Risk of second malignant neoplasms after childhood leukemia and lymphoma: an international study

Risk of Second Malignant Neoplasms After Childhood Leukemia and Lymphoma: An International Study

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Background Survivors of childhood leukemia and lymphoma experience high risks of second malignant neoplasms. We quantified such risk using a large dataset from 13 population-based cancer registries.

Methods The registries provided individual data on cases of leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma occurring in children aged 0–14 years and on subsequent second malignant neoplasms for different time periods from 1943 to 2000. Risks of second malignant neoplasms were assessed through standardized incidence ratios (SIRs) and corresponding 95% confidence intervals (CIs), using the incidence rates in the general populations covered by the registries as a reference. Cumulative absolute risks were also calculated.

Results A total of 133 second malignant neoplasms were observed in 16540 patients (12731 leukemias, 1246 Hodgkin lymphomas, and 2563 non-Hodgkin lymphomas) after an average follow-up of 6.5 years. The most frequent second malignancies after leukemia were brain cancer (19 cases, SIR = 8.52, 95% CI = 5.13 to 13.3), non-Hodgkin lymphoma (nine cases, SIR = 9.41, 95% CI = 4.30 to 17.9), and thyroid cancer (nine cases, SIR = 18.8, 95% CI = 8.60 to 35.7); the most frequent after Hodgkin lymphoma were thyroid cancer (nine cases, SIR = 52.5, 95% CI = 24.0 to 99.6), breast cancer (six cases, SIR = 20.9, 95% CI = 7.66 to 45.4), and neoplasms of skin (non-melanoma) (six cases, SIR = 34.0, 95% CI = 12.5 to 74.0); and the most frequent after non-Hodgkin lymphoma were thyroid cancer (six cases, SIR = 40.4, 95% CI = 14.8 to 88.0) and brain cancer (four cases, SIR = 6.97, 95% CI = 1.90 to 17.9). Cumulative incidence of any second malignant neoplasm was 2.43% (95% CI = 1.09 to 3.78), 12.7% (95% CI = 8.29 to 17.2), and 2.50% (95% CI = 1.04 to 3.96) within 30 years from diagnosis of leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma, respectively.

Conclusions This population-based study provides, to our knowledge, the most precise and up-to-date estimates for relative and absolute risks of second malignant neoplasms after childhood leukemia and lymphoma.

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Survival after childhood cancer has improved greatly over the last three decades. Recent estimates of cumulative survival published since 2000 in Europe (1–6), United States (7), New Zealand (8), and Japan (9) show that 5-year cumulative survival for children with cancer ranges from a minimum of 66% in New Zealand to

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more than 80% in Germany. It has been estimated that, in the United States, one in 570 young adults between the ages of 20 and 34 years is a childhood cancer survivor (10). Because of the young age of this ever-growing population of survivors and their potential longevity, the study of delayed sequelae of childhood cancer and its therapy is of increasing importance. Survivors of childhood cancer are at higher risk of developing a second malignant neoplasm than the general population. Increasing numbers of childhood cancer survivors are still alive when the aging process naturally increases the risk of cancer incidence, adding to the risk caused by childhood cancer.

The most common tumor types in the pediatric age group (0–14 years) are leukemias, central nervous system cancers, and lymphomas. Recent estimates report annual European incidence rates for childhood leukemia and lymphoma of 44.8 and 15.5 per million child-years (standardized to the world standard population) in 1990 to 1999, with statistically significant annual increases of 0.7% and 1.3%, respectively, from 1970 to 1999 (6). In the United States, leukemia and lymphoma incidence rates were 47.8 and 15.1 per million child-years (standardized to the United States standard population) in 2000 to 2003 (7). In Europe, the 5-year survival rate has improved to over 75% in the 1990s for both leukemia and lymphoma (6), and in the United States the most recent 5-year survival rates (for 1996 to 2002) reached 79.5% for leukemia and 86.3% for lymphoma (7).

Childhood leukemia and lymphoma survivors are the largest population of childhood cancer survivors at increased risk of developing second malignant neoplasms. The aim of this study was to quantify this risk, in both relative and absolute terms, using data from a collaborative project involving 13 population-based registries. This study is, to our knowledge, the largest population-based study on this topic.

CONTEXT AND CAVEATS

Prior knowledge

The population of survivors of childhood cancer is growing and aging. Hematolymphopoietic malignancies are among the most common cancers of childhood.

Study design

Population-based registry study in which 13 registries from around the world provided individual data on more than 16500 survivors of childhood leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma. Rates of second malignancies in survivors were compared with those in the general populations covered by the registries.

Contributions

After an average follow-up of 6.5 years, survivors had almost seven times the risk of a second malignant neoplasm than the general population. The most frequent second malignancies after leukemia were brain cancer, non-Hodgkin lymphoma, and thyroid cancer; after Hodgkin lymphoma were thyroid cancer, female breast cancer, and nonmelanoma skin cancer; and after non-Hodgkin lymphoma were thyroid cancer and brain cancer. Cumulative incidence of any second cancer 30 years after diagnosis of leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma was 2.4%, 12.7%, and 2.5%, respectively.

Implications

Survivors of hematolymphopoietic neoplasms are at increased risk of second cancers, with survivors of Hodgkin lymphoma at particularly high risk. Both relative and absolute risks could be evaluated in this large and geographically diverse study.

Limitations

Individual treatment information was not available from the registries. Because of small numbers and multiple comparisons, some associations may have arisen by chance. Some misclassification is possible.

Methods

Data Sources

This study is part of an international multicenter study of second malignant neoplasms that includes data from 13 population-based cancer registries (New South Wales, Australia; British Columbia, Manitoba, and Saskatchewan, Canada; Denmark; Finland; Iceland; Norway; Singapore; Slovenia; Zaragoza, Spain; Sweden; and Scotland) that have been in operation for at least 25 years and that were able to provide high-quality data. There are no relevant differences in how individual registries collect their data: all the registries have contributed data to the series Cancer Incidence in Five Continents (11) and have similar and high proportion of completeness. The population covered by these cancer registries was approximately 47 million in the 1990s. The registries contributed data for different time periods in the years 1943–2000, with a median observation period of 32 years. This dataset partially overlaps with that used in a previous study (12) in the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) that analyzed second malignant neoplasms after cancer in childhood and adolescence diagnosed in the period 1943–1987. In particular, 32 of the 75 second malignancies contributed to this study by the Nordic countries were already included in the earlier Nordic countries' study (12). The data contributed by the Slovenian registry (10 cases) were also included in a previous publication (13).

