Risk of Subsequent Neoplasms During the Fifth and Sixth Decades of Life in the Childhood Cancer Survivor Study Cohort

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Abstract

Childhood cancer survivors are at increased risk for subsequent neoplasms (SNs), but the incidence beyond age 40 and associations with therapeutic exposures have not been well-described. Among 14,364 childhood cancer survivors diagnosed between 1970 and 1986, 3,171 had an attained age ≥40 years at the time of last contact. Cumulative incidence of SNs, standardized incidence ratios (SIRs) and excess absolute risk of subsequent malignant neoplasms (SMNs), and relative risks (RR) for SMNs and non-melanoma skin cancers (NMSCs), were calculated. In total, 679 SNs were diagnosed ≥40 years of age, including 196 SMNs, 419 NMSCs, 21 non-malignant meningiomas, and 43 other benign neoplasms. At age 55, the cumulative incidence of new SNs and SMNs occurring beyond age 40 was 34.6% (95% CI 28.7-40.6) and 16.3% (95% CI 11.7-20.9), respectively. Survivors were twice as likely as the general population to be diagnosed with a SMN after age 40 (SIR=2.2, 95% CI 1.9-2.5). Among SMNs, risk was increased for breast cancer (SIR=5.5, 95% CI 4.5-6.7), renal cancer (SIR=3.9, 95% CI 2.0-7.5), soft tissue sarcoma (SIR=2.6, 95% CI 1.5-4.4), and thyroid cancer (SIR=1.9, 95% CI 1.0-3.5). Female sex (RR=1.9, 95% CI 1.3-2.6, $P<0.001$) and therapeutic radiation exposure (RR=2.2, 95% CI 1.4-3.3, $P<0.001$) were associated with higher risk for SMN in multivariable analysis. Even beyond 40 years of age, survivors of childhood cancer remain at increased risk for treatment-related SNs. These data suggest the need for life-long monitoring and should inform anticipatory guidance provided to childhood cancer survivors.

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List of Abbreviations

CCSS	Childhood Cancer Survivor Study
CI	95% Confidence Interval
CNS	Central Nervous System
E	Expected
EAR	Excess Absolute Risk
GI	Gastrointestinal
HL	Hodgkin Lymphoma
ICD-O	International Classification of Disease for Oncology
NMSC	Non-Melanoma Skin Cancer
O	Observed
PY	Person-Years
RR	Relative Risk
RT	Radiation Therapy
SD	Standard Deviation
SEER	Surveillance, Epidemiology, and End Results
SIR	Standardized Incidence Ratio
SMN	Subsequent Malignant Neoplasm
SN	Subsequent Neoplasm
STS	Soft Tissue Sarcoma

INTRODUCTION

Survival after a diagnosis of childhood cancer has increased substantially over the past four decades, with five-year survival now exceeding 80%.[1] One of the most serious late effects of childhood cancer is the development of subsequent neoplasms (SNs). The current body of literature reports in detail the risk of second cancers in 5-20 year survivors of childhood cancer.[2-8] It is also clear that within the survivor population the incidence of SNs does not plateau with time.[2,8,9] In a 2001 Childhood Cancer Survivor Study (CCSS) report of subsequent malignant neoplasms (SMNs),[8] a 20-year cumulative incidence of 3.2% was reported, and in an updated report from 2010,[2] a 30-year cumulative incidence of 7.9% was reported, with an increased incidence relative to the general population evident in both reports (SIR=6.4, 95% CI 5.7-7.1 and SIR=6.0, 95% CI 5.5-6.4, respectively). These findings highlight the importance of ongoing surveillance over sufficiently long follow-up time. In addition to an increased cumulative incidence of SNs with increasing time from diagnosis, survivors who survive their first SN remain at risk for additional neoplasms. Many survivors will experience multiple SNs with increasing age,[10] a finding that has only become apparent as the cohort has matured. Given this evidence, ongoing surveillance throughout the survivor lifespan is needed.

Presently, limited data exist on the incidence of SNs in childhood cancer survivors in the 5th and 6th decades of life.[11-16] Additionally, it is unknown whether associations with treatment for the primary cancer, which are seen in the first four decades, persist into later adulthood. Based on the importance of this knowledge for predicting risks and providing anticipatory guidance to the aging childhood cancer

survivor population, we present a comprehensive analysis focusing on cumulative incidence of SNs and risk of SMNs in the 5th decade and beyond in survivors from the CCSS.

