Risk of subsequent primary lymphoma in a cohort of 69,460 five-year survivors of childhood and adolescent cancer in Europe: The PanCareSurFup study

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ORIGINAL ARTICLE

Risk of subsequent primary lymphoma in a cohort of 69,460 five-year survivors of childhood and adolescent cancer in Europe: The PanCareSurFup study

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Abstract

Background: Survivors of Hodgkin lymphoma (HL) are at risk of developing non-Hodgkin lymphoma (NHL) after treatment; however, the risks of developing subsequent primary lymphomas (SPLs), including HL and NHL, after different types of childhood cancer are unknown. The authors quantified the risk of SPLs using the largest cohort of childhood cancer survivors worldwide.

Methods: The Pan-European Network for Care of Survivors After Childhood and Adolescent Cancer (PanCare) Survivor Care and Follow-Up Studies (PanCareSurFup) cohort includes 69,460 five-year survivors of childhood cancer, diagnosed during 1940 through 2008, from 12 European countries. Risks of SPLs were quantified by standardized incidence ratios (SIRs) and relative risks (RRs) using multivariable Poisson regression.

Results: Overall, 140 SPLs, including 104 NHLs and 36 HLs, were identified. Survivors were at 60% increased risk of an SPL compared with the general population (SIR, 1.6; 95% confidence interval [CI], 1.4–1.9). Survivors were twice as likely to develop NHL (SIR, 2.3; 95% CI, 1.9–2.8), with the greatest risks among survivors of HL (SIR, 7.1; 95% CI, 5.1–10.0), Wilms tumor (SIR, 3.1; 95% CI, 1.7–5.7), leukemia (SIR, 2.8; 95% CI, 1.8–4.4), and bone sarcoma (SIR, 2.7; 95% CI, 1.4–5.4). Treatment with chemotherapy for any cancer doubled the RR of NHL (RR, 2.1; 95% CI, 1.2–3.9), but treatment with radiotherapy did not (RR, 1.2; 95% CI, 0.7–2.0). Survivors were at similar risk of developing a subsequent HL as the general population (SIR, 1.1; 95% CI, 0.8–1.5).

Conclusions: In addition to HL, the authors show here for the first time that survivors of Wilms tumor, leukemia, and bone sarcoma are at risk of NHL. Survivors

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and health care professionals should be aware of the risk of NHL in these survivors and in any survivors treated with chemotherapy.

KEYWORDS
childhood cancer survivors, Hodgkin lymphoma, late effects, non-Hodgkin lymphoma, second cancers, subsequent primary lymphoma

INTRODUCTION

Approximately 35,000 children and adolescents are diagnosed with cancer in Europe each year.[1] Since the 1970s, 5-year survival rates have improved dramatically and now reach 80% in most European countries, mostly because of combined chemotherapy modalities and improvements in the delivery of radiotherapy.[1–3] There are currently over 500,000 childhood cancer survivors in Europe, and this number continues to increase.[1] The risk of premature morbidity and mortality for childhood cancer survivors compared with the general population is well documented, with many health risks arising 20–30 years after a childhood cancer diagnosis. Approximately 60% of childhood cancer survivors develop at least one chronic health condition during their lifetime, and more than one in four develop severe or life-threatening diseases.[4,5]

A serious long-term consequence of treatment of childhood cancer is the increased risk of developing subsequent primary neoplasms, which is in the range of three to five times greater that of the general population.[6–9] Existing evidence suggests that survivors are at increased risk of several types of subsequent primary neoplasms, particularly central nervous system tumors; nonmelanoma skin cancer; and digestive, breast, bone, and genitourinary cancers. Limited numbers of studies have shown that the overall risk of subsequent primary lymphoma (SPL) is also increased[7,9–11]; however, to our knowledge, few previous large-scale studies have comprehensively investigated the risk of developing SPLs among childhood cancer survivors—with the largest previous study to date including 45 SPLs.[10] Studies of survivors of Hodgkin lymphoma (HL) have found an increased risk of non-Hodgkin lymphoma (NHL) but mostly included HL survivors who were diagnosed in adulthood.[12–21] To date, no large-scale study has characterized the risks of SPLs and of specific SPLs by type of childhood cancer, sex, age at diagnosis, decade of diagnosis, attained age, and treatment factors. Identification of those survivors at highest risk of an SPL would be important for informing survivors and health care professionals of who is at risk, potentially detecting SPLs early, and may give clues about potential biologic mechanisms.

The principal aim of this largest ever cohort study was to quantify the risk of developing an SPL, further subdivided into HL and NHL, among 69,460 survivors of childhood cancer within Europe and compare this risk with that in the general population, including three times the number of SPLs compared with the largest previous study to date.[10] Secondary aims included investigating variations in risk, which may be associated with certain demographic and oncologic factors, and assessing the level of risk sustained in the long term (beyond age 40 years).

MATERIALS AND METHODS

PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies

The Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer (PanCare) is a network of health care professionals, researchers, childhood cancer survivors, and their families that aims to improve both the care and the quality of life for survivors of childhood cancer.[22] Funded by the seventh Framework Program of the European Union, a consortium among several institutions of PanCare members established the largest ever collaborative, comprehensive study for childhood cancer survivors: *The PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies* (PanCareSurFup). The overall objectives of PanCareSurFup are to investigate long-term health risks for childhood cancer survivors, establish clinical guidelines for their follow-up care, and disseminate research results.[23–25] The PanCareSurFup cohort comprises data from 5-year survivors of childhood cancer (diagnosed at ages birth to 20 years between 1940 and 2008) across 12 European countries: France, Italy, Hungary, the Netherlands, Denmark, Sweden, Norway, Finland, Iceland, Slovenia, Switzerland, and the United Kingdom (see Table S1). Data were sourced from both population-based cancer registries and major treatment centers. Ethical approval and consent for data collection were obtained from the ethical and legal bodies in each of the respective countries contributing to PanCareSurFup. Ethical approval was not obtained specifically for this study because it involved pooling of nonidentifiable data.