Data were provided by each cancer registry on selected primary neoplasms occurring during childhood (0–14 years of age), including age and sex of the subject, diagnosis and date of the first malignant neoplasm, follow-up for vital status, and date and diagnosis of the second malignant neoplasm, if any. All children who survived at least 1 day after their first neoplasm diagnosis entered the survivors' cohort. Subjects were no longer followed up if a second malignant neoplasm had occurred or if they died, migrated out of the study area, or were lost to follow-up. Registries used different cancer codes that were systematically converted by the International Agency for Research on Cancer (IARC) to International Classification of Diseases, 9th Revision (ICD-9) codes (14). We analyzed the occurrence of second malignant neoplasms in patients who were diagnosed with leukemia (ICD-9: 204–208), Hodgkin lymphoma (ICD-9: 201), or non-Hodgkin lymphoma (ICD-9: 200, 202) between 0 and 14 years of age and who survived for at least one day. Coding of multiple primary cancers followed a common set of rules proposed by the International Association of Cancer Registries and the IARC (15). According to these rules, a primary cancer is one that originates in a primary site or tissue and is thus not an extension, a recurrence, or a metastasis.

To exclude recurrences, we did not analyze the occurrence of leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma after childhood leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma, respectively. Cancers in the same patient occurring after the first second malignant neoplasm were not analyzed. In situ cancers were not considered to be second primaries. The Saskatchewan registry in Canada did not provide data on non-melanoma skin cancers.

All data were provided in an anonymous fashion with respect to patient identities. Approval for the study was obtained from the ethics committee of IARC. Informed consent was not required because the study was based on anonymized registry records.

Statistical Analysis

To assess the excess of second malignant neoplasms after childhood leukemia or lymphoma, we calculated standardized incidence ratios (SIRs) and corresponding 95% confidence intervals (CIs) of all second malignant neoplasms. These were calculated as the ratio of the observed number of second malignant neoplasms to the expected number, which was obtained by applying the age-, sex-, year-, and registry-specific incidence rates of first primary cancers to the population of survivors of the childhood malignancies under study (16). The reference population is the general population covered by the registries involved in the study. Standardized incidence ratios were calculated for all types of second malignant neoplasms by length of follow-up, age at first neoplasm diagnosis, and calendar period of first neoplasm registration (before and after 1980, approximately at the middle of the observation period). The absolute excess risk was calculated as the difference between observed second malignant neoplasms and expected number of cases of each cancer type, divided by the total number of person-years at risk.

Cumulative incidence of second malignant neoplasms in the survivors' cohort was calculated by taking into account death from any cause as a competing risk event (17). The observed cumulative incidence was estimated nonparametrically in a two-step process: both the Kaplan–Meier estimate of the overall survival from any event (second malignant neoplasm or death) and the conditional probability of second malignant neoplasm were computed. The cumulative incidence of second malignant neoplasms was then computed by summing the products of the overall survival and the hazard rate of second malignant neoplasm for all time intervals. Expected cumulative incidence was calculated using the life-table method (18) without considering competing risks. The entire follow-up period was divided into consecutive 5-year intervals, and the probability of survival within each interval, defined as being free from a second malignant neoplasm, was calculated by dividing the expected number of second malignant neoplasm–free individuals in the interval by the number of first neoplasm survivors who were alive and free from a second malignant neoplasm at the beginning of the interval. This numerator was adjusted for censoring, i.e., second malignant neoplasm–free individuals who died in the interval counted for half an individual in the numerator. The expected cumulative probability of being second malignant neoplasm–free after a given follow-up duration was the product of the probabilities during the relevant intervals, and its complement was the expected cumulative incidence of second malignant neoplasms. The effect of death as a competing risk in the general population was assumed to be negligible, given the young age range considered in our analysis: 0–14 years at diagnosis plus an average follow-up time of 6.5 years. Only 4.7% of the follow-up time of the cohort comprised subjects more than 40 years of age. The standardized death rate for all causes reported in the European mortality database of the World Health Organization for people aged 1–19 years in 2004 was 21.6 per 100 000 (19). All statistical tests were two-sided. The Breslow–Day test was used to assess standardized incidence ratios heterogeneity between registries and trends by age-group (20).

Results

A total of 12 731 survivors of leukemia, 1246 survivors of Hodgkin lymphoma, and 2563 survivors of non-Hodgkin lymphoma, contributing 108 171 person-years of observation, were identified from the pool of 13 registries. The mean follow-up time was 6.5 years. During follow-up, a total of 133 second malignant neoplasms were recorded. The median age and follow-up time at the occurrence of a second malignant neoplasm were 16.0 (interquartile range [IQR] = 10.0–24.0) and 9.5 (IQR = 4.70–16.3) years after leukemia and 26.0 (IQR = 20.0–32.0) and 16.3 (IQR = 9.30–22.2) years after lymphoma, respectively. The distribution of first neoplasms according to various characteristics and the corresponding number of second malignant neoplasms are shown in Table 1.

Table 2 reports the number of observed and expected second malignant neoplasms and the corresponding standardized incidence ratios and absolute excess risks (per 100 000 person-years), in survivors of leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma (separately), for neoplasms with at least one observed case. The overall standardized incidence ratio for having a second malignant neoplasm after any childhood hematolymphopoietic neoplasm was 6.77 (95% CI = 5.67 to 8.02). The most frequent second malignant neoplasms after leukemia were brain cancer (19 cases, SIR = 8.52, 95% CI = 5.13 to 13.3), non-Hodgkin lymphoma (nine cases, SIR = 9.41, 95% CI = 4.30 to 17.9) and thyroid cancer (nine cases, SIR = 18.8, 95% CI = 8.60 to 35.7); the most frequent after Hodgkin lymphoma were thyroid cancer (nine cases, SIR = 52.5, 95% CI = 24.0 to 99.6), breast cancer (six cases, SIR = 20.9, 95% CI = 7.66 to 45.4), and neoplasms of skin (non-melanoma) (six cases, SIR = 34.0, 95% CI = 12.5 to 74.0); and the most frequent after non-Hodgkin lymphoma were thyroid cancer (six cases, SIR = 40.4, 95% CI = 14.8 to 88.0) and brain cancer (four cases, SIR = 6.97, 95% CI = 1.90 to 17.9). Elevated standardized incidence ratios were found for 14 neoplasm types, namely cancers of the tongue, salivary glands, liver, bone, female breast, bladder, brain, thyroid, soft tissue sarcoma, nonmelanoma skin cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, myeloid leukemia, and other leukemias.

