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Second Neoplasms Working Group

CCSS Investigators Meeting
June 2017

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Second Neoplasms Working Group
Overview

- Ongoing review, adjudication and entry of reported neoplasms into data set
  - *Initial review of participant's replies*
  - *Requests for and review of path (and other records)*
  - *Classification of the outcome*
  - *Second tier review of pathologist review*
    - *Markers, location*
  - *Datstat Entry (Turcotte, Green, Armstrong, Neglia)*

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Second Neoplasms Working Group
Overview

- Generation of new AOIs, Concepts, and Results
  - *Expanded Dataset – global reports*
  - *Tumor specific investigations (i.e. breast, thyroid, etc)*
  - *Exposure specific investigations (chemo only, xrt)*
  - *Collaboration with Genetics group integrating host characteristics*

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Second Neoplasms Working Group
Ongoing QA

- Monthly Breast Cancer Calls
  - *Ongoing calls (approx. q month)*
  - *Troubleshooting, looking for duplication*
- As needed with Operations Center at SJCRH re Datstat, data queries

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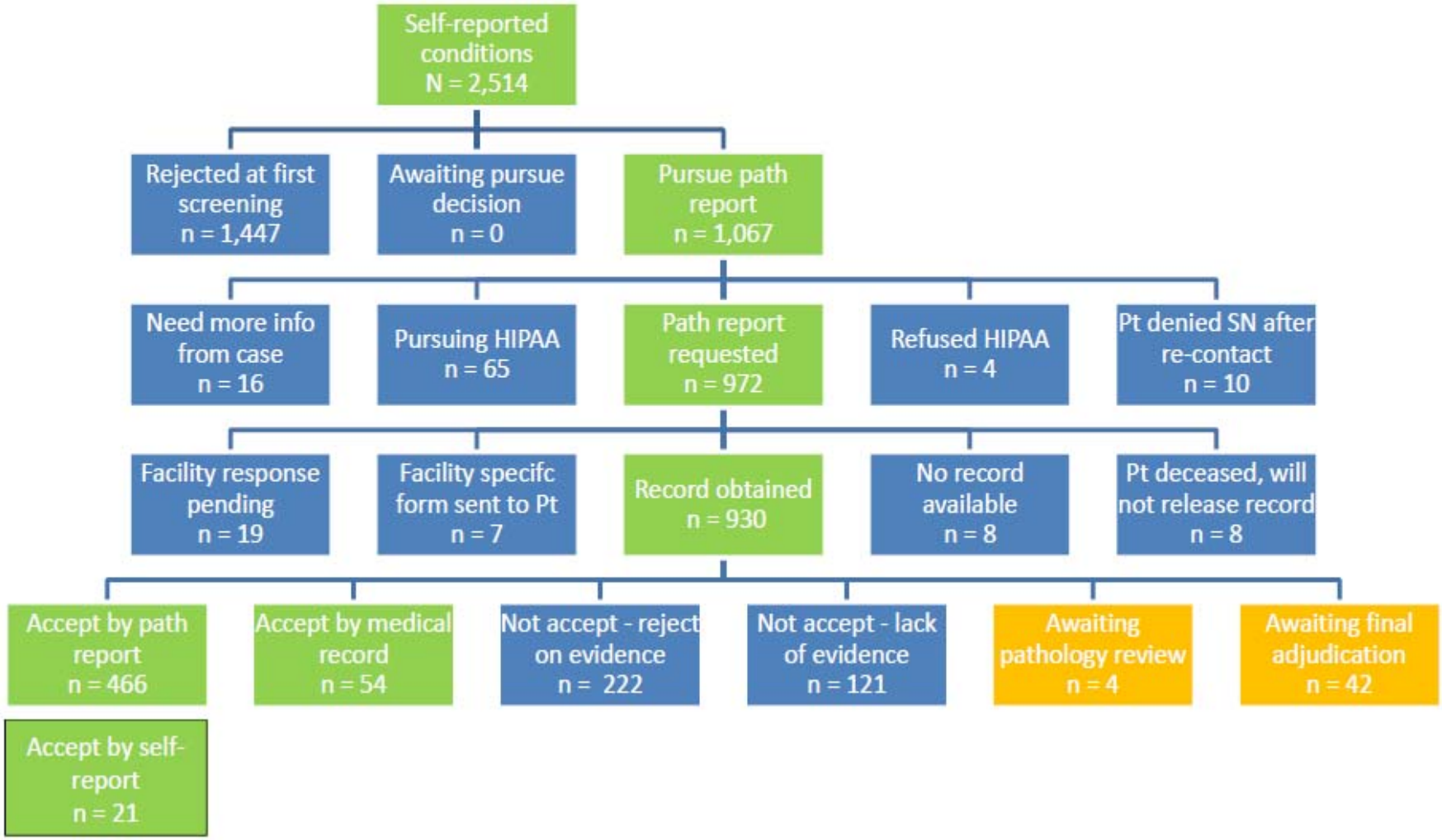
Second Neoplasms Working Group
Committee Membership

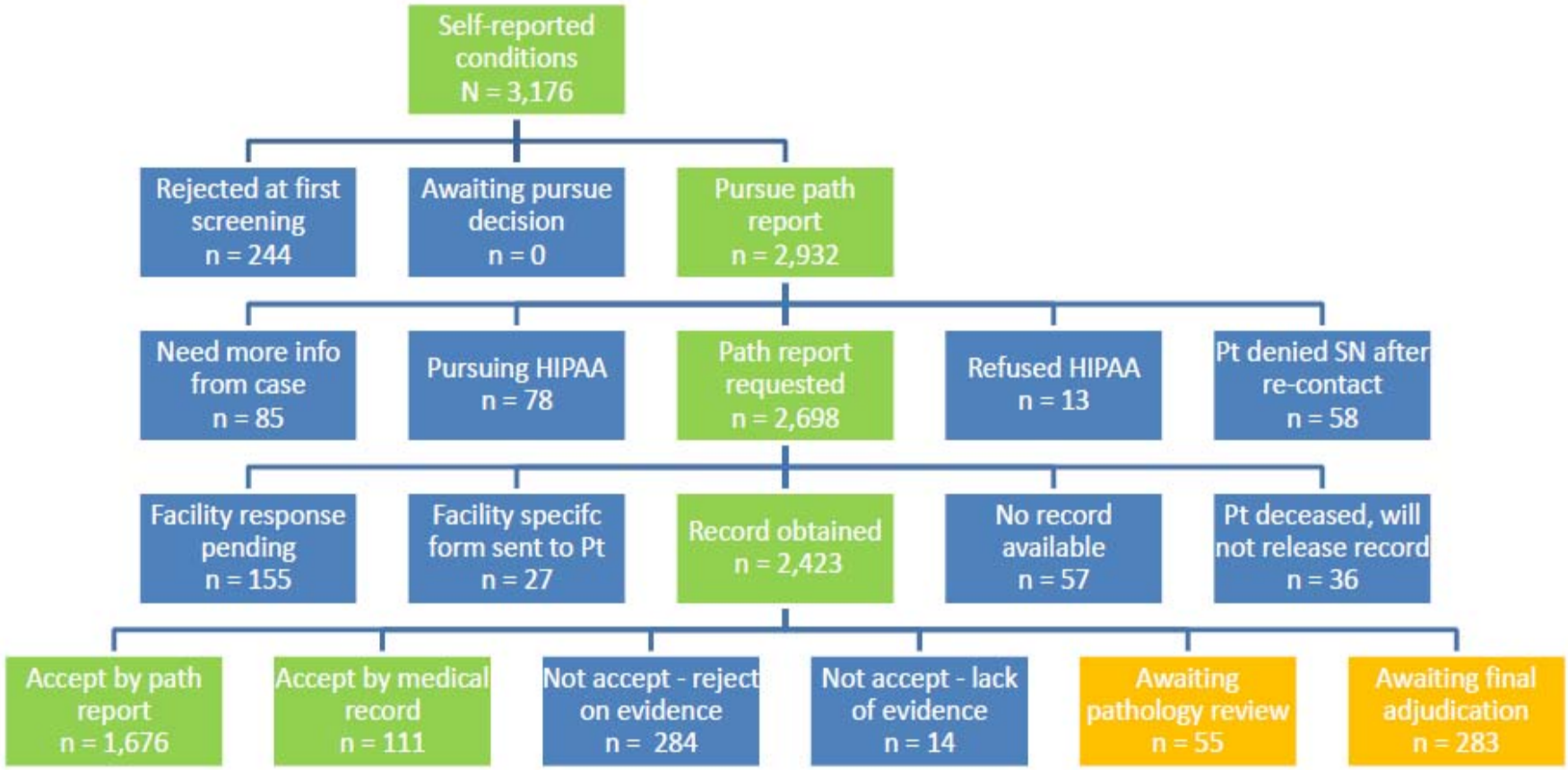
- Joseph Neglia
- Lucie Turcotte
- Mike Arnold
- Greg Armstrong
- Smita Bhatia
- Tara Henderson
- Lindsay Morton
- Rebecca Howell

