Second Malignancies Working Group

A Report from the Childhood Cancer Survivor Study

Joseph P. Neglia, MD, MPH

CCSS
Childhood Cancer Survivor Study

St. Jude Children's Research Hospital

An NCI-funded Resource

Working Group Membership

CCSS

- Lucie Turcotte
- Tara Henderson
- Rebecca Howell
- Mike Arnold
- Chaya Moskowitz
- Greg Armstrong
- Joseph Neglia

Working Group Progress

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- 11 (6): Published/In Press Manuscripts (since Investigator Meeting, 6/2017)
- 1 Currently Submitted Manuscript
- 4 Analysis/Manuscript in Process
- 3 Concepts in development
- 2 New AOIs

Highlights of Recently Completed Research

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- Tara Henderson – HPV-associated Malignancies in Survivors of Childhood Cancer / reanalyzed with expanded cohort / finalizing analysis
- Lucie Turcotte – SMNs among Childhood Cancer Survivors not exposed to radiation therapy / Presented at ASCO 2018 / under review
- Chaya Moskowitz –Mortality following Breast Cancer in Survivors of Childhood Cancer / Presented at ASCO 2018 / accepted J Clin Oncol
- Lene Veiga - Breast cancer risk after childhood cancer according to radiation dose to the breast and anthracyclines / Presented at ASCO 2017 / accepted JAMA Peds

Childhood Cancer Survivor Study

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Human papillomavirus-associated malignancies as subsequent malignant neoplasms in survivors of childhood cancer:

A report from the Childhood Cancer Survivor Study (CCSS)

Henderson, TO, MD, MPH, Fowler, B, MPH, Nathan, PC, MD, MSc, Whitton, J, MS, Leisenring, W, ScD, Oeffinger, KC, MD, Neglia, JP, MD, MPH, Arnold, MA, MD, PhD, Howell, RM, PhD, Robison, LL, PhD, Armstrong, GT, MD, MSCE, Alexander, KA, MD, PhD

Childhood Cancer Survivor Study

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Rationale

- Hypothesized that childhood cancer survivors are at increased risk of SMN due to HPV associated cancers
- Findings could facilitate surveillance guidelines
- Findings could further justify increased HPV vaccination for childhood cancer survivors.

Childhood Cancer Survivor Study

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- HPV-associated SMNs:
  - Oral cavity, oropharynx, pharynx, rectum, cervix uteri, vagina, and vulva

- Genitourinary adenocarcinomas were excluded as they are not associated with HPV

Childhood Cancer Survivor Study
HPV-Associated SMNs

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		Observed	Expected	SIR	95% CI
Overall rate		53	18.56	2.86	2.05-4.00
Sex	Male	24	5.88	4.06	2.51-6.54
	Female	29	12.68	2.31	1.45-3.68
Age at 1st diagnosis	0-4	53	18.56	2.86	2.05-4.00
	5-9	24	5.88	4.06	2.51-6.54
	10-14	29	12.68	2.31	1.45-3.68
	15-20	53	18.56	2.86	2.05-4.00

Childhood Cancer Survivor Study
HPV-Associated SMNs

CCSS

	Observed	Expected	SIR	95 %CI
Leukemia	19	4.91	3.89	1.91-7.92
CNS	2	2.15	0.93	0.23-3.72
Hodgkin	4	4.27	0.94	0.35-2.50
NHL	5	1.48	3.37	1.40-8.12
Kidney (Wilms)	0	0.96	1.00	.
Neuroblastoma	3	0.59	5.07	1.63-15.78
Soft tissue sarcoma	12	1.79	6.71	3.81-11.84
Bone cancer	8	2.41	3.32	1.66-6.66

Childhood Cancer Survivor Study
HPV-Associated SMNs: *Multivariable Cox model*

CCSS

		Hazard Ratio	95% CI
Sex	Male	2.00	1.01-3.98
	Female	1.00	ref
Age at primary dx	0-9	2.35	1.23- 4.49
	10-20	1.00	ref
Platinum (Cis-PT equiv.) dose	0 mg/m2	1.00	ref
	>0 - 400 mg/m2	1.21	0.28-5.24
	>400 mg/m2	3.93	1.58-9.76
Max head, neck, pelvis RT dose	0 cGy	1.00	ref
	>0 - 200 cGy (scatter)	1.26	0.42-3.80
	>200 - 2000 cGy	1.52	0.46-5.07
	>2000 - 3000 cGy	0.96	0.26-3.52
	>3000 cGy	3.24	1.55-6.77

Childhood Cancer Survivor Study
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Childhood Cancer Survivor Study
HPV-Associated SMNs

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Early Conclusions

- Childhood cancer survivors are at increased risk for HPV associated SMNs
- Radiation, high dose platinum are associated with SMN risk
- This work provides support for HPV vaccination in the survivor population
- Additional analyses underway on treatment era effect

Subsequent Malignant Neoplasms Among Non-Irradiated Survivors of Childhood Cancer Treated with Chemotherapy in the Childhood Cancer Survivor Study

Under review, J Clin Oncol 2019

Lucie M. Turcotte, Qi Liu, Yutaka Yasui, Tara O. Henderson, Todd M. Gibson, Wendy Leisenring, Michael A. Arnold, Rebecca M. Howell, Daniel M. Green, Gregory T. Armstrong, Leslie L. Robison, Joseph P. Neglia

