Research Article

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Subsequent Malignant Neoplasms in a Population-Based Cohort of Pediatric Cancer Patients: A Focus on the First 5 Years

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Abstract

Background: The purpose was to describe the development of subsequent malignant neoplasms (SMN) among a population-based cohort of pediatric cancer patients, with a focus on SMNs that occurred within the first 5 years from diagnosis.

Methods: The cohort was identified from POGONIS, an active provincial registry. Cohort members were Ontario residents ages 0 to 14.9 years at primary diagnosis between January 1985 and December 2008. SMNs that developed <18 years were captured by POGONIS, whereas SMNs diagnosed later were identified through linkage. Cumulative incidence and standardized incidence ratios (SIR) were calculated, and proportional hazards models were estimated to examine factors associated with SMN development.

Results: A total of 7,920 patients were eligible. 2.4% (188/7,920) developed 197 SMNs. Mean follow-up time was 10.7 years (SD = 7.6 years; range, 0.0–26.4 years) with mean time to SMN of 8.5 years (SD = 6.3 years; range, 0.0–24.9 years). The SIR for the development of a SMN was 9.9 [95% confidence interval (CI), 8.6–11.4]. 40.6% of SMNs (80/197) developed within 5 years. Early SMNs were more likely to be leukemia and lymphoma. Factors associated with early SMN were primary diagnosis of a bone tumor (OR, 4.88; 95% CI, 1.52–15.60), exposure to radiotherapy (OR, 1.82; 95% CI, 1.02–3.22), and the highest dose of epipodophyllotoxin (OR, 3.74; 95% CI, 1.88–7.42).

Conclusions: Over 40% of SMNs diagnosed in childhood cancer patients occurred in the first 5 years after diagnosis, suggesting a need for early and ongoing surveillance.

Impact: The early development of certain SMNs reinforces the need for early and continued surveillance at all stages for pediatric cancer patients. *Cancer Epidemiol Biomarkers Prev; 24(10); 1585–92. ©2015 AACR.*

Introduction

Over the last 30 years, survival among children diagnosed with cancer has risen dramatically, from 5-year survival rates below 60% in 1975 to rates exceeding 80% today (1). Consequently, the size of the childhood cancer survivor population has expanded. It is estimated that there are over 400,000 survivors (0.11% of the population) in the United States, of whom 24% have survived more than 30 years (2). Although better risk stratification at diagnosis has made it possible to reduce treatment intensity for a proportion of childhood cancers, much of the improvement in survival has been achieved by intensifying therapy for high-risk patients using combinations of surgery, chemotherapy, radiotherapy, and hematopoietic stem cell transplantation (3). In particular, chemotherapy intensity has been escalated for some patients as a result of availability of better supportive care (3, 4). Improvements in survival as a result of intensified treatment place childhood cancer survivors at risk for long-term adverse outcomes.

Childhood cancer survivors have been shown to have elevated risks for the development of diverse chronic physical health conditions (collectively known as "late effects"; refs. 5–7). Among the most consequential late effect is the development of subsequent malignant neoplasms (SMN), which can cause serious morbidity and premature mortality. Although several cohort studies exist that examine the development of SMNs among pediatric cancer patients, most only consider SMNs that develop 5 years or more from the primary diagnosis. This exclusion criterion can lead to an underestimate of the true incidence of SMN development in this population.

The Childhood Cancer Survivor Study (CCSS), a large North American cohort of 14,359 survivors diagnosed between 1970 and 1986 established from eligible and consenting cancer survivors from various participating institutions, reported on 1,402 5-year survivors who developed a total of 2,703 SMNs (8). This represents a 30-year cumulative incidence of 7.9% and a standardized incidence ratios (SIR) of 6.0 [95% confidence interval (CI), 5.5–6.4; ref. 8]. Two additional cohort studies of 5-year survivors compared the incidence of SMNs in childhood cancer survivors with the expected cancer incidence in the age-, sex-, and calendar year–matched general population. In a British population-based cohort of 16,541 survivors, diagnosed between 1926 and 1987, the SIR was 6.2 (95% CI, 5.5–7.1; ref. 9), whereas in a smaller population-based cohort of 2,322 survivors from the Canadian province of British Columbia diagnosed between 1970 and 1995, the SIR was 5.0 (95% CI, 3.8–6.5; ref. 10).