When considering the six registries contributing most person-years to the dataset, standardized incidence ratios for all second malignant neoplasms ranged from 3.30 (95% CI = 1.06 to 7.70) in Finland (five cases) to 9.94 (95% CI = 5.56 to 16.4) in New South Wales (15 cases) after leukemia, from 6.21 (95% CI = 1.67 to 15.9) in Sweden (four cases) to 13.3 (95% CI = 6.07 to 25.2) in Denmark (nine cases) after Hodgkin lymphoma, and from 1.42 (95% CI = 0.02 to 7.90) in Norway (one case) to 4.91 (95% CI = 0.55 to 17.7)

Table 1. Distribution of childhood first malignant neoplasms (leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma) and number of second malignant neoplasms (in parentheses), by selected characteristics

Characteristics	First malignant neoplasm		
	Leukemia	Hodgkin lymphoma	Non-Hodgkin lymphoma
Sex			
Female	5662 (28)	422 (23)	806 (10)
Male	7069 (39)	824 (25)	1757 (8)
Age at first neoplasm registration, y			
<1	318 (0)	0 (0)	79 (0)
1–4	5949 (32)	81 (5)	686 (1)
5–9	4061 (24)	378 (10)	927 (10)
10–14	2403 (11)	787 (33)	871 (7)
Calendar period at first neoplasm diagnosis			
Before 1970	2666 (3)	240 (16)	442 (3)
1970–1979	3201 (29)	295 (20)	629 (6)
1980–1989	3694 (29)	387 (11)	802 (6)
1990 or later	3170 (6)	324 (1)	690 (3)
Duration of follow-up, y			
<1	3754 (4)	122 (1)	890 (2)
1–4	4225 (14)	295 (2)	576 (4)
5–9	1787 (18)	246 (9)	325 (2)
10–14	1258 (8)	181 (7)	282 (2)
15–19	956 (15)	170 (10)	227 (2)
20–24	559 (4)	116 (9)	116 (4)
25–29	135 (3)	68 (7)	70 (2)
30–34	29 (1)	28 (2)	29 (0)
35–39	18 (0)	12 (0)	27 (0)
≥40	10 (0)	8 (1)	21 (0)
Registry (registration period)			
New South Wales, Australia (1972–1997)	1466 (15)	145 (5)	309 (2)
British Columbia, Canada (1970–1998)	780 (6)	98 (3)	169 (1)
Manitoba, Canada (1970–1998)	301 (0)	40 (3)	79 (0)
Saskatchewan, Canada (1967–1998)	289 (1)	28 (1)	55 (1)
Denmark (1943–1997)	2064 (10)	173 (9)	399 (6)
Finland (1953–1998)	1946 (5)	187 (7)	305 (2)
Iceland (1955–2000)	106 (0)	14 (0)	14 (0)
Norway (1953–1999)	1764 (7)	131 (7)	286 (1)
Singapore (1968–1992)	591 (0)	33 (1)	128 (0)
Slovenia (1961–1998)	447 (5)	94 (4)	85 (1)
Zaragoza, Spain (1978–1998)	120 (0)	16 (0)	49 (0)
Sweden (1961–1998)	2019 (14)	187 (4)	524 (3)
Scotland (1975–1996)	838 (4)	100 (4)	161 (1)
Total	12731 (67)	1246 (48)	2563 (18)

in New South Wales (two cases) after non-Hodgkin lymphoma. Heterogeneity among registries was not statistically significant.

Table 3 shows standardized incidence ratios of second malignant neoplasms by period of diagnosis (i.e., before and after 1980) of childhood leukemia and Hodgkin lymphoma diagnosis. There were nine second malignant neoplasms after non-Hodgkin lymphoma diagnosed before 1980 (SIR = 2.75, 95% CI = 1.26 to 5.21) and nine cases after non-Hodgkin lymphoma diagnosed after 1980 (SIR = 5.83, 95% CI = 2.67 to 11.1).

Table 4 shows standardized incidence ratios of the most frequent (at least five observed cases) second malignant neoplasms in survivors of childhood leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma considered together by the time elapsed since the diagnosis of the first neoplasm. In survivors of childhood leukemia, most brain cancers (16 out of 19) occurred between 1 and 14 years after diagnosis of the first neoplasm (with a peak at 5–9 years after diagnosis), seven out of nine of non-Hodgkin lymphomas occurred between 1 and 9 years after diagnosis, and eight out of nine thyroid cancers occurred between 10 and 19 years after diagnosis (data not shown). Standardized incidence ratios of brain cancer and non-Hodgkin lymphoma exhibited a bell-shaped distribution, whereas those of thyroid cancer increased steadily with time since leukemia diagnosis (data not shown). In survivors of childhood Hodgkin lymphoma, all thyroid cancers but one (which occurred in the first 12 months) occurred at least 10 years after diagnosis, all neoplasms of the skin (other than melanoma) but one (which occurred 5–9 years after diagnosis) occurred at least 15 years after diagnosis, all breast cancers occurred at least 10 years after diagnosis, all myeloid leukemias occurred 5–19 years after diagnosis, and all the other leukemias occurred within 9 years after the original Hodgkin lymphoma diagnosis. In survivors of non-Hodgkin lymphoma, all thyroid cancers occurred at least 10 years after diagnosis, whereas three out of four brain cancers occurred within 4 years of diagnosis.