UNIVERSITY OF MINNESOTA

Driven to Discover℠

Department of Pediatrics, Division of Hematology/Oncology

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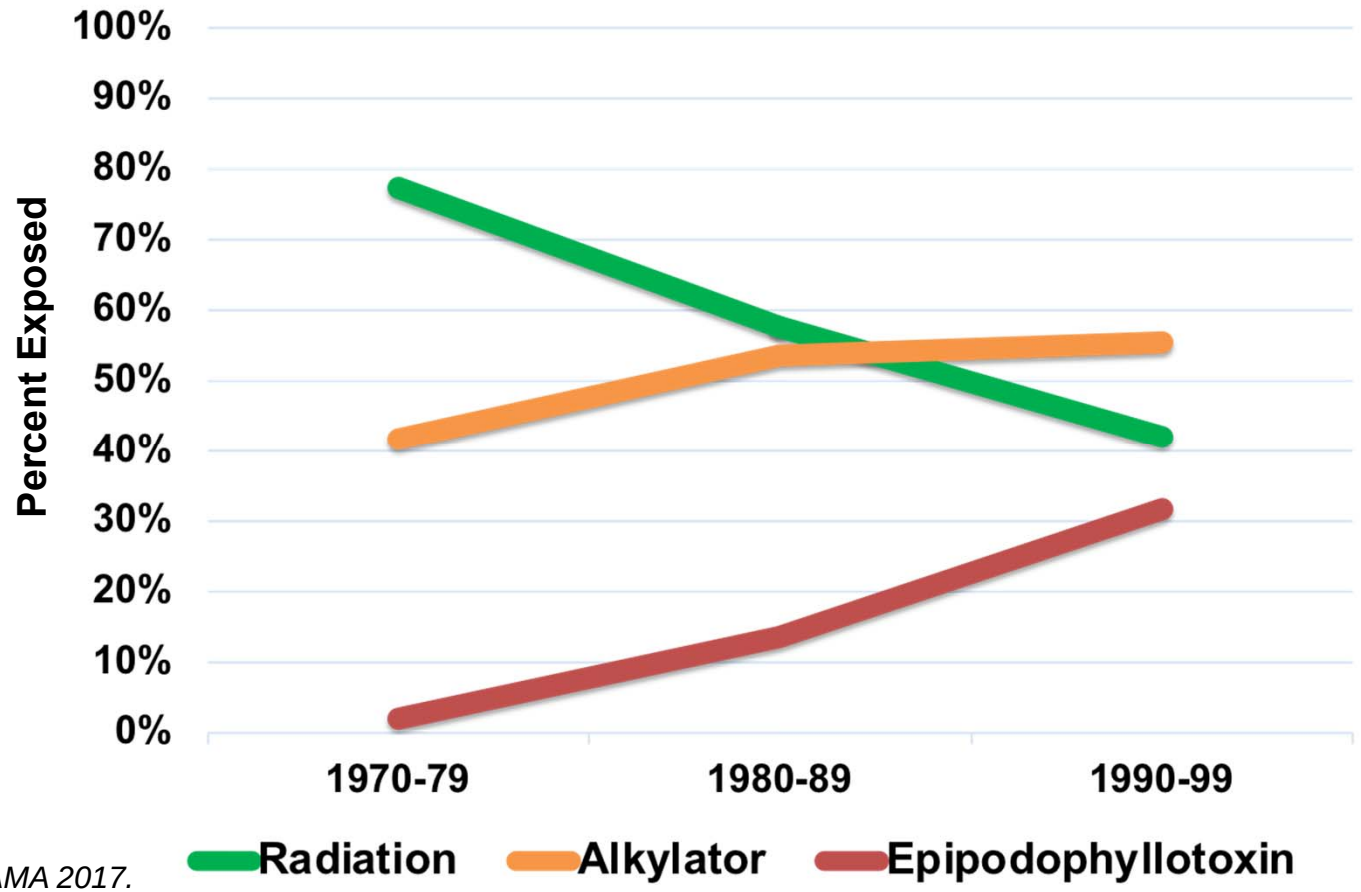
Temporal Changes in Therapeutic Exposures



Turcotte LM et al. JAMA 2017.

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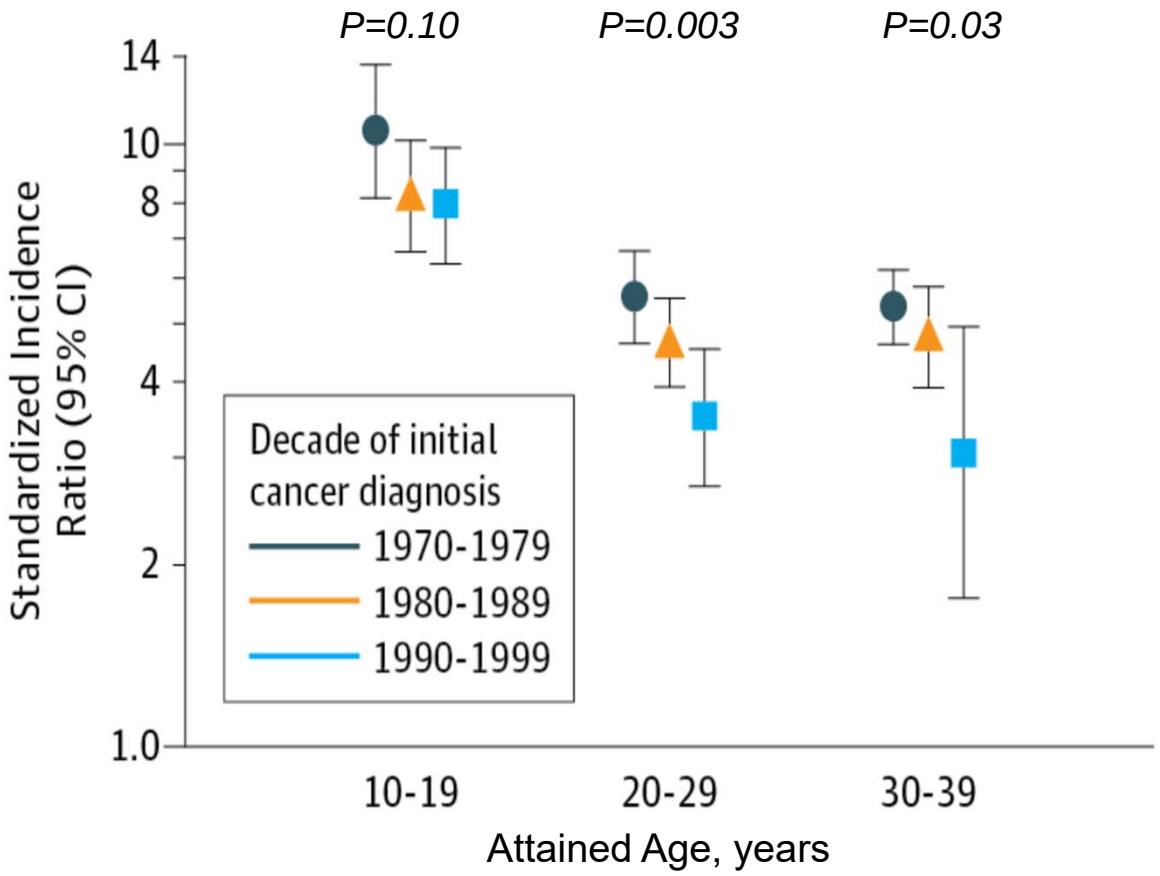
Temporal Changes in Subsequent Malignancies



Turcotte LM et al. JAMA 2017.