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In a Nordic population-based cohort of 47,697 pediatric cancer patients diagnosed between 1943 and 2005, a total of 1,180 SMNs developed in 1,088 patients (11). Unlike the three studies above, this study did not restrict eligibility to 5-year survivors. The overall SIR was 3.3 (95% CI, 3.1–3.5), but this was likely attenuated by follow-up that extended to the age of 79. The SIR for follow-up to age 29 was 7.8 (95% CI, 5.8–8.4); however, many members of the cohort were treated in the era prior to the widespread use of chemotherapy, limiting generalizability of the findings.

Much of the excess risk for SMN development has been linked to specific treatment modalities, in particular radiation therapy and certain classes of chemotherapy such as alkylating agents and epipodophyllotoxins (5, 12–14). Other demonstrated determinants of risk include gender, age at diagnosis of the primary pediatric cancer, and genetic predisposition (6, 10, 15). Cohorts that restrict participants to those that have survived at least 5-years from the primary diagnosis systematically exclude early onset SMNs, particularly acute myeloid leukemia which often occurs in the first several years following therapy (15, 16).

The primary purpose of this study was to describe the development of SMNs among a population-based cohort of pediatric cancer patients, with a focus on those SMNs that occurred within the first 5-years after primary diagnosis. Further, it aimed to quantify the impact of demographic and disease and treatment-related characteristics on the risk for developing a SMN.

Materials and Methods

Patients

The cohort was identified from the Pediatric Oncology Group of Ontario Networked Information System (POGONIS) database, an active provincial registry administered by the Pediatric Oncology Group of Ontario (POGO). POGONIS has collected detailed information for all cases of childhood cancer in Ontario, including demographic, diagnostic and key treatment information, and patient outcomes since 1985. The eligible cohort of patients consisted of all children who were residents of Ontario and ages 0 to 14.9 years at the time of a primary cancer diagnosis between January 1st, 1985, and December 31st, 2008, and who were diagnosed and/or treated at one of five tertiary pediatric oncology centers in the province. POGONIS captures 98% of the incident cancer cases in Ontario diagnosed in the 0 to 14.9-year age range (17).

SMNs that developed prior to age 18 years and which were diagnosed and/or treated at one of the five tertiary pediatric oncology centers were captured by POGONIS. SMNs that were diagnosed outside of a tertiary pediatric center, often in late adolescence or adulthood (aged $\geq$15 years), were identified through record linkage with the Ontario Cancer Registry (OCR). The OCR is a legally mandated cancer registry that requires all Ontario hospitals to submit pathology reports, electronic patient records, electronic hospital discharge records, and electronic reports of deaths for both adults and children with any mention of cancer (18, 19). All SMNs identified in OCR were manually reviewed by two experienced pediatric oncologists (M.L. Greenberg and P.C. Nathan), a senior oncology nurse, and a cancer epidemiologist (J.D. Pole) to confirm that these were true incident cases of SMN.

Diagnostic classification

Diagnoses with an International Classification of Diseases of Oncology, Third Edition, First Revision behavior code of 0 or benign were not considered (20). Diagnoses were classified into 20 groups as outlined in Table 1. The "other leukemia" group includes acute undifferentiated leukemia, chronic leukemia (including juvenile and adult chronic myeloid), acute leukemia with a mixed lineage, and myelodysplastic syndrome. The not elsewhere specified group includes largely malignant melanoma, thyroid carcinoma, malignant carcinoid tumors, and aggressive fibromatosis. Diagnoses were categorized into broader groups for the models given the small number of events in many subgroups.

Treatment information

All treatment-related information for the primary cancer diagnosis was obtained from POGONIS. We captured each chemotherapy agent received as well as cumulative doses of alkylating agents, anthracyclines, epipodophyllotoxins, and platinum agents. All anthracycline doses were converted to doxorubicin equivalents using factors of 0.83, 0.67, 5.0, and 4.0 for daunorubicin, epirubicin, idarubicin, and mitoxantrone, respectively (21). Alkylators were converted to a cyclophosphamide equivalent dose using the methods of Green and colleagues and were categorized into a 4-level variable based on total dose: 0, >0–<4,000, $\geq$4,000–<8,000, $\geq$ 8,000 (22). Dose scores for anthracyclines, epipodophyllotoxins, and platinum agents were determined following the methods proposed by Tucker and colleagues (23) and modified by Friedman and colleagues (8) where the total dose for each agent within a chemotherapy class was determined for each patient and then the tertile for each agent was generated from these distributions where 0 represented no exposure to that agent and 1, 2, and 3 represented the lower, middle, and upper range of the distribution. The tertile scores were then summed for all agents within a given class, and tertiles of these summed scores were used as the final score. Treatment eras were selected such that each was roughly the same amount of time (5 years except for the last period which was 4 years). Radiotherapy and surgery were modeled as a dichotomous variable indicating any receipt. Hematopoietic stem cell transplantation (HSCT) was modeled as a 4-level categorical variable, indicating no HSCT, autologous HSCT, allogeneic-related HSCT, and allogeneic-unrelated HSCT.

