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Cardiovascular disease after childhood acute lymphoblastic leukaemia: a cohort study

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Summary

BACKGROUND AND AIMS: Cardiovascular diseases (CVD) increase late morbidity and mortality in survivors of acute lymphoblastic leukaemia (ALL). We compared the risk of CVD in ALL survivors to siblings, examined time trends, quantified treatment-related risks, and investigated whether risk extends beyond patients treated with anthracyclines and chest radiotherapy.

METHODS: The Swiss Childhood Cancer Survivor Study assessed CVD by patient questionnaire in 5-year ALL survivors diagnosed between 1976 and 2005 and their siblings. Participants were asked whether a physician had ever told them that they had hypertension, arrhythmia, heart failure, myocardial infarction, angina pectoris, stroke, thrombosis or valvular problems. We investigated treatment-related risk factors for CVD using multivariable logistic regression, adjusting for demographic and socioeconomic factors, BMI, smoking, diabetes mellitus, alcohol consumption and physical activity.

RESULTS: We contacted 707 survivors and 1299 siblings, 511 (72%) and 709 (55%) of whom responded, respectively. Survivors had a higher risk of developing CVD than siblings (odds ratio [OR] 1.9, 95% confidence interval 1.3–2.8), in particular heart failure (OR 13.9, 1.8–107.4). Compared to patients treated 1976–85, the risk of CVD was 1.4 (0.7–2.8) for those treated 1985–1994 and 1.5 (0.6–3.7) for those treated 1995–2005. The overall CVD risks after anthracycline treatment (OR 3.1, 2.0–4.7), haematopoietic stem cell transplantation (OR 8.0, 2.4–26.9) or relapse (OR 4.1, 1.9–8.8) were increased compared to those of siblings, while the CVD risks of survivors treated without anthracycline or chest radiotherapy were similar (OR 1.0; 0.5–2.0).

CONCLUSIONS: Despite attempts to reduce cardiotoxicity in childhood cancer treatment, CVD risks in ALL survivors treated more recently do not seem to have declined.

Trial registration number: NCT03297034

Keywords: cardiovascular, late effects, leukaemia, cardiotoxic, heart failure, anthracycline, Swiss Childhood Cancer Registry, Europe

Introduction

Acute lymphoblastic leukaemia (ALL) is the most common malignancy in childhood. Its incidence has increased in recent decades [1]. Better treatments have improved five-year survival rates to 85 percent [1, 2]. A consequence of these effective treatments is damage to normal tissues, which may result in the long-term dysfunction of many organs. The cardiovascular system is particularly vulnerable to cancer treatment, and cardiovascular diseases (CVD) are recognised late effects of cancer treatment [3]. Survivors of childhood ALL have a lifelong increased risk for cardiovascular morbidity and mortality compared to the general population, mainly caused by chemotherapy with anthracyclines or, to a lesser extent, by direct or scattered chest radiotherapy [4]. ALL survivors also have an increased prevalence of insulin resistance and dyslipidaemia [5], and differ from their siblings in health behaviours relevant for CVD, such as physical activity, smoking and alcohol consumption [6–9].

In recent decades, cumulative doses of potentially cardiotoxic treatments for ALL have been reduced. Today,

Author contributions
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low-risk patients receive lower anthracycline doses, and craniospinal radiotherapy is only given to children who relapse [3, 10]. A recent American study reported a reduction of cardiac mortality among ALL survivors [10], but there are no studies of time trends in non-lethal cardiovascular late effects after childhood cancer. Previous studies of cardiovascular morbidity were mostly restricted to survivors diagnosed before 1990, who were treated with protocols that are no longer in use [4, 11–14]. More recent work has suggested that cardiovascular risk may extend beyond survivors who had anthracyclines or chest radiotherapy [15]. Follow-up care after the end of treatment has been intensified and now includes screening for early CVD.

In the Swiss Childhood Cancer Survivor Study (SCCSS), we assessed physician-diagnosed CVD with patient questionnaires. This study compares the risk of CVD reported by ALL survivors to that of their siblings, and changes in risk based on the calendar period of diagnosis. It also examines treatment-related risk factors for CVD in order to determine whether risk increases are confined to patients exposed to cardiotoxic anthracyclines and chest radiotherapy.

Material and methods

Study population

The SCCSS is a population-based, long-term follow-up study of all childhood cancer patients registered in the Swiss Childhood Cancer Registry (SCCR) who have survived for at least five years after cancer diagnosis. Children in the study were diagnosed between 1976 and 2005 and before the age of 20 with leukaemia, lymphoma, central nervous system tumours, malignant solid tumours or Langerhans cell histiocytosis [16]. Between 2007 and 2012, we sent questionnaires (in German, French or Italian) to all survivors. The questionnaire is based on those used in American and British childhood cancer survivor (CCS) studies [17, 18]. It assessed quality of life, health outcomes, current medication and health service use, psychological distress, health behaviour and socioeconomic information. This study includes only participants who were diagnosed with ALL before age 16 years, had survived more than five years after diagnosis, and were 16 years or older and alive at the time of the survey. Those who did not respond to the first mailing received a second copy of the questionnaire. If they again did not respond, we contacted them by phone. Siblings were contacted as a control group. If survivors agreed, we sent a similar questionnaire without cancer-related questions to their siblings. More detailed information on the study design has been published elsewhere [19].

Ethics approval was granted by the Ethics Committee of the Canton of Bern to the SCCR and SCCSS (KEK-BE: 166/2014) and the SCCSS is registered at ClinicalTrials.gov (identifier: NCT03297034).

We reported the results according to the STROBE guidelines [20].

Cardiovascular outcomes

The questionnaire included a separate section on CVD, as in the American and British CCS studies (see figure S1 in appendix 1) [17, 18]. We asked survivors and siblings whether they had ever been diagnosed with arterial hypertension, arrhythmia, heart failure or cardiac dysfunction, myocardial infarction, angina pectoris, stroke, deep vein thrombosis or pulmonary embolism, or valvular problems. Arteriosclerosis, though mentioned in the questionnaire, was not analysed as CVD. Reporting at least one CVD was the primary outcome for the analysis. Respondents could use a free text field to describe additional CVD, including pericarditis. Two authors, CEK and JNC, independently recoded all problems mentioned in the free text fields into the CVD categories mentioned and resolved any discrepancies. We coded missing data in outcomes as "no" based on the assumption that people who did not tick "yes" did not have a clinically relevant disease.

