Subsequent Neoplasm Working Group Report

Lucie Turcotte, MD, MPH, MS

June 19, 2025

CCSS
Childhood Cancer Survivor Study

St. Jude Children's Research Hospital

An NCI-funded Resource

Scope of Research

CCSS

- Oversee the complete and accurate ascertainment of subsequent neoplasms in the CCSS survivor cohort
- Establish the incidence, therapeutic and clinical risk factors, and temporal changes in subsequent neoplasms
- Identify novel associations, in collaborations with other working groups, with subsequent neoplasm risk

Working Group Membership

CCSS

Lucie Turcotte, University of Minnesota
Joseph Neglia, University of Minnesota
Cindy Im, University of Minnesota
Mike Arnold, University of Colorado
Miriam Conces, Nationwide Children's Hospital
Dana Barnea, Tel Aviv Sourasky Medical Center
Sandy Constine, University of Rochester
Taumoha Ghosh, University of Utah
Tara Henderson, Lurie Children's Hospital
Yuehan Wang, NIH/NCI

Rebecca Howell, M.D. Anderson
Constance Owens, M.D. Anderson
Susan Smith, M.D. Anderson
Lenat Joffee, Northwell Health
Andrea Lo, University of British Columbia
Chaya Moskowitz, Memorial Sloan Kettering
Carmen Perez, St. Jude
Stephanie Schaub, University of Washington
Jennifer Yeh, Harvard Medical School

Working Group Progress

CCSS

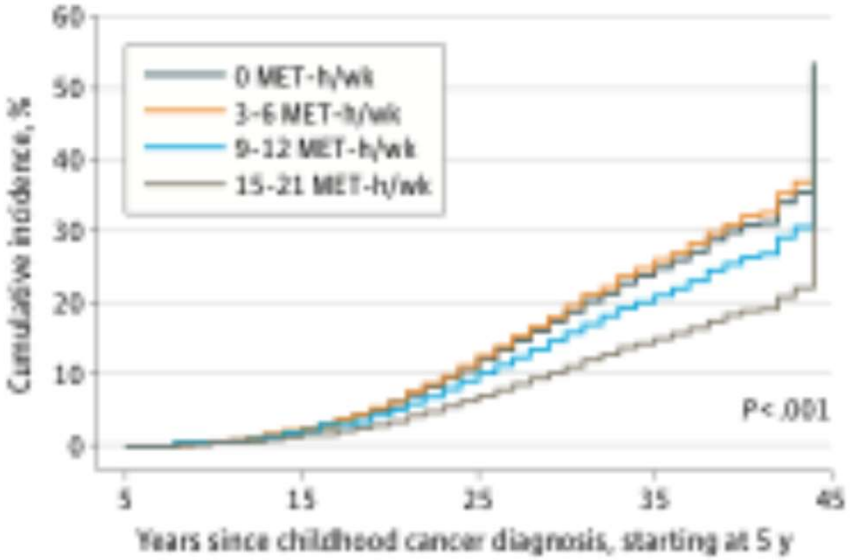
11 Published/In Press Manuscripts (since 1/1/2023)
5 Currently Submitted Manuscripts
6 Analyses/Manuscripts in Process
9 Concepts in development
20 New AOIs (total, since 1/1/2023)

