[a]	(%)[b]
Socio-demographic characteristics																		
Gender				0.109				**0.022**				0.184				0.645		
Female	113	(13)	Ref.		101	(11)	Ref.		14	(2)	Ref.		8	(1)	Ref.		3	(0.3)
Male	102	(10)	0.8	(0.6 - 1.1)	81	(8)	0.7	(0.5 - 0.9)	24	(2)	1.6	(0.8 - 3.0)	7	(1)	0.8	(0.3 - 2.2)	0	(0)
Age at diagnosis				**0.536**				0.802				0.114				**0.019**		
0-5 years	75	(11)	Ref.		63	(9)	Ref.		16	(2)	Ref.		1	(0.1)	Ref.		0	(0)
>5-10 years	47	(11)	0.7	(0.7-1.4)	43	(10)	1.1	(0.7 - 1.6)	4	(1)	0.4	(0.1 - 1.2)	4	(1)	6.3	(0.7 - 56.4)	0	(0)
>10 years	93	(12)	1.0	(0.8-1.6)	76	(10)	1.1	(0.8 - 1.6)	18	(2)	1.0	(0.5 - 2.1)	10	(1)	9.3	(1.2 - 73.2)	3	(0.4)
Lifestyle characteristics																		
Smoking status				0.237				0.805				0.500				0.076		
Never smoked	133	(11)	Ref.		116	(10)	Ref.		21	(2)	Ref.		8	(1)	Ref.		1	(0.1)
Ex-smoker	33	(15)	1.5	(0.9 - 2.1)	24	(11)	1.2	(0.7 - 1.8)	6	(3)	1.6	(0.6 - 4.0)	5	(2)	3.5	(1.1 - 10.8)	0	(0)
Current smoker	49	(11)	1.0	(0.7 - 1.4)	42	(9)	1.0	(0.7 - 1.4)	11	(2)	1.4	(0.7 - 3.0)	2	(0.4)	0.7	(0.1 - 3.2)	2	(0.4)
Performing sports				0.89				0.359				0.055				0.991		
No	85	(11)			67	(9)	Ref.		21	(3)	Ref.		7	(1)	Ref.		2	(0.3)
Yes	130	(11)	1.0	(0.8 - 1.4)	115	(10)	1.2	(0.8 - 1.6)	17	(2)	0.5	(0.3 - 1.0)	8	(1)	0.8	(0.3 - 2.1)	1	(0.1)
BMI at survey				0.517				0.815				0.394				**0.031**		
Underweight	16	(15)	1.4	(0.8 - 2.4)	12	(9)	1.2	(0.6 - 2.3)	4	(2)	1.8	(0.6 - 5.4)	8	(1)	6.1	(1.8 - 20.5)	2	(2)
Healthy	143	(11)	Ref.		119	(11)	Ref.		26	(4)	Ref.		4	(4)	Ref.		1	(0.1)
Overweight/Obese	56	(11)	1.0	(0.7 - 1.3)	51	(10)	1.1	(0.8 - 1.5)	8	(2)	0.8	(0.3 - 1.7)	3	(1)	0.9	(0.2 - 3.5)	0	(0)

Therapy																		
Chemotherapy				**0.035**				**0.028**				0.679						
No pulmotoxic drug	190	(11)	Ref.		161	(9)	Ref.		34	(2)	Ref.		12	(1)			2	(0.1)
BCNU/CCNU	4	(13)	1.3	(0.4 - 3.7)	3	(10)	1.1	(0.3 - 3.7)	1	(3)	1.7	(0.2 - 13.1)	0	(0)			0	(0)
Busulfan	5	(38)	5.1	(1.7 - 15.8)	5	(38)	6.2	(2.0 – 19.1)	1	(8)	4.2	(0.5 – 33.2)	1	(8)			1	(8)
Bleomycin	16	(16)	1.5	(0.9 - 2.7)	13	(13)	1.4	(0.8 - 2.6)	2	(2)	1.0	(0.2 - 4.3)	2	(2)			0	(0)
Radiotherapy to the thorax				**0.035**				**0.028**				0.679						
No RT to the thorax	172	(11)	Ref.		149	(9)	Ref.		28	(2)	Ref.		9	(0.6)	Ref.		2	(0.1)
RT to the thorax	43	(15)	1.5	(1.0 - 2.1)	33	(12)	1.3	(0.9 - 1.9)	10	(4)	2.1	(1.0 - 4.3)	6	(2)	3.8	(1.4 - 10.9)	1	(0.4)
Surgery				0.320				0.787				**0.001**				**0.003**		
No thoracic surgery	203	(11)	Ref.		175	(10)	Ref.		31	(2)	Ref.		11	(1)	Ref.		1	(0.1)
Thoracic surgery	12	(15)	1.4	(0.7 - 2.6)	7	(9)	0.9	(0.4 - 2.0)	7	(9)	5.5	(2.4 - 12.9)	4	(5)	8.6	(2.7 - 27.7)	2	(3)
Hematopoetic stem cell tansplantation				**0.015**				**0.027**				0.197						
No HSCT	195	(11)	Ref.		165	(9)	Ref.		34	(2)	Ref.		14	(1)			2	(0.1)
Autologus	10	(21)	2.2	(1.1 - 4.5)	9	(19)	2.3	(1.1 - 4.9)	1	(2)	1.1	(0.2 - 8.4)	0	(0)			0	(0)
Allogeneic	10	(22)	2.4	(1.1 - 4.8)	8	(18)	2.1	(1.0 - 4.7)	3	(7)	3.7	(1.1 - 12.6)	1	(2)			1	-2

