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Original research

Increased risk of cardiac ischaemia in a pan-European cohort of 36 205 childhood cancer survivors: a PanCareSurFup study

Elizabeth Arnoldina Maria Feijen ,[1] Elvira C van Dalen,[1] Heleen J H van der Pal,[1] Raoul C Reulen,[2] David L Winter,[2] Claudia E Kuehni,[3,4] Vera Morsellino,[5] Daniela Alessi,[6] Rodrigue S Allodji,[7] Julliana Byrne,[8] Edit Bardi,[9] Zsuzsanna Jakab,[10] Desiree Grabow,[11] Stanislaw Garwicz,[12] Nadia Haddy,[13] Momcilo Jankovic,[14] Peter Kaatsch,[11] Gill A Levitt,[15] Cecile M Ronckers,[1] Christina Schindera,[3] Roderick Skinner,[16] Lorna Zalatel,[17] Lars Hjorth,[12] Wim J E Tissing,[1,18] Florent De Vathaire,[7] Mike M Hawkins,[2] Leontien C M Kremer,[1] on behalf of the PanCareSurFup consortium

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For numbered affiliations see end of article.

Correspondence to
Dr Elizabeth Arnoldina Maria Feijen, Princess Maxima Center for Pediatric Oncology, Utrecht 3720 AC, The Netherlands; e.a.m.feijen@prinsesmaximacentrum.nl

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ABSTRACT

Objective In this report, we determine the cumulative incidence of symptomatic cardiac ischaemia and its risk factors among European 5-year childhood cancer survivors (CCS) participating in the PanCareSurFup study.

Methods Eight data providers (France, Hungary, Italy (two cohorts), the Netherlands, Slovenia, Switzerland and the UK) participating in PanCareSurFup ascertained and validated symptomatic cardiac events among their 36 205 eligible CCS. Data on symptomatic cardiac ischaemia were graded according to the Criteria for Adverse Events V.3.0 (grade 3–5). We calculated cumulative incidences, both overall and for different subgroups based on treatment and malignancy, and used multivariable Cox regression to analyse risk factors.

Results Overall, 302 out of the 36 205 CCS developed symptomatic cardiac ischaemia during follow-up (median follow-up time after primary cancer diagnosis: 23.0 years). The cumulative incidence by age 60 was 5.4% (95% CI 4.6% to 6.2%). Men (7.1% (95% CI 5.8 to 8.4)) had higher rates than women (3.4% (95% CI 2.4 to 4.4)) (p<0.0001). Of importance is that a significant number of patients (41/302) were affected as teens or young adults (14–30 years). Treatment with radiotherapy/chemotherapy conferred twofold risk (95% CI 1.5 to 3.0) and cases in these patients appeared earlier than in CCS without treatment/surgery only (15% vs 3% prior to age 30 years, respectively (p=0.04)).

Conclusions In this very large European childhood cancer cohort, we found that by age 60 years, 1 in 18 CCS will develop a severe, life-threatening or fatal cardiac ischaemia, especially in lymphoma survivors and CCS treated with radiotherapy and chemotherapy increases the risk significantly.

BACKGROUND

Treatment for children with cancer has improved considerably over the last decades, resulting in better survival.[1] However, approximately 75% of childhood cancer survivors (CCS) will have at least one chronic health condition at a young age after attaining 5-year survival.[2–4] Symptomatic cardiac adverse events (CEs), that is, heart failure, cardiac ischaemia, arrhythmia, pericarditis and valvular disease, are well-known long-term adverse events following specific treatment for childhood cancer (eg, anthracyclines, radiotherapy where the heart was part of the field). CCS treated with these cardiotoxic treatment were found to have a 10.6% (95% CI 7.4 to 13.9) to develop heart failure, which is the most prevalent CE.[5] These events can lead to long-term morbidity and early mortality among CCS.[6–11]

Several studies have evaluated symptomatic cardiac ischaemia in CCS. The reported prevalences varied between 0.2% and 6%. These reports were often based on self-reported cardiac outcomes, different definitions of symptomatic cardiac ischaemia and varied greatly with respect to treatment histories and/or follow-up durations.[4 6 7 11–17] Unfortunately, most studies did not provide data on detailed risk factors for symptomatic cardiac ischaemia. A large study, the Childhood Cancer Survivor Study (CCSS) provided results of multivariable analyses and male gender, primary cancer diagnosis, treatment era, cardiac irradiation dose were identified as risk factors.[6] Another CCSS study, identified modifiable risk factors (like hypertension and obesity) as risk factors for cardiac ischaemia.[15]

Most aforementioned studies focus on clinically overt cardiac ischaemia, however, ischaemia can be also be detected in an asymptomatic stage. Mulrooney *et al*[18] performed a coronary CT angiography in a small group of 31 asymptomatic Hodgkin's survivors all treated with radiotherapy involving the heart region. It showed that 39% of CCS had plaques in the coronary arteries, after a median follow-up of 24 years. Since the natural incidence of ischaemic heart diseases rises significantly starting in middle-aged populations, the above-mentioned incidences[18] of symptomatic cardiac ischaemia among CCS may well be only the tip of the iceberg.

In order to develop evidence-based clinical follow-up guidelines for CCS and develop new treatment protocols for children with cancer from a risk as well as benefit perspective, it is essential to provide accurate estimates for overall risk of and identify specific risk factors for symptomatic cardiac ischaemia after treatment for childhood cancer. The objectives of the PanCareSurFup (PCSF) cardiac cohort study were to determine the cumulative incidence of symptomatic cardiac ischaemia in European ≥5-year CCS and to determine significant risk factors. We specifically evaluated the effects of treatment, primary cancer diagnosis, sex and attained age on the risk of cardiac ischaemia.

METHODS

Study population

We obtained our study population of ≥5-year survivors from the PCSF cohort study, a collaborative effort of 15 European countries initiated in 2011.[19]

The cardiac outcomes study includes eight European cohorts from seven countries that provided cardiac outcome data: France, Hungary, Italy (two cohorts: population-based and hospital-based), the Netherlands, Slovenia, Switzerland and the UK. The total number of CCS in the eight cohorts was 46 382 (online supplementary eFigure 1 and eTable 1).

Data collection

The methods of the PCSF cardiac study are described in a previous paper.[20] The following data were collected for each ≥5-year CCS included in the cohort analysis: sex, month/year of birth, month/year of first cancer diagnosis, morphology code, topography code, laterality and basis on which the first childhood cancer diagnosis was made, and method of cancer ascertainment of the first cancer diagnosis. In addition, information on surgery (yes/no), chemotherapy (yes/no), radiotherapy (yes/no) and/or bone marrow transplant (yes/no), and the month/year of the start of treatment were collected.[19] The following strategies were used to identify symptomatic cardiac ischaemia cases: linkage to population, hospital or regional-based databases (hospitalisations, medication use, general practitioner (GP) visits) as well as questionnaires sent to survivors and GPs.[20]

Symptomatic cardiac ischaemia

We graded symptomatic cardiac ischaemia according to the Common Terminology Criteria for Adverse Events (CTCAE) V.3.0 as follows: grade 3 (symptomatic and testing consistent with ischaemia or unstable angina or intervention needed), grade 4 (myocardial infarction; life-threatening consequences cardiac ischaemia) or grade 5 (death due to cardiac ischaemia).[21] Any cardiac disease that did not meet these criteria was graded as ≤2. First potential events were identified by questionnaires, outpatient clinic visit or linkages,[20] all potential events were than validated with the help of information from medical records or treating physicians. We then used an extraction and flow chart method described previously to grade the cardiac ischaemia (see online supplementary eFigure 2).[22] We focus on symptomatic cardiac ischaemia because asymptomatic cardiac ischaemia is generally only identified by clinical investigation during follow-up care. Therefore, unless the entire cohort is subject to such standardised clinical investigation, which was not possible, such asymptomatic conditions must be excluded.