Highlights of Recently Completed Research

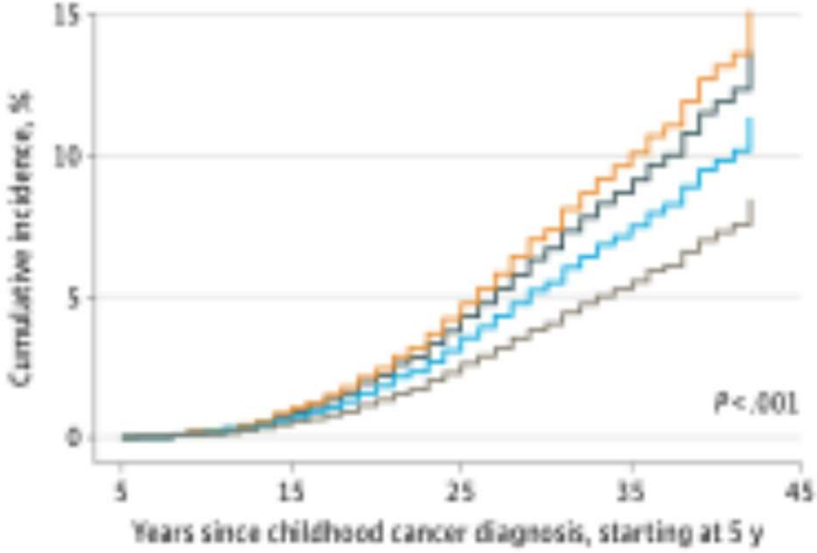
CCSS

Body Mass Index, Physical Activity, and Subsequent Neoplasm Risk Among Childhood Cancer Survivors (Lenat Joffe)

Any Neoplasm



Solid Organ Neoplasm



Joffe L et al. JAMA Oncology 2025.

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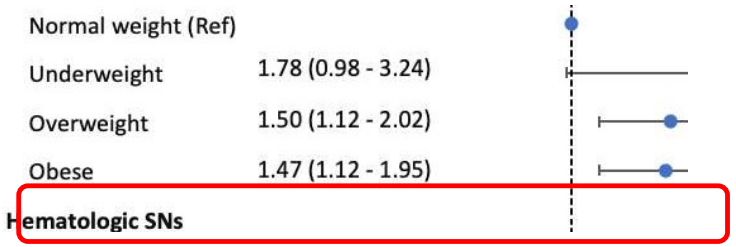
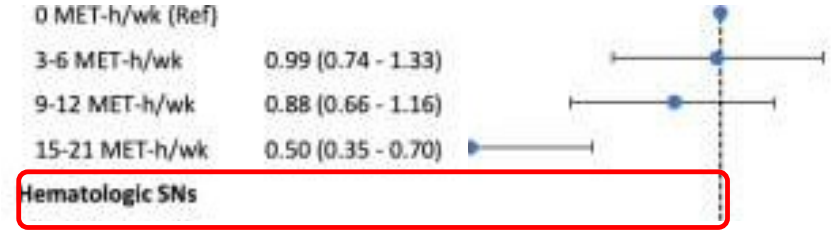


Thyroid 1.64 (1.15-2.34)
Meningioma 1.48 (1.09-2.00)



Thyroid 0.53 (0.34-0.83)
Meningioma 0.51 (0.35-0.75)

Joffe L et al. JAMA Oncology 2025.

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Highlights of Recently Completed Research

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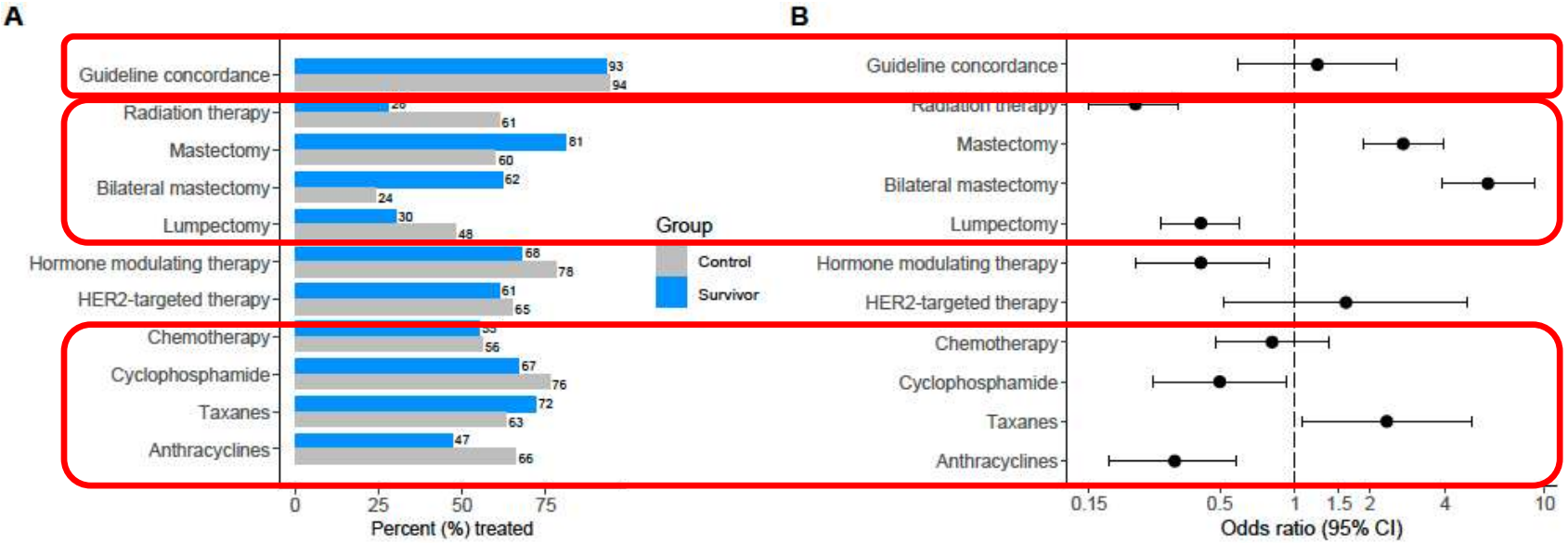
Treatment, toxicity, and mortality after subsequent breast cancer in female survivors of childhood cancer (Cindy Im)



