

Risk of a Second Malignant Neoplasm Among 5-Year Survivors of Cancer in Childhood and Adolescence in British Columbia, Canada

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Background. We examined second malignancies, a recognized late effect of therapy among survivors of childhood and adolescent cancer, among a recent, population-based cohort of 2,322 5-year survivors diagnosed before 20 years of age in British Columbia (BC), Canada between 1970 and 1995. **Procedure.** Survivors and second malignancies were identified from the BC Cancer Registry. Risk of second malignancy was evaluated using standardized incidence ratios (SIRs), absolute excess risk (AER), and cumulative risk. The effect of demographic, temporal, and disease-related characteristics on risk was assessed. **Results.** Fifty-five second malignancies were observed after 26,071 person-years of follow-up. Relative rate of developing a second malignancy among survivors was 5 times higher than expected (SIR = 5.0, 95% CI, 3.8–6.5), and absolute excess risk was 1.7 deaths per 1,000 person-years. Cumulative incidence of a second malignancy was 5.1% at 25 years after

diagnosis of the first cancer. SIRs and absolute excess risk of subsequent cancer was higher among females (SIR = 5.9, 95% CI, 4.5–8.3 and AER = 2.66). While relative risk of second cancer was higher for those diagnosed before 10 years of age (SIR = 10.6, 95% CI, 7.1–16.0), absolute excess risk was slightly higher for those diagnosed after 10 years of age. SIRs were significantly elevated for all follow-up periods, but absolute excess risk of a second cancer was highest among patients surviving more than 15 years. **Conclusions.** Increased risk of a subsequent neoplasm is evident among childhood cancer survivors diagnosed in more recent periods than has been previously reported, continues years after diagnosis, and varies according to several risk factors. Continued surveillance is essential to quantify and characterize long-term and changing risks for appropriate follow-up. *Pediatr Blood Cancer* 2007;48:453–459. © 2006 Wiley-Liss, Inc.

Key words: childhood and adolescent cancers; late effects; second malignant neoplasm; subsequent cancer; survivorship research

INTRODUCTION

As a result of improvements in therapies for childhood and adolescent cancers in the last several decades, survival rates are increasing. However, those same cancer therapies have been shown to increase risk of a subsequent cancer among survivors [1,2]. Recent published reports suggest that the risk of developing a second malignancy in cohorts of 3- or 5-year survivors is 3 to 15 times greater than the incidence in the general population, and that the cumulative risk varies between 2% and 12% at 20 years after the original diagnosis [1–4]. Early studies of small, homogeneous, clinic-based cohorts with short follow-up periods reported somewhat higher incidence ratios, approaching 20-fold excess risks in comparison to the general population [5]. The Childhood Cancer Survivor Study (CCSS), which followed a large multi-center cohort of childhood cancer patients with selected diagnoses in the US and Canada between 1970 and 1986, reported an SIR of observed-to-expected second cancers of 6.4 [6]. Population-based cohorts from the UK and five Nordic countries have reported SIRs of 6.2 and 3.6 respectively [7,8], but these studies did not examine risk among survivors diagnosed during the 1990s. A population-based cohort that followed patients diagnosed with an original cancer before the age of 25 years through the 1990s reported an SIR of 4.4 for second malignancies [9], whereas a small clinic-based study from Slovenia reported an SIR of 8 [10]. Research also indicates that, while the major determinant of a second cancer is treatment (including

high-dose radiation therapy and certain chemotherapy agents), risk may vary according to the patient's gender, age at diagnosis of the original cancer, and genetic predisposition to cancer [2,3,11]. In order to address second cancer risk, more information is needed among the total population of survivors, with extensive follow-up, and on risks to cohorts diagnosed during different treatment eras.