Expansion Cohort Subsequent Neoplasm (SN) Confirmation – Baseline Survey



Report Date: 5/2017

Subsequent Neoplasm (SN) Confirmation – Follow-Up 5 Survey (Overall Cohort)



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Subsequent Neoplasms Identified Prior To and During Most Recent Data Freeze (5/2017)

			SNs Identified Prior To Most Recent Freeze		SNs Identified During Most Recent Freeze[#]		
SN Diagnosis	Participants with SN*	Total SNs	Participants	SNs	Participants	SNs	1st SN of this type since last freeze
Breast	407	486	325	392	89	94	82
Meningioma	326	395	221	254	129	141	105
Other CNS	128	130	105	107	23	23	23
Thyroid	284	287	209	210	76	77	75
Soft tissue sarcoma	113	117	97	100	17	17	16
Leukemia	55	55	48	48	7	7	7
Bone	55	55	53	53	2	2	2
Melanoma	68	70	56	58	12	12	12
Lymphoma	57	61	44	48	13	13	13
Renal carcinoma	47	48	34	34	14	14	13
Other carcinoma	243	249	155	157	91	92	88
NMSC	1,034	3,632	679	2,020	477	1,612	355
All others	61	61	46	46	15	15	15

*SN = Subsequent Neoplasm and includes all invasive neoplasms, in-situ breast cancer, and non-invasive meningiomas

[#]Review and confirmation process for conditions reported during Follow-Up 5 is ongoing

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Second Neoplasms Working Group
Publications 2015 - 2017

- Subsequent Neoplasms in Survivors of Childhood Central Nervous System Tumors: Risk After Modern Multimodal Therapy. Tsui K et al. Neuro Oncol 2015 17(3):448-56.

- Risk of Subsequent Neoplasms in the Fifth and Sixth Decades of Life in the Childhood Cancer Survivor Study Cohort. Turcotte et al. J Clin Oncol 2015 33(31):3568-75.

- Breast Cancer Following Spinal Irradiation for a Childhood Cancer: A Report from the Childhood Cancer Survivor Study. Moskowitz et al. Radiother Oncol 2015 117(2):213-6.

- Radiation-related New Primary Solid Cancers in the Childhood Cancer Survivor Study: Comparative Radiation Dose-response and Modification of Treatment Effects. Inskip et al. Int J Radiat Oncol Biol Phys 2015 94(4):800-7.

- A Comparative Evaluation of Normal Tissue Doses for Patients Receiving Radiation Therapy for Hodgkin Lymphoma on the Childhood Cancer Survivor Study and Recent Children's Oncology Group Trials. Zhou et al. Int J Radiat Oncol Biol Phys 2016 95(2):707-11.

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Second Neoplasms Working Group
Publications 2015 - 2017

- Thyroid Cancer after Childhood Exposure to External Radiation: An Updated Pooled Analysis of 12 Studies. Viega et al. Radiat Res 2016 185(5):473-84.

- Breast Cancer Risk in Childhood Cancer Survivors Without a History of Chest Radiotherapy: A Report from the Childhood Cancer Survivor Study. Henderson, et al. J Clin Oncol 2016 34(9):910-8.

- Morbidity and Mortality Associated with Meningioma After Cranial Radiotherapy: A Report from the Childhood Cancer Survivor Study. Bowers et al. J Clin Oncol 2017 35(14):1570-1576.

- Temporal Trends in Treatment and Subsequent Neoplasm Risk among 5-Year Survivors of Childhood Cancer, 1970-2015. Turcotte et al. JAMA 2017 317(8):814-824.

- Thyroid Cancer Following Childhood Low Dose Radiation Exposure: A Pooled Analysis of Nine Cohorts. Lubin et al. J Clin Endocrinol Metab 2017 Epub Mar 8, 2017.

- Radiation-associated breast cancer and gonadal hormone exposure: a report from the Childhood Cancer Survivor Study. Moskowitz et al. Br J Cancer 2017 In Press.

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Active Concepts

Concept	Investigator	Year
Cause-Specific Mortality among Childhood Cancer Survivors with a Subsequent Thyroid Cancer.	Dana Barnea	2016
Second primary breast cancers among childhood cancer survivors: joint effects of treatment and host factors.	Amy Berrington	2011
The risk of breast and thyroid cancer after radiotherapy for Hodgkin's Lymphoma: Can reconstructed dosimetry data be used to predict secondary malignancies?	David Hodgson	2015
Human papillomavirus (HPV)-associated malignancies as second cancers in childhood cancer survivors: a report from the Childhood Cancer Survivor Study.	Tara Henderson	2015
Secondary Cancers among NF1 Cancer Survivors	Smita Bhatia	2016
Second Neoplasms in Survivors not exposed to Radiation	Lucie Turcotte	2017
Breast Cancer in the Expanded Cohort	Tara Henderson	Pending