Table 2. Standardized incidence ratios with 95% confidence intervals and absolute excess risks per 100 000 person-years of selected second malignant neoplasms after childhood leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma*

Neoplasm sites [ICD-9 code (14)]†	First malignant neoplasm (person-years at risk)											
	Leukemia (75 212)				Hodgkin lymphoma (14 074)				Non-Hodgkin lymphoma (18 886)			
	O	E	SIR (95% CI)	AER‡	O	E	SIR (95% CI)	AER‡	O	E	SIR (95% CI)	AER‡
All malignant neoplasms (140–208)	67	10.9	6.12 (4.74 to 7.77)	74.5	48	3.88	12.4 (9.12 to 16.4)	313.5	18	4.82	3.73 (2.21 to 5.90)	69.8
Tongue (141)	2	0.03	71.9 (8.70 to 260)	2.6	0	0.02	0.00 (0.00 to 234)	−0.1	0	0.02	0.00 (0.00 to 215)	−0.1
Salivary gland (142)	2	0.06	31.5 (3.81 to 114)	2.6	0	0.02	0.00 (0.00 to 170)	−0.1	0	0.02	0.00 (0.00 to 172)	−0.1
Esophagus (150)	0	0.01	0.00 (0.00 to 556)	0.0	1	0.01	120 (3.00 to 669)	7.0	0	0.01	0.00 (0.00 to 313)	−0.1
Small intestine (152)	0	0.02	0.00 (0.00 to 233)	0.0	0	0.01	0.00 (0.00 to 358)	−0.1	1	0.01	105 (2.62 to 583)	5.2
Colon (153)	0	0.24	0.00 (0.00 to 15.4)	−0.3	1	0.11	9.23 (0.23 to 51.4)	6.3	1	0.13	7.48 (0.19 o 41.7)	4.6
Rectum (154)	0	0.05	0.00 (0.00 to 75.8)	−0.1	1	0.04	22.3 (0.56 to 124)	6.8	0	0.06	0.00 (0.00 to 66.0)	−0.3
Liver (155) (excluding 155.2)	2	0.08	24.6 (2.98 to 89.0)	2.6	0	0.02	0.00 (0.00 to 165)	−0.1	1	0.03	34.7 (0.87 to 194)	5.1
Pancreas (157)	0	0.03	0.00 (0.00 to 118)	0.0	1	0.02	44.4 (1.11 to 247)	7.0	0	0.03	0.00 (0.00 to 123)	−0.2
Lung (162)	0	0.10	0.00 (0.00 to 35.2)	−0.1	2	0.08	23.7 (2.87 to 85.6)	13.6	0	0.12	0.00 (0.00 to 30.8)	−0.6
Bone (170)	3	0.60	5.03 (1.04 to 14.7)	3.2	1	0.14	6.99 (0.17 to 39.0)	6.1	1	0.18	5.56 (0.14 to 31.0)	4.3
Soft tissue sarcoma (171)	2	0.48	4.13 (0.50 to 14.9)	2.0	2	0.11	17.8 (2.16 to 64.4)	13.4	0	0.14	0.00 (0.00 to 26.1)	−0.7
Melanoma of skin (172)	2	1.05	1.91 (0.23 to 6.89)	1.3	3	0.45	6.71 (1.38 to 19.6)	18.1	0	0.47	0.00 (0.00 to 7.83)	−2.5
Other neoplasm of skin (173)	4	0.28	14.3 (3.91 to 36.7)	4.9	6	0.18	34.0 (12.5 to 74.0)	41.4	1	0.25	3.94 (0.10 to 21.9)	4.0
Female breast (174)	1	0.41	2.42 (0.06 to 13.5)	0.8	6	0.29	20.9 (7.66 to 45.4)	40.6	0	0.33	0.00 (0.00 to 11.0)	−1.7
Testis (186)	2	0.86	2.32 (0.28 to 8.37)	1.5	0	0.50	0.00 (0.0 to 7.31)	−3.6	0	0.51	0.00 (0.00 to 7.19)	−2.7
Other male genital than testis (187)	0	0.01	0.00 (0.00 to 271)	0.0	1	0.01	142 (3.56 to 794)	7.0	0	0.01	0.00 (0.00 to 421)	−0.1
Bladder (188, 189.3, 189.4)	4	0.07	53.6 (14.6 to 137)	5.2	0	0.05	0.00 (0.00 to 67.3)	−0.4	0	0.07	0.00 (0.00 to 51.7)	−0.4
Kidney (189) (excluding 189.3, 189.4)	1	0.36	2.75 (0.07 to 15.3)	0.9	0	0.06	0.00 (0.00 to 65.1)	−0.4	0	0.10	0.00 (0.00 to 36.1)	−0.5
Brain, nervous system (191–192)	19	2.23	8.52 (5.13 to 13.3)	22.3	3	0.39	7.76 (1.60 to 22.7)	18.5	4	0.57	6.97 (1.90 to 17.9)	18.2
Thyroid gland (193)	9	0.48	18.8 (8.60 to 35.7)	11.3	9	0.17	52.5 (24.0 to 99.6)	62.7	6	0.15	40.4 (14.8 to 88.0)	31.0
Other endocrine gland (194, 164)	1	0.18	5.56 (0.14 to 31.0)	1.1	0	0.03	0.00 (0.00 to 132)	−0.2	0	0.04	0.00 (0.00 to 86.8)	−0.2
Hodgkin lymphoma (201)	4	1.04	3.85 (1.05 to 9.86)	3.9	NA	NA	NA	NA	2	0.35	5.77 (0.70 to 20.8)	8.7
Non-Hodgkin lymphoma (200, 202)	9	0.96	9.41 (4.30 to 17.9)	10.7	1	0.26	3.83 (0.10 to 21.3)	5.3	NA	NA	NA	NA
Lymphoid leukemia (204)	NA	NA	NA	NA	0	0.13	0.00 (0.00 to 27.3)	−0.9	1	0.23	4.36 (0.11 to 24.3)	4.0
Myeloid leukemia (205)	NA	NA	NA	NA	4	0.12	33.9 (9.24 to 86.8)	27.6	0	0.12	0.00 (0.00 to 29.9)	−0.6
Other leukemia (206–208)	NA	NA	NA	NA	5	0.09	53.7 (17.4 to 125)	34.9	0	0.21	0.00 (0.00 to 17.8)	−1.1

* ICD-9 = International Classification for Diseases, 9th Revision; O = observed; E = expected; SIR = standardized incidence ratio; CI = confidence interval; AER = absolute excess risk; NA = not applicable: incidence of leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma after childhood leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma, respectively, were not analyzed.

† Second malignant neoplasms with at least one observed case for any of the three first neoplasm types.

‡ Per 100 000 person-years.