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Subsequent Malignant Neoplasms

Among 7,448 survivors exposed to chemotherapy and no radiation:

- 229 SMNs confirmed among 206 survivors
- Most common SMNs included (SMNs/survivors):
  - Breast (51/45)
  - Thyroid (36/35)
  - Melanoma (18/18)
  - Soft tissue sarcoma (14/13)

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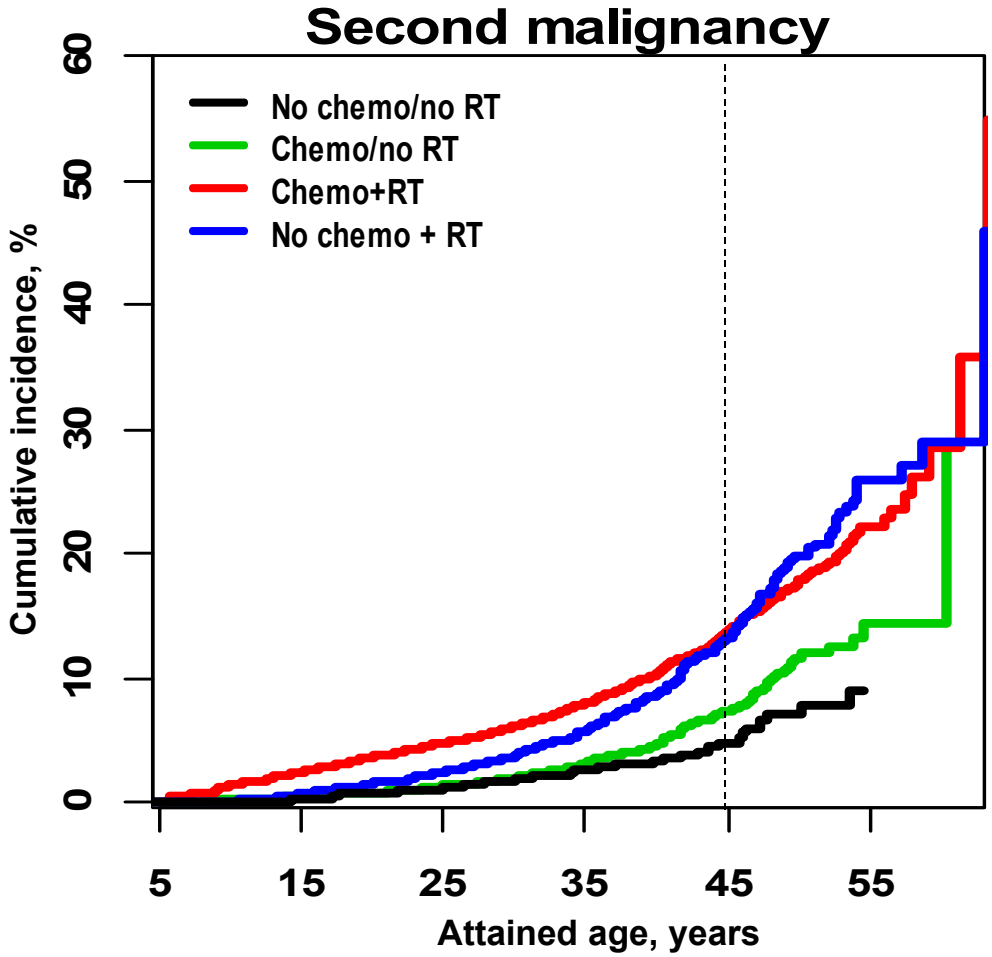
SMN Cumulative Incidence

At attained age of 45 years:

- Chemo + radiation
  13.7% (95% CI 12.4-15.0%)
- Radiation, no chemo
  13.3% (95% CI 11.1-15.3%)
- Chemo, no radiation
  7.4% (95% CI 6.1-8.8%)
- No chemo, no radiation
  4.8% (95% CI 3.0-6.5%)

P=0.015



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SMNs and Chemotherapy

	RR (95% CI)	P
Alkylating agent (mg/m²)*		
None	Ref	
1-3999	1.06 (0.58 - 1.93)	0.85
4000-7999	1.43 (0.89 - 2.32)	0.14
≥ 8000	1.74 (1.09 - 2.79)	0.02
Anthracycline (mg/m²)		
None	Ref	
0-100	0.96 (0.35 - 2.57)	0.93
101-300	1.23 (0.76 - 1.97)	0.40
>300	1.42 (0.89 - 2.24)	0.14
Epipodophyllotoxin (mg/m²)		
None	Ref	
1-1000	0.36 (0.13 - 1.01)	0.05
1001-4000	0.69 (0.33 - 1.45)	0.33
>4000	1.33 (0.61 - 2.93)	0.47
Platinum (mg/m²)^		
None	Ref	
1-400	1.00 (0.51 - 1.94)	0.99
401-750	1.01 (0.51 - 2.02)	0.98
>750	2.70 (1.14 - 6.40)	0.02

- Multivariable models also included:
  - Sex
    Females: RR 1.84 (1.30-2.61)
  - Age at diagnosis (NS)
  - 5 year treatment eras (NS)
  - History of splenectomy (NS)

*Cyclophosphamide equivalent dose
^Platinum correction= 0.25 (carboplatin) + cisplatin