For this study, we utilized the population-based cancer registry to investigate the risk of developing a second malignant neoplasm (SMN) among a cohort of 5-year childhood cancer survivors originally diagnosed with a

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cancer or tumor before age 20 years in British Columbia (BC), Canada from 1970 to 1995, and followed to end 2000. We also examined risk according to several demographic and disease-related characteristics previously determined to affect second cancer risk.

METHODS

Identification of the Survivor Cohort

The cohort consisted of all BC residents diagnosed before age 20 years between January 1, 1970 and December 31, 1995 with a primary cancer or tumor listed in the International Classification of Childhood Cancers (ICCC) [12], who survived at least 5 years from the time of their diagnosis and were reported to the province-wide BC Cancer Registry. In total, 2,322 patients (1,217 males and 1,105 females) were included for the analysis of second cancers, after additional data from health records identified 32 ineligible cases previously counted as eligible cases from the registry and death records. Birth date, gender, and date of death (if applicable) information was provided from the registry. For each new primary diagnosis, the geographic code of address at diagnosis, date of diagnosis, and morphology and histology coded according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O) [13] was also obtained.

Ascertainment of Death and Follow-Up Information

Both routine and study-specific linkages to death certificates and other provincial files of identifiers were carried out in order to obtain follow-up and death information for the cohort. Follow-up began 5 years after diagnosis of the first cancer and continued to occurrence of a second cancer, December 31, 2000, or death, whichever occurred first. Reports of death registrations from the provincial Vital Statistics Agency (VSA), including date, location, and multiple causes of death, are routinely linked to cancer registry records. In order to capture complete data and ensure complete follow-up of all subjects in the event of name changes and missed routine matches, the cohort records were also linked to VSA files of births and marriages by unique lifetime Personal Health Numbers (available since 1986), and relinked to death files. Any subject not linked to a valid death record was considered to be alive at the end of follow-up.

Identification and Verification of Second Malignant Neoplasms

All second primary cancers diagnosed from 5 years post-diagnosis to December 31, 2000, and classified in ICD-O [13], were identified from the BC Cancer Registry. Cancers diagnosed in the 5 years immediately after the original diagnosis were excluded to minimize the misclassification of

progression or recurrence of the childhood cancer as a second malignancy.

A SMN was defined following ICD-O rules [13] as: (i) a neoplasm in a new location that was not direct spread or metastasis of the primary cancer, or (ii) a neoplasm on the same location as the primary cancer but of different histological type. Non-melanoma skin cancers were excluded, as were cases with ICD-O behavioral code 2 or below. Consequently, premalignant and dysplastic conditions, and benign tumors were excluded. Study staff reviewed diagnostic records to distinguish a SMN from progression or recurrence of the original malignancy. Since it was possible that childhood leukemias could relapse as a histologically distinct lymphoma or sarcoma, any second cancers that had the same cell lineage as the original leukemia were categorized as a recurrence of the original diagnosis.

Statistical Analysis

Overall and diagnosis-specific relative risk of a SMN was calculated using standardized incidence ratios (SIRs). SIRs were computed by dividing the observed number of second malignancies by the expected number in the BC population. The expected number of second cancers was calculated by multiplying the number of person-years at risk by age-, gender-, and calendar period-specific incidence rates in the BC population [14]. Calculation of person-years at risk began 5 years after the original diagnosis and continued until occurrence of a SMN, loss to follow-up, death, or December 31, 2000. Risk was also examined according to several demographic and disease-related characteristics, including gender, age at original diagnosis, diagnosis period, and time from original diagnosis to development of a subsequent malignancy. Each point estimate of risk was compared with the Poisson distribution and was considered significant if its 95% confidence interval did not include one [14].