Childhood cancer classification

Because of various practices across different countries in terms of childhood cancer registration, the cancer site and the type of childhood cancer were coded using a range of classification systems. To standardize this across the pooled cohort, all childhood tumor classification codes were converted into codes from the third revision of the *International Classification of Diseases for Oncology* using the Cancer Registry Tools Program.[26,27] These were then categorised into childhood cancers subgroups according to the *International Classification of*

Childhood Cancer, third edition.[28] Individuals were excluded from the pooled cohort if: (1) they had a primary diagnosis of myelodysplastic syndrome, Langerhans cell histiocytosis, or chronic myeloproliferative or lymphoproliferative disorders; (2) tumor coding was nonmalignant, except for intracranial and bladder tumors; and (3) tumor codes were not classifiable according to the third revision of the *International Classification of Childhood Cancer*.

Identification of subsequent primary lymphomas

SPLs were ascertained using various methods, primarily through population-based cancer registries and follow-up clinics and validated through pathology reports or other means of clinical diagnosis. The SPLs were classified by site according to the *International Classification of Diseases* using the revision appropriate to the year of diagnosis (see Table S2). For inclusion as an SPL, the subsequent lymphoma had to have a different morphology classification than the original childhood cancer, as defined by the *International Classification of Diseases for Oncology*, third edition classification. In addition, we excluded subsequent NHLs diagnosed after a primary NHL in childhood ($N = 8$) and subsequent HLs after a primary HL ($N = 1$), regardless of any difference in morphology. Also, all NHL survivors were excluded from analyses relating to subsequent NHLs, and all HL survivors were excluded from analyses relating to subsequent HLs.

Statistical analysis

Individuals entered the cohort at 5-year survival from childhood cancer diagnosis and remained at risk of an SPL until the first occurrence of loss to follow-up, death, or study exit date. Standardized incidence ratios (SIRs) were calculated as the ratio of the observed to expected numbers of lymphomas. Expected rates were calculated by accruing person-years at risk stratified by age, country, sex, and calendar year, and multiplying by the equivalent lymphoma incidence rates for the general population.[29] General population incidence rates (also stratified by age, country, sex, and calendar year) were obtained from the *Cancer Incidence in Five Continents* project.[30] Site-specific incidence rates do not exist for Hungary, hence these were estimated using Slovakian incidence rates because it is their neighboring country with similar demographic characteristics.[31] Absolute excess risks (AERs) were calculated as the observed minus the expected number of lymphomas, divided by person-years at risk, and multiplied by 100,000. This can be interpreted as the number of excess lymphomas observed beyond those expected per 100,000 person-years. Multivariable Poisson regression models were fitted to estimate the relative risk (RR) of all SPLs and subsequent primary NHLs and HLs while adjusting for the effect of potentially confounding factors: sex, childhood cancer diagnosis, country, decade of childhood diagnosis, age at childhood diagnosis, and attained age. RRs can be interpreted as the ratio of SIRs, adjusted for potential confounders. Likelihood-ratio tests were applied to generate p values for linear trend for ordinal factors of interest or heterogeneity for nominal variables. Because of a relatively small number of observations in subsequent primary HLs, AERs could not be calculated.

SIRs, AERs, and RRs were calculated for the treatment factors radiotherapy (*yes/no*) and chemotherapy (*yes/no*) for those countries where <30% of treatment data were missing. Therefore, the Nordic countries and an Italian population-based cohort were completely excluded from analyses involving treatment variables regardless of whether treatment data were available to avoid potential bias. By using this approach, for 10.5% of survivors, the radiotherapy data were missing; and, for 12.4% of survivors, the chemotherapy data were missing. In all, information on radiotherapy was available for 90 SPLs, and information on chemotherapy was available for 88 SPLs.

To assess the probability of developing an SPL with increasing attained age, the cumulative incidence accounting for the competing risk of death was estimated for types of childhood cancer with ≥20 observed SPLs. All statistical analyses were conducted in Stata software (Stata Corporation).[32] All analyses were based on complete case analysis (i.e., list-wise deletion). A two-sided p value $< .05$ was considered statistically significant.

RESULTS

Cohort characteristics

Among 69,460 five-year survivors of childhood cancer, in total, 1,264,624 person-years were accrued, with loss to follow-up not exceeding 6% in any country (see Table S1). Over the follow-up period, 140 SPLs were observed in survivors across an age range from 5 to 88 years. From the 140 SPLs, 104 (74.2%) were classified as NHL, and 36 (25.7%) were classified as HL. Most of the SPLs occurred in males (66.4%) and in those surviving HL ($n = 33$) and leukemia ($n = 31$; Table 1).

Overall risk of any subsequent primary lymphoma

Overall, childhood cancer survivors were 60% more likely to develop an SPL compared with the expected rates from the general population (SIR, 1.6; 95% CI, 1.4–1.9), with four additional cases of lymphoma observed per 100,000 person-years (AER, 4.3; 95% CI, 2.8–6.6; Table 2). In particular, HL survivors (SIR, 4.1; 95% CI, 2.9–5.8), but also Wilms tumor (SIR, 2.2; 95% CI, 1.3–3.8), leukemia (SIR, 2.1; 95% CI, 1.5–3.0), and bone sarcoma (SIR, 2.1; 95% CI, 1.1–3.9) survivors, were at increased risk of developing an SPL. Overall, the SIR decreased with increasing attained age (p for trend $< .001$), but the risk was no longer significantly increased beyond age 50 years (SIR, 1.3; 95% CI, 0.8–2.1). There was a significant increase in SPL risk among those who had received chemotherapy for any childhood cancer compared with those who had not (RR, 1.8; 95% CI, 1.1–2.9; Table 2), independent of whether or not survivors also had received

TABLE 1 Characteristics of 69,460 five-year survivors in the PanCareSurFup cohort and of the 140 individuals who developed a subsequent primary lymphoma (further subdivided into non-Hodgkin and Hodgkin lymphoma, respectively)