Im C et al. Nature Communications 2025.

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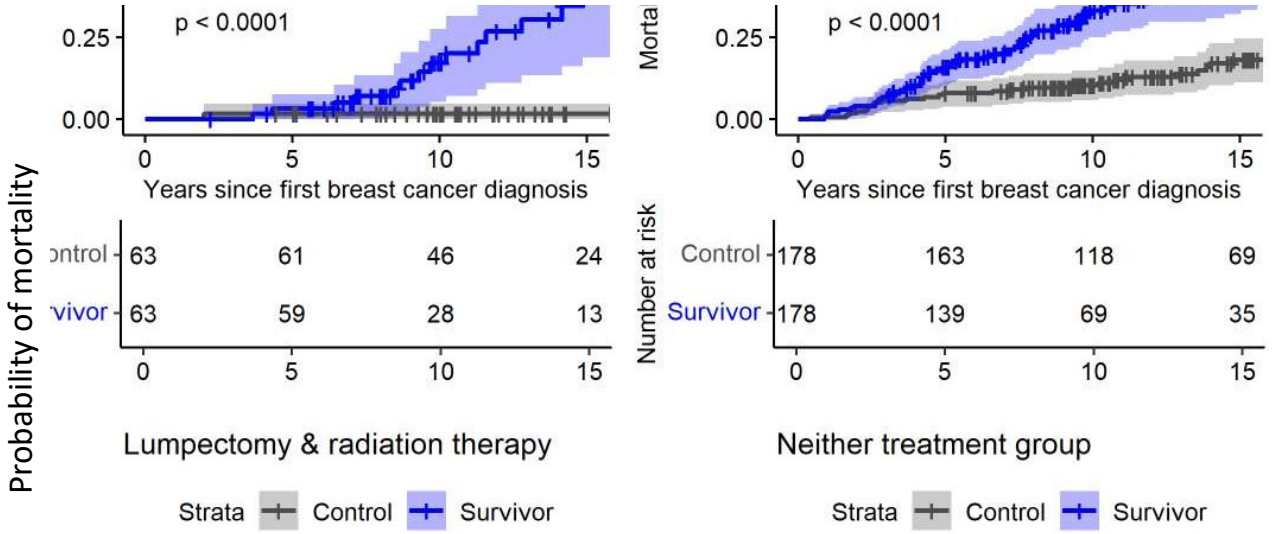

Time since breast cancer diagnosis (years)

Im C et al. Nature Communications 2025.