Absolute excess risk (AER) of a SMN for the entire cohort, and according to several demographic and diagnostic characteristics, was calculated by subtracting the expected number of cases in the general population from those observed in the study cohort, and expressed in relation to the number of person-years at risk [14]. Kaplan–Meier life table procedures were used to estimate the cumulative incidence of a SMN for the cohort [14]. Evaluation of actuarial risks according to several putative risk factors was carried out using a Cox proportional hazards model [14,15]. Annual incidence of a SMN was also calculated for the 5-year survivors, defined as the observed number of cases of SMN divided by the person-years at risk and expressed per 1,000 person-years. All analyses were performed using “R Foundation for Statistical Sciences” (R Development Core Team, Vienna, Austria) and SAS, version 8.2 (SAS Institute, Inc., Cary, NC).

RESULTS

There were 2,322 survivors eligible for inclusion in our study. Characteristics of the study cohort are shown in Table I. Mean age at diagnosis of the first malignancy was 10 (± 6.5) years. During 26,071 person-years of follow-up through December 31, 2000, 55 subsequent cancers occurred, 15 in males and 40 in females. Mean age at diagnosis of a SMN was 27 (± 9.2) years and the mean time from the original diagnosis to development of a SMN was 15 (range, 5.2–29) years.

Overall, relative risk of a SMN in this study was five times higher than expected in the underlying population (SIR = 5.0, 95% CI, 3.8–6.5) (Table II). Increased SIRs for SMN were observed in all diagnostic groups examined except carcinomas, although the number of subsequent cancers was small for all but leukemia (SIR = 4.6, 95% CI, 2.0–11.0), lymphoma (SIR = 6.3, 95% CI, 3.8–11.0), and central nervous system (CNS) tumors (SIR = 5.1, 95% CI, 2.7–9.6).

TABLE I. Characteristics of 5-Year Survivors of Childhood and Adolescent Cancer

Characteristic	Number (%)	
	All survivors (n = 2,322)	Cases with a SMN ^a (n = 55)
Vital status at end of follow-up (alive)	2,143 (92)	33 (60)
Gender		
Male	1,217 (52)	15 (27)
Female	1,105 (48)	40 (73)
Original ICCC ^b diagnosis		
I—Leukemia	471 (20)	5 (9.1)
II—Lymphoma	382 (16)	14 (26)
III—Central nervous system tumors	438 (19)	9 (16)
IV—Sympathetic nervous system tumors	85 (3.7)	3 (5.5)
V—Retinoblastoma	57 (2.5)	2 (3.6)
VI—Renal tumors	125 (5.4)	4 (7.3)
VII—Hepatic tumors	9 (0.4)	1 (1.8)
VIII—Bone tumors	112 (4.8)	8 (15)
IX—Soft tissue sarcomas	146 (6.3)	2 (3.6)
X—Germ cell and other gonadal tumors	167 (7.2)	4 (7.3)
XI—Carcinoma	327 (14)	3 (5.5)
XII—Other unspecified malignant tumors	3 (0.1)	0 (0.0)
Mean age at original diagnosis (years)	10.1 (6.5) ^c	11.7 (5.7) ^c
Mean age at diagnosis of a SMN ^a (years)	N/A ^d	26.7 (9.2) ^c
Mean time from original diagnosis to SMN ^a (years)	N/A ^d	15.0 (6.4) ^c

^aSecond malignant neoplasm.

^bInternational classification of childhood cancers.

^cMean (standard deviation).

^dNot applicable.

The SIR of a SMN was higher for females (SIR = 5.9, 95% CI, 4.3–8.1) than males (SIR = 3.8, 95% CI, 2.4–5.9), and was significantly higher for those originally diagnosed before 10 years of age (SIR = 10.6, 95% CI, 7.1–16.0) than for those diagnosed between 10 and 19 years of age (SIR = 4.0, 95% CI, 2.9–5.7). Furthermore, the relative risk of a SMN was significantly elevated above population levels for survivors in each diagnosis period, from 1970 to 1995, although the number of SMNs was small for the latest group. The SIR for risk of a SMN was highest during the first 5–9 years following the original diagnosis (SIR = 6.7, 95% CI, 4.1–11.0) and decreased with longer duration of follow-up.