		No. of survivors (%)			
Factor		**PanCareSurFup cohort**	**All lymphoma**	**Non-Hodgkin lymphoma**	**Hodgkin lymphoma**
Overall	—	69,460 (100.0)	140 (100.0)	104 (100.0)	36 (100.0)
Sex	Male	37,738 (54.3)	93 (66.4)	67 (64.4)	26 (72.0)
	Female	31,722 (45.7)	47 (33.6)	37 (35.6)	10 (28.0)
Childhood cancer diagnosis	Leukemia	16,646 (24.0)	31 (22.1)	19 (18.3)	12 (33.0)
	Hodgkin lymphoma	6046 (8.7)	33 (23.6)	33 (31.7)	0 (0.0)
	Non-Hodgkin lymphoma	4078 (5.9)	5 (3.6)	0 (0.0)	5 (14.0)
	CNS tumors	14,592 (21.0)	14 (10.0)	9 (8.7)	5 (14.0)
	Neuroblastoma	3178 (4.6)	4 (2.9)	3 (2.9)	1 (3.0)
	Retinoblastoma	2590 (3.7)	3 (2.1)	2 (1.9)	1 (3.0)
	Wilms tumor	4783 (6.9)	14 (10.0)	10 (9.6)	4 (11.0)
	Bone sarcoma	3173 (4.6)	10 (7.1)	8 (7.7)	2 (6.0)
	Soft tissue sarcoma	4531 (6.5)	4 (2.9)	2 (1.9)	2 (6.0)
	Thyroid carcinoma	1295 (1.9)	4 (2.9)	3 (2.9)	1 (3.0)
	Gonadal	2721 (3.9)	2 (1.4)	2 (1.9)	0 (0.0)
	Malignant melanoma	1458 (2.1)	4 (2.9)	3 (2.9)	1 (3.0)
	Other[a]	4369 (6.3)	12 (8.6)	10 (9.6)	2 (6.0)
Data provider country	France	3138 (4.5)	8 (5.7)	7 (6.7)	1 (3.0)
	Hungary	4885 (7.0)	8 (5.7)	7 (6.7)	1 (3.0)
	Italy, population-based[b]	7476 (10.8)	6 (4.3)	3 (2.9)	3 (8.0)
	Italy, hospital-based[c]	1490 (2.1)	3 (2.1)	3 (2.9)	0 (0.0)
	Netherlands	6044 (8.7)	15 (10.7)	9 (8.7)	6 (17.0)
	Denmark	4840 (7.0)	5 (3.6)	2 (1.9)	3 (8.0)
	Sweden	7709 (11.1)	15 (10.7)	9 (8.7)	6 (17.0)
	Norway	3783 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)
	Finland	6229 (9.0)	19 (13.6)	16 (15.4)	3 (8.0)
	Iceland	275 (0.4)	0 (0.0)	0 (0)	0 (0.0)
	Slovenia	1252 (1.8)	1 (0.7)	1 (1.0)	0 (0.0)
	Switzerland	4379 (6.3)	7 (5.0)	5 (4.8)	2 (6.0)
	United Kingdom	17,960 (25.9)	53 (37.9)	42 (40.4)	11 (31.0)
Decade of childhood cancer diagnosis	<1970	8993 (12.9)	39 (27.9)	28 (26.9)	11 (31.0)
	1970–1979	13,479 (19.4)	39 (27.9)	30 (28.8)	9 (25.0)
	1980–1989	20,900 (30.1)	44 (31.4)	33 (31.7)	11 (31.0)
	1990–2008	26,088 (37.6)	18 (12.9)	13 (12.5)	5 (14.0)
Age at childhood cancer diagnosis, years	Birth to 4	26,696 (38.4)	40 (28.6)	27 (26.0)	13 (36.0)
	5–9	15,743 (22.7)	31 (22.1)	21 (20.2)	10 (28.0)
	10–14	15,491 (22.3)	45 (32.1)	37 (35.6)	8 (22.0)
	15–20	11,530 (16.6)	24 (17.1)	19 (18.3)	5 (14.0)

TABLE 1 (Continued)

Factor		No. of survivors (%)			
		PanCareSurFup cohort	All lymphoma	Non-Hodgkin lymphoma	Hodgkin lymphoma
Attained age, years[d]	<20	15,405 (22.2)	35 (25.0)	23 (22.1)	12 (33.0)
	20–29	18,877 (27.2)	39 (27.9)	27 (26.0)	12 (33.0)
	30–39	17,144 (24.7)	24 (17.1)	16 (15.4)	8 (22.0)
	40–49	10,970 (15.8)	24 (17.1)	20 (19.2)	4 (11.0)
	≥50	7064 (10.2)	18 (12.9)	18 (17.3)	0 (0.0)
Follow-up time since 5-year survival, years[d]	0–9	23,923 (34.4)	52 (37.1)	36 (34.6)	16 (44.0)
	10–19	15,801 (22.7)	36 (25.7)	25 (24.0)	11 (31.0)
	20–29	16,103 (23.2)	27 (19.3)	20 (19.2)	7 (19.0)
	≥30	13,633 (19.6)	25 (17.9)	23 (22.1)	2 (6.0)

Abbreviations: 95% CI, 95% confidence interval; AER, absolute excess risk; CNS, central nervous system; PanCareSurFup, the Pan-European Network for Care of Survivors After Childhood and Adolescent Cancer (PanCare) Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies; RR, relative risk; SIR, standardized incidence ratio; SPL, subsequent primary lymphoma.

[a]The category *other* includes: other and unspecified carcinomas ($n = 1181$), other unspecified malignant tumors ($n = 641$), malignant extracranial/extragonadal germ cell tumors ($n = 433$), skin carcinomas ($n = 423$), unspecified lymphomas ($n = 402$), hepatoblastoma ($n = 319$), miscellaneous lymphoreticular neoplasms ($n = 279$), nasopharyngeal carcinomas ($n = 194$), renal carcinomas ($n = 124$), other peripheral nervous cell tumors ($n = 94$), adrenocortical carcinomas ($n = 86$), hepatic carcinomas ($n = 84$), other specified. malignant tumors ($n = 59$), unspecified malignant renal tumors ($n = 35$), and unspecified malignant hepatic tumors ($n = 15$).

[b]Population-based cohort from the Italian Association of Cancer Registries (AIRTUM).

[c]Hospital-based registry from the Italian Registry of Off-Therapy Patients, Genoa.

[d]The number of survivors relates to the highest attained age/follow-up reached, e.g., at exit of cohort.

radiotherapy. The cumulative incidence of developing an SPL by age 65 years was highest after HL, with a probability of developing an SPL of 1.6% (95% CI, 0.7%–3.1%), whereas only 0.6% was expected based on general population rates (Figure 1).

