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Original Research

Risk of subsequent primary leukaemias among 69,460 five-year survivors of childhood cancer diagnosed from 1940 to 2008 in Europe: A cohort study within PanCareSurFup

Rodrigue S. Allodji [a,b,c,*], Mike M. Hawkins [a], Chloe J. Bright [a], Miranda M. Fidler-Benaoudia [a,d], David L. Winter [a], Daniela Alessi [e], Brice Fresneau [b,f], Neige Journy [b], Vera Morsellino [g], Edit Bárdi [h,i], Andrea Bautz [j], Julianne Byrne [k], Elizabeth (Lieke) AM. Feijen [l,m], Jop C. Teepen [l,m], Giao Vu-Bezin [b], Carole Rubino [b], Stanislaw Garwicz [n,†], Desiree Grabow [o], Thorgerdur Gudmundsdottir [i,p], Joyeeta Guha [a], Eva-Maria Hau [q,r], Momcilo Jankovic [s], Peter Kaatsch [o], Melanie Kaiser [o], Helena Linge [n], Monica Muraca [g], Damien Llanas [b], Cristina Veres [b], Hilde Øfstaas [t], Ibrahima Diallo [b], Imene Mansouri [b], Cecile M. Ronckers [l,m], Roderick Skinner [u], Monica Terenziani [v], Finn Wesenberg [w], Thomas Wiebe [n], Carlotta Sacerdote [e], Zsuzsanna Jakab [x], Riccardo Haupt [g], Päivi Lähteenmäki [y], Lorna Zadravec Zaletel [z], Claudia E. Kuehni [q,r], Jeanette F. Winther [j,aa], Gisela Michel [ab], Leontien C.M. Kremer [l,m], Lars Hjorth [n], Nadia Haddy [a,b], Florent de Vathaire [b], Raoul C. Reulen [a]

[a] *Centre for Childhood Cancer Survivor Studies, Institute of Applied Health Research, Robert Aitken Building, University of Birmingham, Birmingham, UK*
[b] *Cancer and Radiation Team, Center for Research in Epidemiology and Population Health, INSERM U1018, University Paris Saclay, Gustave Roussy, Villejuif, France*
[c] *Polytechnic School of Abomey-Calavi (EPAC), University of Abomey-Calavi, 01 P.O. Box 2009, Cotonou, Benin*
[d] *Department of Cancer Epidemiology and Prevention Research, Alberta Health Services, Calgary, Alberta, Canada*

Abbreviations: PanCareSurFup, PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies; CCSS, Childhood Cancer Survivor Study; SIR, standardised incidence ratio; AER, absolute excess risk; AYA, adolescent and young adult; CIs, confidence intervals; ICCC, International Classification of Childhood Cancer; RR, relative risk; SPLs, subsequent primary leukaemias; FPN, first primary neoplasm; SPML, subsequent primary myeloid leukaemias; SPLL, subsequent primary lymphoid leukaemias.

* *Corresponding author:* Radiation Epidemiology Group / CESP - Unit 1018 INSERM, Gustave Roussy, B2M, 114, rue Édouard Vaillant 94805 Villejuif Cedex. Fax: +1 42 11 56 18. Centre for Childhood Cancer Survivor Studies, Institute of Applied Health Research, Robert Aitken Building, University of Birmingham, Birmingham, B15 2TT.
E-mail addresses: rodrigue.allodji@gustaveroussy.fr, A.Rodrigue@bham.ac.uk (R.S. Allodji).
† Deceased 27th November 2018 to whom this research is dedicated.

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[e] Childhood Cancer Registry of Piedmont, Cancer Epidemiology Unit, Department of Medical Sciences, University of Turin and AOU Città Della Salute e Della Scienza di Torino, Italy
[f] Department of Pediatric Oncology, Gustave Roussy, Université Paris-Saclay, Villejuif, France
[g] Epidemiology and Biostatistics Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy
[h] St Anna Kinderspital Wien, Austria
[i] Department of Paediatrics and Adolescent Medicine, Kepler University Hospital, Linz, Austria
[j] Danish Cancer Society Research Center, Childhood Cancer Research Group, Copenhagen, Denmark
[k] Boyne Research Institute, Drogheda, Ireland
[l] Department of Pediatric Oncology, Amsterdam UMC, Emma Children's Hospital, Amsterdam, the Netherlands
[m] Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands
[n] Lund University, Skane University Hospital, Department of Clinical Sciences, Paediatrics, Lund, Sweden
[o] German Childhood Cancer Registry (GCCR), Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Center, Mainz, Germany
[p] Children's Hospital, Landspitali University Hospital, Reykjavik, Iceland
[q] Swiss Childhood Cancer Registry, Institute of Social and Preventive Medicine, University of Bern, Switzerland
[r] Department of Paediatrics, University Children's Hospital of Bern, University of Bern, Switzerland
[s] Foundation MBBM, Hemato-Oncology Center, University of Milano-Bicocca, Via Cadore 38, 20900 Monza, MB, Italy
[t] Norwegian National Advisory Unit on Solid Tumors in Children, Norway
[u] Great North Children's Hospital, Newcastle Upon Tyne Hospitals NHS Foundation Trust, And Northern Institute of Cancer Research, Newcastle University, Newcastle Upon Tyne, UK
[v] Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
[w] Norwegian Cancer Registry and Dept. of Pediatric Medicine, Oslo University Hospital and Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Norway
[x] Hungarian Childhood Cancer Registry, 2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary
[y] Turku University and Turku University Hospital, Department of Pediatric and Adolescent Medicine, Turku, Finland
[z] Institute of Oncology, Ljubljana, Slovenia
[aa] Department of Clinical Medicine, Faculty of Health, Aarhus University and Aarhus University Hospital, Aarhus, Denmark
[ab] Department of Health Sciences and Health Policy, University of Lucerne, Frohburgstrasse 3, PO Box 4466, 6002, Lucerne, Switzerland

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Abstract ***Background:*** Survivors of childhood cancers are at risk of developing subsequent primary leukaemias (SPLs), but the long-term risks beyond 20 years of treatment are still unclear. We investigated the risk of SPLs in five-year childhood cancer survivors using a large-scale pan-European (PanCareSurFup) cohort and evaluated variations in the risk by cancer and demographic factors.
Methods: This largest-ever assembled cohort comprises 69,460 five-year childhood cancer survivors from 12 European countries. Standardised incidence ratios (SIRs) and absolute excess risks (AERs) were calculated.
Results: One hundred fifteen survivors developed an SPL including 86 myeloid leukaemias (subsequent primary myeloid leukaemias [SPMLs]), 17 lymphoid leukaemias and 12 other types of leukaemias; of these SPLs, 31 (27%) occurred beyond 20 years from the first childhood cancer diagnosis. Compared with the general population, childhood cancer survivors had a fourfold increased risk (SIR = 3.7, 95% confidence interval [CI]: 3.1 to 4.5) of developing leukaemia, and eight leukaemias per 100,000 person-years (AER = 7.5, 95% CI: 6.0 to 9.2) occurred in excess of that expected. The risks remained significantly elevated beyond 20 years from the first primary malignancy (SIR = 2.4, 95% CI: 1.6 to 3.4). Overall, the risk ratio for SPML (SIR = 5.8, 95% CI: 4.6 to 7.1) was higher than that for other SPLs.
Conclusions: We demonstrate that beyond 20 years after childhood cancer diagnosis, survivors experience an increased risk for SPLs compared with that expected from the general population. Our findings highlight the need for awareness by survivors and their healthcare providers for potential risk related to SPL.