Statistical analyses

The main outcome of interest was the first occurrence of symptomatic cardiac ischaemia. Time at risk started 5 years after the first primary cancer diagnosis. The following dates were assigned as the end of cardiac follow-up: the date of cardiac ischaemia; the date of death for decedents or the follow-up date given by each data provider. To limit follow-up bias, we fixed the final end-of-follow-up date separately for each country/cohort as the last date on which cardiac follow-up was available for ≥80% of cohort members. This was only necessary for cohorts of patients who were not uniformly followed until a common date (ie, for the Hungarian, Italian and Swiss cohorts (table 1 and online supplementary eFigure 1)). Because only ≥5-year survivors were included, the inclusion criteria based on years of diagnosis (ie, the end years) were adjusted accordingly. We calculated the cumulative incidence for symptomatic cardiac ischaemia, with attained age as the time scale. The cumulative incidence reflects the number of symptomatic cardiac ischaemia events in the ≥5-year CCS cohort and takes into account that some patients died before ever developing symptomatic cardiac ischaemia. When calculating the cumulative incidence, individuals who died before developing symptomatic cardiac ischaemia are not censored but remained in the risk set with a weight. This weight depends on the timing of the last known medical status for those who did not have symptomatic cardiac ischaemia and did not die (ie, competing risk analyses).[23] We report cumulative incidence

Table 1 Completeness of cardiac follow-up in ≥5-year survivors

	Original cohorts				Adjusted cohorts		
Data provider	Inclusion based on years at diagnosis	Original cohort (n)	CCS with cardiac follow-up (n)	CCS with cardiac follow-up (% of the original cohort)	Adjustment of end date (year) of the study*	Adjustment of inclusion based on years of diagnosis†	CCS with cardiac follow-up after adjustment inclusion (n)
France	1940–1986	3171	3143	99.1	2006	No adjustment	3143
Hungary	1971–2008	5162	4883	71.3	2006	1971–2001	3680
Italy—population based	1967–2009	5003	1544	30.8	2010	1967–2005	1541
Italy—hospital based	1960–2008	3004	1569	52.2	2012	1960–2007	1569
The Netherlands	1964–2001	6087	5185	85.2	2012	No adjustment	5185
Slovenia	1961–2002	1256	1147	91.3	2013	No adjustment	1147
Switzerland	1964–2005	4718	3627	67.3	2007	1964–2002	3176
UK	1940–1991	17 981	16 764	93.2	2012	No adjustment	16 764
Total		46 382	37 862	**78.1**			36 205

*CCS with cardiac follow-up >80% in every cohort.
†Years at diagnosis; to exclude <5 years CCS.
CCS, childhood cancer survivors.

Table 2 Patient, cancer, treatment and cardiac outcome of the PCSF cohort members with complete cardiac follow-up

Characteristics	Cardiac follow-up cohort (n=36 205) n (%)	Symptomatic cardiac ischaemia cases (n=302) n (%)
Patient characteristics		
Sex		
Female	16 322 (45.1)	83 (27.5)
Male	19 883 (54.9)	219 (72.5)
Age at diagnosis (years) median (IQR)	*5.8 (2.7–11.0)*	*10.5 (5.4–13.3)*
0–4	16 131 (44.6)	67 (22.2)
5–9	9400 (26.0)	74 (24.5)
10–14	8785 (24.3)	149 (49.3)
≥15	1889 (5.2)	12 (4.0)
Cancer characteristics		
Primary cancer groups		
Leukaemia	9775 (27.0)	22 (7.3)
Lymphoma	5587 (15.4)	123 (40.7)
Central nervous system tumour	6836 (18.9)	42 (13.9)
Bone and soft tissue sarcoma	4270 (11.8)	45 (14.9)
Other tumour	9737 (26.9)	70 (23.2)
Calendar year of diagnosis		
<1980	12 609 (34.8)	240 (79.5)
1980–1989	12 660 (35.0)	53 (17.5)
≥1990	10 936 (30.2)	9 (3.0)
Overall treatment modality		
Without treatment/surgery only	4215 (11.7)	36 (11.9)
Chemotherapy±surgery	7812 (21.6)	22 (7.3)
Radiotherapy±surgery	4810 (13.3)	122 (40.4)
Chemotherapy and radiotherapy±surgery	11 923 (33.0)	91 (30.1)
Missing	7445 (20.6)	31 (10.3)
Vital status at follow-up		
Alive	30 761 (85.0)	212 (70.2)
Deceased	5444 (15.0)	90 (29.8)
Attained age at end of follow-up (year) median (min-max)	*29.7 (5.1–79.8)*	*43.6 (14.6–73.3)*
≤20	7765 (21.4)	8 (2.6)
20–29	10 540 (29.1)	33 (10.9)
30–39	9793 (27.0)	73 (24.2)
40–49	5622 (15.5)	102 (33.8)
50–59	1841 (5.1)	63 (20.9)
≥60	644 (1.8)	23 (7.6)
Follow-up duration from primary cancer diagnosis (year) median (min-max)	*23.0 (5.0–72.5)*	*28.9 (0.1–57.5)*
<10	9944 (27.5)	17 (5.6)
10–19	10 564 (29.2)	55 (18.2)
20–29	9352 (25.8)	95 (31.5)
30–39	4437 (12.3)	69 (22.8)
40–49	1519 (4.2)	56 (18.5)
≥50	389 (1.1)	10 (3.3)
Cardiac events		
Any validated symptomatic cardiac event		
Yes	887 (2.4)	
No	35 318 (97.6)	

Italicised values are the median and IQR of the total cohort.

Type of event	Grade 3	Grade 4	Grade 5	Total
Cardiac ischaemia	43	169	90	**302**
More than one validated symptomatic cardiac event				
Yes	138 (15.6)			
No	749 (84.4)			

ICCC, International Classification Childhood Cancer; PCSF, PanCareSurFup.

by: sex (male and female), treatment groups (no treatment or surgery only (considering this as a proxy for the general population) vs chemotherapy and/or radiotherapy) and specific primary cancer groups (ie, leukaemia, lymphoma, central nervous system (CNS), bone and soft tissue sarcoma and other tumours). We performed a Gray's test to test for unadjusted significant differences between the subgroup-specific cumulative incidences in the different groups.[24] The primary cancer groups as proxy for the level of cardiotoxic treatment. The distribution of known cardiotoxic treatments are shown in online supplementary eTable 2. Potential risk factors were evaluated in two multivariable Cox regression analyses. In one model, we quantified the effect of treatment and sex on the risk of developing symptomatic cardiac ischaemia, while, in a second model we quantified the role of primary cancer diagnosis. In both models, we adjusted for sex, age at diagnosis, year of childhood cancer diagnosis and data provider. CCS with missing data was excluded in the concerning analyses. Two-sided p values are reported and those <0.05 are considered significant. R (V.3.1.1, R Foundation) and SPPS (V.24, IBM SPSS Statistics) were used for analyses.

Patient and public involvement

The PCSF study is a European collaboration of PanCare. PanCare is a multidisciplinary pan-European network of professionals, survivors and their families that aims to reduce the frequency, severity and impact of late side effects of the treatment of children and adolescents with cancer.

RESULTS

Study population and cardiac follow-up

For 81.6% (n=37 862) of study subjects cardiac follow-up was available. The completeness of follow-up in the eight cohorts varied from 30.8% to 99.1%. As a result, the study cohort included 36 205 ≥5-year CCS initially diagnosed with childhood cancer during 1940–2007 (table 1); 16 322 (45.1%) were female and 30 761 (85.0%) CCS were alive at the cohort-specific end of follow-up. Table 2 presents the characteristics of the 36 205 ≥5-year CCS. Median follow-up time after primary cancer diagnosis was 23.0 years (range 5.0–72.5 years) and median attained age at the end of follow-up was 29.7 years (range 5.1–79.8 years).

Symptomatic cardiac ischaemia

Among the 36 205 eligible CCS, we observed symptomatic cardiac ischaemia in 302 individuals (0.83%), including: 43, 169 and 90 events graded as level 3, 4 or 5, respectively (for detailed information for each data provider, see online supplementary eTable 3). The median age at symptomatic cardiac ischaemia was 43.6 years (range 14.6–73.3) and 41 of 302 affected patients were diagnosed prior to age 30 years. Among all cases, 91 (30.1%) received both chemotherapy and radiotherapy (with/without surgery), 22 (7.3%) received chemotherapy (with/without surgery), 122 (40.4%) received radiotherapy (with/without surgery) and the 36 remaining cases (11.9%) received surgery only/no treatment; for another 31 cases (10.3%) this information was missing.