Explanatory variables

We obtained detailed information on sociodemographic characteristics, diagnoses and treatments from the SCCR (see appendix 2). These included gender, nationality, cancer diagnosis, year and age at cancer diagnosis, age at survey, chemotherapy, clinical study participation, treatment protocol, radiotherapy, surgery, haematopoietic stem cell transplantation (HSCT) and history of relapse. Information on follow-up, sociodemographic and behavioural cardiovascular risk factors came from the SCCSS questionnaire.

Statistical analysis

For better comparison to survivors, we weighted the sibling responses for all analyses according to age, gender, language region and migration background, as previously described [8, 21] (supplementary table S1 in appendix 3).

First (analysis 1), we compared the prevalence of CVD reported by ALL survivors and siblings using standardised χ^2 tests. We calculated odds ratios and their 95% confidence intervals (CI) for each outcome, comparing survivors to siblings using weighted univariable logistic regressions.

We then investigated the effects of cancer related variables on our main outcome (≥1 CVD), again using weighted logistic regressions. In the first of these analyses (analysis 2), we investigated whether CVD risks among survivors differed by period of cancer diagnosis (1976–1984, 1985–1994, 1995–2005). This regression model was further adjusted for participation in follow-up care in order to examine any potential effects of detection or recall bias. Survivors attending follow-up care might have been better and/or more recently screened for cardiac problems and therefore report more CVD.

Next (analysis 3), we investigated differences in CVD risk according to treatment-related risk factors (cancer diagnosis, age at diagnosis, history of relapse, chemotherapy, radiotherapy, haematopoietic stem cell transplantation, follow-up care and the different cardiotoxic treatment combinations described above). This analysis included both survivors and siblings (reference group).

Regression models of analyses 2 and 3 were adjusted for recognised cardiovascular risk factors (age, gender, migration background, language region, parents' highest education, BMI, smoking status, diabetes mellitus, alcohol consumption and physical activity). Given this large number of covariates, we followed an approach proposed by Arbogast et al. and Miettinen to reduce dimensionality [22,

23]. In this approach, adjustment for multiple cardiovascular risk factors is done using a summary disease risk score (DRS). To generate the DRS, the outcome is regressed on all the potential confounders and exposures of interest. The results from this intermediate regression are shown in table S2 (appendix 3). For each participant and for each exposure of interest, the DRS was calculated as the log odds of the outcome predicted from this fitted model while treating the individual as unexposed. In the same way, a DRS was calculated for each participant by treating the individual as simultaneously unexposed to all exposures of interest.

All analyses were performed using the statistical software package Stata (Version 13, Stata Corporation, Austin, Texas).

Results

Characteristics of ALL survivors and siblings

We included responses from 511 of the 707 ALL survivors whom we contacted (response rate 72%), and 709 of 1,299 siblings (55%, fig. S2 in appendix 3) in the analysis.

Fifty percent (n = 258) of the 511 ALL survivors were male. Twenty-six percent of survivors were aged 16–20, 49% 21–30, and 25% over 30 at the time of the survey. Cardiovascular risk factors differed between ALL survivors and siblings: ALL survivors had more diabetes mellitus, consumed less alcohol and were less physically active (table S1 in appendix 3). Responders were more often between 21 and 30 years old at survey, female, and diagnosed in earlier time periods than nonresponders. They did not differ by history of relapse or cancer treatment (table S3).

Cardiotoxic treatment has changed in recent decades (table 1). All ALL survivors had received chemotherapy, including 62% (315/511) with anthracyclines. Anthracycline use increased from 42% in 1976–1984, to 71% in 1985–1994, and decreased again to 63% in those diagnosed 1995–2005. Overall, 30% (151/511) of survivors received radiotherapy, and 5% (23/511) radiotherapy to the chest. This last proportion decreased from 9% in 1976–1984 to 4% in 1985–1994 and 1% in 1995–2005. HSCT was performed in 5% (23/511) of all survivors, with no significant change over time.

Risk of CVD in ALL survivors

Compared to siblings, ALL survivors had an increased risk of CVD. Fourteen percent of 511 ALL survivors reported at least one CVD compared to 8% of siblings (OR 1.9, 95% CI 1.3–2.8; p = 0.002) (table 2). Evidence of an increased risk among survivors was strongest for cardiac problems (OR 2.3, CI 1.4–3.8), especially high for heart failure (OR 13.9, CI 1.8–107.4).

We found no evidence for a time trend in self-reported CVD (fig. 1). As figure 1 illustrates, compared to survivors diagnosed 1976–84, the relative odds of CVD were 1.4 (0.7–2.8) for those diagnosed 1985–94 and 1.5 (0.6–3.7) for those diagnosed 1995–2005 (p = 0.567, Model A). Odds ratios remained qualitatively similar when we adjusted for the attendance of follow-up care (Model B): 1.3 (0.7–2.6) for those diagnosed 1985–1994 and 1.1 (0.4–2.9) for those diagnosed 1995–2005.

Treatment-related risk factors for CVD

Adjusting for the baseline DRS, we found increased risks for developing CVD compared to siblings in ALL survivors treated recently (OR 4.1, CI 2.1–7.9), with a history of relapse (OR 4.1, CI 1.9–8.8), those treated with anthra-

Table 1: Treatment related characteristics of acute lymphoblastic leukaemia survivors by calendar period of diagnosis.