1. Introduction

The survival of children with cancer has improved significantly over the past 60 years, with more than 80% of individuals diagnosed recently becoming five-year survivors [1]. Nevertheless, significant long-term morbidities continue to impact the majority of children who survived cancer. One of the most devastating sequelae among childhood cancer survivors (CCSs) is the occurrence of subsequent primary neoplasms [2–8]. Given that the number of survivors continues to increase, it is imperative that studies are undertaken to improve the understanding of the risks and causes of such late effects of treatments for cancer to produce an evidence base to inform clinical guidelines for follow-up.

Subsequent primary leukaemias (SPLs), both myeloid and lymphoid leukaemias, are a concern for long-term CCSs. Previous investigations have reported that the cumulative incidence of SPLs plateaus between 10 and 15 years after the first primary therapy [5,9]. To our knowledge, information on the risk of developing SPLs after 20 years remains unclear because of inadequate statistical power and follow-up time of those previous studies. For example, among 14,358 five-year survivors from the North American Childhood Cancer Survivor Study cohort, 43 SPLs were observed, of which only 13 were diagnosed after 15 years from the original cancer diagnosis [5]. The pan-European cohort of CCSs (PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies [PanCareSurFup]) from several European countries offers a unique opportunity to evaluate the risk of SPLs in a large population of survivors with a variety of first primary malignancies and long follow-up into adulthood [10–15]. The principal aim of the present study was to investigate the risk of occurrence of SPLs in five-year CCSs using the large-scale PanCareSurFup cohort and evaluate variations in the risk by cancer and demographic factors.

2. Methods

2.1. PanCareSurFup cohort

The PanCareSurFup (www.pancaresurfup.eu) consortium pools data from 13 European cohorts, within 12 countries, to establish the largest-ever collaborative study to comprehensively investigate adverse health outcomes in long-term CCSs. The PanCareSurFup cohort comprises data from both population-based cancer registries and major treatment centres [12,13]. A total of 69,460 five-year CCSs diagnosed before the age of 20 years between 1940 and 2008 were included in this cohort as previously described [14,15].

First primary neoplasms (FPNs) were grouped according to the International Classification of Childhood Cancer third edition [16]. Ethical approval was obtained separately for each cohort from the appropriate bodies within each specific country. The main characteristics of the PanCareSurFup cohort are described in Table 1.

2.2. Identification and ascertainment of subsequent primary leukaemias

Follow-up for SPLs began at the date of five-year survival. Exit from risk was the first of date of SPL; date of death (competing risk); date of last follow-up contact and date lost to follow-up. SPLs were coded using the International Classification of Diseases for Oncology (ICD-O) Editions 1, 2 and 3 [16–18], consistent with other publications analysing such data (Appendix Table S1, p 1) [6–8,19,20]. These SPLs were ascertained through (or using a combination of) linkage with population-based national cancer registries, follow-up clinics, questionnaires and available medical records; linkage with national mortality registries and linkage with health insurance registries and validated principally using pathology reports and occasionally other definitive diagnostic reports [14,15].

2.3. Statistical analyses

To compare the observed number of SPLs with that expected from the general population, general population leukaemia incidence rates were classified according to the adolescent and young adult cancer classification based on ICD-O morphology. Incidence rates by ICD-O morphology were available for the United Kingdom (UK) (years 1971–2006: England and Wales, only) [21] and were used as general population rates also for France, Hungary, Italy, the Netherlands, Slovenia and Switzerland. Similarly, Finnish incidence rates by ICD-O morphology (years 1953–2011) were used for Denmark, Norway, Sweden and Iceland [22]. When the range of calendar years for the general population cancer rates did not cover the entire follow-up period, rates from the closest available calendar year were used.

Standardised incidence ratios (SIRs) were calculated as the observed number of SPLs divided by the expected number of leukaemias. Absolute excess risks (AERs) were calculated as the observed minus the expected number of leukaemias, divided by person-years at risk and multiplied by 100,000. The AER can be interpreted as the number of excess leukaemias observed beyond that expected from the general population per 100,000 persons per year. The 95% confidence intervals (CIs) were calculated assuming that the observed number of SPLs followed a Poisson distribution. SIRs and AERs were stratified by country, sex, type of childhood cancer, age at and decade of childhood FPN diagnosis, attained age at exit and years of follow-up. Relative risks (RRs) and the relative excess risk (RER) of developing SPLs associated with these potential explanatory factors were

Table 1
Characteristics of all 69,460 five-year survivors of childhood cancer of the European PanCareSurFup study, 115 survivors who developed a subsequent primary leukaemia (SPL) and 7099 survivors who deceased.

Factors	All five-year survivors, No. (%) or median (range)	Person-years	Survivors who developed an SPL, No. (%) or median (range)	Deceased survivors, No. (%) or median (range)
Overall	69,460	1,126,273	115	7099
Country				
Nordic countries[a]	22,836 (33%)	355,831	29 (25%)	2235 (31%)
France	3138 (5%)	83,064	9 (8%)	539 (8%)
Hungary	4885 (7%)	50,100	11 (10%)	350 (5%)
Italy	8966 (13%)	94,234	9 (8%)	527 (7%)
The Netherlands	6044 (9%)	103,229	13 (11%)	491 (7%)
Slovenia	1252 (2%)	24,821	3 (3%)	146 (2%)
Switzerland	4379 (6%)	46,179	7 (6%)	279 (4%)
UK	17,960 (26%)	368,816	34 (30%)	2532 (36%)
Sex				
Male	37,738 (54%)	601,424	68 (59%)	4125 (58%)
Female	31,722 (46%)	524,848	47 (41%)	2974 (42%)
Type of childhood cancer				
Wilms tumour	4756 (7%)	95,878	8 (7%)	228 (3%)
Leukaemia	16,595 (24%)	219,900	25 (22%)	1776 (25%)
Hodgkin lymphoma	6000 (9%)	87,584	19 (17%)	692 (10%)
Non-Hodgkin lymphoma	3350 (5%)	53,752	6 (5%)	196 (3%)
Central nervous system	14,096 (20%)	228,403	22 (19%)	2338 (33%)
Neuroblastoma	3169 (5%)	55,282	6 (5%)	251 (4%)
Retinoblastoma	2578 (4%)	60,224	3 (3%)	87 (1%)
Bone sarcoma	3147 (5%)	51,767	3 (3%)	401 (6%)
Soft-tissue sarcoma	4501 (6%)	82,501	8 (7%)	453 (6%)
Other and not classifiable	11,268 (16%)	190,982	15 (13%)	677 (10%)
Age at diagnosis of FPN				
Median (range)	*7 (0–20)*		*8 (0–19)*	*8 (0–20)*
0–4 years	26,793 (39%)	463,318	39 (34%)	2232 (31%)
5–9 years	15,702 (23%)	255,543	30 (26%)	1842 (26%)
10–14 years	15,483 (22%)	251,894	34 (30%)	1890 (27%)
15–19 years	11,482 (17%)	155,517	12 (10%)	1135 (16%)
Decade of diagnosis of FPN				
Median (range)	*1986 (1940–2008)*		*1980 (1948–2006)*	*1977 (1940–2008)*
<1970	8993 (13%)	286,777	24 (21%)	1989 (28%)
1970–1979	13,479 (19%)	313,456	27 (23%)	2204 (31%)
1980–1989	20,900 (30%)	339,267	34 (30%)	1858 (26%)
≥1990	26,088 (38%)	186,772	30 (26%)	1048 (15%)
Attained age at exit				
Median (range)	*28 (5–79)*		*20 (6–65)*	*20 (5–76)*
5–19 years	16,243 (23%)	408,724	56 (49%)	3521 (50%)
20–29 years	22,437 (32%)	389,276	33 (29%)	2089 (29%)
30–39 years	17,471 (25%)	214,076	11 (10%)	798 (11%)
≥40 years	13,309 (19%)	114,196	15 (13%)	691 (10%)
Years from FPN diagnosis[b]				
Median (range)	*19 (5–67)*		*10 (5–50)*	*9 (5–63)*
5–9 years	13,211 (19%)	311,750	55 (48%)	3860 (54%)
10–19 years	23,083 (33%)	449,578	29 (25%)	1752 (25%)
20–29 years	17,602 (25%)	236,989	15 (13%)	816 (11%)
30–39 years	10,290 (15%)	96,627	9 (8%)	454 (6%)
≥40 years	5274 (8%)	31,328	7 (6%)	217 (3%)