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CCSS Expansion

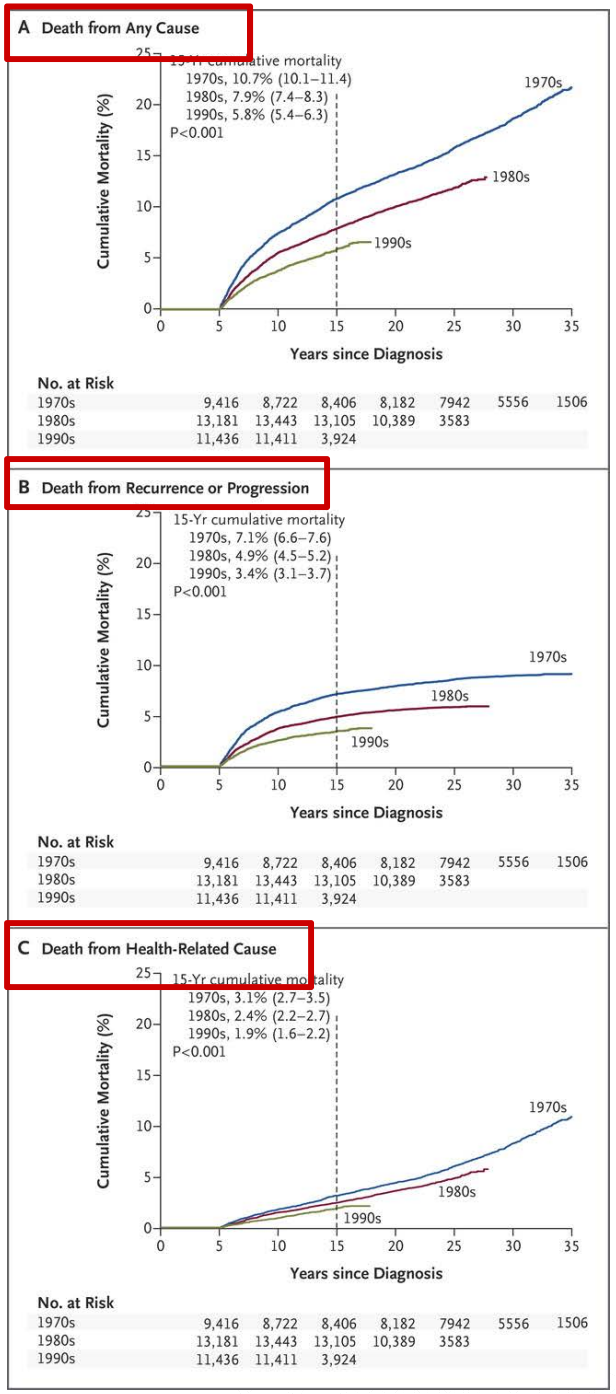
- Original CCSS cohort was inclusive of selected 5-year childhood cancer survivors diagnosed before age 21 at 26 sites between Jan. 1, 1970 and Dec. 31, 1986.
- As of January 2016 over 10,000 additional survivors added, diagnosed between Jan. 1, 1987 and Dec. 31, 1999.
- Cohort was enriched for non-whites through inclusion of 4 new institutions.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer

Gregory T. Armstrong, M.D., M.S.C.E., Yan Chen, M.M., Yutaka Yasui, Ph.D., Wendy Leisenring, Sc.D., Todd M. Gibson, Ph.D., Ann C. Mertens, Ph.D., Marilyn Stovall, Ph.D., Kevin C. Oeffinger, M.D., Smita Bhatia, M.D., M.P.H., Kevin R. Krull, Ph.D., Paul C. Nathan, M.D., Joseph P. Neglia, M.D., M.P.H., Daniel M. Green, M.D., Melissa M. Hudson, M.D., and Leslie L. Robison, Ph.D.



Armstrong GT et al. N Engl J Med 2016.

Research

JAMA | Original Investigation

Temporal Trends in Treatment and Subsequent Neoplasm Risk Among 5-Year Survivors of Childhood Cancer, 1970-2015

Lucie M. Turcotte, MD, MPH, MS; Qi Liu, MS; Yutaka Yasui, PhD; Michael A. Arnold, MD, PhD; Sue Hammond, MD; Rebecca M. Howell, PhD; Susan A. Smith, MPH; Rita E. Weathers, MS; Tara O. Henderson, MD; Todd M. Gibson, PhD; Wendy Leisenring, ScD; Gregory T. Armstrong, MD, MSCE; Leslie L. Robison, PhD; Joseph P. Neglia, MD, MPH

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Turcotte et al.

- Occurrence of SNs was evaluated in 23,603 5-year survivors
- Cumulative SN incidence and 95% confidence intervals (CI) at 15 years from diagnosis and standardized incidence ratios (SIRs - using SEER incidence rates) for subsequent malignant neoplasms (SMNs) were compared over treatment eras.
- Piecewise exponential models assessed changes in rates over treatment eras, adjusting for demographic and clinical characteristics.
- Attenuation of the treatment era coefficient by inclusion of the treatment variable was used to assess impact of therapy

Table 1. Demographic and Treatment Characteristics of Survivors of Childhood Cancer, Overall and by Treatment Era

Characteristics	No. (%)[a]			
	Overall Cohort (N = 23 603)	1970-1979 (n = 6223)	1980-1989 (n = 9430)	1990-1999 (n = 7950)
Age at primary diagnosis, mean (SD), y	7.7 (6.0)	8.4 (5.8)	7.6 (5.8)	7.4 (6.2)
Sex				
Male	12 656 (53.7)	3323 (53.4)	5105 (54.1)	4228 (53.5)
Female	10 947 (46.3)	2900 (46.6)	4325 (45.9)	3722 (46.5)
Race/ethnicity				
White, non-Hispanic	19 269 (80.8)	5533 (88.9)	7795 (82.4)	5941 (74.7)
Black, non-Hispanic	1485 (6.4)	241 (3.9)	574 (6.0)	670 (8.3)
Hispanic/Latino	1783 (8.1)	291 (4.7)	616 (6.8)	876 (11.4)
Other	1066 (4.7)	158 (2.5)	445 (4.9)	463 (5.9)
Primary diagnosis				
Leukemia	7319 (39.4)	2029 (32.6)	3333 (40.1)	1957 (42.9)
Acute lymphoblastic leukemia[b]	6148 (35.1)	1824 (29.3)	2894 (35.8)	1430 (37.9)
Acute myeloid leukemia	868 (3.2)	131 (2.1)	334 (3.3)	403 (3.8)
Other leukemia	303 (1.1)	74 (1.2)	105 (1.0)	124 (1.2)
Lymphoma	4928 (18.3)	1550 (24.9)	1834 (18.0)	1544 (14.7)
Hodgkin lymphoma	2996 (11.1)	1097 (17.6)	1059 (10.4)	840 (8.0)
Non-Hodgkin lymphoma	1932 (7.2)	453 (7.3)	775 (7.6)	704 (6.7)
Central nervous system	4236 (15.7)	736 (11.9)	1503 (14.7)	1997 (19.0)
Astrocytoma	2594 (9.6)	509 (8.2)	946 (9.3)	1139 (10.8)
Medulloblastoma/primitive neuroectodermal tumor	997 (3.7)	148 (2.4)	350 (3.4)	499 (4.8)
Other central nervous system cancer	645 (2.4)	79 (1.3)	207 (2.0)	359 (3.4)
Wilms tumor	2148 (8.0)	534 (8.6)	877 (8.6)	737 (7.0)
Bone cancer	1972 (7.4)	566 (9.1)	760 (7.5)	646 (6.1)
Osteosarcoma	1205 (4.5)	360 (5.8)	474 (4.7)	371 (3.5)
Ewing sarcoma	714 (2.7)	203 (3.3)	277 (2.7)	234 (2.2)
Other bone cancers	53 (0.2)	3 (0.0)	9 (0.1)	41 (0.4)
Neuroblastoma	1838 (6.8)	443 (7.1)	675 (6.6)	720 (6.9)
Rhabdomyosarcoma	1162 (4.3)	365 (5.9)	448 (4.4)	349 (3.3)