ALL Survivors (n = 511)		1976–1984 (n = 135)		1985–1994 (n = 245)		1995–2005 (n = 131)		p-value*
		n	(%)	n	(%)	n	(%)	
Age at questionnaire (years)	16–20	0	0	47	19	88	67	<0.001
	21–30	36	27	172	70	43	33	
	31–40	81	60	26	11	0	0	
	41 or more	18	13	0	0	0	0	
Age at diagnosis (years)	0–4	69	51	140	57	35	27	<0.001
	5–9	48	36	66	27	41	31	
	10 or more	18	13	39	16	55	42	
History of relapse	Yes	29	22	26	11	15	11	0.009
Chemotherapy	Other CT†	78	58	70	29	48	36	<0.001
	Anthracycline	57	42	175	71	83	63	
Radiotherapy	No RT	73	53	185	76	103	79	<0.001
	Other RT‡	52	39	49	20	27	21	
	Chest RT§ <20 Gy	7	5	7	3	0	0	
	Chest RT§ 20–39 Gy	5	3	4	2	1	1	
HSCT	Allogeneic	6	4	7	3	6	5	0.301
	Autologous	0	0	3	1	1	1	
Combination of therapies¶	Other CT†, no or other RT‡	77	57	69	28	48	37	<0.001
	Anthracyclines, no or other RT‡	46	34	165	67	82	63	
	Anthracyclines, chest RT§	11	8	10	4	1	1	
Still in follow-up care‖	Yes	14	11	44	19	77	63	<0.001

ALL = acute lymphoblastic leukaemia; CT = chemotherapy; HSCT = haematopoietic stem cell transplantation; RT = radiotherapy Percentages are based upon available data for each variable. * p-values from chi-squared tests comparing the different time periods † Other chemotherapeutic agents: any chemotherapy other than anthracycline (n = 165) and those who received chemotherapy with unknown details (n = 31) ‡ Other radiotherapy: no history of radiotherapy on the chest (limbs, cranial, neck, pelvis and abdomen) § Chest radiotherapy: mantle field, total body irradiation, thoracic spine radiation, unspecified radiation of the thorax ¶ Patients with HSCT are excluded ‖ Still in clinical follow-up care after cancer treatment at the time of the study (for raw data, see table S4 in appendix 3).

cyclines (OR 3.1, CI 2.0–4.7), and those who had a HSCT (OR 8.0, CI 2.4–26.9) (table 3).

We observed an increased risk of CVD in those treated with both anthracyclines and chest radiotherapy (OR 2.5, CI 0.5–13.7) and in those treated with anthracyclines alone (OR 2.8, CI 1.8–4.5) (fig. 2). ALL survivors treated with chemotherapy other than anthracyclines had a risk similar to that of their siblings (OR 1.0, CI 0.5–2.0).

Discussion

Swiss ALL survivors had a nearly two-fold greater risk for CVD than siblings overall. Risk was most pronounced for heart failure, and CVD risk did not decrease in survivors treated more recently. Only patients treated with anthracyclines, radiotherapy to the chest or HSCT were at risk for CVD, with little evidence of increased risks of other regimens.

Drawing upon the national SCCSS, these results are representative of all Swiss ALL survivors, conditional on being 5-year survivors and alive. Because our study had nationwide coverage, we believe our results are broadly generalisable for ALL patients from developed countries. Patients in Switzerland are treated according to international protocols used in Europe and North America. Of particular relevance is our inclusion of recently treated patients. A further strength of this study is its systematic use of the disease risk score, which allowed us to adjust for many cardiovascular risk factors simultaneously to obtain more precise effect estimates [22].

The main limitation of the study is the low number of cases, caused by the young age of participants. This leads to

Table 2: Prevalence* of self-reported cardiovascular disease in acute lymphoblastic leukaemia survivors compared with siblings.

	ALL survivors (n = 511)		Siblings† (n = 709)		OR	95% CI	p-value§
	n	%‡	n	%‡			
Any CVD¶	73	14.3	58	8.1	1.9	1.3–2.8	0.002
Multiple (≥2) CVD	12	2.4	8	1.1	2.1	0.8–5.6	0.142
Cardiac problems only‖	47	9.2	29	4.2	2.3	1.4–3.8	0.001
Hypertension**	24	4.7	26	3.8	1.3	0.7–2.4	0.438
Arrhythmia**	27	5.3	21	3.0	1.8	1.0–3.5	0.065
Heart failure or cardiomyopathy**	12	2.4	1	0.2	13.9	1.8–107.4	0.012
Myocardial infarction**	1	0.2	2	0.3	0.6	0.0–9.6	0.717
Angina pectoris**	8	1.6	8	1.2	1.4	0.5–3.9	0.512
Stroke**	3	0.6	1	0.2	3.8	0.6–24.2	0.163
Venous thrombosis/pulmonary embolism**	5	1.0	5	0.7	1.5	0.4–4.9	0.532
Valvular problems**	8	1.6	4	0.7	2.6	0.8–8.0	0.094

ALL = acute lymphoblastic leukaemia; CVD = cardiovascular diseases; CI = confidence interval; OR = odds ratio * Missing values coded to 0 † Siblings' numbers and percentages weighted for survivor characteristics (standardised for age, gender, migration background and language region) ‡ Column percentages are given § p-values calculated from logistic regression models for weighted values comparing ALL survivors to siblings ¶ At least one of hypertension, arrhythmia, heart failure or cardiomyopathy, myocardial infarction, angina pectoris, stroke, venous thrombosis/pulmonary embolism or valvular problems ‖ Hypertension, thrombotic problems and strokes excluded ** Missing values for outcome (survivors, siblings): hypertension (1.1%, 5.1%), arrhythmia (1.1%, 4.7%), heart failure or cardiomyopathy (1.2%, 4.5%), myocardial infarction (1.4%, 4.3%), angina pectoris (32.3%, 26.4%), stroke (1.9%, 4.5%), venous thrombosis / pulmonary embolism (1.7%, 4.5%), valvular problems (1.7%, 4.9%)

Table 3: Prevalence and relative odds for any cardiovascular disease in survivors of acute lymphoblastic leukaemia compared to siblings (OR 1.0) adjusted for the baseline risk score.

		No. total	No. CVD	%* CVD	OR†	95% CI	p-value‡
Diagnosis of ALL		511	73	14.3	2.2	1.5–3.4	<0.001
Period of cancer diagnosis	1976–1984	135	19	14.1	1.2	0.6–2.4	0.018
	1985–1994	245	36	14.7	2.7	1.7–4.4	
	1995–2005	131	18	13.7	4.1	2.1–7.9	
Age at diagnosis (years)	0–4	244	29	11.9	2.1	1.3–3.6	0.362
	5–9	155	21	13.5	1.8	1.0–3.3	
	10 or more	112	23	20.5	3.0	1.6–5.6	
History of relapse	No	441	56	12.7	1.9	1.2–3.0	0.047
	Yes	70	17	24.3	4.1	1.9–8.8	
Chemotherapy	Other chemotherapeutic agents§	196	19	9.7	1.2	0.6–2.3	0.005
	Anthracyclines	315	54	17.1	3.1	2.0–4.7	
Radiotherapy	No RT	359	48	13.4	2.3	1.5–3.6	0.645
	Other RT¶	128	21	16.4	2.0	1.0–3.9	
	Chest RT‖ 1–19 Gy	14	1	7.1	0.8	0.1–7.5	
	Chest RT‖ 20 or more Gy	10	3	30	8.5	1.4–51.6	
HSCT**	No	487	66	13.6	2.1	1.3–3.2	0.028
	Yes	24	7	29.2	8.0	2.4–26.9	