FPN = first primary neoplasm.
[a] Nordic countries include Finland, Iceland, Norway, Sweden and Denmark.
[b] Years from FPN diagnosis = Years between FPN diagnosis and SPL diagnosis or date at exit.

estimated using univariable and multivariable Poisson regression. RRs may be interpreted as the ratio of SIRs, adjusted for relevant cofactors fitted. Similarly, RERs may be interpreted as the ratio of AERs, adjusted for relevant cofactors fitted. Tests of homogeneity and trend were based on likelihood ratio tests. For trend tests, ordinal variables were treated as continuous variables in the model. Finally, cumulative incidence curves relating to the first occurrence of an SPL, adjusting for death as a competing risk, were calculated, and Gray's tests were used to evaluate hypotheses of equality of cumulative incidence functions between subgroups where relevant.

Table 2
Characteristics of 115 five-year survivors of childhood cancer of the European PanCareSurFup study who developed a subsequent primary leukaemia (SPL) according the first primary neoplasm (FPN).

Factors	Wilms tumour, No. (%)	Leukaemia, No. (%)	Hodgkin lymphoma, No. (%)	Non-Hodgkin lymphoma, No. (%)	Central nervous system, No. (%)	Neuroblastoma, No. (%)	Retinoblastoma, No. (%)	Bone sarcoma, No. (%)	Soft-tissue sarcoma, No. (%)	Other and not classifiable, No. (%)
Overall	8	25	19	6	22	6	3	3	8	15
Age at diagnosis of FPN										
Median (range)	*2* (1–7)	*7* (1–14)	13 (4–18)	*9* (6–14)	*9* (2–16)	*2* (1–6)	*1* (1–10)	*10* (5–13)	*3* (0–10)	*9* (1–19)
0–4 years	6 (75%)	9 (36%)	1 (5%)	–	7 (32%)	5 (83%)	2 (67%)	1 (33%)	5 (63%)	3 (20%)
5–9 years	2 (25%)	10 (40%)	1 (5%)	3 (50%)	5 (23%)	1 (17%)	–	–	3 (38%)	5 (33%)
10–14 years	–	6 (24%)	13 (68%)	3 (50%)	8 (36%)	–	1 (33%)	2 (67%)	–	1 (7%)
15–19 years	–	–	4 (21%)	–	2 (9%)	–	–	–	–	6 (40%)
Decade of diagnosis of FPN										
Median (range)	*1975 (1954–1989)*	1986 *(1971–2000)*	*1980 (1948–1996)*	*1980 (1963–1991)*	*1989 (1957–2006)*	*1980 (1961–1997)*	*1968 (1953–1980)*	*1970 (1959–1986)*	*1992 (1966–2004)*	*1968 (1954–2001)*
<1970	2 (25%)	–	4 (21%)	1 (17%)	3 (14%)	2 (33%)	2 (67%)	1 (33%)	1 (13%)	8 (53%)
1970–1979	4 (50%)	8 (32%)	5 (26%)	2 (33%)	4 (18%)	1 (17%)	–	1 (33%)	1 (13%)	1 (7%)
1980–1989	2 (25%)	10 (40%)	8 (42%)	2 (33%)	4 (18%)	1 (17%)	1 (33%)	1 (33%)	2 (25%)	3 (20%)
≥1990	–	7 (28%)	2 (11%)	1 (17%)	11 (50%)	2 (33%)	–	–	4 (50%)	3 (20%)
Age at SPL diagnosis										
Median (range)	*20 (10–32)*	*19 (10–31)*	*21 (13–59)*	*17 (13–57)*	*20 (8–65)*	*15 (7–43)*	*41 (21–47)*	*20 (12–40)*	*16 (6–36)*	*25 (11–65)*
5–19 years	4 (50%)	14 (56%)	6 (32%)	4 (67%)	11 (50%)	4 (67%)	–	1 (33%)	7 (88%)	5 (33%)
20–29 years	3 (38%)	10 (40%)	10 (53%)	–	4 (18%)	–	1 (33%)	1 (33%)	–	4 (27%)
30–39 years	1 (13%)	1 (4%)	1 (5%)	–	4 (18%)	1 (17%)	–	–	1 (13%)	2 (13%)
≥40 years	–	–	2 (11%)	2 (33%)	3 (14%)	1 (17%)	2 (67%)	1 (33%)	–	4 (27%)
Years from FPN diagnosis[a]										
Median (range)	*17 (9–31)*	*9* (5–29)	*9 (5–46)*	*10 (5–43)*	*10 (5–50)*	*10 (5–42)*	*37 (20–41)*	*10* (8–27)	*8 (5–36)*	*13 (6–46)*
5–9 years	1 (13%)	15 (60%)	11 (58%)	3 (50%)	11 (50%)	3 (50%)	–	1 (33%)	5 (63%)	5 (33%)
10–19 years	4 (50%)	6 (24%)	6 (32%)	1 (17%)	4 (18%)	1 (17%)	–	1 (33%)	2 (25%)	4 (27%)
20–29 years	2 (25%)	4 (16%)	–	1 (17%)	4 (18%)	–	1 (33%)	1 (33%)	–	2 (13%)
30–39 years	1 (13%)	–	1 (5%)	–	1 (5%)	1 (17%)	1 (33%)	–	1 (13%)	3 (20%)
≥40 years	–	–	1 (5%)	1 (17%)	2 (9%)	1 (17%)	1 (33%)	–	–	1 (7%)

No. = frequency; FPN = first primary neoplasm; SPL = subsequent primary leukaemia.
[a] Years from FPN diagnosis = Years between FPN diagnosis and SPL diagnosis.

Table 3
SIRs and AERs per 100,000 person-years at risk of developing a subsequent primary leukaemia (SPL) among 69,460 five-year survivors of childhood cancer of the European PanCareSurFup study.