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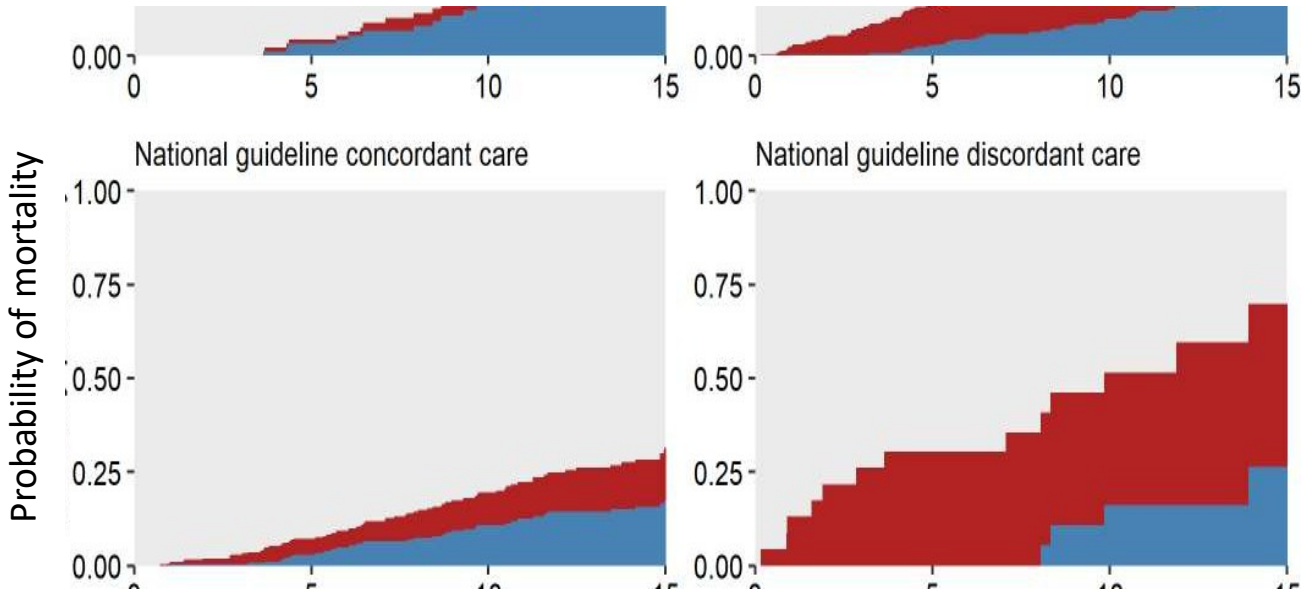

Im C et al. Nature Communications 2025.

Highlights of *Nearly* Completed Research

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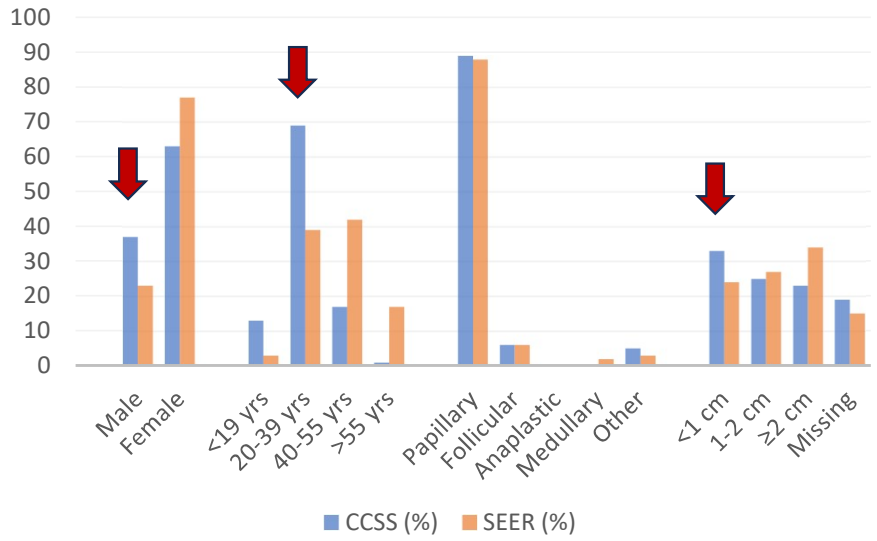
Mortality in survivors of childhood cancer diagnosed with subsequent thyroid cancer: A report from the Childhood Cancer Survivor Study (Dana Barnea)



- Of ***397 childhood cancer survivors with thyroid cancer***, 82 deaths occurred, 7 of which due to thyroid cancer.
- Thyroid cancer survivors were 7 times more likely to die compared to the general population (SMR=6.9, 95% CI 5.5-8.5).
- However, survivors were not at increased risk of thyroid cancer-related mortality compared to thyroid cancer patients in the general population (RR=1.0, 95% CI 0.5-2.3).