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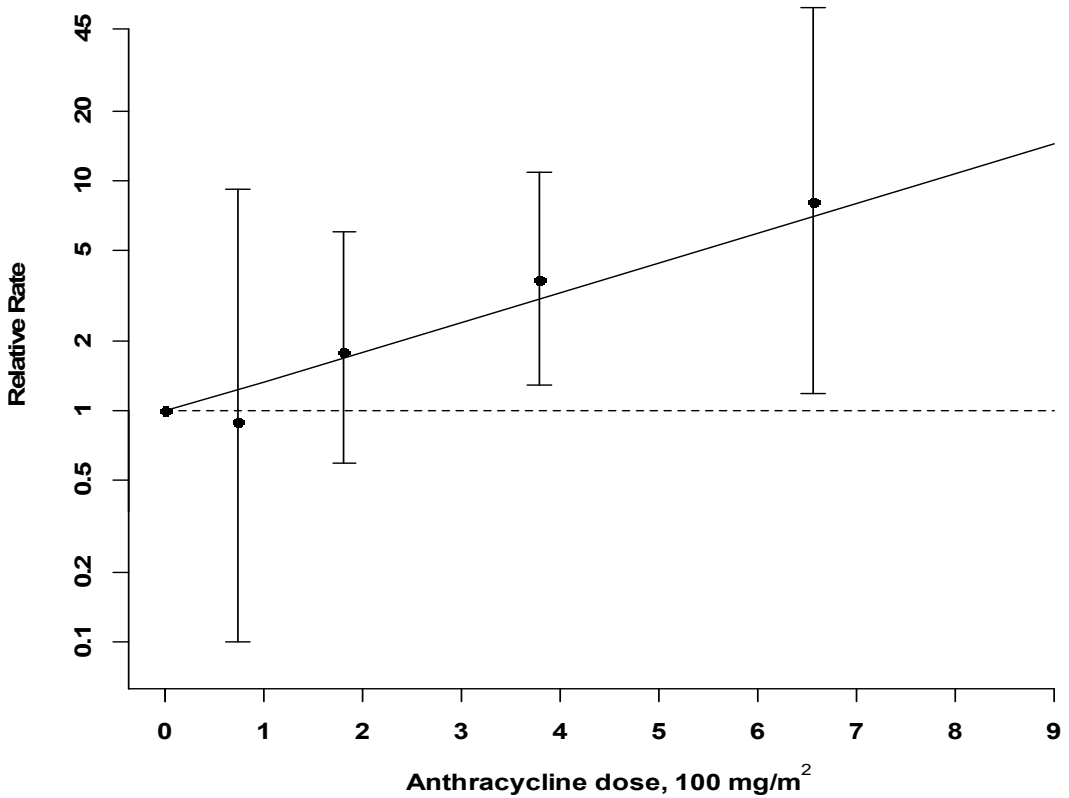
Breast Cancer Dose Response for Anthracycline Exposure



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Subsequent Malignant Neoplasms

Conclusions:

- CCSS participants not treated with radiotherapy are at incresed risk for SNs, though at a rate less than those treated with radiotherapy
- High doses of alkylating agents and platinum compounds are associated with increased risk
- Among women not treated with radiotherapy there appears to be a dose response increase in risk for breast cancer with increased anthracycline dose

Childhood Cancer Survivor Study
Radiation / Anthracylines / Breast Cancer

CCSS

- Veiga et al; in press JAMA Pediatrics
- 271 cases / 1044 controls

Breast dose [b]	Anthracyclines					
	No			Yes		
	Cases/Controls	OR	(95% CI)	Cases/Controls	OR	(95% CI)
	All breast cases					
0-<1 Gy	16/292	1.0	Ref.			
1-<10 Gy	21/116	2.1	(0.9 to 4.8)			
10+ Gy	108/188	9.6	(4.4 to 20.7)			

[a] ORs computed using conditional logistic regression models adjusted for type of first cancer, calendar year of follow-up and family history of breast or ovarian cancer and treatment with alkylating agents (y/n).

[b] Excluded patients with missing information on radiation dose and anthracycline treatment.

Childhood Cancer Survivor Study
Radiation / Anthracylines / Breast Cancer

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	All breast cases					
0-<1 Gy	16/292	1.0	Ref.	43/231	3.3	(1.6 to 6.8)
1-<10 Gy	21/116	2.1	(0.9 to 4.8)	10/36	3.7	(1.4 to 10.3)
10+ Gy	108/188	9.6	(4.4 to 20.7)	33/28	19.1	(7.6 to 48.0)

[a] ORs computed using conditional logistic regression models adjusted for type of first cancer, calendar year of follow-up and family history of breast or ovarian cancer and treatment with alkylating agents (y/n).

[b] Excluded patients with missing information on radiation dose and anthracycline treatment.

Childhood Cancer Survivor Study
Radiation / Anthracylines / Breast Cancer

CCSS

- The combination of anthracyclines and even moderate radiation doses to the breast (10+Gy) can markedly increase breast cancer risks

- These results can inform risk management for childhood cancer patients treated in the past, as well as potential breast cancer risk from current treatment protocols

Mortality Following Breast Cancer In Survivors of Childhood Cancer:

A Report from the Childhood Cancer Survivor Study

In press *J Clin Oncol 2019*

Chaya S. Moskowitz, Joanne Chou, Joseph P. Neglia, Rebecca M. Howell, Lisa R. Diller, Ann H. Partridge, Wendy L. Leisenring, Danielle Novetsky Friedman, Dana Barnea, Lindsay M. Morton, Lucie Turcotte, Gregory T. Armstrong, Leslie L. Robison, Kevin C. Oeffinger, Tara O. Henderson

Memorial Sloan Kettering Cancer Center
Department of Epidemiology and Biostatistics

Supported by the National Cancer Institute (R01CA136783; K07CA134935; U24CA55727), the Meg Berté Owen Fund, and the American Lebanese Syrian Association Charities

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Methods

Women with *de novo* breast cancer

- Surveillance, Epidemiology, and End Results Program (SEER)
- 5 controls for each case
- SEER controls matched to CCSS participants on:
  - Stage of diagnosis
  - Year of diagnosis
  - Age at diagnosis
  - Race / ethnicity

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Childhood cancer survivors

274 females with breast cancer

	Median	Range
Years from childhood cancer to 1st breast cancer	23	7-40
Age at first breast cancer diagnosis, years	38	20-58
Follow-up after breast cancer diagnosis, years	8	1-26