Factors	Overall			By years from diagnosis					
				5–19 years			≥20 years		
	O/E	SIR (95% CI)	AER (95% CI)	O/E	SIR (95% CI)	AER (95% CI)	O/E	SIR (95% CI)	AER (95% CI)
Overall	**115/31**	**3.7 (3.1–4.5)**	**7.5 (6.0–9.2)**	**84/17.9**	**4.7 (3.7–5.8)**	**8.7 (6.8–11.0)**	**31.0/13.1**	**2.4 (1.6–3.4)**	**4.9 (3.1–7.8)**
P-values		***<.0001***	***0.0073***		***<.0001***	***0.0084***		***<.0001***	***0.0152***
Country									
Nordic countries[b]	29.0/10.9	**2.7 (1.8–3.8)**	**5.1 (3.2–8.1)**	20.0/5.7	**3.5 (2.2–5.4)**	**6.1 (3.6–10.2)**	9.0/5.2	**1.7 (0.8–3.3)**	**3.1 (1.1–8.6)**
France	9.0/2.3	**3.9 (1.8–7.4)**	**8.0 (3.8–17.2)**	5.0/1.0	**5.0 (1.6–11.8)**	**9.3 (3.5–24.7)**	4.0/1.3	**3.0 (0.8–7.7)**	**6.7 (2.0–22.2)**
Hungary	11.0/1.2	**9.0 (4.5–16.1)**	**19.5 (10.4–36.5)**	10.0/1.0	**9.8 (4.7–18.0)**	**21.5 (11.2–41.3)**	1.0/0.2	**5.0 (0.1–28.1)**	**9.7 (1.1–86.5)**
Italy	9.0/2.3	**3.9 (1.8–7.4)**	**7.1 (3.3–15.1)**	8.0/1.8	**4.5 (1.9–8.8)**	**8.2 (3.7–18.0)**	1.0/0.5	**1.9 (0.0–10.6)**	**2.5 (0.1–43.8)**
Netherlands	13.0/2.6	**5.0 (2.7–8.6)**	**10.1 (5.5–18.5)**	11.0/1.8	**6.2 (3.1–11.2)**	**12.4 (6.5–23.7)**	2.0/0.8	**2.5 (0.3–8.9)**	**4.1 (0.7–24.8)**
Slovenia	3.0/0.7	**4.3 (0.9–12.4)**	**9.2 (2.5–33.7)**	3.0/0.4	**8.3 (1.7–24.2)**	**16.7 (5.0–55.9)**	0.0/0.3	-	-
Switzerland	7.0/1.2	**6.1 (2.4–12.5)**	**12.7 (5.6–28.5)**	7.0/1.0	**7.2 (2.9–14.8)**	**15.1 (6.8–33.5)**	0.0/0.2	-	-
UK	34.0/9.9	**3.5 (2.4–4.8)**	**6.5 (4.4–9.8)**	20.0/5.4	**3.7 (2.3–5.8)**	**6.2 (3.7–10.4)**	14.0/4.5	**3.1 (1.7–5.2)**	**7.1 (3.8–13.4)**
P for heterogeneity[a]		***0.0393***	***0.0444***		***0.1393***	***0.0453***		***0.9183***	***0.7732***
Sex									
Male	68.0/18.8	**3.6 (2.8–4.6)**	**8.2 (6.2–10.8)**	47.0/11.1	**4.2 (3.1–5.6)**	**8.8 (6.3–12.2)**	21.0/7.7	**2.7 (1.7–4.2)**	**6.9 (4.0–11.9)**
Female	47.0/12.2	**3.9 (2.9–5.2)**	**6.6 (4.8–9.3)**	37.0/6.8	**5.4 (3.8–7.5)**	**8.6 (6.0–12.3)**	10.0/5.4	**1.9 (0.9–3.4)**	**2.7 (1.1–6.6)**
P for heterogeneity[a]		***0.7324***	***0.3446***		***0.2561***	***0.9348***		***0.3207***	***0.0771***
Type of childhood cancer									
Wilms tumour	8.0/2.5	**3.2 (1.4–6.4)**	**5.8 (2.5–13.3)**	5.0/1.5	**3.4 (1.1–7.8)**	**5.9 (2.1–16.7)**	3.0/1.0	**3.1 (0.6–8.9)**	**5.6 (1.4–22.2)**
Leukaemia	25.0/5.4	**4.7 (3.0–6.9)**	**8.9 (5.7–13.9)**	21.0/4.2	**5.0 (3.1–7.7)**	**9.8 (6.1–15.8)**	4.0/1.2	**3.4 (0.9–8.7)**	**5.9 (1.8–18.8)**
Hodgkin lymphoma	19.0/2.4	**7.9 (4.7–12.3)**	**18.9 (11.7–30.6)**	17.0/1.4	**12.5 (7.3–20.0)**	**25.3 (15.4–41.5)**	2.0/1.1	**1.9 (0.2–6.8)**	**3.7 (0.5–27.7)**
Non-Hodgkin lymphoma	6.0/1.5	**3.9 (1.4–8.4)**	**8.3 (3.3–21.0)**	4.0/0.9	**4.6 (1.2–11.7)**	**8.4 (2.8–25.5)**	2.0/0.7	**3.0 (0.4–10.7)**	**7.9 (1.4–43.6)**
Central nervous system	22.0/6.4	**3.5 (2.2–5.2)**	**6.8 (4.2–11.2)**	15.0/3.5	**4.3 (2.4–7.1)**	**7.6 (4.2–13.5)**	7.0/2.9	**2.4 (1.0–5.0)**	**5.4 (2.1–14.2)**
Neuroblastoma	6.0/1.5	**4.1 (1.5–8.9)**	**8.2 (3.3–20.6)**	4.0/1.0	**4.1 (1.1–10.6)**	**8.4 (2.7–26.0)**	2.0/0.5	**4.0 (0.5–14.6)**	**7.8 (1.6–38.4)**
Retinoblastoma	3.0/1.7	**1.8 (0.4–5.3)**	**2.2 (0.4–12.1)**	0.0/0.9	-	-	3.0/0.8	**3.8 (0.8–11.1)**	**8.2 (2.2–30.6)**
Bone sarcoma	3.0/1.6	**1.9 (0.4–5.6)**	**2.8 (0.5–14.2)**	2.0/0.7	**2.7 (0.3–9.9)**	**3.7 (0.7–21.4)**	1.0/0.8	**1.2 (0.0–6.6)**	**0.9 (0.0–124)**
Soft-tissue sarcoma	8.0/2.4	**3.3 (1.4–6.4)**	**6.7 (2.9–15.5)**	7.0/1.2	**5.7 (2.3–11.8)**	**11.2 (4.9–25.3)**	1.0/1.2	**0.8 (0.0–4.6)**	-
Other and not classifiable	15.0/5.7	**2.6 (1.5–4.3)**	**4.9 (2.5–9.2)**	9.0/2.8	**3.3 (1.5–6.2)**	**5.0 (2.3–11.0)**	6.0/3.0	**2.0 (0.7–4.4)**	**4.5 (1.5–13.9)**
P for heterogeneity[a]		***0.0550***	***0.0202***		***0.0392***	***0.0120***		***0.9256***	***0.9927***
Age at diagnosis of FPN									
0–4 years	39.0/12.2	**3.2 (2.3–4.4)**	**5.8 (4.0–8.5)**	26.0/8.2	**3.2 (2.1–4.7)**	**5.8 (3.6–9.2)**	13.0/4.1	**3.2 (1.7–5.5)**	**5.8 (3.0–11.1)**
5–9 years	30.0/6.5	**4.6 (3.1–6.6)**	**9.2 (6.1–13.8)**	25.0/3.9	**6.4 (4.1–9.4)**	**12.1 (7.9–18.6)**	5.0/2.6	**1.9 (0.6–4.5)**	**2.9 (0.8–10.4)**
10–14 years	34.0/7.2	**4.8 (3.3–6.6)**	**10.7 (7.3–15.6)**	26.0/3.5	**7.4 (4.8–10.8)**	**13.2 (8.7–20.0)**	8.0/3.6	**2.2 (0.9–4.3)**	**5.3 (2.1–13.6)**
15–19 years	12.0/5.1	**2.3 (1.2–4.1)**	**4.4 (2.1–9.3)**	7.0/2.3	**3.0 (1.2–6.2)**	**4.3 (1.7–10.6)**	5.0/2.8	**1.8 (0.6–4.1)**	**4.8 (1.3–17.9)**
P for heterogeneity[a]		***0.0780***	***0.0487***		***0.0059***	***0.0113***		***0.6070***	***0.8302***
P-trend[a]		***0.9746***	***0.5241***		***0.1621***	***0.4339***		***0.2485***	***0.8047***
Decade of diagnosis of FPN									
<1970	24.0/10.4	**2.3 (1.5–3.4)**	**4.7 (2.8–8.1)**	8.0/2.7	**3.0 (1.3–5.9)**	**4.5 (1.9–10.4)**	16.0/7.7	**2.1 (1.2–3.4)**	**4.9 (2.5–9.8)**
1970–1979	27.0/7.9	**3.4 (2.3–5.0)**	**6.1 (3.9–9.5)**	15.0/4.1	**3.7 (2.0–6.0)**	**6.0 (3.3–10.9)**	12.0/3.8	**3.2 (1.6–5.5)**	**6.2 (3.1–12.3)**
1980–1989	34.0/8.1	**4.2 (2.9–5.9)**	**7.6 (5.2–11.2)**	31.0/6.5	**4.7 (3.2–6.7)**	**8.9 (6.0–13.2)**	3.0/1.5	**2.0 (0.4–5.8)**	**2.3 (0.5–11.7)**
≥1990	30.0/4.7	**6.4 (4.3–9.2)**	**13.6 (9.2–20.0)**	30.0/4.6	**6.5 (4.4–9.3)**	**13.8 (9.3–20.3)**	0.0/0.0	-	-
P for heterogeneity[a]		***0.0020***	***0.0066***		***0.1317***	***0.0303***		***0.7058***	***0.5400***
P-trend[a]		***0.0002***	***0.0012***		***0.0200***	***0.0033***		***0.7007***	***0.6018***