Risk of subsequent primary non-Hodgkin lymphoma

Overall, childhood cancer survivors were 2.3 times more likely to develop NHL than the general population (SIR, 2.3; 95% CI, 1.9–2.8), with five additional cases of NHL observed per 100,000 person-years (AER, 4.9; 95% CI, 3.5–6.9; Table 3). Male and female childhood cancer survivors were at similar risk when adjusted for confounding factors (p for heterogeneity = .91). Survivors of HL and Wilms tumor were at greatest risk of developing NHL (SIR, 7.1 [95% CI, 5.1–10.0] and 3.1 [95% CI, 1.7–5.7], respectively), but the risk also was great for survivors of leukemia (SIR, 2.8; 95% CI, 1.8–4.4) and bone sarcoma (SIR, 2.7; 95% CI, 1.4–5.4).

More recent decades of childhood cancer diagnosis showed an increase in the SIRs of developing NHL (p for trend < .001), but this effect was not apparent after adjustment for confounders (p for trend = .64), particularly attained age. Increasing attained age and follow-up time demonstrated a decreasing trend in the SIRs of developing NHL (Table 3; p for trend < .001). There was a significantly increased risk of developing NHL among survivors who had received chemotherapy for any childhood cancer (RR, 2.1; 95% CI, 1.2–3.9). However, the RR was not significantly increased for survivors who had received radiotherapy for any childhood cancer (RR, 1.2; 95% CI, 0.7–2.0). The cumulative incidence of developing NHL after HL was 1.6% (95% CI, 0.7%–3.1%) by age 65 years (Figure 1; all SPLs after HL were NHLs).

Risk of subsequent primary Hodgkin lymphoma

Overall, childhood cancer survivors were no more likely to develop HL compared with the general population (SIR, 1.1; 95% CI, 0.8–1.5; Table 4). A childhood cancer diagnosis of NHL conferred an increased risk of developing HL relative to the general population (SIR, 2.4; 95% CI, 1.0–5.9). This was not observed following other types of childhood cancer. The SIR for HL did not vary by decade of diagnosis (p for trend = .21), age at diagnosis ($p = .97$), or with attained age (p for trend = .24), although multivariable analyses suggested that the RRs were lower in those diagnosed in more recent decades (p for trend = .03).

DISCUSSION

Main findings

To our knowledge, this is by far the largest cohort study analyzing the risk of SPLs in childhood cancer survivors and, for the first time within a large-scale study, the risks of NHL and HL individually. Novel

TABLE 2 Standardized incidence ratios, relative risks, and absolute excess risks, with 95% confidence intervals, for developing a subsequent primary lymphoma among a cohort of childhood cancer survivors

Factor		Person-years	Obs/Exp	SIR (95% CI)	RR (95% CI)[b]	AER (95% CI)
Overall	—	1,264,624	140/85.6	1.6 (1.4–1.9)	—	4.3 (2.8–6.6)
Sex[a]	Male	676,132	93/51.5	1.8 (1.5–2.2)	1.0 (Ref)	6.1 (3.9–9.7)
	Female	588,492	47/34.1	1.4 (1.0–1.8)	0.8 (0.5–1.1)	2.2 (0.8–6.2)
	p for heterogeneity			.12	.14	.03
Childhood cancer type[a]	Leukemia	259,372	31/14.8	2.1 (1.5–3.0)	1.0 (Ref)	6.3 (3.2,12.3)
	Hodgkin lymphoma	98,744	33/8.0	4.1 (2.9–5.8)	1.9 (1.1–3.3)	25.3 (16.2–39.7)
	Non-Hodgkin lymphoma	70,165	5/5.4	0.9 (0.4–2.2)	0.4 (0.2–1.1)	0.0 (0.0–0.0)
	CNS tumors	263,500	14/18.6	0.8 (0.4–1.3)	0.4 (0.2–0.7)	0.0 (0.0–0.0)
	Neuroblastoma	61,967	4/3.3	1.2 (0.5–3.3)	0.6 (0.2–1.8)	1.2 (0.0–231.2)
	Retinoblastoma	70,625	3/4.4	0.7 (0.2–2.1)	0.4 (0.1–1.3)	0.0 (0.0–0.0)
	Wilms tumor	109,314	14/6.2	2.2 (1.3–3.8)	1.2 (0.6–2.2)	7.1 (2.8–18.3)
	Bone sarcoma	57,666	10/4.8	2.1 (1.1–3.9)	1.0 (0.4–2.1)	9.1 (2.8–29.7)
	Soft tissue sarcoma	93,042	4/6.8	0.6 (0.2–1.6)	0.3 (0.1–0.8)	0.0 (0.0–0.0)
	Thyroid carcinoma	23,535	4/1.8	2.2 (0.8–5.9)	1.1 (0.4–3.3)	9.3 (1.5–55.9)
	Gonadal	48,850	2/3.6	0.6 (0.1–2.2)	0.3 (0.1–1.2)	0.0 (0.0–0.0)
	Malignant melanoma	24,949	4/1.9	2.1 (0.8–5.5)	1.0 (0.3–3.0)	8.3 (1.2–55.2)
	Other	82,894	12/6.0	2.0 (1.1–3.5)	0.9 (0.5–1.9)	7.2 (2.3–22.5)
	p for heterogeneity			< .001	< .001	< .001
Decade of childhood cancer diagnosis[a]	<1970	310,237	39/28.5	1.4 (1.0–1.9)	1.0 (Ref)	3.4 (1.1–10.9)
	1970–1979	353,278	39/23.1	1.7 (1.2–2.3)	1.0 (0.6–1.6)	4.5 (2.1–9.7)
	1980–1989	399,362	44/23.3	1.9 (1.4–2.5)	1.0 (0.6–1.8)	5.2 (2.8–9.7)
	1990–2008	201,748	18/10.7	1.7 (1.1–2.7)	0.8 (0.4–1.5)	3.6 (1.2–11.3)
	p for trend			.24	.58	.83
Age at childhood cancer diagnosis, years[a]	Birth to 4	526,239	40/28.1	1.4 (1.0–1.9)	1.0 (Ref)	2.3 (0.8–6.4)
	5–9	294,119	31/19.8	1.6 (1.1–2.2)	1.1 (0.7–1.9)	3.8 (1.4–10.1)
	10–14	288,376	45/24.6	1.8 (1.4–2.5)	1.5 (0.8–2.5)	7.1 (3.7–13.5)
	15–20	155,890	24/13.1	1.8 (1.2–2.7)	1.5 (0.8–3.0)	7.0 (2.9–16.9)
	p for trend			.22	.15	.04
Attained age, years[a]	<20	410,373	35/13.3	2.6 (1.9–3.7)	1.0 (Ref)	5.3 (3.1–9.0)
	20–29	419,216	39/26.1	1.5 (1.1–2.0)	0.5 (0.3–0.8)	3.1 (1.2–7.9)
	30–39	262,126	24/19.3	1.2 (0.8–1.9)	0.4 (0.2–0.6)	1.8 (0.2–13.7)
	40–49	120,676	24/13.4	1.8 (1.2–2.7)	0.5 (0.3–1.0)	8.7 (3.5–21.7)
	≥50	52,243	18/13.4	1.3 (0.8–2.1)	0.4 (0.2–0.9)	8.7 (1.4–54.0)
	p for trend			.02	.01	.59
Follow-up time since 5-year survival, years[b]	0–9	565,883	52/23.5	2.2 (1.7–2.9)	0.7 (0.4–1.0)	5.0 (3.1–8.3)
	10–19	370,881	36/23.6	1.5 (1.1–2.1)	0.6 (0.4–1.0)	3.3 (1.3–8.6)
	20–29	212,289	27/18.2	1.5 (1.0–2.2)	0.6 (0.3–1.0)	4.1 (1.3–13.2)
	≥30	115,571	25/20.2	1.2 (0.8–1.8)	0.7 (0.4–1.0)	4.1 (0.5–32.1)
	p for trend			.01	.04	.59