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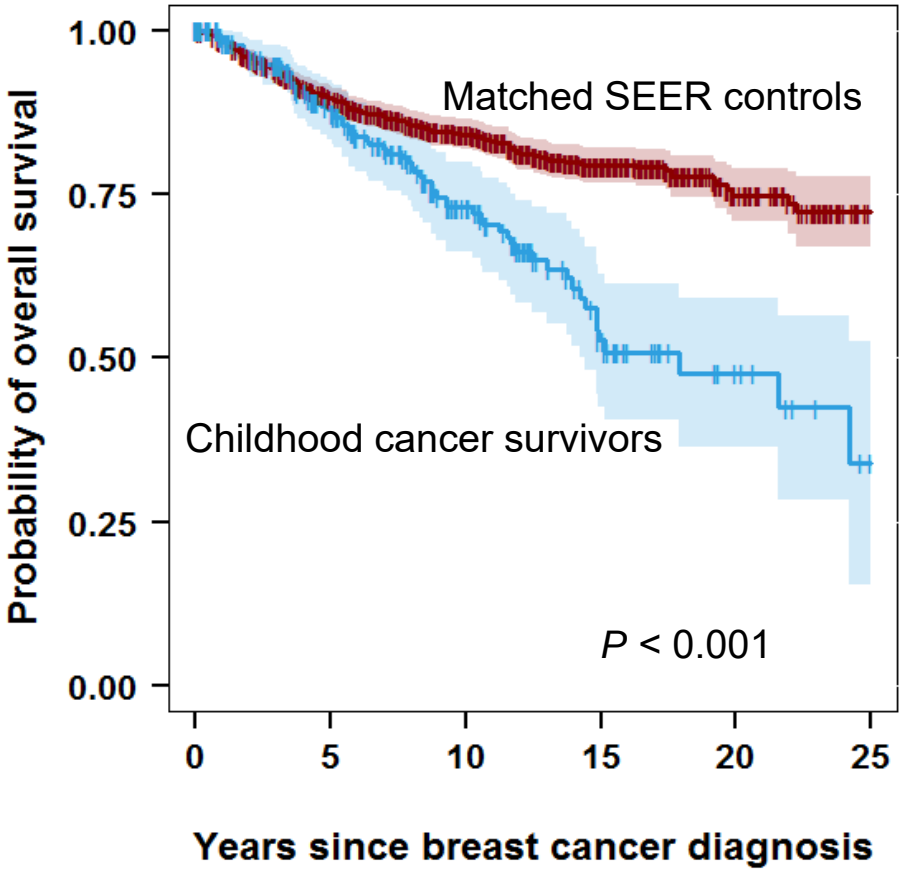
All-cause mortality after breast cancer

- 92 childhood cancer survivors deceased
  - 5-year overall survival: 85%
  - 10-year overall survival: 67%
- HR = 2.2 [95% CI: 1.7-3.0]
- HR similar after adjusting for breast cancer therapy:
  - Radiotherapy: HR = 2.2 [95% CI:1.7-3.1]
  - Chemotherapy: HR = 2.3 [95% CI: 1.8-3.2]
  - Both: HR = 2.4 [95% CI:1.7-3.2]



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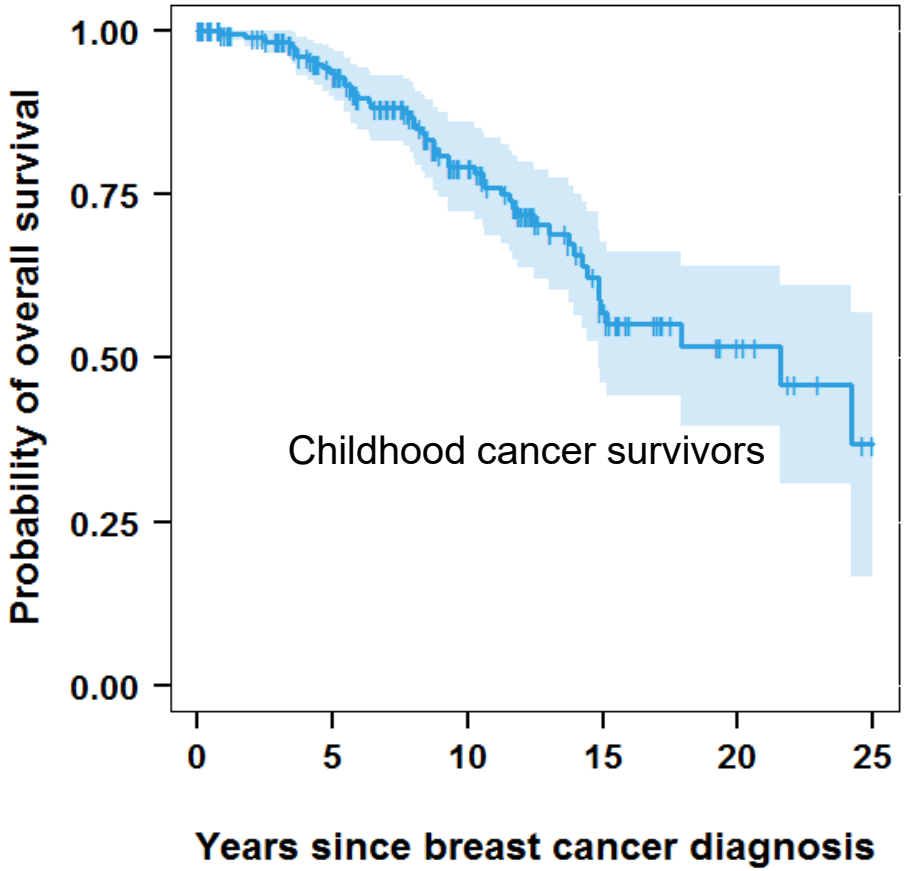
Survival after early stage breast cancer

- 200 childhood cancer survivors
- 50 deceased
  - 5-year overall survival: 94%
  - 10-year overall survival: 79%



CCSS
An NCI-Funded Resource

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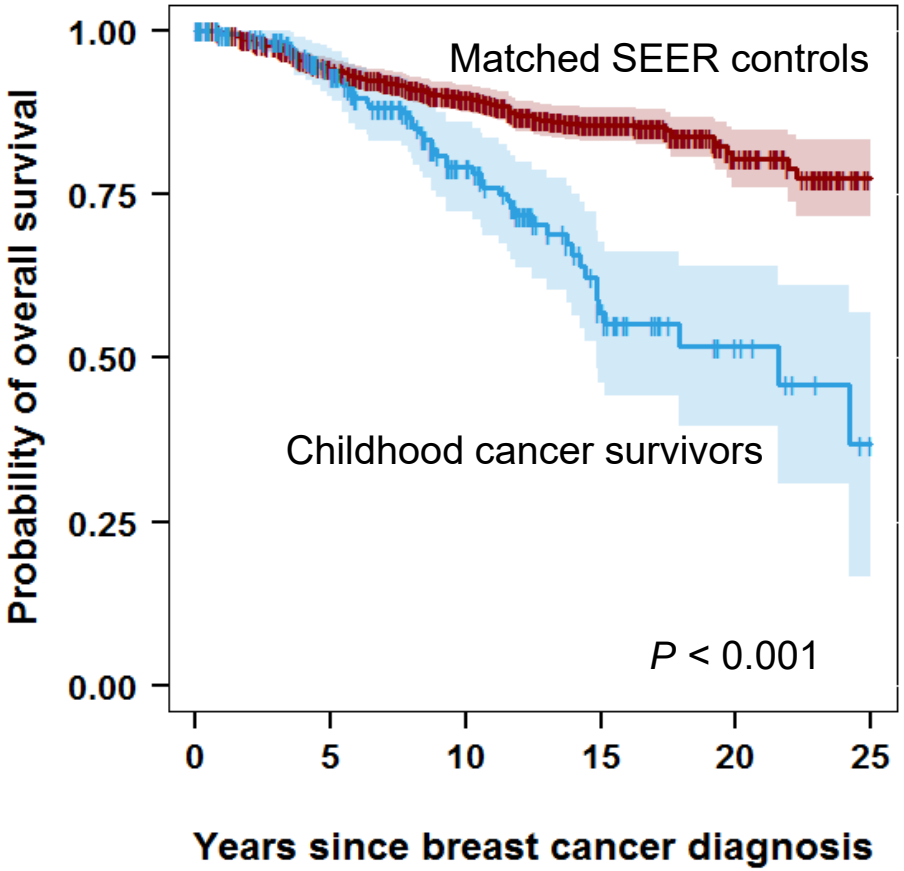