The most common second malignancies were breast cancers (10 of 55 or 18%), thyroid cancers (10 of 55 or 18%), and CNS tumors (8 of 55 or 15%) (Table III). Breast cancers occurred more frequently after a diagnosis of lymphoma, whereas CNS tumors more commonly followed an original CNS tumor or leukemia. Thyroid cancer occurred most often following an original diagnosis of lymphoma or CNS tumor.

The proportion of female survivors that developed a SMN was 3.6% compared to 1.2% for males. Breast cancer as a SMN occurred entirely among women, particularly among those that were diagnosed and treated for their original cancer between the ages of 10–19 years. Second CNS tumors were also more common among females (n = 6), particularly for those diagnosed before 10 years of age, and second thyroid cancers occurred predominantly among females (n = 8) (data not shown).

The mean latency between time of original diagnosis and development of a SMN was 15 (range, 5.2–29) years in this survivor cohort (Table I). Generally, the latency period between diagnosis of the first and second new primary was longer for development of solid tumors than for hematopoietic malignancies, bone cancer, and CNS tumors (Table III). Shorter latency periods were observed for survivors who later developed leukemia (7.6 years) and bone cancer (11.2 years). Patients that developed breast cancer as a SMN had the longest latency following diagnosis of their original cancer (20.8 years). Latency did not vary according to the patient's gender, but was somewhat shorter for those diagnosed with a first cancer before 10 years of age.

The cumulative risk of a second malignancy among survivors in this cohort was higher than expected in the general population and increased with the length of time from first diagnosis. Ten years after the initial diagnosis, the cumulative incidence of a SMN was 0.74% among all survivors. At 15, 20, and 25 years after diagnosis, the cumulative incidence increased to 1.6%, 3.0%, and 5.1%, respectively (Fig. 1). There was no significant difference in the cumulative risk of a SMN according to age at time of the original diagnosis or by diagnosis period. However, the cumulative incidence of a SMN was higher among females than males during all periods of follow-up. This difference was most pronounced after 20 years of follow-up; the

TABLE II. Risk of SMN^a and Absolute Excess Risk by Demographic and Disease-Related Factors

Characteristic	Observed number of SMN ^a	Expected number of SMN ^a	SIR ^b	95% CI ^c	AER ^d
All primary diagnoses ^e	55	11.0	5.0	3.8–6.5	1.69
Leukemia	5	1.09	4.6	2.0–11.0	0.88
Lymphomas	14	2.22	6.3	3.8–11.0	2.75
Central nervous system tumors	9	1.76	5.1	2.7–9.6	1.45
Sympathetic nervous system tumors	3	0.19	15.9	5.8–46.0	2.97
Retinoblastoma	2	0.12	16.1	4.9–58.0	2.82
Renal tumors	4	0.35	11.5	4.7–29.0	2.32
Hepatic tumors	1	0.02	42.1	10.0–230.0	13.37
Bone tumors	8	0.51	15.7	8.0–31.0	6.30
Soft tissue sarcoma	2	0.80	2.5	0.8–8.9	0.69
Germ cell/Gonadal tumors	4	1.00	4.0	1.6–10.0	1.62
Carcinomas	3	3.00	1.0	0.4–2.9	0.00
Gender					
Male	15	4.55	3.8	2.4–5.9	0.77
Female	40	6.56	5.9	4.3–8.1	2.66
Age at diagnosis					
<10 years	22	2.08	10.6	7.1–16.0	1.67
10–19 years	33	8.25	4.0	2.9–5.7	1.75
Diagnosis period					
1970–79	34	7.08	4.8	3.4–6.7	2.15
1980–89	19	3.39	5.6	3.6–8.7	1.44
1990–95	2	0.56	3.6	1.1–13.0	0.54
Time since original diagnosis					
5–9 years	15	2.24	6.7	4.1–11.0	1.24
10–14 years	13	2.45	5.3	3.1–9.0	1.45
15+ years	27	6.43	4.2	2.9–6.2	2.42

^aSecond malignant neoplasm.