Most second malignant neoplasms occurred in patients who had been diagnosed with childhood leukemia when they were 1–4 years old (data not shown), as expected because childhood leukemia incidence peaks at approximately 3 years of age (6). Among survivors of Hodgkin lymphoma, secondary breast cancer and myeloid leukemia occurred exclusively in patients who had their first neoplasm when they were 10–14 years old (data not shown). Incidence of thyroid cancer decreased with increasing age at first diagnosis (age 1–4 years: four cases, SIR = 797 [95% CI = 217 to 2041]; 5 to 9 years: three cases, SIR = 87.1 [95% CI = 18.0 to 254]; 10 to 14 years: two cases, SIR = 15.1 [95% CI = 1.83 to 54.7]; test for trend: $P<.001$). Incidence of other leukemias increased with increasing age at first diagnosis (zero cases in the age-group 1–4 years; one case in the age-group 5–9 years, SIR = 30.1 [95% CI = 0.75 to 167]; four cases in the age-group 10–14 years, SIR = 79.3 [95% CI = 21.6 to 203]; test for trend: $P = .23$).

Cumulative incidence of second malignant neoplasms in survivors of childhood leukemia or lymphoma is shown in Fig. 1. The

Table 3. Standardized incidence ratios and corresponding confidence intervals of selected second malignant neoplasms after childhood leukemia and Hodgkin lymphoma, by calendar period of diagnosis of childhood first malignant neoplasm*

	Calendar period of first neoplasm diagnosis					
	Before 1980			1980 or later		
Neoplasm sites [ICD-9 code (14)]†	O	E	SIR (95% CI)	O	E	SIR (95% CI)
Leukemia‡						
All malignant neoplasms (140–208)	32	5.73	5.58 (3.82 to 7.88)	35	5.22	6.71 (4.67 to 9.33)
Tongue (141)	2	0.02	101 (12.2 to 364)	0	0.01	0.00 (0.00 to 367)
Salivary gland (142)	0	0.03	0.00 (0.00 to 122)	2	0.03	66.8 (8.08 to 241)
Liver (155) (excluding 155.2)	2	0.03	60.5 (7.32 to 219)	0	0.05	0.00 (0.00 to 73.4)
Bone (170)	1	0.24	4.17 (0.10 to 23.2)	2	0.36	5.60 (0.68 to 20.2)
Soft tissue sarcoma (171)	0	0.2	0.00 (0.00 to 18.3)	2	0.29	6.99 (0.85 to 25.2)
Melanoma of skin (172)	1	0.71	1.41 (0.04 to 7.87)	1	0.34	2.93 (0.07 to 16.4)
Other neoplasms of skin (173)	3	0.19	15.7 (3.23 to 45.7)	1	0.09	11.4 (0.29 to 63.8)
Female breast (174)	1	0.40	2.53 (0.06 to 14.1)	0	0.02	0.00 (0.00 to 183)
Testis (186)	0	0.54	0.00 (0.00 to 6.79)	2	0.33	6.15 (0.74 to 22.2)
Bladder (188, 189.3, 189.4)	3	0.05	56.9 (11.7 to 166)	1	0.02	45.7 (1.14 to 254)
Kidney (189) (excluding 189.3, 189.4)	1	0.14	7.10 (0.18 to 39.6)	0	0.22	0.00 (0.00 to 16.7)
Brain, nervous system (191–192)	6	0.79	7.60 (2.79 to 16.6)	13	1.44	9.02 (4.80 to 15.4)
Thyroid gland (193)	5	0.29	17.0 (5.53 to 39.8)	4	0.19	21.6 (5.88 to 55.3)
Other endocrine glands (194, 164)	0	0.05	0.00 (0.00 to 73.4)	1	0.13	7.94 (0.20 to 44.2)
Hodgkin lymphoma (201)	3	0.49	6.14 (1.27 to 17.9)	1	0.55	1.82 (0.05 to 10.1)
Non-Hodgkin lymphoma (200, 202)	4	0.39	10.3 (2.81 to 26.4)	5	0.57	8.79 (2.85 to 20.5)
Hodgkin lymphoma§						
All malignant neoplasms (140–208)	36	2.81	12.8 (8.97 to 17.7)	12	1.07	11.2 (5.79 to 19.6)
Esophagus (150)	1	0.01	130 (3.24 to 723)	0	<0.01	0.00 (0.00 to 6148)
Colon (153)	1	0.09	11.7 (0.29 to 65.1)	0	0.02	0.00 (0.00 to 183)
Rectum (154)	1	0.04	24.0 (0.60 to 134)	0	<0.01	0.00 (0.00 to 1230)
Pancreas (157)	1	0.02	48.7 (1.22 to 272)	0	<0.01	0.00 (0.00 to 1845)
Lung (162)	2	0.08	25.8 (3.13 to 93.4)	0	0.01	0.00 (0.00 to 367)
Bone (170)	1	0.08	13.2 (0.33 to 73.3)	0	0.07	0.00 (0.00 to 52)
Soft tissue sarcoma (171)	2	0.07	29.4 (3.56 to 106)	0	0.04	0.00 (0.00 to 92)
Melanoma of skin (172)	3	0.32	9.27 (1.91 to 27.1)	0	0.12	0.00 (0.00 to 31)
Other neoplasms of skin (173)	5	0.15	34.0 (11.0 to 79.2)	1	0.03	34.1 (0.85 to 190)
Female breast (174)	6	0.27	21.9 (8.03 to 47.6)	0	0.01	0.00 (0.00 to 367)
Other male genital than testis (187)	1	0.01	173 (4.33 to 966)	0	<0.01	0.00 (0.00 to 3689)
Brain, nervous system (191–192)	1	0.23	4.39 (0.11 to 24.5)	2	0.16	12.6 (1.52 to 45.5)
Thyroid gland (193)	6	0.12	51.4 (18.9 to 112)	3	0.05	54.7 (11.3 to 160)
Non-Hodgkin lymphoma (200, 202)	0	0.17	0.00 (0.00 to 21.6)	1	0.09	10.6 (0.26 to 58.9)
Myeloid leukemia (205)	2	0.08	26.1 (3.16 to 94.5)	2	0.04	48.3 (5.84 to 174)
Other leukemia (206–208)	2	0.06	35.7 (4.32 to 129)	3	0.04	80.8 (16.7 to 236)

* ICD-9 = International Classification of Diseases, 9th Revision; O = observed; E = expected; SIR = standardized incidence ratio; CI = confidence interval.