Attained age at exit									
5–19 years	56.0/10.8	**5.2 (3.9–6.7)**	**11.1 (8.3–14.8)**	56.0/10.8	**5.2 (3.9–6.7)**	**11.1 (8.3–14.8)**	–	-	-
20–29 years	33.0/7.7	**4.3 (3.0–6.0)**	**6.5 (4.4–9.6)**	26.0/5.7	**4.6 (3.0–6.7)**	**7.0 (4.6–10.9)**	7.0/2.0	**3.5 (1.4–7.2)**	**5.0 (2.1–12.0)**
30–39 years	11.0/5.3	**2.1 (1.0–3.7)**	**2.7 (1.2–6.0)**	2.0/1.5	**1.4 (0.2–5.0)**	**0.9 (0.1–12.2)**	9.0/3.9	**2.3 (1.1–4.4)**	**3.4 (1.4–8.1)**
≥40 years	15.0/7.2	**2.1 (1.2–3.4)**	**6.8 (3.4–13.8)**	0.0/0.0	-	-	15.0/7.2	**2.1 (1.2–3.4)**	**6.8 (3.4–13.8)**
P for heterogeneity[a]		***0.0017***	***0.0048***		***0.3168***	***0.0489***		***0.5227***	***0.4771***
P-trend[a]		***0.0002***	***0.0035***		***0.0824***	***0.0058***		***0.2932***	***0.5172***
Years from FPN diagnosis[≠]									
5–9 years	55.0/8.0	**6.9 (5.2–9.0)**	**15.1 (11.3–20.1)**	55.0/8.0	**6.9 (5.2–9.0)**	**15.1 (11.3–20.1)**			
10–19 years	29.0/10.0	**2.9 (1.9–4.2)**	**4.2 (2.7–6.6)**	29.0/10.0	**2.9 (1.9–4.2)**	**4.2 (2.7–6.6)**			
20–29 years	15.0/6.0	**2.5 (1.4–4.1)**	**3.8 (2.0–7.3)**				15.0/6.0	**2.5 (1.4–4.1)**	**3.8 (2.0–7.3)**
30–39 years	9.0/4.1	**2.2 (1.0–4.2)**	**5.1 (2.1–12.3)**				9.0/4.1	**2.2 (1.0–4.2)**	**5.1 (2.1–12.3)**
≥40 years	7.0/3.0	**2.3 (0.9–4.8)**	**12.7 (4.8–33.9)**				7.0/3.0	**2.3 (0.9–4.8)**	**12.7 (4.8–33.9)**
P for heterogeneity[a]		***<.0001***	***<.0001***		***0.0002***	***<.0001***		***0.9442***	***0.1334***
P-trend[a]		***<.0001***	***0.0007***		***0.0002***	***<.0001***		***0.8160***	***0.0718***

Abbreviations: O = observed number of leukaemia, E = expected number of leukaemia, SIR = standardised incidence ratio, AER = absolute excess risk per 100,000 person-years, 95% CI = 95% confidence interval (in bold), SPL = subsequent primary leukaemia, FPN = first primary neoplasm; ≠Years from FPN diagnosis = Years between FPN diagnosis and SPL diagnosis or date at exit.

[a] P for heterogeneity or P-trend was calculated using two-sided likelihood ratio tests within a univariable Poisson model.

[b] Nordic countries include Finland, Iceland, Norway, Sweden and Denmark.

All statistical analyses were conducted in SAS software, version 9.4. A two-sided p-value <0.05 was considered statistically significant.

3. Results

3.1. Cohort characteristics

Among 69,460 five-year CCSs, a total of 1,126,273 person-years were accrued and 115 SPLs were observed after a median follow-up of 19 years (range: 5–67 years) and a median age at childhood cancer diagnosis of 7 years (range: 0–20 years). Loss to follow-up did not exceed 6% (Appendix Table S2, p 2). The most commonly observed SPLs were subsequent primary myeloid leukaemias (SPMLs) [86 SPMLs including 44 acute myeloid leukaemias (AMLs), 10 chronic myeloid leukaemias (CMLs) and 32 unspecified/other myeloid leukaemias mainly AML not otherwise specified (NOS) and myeloid leukaemia NOS], followed by subsequent primary lymphoid leukaemias (SPLLs) [17 SPLLs including 5 acute lymphoid leukaemias (ALL), 4 chronic lymphoid leukaemias (CLL) and 8 unspecified/other lymphoid leukaemias mainly precursor B-cell and precursor T-cell lymphoblastic leukaemia] and other types of leukaemias [12 SPLs including 5 acute leukaemias NOS, 2 leukaemia NOS, 2 hairy cell leukaemia and 3 other leukaemias] (Appendix Tables S1 and S3, p 1 and 3). Demographic and cancer characteristics of the study cohort are shown in Table 1. The median attained age at study exit was 28 years (range: 5–79 years), and female survivors accounted for 41% of five-year survivors who developed an SPL. Of those survivors who developed an SPL, 19 (17%) were originally diagnosed with Hodgkin lymphoma as childhood cancer, despite only 9% of the survivors in this cohort being diagnosed with Hodgkin lymphoma in the all five-year survivors. There were 31 (27%) SPLs diagnosed beyond 20 years after the FPN and 15 SPLs diagnosed beyond attaining 40 years of age (Table 1).

3.2. First primary neoplasm characteristics of survivors with a subsequent primary leukaemia

The characteristics of the 115 five-year survivors who developed an SPL are summarised in Table 2 by the type of FPNs. Among these, 39 (34%) were diagnosed with their FPN within five years of age; specifically, 5 of 6 (83%) and 6 of 8 (75%) SPLs occurring among neuroblastoma or Wilms tumour survivors were originally diagnosed before five years of age, respectively (Table 2). The median latency between the FPN and SPL was 10 years (Table 1), with the shortest delay noted for survivors of soft-tissue sarcoma (8 years) and leukaemia (9 years). In contrast, survivors whose first malignancy was either Wilms tumour or retinoblastoma had the