ALL=- acute lymphoblastic leukaemia; DRS=- disease risk score; CVD = cardiovascular diseases; HSCT = haematopoietic stem cell transplantation; OR = odds ratio; RT = radiotherapy; CI = confidence interval Percentages are based upon available data for each variable. * Row percentages are given † Adjusted with Baseline DRS for age at questionnaire, gender, migration background, language region, parents' education, smoking status, BMI, diabetes mellitus, alcohol consumption and physical activity ‡ P-values calculated from Wald test for comparison within survivors only § Other chemotherapeutic agents: any chemotherapy other than anthracycline (n = 165) and those who received chemotherapy with unknown details (n = 31) ¶ Other radiotherapy: no history of radiotherapy on the chest ‖ Chest radiotherapy: mantle field, total body irradiation, thoracic spine radiation, unspecified radiation of the thorax ** Includes both autologous and allogeneic, and both peripheral blood cell and bone marrow transplantation

large confidence intervals. A further limitation is that cardiovascular conditions were self-reported without external validation. Some participants could actually have hypertension but not be aware of it because their blood pressure has never been measured. As a sensitivity analysis, we excluded ALL survivors who reported only hypertension from the analysis of risk factors. The directions and strength of the associations did not change (period of cancer 1976–1984, OR 1.7, CI 0.7–3.7; 1985–1994, OR 2.9, CI 1.7–5.1; 1995–2005, OR 3.9, CI 1.9–8.1). However, period of cancer diagnosis was no longer significantly associated (p = 0.22) (see table S5 in appendix 3). We interpret this as a lack of statistical power due to the lower numbers of cardiac outcomes in the analysis. Although this could lead to either under- or overestimation of CVD [24], good agreement is possible between self-reported CVD and medical records [25]. We did not include deceased cases; however, few patients in our population died from a cardiac cause [26]. We could not retrieve the anthracycline status for 6% of the patients, and their treatment was classified as other chemotherapeutic agent. This might have introduced bias, leading to an underestimation of the effect of anthracyclines and an overestimation of the risk in those exposed to other chemotherapy. We could not grade severity of CVD according to the Common Terminology Criteria for Adverse Events (CTCAE) with the available information [27].

Figure 1: Odds ratios for reporting a cardiovascular disease by calendar period of diagnosis, adjusted for baseline risk (model A) and for baseline risk and follow-up care (model B).* p-values calculated from likelihood ratio tests.

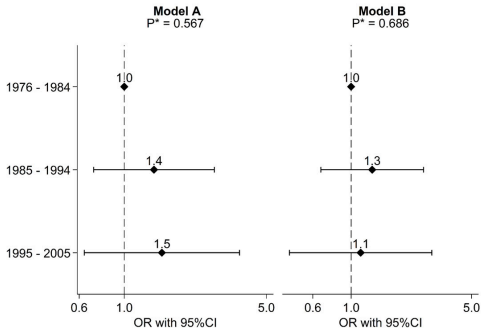
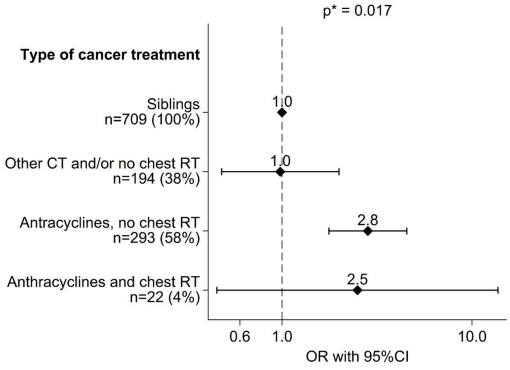


Figure 2: Odds ratios and 95% confidence intervals for reporting any cardiovascular disease in acute lymphoblastic leukaemia survivors by type of treatment. Results are adjusted for the baseline disease risk score†.* p-values calculated from Wald test for survey statistics comparing only inter-survivor responses; † Baseline disease risk score: adjusting for age at questionnaire, gender, migration background, language region, parents' education, smoking status, body mass index, diabetes mellitus, alcohol consumption and physical activity.Other CT: any chemotherapy other than anthracyclines and those who received chemotherapy with unknown details; Chest RT: mantle field, total body irradiation, thoracic spine radiation, unspecified radiation of the thorax.NOTE: Patients with haematopoietic stem cell transplantation (n = 24) were excluded from these analyses. There were no patients without chemotherapy and only two patients with chest radiotherapy but no anthracycline treatment.



Overall, the prevalence of CVD in our ALL-survivor cohort is similar to that reported from questionnaire surveys in other childhood cancer survivors such as the assessment of CVD in a large American childhood cancer survivor study that used the same questions [12]. Respective prevalences in that study and ours were broadly comparable: 0.7% and 0.2% for myocardial infarction, 1.3% and 0.2% for pericardial disease, 1.7% and 2.4% for cardiomyopathy, and 1.6% and 1.6% for valvular diseases. Prevalence of CVD in siblings was comparable in both. Hazard ratios (odds ratios) for CVD, comparing ALL survivors with siblings in this American (and our) study were 4.2 (13.9, 95% CI 1.8–107.4) for congestive heart failure, 3.3 (0.6, 95% CI 0.0–6.5) for myocardial infarction, and 2.6 (2.6, 95% CI 0.8–8.0) for pericardial disease and valvular abnormalities.

A Dutch study that assessed CVD during follow-up consultations and by questionnaire reported a prevalence of 3.7% for cardiac events (congestive heart failure, cardiac ischemia, valvular disease, cardiac arrhythmia, pericarditis) in a population of 1,362 CCS with a median age of 29.1 years at study [14]. The reason why this prevalence is lower than our figure of 14.3% might be because the Dutch study only included CVD with a CTCAE grade higher than 2, whereas we might also have included less severe manifestations. Both that study and ours contrast with a recent study that assessed CVD by physical examinations and echocardiography, which reported a prevalence of 7.4% for cardiomyopathy, 3.8% for coronary artery disease, 28% for valvular disease and 4.4% for conduction/rhythm disorders [28]. However, only high-risk patients treated with anthracyclines or chest radiotherapy were included in the study, and subclinical disease was also detected by these examinations.