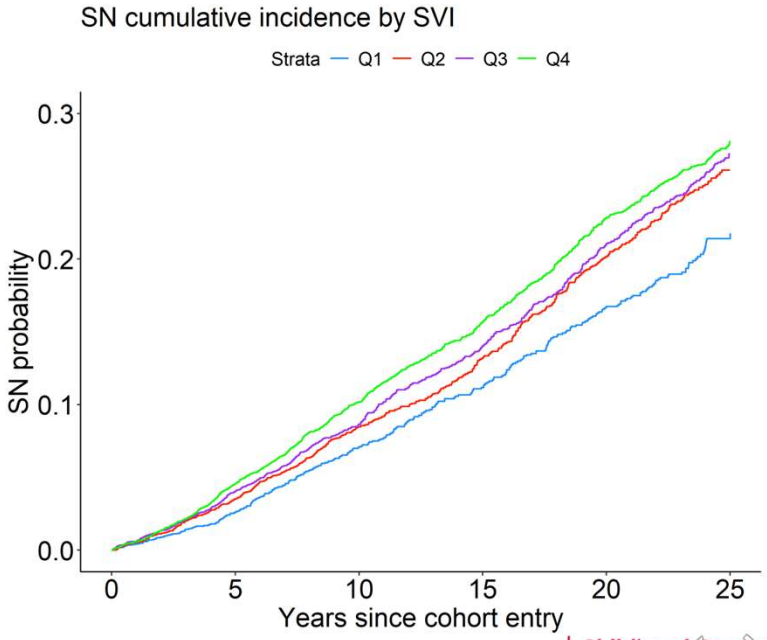
Highlights of *Nearly* Completed Research

CCSS

Socioeconomic status and associations with subsequent neoplasms among survivors of childhood cancer (Taumoha Ghosh)

Social vulnerability index	Multivariable model, adjusted for demographics, cancer/treatment features (n=17,895)	
	HR (95% CI)	P
Overall score (ref=Q1)		
Q2	1.15 (1.03 - 1.28)	0.0117
Q3	1.27 (1.14 - 1.4)	< 0.001
Q4	1.42 (1.29 - 1.57)	< 0.001
	P-trend:	< 0.001

Q1 = most vulnerability, Q4 = least vulnerability



Active Ancillary Study Highlights—IPD Cohort

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Consortium Core Group	
Dutch KiKa grant	Study Group Representatives
Principal investigators Cecile Ronckers Leontien Kremer Flora van Leeuwen	North American Childhood Cancer Survivor Study
	St. Jude Lifetime Cohort
	US National Wilms' Tumor Study
Post doctoral researcher Jop Teepen	Dutch Childhood Oncology Group LATER
	French Childhood Cancer Survivor Study
Post doctoral fellow Yuehan Wang	Swiss Childhood Cancer Survivor Study
	ALiCCS collaborative study (Nordic Countries; Danish part)
	Dutch Hodgkin Late Effects cohort

1. To address 3 clinically relevant research questions on treatment-related subsequent breast cancer risk

- Chest Radiotherapy: prescribed chest-radiotherapy doses <20Gy
- Chemotherapy: role of specific anthracyclines
- Attained Age: to examine whether excess risks remain increased across the lifespan, especially after age 50 yrs

2. To establish a harmonized database of international cohorts

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Active Ancillary Study Highlights—IPD Cohort

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IPD lung cancer, thyroid cancer, melanoma (Jop Teepen)