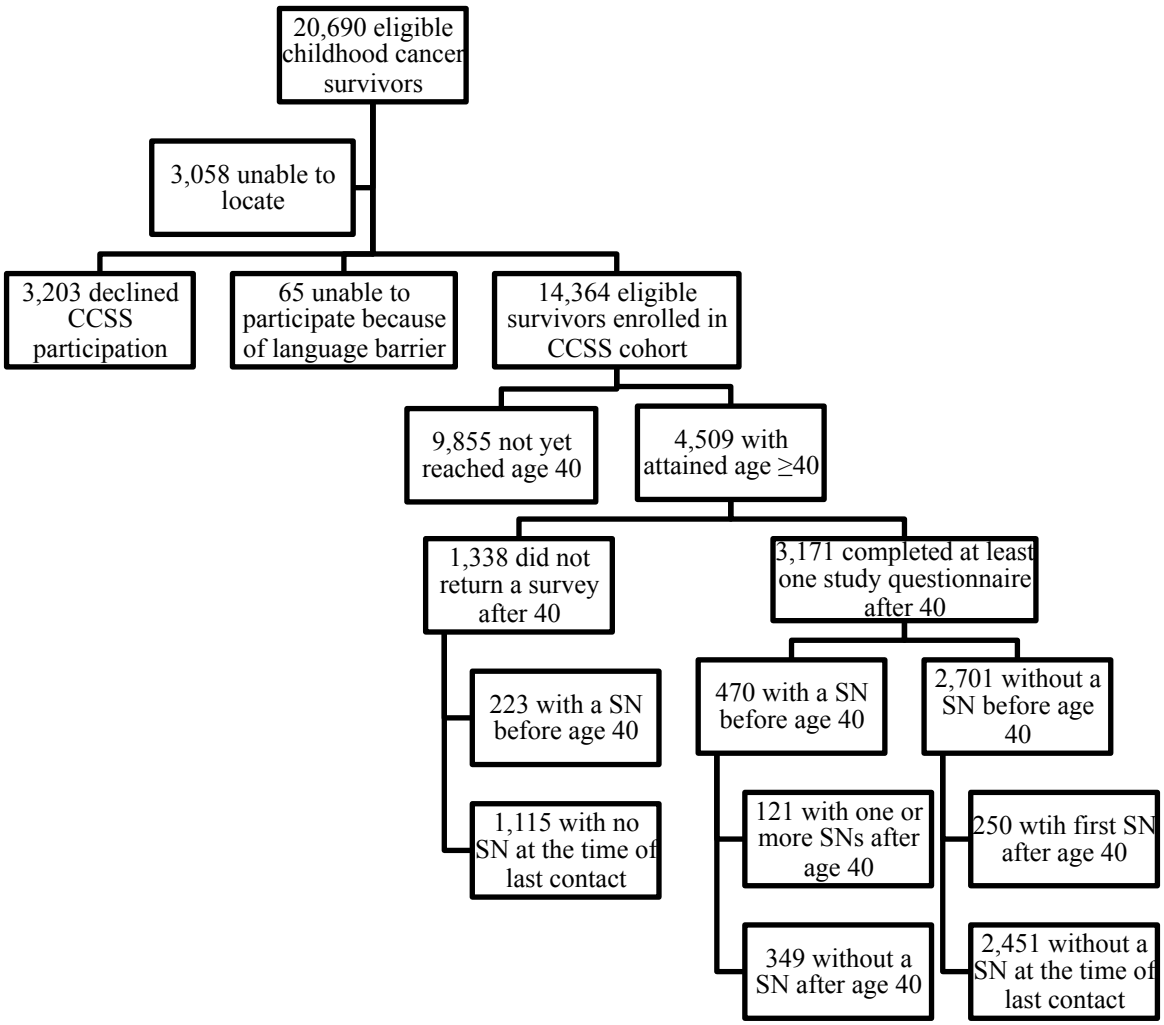
MATERIALS AND METHODS

The CCSS Cohort

The CCSS, initiated in 1994, is a retrospective cohort with ongoing, longitudinal follow-up of survivors of childhood cancer. Cohort characteristics and methods have been previously reported.[17-19] Initial diagnoses included: leukemia, Hodgkin lymphoma (HL), non-Hodgkin lymphoma, neuroblastoma, soft tissue sarcoma, bone cancer, central nervous system malignancy, and Wilms tumor. Eligible patients were diagnosed at one of 26 collaborating institutions within the United States or Canada between January 1, 1970 and December 31, 1986, were <21 years old at the time of diagnosis, and survived ≥5 years from the time of initial cancer diagnosis. Human subjects committee approval was granted at participating institutions prior to participant recruitment and participants provided informed consent. Participants completed a baseline questionnaire and were provided with four follow-up questionnaire opportunities.

The CCSS cohort consists of 14,364 participating survivors (Figure 1). The current analysis is limited to cohort participants who completed at least one study questionnaire after reaching age 40 (N = 3,171), including those who died after questionnaire completion.

Figure 1. CONSORT diagram of eligible CCSS survivors ≥40 years of age.



Identification and Validation of Subsequent Neoplasms

SNs were initially identified via self- or proxy-report questionnaires and/or death certificates and were confirmed by pathology report, or when unavailable, by death certificate or medical records. SNs were further classified into four mutually exclusive groups: 1) SMNs, which include invasive neoplasms classified as International Classification of Disease for Oncology (ICD-O, 2nd version), behavior code of 3,[20]

excluding non-melanoma skin cancers (NMSCs), 2) NMSCs (including ICD-O morphology codes 8070, 8071, 8081, 8090 and 8094), 3) non-malignant meningiomas and 4) other benign neoplasms with an ICD-O behavior code of 0, 1, or 2, regardless of site or morphology. Therapeutic exposures, including surgery, chemotherapy and radiation, were ascertained through medical record abstraction, as previously described.[17,18]

Statistical Analysis

Cumulative incidence estimates were calculated beginning at age 40 for all SN events and for SN subgroups (SMN, NMSC, meningioma), using age as the time scale, treating death as a competing risk event, with follow-up censored at the time of last contact. Risk for SMN was calculated using standardized incidence ratios (SIR) and excess absolute risk (EAR) per 1,000 person-years (PY). SIRs and EARs were calculated for SMNs reported after age 40, using age, gender and calendar year U.S. cancer rates from the Surveillance, Epidemiology, and End Results (SEER) program[21] to evaluate expected numbers of events. NMSCs and non-malignant meningiomas were not included in SIR or EAR calculations since NMSCs are not reported by SEER and benign meningiomas were not reported by SEER during the study time period.

Poisson multivariable regression models, with age as the time scale, were performed to estimate relative risks (RRs) of developing a SMN or NMSC for several host characteristics and treatment variables, as well as the effect of SN prior to age 40. For SMN models, SEER rates were used as the offset terms so that risks are standardized

by expected rates for same age, sex and calendar year subjects. Thus, RRs for SMNs can be interpreted as ratios of SIRs for different covariate levels. NMSC models are not standardized in this way. Multivariable models were developed by adding and subtracting risk factors sequentially, and selecting the best-fitting model, as measured by the quasi-likelihood information criterion, while taking into consideration the non-independence of some combinations of risk factors.[22] All statistical tests were two-sided and statistical significance was defined as $P<0.05$.

RESULTS

Cohort Characteristics

Among 14,364 cohort members, 3,171 completed at least one study questionnaire after age 40. These individuals accrued 15,985 person-years of follow-up after age 40. The median age of this group was 44 years (range 40-58). Demographic and treatment characteristics are included in Table 1. A total of 679 SNs were diagnosed ≥40 years of age, including 196 SMNs, 419 NMSCs, 21 non-malignant meningiomas, and 43 other non-invasive neoplasms. Of these survivors, 470 (14.8%) experienced a SN prior to age 40 (Table 2), and 2,701 did not. Among those without a prior SN, 250 experienced their first SN after turning 40, leaving 2,451 without a SN at the time of last contact (Figure 1).

Table 1. Demographic and treatment characteristics of CCSS cohort survivors with attained age ≥40 years.