Table 3 Cumulative incidence of symptomatic cardiac ischaemia, by attained age

	Attained age 10 **years**	Attained age 20 **years**	Attained age 30 **years**	Attained age 40 **years**	Attained age 50 **years**	Attained age 60 **years**
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Overall	**0.00% (0.00 to 0.00)**	**0.02% (0.01 to 0.04)**	**0.16% (0.11 to 0.21)**	**0.71% (0.58 to 0.85)**	**2.46% (2.08 to 2.84)**	**5.39% (4.55 to 6.22)**
Sex						
Male	0.00% (0.00 to 0.00)	0.01% (0.00 to 0.03)	0.20% (0.13 to 0.28)	0.98% (0.76 to 1.20)	3.40% (2.80 to 4.01)	7.09% (5.81 to 8.37)
Female	0.00% (0.00 to 0.00)	0.04% (0.01 to 0.08)	0.10% (0.05 to 0.16)	0.40% (0.26 to 0.55)	1.36% (0.95 to 1.77)	3.39% (2.39 to 4.39)
Treatment						
No treatment/surgery only	0.00% (0.00 to 0.00)	0.00% (0.00 to 0.00)	0.04% (0.00 to 0.11)	0.45% (0.15 to 0.74)	1.45% (0.78 to 2.11)	3.61% (2.14 to 5.08)
Chemotherapy and/or radiotherapy	0.00% (0.00 to 0.00)	0.04% (0.01 to 0.06)	0.20% (0.13 to 0.26)	0.77% (0.61 to 0.94)	2.84% (2.34 to 3.34)	6.20% (5.09 to 7.31)
Treatment and sex						
Male no treatment/surgery only	0.00% (0.00 to 0.00)	0.00% (0.00 to 0.00)	0.00% (0.00 to 0.00)	0.43% (0.01 to 0.85)	2.01% (0.90 to 3.13)	5.53% (2.92 to 8.13)
Male chemotherapy and/or radiotherapy	0.00% (0.00 to 0.00)	0.02% (0.00 to 0.04)	0.25% (0.15 to 0.35)	1.06% (0.80 to 1.33)	3.77% (3.00 to 4.55)	7.73% (6.11 to 9.35)
Female no treatment/surgery only	0.00% (0.00 to 0.00)	0.00% (0.00 to 0.00)	0.07% (0.00 to 0.22)	0.47% (0.05 to 0.89)	0.92% (0.17 to 1.66)	1.74% (0.35 to 3.13)
Female chemotherapy and/or radiotherapy	0.00% (0.00 to 0.00)	0.06% (0.01 to 0.11)	0.13% (0.05 to 0.21)	0.42% (0.25 to 0.59)	1.65% (1.09 to 2.20)	4.18% (2.76 to 5.61)
Primary cancer groups						
Leukaemia	0.00% (0.00 to 0.00)	0.02% (0.00 to 0.06)	0.15% (0.06 to 0.25)	0.30% (0.11 to 0.49)	1.58% (0.33 to 2.84)	3.81% (0.49 to 7.13)
Lymphoma	0.00% (0.00 to 0.00)	0.06% (0.00 to 0.13)	0.38% (0.19 to 0.56)	1.93% (1.39 to 2.46)	5.79% (4.50 to 7.08)	10.75% (8.22 to 13.28)
Central nervous system tumour	0.00% (0.00 to 0.00)	0.00% (0.00 to 0.00)	0.04% (0.00 to 0.10)	0.35% (0.16 to 0.55)	0.98% (0.56 to 1.40)	2.86% (1.81 to 3.90)
Bone and soft tissue sarcoma	0.00% (0.00 to 0.00)	0.05% (0.00 to 0.13)	0.20% (0.05 to 0.35)	0.76% (0.38 to 1.13)	2.20% (1.26 to 3.13)	6.01% (3.62 to 8.40)
Other tumour	0.00% (0.00 to 0.00)	0.01% (0.00 to 0.04)	0.10% (0.02 to 0.18)	0.51% (0.28 to 0.74)	2.43% (1.66 to 3.20)	4.82% (3.31 to 6.33)

Cumulative incidence

Table 3 shows the cumulative incidences by attained age. The overall cumulative incidence of symptomatic cardiac ischaemia at the age of 60 years was 5.4% (95% CI 4.6 to 6.2) (figure 1). Males were at a higher risk of developing symptomatic cardiac ischaemia: at the age of 60 years the cumulative incidence was 7.1% (95% CI 5.8 to 8.4), while for females this was 3.4% (95% CI 2.4 to 4.4) (see figure 2). The cumulative incidence of symptomatic cardiac ischaemia at the age of 60 years was 3.6% (95% CI 2.1 to 5.1) in the no treatment/surgery only group and 6.2% (95% CI 4.1 to 7.3) in the chemotherapy and/or radiotherapy group (figure 3A; for attained age online supplementary eFigure 3). The first symptomatic cardiac ischaemia event in the no treatment/surgery only group occurred at 29.9 years of age, while the first event in the chemotherapy-treated and/or radiotherapy-treated group occurred at 14.5 years of age. Figure 3B shows cumulative incidence restricted to attained ages 15–30 years; the cumulative incidence at 30 years of age for CCS treated with chemotherapy and/or radiotherapy and CCS receiving neither treatment was 0.20% (95% CI 0.13 to 0.26) and 0.04% (95% CI 0 to 0.11), respectively (p=0.04).

Males treated with chemotherapy and/or radiotherapy had the highest cumulative incidence at the age of 60 years (7.7% (95% CI 6.1 to 9.4)) and females without treatment/surgery only had the lowest cumulative incidence at 60 years of age (1.7% (95% CI 0.4 to 3.1)). There was no significant difference between males without treatment/surgery only and females treated with chemotherapy and/or radiotherapy overall (online supplementary

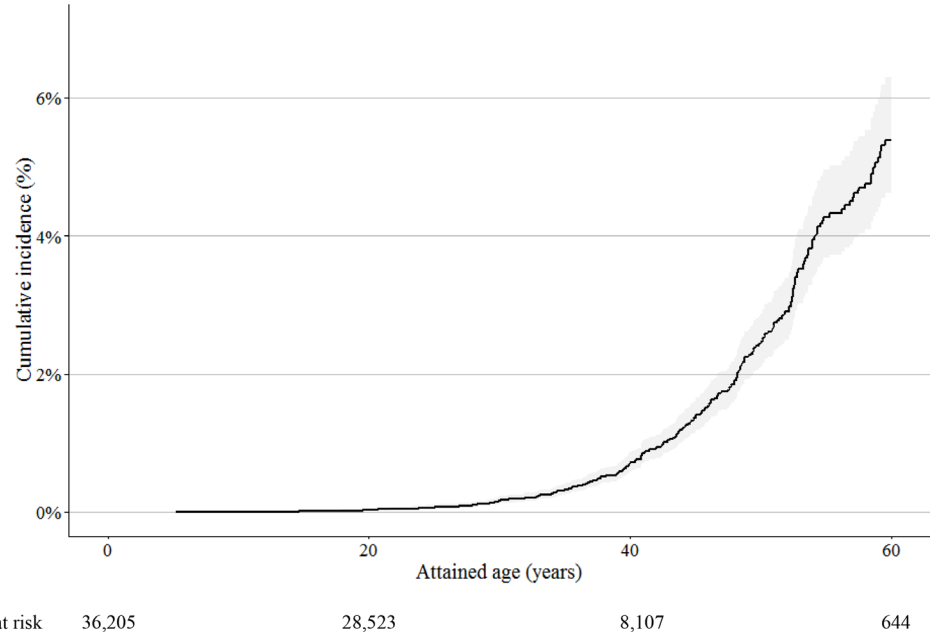
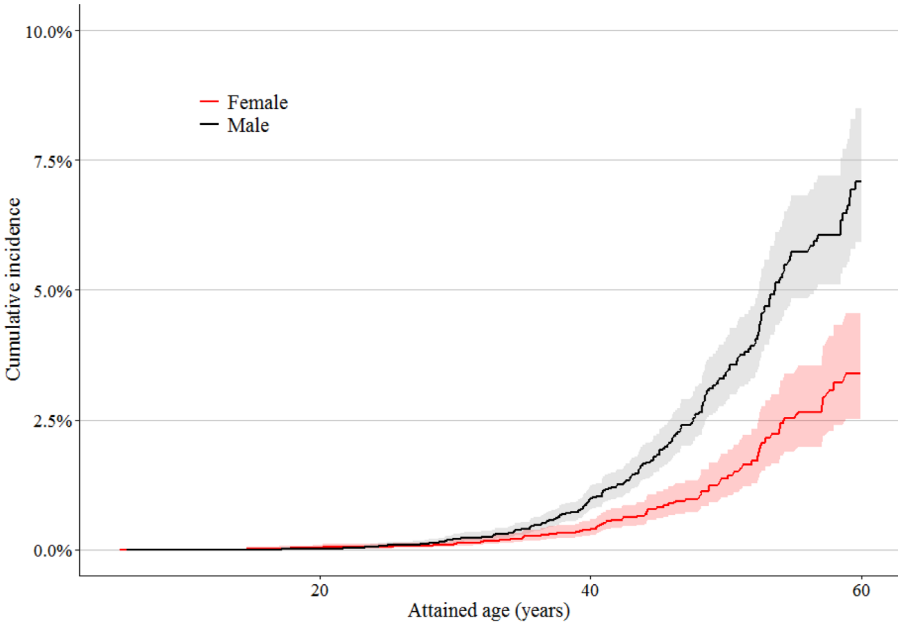
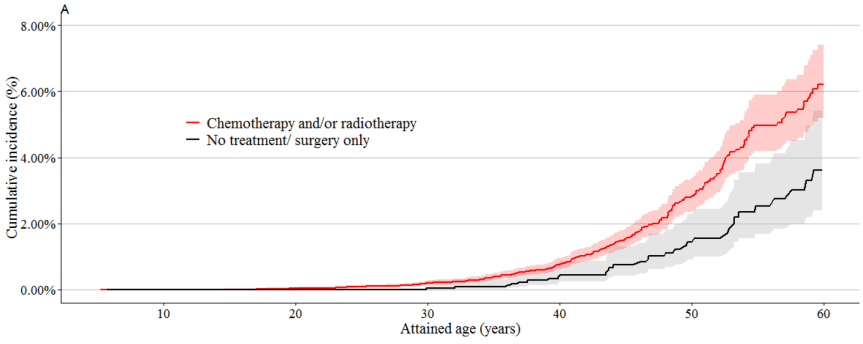


Figure 1 Cumulative incidence and 95% CI of symptomatic cardiac ischaemia by attained age for 5-year survivors participating in the PanCareSurFup consortium.