Table 1. Demographic and Treatment Characteristics of Survivors of Childhood Cancer, Overall and by Treatment Era

Characteristics	No. (%)[a]			
	Overall Cohort (N = 23 603)	1970-1979 (n = 6223)	1980-1989 (n = 9430)	1990-1999 (n = 7950)
Maximum radiation treatment dose to any body region, Gy				
None	9369 (49.3)	1232 (23.3)	3649 (45.6)	4488 (66.9)
0.1-10	308 (1.3)	58 (1.1)	140 (1.6)	110 (1.2)
10.1-20	2995 (14.7)	602 (11.4)	1642 (20.6)	751 (11.1)
20.1-30	2833 (12.5)	1396 (26.4)	852 (10.2)	585 (6.9)
30.1-40	1489 (6.3)	779 (14.7)	493 (5.5)	217 (2.3)
40.1-50	1738 (7.3)	749 (14.2)	698 (7.8)	291 (3.0)
≥50.1	2066 (8.6)	467 (8.8)	767 (8.6)	832 (8.6)
Median (IQR) dose	26.0 (18.0-45.0)	30.0 (24.0-44.0)	24.0 (18.0-45.0)	26.0 (18.0-52.0)

Table 1. Demographic and Treatment Characteristics of Survivors of Childhood Cancer, Overall and by Treatment Era (continued)

Characteristics	No. (%)[a] Overall Cohort (N = 23 603)	1970-1979 (n = 6223)	1980-1989 (n = 9430)	1990-1999 (n = 7950)
Cyclophosphamide equivalent dose, mg/m^2[d]				
None	9743 (47.8)	2793 (58.5)	3668 (46.6)	3282 (43.7)
1-3999	2560 (15.2)	341 (7.1)	1192 (15.6)	1027 (18.8)
4000-7999	2640 (12.7)	406 (8.5)	1047 (12.7)	1187 (14.6)
≥8000	5077 (24.3)	1231 (25.8)	1998 (25.1)	1848 (22.8)
Anthracycline, mg/m^2				
None	11 192 (48.9)	3720 (72.0)	4267 (49.9)	3205 (36.1)
0-100	1392 (10.8)	118 (2.3)	552 (10.0)	722 (15.8)
101-300	4994 (25.7)	529 (10.2)	1788 (21.5)	2677 (37.5)
>300	3278 (14.6)	798 (15.5)	1565 (18.5)	915 (10.6)
Epipodophyllotoxin, mg/m^2				
None	17 577 (80.0)	5251 (97.9)	7191 (84.0)	5135 (66.6)
1-1000	1013 (5.0)	60 (1.1)	351 (4.4)	602 (7.7)
1001-4000	1771 (9.4)	34 (0.6)	412 (5.9)	1325 (17.3)
>4000	829 (5.6)	21 (0.4)	373 (5.6)	435 (8.4)
Platinum agent, mg/m^2				
None	19 066 (90.7)	5332 (98.9)	7613 (91.4)	6121 (85.7)
1-400	807 (3.3)	28 (0.5)	343 (3.8)	436 (4.3)
401-750	711 (2.9)	18 (0.3)	325 (3.6)	368 (3.7)
>750	765 (3.1)	12 (0.2)	117 (1.3)	636 (6.3)