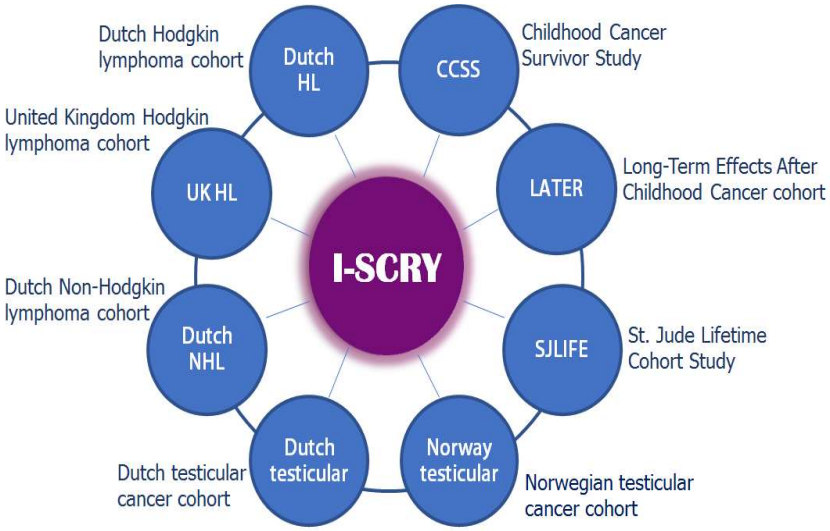
- Expand the IPD cohort (currently 22,000 females) to include up to 50,000 female and male survivors of childhood and adolescent cancer
- Investigate risks and risk factors for:
  - Lung cancer, including sub-types such as mesothelioma
  - Thyroid cancer
  - Melanoma
- SMN (primary) and Genetics (secondary) working groups

Active Ancillary Study Highlights– I-SCRY

CCSS

Purpose

- To create a large pooled source of harmonized data with detailed information on treatment exposures and outcomes in childhood, adolescent, and young adult cancer survivors
- To evaluate the association of childhood, adolescent, and young adult cancer therapy on colorectal cancer risk in a large, multi-cohort, international survivor population



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Active Ancillary Study Highlights— I-SCRY

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56,202 childhood, adolescent, and young adult cancer survivors

Inclusion criteria:

- In one of 8 contributing cohorts
- Diagnosed with a cancer:
  - Ages 0 - 39 yrs
  - 1953 - 2012
- Survived ≥ 5 yrs after primary dx

- 277 survivors diagnosed with colorectal cancer
- Age at primary cancer, years:
  - Median 17, range 0-39
- Latency period, years:
  - Median 27, range 5-51

Plan to Use FU7 Frozen Data

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- Develop clinically relevant risk prediction models for:
  - Basal cell carcinoma → inform current guidelines for timing of screening (submitted)
  - Meningioma-associated morbidity → incorporate germline and somatic genetics, phenotypic features, treatment exposures → identify high-risk tumors that are likely to cause morbidity/require intervention (under development)
- Provide deeper phenotyping of identified SMNs (ancillary study proposed):
  - Abstract tumor size, location, cytogenetic and molecular characteristics
  - Abstract treatment and outcomes data

Plan for Concept Development Using FU8 Survey Data Focused on Aging

CCSS

- Assess frailty and measures of aging (both clinical and genetic) as risk factors for subsequent neoplasms: analyses underway led by Dr. Amy Berkman (CDA Awardee)

- Investigate how subsequent neoplasm development impacts measures of frailty and aging

Opportunities for Collaboration with Other Working Groups

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- Epi/Biostatistics: So many opportunities...
- Genetics: Identifying therapy associated mutational signatures in SNs (Wednesday plenary); Incorporating genetic data into SMN risk prediction (concepts in development)
- Chronic Disease: Trajectory of CHCs after SMNs; burden of CHCs and SMN risk
- Psychology: Chronic emotional stress and SMN risk and SMN-associated mortality (concept in development)
- Cancer Control: SES (and SDOH) as risk factors for SMNs (analyses in progress); impact of screening practices on SMN outcomes (concept in development)

As CCSS Engages with Participants This Year What Would You Like to Learn From Them?