^bStandardized incidence ratio.

^c95% confidence interval.

^dAbsolute excess risk per 1,000 person-years.

^eDiseases described are the primary cancer diagnosis classified according to the ICCC.

cumulative risk of developing a second primary cancer at 20 years was 4.7% among females compared to only 1.5% among males (data not shown). The annual incidence of a SMN in our study cohort was 2.1 per 1,000 person-years (data not shown). The annual incidence was greatest for those originally diagnosed with bone tumors (6.7 per 1,000 person-years), and was higher for females than males (3.2 per 1,000 person-years vs. 1.1 per 1,000 person-years).

Despite a five-fold relative risk of second malignancies among survivors when compared to the general population, the AER of SMN was only 1.7 cases per 1,000 person-years at risk (Table II). A high AER was found for those originally diagnosed with bone tumors (AER = 6.3 per 1,000 person-years). Other diagnosis-specific AERs remained below 3 cases per 1,000 person-years at risk. The absolute excess risk of SMN among female survivors was much larger than for male survivors (AER = 2.7 per 1,000 person-years vs. AER = 0.8 per 1,000 person-years). In addition, AERs were somewhat greater for those diagnosed before 1980 and for those with a longer duration of follow-up (15+ years).

Conversely, the AER was very similar for patients diagnosed with an original primary malignancy before and after 10 years of age.

DISCUSSION

This study reports on second cancer risk in a geographically defined population of survivors in a recent, population-based cohort with long follow-up. Use of a high-quality cancer registry and health records to identify and verify second cancers resulted in virtually complete and unbiased reporting, avoiding potential selection bias due to lack of participation, loss to follow-up, or differential reporting due to treatment center referral patterns. Follow-up using data linkage reduced differential and non-differential loss of subjects over time.

We examined the risk of second primary cancers in a relatively recent cohort. This allowed for examination of risks and patterns of second cancers for those who had

TABLE III. Number of SMN^a by Diagnosis According to Original Diagnosis Type

ICCC ^b code of original diagnosis (number of cases)	ICDO ^c SMN diagnosis (number of patients)											Total	
	Bone	CNS	Breast	FR organs ^d	Digestive organs	Leukemia	Lung	Lymphoma	Skin	Testis	Thyroid		All other cancers
I (471)	1	2										2	5
II (382)		1	4			1	1	2	1		4		14
III (438)		3	1					1		1	3		9
IV (85)		1									2		3
V (57)		1	1										2
VI (125)	1		1			1		1					4
VII (9)				1									1
VIII (112)	1		2		1	1			1		1	1	8
IX (146)	1											1	2
X (167)	1		1							2			4
XI (327)				1					1			1	3
XII (3)													0
Total (2322)	5	8	10	2	1	3	1	4	3	3	10	5	55
Latency ^e (yrs)	11.2	13.3	20.8	N/A ^f	N/A ^f	7.6	N/A ^f	17.7	12.9	17.2	14.4	13.1	15.0

^aSecond malignant neoplasm.

^bInternational Classification of Childhood Cancers: I—leukemia; II—lymphoma; III—CNS tumors; IV—sympathetic nervous system tumors; V—retinoblastoma; VI—renal tumors; VII—hepatic tumors; VIII—bone tumors; IX—soft tissue sarcoma; X—germ cell and gonadal tumors; XI—carcinomas; XII—other and unspecified malignant tumors.

^cInternational classification of diseases for oncology.

^dFemale reproductive organs (Including ovary, cervix and endometrium).

^eMean latency period from original diagnosis to diagnosis of a second malignant neoplasm (years).