Characteristic	All Survivors with attained age ≥40 years (n = 3171)	Survivors ≥40 years with 1st SN prior to age 40 (n = 470)	Survivors ≥40 years with 1st SN after age 40 (n = 250)	Survivors ≥40 years without SN (n = 2451)
Mean age at diagnosis of primary cancer, years (SD)	13.9 (4.2)	13.7 (4.2)	15.9 (3.3)	13.7 (4.2)
Sex, N (%)				
Male	1661 (52.4)	170 (36.2)	103 (41.2)	1388 (56.6)
Female	1510 (47.6)	300 (63.8)	147 (58.8)	1063 (43.4)
Race, N (%)				
White, non-Hispanic	2797 (88.2)	428 (91.1)	234 (93.6)	2135 (87.1)
Black, non-Hispanic	89 (2.8)	3 (0.6)	2 (0.8)	84 (3.4)
Hispanic	107 (3.4)	15 (3.2)	3 (1.2)	89 (3.6)
Other	171 (5.4)	23 (4.9)	11 (4.4)	137 (5.6)
Unknown	7 (0.2)	1 (0.2)		6 (0.2)
Primary cancer diagnosis, N (%)				
Leukemia	589 (18.6)	91 (19.4)	30 (12.0)	468 (19.1)
CNS malignancy	338 (10.7)	45 (9.6)	20 (8.0)	273 (11.1)
Hodgkin lymphoma	952 (30.0)	215 (45.7)	137 (54.8)	600 (24.5)
Non-Hodgkin lymphoma	336 (10.6)	36 (7.7)	15 (6.0)	285 (11.6)
Wilms tumor	59 (1.9)	5 (1.1)	1 (0.4)	53 (2.2)
Neuroblastoma	26 (0.8)	3 (0.6)		23 (0.9)
Soft tissue sarcoma	348 (11.0)	33 (7.0)	20 (8.0)	295 (12.0)
Bone cancer	523 (16.5)	42 (8.9)	27 (10.8)	454 (18.5)
Year of diagnosis of childhood cancer, N (%)				
1970-74	1179 (37.2)	176 (37.4)	132 (52.8)	871 (35.5)
1975-79	1200 (37.8)	189 (40.2)	86 (34.4)	925 (37.7)
1980-86	792 (25.0)	105 (22.3)	32 (12.8)	655 (26.7)
Childhood cancer therapy, N (%)				
Chemotherapy only	83 (2.6)	9 (1.9)	3 (1.2)	71 (2.9)
Radiation only	11 (0.3)	1 (0.2)	1 (0.4)	9 (0.4)
Surgery only	251 (7.9)	17 (3.6)	12 (4.8)	222 (9.1)
Chemotherapy and radiation	214 (6.7)	42 (8.9)	15 (6.0)	157 (6.4)
Chemotherapy and surgery	482 (15.2)	26 (5.5)	19 (7.6)	437 (17.8)
Radiation and surgery	600 (18.9)	121 (25.7)	79 (31.6)	400 (16.3)
Chemotherapy and radiation and surgery	1248 (39.4)	235 (50.0)	108 (43.2)	905 (36.9)
Unknown	282 (8.9)	19 (4.0)	13 (5.2)	250 (10.2)
Splenectomy, N (%)	720 (23.9)	179 (40.6)	102 (42.3)	439 (18.8)
Vital status, N (%) (alive)	2993 (94.4)	422 (89.8)	224 (89.6)	2347 (95.8)
Type of SN, after 40 years (individuals : occurrences)				
Total	445 : 679	145 : 254	300 : 425	0
SMN	180 : 196	38 : 42	142 : 154	0
NMSC	206 : 419	84 : 187	122 : 232	0
Meningioma	19 : 21	6 : 6	13 : 15	0
Other benign neoplasm	40 : 43	17 : 19	23 : 24	0

Table 2. Subsequent neoplasms experienced among childhood cancer survivors, prior to 40 years of age.

Subsequent Neoplasm Type	Frequency
SMN	**210**
Breast	*85*
Thyroid	*41*
Soft tissue sarcoma	*11*
Osteosarcoma	*5*
Other bone	*3*
CNS malignancy	*7*
Lymphoma	*10*
Melanoma	*18*
Leukemia	*2*
Lung	*1*
Female genitourinary	*4*
Head and neck	*9*
Renal	*1*
Gastrointestinal	*6*
Other	*7*
NMSC	**477**
Meningioma	**41**
Other non-invasive	**54**

Female survivors made up 47.6% of survivors ≥40 years, but represented 62% of individuals with a SN (Table 1). HL survivors experienced a disproportionate number of SNs compared to other primary diagnoses (48.9%). The distribution of SNs, specifically, SMN, NMSC, or meningioma, is shown in Table 1. Patterns of multiple SNs within individuals are shown in Figure 2.

Figure 2. Patterns of multiple SNs within survivors ≥40 years of age.

SN1		SN2		SN3		SN4+	
NMSC	194	NMSC	74	NMSC	35	NMSC	81
						Breast	3
						Other invasive	1
				Breast	2	NMSC	2
						Breast	1
				Other invasive	2	NMSC	1
				Other non-invasive	1	NMSC	1
		Breast	6	Breast	1		
				STS	1		
		STS	1				
		Thyroid	2	NMSC	1		
		Other invasive	5	Other invasive	1	NMSC	5
		Meningioma	1	NMSC	1	NMSC	2
		Other non-invasive	3	NMSC	2	NMSC	4
Breast	83	NMSC	2	NMSC	1	STS	1
		Breast	4				
		STS	1				
		Other invasive	1				
		Other non-invasive	2				
STS	9						
GI	9	NMSC	1	NMSC	1	NMSC	1
Thyroid	8	Breast	1	Other non-invasive	1		
Other invasive	47	NMSC	5	NMSC	1		
		Other invasive	1	Other invasive	1		
		Meningioma	1				
		Other non-invasive	1	NMSC	1		
Meningioma	17	NMSC	1				
		Breast	1				
		Meningioma	1	Meningioma	1	NMSC	1
Other non-invasive	32	NMSC	1				
		Breast	1				
		Other non-invasive	3	Thyroid	1	Other invasive	1

Cumulative Incidence of Subsequent Neoplasms

The cumulative incidence of a SN after age 40 increased rapidly, reaching 34.6% (95% confidence interval [CI] 28.7-40.6) at age 55 (Figure 3, Table 3). The cumulative incidence at age 55 was higher among survivors with a SN prior to age 40 (57.6%, 95% CI 46.7-68.6) compared to those with no prior history of SN (30.4%, 95% CI 23.8-37, *P*=0.001) (Table 3). The cumulative incidence of a SMN after age 40 reached 16.3% (95% CI 11.7-20.9) at age 55 (Figure 3) and was similar for survivors with and without a previous SN (20.8%, 95% CI 12.5-29.1 and 15.4%, 95% CI 10.2-20.5, *P*=0.35) (Table 3). By age 55, the cumulative incidence of NMSCs was 19.6% (95% CI 14.7-24.5), with a higher cumulative incidence of NMSCs observed in survivors with a previous SN (38.2%, 95% CI 27.9-48.5) compared to those without (16.2%, 95% CI 10.8-21.6). Treatment with radiation, combined with history of SN, was associated with the highest cumulative incidence of SN (62.3%, 95% CI 51.2-73.5), compared to the lowest cumulative incidence among survivors without prior radiation therapy and no prior SN (13.3%, 95% CI 4.8-21.8) (Figures 4-1,4-2).