Statistical analysis

All statistical analyses were performed using SAS 9.2. The number of person-years at risk was calculated for the entire cohort as the time from the date of primary diagnosis until the earliest of the first SMN diagnosis, death, or the end of the follow-up period (June 30, 2011). A cumulative incidence curve for the development of SMN was generated where death was treated as a competing risk. The CUMINCID macro from the SAS autocall library was utilized to create this curve.

SIRs were calculated by calculating the ratio of the observed number of SMN to the expected incident cancers, derived from age- and sex-specific Ontario population cancer incidence data from Statistics Canada (24, 25). Given the cancer incidence data from Statistics Canada do not include nonmelanoma skin cancers, these cancers were not included in the observed SMN counts used to calculate SIRs.

A series of models that examined factors associated with the development of an SMN were developed using a proportional hazards approach utilizing the person-years at risk described above. Three models were developed: the first examined all SMNs, the second examined SMN that occurred in the first 60 months

Table 1. Demographics for patients 0 to 14 years old who were diagnosed with cancer between 1985 and 2008 in Ontario, stratified by SMN

		SMN		
	Overall cohort	No	Yes	
Characteristic	***n* (%)**	***n* (%)**	***n* (%)**	***P***
Total	7,920 (100.0)	7,732 (100.0)	188 (100.0)	
Age at primary diagnosis (years)				0.32
Mean (SD)	5.8 (4.5)	5.8 (4.4)	6.2 (4.8)	
0–4	3,770 (47.6)	3,681 (47.6)	89 (47.3)	
5–9	2,106 (26.6)	2,061 (26.7)	45 (23.9)	
10–14	2,044 (25.8)	1,990 (25.7)	54 (28.7)	
Sex				0.29
Female	3,589 (45.3)	3,511 (45.4)	78 (41.5)	
Male	4,331 (54.7)	4,221 (54.6)	110 (58.5)	
Primary cancer diagnosis				0.00
Leukemia	2,428 (30.7)	2,381 (30.8)	47 (25.0)	
Acute lymphoblastic	1,944 (24.5)	1,907 (24.7)	37 (19.7)	
Acute myeloid	363 (4.6)	358 (4.6)	5 (2.7)	
Other	121 (1.5)	116 (1.5)	5 (2.7)	
Lymphoma and reticuloendothelial	1,044 (13.2)	1,009 (13.0)	35 (18.6)	
Hodgkin lymphoma	317 (4.0)	298 (3.9)	19 (10.1)	
Non-Hodgkin lymphoma	437 (5.5)	424 (5.5)	13 (6.9)	
Other	290 (3.7)	287 (3.7)	3 (1.6)	
CNS	1,897 (24.0)	1,855 (24.0)	42 (22.3)	
Astrocytoma	706 (8.9)	694 (9.0)	12 (6.4)	
Medulloblastoma	316 (4.0)	307 (4.0)	9 (4.8)	
Other CNS	875 (11.0)	854 (11.0)	21 (11.2)	
Sympathetic nervous system	748 (9.4)	733 (9.5)	15 (8.0)	
Neuroblastoma	542 (6.8)	529 (6.8)	13 (6.9)	
Retinoblastoma	205 (2.6)	203 (2.6)	2 (1.1)	
Other	1 (0.0)	1 (0.0)	0 (0.0)	
Kidney tumors	446 (5.6)	442 (5.7)	4 (2.1)	
Liver tumors	117 (1.5)	115 (1.5)	2 (1.1)	
Bone tumors	332 (4.2)	315 (4.1)	17 (9.0)	
Osteosarcoma	165 (2.1)	158 (2.0)	7 (3.7)	
Ewing	159 (2.0)	150 (1.9)	9 (4.8)	
Other	8 (0.1)	7 (0.1)	1 (0.5)	
Germ cell tumors	171 (2.2)	164 (2.1)	7 (3.7)	
Soft tissue sarcoma	418 (5.3)	406 (5.3)	12 (6.4)	
Not elsewhere specified	319 (4.0)	312 (4.0)	7 (3.7)	
Childhood cancer therapy				
Surgery (yes/no)	3,988 (50.4)	3,892 (50.3)	96 (51.1)	0.84
Radiation therapy (yes/no)	2,720 (34.3)	2,618 (33.9)	102 (54.3)	0.00
Chemotherapy therapy (yes/no)	5,715 (72.2)	5,553 (71.8)	162 (86.2)	0.00
HSCT (yes/no)	780 (9.8)	732 (9.5)	48 (25.5)	0.00
Vital status				0.00
Alive	6,070 (76.6)	5,958 (77.1)	112 (59.6)	
Deceased	1,850 (23.4)	1,774 (22.9)	76 (40.4)	