n.a.: Not applicable; Ref.: Reference group; RT: Radiotherapy
[a] Absolute numbers of survivors reporting pulmonary outcome.
[b] Row percentage are given.
[c] Global P-value was calculated with likelihood ratio-tests.
[d] Proportions only are reported for Emphysema, as there were too few events reported.

Respiratory System (Lungs)

Have you ever been told by a doctor that you have, or have had …	Ever in life? Yes	Ever in life? No	Since when?	Currently? Yes	Currently? No
Asthma	☐	☐	_____ (Year)	☐	☐
Chronic cough (for more than 3 month)	☐	☐	_____ (Year)	☐	☐
Pneumonia **If yes,** how many in the last two years? _____ pneumonia	☐	☐	_____ (Year)	☐	☐
Lung fibrosis (scarring of the lung)	☐	☐	_____ (Year)	☐	☐
Changes on your thorax and/or ribs	☐	☐	_____ (Year)	☐	☐
Emphysema	☐	☐	_____ (Year)	☐	☐
Have you ever had an examination by a respiratory specialist, for example a spirometry or ergometry?	☐	☐	_____ (Year)	☐	☐
Any other breathing or lung problem? **If yes, describe this problem.** _____ _____	☐	☐	_____ (Year)	☐	☐

FIGURE S1 English translation of original questions for adults on pulmonary health in the SCCSS questionnaire

Original questions in German, French and Italian as well as for adolescents are available on request.

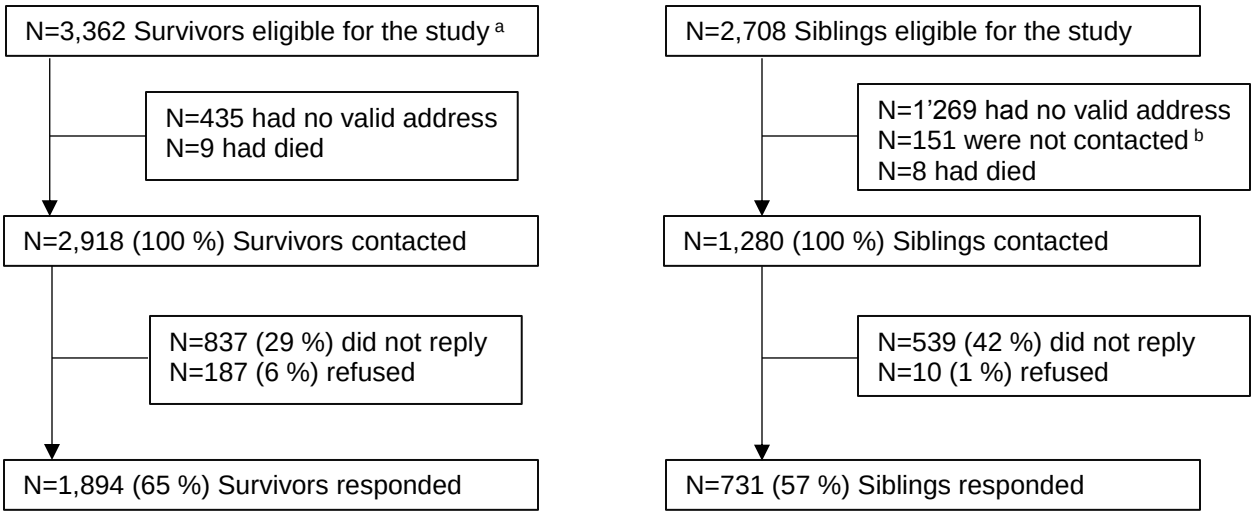


FIGURE S2 Response rates in the Swiss Childhood Cancer Survivor Study for both, childhood cancer survivors and siblings, ≥16 years old at survey