Our study supports observations that HSCT and anthracycline therapy are risk factors for CVD [3]. We found no evidence suggesting that anthracycline and chest radiotherapy have a synergistic effect, which is consistent with no interaction between radiation dose and anthracycline exposure in relation to cardiac deaths [29], although our study was underpowered for assessing such interactions. Our results do not support the hypothesis that all cancer treatments, in addition to anthracyclines and chest radiotherapy, lead to an increased risk of CVD [28].

Over the past 20 years, anthracycline doses have been reduced in low-risk ALL patients, and craniospinal radiotherapy is now limited to patients with relapse. The American childhood cancer survivor study reported a decrease in the incidence of cardiac deaths from 0.6 in 1970–74 to 0.1 in 1990–1994 [10]. It is perhaps surprising, then, that although cardiac mortality has declined, we observed no relative reduction of risk for CVD in recently treated ALL survivors compared to ALL survivors treated earlier. We

offer two possible explanations for this finding. First, if the incidence of CVD has remained constant while follow-up care has improved, then we might detect CVD earlier and offer better treatment options, and decreased cardiac mortality ensues. Second, a small group of high-risk ALL-patients has received even higher doses of anthracyclines. Treatment of this small, high-risk group may have offset an otherwise small decline to produce an incidence of CVD that appears little changed. Engagement in more intense follow-up may have led to the detection of more CVD in recent years. In Model B (fig. 1), we adjusted for follow-up care. However, we cannot fully rule out possible residual confounding.

New studies should include clinical assessment of CVD and more recently treated patients, and also assess both morbidity in relation to mortality of CVD to avoid survivor bias. In the clinic, closer, prospective follow-up of those patients at risk may improve detection of subclinical CVD, thus permitting earlier intervention that could reduce the severity of outcomes.

Conclusion

Our national study of ALL survivors demonstrates the higher risk of CVD in ALL survivors treated with known cardiotoxic treatment regimens. Survivors treated with other regimens did not seem to have increased risk compared to siblings. Despite attempts to reduce cardiotoxicity in cancer treatment regimens during the past decades, we found no decrease in CVD risk over time.

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Potential competing interests

None of the authors report any conflict of interest related to the study. 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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Appendix 1

Questions on cardiovascular problems in the Swiss Childhood Cancer Survivor Study

The questions on cardiovascular problems in the Swiss Childhood Cancer Survivor Study are shown in figure S1.

Appendix 2: Explanatory variables from the Swiss Childhood Cancer Survivor Study (SCCSS)

We obtained detailed information on sociodemographic characteristics, diagnoses and treatments from the SCCR. These included gender, nationality, cancer diagnosis, year and age at cancer diagnosis, age at survey, chemotherapy (yes/no), clinical study participation (yes/no, study protocol, treatment arm), treatment protocol, radiotherapy (yes/no, area, dose), surgery (yes/no, area, type), haematopoietic stem cell transplantation (yes, including autologous or allogeneic/no), and history of relapse (yes/no). We determined anthracycline and other chemotherapeutic agent use (yes/no) through information on clinical study participation and treatment protocol from the SCCR. Other chemotherapeutic agents included any chemotherapy not containing anthracyclines and chemotherapy with unknown details. We classified radiotherapy into four categories: No radiotherapy, Other radiotherapy, Chest radiotherapy 1-19 Gray (Gy) and Chest radiotherapy 20 Gy or more. Chest radiotherapy included total body irradiation, mantle field irradiation or irradiation to the thorax, mediastinum, or thoracic spine. Cardiotoxic treatment was divided into other chemotherapeutic agents and/or other radiotherapy, other chemotherapeutic agents and chest radiotherapy, anthracyclines and other radiotherapy, and anthracyclines and chest radiotherapy. We also categorised period of diagnosis (1976-84, 1985-94, ≥1995), age at diagnosis (0-4, 5-9, ≥10 years) and age at questionnaire (16-20, 21-30, 31-40, or 41 or more years).

Information on follow-up, sociodemographic and behavioural cardiovascular risk factors came from the SCCSS questionnaire. We used data on parents' highest education (primary, secondary, tertiary), migration background (yes/no), smoking status (current/ever), height (cm) and weight (kg), diabetes mellitus (yes/no), alcohol consumption (Occasionally/never, >=1 standard drink weekly, not daily, 1 standard drink daily and >1 standard drink daily) and physical activity (yes/no). We asked survivors if they were still under regular follow-up care for their former childhood cancer (still in follow-up care/not in follow-up care). We coded migration status as yes if a participant was born abroad, had no Swiss citizenship at birth, or had at least one parent with no Swiss citizenship. We defined participants as physically active if they reported being engaged in any fitness training or sports. We calculated the body mass index (BMI) for each participant (kg/m2) and divided it into four categories: underweight, BMI <18; normal weight, BMI 18-24.9; overweight, BMI 25-30; and obese, BMI >30.

Appendix 3: Supplementary data

Figure S1: Questions on cardiovascular problems in the Swiss Childhood Cancer Survivor Study (German version)

43. **Herz und Kreislaufsystem**

	Irgendwann im Leben		Seit wann?	Aktuell noch vorhanden?	
	Ja	Nein		Ja	Nein
Wiederholt gemessener hoher Blutdruck (arterielle Hypertonie)	☐	☐	____ (Jahr)	☐	☐
Herzrhythmusstörungen (Arrhythmien, unregelmässige Herzschläge), welche von einem Kardiologen (Herzspezialisten) abgeklärt werden mussten	☐	☐	____ (Jahr)	☐	☐
Herzinsuffizienz (Herzmuskelschwäche, ev. mit Wassereinlagerungen in Beinen und Lunge und ev. Atemschwäche bei körperlicher Betätigung)	☐	☐	____ (Jahr)	☐	☐
Herzinfarkt	☐	☐	____ (Jahr)	☐	☐
Angina Pectoris (Engegefühl mit Schmerzen in der Brust, das durch einen Sauerstoffmangel im Herzen auftritt)	☐	☐	____ (Jahr)	☐	☐
Schlaganfall	☐	☐	____ (Jahr)	☐	☐
Arteriosklerose (Arterienverkalkung)	☐	☐	____ (Jahr)	☐	☐
Tiefe Venenthrombose oder Lungenembolie	☐	☐	____ (Jahr)	☐	☐
Probleme mit den Herzklappen (Insuffizienz, Verengungen, künstliche Herzklappen etc.)	☐	☐	____ (Jahr)	☐	☐
Haben Sie je spezielle Abklärungen bei einem Herzspezialisten (Kardiologen) durchführen müssen, bspw. eine Biopsie oder Setzen eines Katheters?	☐	☐	____ (Jahr)	☐	☐
Andere Probleme, die das Herz- und Kreislaufsystem betreffen, z.B. Perikarditis **Falls Ja**, bitte beschreiben Sie die Probleme näher _____ _____	☐	☐	____ (Jahr)	☐	☐

Figure S2: Study participants flow chart.* Not contacted because another sibling of the same family in the same age category was already contacted.