(five years) after the primary diagnosis, and the third examined SMN that occurred 60 months or more from the primary diagnosis.

Results

There were 7,920 patients diagnosed with cancer prior to age 15 years in Ontario between 1985 and 2008 who were treated at a pediatric tertiary care center (Table 1). Of these patients, 2.4% (188/7,920) developed a total of 197 SMN. The mean follow-up time was 10.7 years (SD = 7.6 years; range, 0.0–26.4 years) with the mean time to development of an SMN of 8.5 years (SD = 6.3 years; median, 7.3; range, 0.0–24.9 years). Patients who experienced an SMN were nearly twice as likely to die compared with those who did not experience an SMN (40.4% vs. 22.9%, $P < 0.01$). The SIR for the development of an SMN was 9.9 (95% CI, 8.6–11.4; Table 2).

There were no differences by age at primary diagnosis ($P = 0.32$) or sex ($P = 0.29$) between those who did or did not develop an SMN (Table 1). Differences in the development of SMNs by primary diagnosis were significant ($P < 0.01$; Table 1) with increased SIRs for patients with a primary diagnosis of leukemia other than acute lymphoblastic leukemia or acute myeloid leukemia (SIR, 20.2; 95% CI, 6.4–41.7; in this group of 121 patients, 22 patients were diagnosed with primary myelodysplastic syndrome and only two went on to develop a SMN), Hodgkin lymphoma (SIR, 15.7; 95% CI, 9.4–23.5), medulloblastoma (SIR, 16.8; 95% CI, 7.2–30.4), neuroblastoma (SIR, 15.1; 95% CI, 8.0–24.4), bone tumors (SIR, 18.3; 95% CI, 10.6–28.1), and germ cell tumors (SIR, 15.6; 95% CI, 6.2–29.2; Table 2).

The SMNs that developed were predominantly leukemia (23.9%), other tumors not elsewhere specified (25.9%, 27/51 were thyroid carcinoma), CNS tumors (21.3%), and lymphoma and reticuloendothelial cancers (9.6%; Table 3).

The complete distribution of SMN type by primary diagnosis is not shown. But of the 38 SMNs that developed among primary acute lymphoblastic leukemia patients, 18.4% (7/38) were acute