TABLE 2 (Continued)

Factor		Person-years	Obs/Exp	SIR (95% CI)	RR (95% CI)[b]	AER (95% CI)
Radiotherapy[c,d]	No	272,789	31/18.2	1.7 (1.2–2.4)	1.0 (Ref)	4.7 (2.0–11.0)
	Yes	478,392	59/33.9	1.7 (1.3–2.2)	1.1 (0.7–1.7)	5.3 (2.9–9.6)
	Missing	86,824	5/5.3	—	—	—
	p for heterogeneity			.92	.63	.83
Chemotherapy[c,d]	No	275,213	29/23.0	1.3 (0.9–1.8)	1.0 (Ref)	2.2 (0.4–12.6)
	Yes	447,974	59/27.0	2.2 (1.7–2.8)	1.8 (1.1–2.9)	7.1 (4.5–11.4)
	Missing	114,818	7/7.4	—	—	—
	p for heterogeneity			.01	.02	.07

Abbreviations: 95% CI, 95% confidence interval; AER, absolute excess risk; CNS, central nervous system; Exp, expected; Obs, observed; Ref, reference category; RR, relative risk; SIR, standardized incidence ratio.

[a]RRs were derived from a model including sex, childhood cancer diagnosis, country, decade of childhood diagnosis, age at childhood diagnosis, and attained age.

[b]RRs were derived from a model including sex, childhood cancer diagnosis, country, decade of childhood diagnosis, age at childhood diagnosis, and follow-up time.

[c]RRs were derived from a model including sex, country, age at childhood diagnosis, attained age and treatment.

[d]Analyses relating to treatment included data from data providers that had <30% of missing data (Nordic countries and Italian population-based cohort were excluded; treatment data were not available at all for Nordic countries).

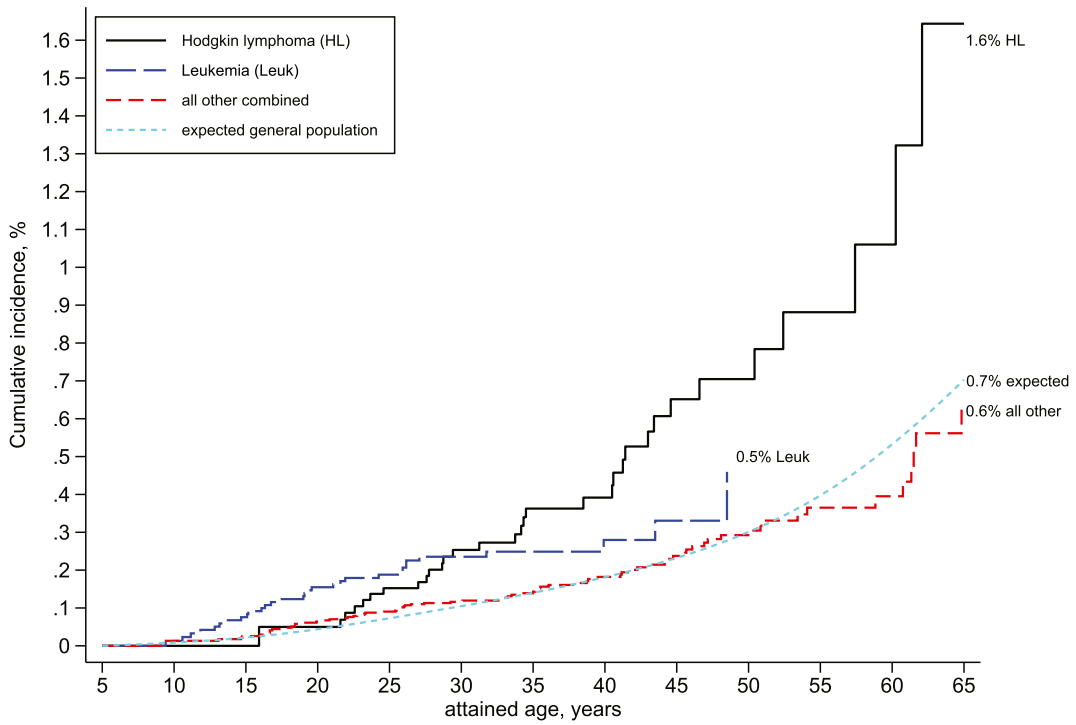

FIGURE 1 Cumulative incidence of developing a subsequent primary lymphoma (all types) for types of childhood cancer with at least 20 observed lymphomas, as a function of attained age.

findings include that childhood cancer survivors are 2.3 times more likely to develop NHL than the general population, with survivors of HL, Wilms tumor, leukemia, and bone sarcoma at greatest risk. Conversely, the risk of HL among childhood cancer survivors is not increased, except in survivors of NHL. This study has further found that childhood cancer survivors who have received chemotherapy are almost twice as likely to develop a subsequent primary NHL than survivors treated without chemotherapy. This increase in risk, however, does not extend to survivors who received radiotherapy for any childhood cancer.