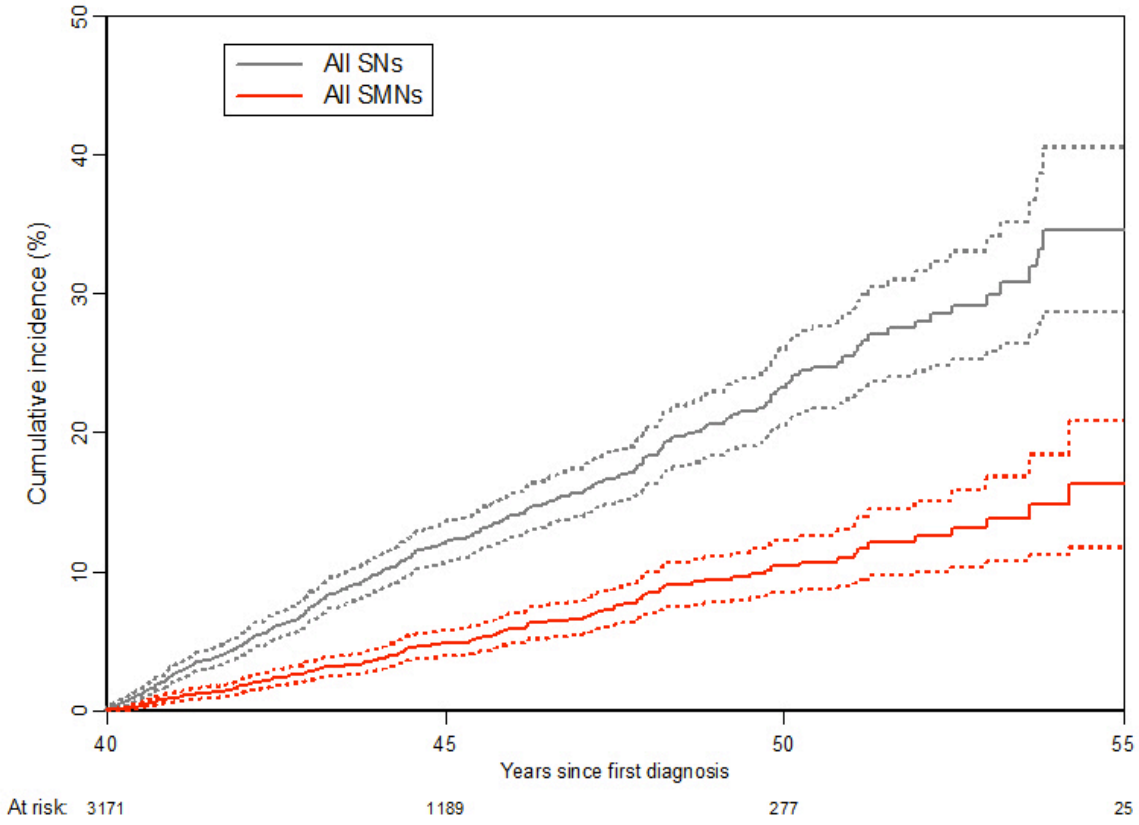


Figure 3. Cumulative incidence of new subsequent neoplasms diagnosed in CCSS survivors ≥40 years of age.

Table 3. Comparison of cumulative incidence of subsequent neoplasms after 40 years of age based on history of subsequent neoplasm before 40 years.

		Survivors ≥40 years of age					
		All		SN before 40		No SN before 40	
	Age	Patients at Risk	Cumulative Incidence, % (CI)	Patients at Risk	Cumulative Incidence, % (CI)	Patients at Risk	Cumulative Incidence, % (CI)
All SNs	40	3171	0	470	0	2701	0
	45	1190	12.1 (10.7-13.5)	150	27.4 (22.3-32.6)	1040	9.4 (8.0-10.8)
	50	278	23.3 (20.6-26.0)	28	48.2 (40.1-56.3)	250	18.7 (16.0-21.5)
	55	26	34.6 (28.7-40.6)	5	57.6 (46.7-68.6)	21	30.4 (23.8-37.0)
SMN	40	3171	0	470	0	2701	0
	45	1307	4.8 (3.9-5.8)	196	7.7 (4.6-10.8)	1111	4.3 (3.4-5.3)
	50	338	10.4 (8.5-12.2)	50	16.4 (10.5-22.3)	288	9.2 (7.3-11.2)
	55	42	16.3 (11.7-20.9)	8	20.8 (12.5-29.1)	34	15.4 (10.2-20.5)
NMSC	40	3171	0	470	0	2701	0
	45	1260	6.8 (5.7-7.9)	169	19.1 (14.7-23.6)	1092	4.6 (3.6-5.6)
	50	310	12.2 (10.1-14.2)	34	30.9 (23.6-38.1)	276	8.8 (6.8-10.8)
	55	37	19.6 (14.7-24.5)	6	38.2 (27.9-48.5)	31	16.2 (10.8-21.6)
Mening-ioma	40	3171	0	470	0	2701	0
	45	1368	0.4 (0.2-0.7)	212	1.1 (0.0-2.2)	1156	0.3 (0.1-0.6)
	50	369	1.2 (0.4-1.9)	60	1.1 (0.0-2.2)	309	1.2 (0.3-2.0)
	55	53	1.4 (0.5-2.4)	8	2.8 (0.0-6.3)	45	1.2 (0.3-2.0)