Table 2. SIR for second malignant neoplasm by primary cancer diagnosis

Primary cancer diagnosis			Time to SMN (years)	
Type	**Total**	**SIR (95% CI)**	**Mean (SD)**	**Median (range[a])**
Total for all cancers	7,920	9.9 (8.6–11.4)	8.6 (6.0)	7.3 (0.0–24.9)
Leukemia	2,428	8.4 (6.1–10.9)	8.9 (6.2)	8.3 (0.3–22.7)
Acute lymphoblastic	1,944	7.7 (5.4–10.4)	9.1 (6.2)	8.3 (0.3–22.7)
Acute myeloid	363	8.6 (2.7–17.7)	10.8 (6.2)	10.8 (2.2–17.5)
Other	121	20.2 (6.4–41.7)	5.4 (6.3)	3.5 (0.6–16.3)
Lymphoma and reticuloendothelial	1,044	11.3 (7.8–15.3)	10.0 (7.0)	11.6 (0.0–23.8)
Hodgkin lymphoma	317	15.7 (9.4–23.5)	12.6 (6.1)	12.6 (2.1–23.8)
Non-Hodgkin lymphoma	437	12.1 (6.4–19.6)	7.6 (7.4)	3.0 (1.2–21.2)
Other	290	3.6 (0.7–8.9)	3.8 (3.6)	4.2 (0.0–7.1)
CNS	1,897	9.6 (6.9–12.7)	8.7 (5.2)	8.9 (0.3–20.3)
Astrocytoma	706	6.1 (3.1–10.0)	11.0 (5.5)	11.5 (1.6–20.3)
Medulloblastoma	316	16.8 (7.2–30.4)	5.4 (4.4)	3.9 (1.5–14.8)
Other CNS	875	11.4 (7.1–16.9)	8.5 (4.7)	9.2 (0.3–18.8)
Sympathetic nervous system	748	11.2 6.3–17.6)	8.4 (5.7)	5.6 (1.3–18.2)
Neuroblastoma	542	15.1 (8.0–24.4)	9.0 (5.9)	6.2 (1.3–18.2)
Retinoblastoma	205	4.2 (0.4–12.1)	4.2 (1.1)	4.2 (3.4–4.9)
Other	1	0.0		
Kidney tumors	446	3.6 (0.9–8.0)	13.2 (7.4)	15.0 (2.7–20.0)
Liver tumors	117	10.4 (1.0–29.7)	3.3 (0.8)	3.3 (2.7–3.8)
Bone tumors	332	18.3 (10.6–28.1)	8.1 (8.0)	4.2 (1.2–24.9)
Osteosarcoma	165	13.8 (5.5–25.9)	7.6 (10.1)	2.3 (1.2–24.9)
Ewing	159	22.0 (10.0–38.7)	8.5 (7.3)	4.2 (1.7–21.8)
Other	8	97.6 (0.0–382.7)	8.8	8.8 (8.8–8.8)
Germ cell tumors	171	15.6 (6.2–29.2)	3.0 (4.1)	1.8 (0.2–12.0)
Soft tissue sarcoma	418	11.7 (6.0–19.3)	7.5 (6.6)	5.8 (0.2–24.5)
Not elsewhere specified	319	9.6 (3.8–18.0)	6.5 (5.3)	4.9 (0.0–13.3)

[a]Some malignances are identified less than 36 days apart (0.1 of a year) and hence the time to develop SMN is shown. Subsequent development of basal cell or squamous cell skin cancers was not included in the SIR calculations.

myeloid leukemia, 26.3% (10/38) were CNS tumors, and 28.9% (11/38) were other tumors comprised mainly of thyroid carcinoma (6/11). Of the 6 SMNs that developed among primary acute myeloid leukemia patients, 50.0% (3/6) were other tumors (two thyroid carcinoma and a basal cell carcinoma). Of the 20 SMNs that developed among primary Hodgkin patients, 45.0% (9/20) were other tumors comprised mainly of thyroid carcinoma ($n = 3$) and carcinoma of the breast ($n = 3$). Of the 43 SMNs that developed among primary CNS tumor patients, 41.8% (18/43) developed another CNS tumor. Of the 17 SMNs

Table 3. SMN for patients diagnosed with a primary neoplasm between 0 to 14 years of age and 1985–2008 in Ontario, overall and within 5 years of primary diagnosis

	Total SMN		SMN within 5 years		
	N	**Col %**	***N***	**Col %**	**Row %**
SMN	197	100.0	80	100.0	40.6
Leukemia	47	23.9	41	51.3	87.2
Acute lymphoblastic	7	3.6	6	7.5	85.7
Acute myeloid	26	13.2	23	28.8	88.5
Other	14	7.1	12	15.0	85.7
Lymphoma and reticuloendothelial	19	9.6	12	15.0	63.2
Hodgkin lymphoma	2	1.0	2	2.5	100.0
Non-Hodgkin lymphoma	15	7.6	8	10.0	53.3
Other	2	1.0	2	2.5	100.0
CNS	42	21.3	6	7.5	14.3
Astrocytoma	11	5.6	1	1.3	9.1
Medulloblastoma	4	2.0	0	0.0	0.0
Other CNS	27	13.7	5	6.3	18.5
Sympathetic nervous system	3	1.5	3	3.8	100.0
Neuroblastoma	1	0.5	1	1.3	100.0
Retinoblastoma	2	1.0	2	2.5	100.0
Other	0	0.0	0	0.0	
Kidney tumors	6	3.0	2	2.5	33.3
Liver tumors	0	0.0	0	0.0	
Bone tumors	8	4.1	3	3.8	37.5
Osteosarcoma	8	4.1	3	3.8	37.5
Ewing	0	0.0	0	0.0	
Other	0	0.0	0	0.0	
Germ cell tumors	3	1.5	1	1.3	33.3
Soft tissue sarcoma	18	9.1	6	7.5	33.3
Not elsewhere specified	51	25.9	6	7.5	11.8
Thyroid carcinoma	27	13.7	2	2.5	7.4

that developed among primary bone tumor patients, 41.2% (7/17) developed acute myeloid leukemia.