TABLE 3 Standardized incidence ratios, relative risks, and absolute excess risks, with 95% confidence intervals, for developing a subsequent primary non-Hodgkin lymphoma among a cohort of childhood cancer survivors (excluding non-Hodgkin lymphoma survivors)

Factor		Obs/Exp	SIR (95% CI)	RR (95% CI)	AER (95% CI)
Overall		104/45.0	2.3 (1.9–2.8)	—	4.9 (3.5–6.9)
Sex[a]	Male	67/27.5	2.4 (1.9–3.1)	1.0 (Ref)	6.3 (4.2–9.5)
	Female	37/17.6	2.1 (1.5–2.9)	1.0 (0.6–1.5)	3.4 (1.9–6.3)
	p for heterogeneity		.47	.91	.09
Childhood cancer type[a]	Leukemia	19/6.8	2.8 (1.8–4.4)	1.0 (Ref)	4.7 (2.3–9.5)
	Hodgkin lymphoma	33/4.6	7.1 (5.1–10.0)	3.2 (1.7–6.0)	28.7 (19.3–42.7)
	CNS tumors	9/10.8	0.8 (0.4–1.6)	0.4 (0.2–0.9)	0.0
	Neuroblastoma	3/1.7	1.8 (0.6–5.6)	0.8 (0.2–2.7)	2.1 (0.2–27.6)
	Retinoblastoma	2/2.6	0.8 (0.2–3.0)	0.5 (0.1–2.0)	0.0
	Wilms tumor	10/3.2	3.1 (1.7–5.7)	1.4 (0.6–3.2)	6.2 (2.5–15.5)
	Bone sarcoma	8/2.9	2.7 (1.4–5.4)	1.2 (0.5–3.1)	8.8 (2.9–26.2)
	Soft tissue sarcoma	2/4.1	0.5 (0.1–2.0)	0.2 (0.1–1.0)	0.0
	Thyroid carcinoma	3/1.2	2.6 (0.8–8.1)	1.3 (0.4–4.9)	7.9 (1.3–49.3)
	Gonadal	2/2.2	0.9 (0.2–3.7)	0.4 (0.1–2.0)	0.0
	Malignant melanoma	3/1.2	2.4 (0.8–7.5)	1.3 (0.4–4.7)	7.1 (1.0–48.4)
	Other	10/3.7	2.7 (1.4–5.0)	1.3 (0.6–3.1)	7.6 (2.8–20.3)
	p for heterogeneity		< .001	< .001	< .001
Decade of childhood cancer diagnosis[a]	<1970	28/19.5	1.4 (1.0–2.1)	1.0 (Ref)	2.9 (0.8–9.7)
	1970–1979	30/12.2	2.5 (1.7–3.5)	1.3 (0.7–2.3)	5.3 (2.9–9.7)
	1980–1989	33/9.7	3.4 (2.4–4.8)	1.5 (0.7–2.9)	6.2 (3.9–10.1)
	1990–2008	13/3.7	3.5 (2.1–6.1)	1.1 (0.5–2.7)	5.0 (2.3–10.7)
	p for trend		< .001	.64	.58
Age at childhood cancer diagnosis, years[a]	0–3	27/13.9	1.9 (1.3–2.8)	1.0 (Ref)	2.6 (1.2–5.6)
	4–7	21/9.7	2.2 (1.4–3.3)	1.1 (0.6–2.1)	4.2 (1.9–9.3)
	8–11	37/13.6	2.7 (2.0–3.8)	1.5 (0.8–2.9)	8.8 (5.3–14.7)
	12–21	19/7.9	2.4 (1.5–3.8)	1.4 (0.6–3.4)	7.5 (3.5–16.2)
	p for trend		.59	.28	.03
Attained age, years[a]	<20	23/4.9	4.7 (3.1–7.1)	1.0 (Ref)	4.6 (2.8–7.8)
	20–29	27/8.5	3.2 (2.2–4.6)	0.5 (0.3–1.0)	4.7 (2.7–8.2)
	30–39	16/10.2	1.6 (1.0–2.6)	0.3 (0.1–0.5)	2.4 (0.6–9.1)
	40–49	20/1	2.0 (1.3–3.1)	0.4 (0.2–0.8)	8.7 (3.6–21.1)
	≥50	18/11.5	1.6 (1.0–2.5)	0.3 (0.1–0.8)	13.3 (3.7–47.6)
	p for trend		< .001	< .001	.39
Follow-up time since 5-year survival, years[b]	0–9	36/8.1	4.4 (3.2–6.1)	1.0 (Ref)	5.2 (3.4–8.0)
	10–19	25/9.5	2.6 (1.8–3.9)	0.6 (0.3–1.0)	4.4 (2.4–8.3)
	20–29	20/11.0	1.8 (1.2–2.8)	0.4 (0.2–0.8)	4.5 (1.7–11.8)
	≥30	23/16.4	1.4 (0.9–2.1)	0.4 (0.2–0.8)	6.0 (1.4–25.0)
	p for trend		< .001	< .001	.82
Radiotherapy[c,d]	No	21/9.5	2.2 (1.4–3.4)	1.0 (Ref)	4.5 (2.1–9.8)
	Yes	48/18.1	2.7 (2.0–3.5)	1.2 (0.7–2.0)	6.6 (4.2–10.4)

TABLE 3 (Continued)

Factor		Obs/Exp	SIR (95% CI)	RR (95% CI)	AER (95% CI)
	Missing	5/2.3	—	—	—
	p for heterogeneity		.48	.32	.38
Chemotherapy[c,d]	No	22/14.3	1.5 (1.0–2.3)	1.0 (Ref)	2.9 (0.9–9.5)
	Yes	46/12.1	3.8 (2.8–5.1)	2.1 (1.2–3.9)	8.2 (5.5–12.1)
	Missing	6/3.6	—	—	—
	p for heterogeneity		< .001	.01	.04

Abbreviations: 95% CI, 95% confidence interval; AER, absolute excess risk; CNS, central nervous system; Exp, expected; Obs, observed; Ref, reference category; RR, relative risk; SIR, standardized incidence ratio.

[a]RRs were derived from a model including sex, childhood cancer diagnosis, country, decade of childhood diagnosis, age at childhood diagnosis, and attained age.

[b]RRs were derived from a model including sex, childhood cancer diagnosis, country, decade of childhood diagnosis, age at childhood diagnosis, and follow-up time.