^fMean latency period not reported for ICDO diagnoses with <3 cases.

therapies similar to those for current patients. Furthermore, we only considered second cancers that occurred 5 years or more after the original diagnosis. This restriction minimized the possibility of including recurrent or progressive cancers misclassified as a SMN. Two limitations of this study are the small numbers for some categories of risk, which preclude meaningful examination of some types of cancer diagnoses

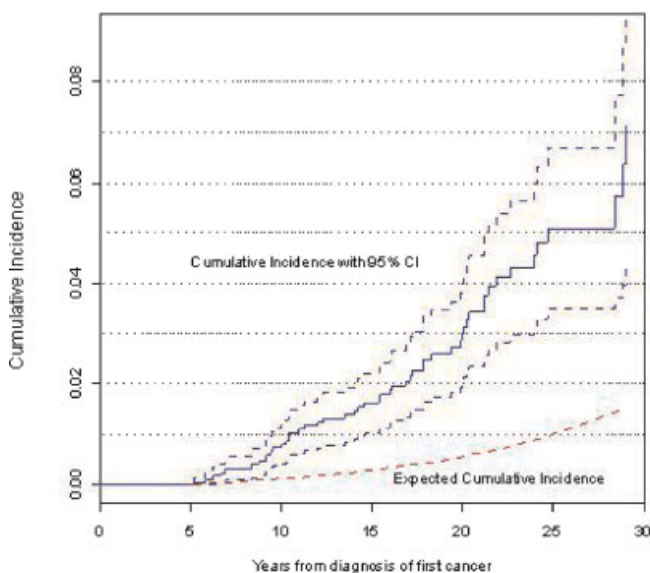


Fig. 1. Cumulative incidence of second malignant neoplasm among 5-year survivors of childhood and adolescent cancer.

and SMNs, and the lack of information on treatment which is a major risk factor for SMNs.

Overall, our cohort exhibited a statistically significant five-fold relative risk of SMN compared with the incidence in the BC population, and an AER of 1.7 per 1,000 person-years. Our results are comparable to those reported in other population-based cohorts, such as the UK's Childhood Cancer Research Group (CCRG) [7] who reported an SIR of SMN in 3-year survivors of 6.2, the Nordic countries study [8] which reported an SIR of SMN from diagnosis of 3.6, and the UK study from the Northern Region Young Person Malignant Disease Registry (NRYPMDR) [9] that reported an SIR of second malignancy of 4.4. Studies of cohorts identified from treatment centres have reported somewhat higher relative risks of SMN, with SIRs ranging from 8.7 to 21.4 [10,16–18]. The large multi-centre CCSS study of 5-year survivors recently reported an overall SIR of 4.3 [19]. Most of this excess risk relative to the background population is probably due to the effects of therapy for the first cancer (radiation and/or chemotherapy), but genetic predisposition and other environmental exposures may also be factors. Differences in the size, time period and composition of survivor cohorts, and in follow-up methodologies most likely accounted for the variation in SIR estimates reported to date.

The SIR of a second malignancy in our cohort was significantly elevated for all categories of initial diagnosis except carcinomas, and incidence ratios varied according to the original cancer diagnosis, although reliability of risk

estimates were affected in some categories due to small numbers. The highest relative risk of SMN was found for patients originally diagnosed with bone tumors (SIR = 15.7). Similarly, a high AER was observed for patients originally diagnosed with bone tumors (AER = 6.3). A cohort of French and British children reported increased SIR for second malignancies among survivors originally diagnosed with retinoblastoma during childhood [17], which may be linked to an increased genetic susceptibility following heritable retinoblastoma [2,3,5]. The US CCSS, the UK CCRG, and the UK NRYPMR cohorts observed that the highest relative risk of a SMN was after a diagnosis of Hodgkin disease (SIRs ranging from 7.3 to 9.7) [6,7,9].