† Second malignant neoplasms with at least one observed case.

‡ Person-years at risk were 30 678 for the period before 1980 and 44 534 for 1980 or later.

§ Person-years at risk were 8148 for the period before 1980 and 5926 for 1980 or later.

cumulative incidence of any malignancy within 30 years since the first neoplasm diagnosis was 2.43% (95% CI = 1.09 to 3.78) after leukemia, three times the expected cumulative incidence of any malignancies in the general population; 12.7% (95% CI = 8.29 to 17.2) after Hodgkin lymphoma, 11 times the expected incidence; and 2.50% (95% CI = 1.04 to 3.96) after non-Hodgkin lymphoma, 2.5 times the expected incidence. The cumulative incidence reached 3.40% (95% CI = 1.12 to 5.68) 35 years after leukemia, and 31.9% (95% CI = 20.1 to 43.7) 45 years after Hodgkin lymphoma.

Discussion

In this study of second cancers after childhood leukemia and lymphoma, we found that survivors had an increased risk of developing a second malignant neoplasm compared with the general population. The highest risk was found in Hodgkin lymphoma survivors, confirming previous findings from population-based and clinical studies (12,13,21–33). The most frequent second malignant neoplasms were, in descending order, brain cancer, non-Hodgkin lymphoma, and thyroid cancer after leukemia; thyroid cancer, female breast cancer, and non-melanoma skin cancer after Hodgkin lymphoma; and thyroid cancer and brain cancer after non-Hodgkin lymphoma.

Large cohorts of childhood cancer survivors have been studied to estimate the risk of developing a second malignant neoplasm and to disentangle the role of various risk factors (i.e., factors related to the host, initial cancer type, and cancer therapies) (21). The main risk factors for second malignant neoplasms in survivors of childhood cancer are radiotherapy and chemotherapy (34). At

Table 4. Standardized incidence ratios and 95% confidence intervals of the most frequent (at least five observed cases) second malignant neoplasms after childhood leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma, by length of follow-up after childhood first malignant neoplasm*

Years since the first neoplasm	Person-years at risk	All malignant neoplasms (140–208)			Bone (170)			Melanoma of skin (172)			Other neoplasm of skin (173)			Female breast (174)		
		O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)
<1	13649	7	1.29	5.42 (2.18 to 11.2)	0	0.07	0.00 (0.00 to 52.4)	0	0.02	0.00 (0.00 to 183)	0	0.01	0.00 (0.00 to 367)	0	<0.01	0.00 (0.00 to 7378)
1–4	34465	20	3.22	6.22 (3.80 to 9.61)	1	0.24	4.15 (0.10 to 23.1)	0	0.09	0.00 (0.00 to 40.8)	0	0.03	0.00 (0.00 to 122)	0	<0.01	0.00 (0.00 to 1845)
5–9	27029	29	3.13	9.26 (6.20 to 13.3)	2	0.28	7.20 (0.87 to 26.0)	1	0.25	3.970 (10 to 22.1)	2	0.06	33.2 (4.02 to 120)	0	0.01	0.00 (0.00 to 367)
10–14	17060	17	3.43	4.96 (2.89 to 7.94)	0	0.19	0.00 (0.00 to 19.3)	0	0.45	0.00 (0.00 to 8.15)	0	0.10	0.00 (0.00 to 36.7)	2	0.04	49.5 (5.99 to 179)
15–19	9469	27	3.16	8.55 (5.63 to 12.4)	2	0.07	30.0 (3.39 to 101)	3	0.50	5.99 (1.24 to 17.5)	4	0.13	31.6 (8.62 to 81.0)	1	0.12	8.17 (0.20 to 45.5)
≥20	6498	33	5.03	6.56 (4.52 to 9.22)	0	0.03	0.00 (0.00 to 122)	1	0.65	1.53 (0.04 to 8.52)	5	0.38	13.1 (4.27 to 30.7)	4	0.86	4.63 (1.26 to 11.9)
		Brain, nervous system (191–192)			Thyroid gland (193)			Hodgkin lymphoma (201)			Non-Hodgkin lymphoma (200, 202)			Leukemia (204–208)		
		O	E	SIR (95% CI	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)
<1	13649	3	0.43	6.91 (1.43 to 20.2)	1	0.01	88.9 (2.22 to 496)	1	0.05	21.0 (0.52 to 117)	1	0.12	8.49 (0.21 to 47.3)	0	0.13	0.00 (0.00 to 28.2)
1–4	34465	6	1.06	5.65 (2.07 to 12.3)	0	0.06	0.00 (0.00 to 61.1)	2	0.20	10.0 (1.21 to 36.3)	4	0.33	12.2 (3.32 to 31.2)	3	0.31	9.82 (2.03 to 28.7)
5–9	27029	11	0.71	15.5 (7.72 to 27.7)	1	0.13	7.71 (0.19 to 42.9)	0	0.32	0.00 (0.00 to 11.5)	3	0.26	11.7 (2.42 to 34.3)	4	0.20	20.2 (5.51 to 51.8)
10–14	17060	4	0.43	9.31 (2.54 to 23.8)	6	0.20	30.4 (11.2 to 66.2)	0	0.39	0.00 (0.00 to 9.41)	2	0.21	9.66 (1.17 to 34.9)	1	0.12	8.47 (0.21 to 47.2)
15–19	9469	1	0.26	3.78 (0.09 to 21.1)	7	0.19	35.9 (14.4 to 73.9)	2	0.28	7.21 (0.87 to 26.0)	0	0.15	0.00 (0.00 to 24.5)	2	0.07	29.6 (3.58 to 107)
≥20	6498	1	0.29	3.48 (0.09 to 19.4)	9	0.20	44.2 (20.2 to 83.9)	1	0.15	6.60 (0.17 to 36.8)	0	0.16	0.00 (0.00 to 22.9)	0	0.10	0.00 (0.00 to 36.7)

* Neoplasm codes from the International Classification of Diseases, 9th Revision (14) are given in parentheses. O = observed; E = expected; SIR = standardized incidence ratio; CI = confidence interval.