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- How survivors make decisions about SMN screening/surveillance practices?
- Treatment decision-making considerations for SMNs → how do survivors engage with oncologists and what are drivers in how they approach SMN treatment? What have they learned in survivorship care that has shaped how they approach a subsequent cancer diagnosis and treatment?
- How/if survivors with SMNs want to engage with CCSS after being diagnosed with subsequent malignancies?

Value Added to Your Working Group by a 2000-2025 Cohort Expansion

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- Important changes in childhood cancer treatments that may impact SMN incidence/risk:
  - Reduced use of therapeutic radiation, changes in radiation modality
  - Introduction of targeted immunotherapies (CAR-T, blinatumomab, rituximab, brentuximab)
  - Continued improvements in risk stratification in many diseases
- Growing population of survivors with high-risk primary cancers (more heavily treated)
- Increasing recognition of SMN risk/need for early cancer screening
- Interest in how changes in racial and ethnic make-up of contemporary population may impact SN risk and outcomes

Special Considerations for a Cohort Expansion Specific to Your Working Group

CCSS

Targeted recruitment of certain diseases/treatments may be higher yield for SN learning

- Radiation modalities (3D, IMRT, protons) to understand differences and compare to historical modalities
- Immunotherapies/targeted therapies

Important to collect SN tumor tissue, imaging, germline genetic data, potentially immune function (quantitative), treatment, etc.

Five Year Plan: Progress Update

CCSS

- Evaluate changes in incidence of and risk factors, including obesity, for SNs based on temporal changes in primary therapy
- Identify genetic susceptibility for SNs that modifies risk conferred by therapeutic exposure
- Utilize the large CCSS cohort to identify populations at high risk for SNs among aging survivors
- Describe treatment of SNs and associated toxicities and outcomes

Five Year Plan: Progress Update

CCSS

Evaluate changes in incidence of and risk factors, including obesity, for SNs based on temporal changes in primary therapy

- *Examined obesity and physical activity as SN risk factors, have not examined temporal changes*

Identify genetic susceptibility for SNs that modifies risk conferred by therapeutic exposure

Utilize the large CCSS cohort to identify populations at high risk for SNs among aging survivors

Describe treatment of SNs and associated toxicities and outcomes

Five Year Plan: Progress Update

CCSS

- Evaluate changes in incidence of and risk factors, including obesity, for SNs based on temporal changes in primary therapy
- Identify genetic susceptibility for SNs that modifies risk conferred by therapeutic exposure
  - *Im C, Sharafeldin N, et al. Polygenic Risk and Chemotherapy-Related Subsequent Malignancies in Childhood Cancer Survivors: A Childhood Cancer Survivor Study and St Jude Lifetime Cohort Study Report. JCO 2023.*
  - *Gibson TM et al. Polygenic risk scores, radiation treatment exposures and subsequent cancer risk in childhood cancer survivors. Nat Med 2024.*
  - *Watt G. Germline genetic variation and the risk of chemotherapy-associated SMNs for survivors of childhood cancers. Oral presentation at ISLCCC 2024; manuscript in progress.*
  - *Brady S. The Genomic Landscape of SMNs in Childhood Cancer Survivors. Manuscript submitted*.
- Utilize the large CCSS cohort to identify populations at high risk for SNs among aging survivors
- Describe treatment of SNs and associated toxicities and outcomes

Five Year Plan: Progress Update

CCSS

- Evaluate changes in incidence of and risk factors, including obesity, for SNs based on temporal changes in primary therapy
- Identify genetic susceptibility for SNs that modifies risk conferred by therapeutic exposure
- Utilize the large CCSS cohort to identify populations at high risk for SNs among aging survivors
  - *Bhandari R et al. Mortality and burden of subsequent malignant neoplasms in survivors of childhood cancer beyond age 50: A report from the CCSS. Manuscript submitted.*
- Describe treatment of SNs and associated toxicities and outcomes

Five Year Plan: Progress Update

CCSS

- Evaluate changes in incidence of and risk factors, including obesity, for SNs based on temporal changes in primary therapy
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- Describe treatment of SNs and associated toxicities and outcomes
  - *Im C et al. Treatment, toxicity, and mortality after subsequent breast cancer in female survivors of childhood cancer. Nat Comm 2025.*
  - *Im C et al. Breast cancer recurrence and mortality among survivors of childhood cancer. Manuscript in progress.*