Female survivors in our cohort were at a greater absolute and relative risk for SMN than that observed for males. Female gender was also associated with an increased SIR in the CCSS study [6] which reported that women were 64% more likely to experience a second cancer than men. These findings may be attributable to cases of secondary breast cancer experienced among women but not men. The US CCSS has also shown that the relative risk of secondary breast cancers may be increased following treatment with chest radiation therapy [20].

Younger age at diagnosis of the original cancer or tumor has been associated with an increased relative risk (SIR) of second primary cancers [6–9,21], as was also observed in our study. This pattern is typical in the development of radiation-associated second cancers [3,6,8,11,21]. For example, Garwicz et al. [21] found that the SIR of a SMN after radiotherapy was highest for children diagnosed and treated before the age of 5 years. Similarly, Neglia et al. [6] found that younger age at initial radiation treatment was an independent risk factor for second CNS malignancies. However, the absolute excess risk of a SMN in our cohort was similar for those diagnosed between 10–19 years of age (AER = 1.8) and those diagnosed younger (AER = 1.7). This difference between relative and absolute risk of SMNs reflects the higher background cancer rate with increasing age in the general population [15]. Our results are similar to recent findings from the CCSS that indicate that age at diagnosis is not significantly associated with an increased risk of breast cancer [20].

Relative risk of a SMN decreased with time since first cancer diagnosis, as supported by findings from earlier studies [6–8,10,17]. The CCSS noted that almost 50% of second primary cancers occurred within 15 years of the original childhood cancer diagnosis [6], while Jenkinson et al. [7] found that the relative risk of SMN was greatest during the first 3–9 years after diagnosis of the original cancer. It is expected that the relative risk of a SMN would decrease over time because the background incidence of cancer in the general (comparative) population increases with age. However, the AER of a SMN increased with time from original diagnosis in our cohort. At more than 15 years after the original diagnosis, patients' absolute excess risk of

developing a SMN was almost two times higher than during the first 10 years after diagnosis.

We found no clear effect of diagnosis period on the standardized incidence of a SMN, as also observed previously [6,7,9]. However, the absolute risk of developing a SMN decreased over time, being highest for patients diagnosed from 1970 to 1979. Olsen et al. [8] also found that risk varied according to the time of diagnosis and treatment of the original cancer; however, their cohort was diagnosed in an earlier period (1943–1987).

We observed a 15-year mean latency between diagnosis of the initial cancer and diagnosis of a SMN, with a shorter latency to development of a second primary leukemia than for non-hematopoietic or solid second malignancies. Our diagnosis-specific mean latencies were longer than those reported previously [6,10,16,17,21], which may be due to the exclusion of secondary leukemias that occurred prior to 5 years from diagnosis, or reflect differences in our study cohort, including the heterogeneity of survivors according to their original cancer diagnosis, and the definition of “period at risk” for a SMN.

The cumulative incidence of SMN in our study was 3.0% at 20 years and 5.1% at 25 years after diagnosis, which is comparable to the CCSS and the CCRG survivor cohorts that reported actuarial risks of 3.2% and 3.1% at 20 years after diagnosis, and 4.7% and 4.2% at 25 years after diagnosis, respectively [6,7]. The Nordic countries study observed the same trend, although they reported slightly lower actuarial risks at each follow-up period [8]. Conversely, the population-based UK cohort found that the cumulative probability of second malignancy was 8.9% by 30 years following initial diagnosis [9], but this finding may be due to the inclusion of survivors aged 20–24 years who have a higher probability of second malignancy than those diagnosed in childhood [9].

In conclusion, our study results are consistent with other recent cohort studies, suggesting that the registry-based record linkage methodology is sufficiently robust to provide reliable risk estimates. We extend knowledge gained from earlier cohorts and selected diagnostic groups to show that excess risk of second cancer persists many years after diagnosis, and occurs even among more recently diagnosed survivors of a cancer or tumor. Overall, the evidence for continued excess risk highlights the need for further monitoring of second cancers, in order to identify high-risk groups for follow-up care, and for further research to mitigate second cancer risk in this population.