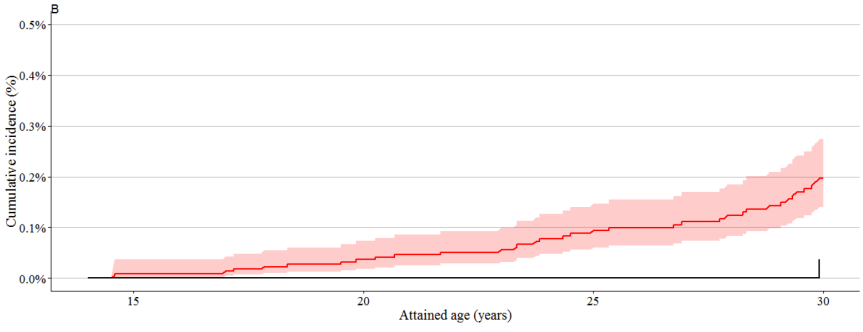


N at risk *male*	19,883	15,435	4,276	328
N at risk *female*	16,322	13,088	3,831	316

Figure 2 Cumulative incidence and 95% CI of symptomatic cardiac ischaemia for female and male survivors by attained age. P value for unadjusted Gray's test is p<0.0001.

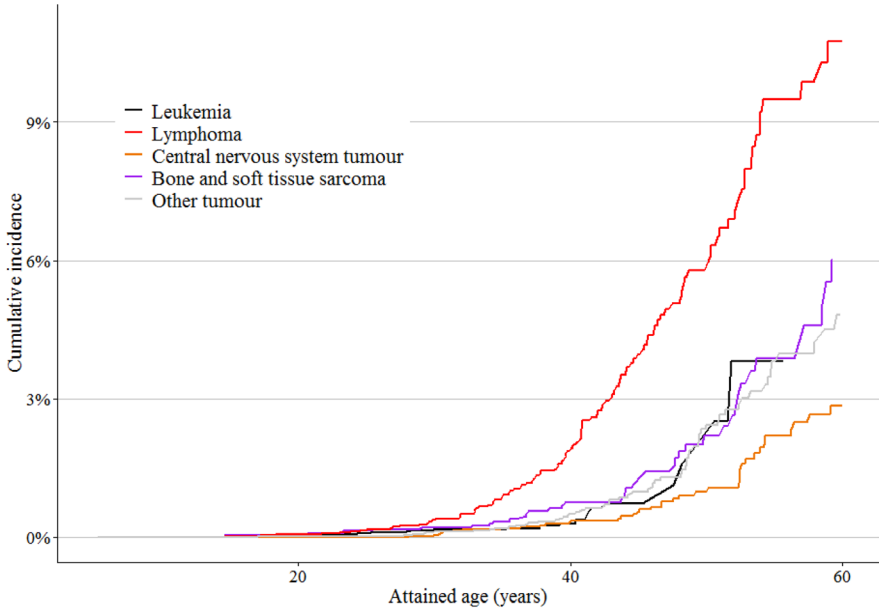


N at risk CT and/or RT	24,545	23,818	18,942	12,270	5,628	1,509	374
N at risk no treatment/ surgery only	4,215	4,067	3,336	2,416	1,498	706	219



N at risk CT and/or RT	21,883	18,942	15,713	12,270
N at risk no treatment/ surgery only	3,772	3,336	2,894	2,416

Figure 3 Cumulative incidence of symptomatic cardiac ischaemia per treatment group with attained age as time scale. (A) All attained ages, p value for unadjusted Gray's test is p<0.0002. (B) Zoomed in on attained ages 15–30 years, p value for unadjusted Gray's test is p=0.04. RT, radiotherapy.



Leukemia	9,775	6,957	1,194	6
Lymphoma	5,587	4,863	1,500	112
Central nervous system	6,836	5,346	1,916	209
Bone and soft tissue sarcoma	4,270	3,542	1,141	123
Other tumour	9,736	7,814	2,356	194

Figure 4 Cumulative incidence of symptomatic cardiac ischaemia per malignancy group with attained age as time scale. Unadjusted Gray's test: leukaemia versus lymphoma p<0.0001; leukaemia versus central nervous system (CNS) tumour p=0.16; leukaemia versus bone and soft tissue sarcoma p=0.16; leukaemia versus other tumour p=0.72; lymphoma versus CNS, bone and soft tissue sarcoma, other tumour p<0.0001; CNS versus bone and soft tissue sarcoma, other tumour p<0.0001; bone and soft tissue sarcoma versus other tumour p=0.32.

eFigure 4A; p=0.47) nor for specific groups aged 5–30 years during follow-up (online supplementary eFigure 4B; shows cumulative incidence restricted to attained ages 5–30 years, p value for Gray's test for male chemotherapy and/or radiotherapy vs female chemotherapy and/or radiotherapy is p=0.12).

Survivors of paediatric lymphoma had a significantly higher cumulative incidence of symptomatic cardiac ischaemia at the age of 60 years (10.8%; 95% CI 8.2 to 13.3) when compared with all other malignancy groups. Survivors with bone and soft tissue sarcoma and survivors from the other tumour groups had a significantly higher cumulative incidence than CNS tumour survivors (6.0% (95% CI 3.6 to 8.4), 4.8% (95% CI 3.3 to 6.3) and 2.9% (95% CI 1.8 to 3.9) respectively), but not leukaemia (3.8% (95% CI 0.5 to 7.1). Leukaemia and CNS did also not differ significantly from each other (figure 4).

Risk factors

A multivariable Cox proportional hazards model showed that CCS treated with chemotherapy and/or radiotherapy have a twofold risk of developing symptomatic cardiac ischaemia (HR 2.1; 95% CI 1.5 to 3) compared with CCS without treatment/surgery only (table 4). There was no significant interaction term between sex and treatment. A model where treatment was divided in four mutually exclusive groups (no treatment/surgery only, radiotherapy (±surgery), chemotherapy (±surgery), radiotherapy and chemotherapy (±surgery)) showed that compared with no treatment/surgery only, radiotherapy (±surgery) and radiotherapy and chemotherapy (±surgery) had a more than twofold risk of developing symptomatic cardiac ischaemia, chemotherapy (±surgery) failed the widely accepted significance level of 0.05 (p=0.12) (online supplementary eTable 4).

In the Cox model with primary cancer diagnoses, we found that only survivors of lymphoma has a significantly higher risk than leukaemia survivors (HR 3.4; 95% CI 2.0 to 5.3) (table 4).

Table 4 Cox regression analyses for symptomatic cardiac ischaemia, with attained age as time scale

	n/total n	HR	P value	n events
Model 1				
Age at primary childhood cancer diagnosis		1.0 (0.97 to 1.03)	0.87	
Sex				
Male	15 839/28 760	Ref		213/292
Female	12 921/28 760	**0.4 (0.3 to 0.6)**	<0.0001	79/292
Treatment				
No treatment/surgery only	4215/28 760	Ref		36//292
Chemotherapy and/or radiotherapy	24 545/28 760	**2.1 (1.5 to 3.0)**	<0.0001	256/292
Model 2				
Age at primary childhood cancer diagnosis		**0.97 (0.93 to 0.99)**	0.04	
Sex				
Male	19 883/36 204	Ref		238/324
Female	16 312/36 204	**0.5 (0.4 to 0.6)**	<0.0001	86/324
Primary cancer diagnosis				
Leukaemia	9775/36 204	Ref		24/324
Lymphoma	5587/36 204	**3.4 (2.0 to 5.3)**	<0.0001	137/324
Central nervous system	6836/36 204	0.9 (0.5 to 1.4)	0.57	43/324
Bone and soft tissue sarcoma	4270/36 204	1.5 (0.9 to 2.5)	0.14	46/324
Other tumours	9736/36 204	1.3 (0.8 to 2.1)	0.34	74/324

Each model is also corrected for data provider and year of childhood cancer diagnosis.
Bold values are statistically significant.

DISCUSSION

In this large European CCS cohort of 36 205 CCS, we showed that at 60 years of age, almost 1 in 18 CCS (5.4%) developed a severe, life-threatening or fatal cardiac ischaemia. When we compare CCS who received chemotherapy and/or radiotherapy with CCS without treatment/surgery only we identified a twofold higher risk in the former group, however in a sensitivity analyses (online supplementary eTable 4) we found that radiotherapy only or with chemotherapy yields the highest risk, chemotherapy alone just failed the accepted significance level of 0.05.