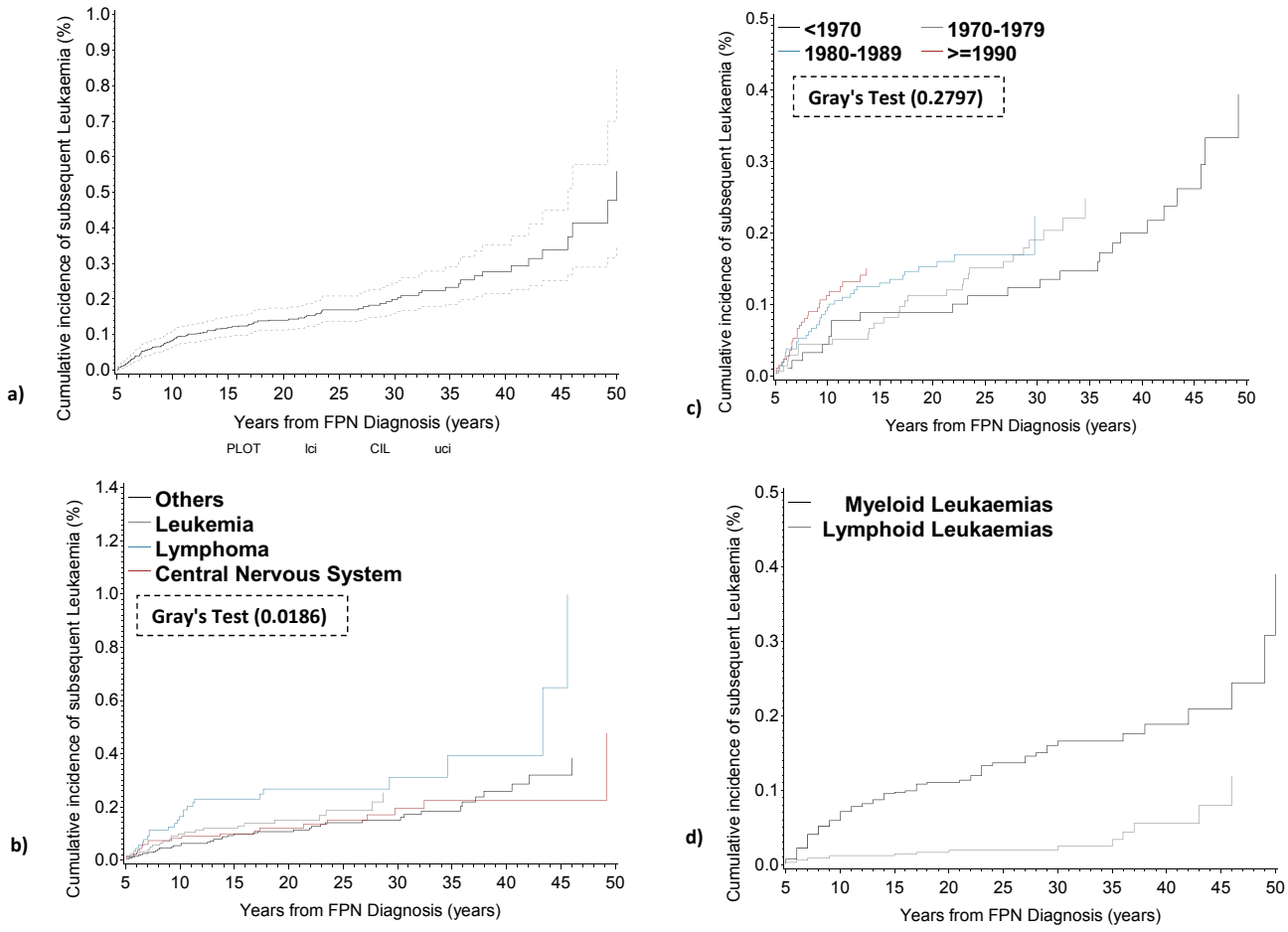

Fig. 1. (a) Cumulative incidence of new subsequent leukaemia diagnosed in survivors from the five-year survivors of childhood cancer of the largest-ever European PanCareSurFup study. Whole cohort: Solid lines are calculated cumulative incidence values; dashed lines are 95% CIs. Cumulative incidence curves (b) for the main type of childhood cancer, (c) for decade of diagnosis of FPN and (d) by leukaemia type. CI, confidence interval; FPN, first primary neoplasms.

longest mean latency—17 and 37 years, respectively. The median attained age at SPL diagnosis was 20 years (Table 1), while the median age at the development of SPL was highest for Hodgkin lymphoma (21 years), not classifiable childhood cancers (25 years) and retinoblastoma (41 years) survivors (Table 2).

3.3. Overall risk of subsequent primary leukaemias

Compared with that expected from the general population, CCSs had an almost fourfold risk (SIR: 3·7, 95% CI: 3·1–4·5) of developing an SPL and almost eight leukaemias per 100,000 person-years (AER: 7·5, 95% CI: 6·0–9·2) in excess of that expected (Table 3). The cumulative incidence for the development of SPLs steadily increased after FPN diagnosis, from 0·1% (95% CI: 0·1–0·2) at 20 years to 0·6% (95% CI: 0·4–0·9) at 50 years (Fig. 1a).

All survivors of each specific type of primary childhood cancer—except retinoblastoma and bone sarcoma—had both a statistically significantly increased relative excess risk and AER of developing an SPL, with the greatest excess risks among Hodgkin lymphoma survivors (SIR: 7·9, 95% CI: 4·7–12·3; AER: 18·9, 95% CI: 11·7–30·6) (Table 3). However, the large excess risk for Hodgkin lymphoma survivors seen before 20 years of follow-up (SIR of 12·5) disappears with longer follow-up (SIR: 1·9, 95% CI: 0·2–6·8). When stratifying into 4 FPN tumour types [leukaemia, lymphoma included also the non-Hodgkin lymphoma (NHL), central nervous system (CNS) and others], the cumulative incidence at 20 years was highest among lymphoma survivors (0·3%, 95% CI: 0·2–0·4) (Fig. 1b).

Although SIRs appeared to be higher among survivors diagnosed in most recent decades (p-trend = 0·0002; Table 3 & Appendix Table S4, p 4), this finding was not confirmed by multivariable analyses adjusted for country, sex, type of childhood cancer, age at diagnosis, decade of diagnosis and years from diagnosis at exit (p-trend = 0·5180; Table 4). In addition, we observed no significant differences in cumulative incidence of SPLs among categories of decade of diagnosis of FPNs (p = 0·2797) (Fig. 1c).

Table 4
Relative risk (RR) and relative excess risk (RER) of developing a subsequent primary leukaemia (SPL) by demographic and treatment factors among 69,460 five-year survivors of childhood cancer of the European PanCareSurFup study (multivariable analyses).

Factors	RR (95% CI)	RER (95% CI)
Sex		
Male	Ref	Ref
Female	1.2 (0.8–1.7)	1.0 (0.6–1.6)
P for heterogeneity[a]	*0.4328*	*0.9621*
Type of childhood cancer		
Wilms tumour	Ref	Ref
Leukaemia	1.1 (0.5–2.6)	0.5 (0.2–1.3)
Hodgkin lymphoma	2.2 (0.9–5.4)	1.6 (0.5–4.7)
Non-Hodgkin lymphoma	1.1 (0.3-3.2)	3.7 (1.1–12.8)
Central nervous system	1.0 (0.4–2.3)	0.8 (0.3–2.2)
Neuroblastoma	1.2 (0.4–3.5)	2.5 (0.8–7.8)
Retinoblastoma	0.7 (0.2-2.7)	2.3 (0.4–12.8)
Bone sarcoma	0.5 (0.1–2.1)	2.5 (0.6–11.6)
Soft-tissue sarcoma	1.0 (0.4–2.8)	2.2 (0.7–6.6)
Other and not classifiable	0.9 (0.3–2.2)	0.8 (0.3–2.5)
P for heterogeneity[a]	*0.2471*	*0.0005*
Age at diagnosis of FPN		
0–4 years	1.1 (0.5–2.3)	1.8 (0.7–4.4)
5–9 years	1.6 (0.7–3.3)	3.2 (1.2–8.1)
10–14 years	1.7 (0.9–3.5)	2.5 (1.0–6.2)
15–19 years	Ref	Ref
P for heterogeneity[a]	*0.1918*	*0.0542*
P-trend[a]	*0.5536*	*0.9484*
Decade of diagnosis of FPN		
<1970	Ref	Ref
1970–1979	1.1 (0.6–2.2)	0.9 (0.4–2.0)
1980–1989	1.2 (0.6–2.3)	0.7 (0.3–1.5)
≥1990	1.4 (0.7–3.0)	0.5 (0.2–1.2)
P for heterogeneity[a]	*0.8251*	*0.3701*
P-trend[a]	*0.5180*	*0.1187*
Years from FPN diagnosis[≠]		
5–9 years	2.1 (0.8–5.4)	1.4 (0.4-4.7)
10–19 years	0.9 (0.3–2.4)	0.8 (0.2-2.8)
20–29 years	0.8 (0.3–2.3)	1.1 (0.3-3.6)
30–39 years	0.8 (0.3–2.3)	1.7 (0.5–6.1)
≥40 years	Ref	Ref
P for heterogeneity[a]	*0.0018*	*0.2498*
P-trend[a]	*0.0040*	*0.4488*

Abbreviations: Relative risk (RR) and relative excess risk (RER) from multivariable Poisson regression model adjusted for country, sex, type of childhood cancer, age at diagnosis, decade of diagnosis and years from diagnosis. Ref-reference category, 95% CI - 95% confidence interval, FPN = first primary neoplasm; [≠]Years from FPN diagnosis = Years between FPN diagnosis and SPL diagnosis or date at exit.
[a] P for heterogeneity or P-trend was calculated using two-sided likelihood ratio tests within a multivariable Poisson model.