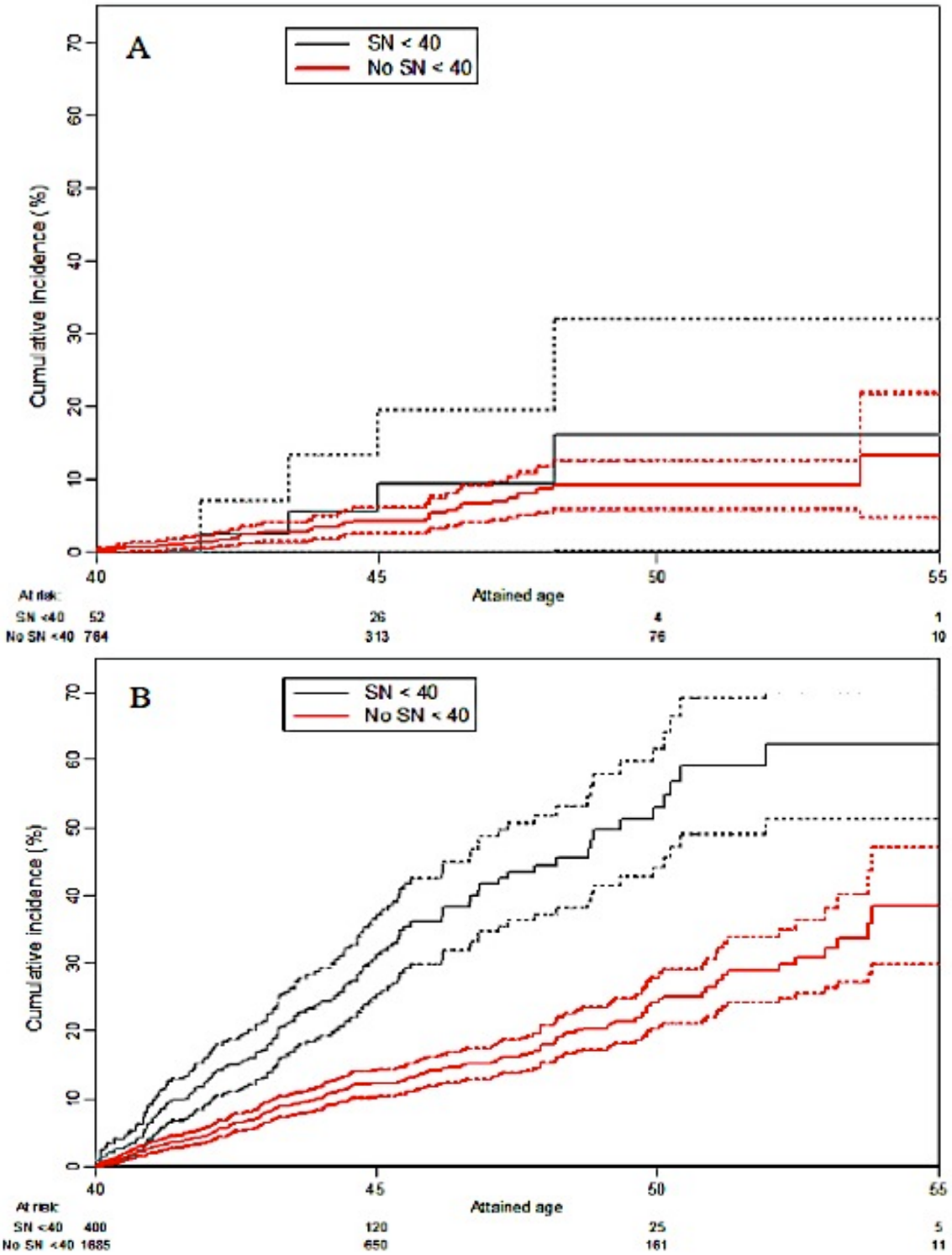


Figure 4-1. Cumulative incidence curves based on previous SN and RT history. A) SNs after age 40 in individuals who did not receive RT for their primary disease, B) SNs after age 40 in individuals who did receive RT for their primary disease.

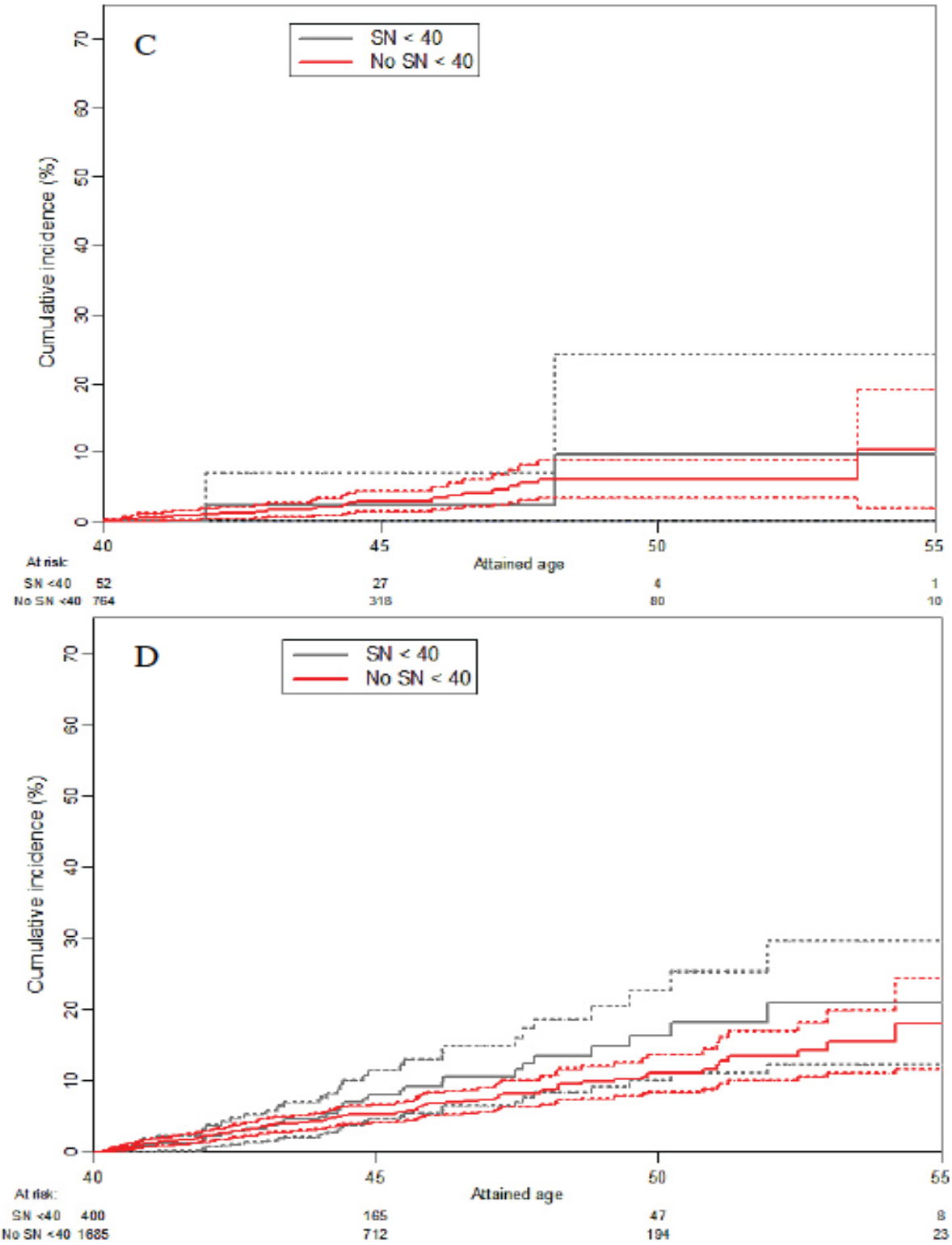


Figure 4-2. Cumulative incidence curves based on previous SN and RT history. C) SMNs after age 40, without previous RT, D) SMNs after age 40, with previous RT.

Risk of Subsequent Malignant Neoplasms Among Survivors With a History of Subsequent Neoplasm Before Age 40

Among the 470 survivors with a SN before age 40, 121 experienced one or more SNs after age 40. Forty-two SMNs were observed, with 30 occurring in females (SIR=3.0, 95% CI 2.2-4.0). HL survivors had the greatest risk among the primary diagnoses (SIR=3.8, 95% CI 2.5-5.6, EAR 3.81 per 1,000 PY). Treatments associated with increased risk of SMN include radiation (SIR=3.0, 95% CI 2.2-4.2) and alkylating agents (SIR=2.9, 95% CI 1.9-4.6). Among SMNs, risk was increased for breast cancer (SIR=5.0, 95% CI 3.1-7.9), cancers of the thyroid (SIR=4.4, 95% CI 1.9-10.6), head and neck (SIR=8.6, 95% CI 2.8-26.6), kidney (SIR=6.3, 95% CI 1.6-25.3), and soft tissue sarcomas (SIR=4.8, 95% CI 1.6-14.8).

Risk of Subsequent Malignant Neoplasms Among Survivors Without a History of Subsequent Neoplasm Before Age 40

Of the survivors without a prior SN, 250 experienced one or more SNs after age 40, including 154 SMNs (Table 1). Risk was significantly increased among females (SIR=2.7, 95% CI 2.3-3.3, EAR 2.3 per 1,000 PY) and HL survivors (SIR=3.6, 95% CI 2.9-4.4, EAR 3.28 per 1,000 PY). Among SMNs, risk was increased for breast (SIR=5.7, 95% CI 4.6-7.0) and renal (SIR=3.5, 95% CI 1.7-7.3) cancers and soft tissue sarcoma (SIR=2.2, 95% CI 1.2-4.2). Of the therapeutic exposures, radiation (SIR=2.5, 95% CI 2.1-3.0), alkylating agents (SIR=2.2, 95% CI 1.8-2.8), anthracyclines (SIR=2.1, 95% CI 1.6-3.0), epipodophyllotoxins (SIR=3.3, 95% CI 1.3-8.5) and platinum (SIR=2.6, 95% CI

1.1-6.2) were all associated with increased risk of SMN. The risk of SMN was not increased among individuals with no history of SN prior to age 40 who did not receive therapeutic radiation (Tables 4a-c).