Furthermore, an important finding of this study is that even at a young age (<30 years) CCS are at risk of symptomatic cardiac ischaemia; the earliest event affected a girl aged 15 years. The average age at first myocardial infarction in the general population is 64.5 years for males and 70.4 years for females.[25] We showed that symptomatic cardiac ischaemia occurs in CCS treated with chemotherapy and/or radiotherapy at a much younger age than CCS in the without treatment/surgery only group. Almost 15% of CCS treated with chemotherapy and/or radiotherapy who developed symptomatic cardiac ischaemia, developed it before 30 years of age (figure 3B). In the without treatment/surgery only group, 3% of CCS who developed symptomatic cardiac ischaemia, developed it before 30 years of age. Streefkerk *et al*[26] and Gudmundsdottir *et al*[27] compared the hospitalisation rate for ischaemic heart disease between a cohort of childhood cancer survivors and a matched general population and found a relative rate of 1.6 and 1.7 (95% CI 1.5 to 1.9), respectively, which are in line with our result. Gudmundsdottir *et al* also found a larger difference in the younger age groups (aged 20–50 years).

We confirmed that males had a higher risk of developing symptomatic cardiac ischaemia. This was previously shown in CCS[6 11] and is also the case in the general population.[28] When we focus on the first 30 years of age, there is no statistically significant difference between male and female CCS. However, after 30 years of age the risk of ischaemic heart disease in males increases steadily. Females treated with chemotherapy and/or radiotherapy seem to have the same risk as males treated without treatment/surgery only, again the difference did not reach statistical significance.

Lymphoma survivors had a more than threefold higher risk of developing symptomatic cardiac ischaemia than CCS who had leukaemia. This implies that there is an important role of radiotherapy involving the heart region as a risk factor, since one in three patients with lymphoma received radiotherapy involving the heart region as part of treatment (online supplementary eTable 2). Other studies also identified radiotherapy involving the heart region as a risk factor for cardiac ischaemia.[6 17] The other malignancy groups did not significantly differ from leukaemia survivors. However, overall CNS tumour survivors were at low risk of developing symptomatic cardiac ischaemia (table 3 and online supplementary eTable 5).

A strength of this study is that the PCSF cardiac cohort is the largest cohort of CCS with cardiac outcome information. Our analyses provide information on time of onset and the risk factors, such as radiotherapy and gender that will improve the prediction of the long-term risk of cardiac ischaemia. Moreover, we validated the cardiac outcomes, based on a previously reported method.[22] Also, most studies conducted to date mainly included follow-up prior to age 50 years, that is, before the significant rise in background rates of ischaemic heart disease in the general population,[25] while in our study we were able to assess patients with an attained age of 50 years and older.

Potential limitations of this study are the variation between data providers in inclusion criteria and method of follow-up. We carried out a sensitivity analysis evaluating inclusion criteria (incidence year 1970–1986 and age at diagnosis <15 years), and showed no clear differences in results (online supplementary eTable 6). It is possible that identification of cardiac ischaemia cases were less optimal for some data providers, however we corrected for data provider in the multivariable model. Another limitation is the lack of detail on risk factors, like chemotherapy and radiation doses, which is not uncommon for cohort studies of this size.[29] We are conducting a nested case-control study in which we do have detailed treatment information necessary to assess the influence of specific cancer treatments and of lifestyle-related factors on the occurrence of symptomatic cardiac ischaemia.[20]

In conclusion, in this large European CCS cohort in 36 205 CCS demonstrated that survivors are at increased risk of severe, life-threatening or fatal cardiac ischaemia. Cardiac ischaemia in CCS can develop at a very young age, as early as 15 years of age. We were also able to have accurate estimations of the risk at an older age (>50 years of age). At an attained age of 60 years, 1 in 18 CCS developed symptomatic cardiac ischaemia. Compared with a group CCS without treatment/surgery only group, CCS treated with radiotherapy and/or chemotherapy had a twofold higher risk of developing cardiac ischaemia. Compared with CCS with a CNS tumour, survivors of lymphoma had a 3.4-fold higher risk of developing ischaemia.

The results from this study indicate that a cardiac ischaemia long-term follow-up surveillance guideline is needed. The International Guideline Harmonisation Group[30] is currently developing such a guideline. All medical professionals and survivors should be aware that symptomatic

Key questions

What is already known on this subject?

- Several studies have evaluated symptomatic cardiac ischaemia in childhood cancer survivors (CCS).
- The reported prevalences varied between 0.2% and 6%.
- A large study showed that male gender, primary cancer diagnosis, treatment era, cardiac irradiation dose were identified as risk factors.
- Information on excess risk of ischaemic diseases after age 50 is currently lacking.

What might this study add?

- In this largest CCS cohort of 36 205 survivors, we showed that at 60 years of age, 5.4% of the CCS developed a severe, life-threatening or fatal cardiac ischaemia, which were all validated events by medical records or treating physician.
- An important finding of this study is that even at a young age (<30 years), CCS are at risk of symptomatic cardiac ischaemia.

How might this impact on clinical practice?

- Medical professionals and CCS should be aware that cardiac ischaemia occurs in this population, even at a very young age.
- When symptoms, such as chest pain, occur, there should be a low threshold for performing diagnostic tests and starting treatment.
- A cardiac ischaemia long-term follow-up surveillance guideline is needed for CCS.

cardiac ischaemia occurs in this population, even at a young age. When symptoms, such as chest pain, occur, there should be a low threshold for performing diagnostic tests and starting treatment.

Author affiliations
[1]Pediatric Oncology, Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands
[2]University of Birmingham, Birmingham, UK
[3]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
[4]Pediatric Hematology and Oncology, University Children's Hospital Bern, University of Bern, Bern, Switzerland
[5]Giannina Gaslini Children's Hospital, Genova, Italy
[6]Childhood Cancer Registry of Piedmont, Torino, Italy
[7]Gustave Roussy, Villejuif, Île-de-France, France
[8]Boyne Institute, Drogheda, Ireland
[9]Kepler University Clinic, Linz, Austria
[10]Markusovszky University Teaching Hospital, Szombathely, Vas, Hungary
[11]University Medical Center Mainz, Mainz, Germany
[12]Skåne University Hospital Lund, Lund, Sweden
[13]INSERM, Paris, France
[14]Hospital San Gerardo, Monza, Italy
[15]Great Ormond Street Hospital for Children, London, UK
[16]Newcastle University, Newcastle upon Tyne, UK
[17]Institute of Oncology Ljubljana, Ljubljana, Slovenia
[18]Pediatric Oncology, University of Groningen, Groningen, The Netherlands

Correction notice This article has been corrected since it was first published. The author Claudia E Keuhni should have been listed as Claudia E Kuehni, and the corresponding affiliations have been updated to include the specific departments: 'Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland' and 'Pediatric Hematology and Oncology, University Children's Hospital Bern, University of Bern, Bern, Switzerland'.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the 'Methods' section for further details.

Patient consent for publication Not required.

Ethics approval Medical ethical approval was obtained by each country (France, Hungary, Italy, the Netherlands, Switzerland, Slovenia, the UK).

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iD
Elizabeth Arnoldina Maria Feijen http://orcid.org/0000-0001-8930-3160

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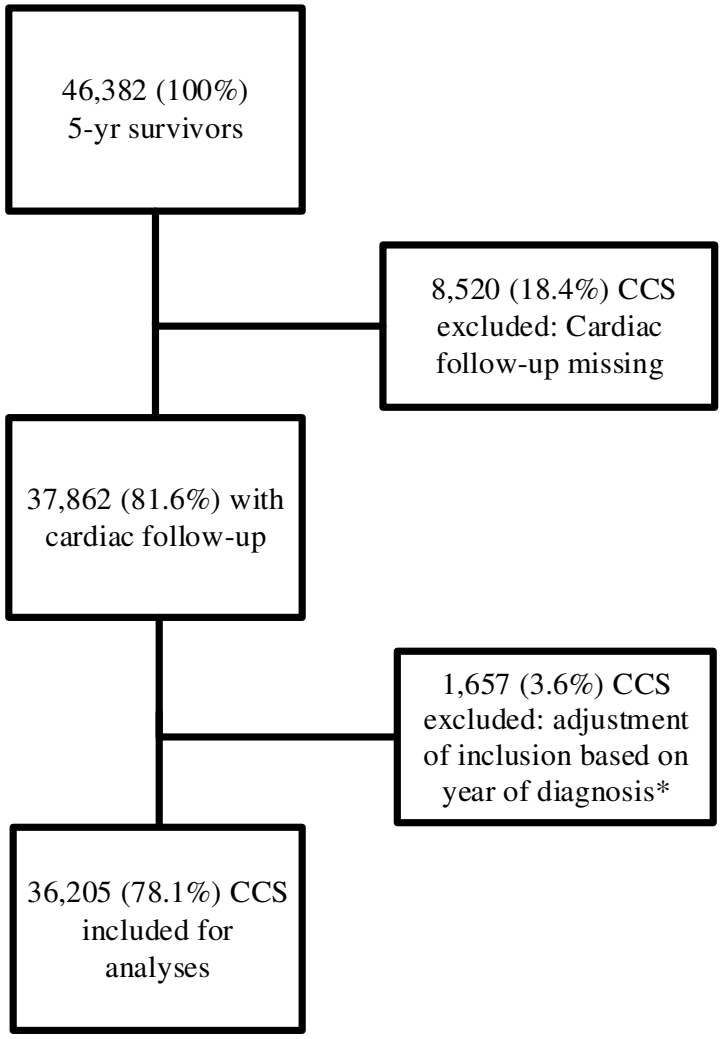
Correction: *Increased risk of cardiac ischaemia in a pan-European cohort of 36 205 childhood cancer survivors: a PanCareSurFup study*

Feijen EAM, van Dalen EC, van der Pal HJH on behalf of the PanCareSurFup consortium, *et al*. Increased risk of cardiac ischaemia in a pan-European cohort of 36 205 childhood cancer survivors: a PanCareSurFup study. *Heart* 2021;107:33-40.doi:10.1136/heartjnl-2020-316655.