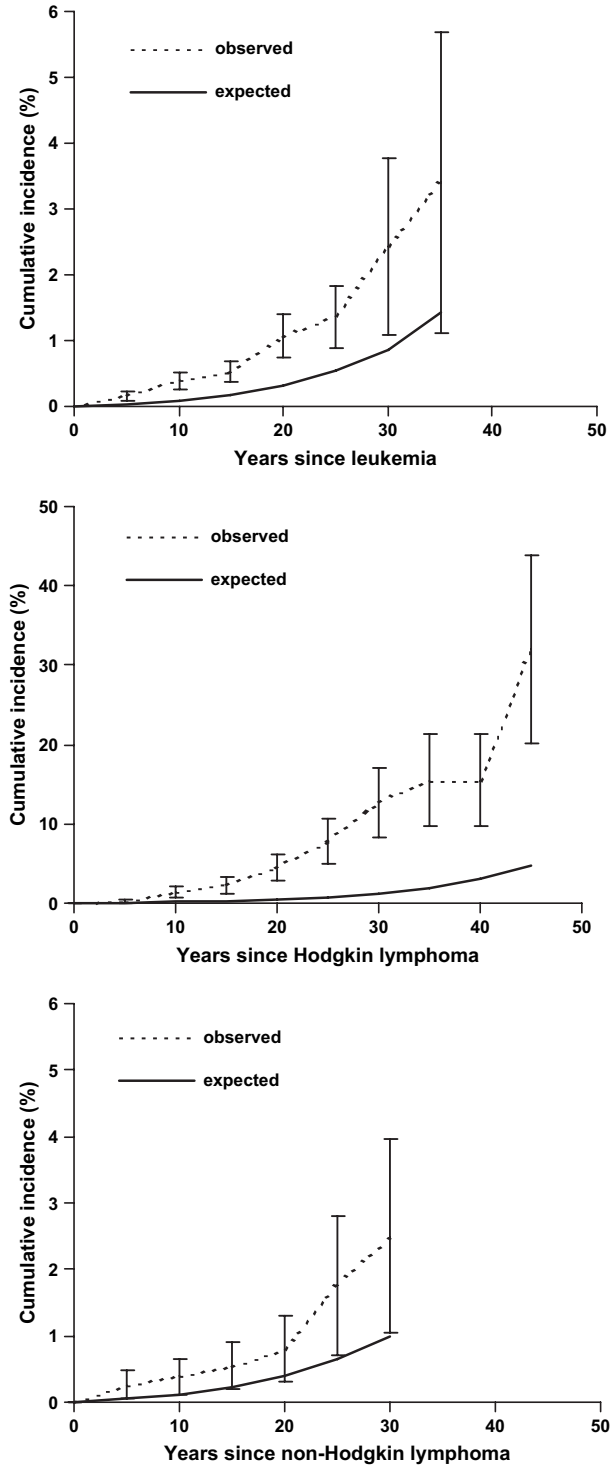

Fig. 1. Cumulative incidence (%) of second malignant neoplasms after childhood leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma by time since childhood first malignant neoplasm diagnosis. **Error bars** represent 95% confidence intervals. (*Y*-axis scale differs for Hodgkin lymphoma.)

least 80% of second malignant neoplasms in childhood cancer survivors develop in the radiotherapy field, with a median latency of at least 10 years and no risk plateau (35). Different tissues are not equally sensitive to radiation, and host factors such as repair enzymes, rate of cell division, endocrine, and immune function may be important cofactors. For a given radiation dose, orthovoltage (voltage in the range of 140–400 kV) in use until the middle of the 1970s and the 1980s was more oncogenic than megavoltage (voltage > 1 MV) (35,36). Other possible risk factors include rare genetic/host predisposition to developing multiple cancers and underlying factors common to different diseases or treatment, such as immunosuppression due to infection with human immunodeficiency virus or bone marrow transplantation (36). Environmental and behavioral shared risk factors are less likely to have played a role in the development of a second malignant neoplasm after childhood hematolymphopoietic neoplasms, given the short latency of childhood cancer.

Individual treatment information was not available from the registries contributing data to our study, and hence no causal inference on the effects of therapies can be drawn. Nevertheless, knowledge of temporal changes in treatment practice in pediatric hematology may help the interpretation of our results, if it is assumed that intercountry variations in treatment procedures were small among the high-income countries of the 13 cancer registries included in our analysis. Similar trends in survival after childhood cancer in European countries and the United States confirm a general uniformity of procedures and treatments (37,38).

Among second malignant neoplasms that may be related to radiotherapy are brain, thyroid, breast, and nonmelanoma skin cancers (36). Brain cancers are the most common second malignant neoplasms after lymphoid leukemia, with a median latency of 7–11 years (25,39,40). A causal link between brain cancer and cranial irradiation has been suggested (41). In the 1970s and 1980s, cranial and spinal radiotherapy was used with doses in the range of 18–24 Gy as prophylaxis to central nervous system involvement (42,43). In addition, brain cancers have been reported in children who had lymphoid leukemia and were not treated with radiotherapy (44). Thyroid cancer induced by radiation is frequently observed in long-term survivors of childhood cancer, although it is not a leading cause of death among them. Those treated for childhood cancer before age 10 years have the highest risk (45). The frequency of thyroid cancer increases linearly with radiation doses up to 30 Gy and decreases at higher doses (46). In the 1970s and 1980s, children treated for lymphoid leukemia received small quantities of radiation at the thyroid because of the unclear borders of the cranial irradiation field (42,43), whereas children with lymphomas were often treated with supradiaphragmatic radiotherapy (including mediastinal, sovraclavear, and laterocervical nodes) (47). Patients treated with radiotherapy also have increased risk of developing nonmelanoma skin neoplasms in the treatment field (48). Second malignant neoplasms are a leading cause of death among long-term survivors of Hodgkin lymphoma, and breast cancer is the most frequent second malignant neoplasm among female survivors (32). A previous study found that the risk starts to increase 5–9 years after completion of radiotherapy, is highest among girls treated at an age of 10 years or older, and is lower for women diagnosed when they were more than 30 years of age (49). The effect of radiation is likely to be stronger during puberty, when breast cells proliferate rapidly due to the hormonal stimulation, resulting in an increased risk of

developing breast cancer. The main concern for Hodgkin lymphoma survivors is thus the risk of subsequent breast cancer among adolescents and young women treated with supradiaphragmatic radiotherapy (47). Recently, it was estimated that cumulative absolute risks of breast cancer after Hodgkin lymphoma range from 0% to 39.6% (based on 3817 women diagnosed up to 30 years of age), depending on age at Hodgkin lymphoma diagnosis, duration of follow-up, and type of treatment. For patients diagnosed by 15 years of age who received a mediastinal dose of at least 40 Gy and no alkylating agents, the cumulative projected risk of breast cancer at 30 years of follow-up was 10.3% (95% CI = 6.8% to 15.2%) (50). Women treated with radiotherapy or alkylating agents and who had early menopause (i.e., before age 40 years) had a lower risk of breast cancer than those who maintained normal ovarian function (51).