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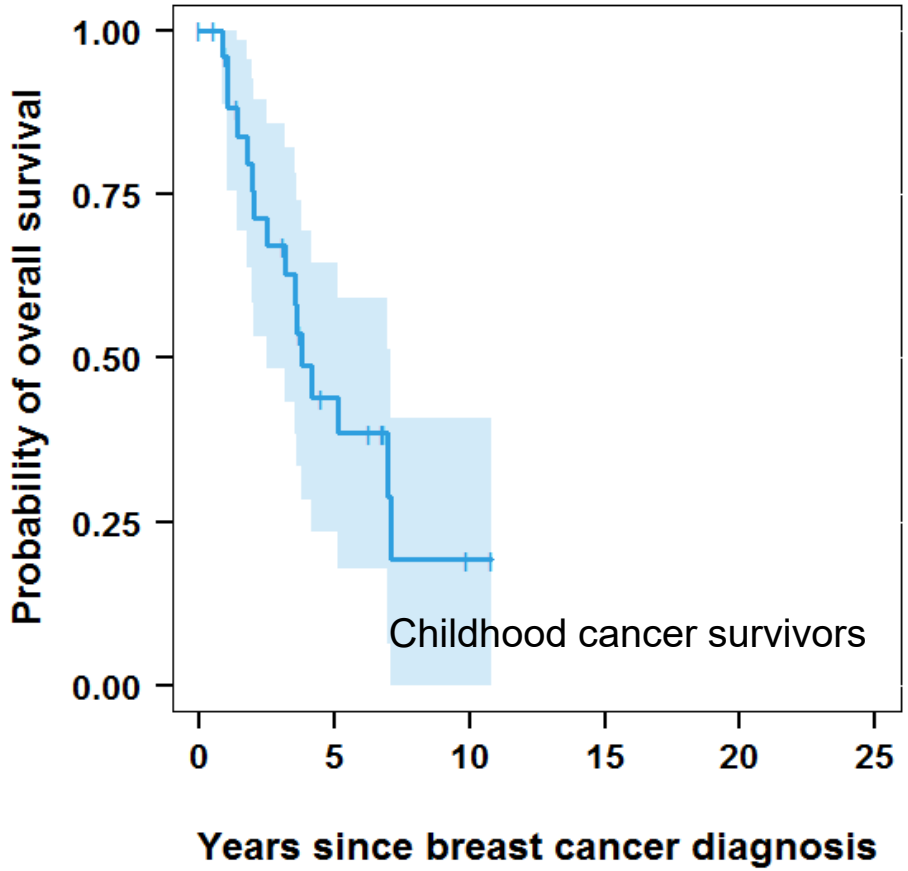
Survival after advanced stage breast cancer

- 28 childhood cancer survivors
- 16 deceased
  - 5-year overall survival: 44%



CCSS
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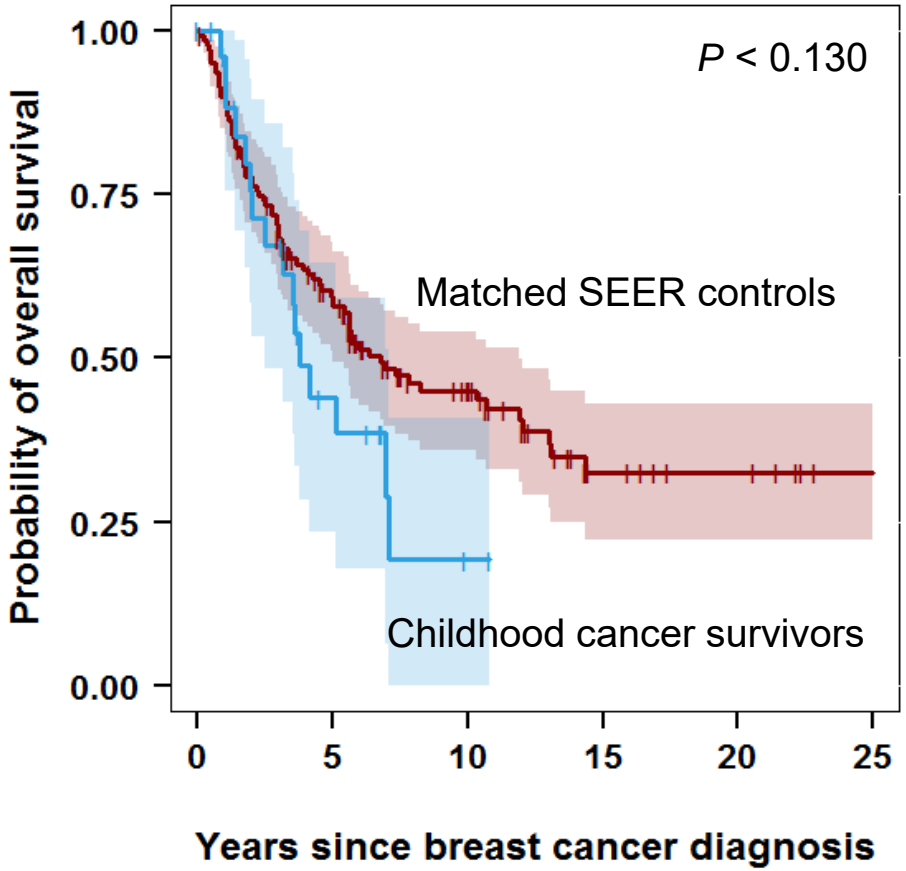
Survival after advanced stage breast cancer

- 28 childhood cancer survivors
- 16 deceased
  - 5-year overall survival: 44%
- HR = 1.5 [95% CI: 0.9-2.7]