This article has been corrected since it was first published. The author Claudia E Keuhni should have been listed as Claudia E Kuehni, and the corresponding affiliations have been updated to include the specific departments: 'Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland' and 'Pediatric Hematology and Oncology, University Children's Hospital Bern, University of Bern, Bern, Switzerland'.

Heart 2021;**107**:e1. doi:10.1136/heartjnl-2020-316655corr1

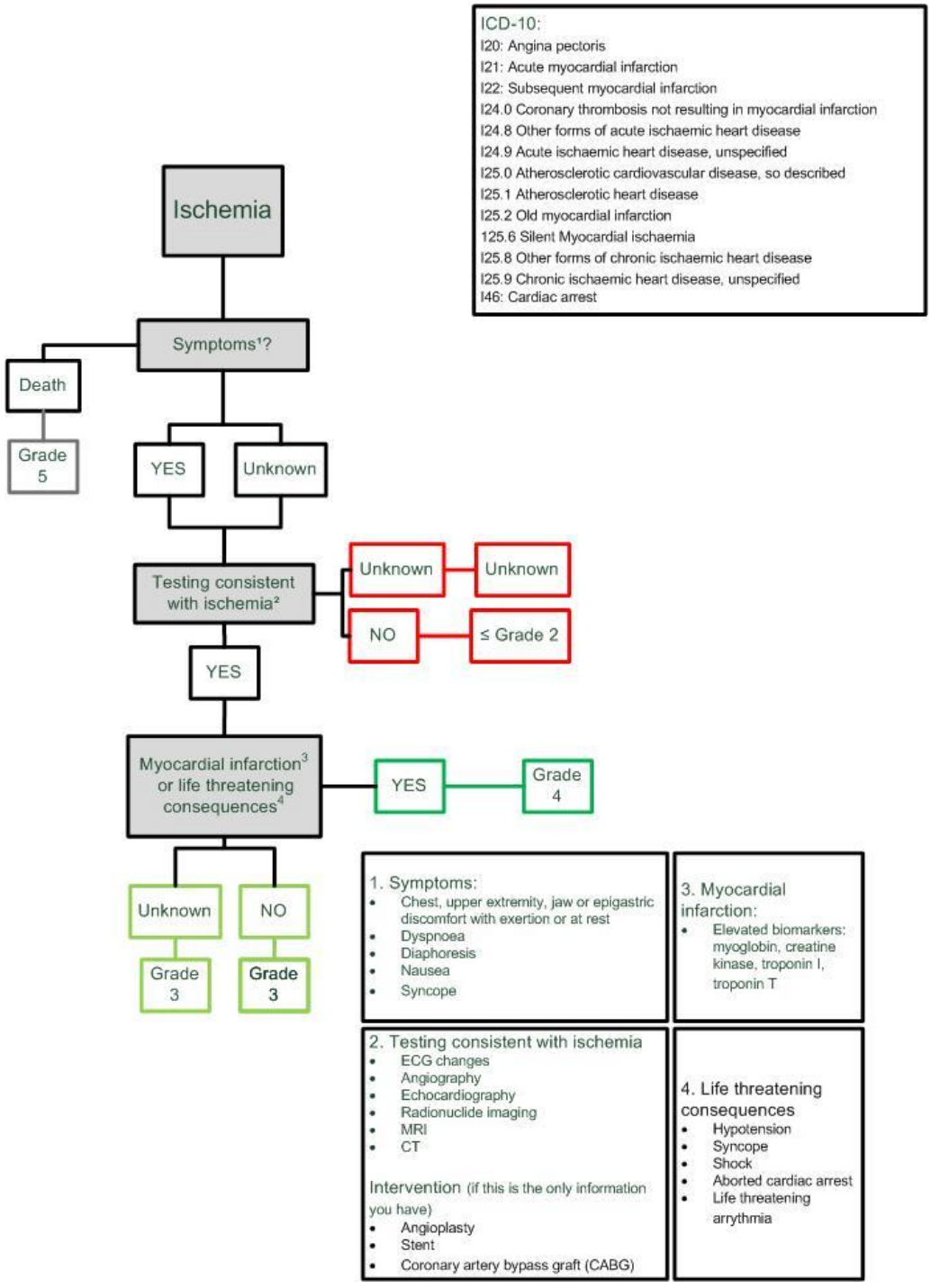
Supplemental figures and tables



eFigure 1. Flow diagram of childhood cancer survivors, part of the eight PCSF cohorts used in the analyses.

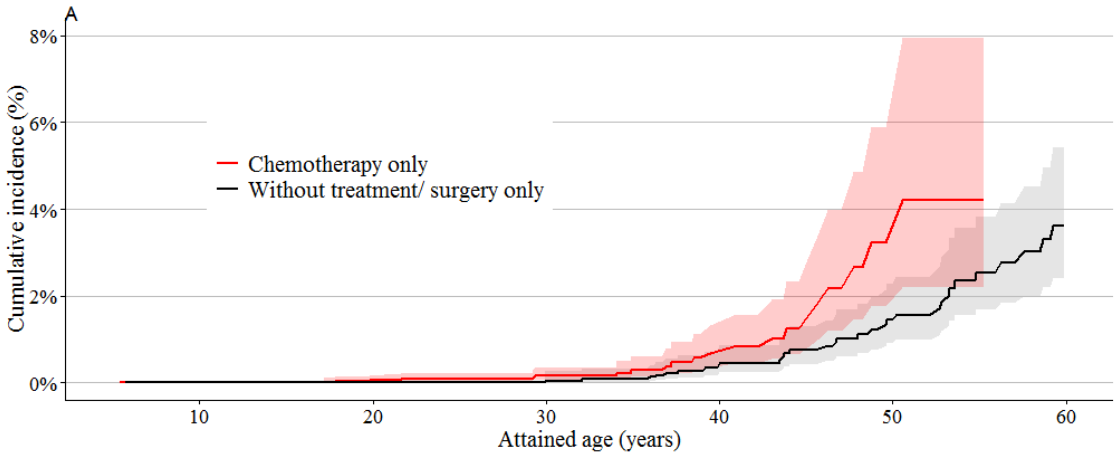
CCS= childhood cancer survivors; PCSF=PanCareSurFup

* Based on adjustment of end date of study to have > 80% completeness of follow-up for all included survivors.

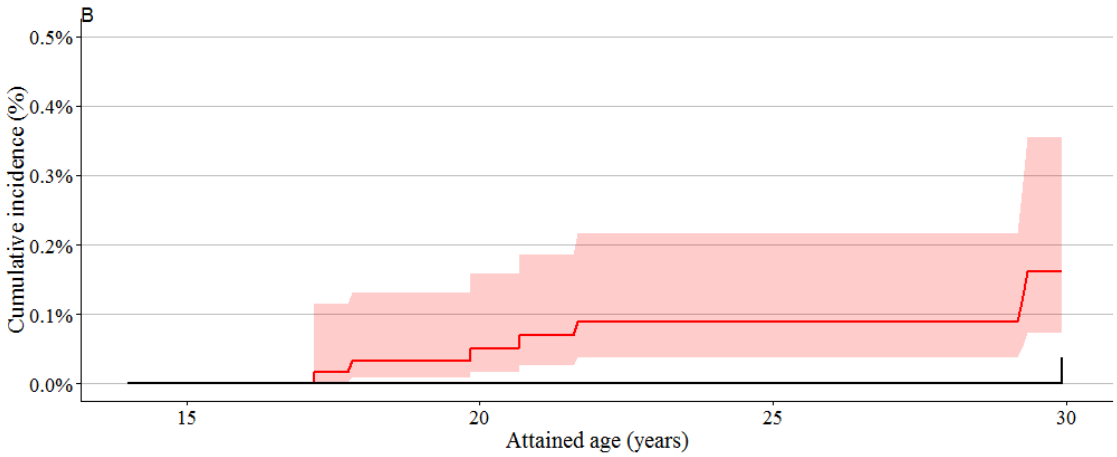


eFigure 2. Flowchart cardiac ischemia.