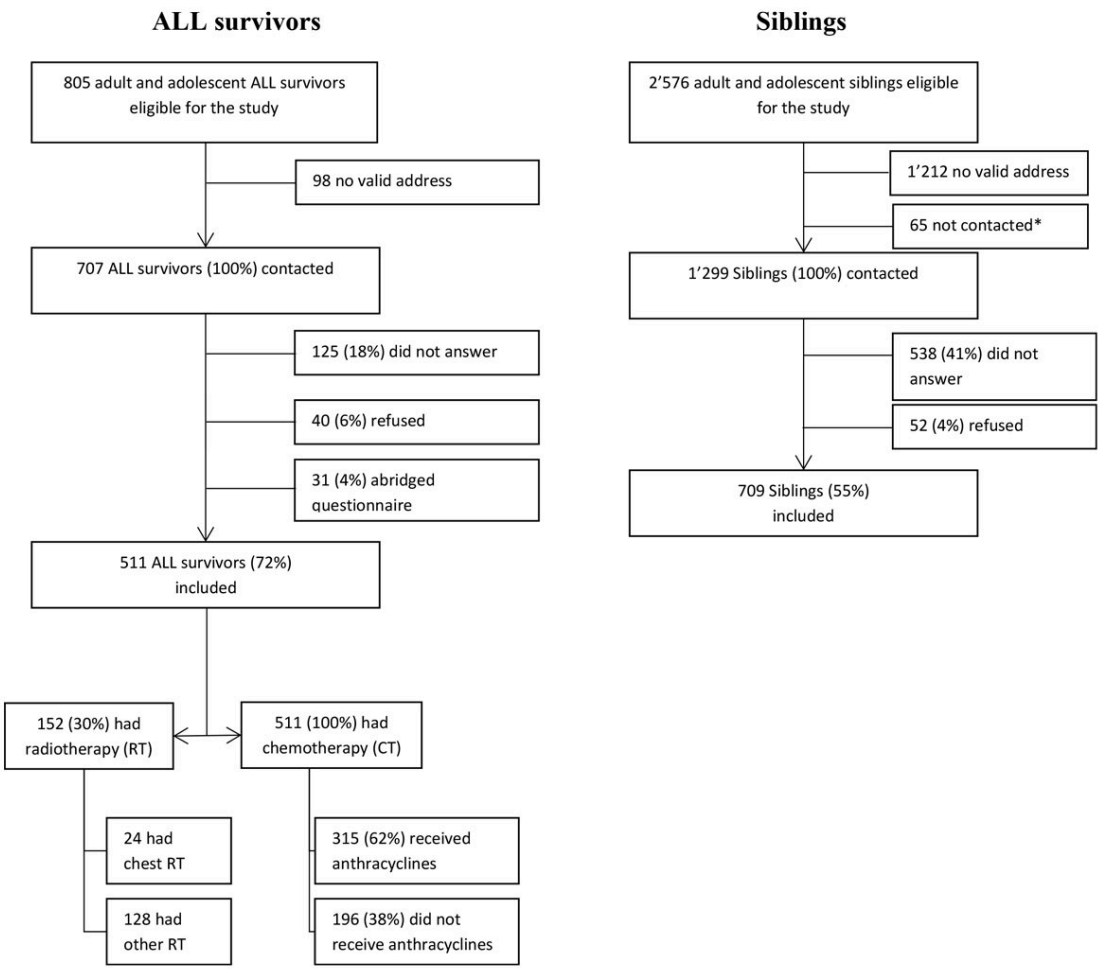

Table S1: Characteristics of acute lymphatic leukaemia survivors and siblings participating in the study.

	ALL survivors (n = 511)		Siblings (n = 709)				
			Unweighted			Weighted[a]	
	n	(%[b])	n	(%[b])	p-value[c]	(%[b])	p-value[d]
Sociodemographic conditions							
Age at questionnaire (years)							
– 16–20	135	(26.4)	120	(16.9)		(27.6)	
– 21–30	251	(49.1)	319	(45.0)		(48.9)	
– 31–40	107	(20.9)	195	(27.5)		(20.0)	
– 41 or more	18	(3.5)	75	(10.6)	<0.001	(3.5)	n.a.[a]
Gender							
– Male	258	(50.5)	291	(41.0)		(52.9)	
– Female	253	(49.5)	418	(59.0)	0.001	(47.1)	n.a.[a]
Migration background[e]							
– No migration background	466	(91.2)	679	(95.8)		(76.7)	
– Migration background	45	(8.8)	26	(4.2)	<0.001	(23.3)	n.a.[a]
Language region							
– German	384	(75.1)	591	(83.4)		(76.8)	
– French or Italian	127	(24.9)	118	(16.6)	<0.001	(23.2)	n.a.[a]
Parents' highest education[f]							
– Primary education	55	(10.8)	62	(8.7)		(7.3)	
– Secondary	337	(66.0)	499	(70.4)		(67.2)	
– Tertiary	104	(20.4)	132	(18.6)		(20.7)	
– Unknown	15	(2.9)	16	(2.3)	0.375	(4.8)	0.141
Lifestyle conditions							
Smoking							
– Never	308	(62.6)	446	(63.7)		(66.4)	
– Ever	184	(37.4)	254	(36.3)	0.695	(33.6)	0.202
– Current	111	(22.6)	135	(19.3)	0.169	(19.5)	0.233
Body mass index (kg/m^2)							
– Underweight (<18)	26	(5.4)	16	(2.3)		(2.9)	
– Normal weight (18–24.9)	336	(69.1)	499	(71.2)		(75.0)	
– Overweight (25–30)	102	(21.0)	149	(21.3)		(18.6)	
– Obese (>30)	22	(4.5)	37	(5.3)	**0.043**	(3.5)	0.098
Diabetes mellitus							
– No	500	(97.9)	706	(99.6)		(99.7)	
– Yes	11	(2.1)	3	(0.4)	**0.005**	(0.3)	**0.002**
Alcohol consumption(standard drink)							
– Occasionally/never	198	(40.7)	233	(33.3)		(28.2)	
– ≥1 weekly, not daily	261	(53.7)	422	(60.4)		(66.0)	
– Daily	27	(5.5)	44	(6.3)	0.020	(5.8)	**<0.001**
Physical activity[g]							
– Low	163	(33.2)	209	(29.9)		(26.5)	
– Sufficient	328	(66.8)	491	(70.1)	0.221	(73.5)	**0.020**