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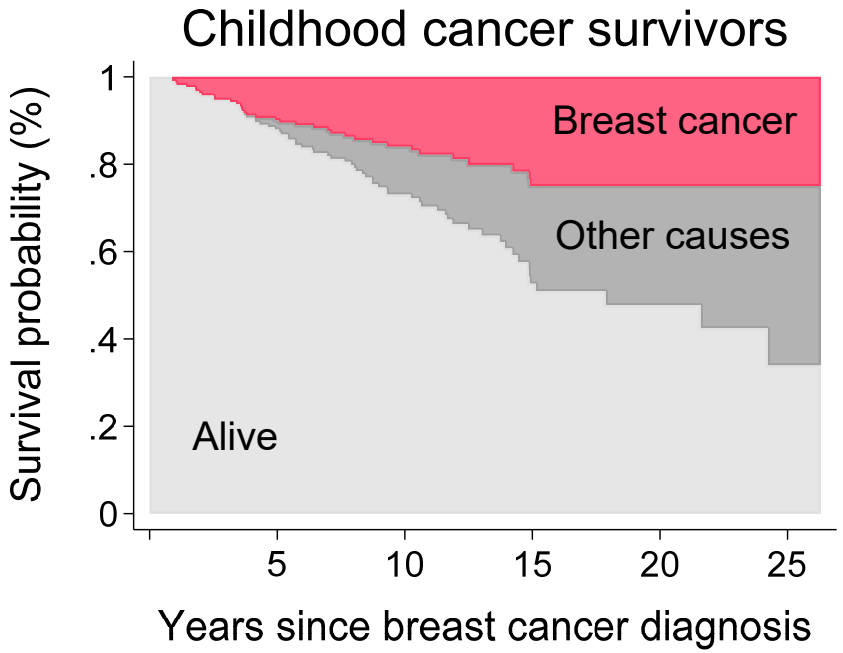
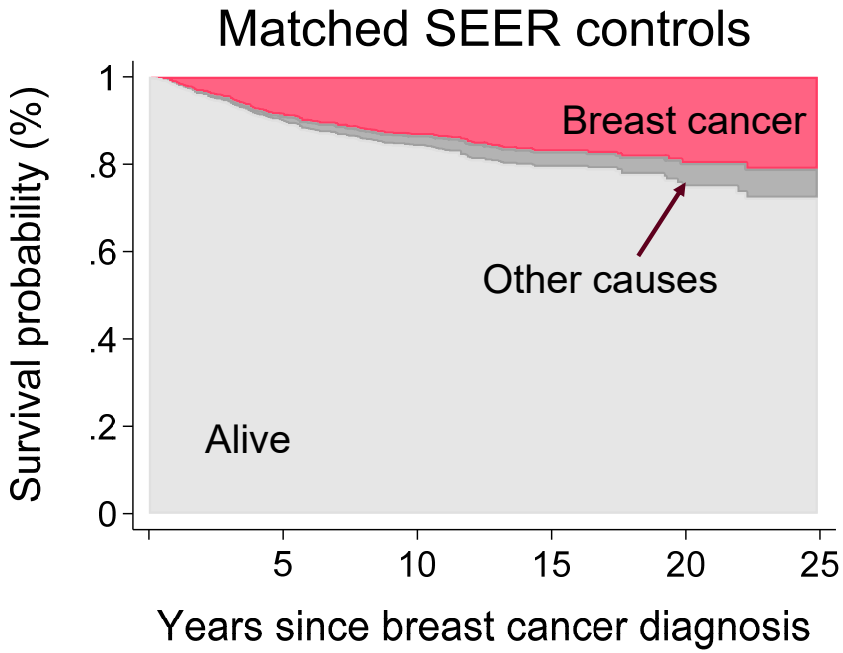
Cause-specific mortality

Other-cause mortality: HR=5.5; 95% CI (3.4, 9.0); p<0.001





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Other causes of death

- 43 childhood cancer survivor died from causes not attributed to breast cancer:
  - Other subsequent malignant neoplasm (SMN) 18
  - Cardiovascular disease (CVD) 14
  - Pulmonary / infectious 7
  - Other health cause 1
  - External 1
  - Unknown 2

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Conclusions

- Mortality after breast cancer is substantially elevated in childhood cancer survivors relative to women with *de novo* breast cancer
- Health conditions other than breast cancer are critical contributors to this elevated mortality
- Results highlight the need for childhood cancer survivors with breast cancer to be followed by clinicians familiar with their unique risks
- Future research should determine if this increased mortality reflects co-morbidity, limited therapeutic options and/or missed opportunities for risk-reducing interventions at the time of breast cancer diagnosis.

Career Development Award

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Lucie Turcotte K08

- *Treatment Modifications, Outcomes, and Provider Decision Making in the management of Subsequent Breast Cancers Among Survivors of Childhood Cancer*

Working Group Work

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- The SMN Working Group acts (in some ways) as a core resource
  - Adjudication and validation of reported events
  - High commitment to quality of the data
    - Multi-step process for SMN inclusion
    - Review and development of chemo / radiotherapy exposures
  - Foundational for many of our analyses

- The SMN Working Group also:
  - Generates and pursues new lines of investigation
  - Works to develop studies that add to knowledge and offer immediate guidance for surveillance and possibly prevention strategies

Validation of Second Neoplasms

CCSS

- Yield from Follow Up 5 and Follow Up 6:
  - 5979 self reported conditions
  - 4649 cases reviewed
  - 3392 cases validated and entered

- Final entry of approximately 1,100 of these conditions took over 44 person-hours of review. An estimated 200 hours was committed to pathology review prior to final review.