Table 4a. Standardized incidence ratios for subsequent malignant neoplasms after 40 years of age.

	All Survivors ≥40y			
	O	E	SIR (CI)	EAR
All patients	196	89.7	2.2 (1.9-2.5)	1.31
Sex				
Male	54	38.1	1.4 (1.1-1.9)	0.37
Female	142	51.6	2.8 (2.3-3.3)	2.34
Primary cancer diagnosis				
Leukemia	23	14.6	1.6 (1.0-2.4)	0.54
CNS malignancy	9	8.7	1.0 (0.5-2.1)	0.03
Hodgkin lymphoma	112	30.7	3.6 (3.0-4.4)	3.4
Non-Hodgkin lymphoma	13	8.5	1.5 (0.9-2.6)	0.52
Wilms tumor	1	1.4	0.7 (0.1-5.1)	0.21
Neuroblastoma	0			
Soft tissue sarcoma	16	10.4	1.5 (0.9-2.8)	0.62
Bone cancer	22	14.7	1.5 (1.0-2.3)	0.56
Type of SMN				
Breast	103	18.7	5.5 (4.5-6.7)	1.04
Thyroid	12	6.3	1.9 (1.0-3.5)	0.07
Soft tissue sarcoma	13	5.1	2.6 (1.5-4.4)	0.1
Osteosarcoma	1	0.2	5.2 (0.7-36.7)	0.01
CNS malignancy	4	2.9	1.4 (0.5-3.7)	0.01
Lymphoma	8	9.3	0.9 (0.4-1.9)	0.02
Melanoma	9	8.9	1.0 (0.5-1.9)	0
Leukemia	3	2.6	1.2 (0.4-3.6)	0.01
Lung	5	3.7	1.3 (0.6-3.2)	0.02
Female genitourinary	6	7.9	0.8 (0.3-1.7)	0.05
Head and neck	5	2.7	1.8 (0.8-4.4)	0.03
Renal	9	2.3	3.9 (2.0-7.5)	0.08
Gastrointestinal	10	13.1	0.8 (0.4-1.4)	0.04
Other	8	6	1.3 (0.6-2.9)	0.02
Treatment Exposure				
Radiation therapy	156	60.1	2.6 (2.2-3.1)	1.78
Alkylating agents	95	40.5	2.4 (1.9-2.9)	1.46
Anthracyclines	45	23.9	1.9 (1.4-2.6)	0.92
Epipodophyllotoxins	5	1.5	3.4 (1.5-8.0)	2.22
Platinum	6	2	3.1 (1.4-6.7)	1.98
Radiation, no chemo	59	20.2	2.9 (2.3-3.8)	2.44
Chemo, no radiation	22	15.1	1.5 (1.0-2.2)	0.49
Radiation and chemo	97	39.7	2.4 (2.0-3.0)	1.51

Table 4b. Standardized incidence ratios for subsequent malignant neoplasms after 40 years of age.

	Cohort members treated with previous radiation*							
	No SN before 40y				SN before 40y			
	O	E	SIR (CI)	EAR	O	E	SIR (CI)	EAR
All patients	119	47.9	2.5 (2.1-3.0)	1.63	37	12.2	3.0 (2.2-4.2)	2.39
Sex								
Male	32	21.8	1.5 (1.0-2.1)	0.42	12	3.1	3.9 (2.3-6.6)	2.42
Female	87	26	3.3 (2.7-4.1)	3.16	25	9.1	2.7 (1.8-4.2)	2.38
Primary cancer diagnosis								
Leukemia	9	8.3	1.1 (0.6-2.1)	0.08	4	2	2.0 (0.8-5.2)	0.95
CNS malignancy	5	4.6	1.1 (0.5-2.6)	0.09	1	0.9	1.2 (0.2-8.0)	0.14
Hodgkin lymphoma	77	20	3.9 (3.1-4.8)	3.64	27	7.2	3.8 (2.5-5.6)	3.85
Non-Hodgkin lymphoma	6	5.2	1.2 (0.5-2.5)	0.16	3	0.8	3.8 (1.4-10.6)	2.91
Wilms tumor	1	1.1	1.0 (0.1-6.6)	0.04	0			
Neuroblastoma	0				0			
Soft tissue sarcoma	13	4.5	2.9 (1.5-5.6)	2.08	0			
Bone cancer	8	3.8	2.1 (1.0-4.4)	1.23	2	0.7	3.0 (0.9-10.1)	2.3
Type of SMN								
Breast	68	9.5	7.2 (5.7-9.0)	1.34	17	3.3	5.1 (3.1-8.4)	1.32
Thyroid	7	3.2	2.2 (0.9-5.0)	0.09	5	1	5.2 (2.2-12.3)	0.39
Soft tissue sarcoma	6	2.8	2.1 (1.0-4.7)	0.07	3	0.5	5.7 (1.8-17.4)	0.24
Osteosarcoma	0				1	0	42.1 (6.0-298)	0.09
CNS malignancy	3	1.6	1.9 (0.6-6.0)	0.03	1	0.3	2.9 (0.4-20.5)	0.06
Lymphoma	4	5	0.8 (0.2-2.6)	0.02	3	1.1	2.8 (0.9-8.5)	0.18
Melanoma	4	4.7	0.8 (0.3-2.3)	0.02	0			
Leukemia	1	1.4	0.7 (0.1-5.1)	0.01	0			
Lung	5	2.1	2.4 (1.0-5.9)	0.07	0			
Female genitourinary	3	4	0.8 (0.3-2.3)	0.05	0			
Head and neck	1	1.5	0.7 (0.1-4.7)	0.01	2	0.3	6.7 (1.7-26.7)	0.16
Renal	5	1.3	3.9 (1.6-9.4)	0.09	1	0.3	3.7 (0.5-26.1)	0.07
Gastrointestinal	6	7.2	0.8 (0.4-1.9)	0.03	2	1.8	1.1 (0.3-4.4)	0.02
Other	6	3.5	1.7 (0.7-4.3)	0.06	2	0.2	11.3 (2.9-44)	0.18
Treatment Exposure								
Radiation therapy	119	47.9	2.5 (2.1-3.0)	1.63	37	12.2	3.0 (2.2-4.2)	2.39
Alkylating agents	59	23.9	2.5 (1.9-3.2)	1.57	19	6.1	3.1 (2.0-4.9)	2.39
Anthracyclines	27	10.9	2.5 (1.6-3.8)	1.49	0			
Epipodophyllotoxins	4	0.9	4.6 (1.8-11.6)	3.25	1	0.2	4.1 (0.6-28.6)	2.88
Platinum	2	0.4	4.9 (1.3-17.9)	3.58	0			
Radiation, no chemo	45	15.7	2.9 (2.2-3.8)	2.3	14	4.4	3.2 (1.8-5.6)	3
Chemo, no radiation	0				0			
Radiation and chemo	74	32	2.3 (1.8-2.9)	1.37	23	7.8	3.0 (2.0-4.5)	2.12

*Note: The total number of observed events in the with and without previous radiation groups is equal to 186; there were 10 SMNs for which the radiation status of the individual was unknown.