ALL = acute lymphoblastic leukaemia; n.a. = not applicable; RT = radiotherapy Percentages are based upon available data for each variable [a] Standardised (for age, gender, migration background and language region) numbers and percentages are given for siblings. N.A.: not applicable because this variable was used for standardisation [b] Column percentages are given [c] P-values calculated from chi-square statistics for unweighted values comparing survivors to siblings [d] P-values calculated from chi-square statistics for unweighted values comparing survivors to siblings [e] Migration background was defined as not born in Switzerland, no Swiss citizenship from birth or at least one parent with no Swiss citizenship [f] Secondary education included high school, teacher training, vocational education and professional school; primary education involved compulsory schooling; tertiary education included university or upper professional high school [g] Physical activity is defined as workout training, gym or sport (general)

Table S2: Results from the unconditional logistic regression model[a] used for creating the disease risk score.

	Cardiovascular disease (n = 1122)			
	n[b]	(%)[c]	Odds ratio	(95% CI)
Survivor				
– Sibling	65	(9)	1.0	
– Survivor	73	(14)	42.9	(5.2–353.9)
Age at questionnaire (years)				
– 16–20	17	(7)	1.0	
– 21–30	61	(11)	2.6	(1.3–5.4)
– 31–40	45	(15)	5.6	(2.6–12.4)
– 41 or more	15	(16)	7.9	(2.9–21.4)
Sex				
– Male	65	(12)	1.0	
– Female	73	(11)	0.7	(0.4–1.1)
Migration background[e]				
– No migration background	105	(11)	1.0	
– Migration background	33	(15)	1.9	(1.0–3.4)
Language region				
– German	115	(12)	1.0	
– French or Italian	23	(9)	0.7	(0.3–1.2)
Parents' highest education[f]				
– Primary education	97	(12)	1.0	
– Secondary	15	(13)	1.2	(0.5–2.9)
– Tertiary	25	(11)	1.1	(0.6–1.9)
– Unknown	1	(3)	6.1	(0.9–42.4)
Currently smoking				
– No	108	(11)	1.0	
– Yes	29	(12)	0.9	(0.4–2.0)
Ever smoked				
– No	84	(11)	1.0	
– Yes	53	(12)	1.0	(0.6–1.9)
Body mass index (kg/m^2)				
– Underweight (<18)	6	(14)	1.1	(0.5–2.5)
– Normal weight (18–24.9)	88	(11)	1.0	
– Overweight (25–30)	28	(11)	1.1	(0.6–2.0)
– Obese (>30)	12	(20)	1.7	(0.7–4.0)
Diabetes				
– No	49	(13)	1.0	
– Yes	87	(11)	1.0	omitted [d]
Alcohol consumption (standard drink)				
– Occasionally/never	59	(14)	1.0	
– ≥1 weekly, not daily	70	(10)	1.0	(0.6–1.7)
– Daily	3	(6)	0.6	(0.1–2.6)
– >Daily	5	(23)	1.9	(0.6–6.2)
Physical activity[g]				
– Low	49	(13)	1.0	
– Sufficient	87	(11)	0.7	(0.4–1.3)
Year at diagnosis				
Sibling	65	(9)	1.0	
– 1976–1984	19	(14)	0.4	(0.1–1.3)
– 1985–1994	36	(15)	0.8	(0.3–1.8)
– 1995–2005	18	(14)	1.0	omitted [d]
Age at diagnosis				
Sibling	65	(9)	1.0	
– 0–4	29	(12)	1.0	(0.5–2.3)
– 5–9	21	(14)	0.7	(0.3–1.7)
– ≥10	23	(21)	1.0	omitted [d]
Relapse				
– Sibling	65	(9)	1.0	
– No history of relapse	56	(13)	0.6	(0.2–1.4)
– Relapse	17	(24)	1.0	omitted [d]
Chemotherapy				
– Sibling	65	(9)	1.0	

	Cardiovascular disease (n = 1122)			
	n[b]	(%)[c]	Odds ratio	(95% CI)
– Other chemotherapy	19	(10)	0.6	(0.3–1.0)
– Anthracycline	54	(17)	1.0	omitted [d]
Radiotherapy (RT)				
– Siblings	65	(9)	1.0	
– No RT	48	(13)	0.7	(0.1–4.9)
– Other RT	21	(16)	0.7	(0.1–4.8)
– RT heart <20 Gy	1	(7)	0.1	(0.0–2.2)
– RT heart 20–39 Gy	3	(30)	1.0	omitted [d]
HSCT				
– Siblings	65	(9)	1.0	
– No HSCT	66	(14)	0.3	(0.1–1.4)
– HSCT	7	(29)	1.0	omitted [d]
Follow–up				
– Siblings	65	(9)		
– No follow–up	48	(14)	0.7	(0.3–1.4)
– Follow–up	24	(18)	1.0	omitted [d]

[a] Model adjusted for all factors shown [b] Absolute numbers of participants reporting to have a cardiovascular disease [c] Row percentages are given [d] Category omitted due to collinearity or perfect prediction of outcome

Table S3: Comparison of responding and nonresponding ALL-survivors in the Swiss Childhood Cancer survivor study.