[c]RRs were derived from a model including sex, country, age at childhood diagnosis, attained age, and treatment.

[d]Analyses relating to treatment included data from data providers that had <30% of missing data (Nordic countries and Italian population-based cohorts were excluded; treatment data were not available at all for Nordic countries).

Previous studies

When evaluating the overall risk of childhood cancer survivors developing SPLs, the SIR of 1.6 for total lymphoma found in this analysis was consistent with the results of the North American Childhood Cancer Survivor Study conducted in a cohort of 14,359 childhood cancer survivors (SIR, 1.6; 95% CI, 1.2–2.1).[10] In that North American study, the SIR beyond age 40 years was still increased 2.6-fold (95% CI, 1.5–5.6); however, in our data, the risk was not increased beyond age 50 years (SIR, 1.3; 95% CI, 0.8–2.1),[11] although overlapping confidence intervals suggest that these SIRs are not necessarily inconsistent. There have been suggestions that, for the generality of survivors, historic treatment regimens across North America may have been more aggressive than across Europe, which may translate into a higher risk of long-term complications of treatment, including subsequent primary malignancies.[33] Other studies documenting the risk of developing SPLs derived their data from European cohorts (Nordic countries and the Netherlands, respectively), which also contributed to the current PanCareSurFup cohort. Consistent with our findings, the Nordic study reported a moderately increased risk for bone marrow and lymphatic system malignancies, although this includes a wider range of diagnoses and thus is less valid to interpret for SPL alone (SIR, 2.6; 95% CI, 2.2–3.2).[7] A Dutch study among 6165 childhood cancer survivors quoted a slightly higher, but not inconsistent, risk of NHL (SIR, 3.9; 95% CI, 2.0–7.0).[8] Furthermore, the Dutch study observed only six cases of HL and, as a result, reported a lower and insignificant risk of HL (SIR, 1.9; 95% CI, 0.7–4.1), which supports our finding that childhood cancer survivors are no more likely to develop HL than the general population.

Although very few studies have investigated the risk of NHL among the generality of childhood cancer survivors, several studies have reported increased risks of NHL after (mostly) adult HL, with a wide range in SIRs from 3.0 to 32.0, which is not inconsistent with the SIR of 7.1 found in the current analysis.[12–17,20,21] Postulated risks factors include immunodeficiency, because Zarate-Osorno et al.[34] concluded that the types of NHL diagnosed among patients with HL were clinically, histologically, and immunophenotypically similar to that found in immunosuppressed patients. Here, we found that survivors who received chemotherapy were at the highest risk. Whether any specific chemotherapeutic agent or whether chemotherapy-induced immunosuppression may be implicated in the development of NHL, however, is not clear. Swerdlow et al[16] found increased risks of NHL among HL survivors after various different chemotherapy regimens, suggesting that not one specific chemotherapy agent is implicated. We also found increased risks of NHL among survivors of Wilms tumor, leukemia, and bone sarcoma who likely have received different chemotherapy regimens. Exposure to prolonged chemotherapy has been shown to be immunosuppressive and thus may create an environment in which latent oncogenic viruses, such as Epstein–Barr virus, that have been associated with NHL development may be reactivated.[35,36] Among (bilateral) Wilms tumor survivors, the increased risk may to some extent also be related to immunosuppressive therapy for a kidney transplant, which could cause posttransplantation lymphoproliferative disorders,[37] including NHL, although typically this occurs in the first few years after kidney transplantation, with a potential second peak 7–10 years later.[38] However, in our data, all Wilms tumor survivors who developed NHL had unilateral Wilms tumor; and, for 9 of 10 Wilms tumor survivors who developed NHL, this occurred at least 13 years after the original Wilms tumor diagnosis (range, 6–53 years), suggesting that this is probably an unlikely explanation. Similarly, stem cell transplantation among leukemia survivors may have increased the risk of post-transplantation lymphoproliferative disorders, including NHL; but, in our cohort, only one leukemia survivor with NHL had undergone stem cell transplantation. Further studies evaluating detailed

treatment factors and the role of specific chemotherapy exposures in relation to immunosuppression and Epstein–Barr virus infection status are warranted.

In the current study, there was no indication of any significant difference in the risk of SPL between those who received radiotherapy only during childhood and those who did not. This is

TABLE 4 Standardized incidence ratios, relative risks, and absolute excess risks, with 95% confidence intervals, for developing a subsequent primary Hodgkin lymphoma among a cohort of childhood cancer survivors (excluding Hodgkin lymphoma survivors)

Factor		Obs/Exp	SIR (95% CI)	RR (95% CI)[b]
Overall		36/34.2	1.1 (0.8–1.5)	-
Sex	Males	26/19.4	1.3 (0.9–2.0)	1.0 (ref.)
	Females	10/14.7	0.7 (0.4–1.3)	0.5 (0.3–1.1)
	p for heterogeneity		.06	.09
Childhood cancer diagnosis	Leukemia	12/8.0	1.5 (0.9–2.6)	1.0 (Ref)
	Non-Hodgkin lymphoma	5/2.0	2.4 (1.0–5.9)	1.2 (0.4–3.7)
	CNS tumors	5/7.8	0.6 (0.3–1.5)	0.3 (0.1–0.9)
	Other[c]	14/16.3	0.9 (0.5–1.4)	0.3 (0.1–0.8)
	p for heterogeneity		.19	.02
Decade of childhood cancer diagnosis	<1970	11/7.3	1.5 (0.8–2.7)	1.0 (Ref)
	1970–1979	9/9.2	1.0 (0.5–1.9)	0.4 (0.2–1.1)
	1980–1989	11/11.8	0.9 (0.5–1.7)	0.4 (0.1–0.9)
	1990–2008	5/5.9	0.8 (0.4–-2.0)	0.3 (0.1–0.9)
	p for trend		.23	.03
Age at childhood cancer diagnosis, years	Birth to 3	13/13.6	1.0 (0.6–1.6)	1.0 (Ref)
	4–7	10/8.5	1.2 (0.6–2.2)	1.2 (0.5–2.9)
	8–11	8/8.1	1.0 (0.5–2.0)	1.2 (0.5–3.2)
	12–21	5/3.9	1.3 (0.5–3.1)	2.0 (0.7–6.3)
	p for trend		.69	.29
Attained age, years	<20	12/7.8	1.5 (0.9–2.7)	1.0 (Ref)
	20–29	12/15.4	0.8 (0.4–1.4)	0.4 (0.2–1.0)
	30–39	8/7.5	1.1 (0.5–2.1)	0.5 (0.2–1.3)
	40–49	4/2.5	1.6 (0.6–4.3)	0.7 (0.2–2.3)
	≥50	0/1.0	—	0.0
	p for trend		.31	.09
Follow-up time since 5-year survival, years[a]	0–9	16/13.1	1.2 (0.7–2.0)	1.0 (Ref)
	10–19	11/12.5	0.9 (0.5–1.6)	0.4 (0.2–0.9)
	20–29	7/6.1	1.2 (0.6–2.4)	0.5 (0.2–1.2)
	≥30	2/2.6	0.8 (0.2–3.1)	0.6 (0.2–2.0)
	p for trend		.58	.05
Radiotherapy[c,d]	No	10/7.7	1.3 (0.7–2.4)	1.0 (Ref)
	Yes	11/12.9	0.9 (0.5–1.5)	0.8 (0.3–2.0)
	Missing	0/2.4	—	—
	p for heterogeneity		.34	.71
Chemotherapy[c,d]	No	7/7.3	1.0 (0.5–2.0)	1.0 (Ref)
	Yes	13/12.6	1.0 (0.6–1.8)	1.1 (0.4–2.9)