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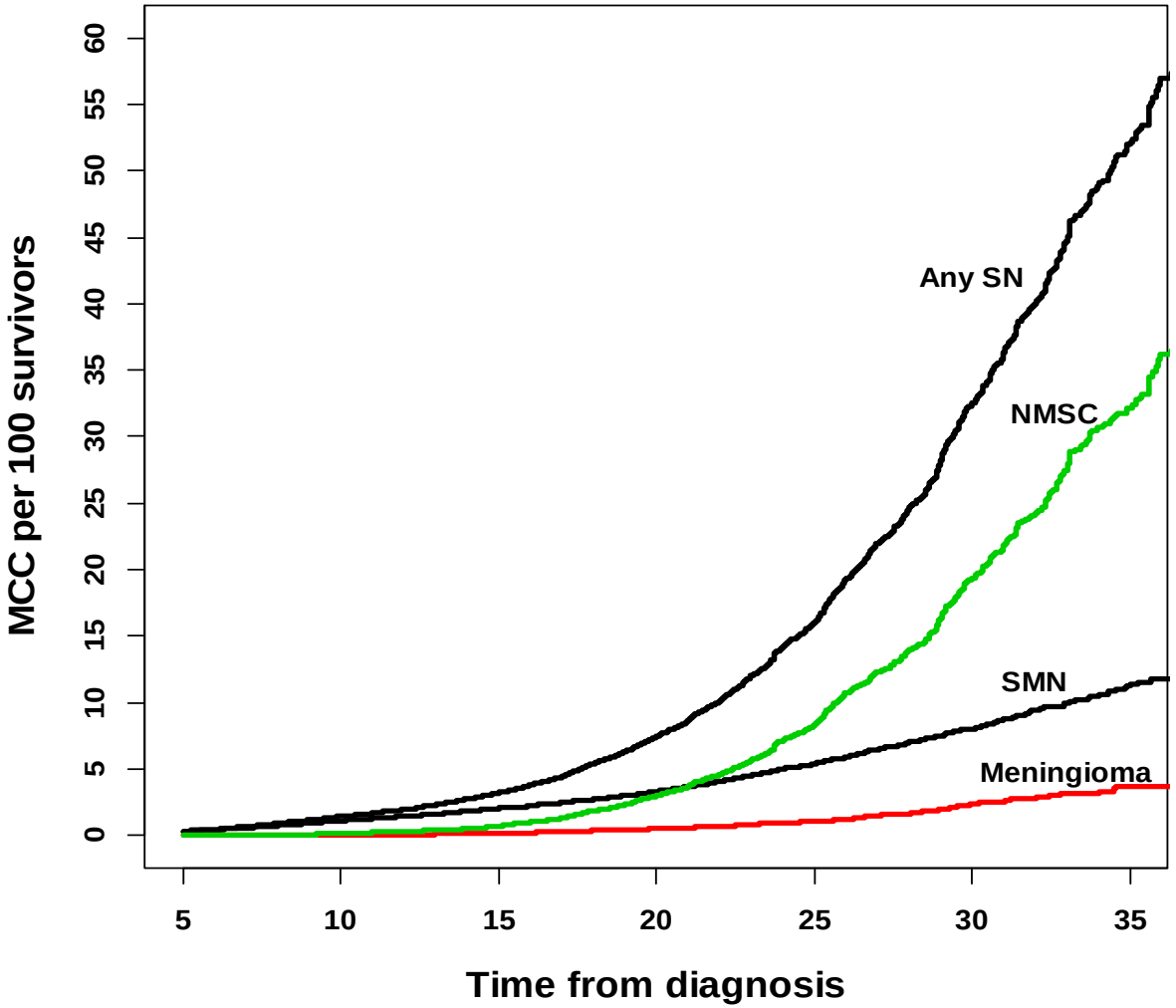
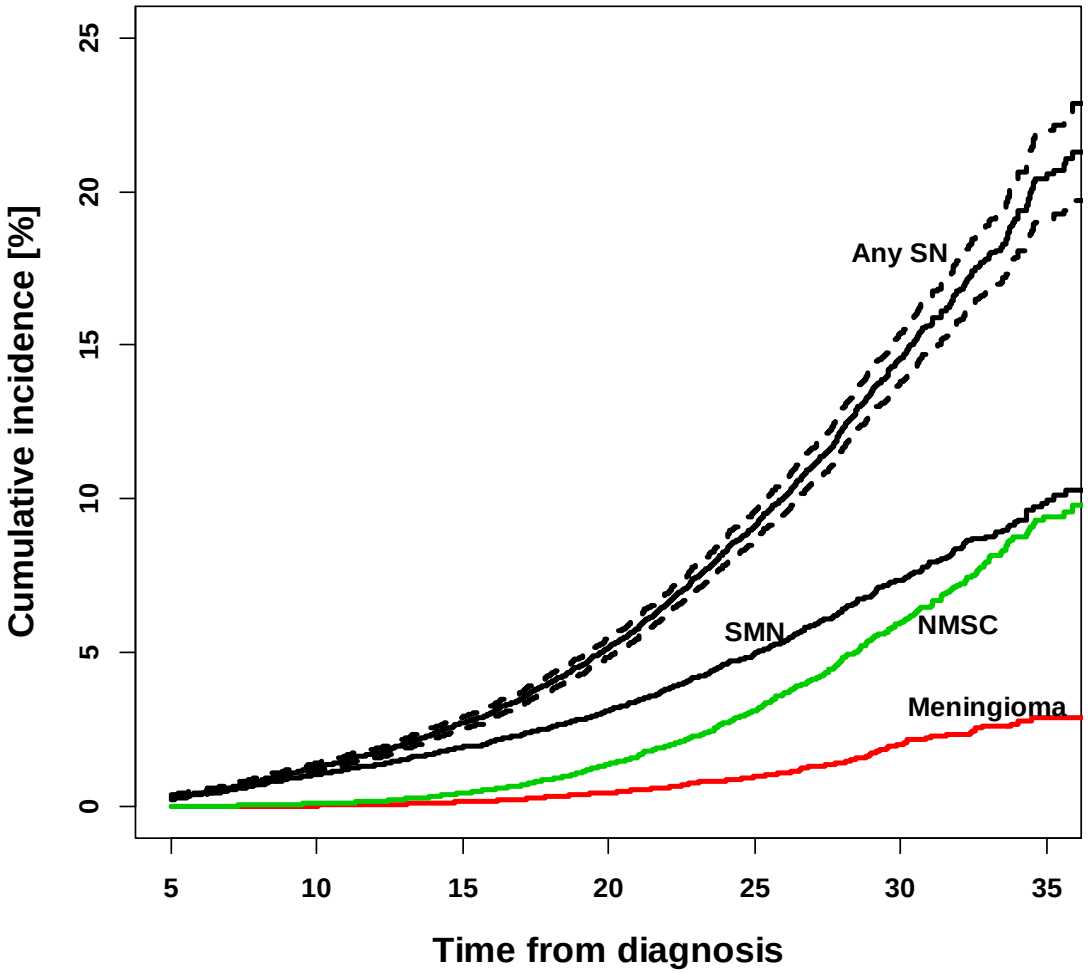
- 374,638 person-years at risk.
- 3315 SNs (including 1026 SMNs, 233 benign meningiomas, 1856 non-melanoma skin cancers [NMSCs]) among 1639 survivors were reported and validated.
- Exposure to therapeutic radiation decreased by treatment decade (77%, 54%, 33%).
- Exposure to chemotherapy agents increased.
  - Median doses of anthracyclines and alkylators decreased
  - Median platinum dose increased
  - Median epipodophyllotoxin dose increased in 80's, fell in the 90's

Mean Cumulative Count of SNs



Cumulative incidence of second neoplasms

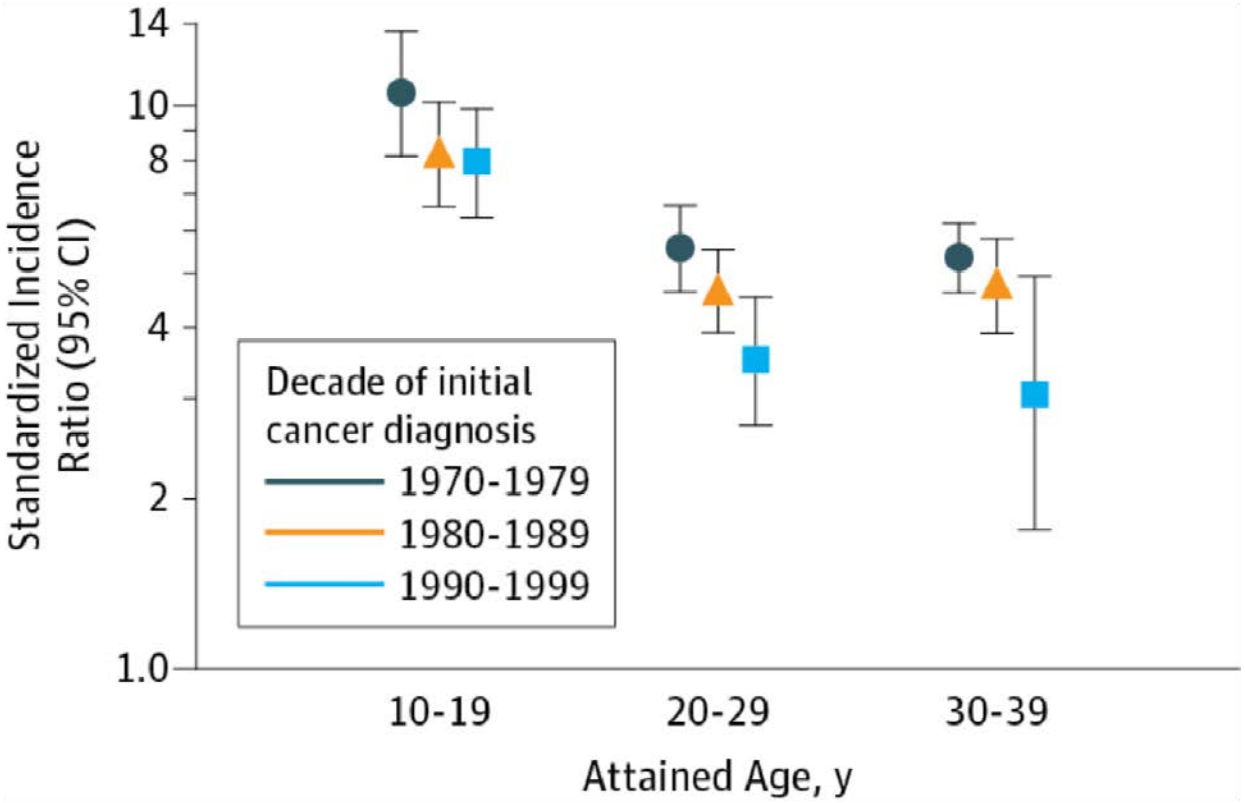


Cumulative Incidence %	15 yrs	30 yrs
Any SN	2.7	14.6
SMN	1.9	7.4
NMSC	0.4	6.0
Meningioma	0.2	2.0