SIRs decreased significantly with increasing attained age at exit (p-trend = 0·0002) but were still twofold elevated beyond 30 years of age compared with the general population (Table 3). Similarly, the SIR declined with time since FPN diagnosis (p-trend<0·0001) but remained significantly elevated (SIR: 2·4, 95% CI: 1·6–3·4) after 20 years of follow-up (Table 3). The multivariable analysis revealed that SIRs varied substantially with follow-up time from FPN diagnosis (p = 0·0018) (Table 4). AERs were particularly high between 5 and 9 years of follow-up (AER: 15·1, 95% CI: 11·3–20·1) and then declined substantially to 3·8–4·2 between 10 and 39 years and then increased sharply (AER: 12.7, 95% CI: 4.8–33.9) beyond 40 years of follow-up (Table 3).

3.4. Risks of subsequent primary myeloid leukaemias and subsequent primary lymphoid leukaemias

Differences in the cumulative incidence rates of SPMLs and SPLLs were observed (Fig. 1d). Overall, survivors had significantly and substantially elevated risks for myeloid neoplasms, with a relative risk of sixfold (SIR: 5.8, 95% CI: 4.6–7.1) and six myeloid leukaemias per 100,000 person-years (AER: 6.3, 95% CI: 5.0–8.0) in excess of that expected (Table 5). Survivors of each specific type of childhood cancer—except retinoblastoma and bone sarcoma—had both a statistically significantly increased SIR and AER for developing an SPML, although Hodgkin lymphoma survivors experienced the greatest SIR and AER (SIR: 12.1, 95% CI: 6.9–19.6; AER: 16.8, 95% CI: 10.0–27.9). SPML AERs varied with age at diagnosis. Those diagnosed within five years of age and after 15 years of age experienced an excess of four SPMLs per 100,000 person-years, while those diagnosed at ages 5–14 years experienced an excess of eight to ten SPMLs per 100,000 person-years. Most SPMLs were diagnosed within the age of 30 years (81.4%), and 76.7% occurred within 20 years of FPN diagnosis (Appendix Table S3, p 3).

In contrast, the SIR was not significantly elevated for lymphocytic leukaemia (SIR: 1.2, 95% CI: 0.7–2.0) and the AER for developing an SPLL was only 0.3 per 100,000 person-years (Appendix Table S5, p 5). No significantly increased SIRs or AERs were noted for SPLLs when stratified by sex, FPN, age at diagnosis, decade of diagnosis and attained age at exit, nor years from diagnosis at exit.

4. Discussion

4.1. Main findings

In this largest-ever cohort study investigating the risk of SPLs in five-year CCSs, we showed that the risk of developing an SPL remained elevated for at least 20 years from FPN diagnosis and only the risk of SPML is increased and not for SPLL. Owing to the collaborative nature of this study, we were able to expand upon previous individual studies from the UK [8], France [6], Italy [23], Nordic countries [19] and the United States [5,20] and overcome their limitations of low statistical power. Indeed, compared with the largest previous study investigating SPL risk in CCSs from the North American Childhood Cancer Survivor Study [5], we observed

Table 5
SIRs and AERs per 100,000 person-years at risk of developing a subsequent myeloid primary leukaemia (SPLM) and relative risk (RR) and relative excess risk (RER) of developing an SPLM by demographic and treatment factors among 69,460 five-year survivors of childhood cancer of the European PanCareSurFup study (multivariable analyses).

Factors	O/E	SIR (95% CI)	RR (95% CI)	AER (95% CI)	RER (95% CI)
Overall	86.0/14.9	**5.8 (4.6–7.1)**		**6.3 (5.0–8.0)**	
P-values		**<0001**		**0.0078**	
Sex					
Male	49.0/8.5	**5.7 (4.3–7.6)**	Ref	**6.7 (4.9–9.2)**	Ref
Female	37.0/6.4	**5.8 (4.1–8.0)**	1.1 (0.7–1.7)	**5.8 (4.1–8.3)**	1.2 (0.7–2.1)
P for heterogeneity		***0.9757***	*0.6891*	***0.5498***	*0.4485*
Type of childhood cancer					
Wilms tumour	6.0/1.1	**5.5 (2.0–12.0)**	Ref	**5.1 (2.1–12.4)**	Ref
Leukaemia	22.0/2.3	**9.6 (6.0–14.5)**	1.3 (0.5–3.3)	**9.0 (5.8–13.9)**	0.5 (0.2–1.6)
Hodgkin lymphoma	16.0/1.3	**12.1 (6.9–19.6)**	2.0 (0.7–5.7)	**16.8 (10.0–27.9)**	1.3 (0.3–4.8)
Non-Hodgkin lymphoma	4.0/0.8	**5.1 (1.4–13.1)**	0.9 (0.2–3.2)	**6.0 (2.0–17.9)**	3.6 (0.7–19.3)
Central nervous system	16.0/3.2	**5.1 (2.9–8.2)**	0.9 (0.3–2.4)	**5.6 (3.3–9.7)**	0.8 (0.2-2.7)
Neuroblastoma	4.0/0.6	**7.0 (1.9–17.9)**	1.2 (0.3–4.2)	**6.2 (2.1–17.9)**	1.9 (0.4–9.5)
Retinoblastoma	0.0/0.7	**-**	–	**-**	–
Bone sarcoma	1.0/0.8	**1.2 (0.0–6.6)**	0.2 (0.0–1.8)	**0.3 (0.0–41.3)**	1.1 (0.1–11.3)
Soft-tissue sarcoma	6.0/1.2	**5.0 (1.9–11.0)**	1.0 (0.3-3.1)	**5.8 (2.4–14.3)**	2.9 (0.7–12.3)
Other and not classifiable	11.0/3.0	**3.7 (1.9–6.7)**	0.8 (0.3–2.2)	**4.2 (2.1–8.4)**	0.9 (0.3-3.2)
P for heterogeneity		***0.0421***	*0.2457*	***0.0330***	*0.0168*
Age at diagnosis of FPN					
0–4 years	25.0/4.8	**5.2 (3.3–7.6)**	1.7 (0.7–4.2)	**4.3 (2.8–6.7)**	1.5 (0.5–4.6)
5–9 years	24.0/3.2	**7.4 (4.7–11.0)**	2.2 (1.0–5.2)	**8.1 (5.3–12.5)**	3.0 (0.9-9.6)
10–14 years	28.0/4.0	**6.9 (4.6–10.0)**	2.2 (1.0–4.9)	**9.5 (6.4–14.2)**	2.9 (1.0–8.2)
15–19 years	9.0/2.8	**3.2 (1.5–6.1)**	Ref	**4.0 (1.8–8.8)**	Ref
P for heterogeneity		***0.1272***	*0.2192*	***0.0275***	*0.0629*
P-trend		***0.5240***	*0.5719*	***0.2793***	*0.8119*
Decade of diagnosis of FPN					
<1970	8.0/3.7	**2.2 (0.9–4.3)**	Ref	**2.4 (0.9–6.2)**	Ref
1970–1979	15.0/3.6	**4.2 (2.4–7.0)**	1.6 (0.6–4.2)	**4.7 (2.6–8.3)**	1.9 (0.5–7.2)
1980–1989	25.0/4.4	**5.7 (3.7–8.5)**	1.5 (0.6–3.9)	**5.7 (3.7–8.8)**	0.9 (0.2–3.7)
≥1990	38.0/3.3	**11.4 (8.1–15.7)**	2.0 (0.7–5.3)	**10.1 (7.3–14.1)**	0.5 (0.1–2.0)
P for heterogeneity		***<.0001***	*0.5264*	***0.0064***	*0.1036*
P-trend		***<.0001***	*0.4096*	***0.0006***	*0.0520*
Years from FPN diagnosis[≠]					
5–9 years	42.0/2.6	**16.0 (11.5–21.6)**	2.6 (0.8–9.1)	**12.6 (9.2–17.3)**	0.5 (0.1–3.0)
10–19 years	24.0/4.9	**4.9 (3.1–7.2)**	0.8 (0.2-2.9)	**4.2 (2.7–6.6)**	0.2 (0.0–1.6)
20–29 years	13.0/3.8	**3.4 (1.8–5.9)**	0.7 (0.2-2.4)	**3.9 (2.0–7.4)**	0.3 (0.0–1.8)
30–39 years	3.0/2.3	**1.3 (0.3–3.9)**	0.3 (0.1-1.5)	**0.7 (0.1–7.5)**	1.1 (0.2–8.6)
≥40 years	4.0/1.3	**3.1 (0.8–7.9)**	Ref	**8.6 (2.6–28.4)**	Ref
P for heterogeneity		***<.0001***	*< .0001*	***<.0001***	*0.1056*
P-trend		***<.0001***	*< .0001*	***0.0001***	*0.9415*