[a] Eligible: registered in SCCR, diagnosed 1976-2005, aged ≤20 years at diagnosis, survived for ≥5 years from initial cancer diagnosis and were aged ≥16 years at survey
[b] Not contacted because of different reasons: sibling refused through survivor/parent; survivor does not want contact anymore, survivor has no contact with sibling, half-sibling, several siblings aged <16 years, survivor died.

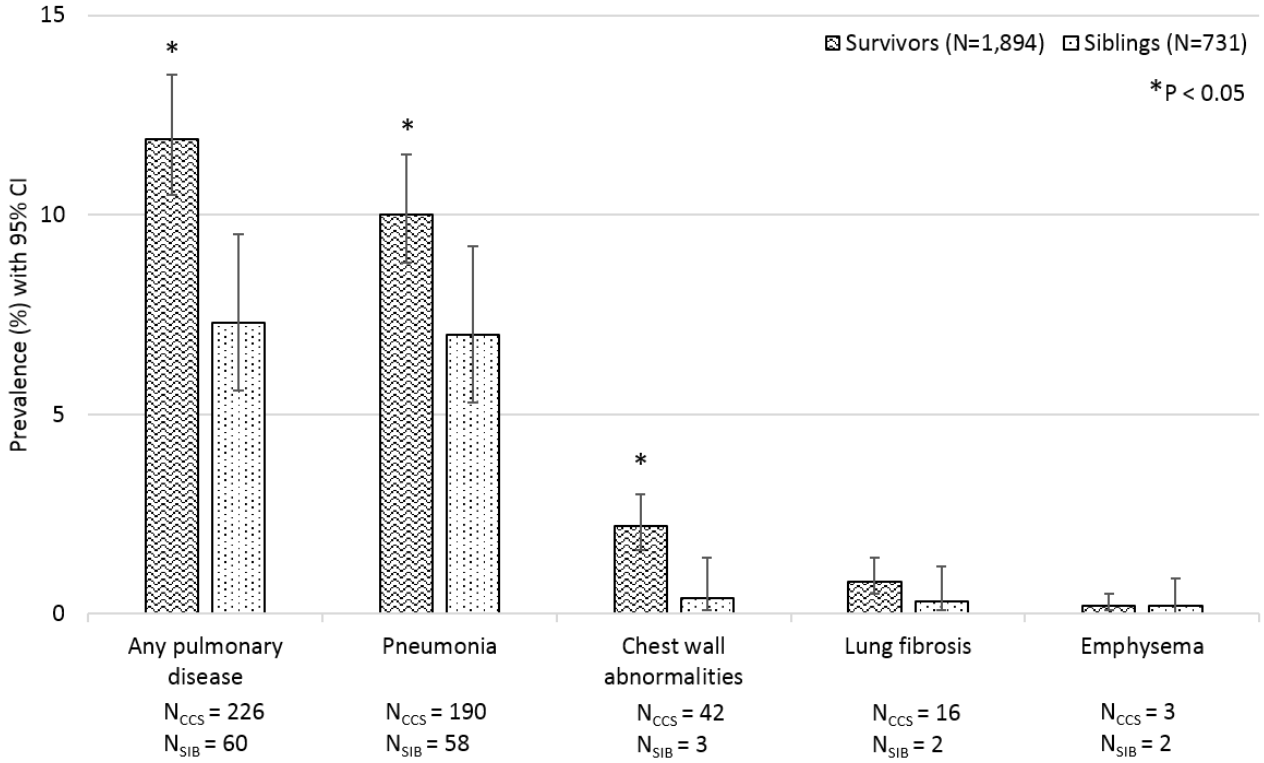


FIGURE S3 Long-term prevalence of self-reported pulmonary diseases in childhood cancer survivors and siblings

N_{CCS}: Number in survivors; N_{SIB}: number in siblings
Prevalence of siblings is weighted for gender, age at survey Swiss language region and migration background of survivors; Numbers are absolute values.