TABLE 4 (Continued)

Factor		Obs/Exp	SIR (95% CI)	RR (95% CI)[b]
	Missing	1/3.2	—	—
	p for heterogeneity		.87	.79

Abbreviations: 95% CI, 95% confidence interval; CNS, central nervous system; Exp, expected; Obs, observed; Ref, reference category; RR, relative risk; SIR, standardized incidence ratio.

[a]RRs were derived from a model including sex, childhood cancer diagnosis, country, decade of childhood diagnosis, age at childhood diagnosis, and attained age.

[b]RRs were derived from a model including sex, childhood cancer diagnosis, country, decade of childhood diagnosis, age at childhood diagnosis, and follow-up time.

[c]RRs were derived from a model including sex, country, age at childhood diagnosis, attained age and treatment.

[d]Analyses relating to treatment included data from data providers that had <30% of missing data (Nordic countries and Italian population-based cohorts were excluded; treatment data were not available at all for Nordic countries).

consistent with research conducted in individuals who were exposed to radiation after the atomic bomb, in whom no increased risk was observed either.[39]

Clinical implications

Current guidelines from the Children's Oncology Group for the long-term surveillance of childhood cancer survivors do not include details of an increased SPL risk.[40] Although we do not advocate surveillance of survivors because the absolute risks are small, survivors of HL, Wilms tumor, leukemia, and bone sarcoma should be encouraged to seek clinical advice from a medical professional if potentially relevant symptoms of NHL develop, including swellings, fever, and night sweats. Previous studies identified HL survivors to be at risk of NHL, but here we found that survivors of Wilms tumor, leukemia, and bone sarcoma are also at risk; it would be important for health care professionals responsible for the long-term follow-up of these survivors to be aware of the increased risk. Finally, it may be worth emphasizing to survivors that treatment with radiotherapy does not seem to suggest an increased risk of SPLs.

Study limitations

One of the potential limitations of this study is the lack of detailed data concerning childhood treatment variables, such as cumulative doses of radiotherapy (including radiotherapy field) and chemotherapy. To fully assess the effect of treatment modalities on SPL risk, it would be beneficial to perform further analysis in the form of a nested case–control study in which detailed treatment information would be collected so that the risk of developing an SPL by cumulative doses of both radiation and chemotherapy agents can be calculated.

Another potential limitation of the study is the relatively small number of subsequent primary HLs observed, meaning that some components of the study may lack statistical power for further detailed analyses. That said, with more than three times the number of SPLs compared with the next largest study, this study is the largest cohort of childhood cancer survivors with subsequent HLs to date and hence provides the most accurate estimates of these risks.[10]

Furthermore, it is feasible that, in some instances, the first primary lymphoma was misdiagnosed as HL instead of NHL.[12] In such cases, the subsequent primary NHL would not have been a true subsequent primary and thus resulted in an overestimate of the risk of developing NHL after HL. Although we cannot investigate the extent to which such misclassification has occurred, in a German study among adult patients with HL (aged 19–71 years), misclassification of the first primary lymphoma as HL instead of NHL occurred only for 2.1% of patients, suggesting that the extent to which potential misclassification might affect our results is likely minimal.[19] Also, we observed increased risks of NHL in survivors of Wilms tumor, leukemia, and bone sarcoma, suggesting that there is a critical role of treatment or immunodeficiency in the development of NHL after childhood cancer, and the increase cannot be caused only by misclassification of the first primary cancer.

Another potential limitation relates to heterogeneity in subtypes of subsequent primary NHL, with each subtype potentially having a different etiology. An investigation of treatment-related risk factors for subtypes of NHL is simply not feasible within this large-scale cohort study and would require a case–control study.

CONCLUSION

In conclusion, in this largest cohort study to date, we demonstrate that the risk of developing NHL was increased particularly among those surviving HL, Wilms tumor, leukemia, and bone sarcoma and those who were treated with chemotherapy for any cancer. Only NHL survivors were at increased risk of HL. Although, for most childhood cancer survivors, the absolute risk of developing an SPL is low, health care professionals should be aware of the increased risk of developing NHL among survivors of HL, Wilms tumor, leukemia and bone sarcoma and in any survivors treated with chemotherapy. Survivors should be encouraged to seek clinical advice from a medical

professional if potentially relevant symptoms of NHL develop, including swellings, fever, and night sweats.

AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

Zsuzsanna Jakab reports personal fees from Semmelweis Egyetem outside the submitted work. Lars Hjorth reports personal fees from Bayer and F. Hoffmann-La Roche outside the submitted work. The remaining authors made no disclosures.

DATA AVAILABILITY STATEMENT

Access to anonymized data may be granted under conditions agreed with the relevant (local) legal and research ethics committees and with appropriate data sharing agreements and permissions from each data provider in place. Any data sharing would have to comply with the EU General Data Protection Regulation. The data that support the findings of this study are not publicly available because of privacy and ethical restrictions. Aggregated data in the form of tables may be available on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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