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REFERENCES

1. Hewitt M, Weiner SL, Simone JV, editors. Childhood cancer survivorship: improving care and quality of life. Washington, DC: National Academic Press; 2003. 224p.
2. Green DM. Late effects of treatment for cancer during childhood and adolescence. *Curr Probl Cancer* 2003;27:127–142.
3. Bhatia S, Sklar C. Second cancers in survivors of childhood cancer. *Nat Rev Cancer* 2002;2:124–132.
4. Robison LL. Survivors of childhood cancer and risk of a second tumor. *J Natl Cancer Inst* 1993;85:1102–1103.
5. Robison LL, Mertens A. Second tumors after treatment of childhood malignancies. *Hematol/Oncol Clin North America* 1993;7:401–415.
6. Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: Childhood cancer survivor study. *J Natl Cancer Inst* 2001;93:618–629.
7. Jenkinson HC, Hawkins MM, Stiller CA, et al. Long-term population-based risks of second malignant neoplasms after childhood cancer in Britain. *Br J Cancer* 2004;91:1905–1910.
8. Olsen J, Garwicz S, Hertz H, et al. Second malignant neoplasms after cancer in childhood or adolescence. *BMJ* 1993;307:1030–1036.
9. Hammal DM, Bell CL, Craft AW, et al. Second primary tumors in children and young adults in the North of England (1968–99). *Pediatr Blood Cancer* 2005;45:155–161.
10. Jazbec J, Ecimovic P, Jereb B. Second neoplasms after treatment of childhood cancer in Slovenia. *Pediatr Blood Cancer* 2004;42:574–581.
11. Schwartz CL. Long-term survivors of childhood cancer: The late effects of therapy. *The Oncologist* 1999;4:45–54.
12. Kramarova E, Stiller CA, Ferlay J, et al., editors. International classification of childhood cancer. Lyon, France: International Agency for Research on Cancer; 1996. (IARC Technical Report No. 29).
13. Fritz A, Percy C, Jack A, et al., editors. International Classification of Diseases for Oncology, 3rd edn. Geneva, Switzerland: World Health Organization; 2000.
14. Breslow NE, Day NE. Statistical Methods in Cancer Research: The Design and Analysis of Cohort Studies. Lyon, France: International Agency for Research on Cancer; 1987. (IARC Scientific Publications No. 82).
15. Yasui Y, Liu Y, Neglia JP, et al. A methodological issue in the analysis of second-primary cancer incidence in long-term survivors of childhood cancer. *Am J Epidemiol* 2003;158:1108–1113.
16. de Vathaire F, Schweisguth O, Rodary C, et al. Long-term risk of second malignant neoplasm after a cancer in childhood. *Br J Cancer* 1989;59:448–452.
17. de Vathaire F, Hawkins M, Campbell S, et al. Second malignant neoplasms after a first cancer in childhood: Temporal pattern of risk according to type of treatment. *Br J Cancer* 1999;79:1884–1893.
18. Li FP, Cassady JR, Jaffe N. Risk of second tumors in survivors of childhood cancer. *Cancer* 1975;35:1230–1235.
19. Friedman DL, Whitton J, Yasui Y, et al. Risk of second malignant neoplasms 15 years after childhood cancer: The updated experience of the Childhood Cancer Survivor Study (CCSS). American Society of Clinical Oncology: Annual Meeting 2004. New Orleans, LA: June 5–8, 2004.
20. Kenney LB, Yasui Y, Inskip PD, et al. Breast cancer after childhood cancer: A report from the childhood cancer survivor study. *Ann Intern Med* 2004;141:590–597.
21. Garwicz S, Anderson H, Olsen J, et al. Second malignant neoplasms after cancer in childhood and adolescence: A population-based case-control study in the 5 Nordic countries. *Int J Cancer* 2000;88:672–678.