Table 4c. Standardized incidence ratios for subsequent malignant neoplasms after 40 years of age.

	Cohort members not treated with previous radiation*							
	No SN before 40y				SN before 40y			
	O	E	SIR (CI)	EAR	O	E	SIR (CI)	EAR
All patients	28	21.4	1.3 (0.9-1.9)	0.34	2	1.5	1.3 (0.3-5.0)	0.35
Sex								
Male	9	9.4	1.0 (0.5-1.8)	-0.04	0			
Female	19	12	1.6 (1.0-2.6)	0.77	2	1.1	1.7 (0.5-6.6)	1.03
Primary cancer diagnosis								
Leukemia	8	2.8	2.9 (1.4-6.0)	1.75	1	0.3	3.2 (0.6-18.2)	2.58
CNS malignancy	3	2.4	1.3 (0.3-5.1)	0.25	0			
Hodgkin lymphoma	0				0			
Non-Hodgkin lymphoma	3	1.6	1.8 (0.6-5.5)	0.86	0			
Wilms tumor	0				0			
Neuroblastoma	0				0			
Soft tissue sarcoma	3	4.3	0.7 (0.2-2.1)	-0.38	0			
Bone cancer	11	8.7	1.3 (0.7-2.3)	0.31	1	0.6	1.8 (0.3-12.0)	0.93
Type of SMN								
Breast	13	4.3	3.0 (1.6-5.5)	0.45	0			
Thyroid	0				0			
Soft tissue sarcoma	3	1.2	2.5 (0.8-7.6)	0.09	0			
Osteosarcoma	0				0			
CNS malignancy	0				0			
Lymphoma	1	2.2	0.5 (0.1-3.2)	-0.06	0			
Melanoma	5	2.1	2.3 (1.0-5.6)	0.15	0			
Leukemia	1	0.6	1.6 (0.2-11.6)	0.02	0			
Lung	0				0			
Female genitourinary	2	1.8	1.1 (0.3-4.4)	0.02	1	0.2	5.7 (0.9-38.3)	1
Head and neck	1	0.7	1.5 (0.2-10.7)	0.02	1	0	27.0 (3.8-191.4)	0.74
Renal	2	0.6	3.6 (0.9-14.2)	0.07	0			
Gastrointestinal	0				0			
Other	0				0			
Treatment Exposure								
Alkylating agents	16	9.6	1.7 (1.0-2.8)	0.72	1	0.7	1.4 (0.2-9.5)	0.44
Anthracyclines	17	9.6	1.8 (1.1-2.9)	0.83	1	0.7	1.5 (0.2-10.0)	0.53
Epipodophyllotoxins	0				0			
Platinum	3	1.5	2.1 (0.7-6.3)	1.03	1	0	21.8 (9.6-49.4)	22.37
Chemo	20	14.1	1.4 (0.9-2.2)	0.45	2	1	1.9 (0.5-7.2)	1.06
No chemo	8	7.3	1.1 (0.5-2.3)	0.11	0			

*Note: The total number of observed events in the with and without previous radiation groups is equal to 186; there were 10 SMNs for which the radiation status of the individual was unknown.

Multivariable Analyses

In the multivariable Poisson regression model for SMNs, candidate risk factors included: sex, age at primary diagnosis, history of SN before age 40, therapeutic radiation for primary diagnosis, chemotherapy for primary diagnosis and specific classes of chemotherapeutic agents (alkylating agents, anthracyclines, epipodophyllotoxins, and platinum). Female sex (RR=1.9, 95% CI 1.3-2.6), platinum chemotherapy (RR=2.3, CI 1.0-5.2), and therapeutic radiation (RR=2.2, CI 1.4-3.3) remained significantly associated with increased risk of SMN (Table 5). History of SN prior to age 40 was not significant in this model.

Table 5. Multivariable Poisson regression model for subsequent malignant neoplasms.

Risk Factor		**RR (95% CI)**	***P*-value**
Sex	Female	1.9 (1.3-2.6)	<0.001
	Male	1.0 (ref)	
Platinum	Yes	2.3 (1.0-5.2)	0.05
	No	1.0 (ref)	
Radiation therapy	Yes	2.2 (1.4-3.3)	<0.001
	No	1.0 (ref)	

A multivariable analysis for NMSC, including sex, SN before age 40, therapeutic radiation exposure for primary diagnosis, and anthracycline exposure, was performed. Male sex was associated with increased risk (RR=1.2, 95% CI 1.0-1.4). A significant interaction between therapeutic radiation exposure and history of SN before age 40 was observed, such that individuals with previous radiation exposure and a history of SN (RR=1.3, 95% CI 1.0-1.6) and individuals without exposure to radiation and a SN prior to age 40 (RR=2.4, 95% CI 1.7-3.4) were at increased risk for NMSC as compared to

those with neither, while survivors with prior radiation exposure, but lack of SN history before age 40 did not have a significantly elevated risk of NMSC (Table 6).

Table 6. Multivariable Poisson regression model for non-melanoma skin cancers.

Risk Factor		**RR (95% CI)**	***P*-value**
Sex	Male	1.2 (1.0-1.4)	0.02
	Female	1.0 (ref)	
Anthracycline exposure	Yes	0.8 (0.7-1.0)	0.02
	No	1.0 (ref)	
Radiation therapy and SN interaction	RT, SN<40	1.3 (1.0-1.6)	0.03
	RT, No SN <40	1.2 (0.9-1.5)	0.14
	No RT, SN <40	2.4 (1.8-3.4)	<0.001
	No RT, No SN <40	1.0 (ref)	

DISCUSSION

We present a comprehensive report on the occurrence of new SNs experienced beyond 40 years of age among survivors of childhood cancer with assessment of risk based on therapeutic exposures during childhood. We found that the risk of developing a SN remains elevated beyond that expected in the general population, even as survivors are entering an age range where cancer risk increases for the general population. Additionally, survivors with a SN prior to age 40, compared to those with no previous SN, had an increased incidence of NMSCs, but this was not a risk factor for SMNs or meningiomas. Thus, individuals with and without a previous SN have a substantial risk of a new malignancy in the 5th and 6th decades, in excess of what is expected among the general U.S. population. Being free of SNs prior to age 40 does not preclude survivors from an increased risk of future SNs. This latency period supports potential genetic

susceptibility or underlying biologic mechanisms, in addition to treatment exposures, for the development of SNs.