Feijen EAM, van der Pal HJ, van Dalen EC, Mulder RL, Bardi E, Kuehni C, et al. A new method to facilitate valid and consistent grading cardiac events in childhood cancer survivors using medical records. PloS one. 2014;9(7):e100432.

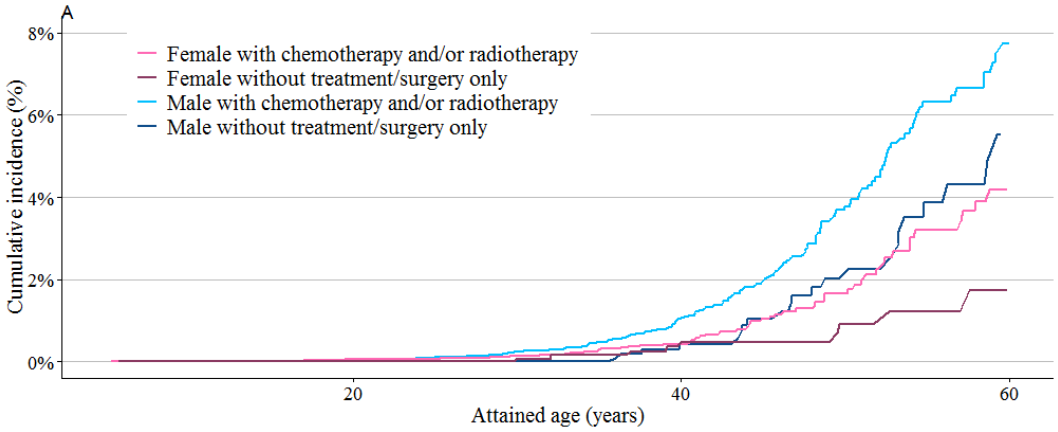


N at risk CT and/or RT	7,812	7,461	5,175	2,380	691	98	7
N at risk OK only/no treatment	4,215	4,067	3,336	2,416	1,498	706	219

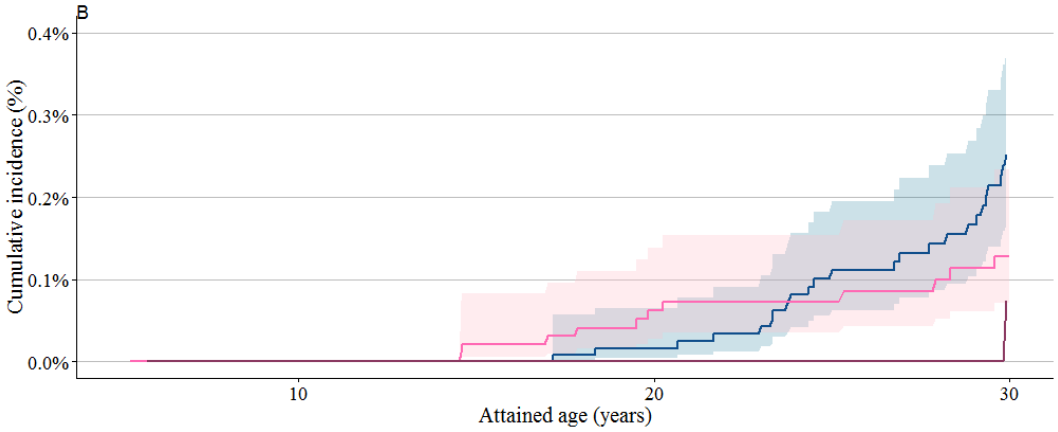


N at risk CT and/or RT	6,534	5,175	3,749	2,380
N at risk OK only/no treatment	3,772	3,336	2,894	2,416

eFigure 3. Cumulative incidence of symptomatic cardiac ischemia per treatment group (without treatment/surgery only & chemotherapy only) attained age as time-scale. **A** is for all ages at follow-up, p-value for unadjusted Gray's test for without treatment/surgery only vs chemotherapy only is p=0.016. **B** is focussed on 15-30 year of age at follow-up, p-value for unadjusted Gray's test for without treatment/surgery only vs chemotherapy only is p=0.08.



Male without treatment/ surgery only	2173	1653	708	103
Male with chemotherapy and/ or radiotherapy	13666	10423	3057	205
Female without treatment/ surgery only	2042	1683	790	116
Female with chemotherapy and/ or radiotherapy	10879	8519	2571	169



Male without treatment/ surgery only	2173	2079	1653	1181
Male with chemotherapy and/ or radiotherapy	13666	13261	10423	6688
Female without treatment/ surgery only	2042	1988	1683	1235
Female with chemotherapy and/ or radiotherapy	10879	10557	8519	5582

eFigure 4. Cumulative incidence of symptomatic cardiac ischemia per treatment group and sex with attained age as time-scale. A is for all ages at follow-up, p-value for unadjusted Gray's test for males without treatment/surgery only vs female chemotherapy and/ or radiotherapy is p=0.47.

B is focussed on 5-30 year of age at follow-up, p-value for Gray's test for male chemotherapy and/ or radiotherapy vs female chemotherapy and/ or radiotherapy is p=0.12.

eTable 1. Inclusion criteria for each data provider within PCSF

	Type of cohort (>5 year survivors)	Number of childhood cancer survivors in cohort	Age at primary cancer diagnosis	Type of malignancy	Period of primary cancer diagnosis
France	Hospital data (5 paediatric oncology centres) , clinical trials, and cancer registry	3,171	0-<21 years	Solid tumours	1940-1986
Hungary	Hospital data, clinical trials, and nationwide cancer registry	5,162	0-<18 years	All, including benign CNS tumours	1971-2008
Italy (hospital based)	Nationwide cancer registry	3,004	0-<15 years	All	1960-2008
Italy (population based)	CCRP (Childhood Cancer Registry of Piedmont) and AIRTUM (Italian Association of Cancer Registries)	5,003	0-<18 years	All	1967-2009
The Netherlands	DCOG LATER (= Dutch Childhood Oncology Group Long-term effects) registry based on nationwide hospital based cohorts	6,087	0-<18 years	All	1964-2001
Slovenia	Nationwide Slovenian cancer registry, follow-up clinic	1,256	0-<16 years	All	1961-2002
Switzerland	Nationwide Swiss Childhood Cancer Registry	4,718	0-<21 years	All, including LCH	1964-2005
United Kingdom	Nationwide cancer registration	17,981	0-<15 years	All	1940-1991

CNS= central nervous system; LCH= Langerhans Cell Histiocytosis; PCSF= PanCareSurFup

eTable 2. Primary cancer groups and cardiotoxic treatment

Primary cancer	% of CCS received anthracyclines*	% of CCS received chest radiotherapy*	% of CCS received anthracyclines and chest radiotherapy*	Median dose of anthracyclines*
Leukemia	60%	12%[#]	10%[#]	114 mg/m^2
Lymphoma	67%	20%[¶]	14%[¶]	180 mg/m^2
Bone and soft tissue sarcoma	61%	10%[□]	7%[□]	400 mg/m^2
Central nervous system	1%	7%[□]	0%[□]	-
Other tumours	25%	5%[□]	2%[□]	180 mg/m^2

*Based on Dutch nationwide cohort study

[#] Mainly cranio-spinal radiotherapy

[¶] Mainly total node, mantle field radiotherapy

[□] Tumor location in the chest area

eTable 3. Sensitivity analyses Cox regression analyses for symptomatic cardiac ischemia, with attained age as time scale. Inclusion criteria: incidence year 1970-1986, age at diagnosis <15 year old.

	cohort n	grade 3	grade 4	grade 5	Total	median attained age (min-max)	Median follow-up time (min-max)
France	3143	13 (59%)	7 (32%)	2 (9%)	22	32.2 (5.3-68.3)	25.8 (5.1-57.8)
Hungary	3680	4 (50%)	2 (25%)	2 (25%)	8	20.5 (5.3-47.7)	12.9 (5.0-35.8)
Italian Population based	1541	4 (44%)	4 (44%)	1 (11%)	9	25.3 (5.1-55.3)	14.1 (5.1-47.1)
Italian Hospital based	1569	3 (50%)	2 (33%)	1 (17%)	6	26.6 (5.2-61.0)	18.9 (5.1-52.9)
Netherlands	5185	7 (41%)	10 (59%)	0 (0%)	17	27.3 (5.1-64.6)	19.8 (5.1-49.8)
Slovenia	1147	3 (33%)	3 (33%)	3 (33%)	9	29.8 (5.8-64.8)	21.0 (5.1-48.4)
Switzerland	3176	2 (33%)	4 (67%)	0 (0%)	6	21.4 (5.3-55.3)	13.1 (5.0-38.0)
The United Kingdom	16764	7 (3%)	137 (56%)	81 (36%)	225	35.3 (5.8-79.8)	28.5 (5.0-72.5)
Total	**36205**	**43 (14%)**	**169 (56%)**	**90 (30%)**	**302**	**29.7 (5.1-79.8)**	**23.0 (5.0-72.5)**

eTable 4. Sensitivity analyses Cox regression analyses for symptomatic cardiac ischemia, with attained age as time scale. Four mutually exclusive treatment groups.