Friedman, JNCI 2010	15 yrs	30 yrs
Any SN		20.5
SMN		7.9
NMSC		9.1
Meningioma		3.1

From: **Temporal Trends in Treatment and Subsequent Neoplasm Risk Among 5-Year Survivors of Childhood Cancer, 1970-2015**

JAMA. 2017;317(8):814-824. doi:10.1001/jama.2017.0693



From: **Temporal Trends in Treatment and Subsequent Neoplasm Risk Among 5-Year Survivors of Childhood Cancer, 1970-2015**

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Table 3. Relative Rates of Overall and Subsequent Neoplasm Subtypes, per 5-Year Treatment Era, Without and With Adjustment for Treatment Variables[a]

		Subsequent Neoplasm		Subsequent Malignant Neoplasm		Meningioma		Nonmelanoma Skin Cancer	
Treatment Era		RR (95% CI)	*P* Values	RR (95% CI)	*P* Values	RR (95% CI)	*P* Values	RR (95% CI)	*P* Values
Not adjusted for any treatment (A)		0.81 (0.76-0.86)	<.001	0.87 (0.82-0.93)	<.001	0.85 (0.75-0.97)	.03	0.75 (0.67-0.84)	<.001
Adjusted for:									
All treatments except maximum radiation dose (B)		0.84 (0.78-0.90)	<.001	0.87 (0.81-0.94)	<.001	0.80 (0.68-0.92)	.003	0.81 (0.71-0.92)	.001
Maximum radiation dose (C)		0.93 (0.87-0.99)	.02	0.96 (0.90-1.02)	.20	1.01 (0.87-1.17)	.90	0.87 (0.78-0.97)	.01
All treatments (D)		0.91 (0.84-0.98)	.01	0.93 (0.86-1.00)	.047	0.94 (0.81-1.10)	.47	0.87 (0.76-1.00)	.048
Statistical significance for the coefficient difference	A vs B		.10	A vs B	>.99	A vs B	.02	A vs B	.046
	A vs C		<.001	A vs C	<.001	A vs C	<.001	A vs C	<.001
	A vs D		<.001	A vs D	<.001	A vs D	<.001	A vs D	.03
	B vs C		<.001	B vs C	<.001	B vs C	.02	B vs C	<.001
	B vs D		<.001	B vs D	<.001	B vs D	<.001	B vs D	<.001
	C vs D		.24	C vs D	.046	C vs D	.90	C vs D	.10

Abbreviation: RR, relative rate.

[a] Separate models were developed for each outcome, adjusting for sex, age at initial cancer diagnosis, attained age as cubic spline. Models adjusting for treatment included maximum radiation dose to the body, splenectomy, cyclophosphamide equivalent dose, anthracycline dose, epipodophyllotoxin dose, and platinum dose.

Relative Rates of Overall and Subsequent Neoplasm Subtypes, per 5-Year Treatment Era, Without and With Adjustment for Treatment Variables[a]

From: **Temporal Trends in Treatment and Subsequent Neoplasm Risk Among 5-Year Survivors of Childhood Cancer, 1970-2015**

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Adjusted for:								
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Maximum radiation dose (C)	0.93 (0.87-0.99)	.02	0.96 (0.90-1.02)	.20	1.01 (0.87-1.17)	.90	0.87 (0.78-0.97)	.01
All treatments (D)	0.91 (0.84-0.98)	.01	0.93 (0.86-1.00)	.047	0.94 (0.81-1.10)	.47	0.87 (0.76-1.00)	.048
Statistical significance for the coefficient difference	A vs B	.10	A vs B	>.99	A vs B	.02	A vs B	.046
	A vs C	<.001	A vs C	<.001	A vs C	<.001	A vs C	<.001
	A vs D	<.001	A vs D	<.001	A vs D	<.001	A vs D	.03
	B vs C	<.001	B vs C	<.001	B vs C	.02	B vs C	<.001
	B vs D	<.001	B vs D	<.001	B vs D	<.001	B vs D	<.001
	C vs D	.24	C vs D	.046	C vs D	.90	C vs D	.10

Abbreviation: RR, relative rate.

[a] Separate models were developed for each outcome, adjusting for sex, age at initial cancer diagnosis, attained age as cubic spline. Models adjusting for treatment included maximum radiation dose to the body, splenectomy, cyclophosphamide equivalent dose, anthracycline dose, epipodophyllotoxin dose, and platinum dose.

Relative Rates of Overall and Subsequent Neoplasm Subtypes, per 5-Year Treatment Era, Without and With Adjustment for Treatment Variables[a]

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Multivariable Analysis

- After adjusting for demographics and cancer diagnosis, incidence rates declined every 5-year era
- Inclusion of treatment exposures attenuated the treatment era-associated decline of SN rates, indicating the decline was at least partially attributable to changes in treatment exposure.
- Females at increased risk of SMN, meningioma
- Increased risk with xrt (all categories).
- Increase in SMN with increased cyclophosphamide equivalent dose and platinum dose.

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Selected Publications

Concept

- Breast Cancer Risk in Survivors Not Exposed to Chest Radiation

PI

- Tara Henderson

Aims

- Aim 1: To describe the cumulative incidence, standardized incidence ratio and absolute excess risk of breast cancer in women not exposed to chest radiation for a pediatric malignancy.
- Aim 2: To describe the risk factors (treatment related, familial and behavioral) associated with the development of breast cancer tract among female childhood cancer survivors not exposed to chest radiation.
- Aim 3: To describe the clinical and pathological characteristics of the breast cancer cases in women not exposed to chest radiation.