Current Top Priorities: One-Year Deliverables

CCSS

- Expand cross-working group collaborations to enhance opportunities for studies on etiology or interventions
  - Deliverable: Identify at least 3 new partnerships within other working groups (Genetics, Cancer Control, Psychology, etc.) that lead to new Concepts
- Develop projects that leverage existing biospecimen data
  - Deliverable: Develop ≥ 2 subsequent neoplasm working group projects that use existing clinical and biospecimen data
- Continue to engage early career faculty in working group activities
  - Deliverable: Have 1-2 junior investigators apply for CCSS CDA with SMN-focused projects

Working Group Threats and Opportunities

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- Major Threat or Challenges:
  - Outdated treatment exposures among current cohort—outcomes may not be applicable to contemporary survivors
  - Accelerating number of subsequent neoplasm events for validation

- Major Opportunity:
  - Using the Virtual Pooled Registry (VPR) to capture subsequent malignancies—pilot captured data from 26 registries, now increased to 43+ registries
  - Leveraging new/possible genetic data (somatic data, +/- CHIP)

Final Reminder: An Amazing Resource

CCSS

Subsequent Neoplasm	Total Cases Ascertained		Initial Cohort		Expansion Cohort		Ascertained from FU7 or diagnosed since June 2020	
	N	%	N	%	N	%	N	%
All Subsequent Neoplasms	**11325**	**100.0**	**8651**	**100.0**	**2674**	**100.0**	**1663**	**100.0**
Leukemia	106	0.9	68	0.8	38	1.4	7	0.4
ALL	18	0.2	15	0.2	3	0.1	0	0
AML	56	0.5	35	0.4	21	0.8	3	0.2
Other leukemia	32	0.3	18	0.2	14	0.5	4	0.2
Lymphoma	**104**	**0.9**	**72**	**0.8**	**32**	**1.2**	**10**	**0.6**
Hodgkin	24	0.2	15	0.2	9	0.3	2	0.1
Non-Hodgkin	79	0.7	56	0.6	23	0.9	8	0.5
Other lymphoma	1	0.0	1	0.0	0	0.0	0	0.0
CNS	**1205**	**10.6**	**929**	**10.7**	**276**	**10.3**	**189**	**11.4**
Glial	163	1.4	93	1.1	70	2.6	10	0.6
Medullo/PNET	10	0.1	7	0.1	3	0.1	0	0.0
Meningioma	992	8.8	797	9.2	195	7.3	177	10.6
Other CNS	40	0.4	32	0.4	8	0.3	2	0.1

Final Reminder: An Amazing Resource

CCSS

Subsequent Neoplasm	Total Cases Ascertained		Initial Cohort		Expansion Cohort		Ascertained from FU7 or diagnosed since June 2020	
	N	%	N	%	N	%	N	%
Solid Organ	**2195**	**19.4**	**1623**	**18.8**	**572**	**21.4**	**231**	**13.9**
Breast	767	6.8	606	7.0	161	6.0	74	4.4
Bone	68	0.6	52	0.6	16	0.6	2	0.1
Soft tissue sarcoma	246	2.2	174	2.0	72	2.7	19	1.1
Thyroid	429	3.8	264	3.1	165	6.2	28	1.7
Other solid organ	685	6.0	527	6.1	158	5.9	108	6.5
Skin	**7501**	**66.2**	**5800**	**67.0**	**1701**	**63.6**	**1215**	**73.1**
Melanoma	182	1.6	134	1.5	48	1.8	18	1.1
Non-melanoma Skin Cancer	7319	64.6	5666	65.5	1653	61.8	1197	72.0
Unspecified Cancer	**214**	**1.9**	**159**	**1.8**	**55**	**2.1**	**11**	**0.7**

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Childhood Cancer Survivor Study

Questions?

Join our Subsequent Neoplasm Working Group Meetings! Second Mondays of the month, 10:00am CST, via Zoom.

Email turc0023@umn.edu if you are interested or if you have questions.

St. Jude Children's Research Hospital