	Responders (n=511)		Nonresponders (n=196)		p-value[b]
			unweighted		
	n	(%[a])	n	(%[a])	
Sociodemographic characteristics					
Age at questionnaire (years)					0.043
– 16–20	135	(26)	69	(35)	
– 21–30	251	(49)	74	(38)	
–	107	(21)	45	(23)	
– 41 or more	18	(4)	8	(4)	
Gender					0.001
– Male	258	(50)	127	(65)	
– Female	253	(50)	69	(35)	
Language region					0.646
– German	384	(75)	384	(73)	
– French or Italian	127	(25)	127	(27)	
Cancer related characteristics					
Age at diagnosis (years)					
– 0–4	244	(48)	93	(47)	0.771
– 5–9	155	(30)	64	(33)	
– 10 or more	112	(22)	39	(20)	
Year at diagnosis					0.005
– 1976–1984	135	(26)	53	(27)	
– 1985–1994	245	(48)	71	(36)	
– 1995–2005	131	(26)	72	(37)	
History of relapse					0.104
– No	442	(86)	160	(82)	
– Yes	69	(14)	36	(18)	
Chemotherapy					n.a.
– Yes	511	(100)	196	(100)	
Radiotherapy					0.365
– No	362	(71)	132	(67)	
– Yes	149	(29)	64	(33)	
HSCT					0.440
– No	487	(95)	184	(94)	
– Yes	24	(5)	12	(6)	

[a] Column percentages are given [b] p-values calculated from chi-squared tests comparing nonresponders to responders

Table S4: Numbers of patients with current follow-up care among all children diagnosed with ALL, by diagnostic period.

	1976–1984				1985–1995				1995–2005			
	No FU	% [a]	FU	%	No FU	%	FU	%	No FU	%	FU	%
Sociodemographic characteristics												
Age at questionnaire (years)												
16–20					30	15.7	11	25.0	26	57.8	54	70.1
21–30	31	26.1	4	28.6	141	73.8	27	61.4	19	42.2	23	29.9
31–40	72	60.5	8	57.1	20	10.5	6	13.6				
40 or more	*16*	13.4	2	14.3								
Gender												
Male	67	56.3	4	28.6	84	44.0	22	50.0	28	62.2	43	55.8
Female	52	43.7	10	71.4	107	56.0	22	50.0	17	37.8	34	44.2
Language region												
German	94	79.0	13	92.9	144	75.4	35	79.6	27	60.0	55	71.4
French or Italian	25	21.0	1	7.1	47	24.6	9	20.5	18	40.0	22	28.6
Cancer related characteristics												
Age at diagnosis (years)												
0–4	59	49.6	8	57	110	57.6	21	47.7	14	31.1	21	27.3
5–9	42	35.3	6	42.9	52	27.2	13	29.6	13	28.9	22	28.6
10 or more	18	15.1	0	0.0	29	15.2	10	22.7	18	40.0	34	44.2
History of relapse												
No	95	79.8	9	64.3	174	91.1	36	81.8	43	95.6	66	85.7
Yes	24	20.2	5	35.7	17	8.9	8	18.2	2	4.4	11	14.3
Chemotherapy												
Yes	119	100	14	100	191	100	44	100	45	100	77	100
Radiotherapy												
No	63	52.9	8	57.1	156	81.7	21`	47.7	33	73.3	66	85.7
Yes	56	47.1	6	42.9	35	18.3	23	52.3	12	26.7	11	14.3
HSCT [b]												
No	115	96.6	11	78.6	186	97.4	40	90.9	44	97.8	72	93.5
Yes	4	3.4	3	21.4	5	2.6	4	9.1	1	2.2	5	6.5

FU = current follow-up care, HSCT = haematopoietic stem cell transplantation Percentages are based upon available data for each variable [a] Row percentages are given, NOTE: Percentages are based upon available data for each variable [b] Includes both autologous and allogeneic, and both peripheral blood cell and bone marrow transplantation

Table S5: Prevalence and relative odds for any cardiovascular disease without hypertension in survivors of acute lymphoblastic leukaemia compared with siblings (OR 1.0) adjusted for the baseline risk score.

	No. total	No. CVD	%[a] CHD	OR[b]	95% CI	p-value[c]
Diagnosis of ALL	511	54	10.5	2.6	1.6–4.3	0.013
Period of cancer diagnosis						0.219
1976–1984	135	14	10.3	1.7	0.7–3.7	
1985–1994	245	26	10.6	2.9	1.7–5.1	
1995–2005	131	14	10.7	3.9	1.9–8.1	
Age at diagnosis (years)						0.431
0–4	244	24	16.7	2.7	1.5–4.9	
5–9	155	14	9.0	2.0	1.0–4.0	
10 or more	112	16	14.3	3.3	1.7–6.8	
History of relapse						0.078
No	441	42	9.5	2.3	1.4–3.9	
Yes	70	12	17.1	4.6	2.1–10.3	
Chemotherapy						0.01
Other chemotherapeutic agents[d]	196	13	6.6	1.3	0.6–2.9	
Anthracyclines	315	41	13.0	3.5	2.1–5.9	
Radiotherapy						0.910
No RT	359	35	9.7	2.5	1.5–4.3	
Other RT[e]	128	15	11.7	2.5	1.2–5.4	
Chest RT[f] 1–19 Gy	14	1	7.1	1.6	0.2–13.6	
Chest RT[f] 20 or more Gy	10	3	30.0	13.5	2.5–72.6	
HSCT[g]						0.532
No	487	51	10.5	2.6	1.5–4.2	
Yes	24	3	12.5	4.0	1.0–16.5	

ALL = acute lymphoblastic leukaemia; DRS = disease risk score; CVD = cardiovascular diseases; HSCT = haematopoietic stem cell transplantation; OR = odds ratio; RT = radiotherapy; CI = confidence interval Percentages are based upon available data for each variable [a] Row percentages are given [b] Adjusted with Baseline DRS for age at questionnaire, gender, migration background, language region, parents' education, smoking status, BMI, diabetes mellitus, alcohol consumption and physical activity [c] P-values calculated from Wald test for comparison within survivors only [d] Other chemotherapeutic agents: any chemotherapy other than anthracycline (n = 165) and those who received chemotherapy with unknown details (n = 31) [e] Other radiotherapy: no history of radiotherapy on the chest [f] Chest radiotherapy: mantle field, total body irradiation, thoracic spine radiation, unspecified radiation of the thorax [g] Includes both autologous and allogeneic, and both peripheral blood cell and bone marrow transplantation