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Breast Cancer Clinical Characteristics

Characteristic	No Chest RT (N=47)	Chest RT	General Population
Median age at BC, yr (range)	38 (22-47)	39[1] (24-59)	61[2]
Bilateral BC, N (%)	15%	13-17%[3]	3-5%[3]

[1]Moskowitz et al. J Clin Oncol 2014
[2]SEER, 2007-2011
[3]Henderson et al. Ann Int Med 2010

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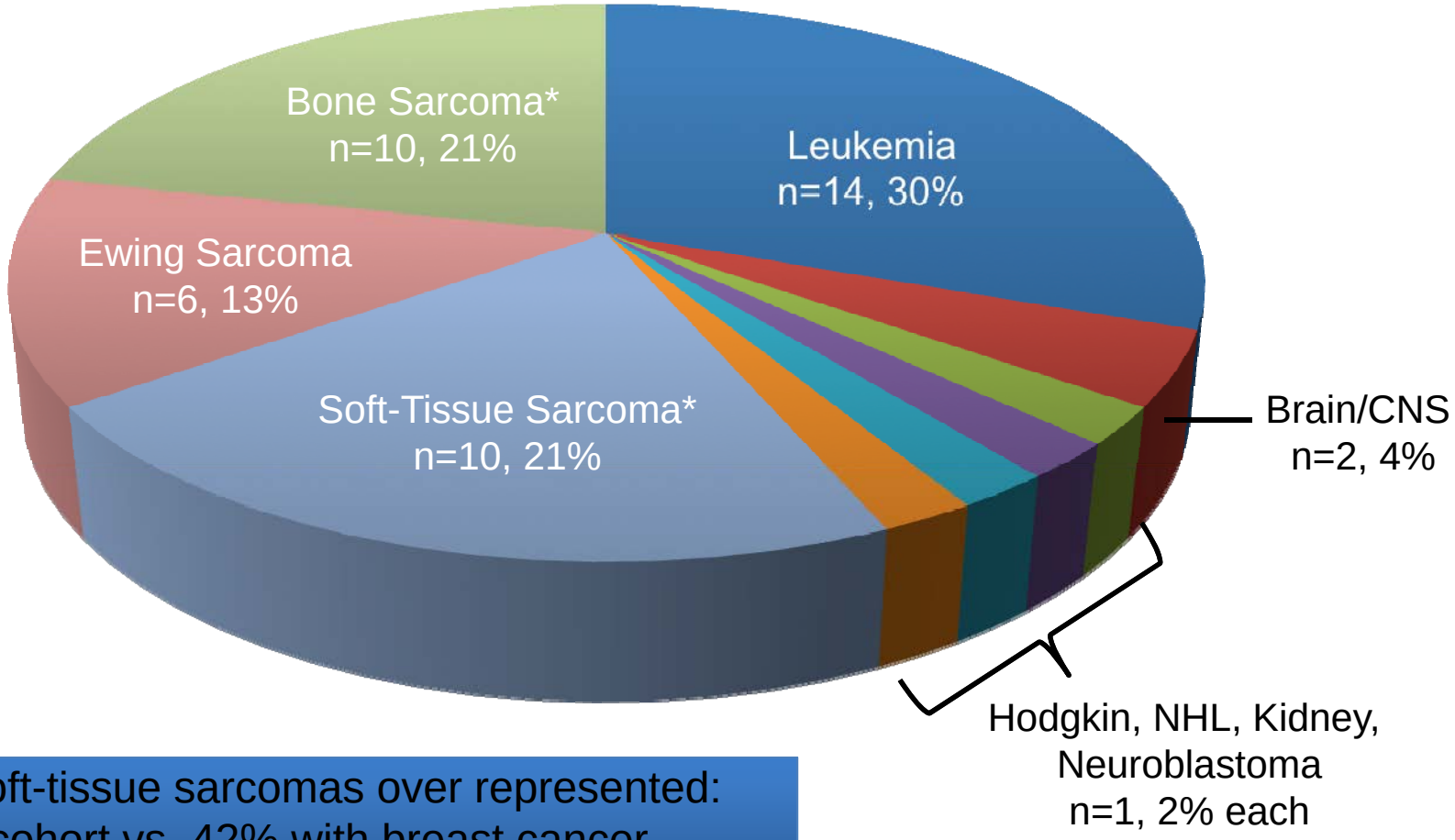
Results – Primary Diagnoses

- Primary diagnoses of women with breast cancer (N=47):

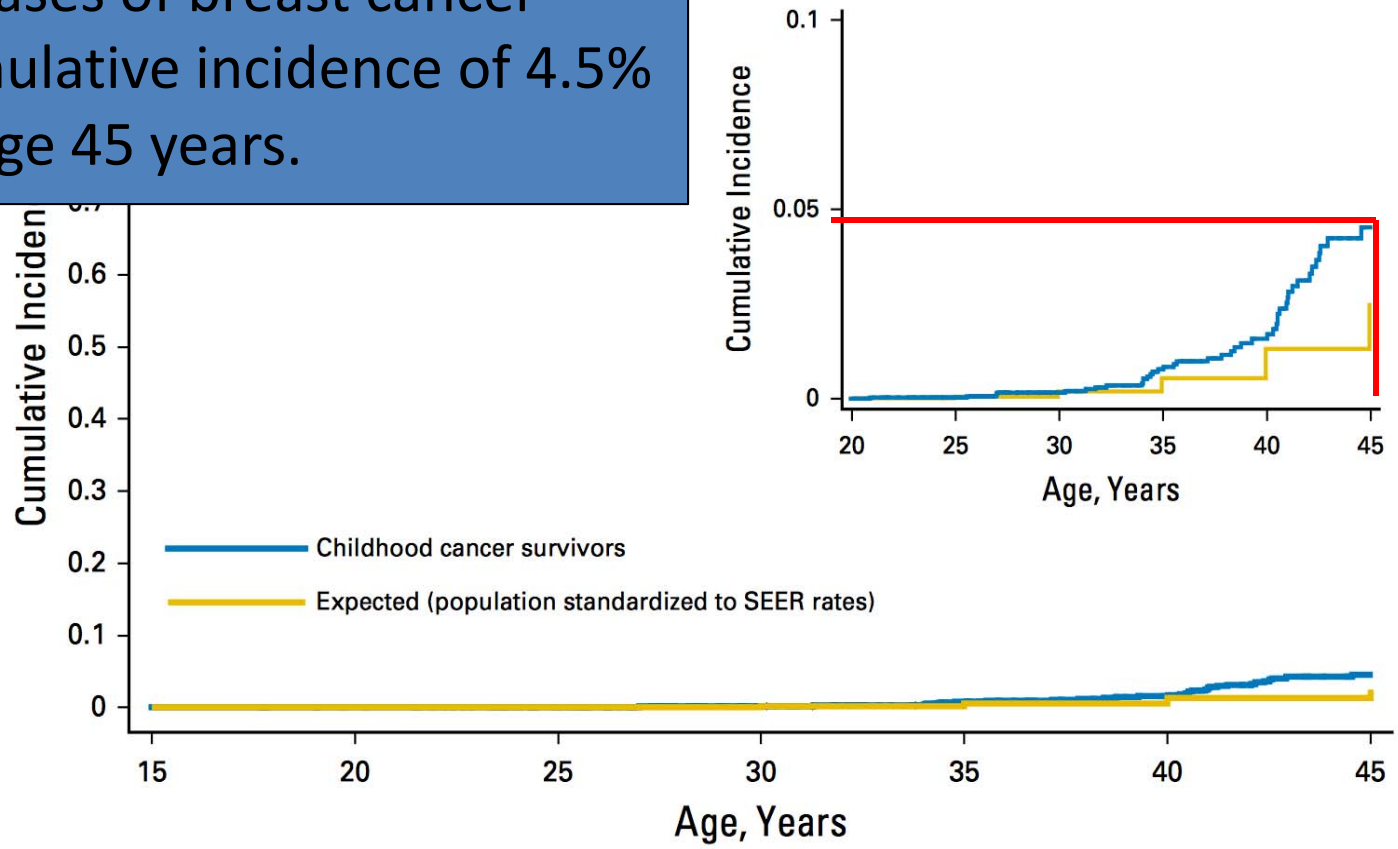


*Bone and soft-tissue sarcomas over represented:
18% of total cohort vs. 42% with breast cancer

CCSS: Breast Cancer Risk in Women Not Exposed to Chest RT

Among 3,758 women never exposed to chest RT:

- 47 cases of breast cancer
- Cumulative incidence of 4.5% by age 45 years.