Studies from the Nordic countries[11] and the British Childhood Cancer Survivor Study[12] have also reported on late occurring SNs. Across cohorts, all describe similar risk of any SMN between 40-60 years of age (CCSS: ≥40y SIR = 2.2, 95% CI 1.9-2.5; Nordic: 40-49y SIR = 2.3, 95% CI NA, 50-59y SIR = 1.7, 95% CI NA; British: 40-49y SIR = 2.5, 95% CI 2.1-3.0, ≥50y SIR 1.7, 95% CI 1.4-2.1); however, there are some differences across cohorts. Our study is limited to individuals treated in the current era of multi-agent chemotherapy, whereas, both the British and Nordic cohorts include survivors treated between 1940 and 1970. This accounts for larger numbers of survivors ≥40 years of age within both cohorts, but a large proportion of those individuals were treated prior to the current treatment era. Moreover, the Nordic study did not have data on cancer treatment exposures. Because the CCSS is a younger cohort, childhood tumors typically occurring at later ages, such as HL, are overrepresented, and malignancies of younger childhood, such as neuroblastoma and Wilms, are relatively underrepresented. This likely alters the pattern of SMNs observed; specifically, SIRs for breast cancer were not significantly increased in older age groups in the Nordic or British studies, but are increased in our study and gastrointestinal and genitourinary cancers were increased in the British study, but not in ours.

As anticipated, our analysis of therapeutic exposures documents that therapeutic radiation exposure continues to place survivors at increased risk for SMNs compared to their non-irradiated counterparts well into their 5th and 6th decades of life, indicating need

for ongoing monitoring of this at-risk subgroup. Interestingly, and somewhat encouraging, male survivors with an attained age ≥40 years who were not exposed to therapeutic radiation, were not at increased risk for SMN after age 40, regardless of their SN history before age 40. Of the chemotherapeutic exposures, only platinum agents were significantly associated with developing a SMN after 40 years of age.

Hodgkin lymphoma survivors compose 30% of survivors ≥40 years of age in our cohort and they experienced a disproportionately high number of new SMNs (57%) after age 40 compared to other primary diagnoses, due to the high incidence of breast cancer in this group. Breast cancer risk among HL survivors has previously been reported from the CCSS cohort and others.[13,23,24] Additionally, HL survivors composed over half of survivors who experienced a SMN after age 40 without a history of SN before age 40, confirming that risk persists with increasing age, regardless of SN history. High dose chest-directed radiation therapy was previously a central component of HL therapy and is the primary driver for the high incidence of SNs and risk for SMNs; notably, when HL patients were compared to non-HL patients in separate multivariable models, the radiation effect was only significant in the HL survivors.

We identified a significant interactive association between radiation exposure and SN history with risk of NMSC, with highest risk among the subjects with prior SN and no radiation exposure, though there remained significantly increased risks for the group with radiation exposure and previous SN. This is unexpected based on previous CCSS analyses, which have shown a strong association between therapeutic radiation and NMSCs,[25] as well as the frequent occurrence of multiple NMSCs within individuals.[10]

This effect is further illustrated by the significant increase in cumulative incidence of NMSCs among individuals with a history of SN prior to age 40 compared to those without. It is possible that the role of previous treatment exposures was more important at younger ages, or that other factors, such as underlying genetic susceptibility are responsible for the high cumulative incidence observed in this population.

Importantly, we did not observe an excess risk for subsequent head and neck, lung, colon or female genital tract malignancies even though rates of these common malignancies increase in the general population in this age group. This contrasts with the previous CCSS publications reporting increased risk for these malignancies among survivors, with the reported median time to occurrence ranging from 15-23 years.[2,26] It is possible that the highest risk period for these malignancies among survivors is prior to 40 years, and that as the incidence of these cancers increase within the general population with age, the risk beyond what is experienced by the general population is diminished.

A number of limitations should be considered. Although this analysis represents a large cohort of childhood cancer survivors, given the dates of inclusion, the cohort remains relatively young. There are limited numbers of survivors who have reached the 5th decade; specifically, survivors with malignancies diagnosed at very young ages, such as Wilms tumor or neuroblastoma, are underrepresented. Similarly the average age at childhood cancer diagnosis in this cohort is skewed by the overrepresented diagnoses of later childhood, such as HL, bone cancer and sarcoma. Treatment exposures for SNs were not included in this analysis and may contribute to additional SNs. Lifestyle and behavior data, as well as UV exposure, were not utilized for this analysis and would be expected to

become increasingly important as the cohort ages. Additionally, although family history may play a role in the development of late SNs, these data were only collected at baseline, without subsequent updates, and are thus not presented here.

As cancer therapies have changed over time, it is anticipated that the occurrence of subsequent late effects will change as well. Investigations of more recently treated survivors will help inform how adoption of newer therapeutic strategies for childhood cancer have changed the pattern of observed late effects, including second cancers. Specifically, we will need to investigate how removal of prophylactic radiation therapy in B-cell acute lymphoblastic leukemia, use of chemotherapy-only or response-based radiation therapy in HL, and use of conformal radiation therapy will impact risk for SNs. Few changes in chemotherapy have occurred during this time period that are likely to impact late occurring SN risk.[27,28]

The data presented here have important implications for long-term screening practices among childhood cancer survivors and for medical practitioners providing their care. Routine cancer screening, such as mammography, is typically initiated around this age amongst the general population; however, the risks experienced by the survivor population are unique. Survivors without a SN prior to age 40 may be particularly vulnerable, since they have not experienced previous neoplasms that may have altered their screening practices, and based on these data, it is evident that risk persists with age, even in those without a history of SN. The data presented here solidify the importance of future investigations of the underlying biologic mechanisms of SNs, as well as ongoing

close surveillance for survivors of childhood cancer. These findings should help inform anticipatory guidance and recommended cancer screening in the 5th decade and beyond.

FUTURE DIRECTIONS

There remains much work to be done to fully understand the ongoing risks experienced by the aging childhood cancer survivor population. Genome wide association studies and whole exome sequencing studies are currently underway to better define risk alleles for the development of subsequent neoplasms. It will also be important to follow the CCSS cohort as it continues to mature, since the present study was strongly influenced by its current relative youth; HL composes a disproportionately large percent of this study population compared to the general pediatric cancer population. As patients with tumors of earlier childhood, such as Wilms or neuroblastoma age into the 5th and 6th decades of life, it will be necessary to re-examine the patterns and cumulative incidence of SNs. Additionally, the CCSS has recently expanded the study cohort to include individuals treated between January 1, 1987 to December 31, 1999. Greater insight into the importance of therapeutic modifications over time on development of subsequent neoplasms will be gained once analyses of the entire cohort can be performed; specifically, it will be important to determine whether decreased use of high-dose radiation in HL has resulted in lower rates of SNs and SMNs, or whether use of intensified intrathecal therapy in place of cranial or craniospinal radiation in acute lymphoblastic leukemia has reduced rates of subsequent meningiomas or other CNS neoplasms.

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