Abbreviations: O = observed number of leukaemia, E = expected number of leukaemia, SIR = standardised incidence ratio, AER = absolute excess risk per 100,000 person-years, 95% CI = 95% confidence interval (in bold), Ref = reference category, FPN = first primary neoplasm.
[≠]Years from FPN diagnosis = Years between FPN diagnosis and SPLM diagnosis or date at exit.
*Nordic countries include Finland, Iceland, Norway, Sweden, and Denmark.
P for heterogeneity or P-trend was calculated using two-sided likelihood ratio tests within an univariable Poisson model. Relative risk (RR) and relative excess risk (RER) from multivariable Poisson regression model adjusted for country, sex, type of childhood cancer, age at diagnosis, decade of diagnosis and years from diagnosis.
P for heterogeneity or P-trend was calculated using two-sided likelihood ratio tests within a multivariable Poisson model.

three times the number of SPLs both overall (115 vs. 43) and beyond 15 years from FPN diagnosis (40 vs. 13). As a result, we provide the most robust estimates of SPL risks among CCSs to date, which substantially adds to the literature and will aid the long-term follow-up of CCSs.

The overall SIR was 3.7 for an SPL, which was slightly higher than the SIR from the previous Nordic countries study with 30,880 childhood cancer patients diagnosed between 1943 and 1987 (SIR of 2.8) [19]. However, our SIR was slightly lower than that reported in a previous CCS publication with 14,358 survivors showing a sixfold increased risk (SIR: 6.3, 95% CI: 4.6–8.5) [5] and two previous European articles: a British cohort of 16,422 including CCSs diagnosed between 1962 and 1983 who survived at least one year (SIR of 8) and the French-British Euro2K cohort including 4204 3-year CCSs diagnosed between 1947 and 1986 (SIR of 7.8) [8,6]. This difference could be explained, in part, by the latency of at least 5 years in the

present study, whereas the two previous European studies began follow-up at the time of FPN diagnosis, 1-year or 3-year survival [6,8,19]. Although SPL risk is mainly elevated/peaks in the first 5 years, as in the CCSs [5], the PanCareSurFup study includes only five-year survivors; therefore, all SPLs occurring in the first 5 years after treatment were not considered in the present study. The AER ≥20 years in our study (AER of 4.8 events per 100,000 person-years of follow-up) is higher than that found in a previous analysis [5] ≥ 15 years in CCSs (AER of 2 per 100,000 person-years).

Previous reports have indicated that the risk of SPL reaches a plateau at approximately 10 years [9,24,25]; in this study, we reported that SIRs and AER are still increased after 10 years, so there is no plateau.

Furthermore, consistent with previous studies [26–28], the highest SPL risks (SIR and AER) were found in Hodgkin lymphoma survivors in this study, mainly before 20 years of follow-up. Therefore, the awareness of this risk remains crucial for survivors of Hodgkin lymphoma [29].

Statistically significant risks (SIRs or AERs) of SPLs were also found after leukaemia, soft-tissue sarcoma, CNS tumours, non-Hodgkin lymphoma, neuroblastoma and Wilms tumour. Clinicians should be aware of these risks during long-term follow-up care of these survivors given that both chemotherapy (alkylating agents and/or topoisomerase II inhibitors) and radiation therapy can increase the risk of SPL after treatment [5–8].

4.2. Study strengths, limitations and sensitivity analyses

The main advantages of the present study are its large size with nearly 70,000 survivors and its great range of follow-up time; as a result, we were able to quantify risks of SPL several decades (>20 years) after FPN diagnosis and to show that increased risk was only seen for SPMLs and not for SPLLs. These had not been possible in previous articles and thus provide increased reliability in our findings for clinicians and future research. However, an inherent limitation of large-scale cohort studies with long durations of follow-up is that it is often not feasible to collect detailed information on exposures. Thus, the main limitation of our study is the lack of treatment information on cumulative radiation dose (dose to active bone marrow), bone marrow transplantation, family history or syndromes and cumulative chemotherapy dose exposures given as treatment for the childhood cancer; as a result, we were unable to look specifically at the effect of treatment protocols on the risk of SPLs. To address this point, we are currently conducting an international pooled study of all existing cohort and case-control studies relating to leukaemia after childhood cancer (RadLeuk project). Although smaller in size than the present study, this study will have available cumulative doses of individual cytotoxics and cumulative doses of radiation to the active bone marrow for each individual included [7,8,20,30]. Therefore, the RadLeuk study should address the risks associated with cumulative radiation and chemotherapeutic doses and development of SPLs. Further research is warranted to assess the influence of family history or syndromes, genetic predispositions, genes involved in drug metabolism and cytogenetic and molecular features in the development of SPLs. Another limitation is that we did not have general population rates for all the countries included in this study, with only UK or Finnish rates being used for all countries. We have nonetheless performed SIR or AER sensitivity analyses to determine if the risk estimates reported were sensitive to the general population rates applied, and these additional analyses revealed that excess risk estimates were very similar regardless of the general population rates applied (Appendix Tables S6 and S7, p 6 and 7).

5. Conclusions

Our findings show that increased risk was only seen for SPMLs and not for SPLLs. We demonstrate also that the cumulative incidence of SPL does not reach a plateau but continues to increase long after five-year survival, with CCSs experiencing increased risks for SPLs beyond 20 years after their treatment compared with the general population. More efforts are needed to collect information on the long-term risk factors of SPLs in the increasingly large and ageing population of CCSs; such a thorough understanding of the epidemiology of SPLs is essential to identify patients at the highest risk of SPL. Our findings highlight the need for awareness by survivors and their healthcare providers for potential risk related to SPL several decades after childhood cancer treatment.

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Conflict of interest statement

No conflicts of interest declared.

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Appendix A. Supplementary data

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