Overall, 40.6% of SMNs (80/197) developed within the first 5 years from the primary diagnosis. Early SMNs were more likely to be leukemia, lymphoma, or sympathetic nervous system tumors, with 87.2%, 63.2%, and 100.0% of these SMN cases developing prior to 5 years, respectively. However, 33.8% of the SMNs developing before 5 years (27/80) were solid tumors, and those 27 cases constituted 20.6% of all solid tumor SMNs.

At 5, 10, and 15 years from the primary diagnosis, the cumulative incidence of an SMN was 1.0% (95% CI, 0.8–1.3), 1.6% (95% CI, 1.4–2.0), and 2.6% (95% CI, 2.2–3.1), respectively (Fig. 1). Among cohort members who did not develop an SMN, 23.4% died during follow-up, whereas among those who did develop an SMN 41.6% died. Among those cohort members who experienced an early SMN, 56.3% died during follow-up, whereas among those who developed a late SMN only 30.5% died with both groups having similar follow-up times after the diagnosis of the SMN (4.2 compared with 4.0 years, respectively).

Table 4 presents the three models that examine factors associated with the development of all SMN, early SMN, and late SMN. Factors significantly associated with an early SMN were primary diagnosis of a bone tumor compared with leukemia, exposure to the highest dose level of epipodophyllotoxin agents, and receipt of radiotherapy. Factors significantly associated with a late SMN were younger age at primary diagnosis, primary diagnosis of a central nervous system (CNS) tumor or bone tumor compared to leukemia, receipt of radiotherapy, and receipt of either a related or unrelated allogeneic HSCT.

Discussion

This study reports on the development of SMN in a geographically defined population of survivors of childhood cancer. The use of an active pediatric-specific cancer registry along with linkage to a passive adult cancer registry to identify and verify subsequent cancers results in virtually complete and unbiased reporting of malignancies, in contrast with ascertaining SMN from patient self-report (16). Further, this study captured SMNs that develop in the first 5 years after the primary cancer diagnosis, a time period that is infrequently reported in the literature as many survivor cohorts have only included 5-year survivors (9, 10, 16, 26). The methodology employed in this study avoids potential selection bias due to lack of participation and loss to follow-up. Although follow-up duration is not as long as other studies, this study provides an examination of a contemporary treatment period and allows for an exploration of the relationship between various current treatment exposures and the development of SMNs.

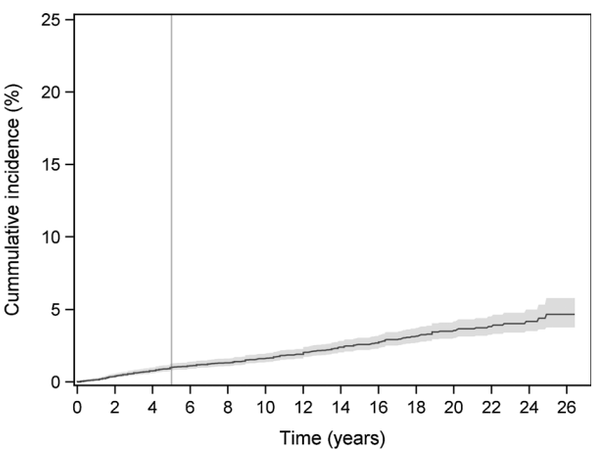

Figure 1.
Cumulative incidence of second malignant neoplasm (SMN) and corresponding 95% CI for patients 0 to 14 years old who were diagnosed between 1985 and 2008 in Ontario.

In this population-based study, 2.4% of the patients developed an SMN with a mean follow-up of 10.7 years. Nearly half (41%) of the SMNs occurred within 5 years of the primary diagnosis. The cumulative incidence of SMN at 15 years was 2.6%. If events that occurred prior to 5 years were excluded (to establish a cohort of 5-year survivors), the predicted cumulative incidence of SMN at 15 years is 2.0%. This restricted cumulative incidence of SMN at 15 years is comparable with that in much of the published literature, which ranges from 1.6% to 2.1% (9, 10, 15, 16, 26). Including events that occur prior to 5 years of survival raises the cumulative incidence by 0.6%, suggesting that many studies underestimate the true risk for developing an SMN in patients newly diagnosed with a first cancer.