- At present, 17% of all patients with a BCC have had > 10
  - One individual has 106 validated BCCs
  - Now 4,000 validated NMSCs in the CCSS (2/3 of all SNs)

Ascertainment / Validation
VPR-CLS

CCSS

- Challenge – identify the occurrence of new primary neoplasms in our cohort
  - Current system is very labor intensive but likely very specific and we assume sensitive
- Opportunity – Cancer Databases exist in all of the states
  - Unfortunately, there is not national registry, so accessing them requires 50 applications
- Potential Solution –

  Virtual Pooled Registry – Cancer Linkage System

VPR-CLS

CCSS

- Virtual Pooled Registry Cancer Linkage System
  - Funded by NCI SEER, managed by North American Association of Central Cancer Registries (NAACCR)
  - Dennis Deapen, DrPH, Keck School of Medicine of USC

- Goal of VPR: To provide a single portal to facilitate efficient, standardized linkages between study cohorts and multiple state cancer registries
  - Potential for huge benefit to CCSS: Improve on self-report, reduce burden of record reviews for SMN confirmation

- CCSS selected for pilot testing of Phase 1
  - Initial linkage and release of registry-specific match counts

VPR-CLS

CCSS

- Phase 1 successfully completed:
- Test linkage performed by 34 state registries (74.5% of U.S. population)
- Varying coverage through 2016 (23 registries included data from 1995+)
  - 10,440 total high quality matches (not requiring manual review)
  - 6,541 matched with the primary childhood cancer (2 year window)
  - **3,899** matches classified as a subsequent neoplasm
  - CCSS self-report and review identified **2,014** SNs through 2016

VPR-CLS Next Steps

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Phase 2: Obtain individual-level data on the matched cases

- Each registry has its own requirements for releasing data
- VPR working to develop and get registry approvals for:
  - Templated Data Use Agreement
  - Templated IRB/Registry application

} Avoid need for 50 separate applications

To date, 13 registries have accepted VPR Template (cover 22% of population)

- If we also add Texas and California, coverage increases to 43% (52% of Phase 1 matches)

Next Steps: Complete VPR Templated Application when finalized

Plan to also apply individually to Texas and California registries

VPR-CLS

CCSS

- Early Challenges
  - Lack of SSN for many patients limits matching
  - Not all state registries have been in place long enough to include cohort participants diagnosed in the 1970s
  - Early work still required manual match for a subset of cases

Approved Concept Proposals / Not yet published

CCSS

- Concepts **Progressing** as Planned
  - Reducing Risk of Skin Cancer Among Childhood Cancer Survivors (Geller, 2017) *Baseline Paper published J Investigative Dermatology*
  - Cause-Specific Mortality among Childhood Cancer Survivors with a Subsequent Thyroid Cancer (Barnea, 2016)
  - The risk of breast and thyroid cancer after radiotherapy for Hodgkin's Lymphoma: Can reconstructed dosimetry data be used to predict secondary malignancies? (Hodgson, 2015)
  - Human papillomavirus (HPV)-associated malignancies as second cancers in childhood cancer survivors: a report from the Childhood Cancer Survivor Study (Henderson 2015)

Approved Concept Proposals / Not yet published

CCSS

- Concept **Progressing as Planned**
  - Breast Cancer Risk in the Modern Treatment Era: A Report from the Childhood Cancer Survivor Study (Henderson, 2017)
  - Subsequent Neoplasms Among Survivors of Childhood Cancer Not Previously Treated with Radiation (Turcotte 2017)
  - Lung Cancer as a Subsequent Malignant Neoplasm in Survivors of Childhood Cancer (Ghosh, 2019)

Approved AOIs / No Concept

CCSS

- AOIs approved **since June 2017** Investigator Meeting
  - Treatment Modifications and Provider Decision Making in the Management of Subsequent Breast Cancers Among Survivors - Turcotte (Ancillary Study) (Approved 9/2017)
  - International Pooled Analysis of Breast Cancer Risk after Treatment for Childhood and Young Adult Cancer – Ronckers (Approved 11/2017)

Ancillary Study -

CCSS

- **Treatment Modifications, Outcomes, and Provider Decision Making in the management of Subsequent Breast Cancers Among Survivors of Childhood Cancer – Funded through Turcotte K08 & UMN sources**

Specific Aims:

1. **Survival Following Subsequent Breast Cancers.** Quantify OS and EFS among CCSS participants with breast cancer and compare with SEER OS estimates, and with OS and EFS in an age-, breast cancer stage- and treatment era-matched comparison cohort of women with primary breast cancer.
2. **Treatment and Treatment-Related Toxicity for Subsequent Breast Cancer.** Compare prescribed treatment and breast cancer treatment-related toxicity between CCSS participants with breast cancer and a comparison cohort of women with primary breast cancer, matched on age, breast cancer stage and treatment era. Explore differences between subsequent breast cancer treatment and National Comprehensive Cancer Network treatment guidelines.
3. **Treatment Decision Making for Subsequent Breast Cancer.** Perform semi-structured interviews with medical and radiation oncologists to understand drivers of treatment decision-making, and use responses to create a broad-reaching survey for distribution to medical and radiation oncologists.

Five Year Plan: Aim 1

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Aim 1 - evaluate changes in incidence of and risk factors for second neoplasms based on temporal changes in primary therapy

- 5 year plans
  - Specific cancer group
    - By original dx (Leukemia, HD, CNS, other)
    - By unique SN (Breast, Carcinoma, Melanoma, other)
  - Changes in XRT technique and impact on SN
  - Utility of first past XRT data for SN analysis (i.e. CNS tumors)

Five Year Plan: Aim 2

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- Aim 2: Identify genetic susceptibility for specific subsequent neoplasms that modifies risk conferred by therapeutic exposure.
    - Engaged with the Genetics Working Group regarding classification of out identified SMNs

Five Year Plan: Aim 3

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- Aim 3: Utilize the large CCSS cohort to identify high-risk populations among aging survivors.
  - New AOI on colorectal cancer (Henderson)
  - New collaboration with Dutch cohort for breast cancer analysis

Top Priorities

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- Continue to provide timely, complete, and accurate data on newly occurring second neoplasms in the cohort
- Move forward publications including
  - Chemo only SMNs
  - HPV associate SMNs
  - Further Breast Cancer analyses (in collaboration with NCI, Dutch)
  - Facilitate studies of risk modeling (Wong, Moskowitz)

Top Priorities

CCSS

- Integration of VPR-CLS into SMN validation work flow
- Ongoing interactions with the Genetics WG for SN analyses
- Periodically review the SMN status of the cohort – what is changing overall and within specific subgroups

Immediate Opportunities for Investigators

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- Second Neoplasms of the CNS
  - No update since 2006
  - Significant increase in cases:
    - Meningioma 66 to 456
    - Glioma/other 40 to 133
  - Investigate newer methods for determining radiation dose
  - Re-visit chemotherapy & age associations
- Renal Cell Carcinoma
  - Now 55 cases (26 in prior report) – re-explore chemotherapy and radiotherapy
- Further exploration of non-melanoma skin cancers
  - Reassess burden on survivors, risk factors (4000 NMSC in the data set)

Topics for SMN Working Group Break Out

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- Other ideas for analysis in the expanded cohort?
- International Collaborations – opportunities? Process?
- How many BCCs is enough? How do we handle continued validation