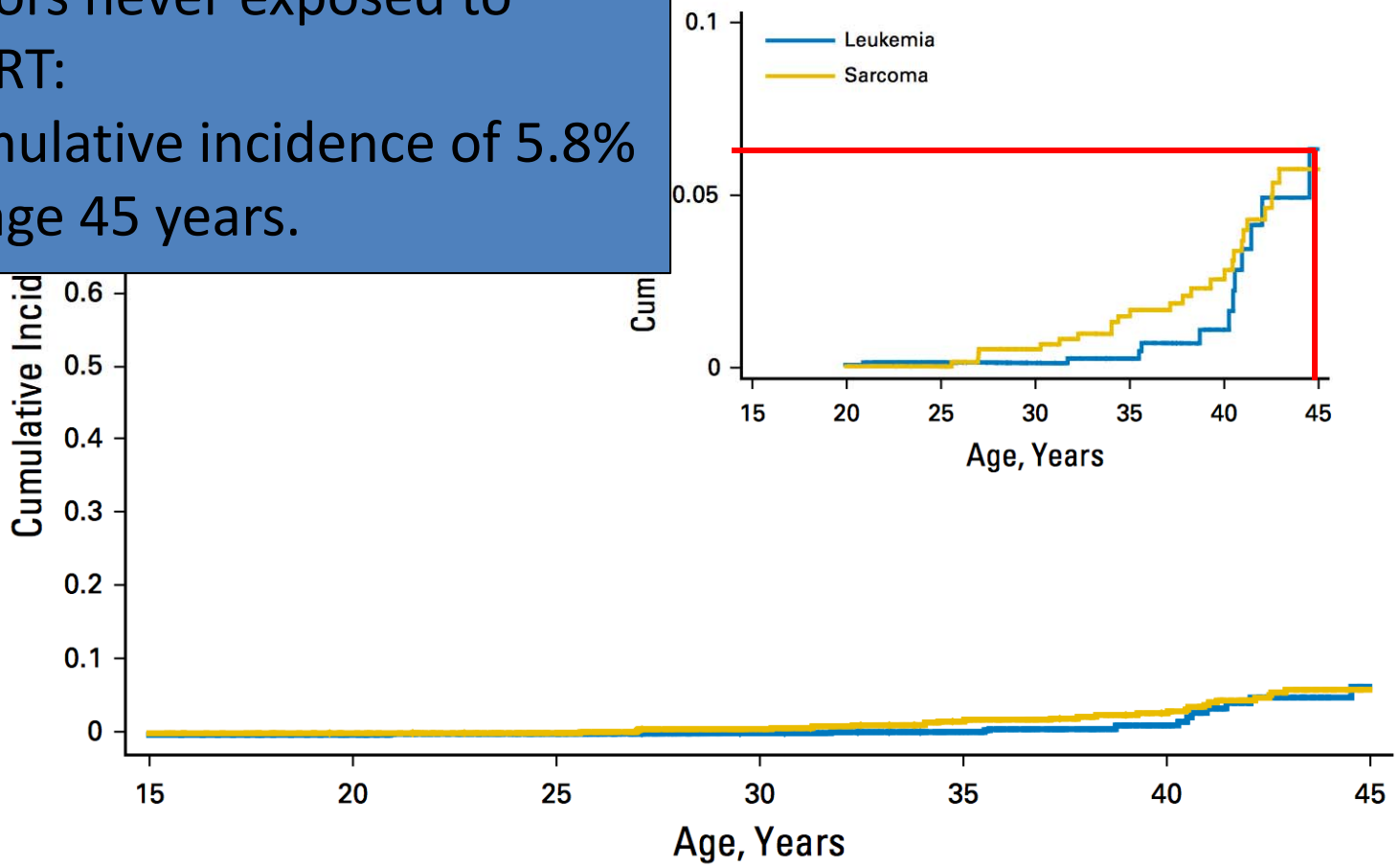


Henderson et al. J Clin Oncol. 2016.

CCSS: Breast Cancer Risk in Women Not Exposed to Chest RT

Among leukemia and sarcoma survivors never exposed to chest RT:

- Cumulative incidence of 5.8% by age 45 years.



Henderson et al. J Clin Oncol. 2016.

Multivariable Risk Factor Analysis in Women Not Exposed to Chest RT

Variable	Whole Cohort			Leukemia/Sarcoma		
	No. of Patients With Breast Cancer	Relative SIRs (95% CI)	*P*	No. of Patients With Breast Cancer	Relative SIRs (95% CI)	*P*
Cyclophosphamide equivalent dose, mg/m^2						
0	15	—	.044	10	—	.045
1-5,999	4	0.6 (0.2 to 2.0)		4	0.7 (0.2 to 2.3)	
6,000-17,999	16	1.6 (0.7 to 3.5)		15	1.9 (0.8 to 4.5)	
≥ 18,000	7	3.0 (1.2 to 7.7)		6	3.4 (1.2 to 9.7)	
Anthracycline dose, mg/m^2						
0	12	—	.004	6	—	.005
1-249	4	2.6 (0.8 to 8.7)		4	4.3 (1.1 to 16.6)	
≥ 250	26	3.8 (1.7 to 8.3)		25	5.1 (1.9 to 13.7)	
Age at primary cancer diagnosis, years						
0-9	6	—	.077	4	—	.147
10-20	36	2.3 (0.9 to 5.8)		31	2.3 (0.7 to 7.0)	
Ethnicity			.849			.944
White, non-Hispanic	37	—		31	—	
Minorities	5	1.1 (0.4 to 2.8)		4	1.0 (0.4 to 3.0)	
Current age, years			.380			.661
5-29	4	—		4	—	
30-34	11	1.3 (0.4 to 4.1)		7	0.8 (0.2 to 2.7)	
35-39	8	0.6 (0.2 to 1.9)		7	0.5 (0.1 to 1.7)	
40+	19	0.8 (0.3 to 2.5)		17	0.7 (0.2 to 2.2)	

NOTE. Survivors with complete data on all risk factors were included.
Abbreviation: SIR, standardized incidence ratio.

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Exploiting the expanded cohort:

- New associations between exposures and SNs - chemo only analysis, late leukemias, others
- More detailed investigations of earlier reports - breast ca, colon ca & other carcinomas, lung ca - within these we could look at temporal changes depending on number
- XRT impact over time - are newer modalities and better targeting changing risk

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Investigating Genomic Variants

- Collaborate on ongoing and future analyses of GWAS and WES data related to SN development
  - Joint effects of treatment and genetic susceptibility for major treatment-related SN types (e.g., breast, thyroid, meningioma, BCC, sarcoma)
  - Consideration of unique genetic susceptibility for other, more rare tumors
  - Combination meeting of Genetics and SN Working Group today

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Interventions

- Work with Cancer Control Committee for further screening efforts in high-risk survivors