Interestingly, the estimates from this cohort, with patients who were treated with contemporary regimes, demonstrate similar cumulative incidence to studies examining patients treated from 1926 to 1986. Although risk stratification has reduced the overall intensity of therapy received over time for some children, advances in supportive care and improvements in therapy have translated into increased survival for high-risk patients. These high-risk survivors might be at incremental risk of developing late effects such as SMNs and hence no radical difference in SMN cumulative incidence is noted across treatment era.

After expert review of each potential SMN to prevent the misclassification of recurrent or progressive cancer, this study demonstrated that SMNs that develop in the first 5 years after diagnosis represent a substantial proportion of overall SMNs. SMNs that developed prior to 5 years from primary diagnosis were predominantly hematologic (leukemia, lymphoma), whereas SMNs that developed after 5 years were predominantly solid cancers of the CNS and thyroid. However, 21% of the non hematopoietic SMNs occurred prior to 5 years from the completion of therapy. Within this group of early solid SMNs, only 37.0% were exposed to radiotherapy as part of treatment for their primary tumor compared with 67.3% of the later onset SMNs. This raises the possibility of hereditable genetic predisposition to the development of malignancy in this group in particular.

The increased risk for development of subsequent CNS and thyroid carcinoma is consistent with previous pediatric data and is likely a result of the latency associated with exposure to radiotherapy (9, 10, 16). Interestingly, the incidence of breast cancer as an SMN is high in many prior studies, but this was not the case in this cohort. Only three carcinomas of the breast were identified. This is likely a result of several factors including the age criteria for eligibility and the relatively young age and short follow-up of the cohort where only 21% of the females were followed to the age of 25 years or beyond. Future examinations of this cohort with longer follow-up may reveal higher incidence of solid tumors, including breast cancers.

In this study, previously established risk factors for the development of SMNs including exposure to radiotherapy

Table 4. Multivariable HRs and 95% CIs for the development of second malignant neoplasms (SMN) in pediatric cancer patients 0 to 14 years old in Ontario, by time since primary diagnosis

	All SMN		SMN within 5 years		SMN after 5 years	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Sex		0.97		0.51		0.65
Female	1.01 (0.74–1.36)		0.85 (0.52–1.38)		1.10 (0.74–1.63)	
Male	1.00		1.00		1.00	
Age at primary diagnosis (years)		0.09		0.16		0.06
0–4	1.00					
5–9	0.69 (0.46–1.03)		0.53 (0.26–1.07)		0.77 (0.47–1.26)	
10–14	0.67 (0.44–1.04)		0.97 (0.53–1.78)		0.50 (0.28–0.89)	
Treatment era		0.03		0.10		0.10
1985–1989	1.00		1.00		1.00	
1990–1994	0.86 (0.55–1.63)		0.83 (0.33–2.07)		0.87 (0.53–1.45)	
1995–1999	1.55 (0.97–2.47)		2.18 (1.00–4.76)		1.18 (0.65–2.17)	
2000–2004	1.68 (0.98–2.86)		1.73 (0.78–3.86)		1.65 (0.73–3.72)	
2005–2008	1.95 (0.99–3.84)		1.73 (0.71–4.18)		7.80 (1.49–40.93)	
Type of primary cancer diagnosis		0.01		0.06		0.21
Leukemia	1.00		1.00		1.00	
Lymphoma and reticuloendothelial	2.02 (1.13–3.62)		1.93 (0.80–4.64)		2.13 (0.98–4.64)	
CNS	1.93 (0.98–3.80)		1.03 (0.36–2.91)		2.90 (1.15–7.31)	
Sympathetic nervous system	1.44 (0.64–3.24)		0.74 (0.18–3.10)		2.03 (0.72–5.69)	
Kidney tumors	0.61 (0.20–1.85)		0.47 (0.06–3.96)		0.62 (0.16–2.33)	
Liver tumors	1.66 (0.34–8.08)		4.76 (0.82–27.49)		0.00 (0.00–0.00)	
Bone tumors	4.69 (2.11–10.44)		4.88 (1.52–15.60)		3.82 (1.23–11.89)	
Germ cell tumors	3.13 (1.03–9.50)		3.85 (0.91–16.23)		1.24 (0.13–11.67)	
Soft tissue sarcoma	1.92 (0.85–4.31)		1.73 (0.52–5.75)		1.86 (0.62–5.59)	
Not elsewhere specified	3.05 (1.17–7.94)		2.44 (0.65–9.15)		3.28 (0.81–13.37)	
Radiotherapy		<0.01		0.04		<0.01
No	1.00		1.00		1.00	
Yes	2.35 (1.66–3.33)		1.82 (1.02–3.22)		2.72 (1.72–4.30)	
Alkylating dose (mg/m^2)		0.50		0.17		0.28
None	1.00		1.00		1.00	
>0–<4,000	1.13 (0.64–2.01)		0.52 (0.14–1.88)		1.43 (0.74–2.76)	
≥4,000–<8,000	2.08 (0.76–5.71)		0.85 (0.10–7.09)		3.07 (0.93–10.06)	
≥8,000	2.05 (0.27–15.60)		7.73 (0.93–64.19)		0.00 (0.00–0.00)	
Anthracycline score		0.70		0.30		0.46
0	1.00		1.00		1.00	
1	0.89 (0.49–1.64)		0.42 (0.15–1.20)		1.50 (0.69–3.26)	
2	1.24 (0.71–2.16)		0.93 (0.41–2.10)		1.53 (0.70–3.33)	
3	1.18 (0.68–2.03)		0.61 (0.26–1.43)		1.82 (0.87–3.78)	
Epipodophyllotoxin score		0.06		<0.01		0.71
0	1.00		1.00		1.00	
1	1.41 (0.79–2.54)		1.65 (0.61–4.45)		1.28 (0.62–2.68)	
2	1.11 (0.61–2.03)		0.66 (0.19–2.26)		1.47 (0.73–2.98)	
3	1.87 (1.18–2.96)		3.74 (1.88–7.42)		1.10 (0.56–2.14)	
Platinum score		0.16		0.54		0.24
0	1.00		1.00		1.00	
1	1.65 (0.84–3.26)		1.19 (0.34–4.14)		2.00 (0.88–4.58)	
2	0.58 (0.20–1.67)		0.57 (0.12–2.62)		0.59 (0.13–2.63)	
3	1.52 (0.81–2.87)		1.66 (0.66–4.21)		1.52 (0.63–3.66)	
HSCT type		0.11		0.94		0.02
None	1.00		1.00		1.00	
Allogeneic related	2.45 (1.11–5.41)		1.37 (0.30–6.16)		3.50 (1.35–9.05)	
Allogeneic unrelated	1.95 (0.73–5.19)		0.76 (0.10–5.99)		3.35 (1.06–10.55)	
Autologous	0.90 (0.36–2.24)		1.28 (0.33–4.90)		0.79 (0.22–2.86)	
Surgery		0.20		0.04		0.84
No	1.00		1.00		1.00	
Yes	0.77 (0.52–1.15)		0.52 (0.28–0.96)		1.06 (0.62–1.79)	