In our study, all six breast cancers occurred 10–29 years after a Hodgkin lymphoma diagnosis among women who were 10–14 years of age at the time of the first diagnosis and who had originally been diagnosed before 1980 (when radiotherapy was used intensively). This pattern is consistent with the radiosensitivity of the breast at ages near puberty. The estimated cumulative incidence of any second malignant neoplasm among Hodgkin lymphoma survivors was 12.7% (95% CI = 8.29% to 17.2%) and 31.9% (95% CI = 20.1% to 43.7%) at 30 and 45 years of follow-up, respectively. These findings highlight the importance of careful follow-up of long-term Hodgkin lymphoma survivors. However, therapies that may be related to the high estimated risk of second malignant neoplasms in these women were in use two to three decades ago and do not reflect the optimal treatment protocols in use currently, which, by using lower doses and smaller radiotherapy fields, are expected to decrease the risk of late effects (52,53). Radiation therapy may also be related to risk of head and neck cancers. In a recent report (54), elevated risk of head and neck neoplasms (SIR = 20.9, 95% CI = 10.5 to 41.8, based on eight cases) was found in 4834 patients who survived childhood leukemia. In the group of patients for whom radiation therapy data were available, this treatment was associated with head and neck carcinomas.

With regard to chemotherapy, secondary acute myeloid leukemia is the most frequent hematologic second malignant neoplasm among Hodgkin lymphoma survivors (55). In our study, we found an increased risk for myeloid leukemia among Hodgkin lymphoma survivors (SIR = 33.9, 95% CI = 9.24 to 86.8, based on four cases). MOPP (mechloretamine, vincristine, prednisone, and procarbazine), the standard chemotherapy for Hodgkin lymphoma in the 1970s and the early 1980s, has been linked to increased risk of secondary leukemias, with a plateau 10–14 years after the end of the therapy (23,24). In the early 1980s, treatment procedures shifted from intense to less aggressive radiotherapy and the introduction of less leukemogenic chemotherapy (such as ABVD [adriamycin, bleomycin, vinblastine, and dacarbazine]) (36). Recently, an elevated risk of bladder cancer (SIR = 10.6, 95% CI = 2.7 to 42.3, based on two cases) was found in a cohort of 4834 childhood leukemia survivors (54). An increased risk of bladder cancer in adults has been associated with cyclophosphamide, which is often used to treat non-Hodgkin lymphomas (56,57) and, more rarely, childhood leukemia (58).

In our study, we found that childhood cancer survivors had increased risk for second malignant neoplasms that have been associated with radiotherapy (cancers of the brain, thyroid, skin [nonmelanoma], breast, and head and neck [the tongue and salivary glands in particular]) and chemotherapy (acute nonlymphocytic leukemia and bladder cancer). Although we cannot draw conclusions on the causative role of treatments on second malignancies, the risk pattern that emerges from our study is generally consistent with the late effects of therapies for childhood cancer in use during the study period.

This study allowed a precise and up-to-date estimation of cumulative incidence of second malignant neoplasms after childhood hematolymphopoietic neoplasms. The cumulative incidence of any malignancies for survivors ranged from 2.43% (95% CI = 1.09 to 3.78) 30 years after leukemia to 31.9% (95% CI = 20.1 to 43.7) 45 years after Hodgkin lymphoma. Compared with the general population, survivors of childhood Hodgkin lymphoma had an 11-fold increased risk of having any malignancy in 30 years since the first neoplasm diagnosis. Cumulative incidence of second malignant neoplasms was higher for children who had a leukemia or lymphoma diagnosed after 1980. This phenomenon may be related to the more intensive and aggressive chemotherapies that have been used in more recent years as opposed to less toxic although less effective therapies before 1980.

The data analyzed in this study came from 13 well-established cancer registries and form a large dataset for a population-based study of second malignant neoplasms in childhood cancer survivors. Nevertheless, several possible limitations have to be considered in interpreting our results, including the small number of second malignant neoplasms, the possibility of chance associations due to multiple comparisons, and misclassification due to the unspecialized coding used to classify childhood cancer. However, for the first primary malignancies considered in this work, conversion between ICD-9 and childhood cancer classification is straightforward, and, because second malignant neoplasms may occur several years after the first neoplasm, adult cancer classification may be the appropriate one to use for many of the second malignant neoplasms identified.

In addition, the analysis of lymphoid leukemia data was not possible in our study. Reliable diagnoses of lymphoid leukemia are available starting from the 1970s (59), whereas some of the registries included cases diagnosed as early as 1943. The number of lymphoid leukemias, which generally account for approximately 80% of all leukemias in children, was therefore likely to be underestimated. The analysis of the lymphoid leukemia subgroup, however, yielded risk estimates of second malignant neoplasms that were essentially identical to those for all leukemias but less precise because of the smaller number of events (data not shown).

Sometimes more than one second malignant neoplasm occurs in childhood cancer survivors. In this study, underestimation of the total number of malignancies following a primary neoplasm should therefore be expected because the study design implied that subjects exited from the cohort after the occurrence of one second malignant neoplasm.

The major strength of this population-based study is the size of the cohort, which has provided a unique opportunity to evaluate

both the relative and the absolute risks of second malignant neoplasms for long-term survivors. The geographical heterogeneity of the registries contributing to this study and the high quality of their data make the described pattern of second malignant neoplasm risk for childhood leukemia and lymphoma survivors valid for many areas in the world. Extensive efforts are still needed to collect information on the long-term risk of second cancers in the increasingly large and aging population of childhood cancer survivors. A thorough understanding of the epidemiology of second cancers is essential for developing preventive strategies (60) targeted at individuals who survived childhood cancer.

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Notes

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