Model 1	***n / total n***	**Hazard Ratio**	***p-value***	***n events***
Age at primary childhood cancer diagnosis		1.01 (0.98-1.04)	0.44	
Sex				
Male	*15839/28760*	REF		*219/271*
Female	*12921/28760*	**0.5 (0.35-0.60)**	**<0.0001**	*83/271*
Treatment group				
No treatment/ surgery only	*4215/28760*	REF		*36/271*
Chemotherapy +/- surgery	*7812/28760*	1.6 (0.89-2.8)	0.12	*22/271*
Radiotherapy +/- surgery	*4810/28760*	**2.0 (1.4-2.9)**	**0.0004**	*122/271*
Chemotherapy and radiotherapy +/- surgery	*11923/28760*	**2.4 (1.6-3.7)**	**<0.0001**	*91/271*

Also corrected for data provider and year of childhood cancer diagnosis.

* significant result (p<0.05)

eTable 5. Cumulative incidence of symptomatic cardiac ischemia per diagnosis group, by attained age.

	Attained age 10 yr	Attained age 20 yr	Attained age 30 yr	Attained age 40 yr	Attained age 50 yr	Attained age 60 yr
Leukeamia	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Overall	0.00% (0.00-0.00)	0.02% (0.00-0.06)	0.15% (0.06-0.25)	0.30% (0.11-0.49)	1.58% (0.33-2.84)	3.81% (0.49-7.13)
Treatment						
No treatment/ surgery-only[a]	NA	NA	NA	NA	NA	NA
Chemotherapy (± surgery)	0.00% (0.00-0.00)	0.00% (0.00-0.10)	0.00% (0.00-0.10)	0.00% (0.00-0.10)	0.00% (0.00-0.10)	2.2% (0.00-6.4)
Radiotherapy (± surgery)[b]	NA	NA	NA	NA	NA	NA
Chemotherapy and radiotherapy (± surgery)	0.00% (0.00-0.00)	0.02% (0.00-0.06)	0.19% (0.06-0.33)	0.26% (0.07-0.46)	2.35% (0.17-4.52)	6.71% (0.00-15.25)
	Attained age 10 yr	Attained age 20 yr	Attained age 30 yr	Attained age 40 yr	Attained age 50 yr	Attained age 60 yr
Lymphoma	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Overall	0.00% (0.00-0.00)	0.06% (0.00-0.13)	0.38% (0.19-0.56)	1.93% (1.39-2.46)	5.79% (4.50-7.08)	10.75% (8.22-13.28)
Treatment						
No treatment/ surgery-only	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	2.23% (0.00-6.55)	5.49% (0.00-13.03)
Chemotherapy (± surgery)	0.00% (0.00-0.00)	0.07% (0.00-0.22)	0.16% (0.00-0.38)	0.69% (0.00-1.46)	2.56% (0.00-5.33)	2.56% (0.00-5.33)
Radiotherapy (± surgery)	0.00% (0.00-0.00)	0.28% (0.00-0.66)	0.80% (0.16-1.44)	2.58% (1.40-3.76)	5.63% (3.72-7.55)	10.19% (7.01-13.37)
Chemotherapy and radiotherapy (± surgery)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.46% (0.12-0.80)	2.59% (1.58-3.59)	7.88% (5.23-10.52)	14.51% (7.67-21.35)
	Attained age 10 yr	Attained age 20 yr	Attained age 30 yr	Attained age 40 yr	Attained age 50 yr	Attained age 60 yr
CNS tumours	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Overall	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.04% (0.00-0.10)	0.35% (0.16-0.55)	0.98% (0.56-1.40)	2.86% (1.81-3.90)
Treatment						
No treatment/ surgery-only	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.09% (0.00-0.26)	0.58% (0.06-1.10)	1.41% (0.44-2.37)	3.27% (1.19-5.35)
Chemotherapy (± surgery)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.00% (0.00-0.00)
Radiotherapy (± surgery)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.10% (0.00-0.24)	0.57% (0.09-1.06)	2.57% (1.17-3.97)
Chemotherapy and radiotherapy (± surgery)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.80% (0.00-1.73)	1.97% (0.00-4.42)	1.97% (0.00-4.42)
	Attained age 10 yr	Attained age 20 yr	Attained age 30 yr	Attained age 40 yr	Attained age 50 yr	Attained age 60 yr
Bone and soft tissue sarcoma	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Overall	0.00% (0.00-0.00)	0.05% (0.00-0.13)	0.20% (0.05-0.35)	0.76% (0.38-1.13)	2.20% (1.26-3.13)	6.01% (3.62-8.40)

Treatment						
No treatment/ surgery-only	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.45% (0.00-1.32)	2.82% (0.00-6.32)
Chemotherapy (± surgery)	0.00% (0.00-0.00)	0.10% (0.00-0.30)	0.20% (0.00-0.48)	1.12% (0.03-2.20)	5.92% (0.07-11.77)	5.92% (0.07-11.77)
Radiotherapy (± surgery)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.22% (0.00-0.66)	0.48% (0.00-1.15)	2.14% (0.55-3.72)	8.10% (4.09-12.11)
Chemotherapy and radiotherapy (± surgery)	0.00% (0.00-0.00)	0.08% (0.00-0.25)	0.28% (0.00-0.61)	1.00% (0.22-1.78)	1.00% (0.22-1.78)	1.00% (0.22-1.78)
Other Tumours	Attained age 10 yr % (95% CI)	Attained age 20 yr % (95% CI)	Attained age 30 yr % (95% CI)	Attained age 40 yr % (95% CI)	Attained age 50 yr % (95% CI)	Attained age 60 yr % (95% CI)
Overall	0.00% (0.00-0.00)	0.01% (0.00-0.04)	0.10% (0.02-0.18)	0.51% (0.28-0.74)	2.43% (1.66-3.20)	4.82% (3.31-6.33)
Treatment						
No treatment/ surgery-only	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.52% (0.01-1.03)	1.84% (0.58-3.10)	4.07% (148-6.67)
Chemotherapy (± surgery)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.29% (0.00-0.70)	1.03% (0.00-2.53)	9.61% (0.00-20.60)	9.61% (0.00-20.60)
Radiotherapy (± surgery)	0.00% (0.00-0.00)	0.00% (0.00-0.00)	0.09% (0.00-0.28)	0.44% (0.01-0.87)	2.73% (1.46-4.00)	5.41% (3.20-7.62)
Chemotherapy and radiotherapy (± surgery)	0.00% (0.00-0.00)	0.05% (0.00-0.14)	0.11% (0.00-0.25)	0.45% (0.08-0.81)	3.07% (0.49-5.65)	3.07% (0.49-5.65)

CNS = Central nervous system

[a] n=15, not sufficient for anlayses

[b] n=8, not sufficient for anlayses

eTable 6. Sensitivity analyses Cox regression analyses for symptomatic cardiac ischemia, with attained age as time scale. Inclusion criteria: incidence year 1970-1986, age at diagnosis <15 year old.

Model 1	***n / total n***	**Hazard Ratio**	***p-value***	***n events***
Age at primary childhood cancer diagnosis		1.1 (1.0-1.1)	*0.053*	
Sex				
Male	*7804/14082*	REF		*99/130*
Female	*6278/14082*	**0.4 (0.2-0.5)***	*< 0.0001*	*31/130*
Treatment				
No treatment/ surgery only	*1750/14082*	REF		*11/130*
Chemotherapy and/ or radiotherapy	*12332/14082*	**2.0 (1.1-3.7)***	*< 0.0001*	*119/130*
Model 2	***n / total n***	**Hazard Ratio**		***n events***
Age at primary childhood cancer diagnosis		1.0 (0.94-1.0)	*0.96*	
Sex				
Male	*7804/14081*	REF		*99/130*
Female	*6277/14081*	**0.4 (0.3-0.7)***	*<0.0001*	*31/130*
Primary cancer diagnosis				
Leukaemia	*4154/14081*	REF		*13/130*
Lymphoma	*2110/14081*	**5.3 (2.8-10.0)***	*<0.0001*	*72/130*
Central nervous system	*2565/14081*	1.5 (0.7-3.1)	*0.29*	*18/130*
Bone and soft tissue sarcoma	*1643/14081*	1.6 (0.7-3.6)	*0.25*	*12/130*
Other tumours	*3609/14081*	1.6 (0.7-6.4)	*0.25*	*15/130*

Also corrected for data provider and year of childhood cancer diagnosis.

* significant result (p<0.05)