were demonstrated. Radiotherapy was a significant risk factor for the development of both early and late SMNs with a stronger relationship with SMNs that develop 5 or more years after the primary diagnosis. Patients who had an allogeneic stem cell transplant were also independently at risk for the development of late SMN but not early SMN. This is also consistent with previous studies that have shown that stem cell transplant is a risk factor for the development of solid SMNs (27–29).

Cohort members that experienced an early SMN were 1.8 times more likely to die compared with those with who developed a late SMN. This finding is not explained by differences in follow-up time after the development of SMN, but is likely related to relative differences in survival after the development of acute myeloid leukemia and non-Hodgkin lymphoma which predominate as early SMNs in this cohort.

Although this study was population-based and did not rely on patient recall, it does have several limitations. Patients who were

treated in Ontario but moved out of the province may have their SMNs missed. Using data available from Statistics Canada, out-migration for the Ontario population ages 0 to 49 years from 1985 to 2013 has averaged 0.6% per annum and peaks in the 25- to 29-year age range at an average of 1.3% per annum (30, 31). Therefore, we may be underestimating the number of SMNs, though we expect very few such cases. The relatively small number of SMNs also precludes a more detailed analysis examining difference in predictive factors specific to tumor subgroups.

The findings of our study further corroborate the observation that children who experience a cancer diagnosis are at significantly increased risk for developing SMNs. The early development of many of these SMNs reinforces the need for early and continued surveillance at all stages. Future studies should focus on assessing the potential for less toxic treatment regimens, and on the identification of potential hereditable genetic predisposition syndromes, in order to reduce the incidence of therapy-related SMNs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.D. Pole, M.L. Greenberg
Development of methodology: J.D. Pole, M.L. Greenberg, P.C. Nathan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.D. Pole
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.D. Pole, L.Y. Gu, P.C. Nathan
Writing, review, and/or revision of the manuscript: J.D. Pole, V. Kirsh, M.L. Greenberg, P.C. Nathan
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.D. Pole, L.Y. Gu
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