CHILDHOOD CANCER SURVIVOR STUDY
ANALYSIS CONCEPT PROPOSAL

1. **Study title:** Changing Patterns of Second Neoplasms in Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study
2. **Working group and investigators:** This project will be developed through the SMN Working Group with secondary oversight by the Epidemiology and Biostatistics Working Group. Proposed investigators include:

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3. **Background and rationale:**

Through the initiation of the Childhood Cancer Survivor Study (CCSS)[1] and other large cohorts of childhood cancer survivors[2-8], a tremendous amount has been learned about late health consequences of cancer therapies. One of the outcomes associated with the greatest morbidity and mortality for survivors is subsequent neoplasms (SN).[9-14] Multiple reports from the CCSS and others have reported extensively on SN and associated risk factors.[15-35] One of the strongest risk factors associated with SN to date has been radiation therapy.[36-42] As we have gained this knowledge, treatments have been modified in efforts to enhance outcomes while limiting late toxicities. The initial CCSS cohort included patients treated from 1970 to 1986. The most recent comprehensive report on SN within CCSS was published in 2010.[15] Recently, the CCSS cohort has been expanded to include individuals treated from 1987 to 1999. The goal of this analysis is to provide an update on SN within the complete CCSS cohort and to identify changing patterns of SN over time. We hypothesize that based on treatment modifications made as a result of previously reported second neoplasms and other toxicities, we will observe changes in the incidence and pattern of second neoplasms experienced by survivors over time.

4. **Specific aims:**
   1. Describe cumulative incidence, risk and risk factors for subsequent neoplasms (subsequent malignant neoplasms (SMN), non-melanomatous skin cancers (NMSC) and meningiomas) in the complete CCSS (Original + Expansion) cohort
   2. Identify how patterns of SN have changed over time, based on decade of diagnosis and treatment (1970-79, 1980-89, 1990-99)

5. **Hypotheses:**
   1. There will be a measurable downtrend in the receipt of radiation therapy by decade (1970s vs. 1980s vs. 1990s)
   2. Rates of SNs felt to be primarily radiation-driven will decrease over time
      a. Breast
      b. Gastrointestinal
      c. CNS
      d. Meningioma
      e. Lung

f. Thyroid
g. Bone
h. Soft tissue sarcoma
i. NMSC

3. Chemotherapy-associated SN (leukemia) may be increased over time, as chemotherapy is intensified in the setting of decreased use of radiation therapy.

6. Analysis framework: This analysis will include survivors enrolled in the complete CCSS Cohort (1970-1999). Our initial analysis approach will look at changes in SN patterns by decade of initial cancer diagnosis; however, we will attempt to look at changes in treatment over time and define specific relevant exposure eras, where applicable. Subsequent neoplasms will be analyzed by:

A. Descriptive characteristics will be reported:
   a. Age, sex, race/ethnicity, age at initial diagnosis, time from initial diagnosis, original malignancy, decade of diagnosis
   b. Therapeutic exposures, by treatment decade (1970-79, 1980-89, 1990-99)
      i. Chemotherapy agents and doses
         1. Alkylating agents (yes/no/cumulative dose* based on alkylator score)
         2. Anthracyclines (yes/no/cumulative dose*)
         3. Epipodophyllotoxins (yes/no/cumulative dose*)
         4. Platinums (yes/no/cumulative dose*)
      ii. Radiotherapy site and doses
         1. CNS (yes/no/cumulative dose*)
         2. Chest (yes/no/cumulative dose*)
         3. Abdomen (yes/no/cumulative dose*)
         4. Pelvis (yes/no/cumulative dose*)
         5. Extremities (yes/no/cumulative dose*)
      iii. Splenectomy (yes/no)

   **cumulative dose data will include exposure between time of initial childhood cancer diagnosis to 5 years post-diagnosis*

B. Cumulative incidence curves will be constructed and mean cumulative counts[43] calculated for the following:
   a. All subsequent neoplasms
   b. NMSCs
   c. Meningiomas
   d. Malignant neoplasms
      i. Breast
      ii. Thyroid
      iii. Soft tissue sarcoma
      iv. Bone
      v. CNS
      vi. Lung
      vii. Gastrointestinal
      viii. Leukemia

   For each of the second neoplasm outcome definitions (NMSC, meningioma and malignant neoplasm), cumulative incidence and mean cumulative count will be reported using time from initial diagnosis as the time scale for presentation and treating death as a competing risk event. Subsets of subjects may be presented, divided by type of SMN, prior SN and/or diagnosis, for example (results from variables to be examined in Cox regression models may influence choices of subgroups). Log-rank testing will be done to

compare cumulative incidence curves and mean cumulative counts for decade of diagnosis.

C. Standardized incidence ratios (SIR) and absolute excess risk (AER) will be calculated for all malignant neoplasms (ICD-O, 5^{th} digit = 3)
For all second malignant neoplasms, standardized incidence ratios and excess absolute risk will be reported, using age, gender and calendar year U.S. cancer rates from SEER to evaluate expected numbers of events. SIRs will be reported by attained age, decade of diagnosis, primary diagnosis, as well as by type of SMN. We will evaluate the impact of age at diagnosis and treatment, including exposure (y/n) to specific chemotherapy subgroups (anthracyclines, epipodophyllotoxins, platinums and alkylators) and to radiation therapy, on SIRs.

D. Multivariable modeling with years since diagnosis as the time scale will be performed to look at the impact of primary cancer diagnosis, therapeutic variables described above, treatment decade (1970-1979, 1980-1989, 1990-1999), and demographic factors (sex, age at primary cancer diagnosis).

7. Tables/figures

Table 1: Demographics/cohort characteristics

	All Cohort members N=	Survivors with SN N=	Survivors without SN N=
Mean age at primary diagnosis, years			
Sex			
Male			
Female			
Race			
White			
Black			
Hispanic			
Other			
Unknown			
Primary diagnosis			
Leukemia			
CNS tumor			
Hodgkin lymphoma			
Non-Hodgkin lymphoma			
Wilms tumor			
Neuroblastoma			
Soft tissue sarcoma			
Osteosarcoma			
Other bone cancer			
Initial therapy			
Chemotherapy only			
Radiation only			
Surgery only			
Chemo+Rad			
Any Radiation			
No treatment			
Unknown			
History of splenectomy			
Vital status			
Alive			
Deceased			
Second neoplasm			
SMN			
Meningioma			
NMSC			
Other			
Mean time from primary cancer diagnosis to development of second neoplasm, years			

Table 2: Second neoplasm diagnoses by primary cancer diagnosis. (Could expand this to include all subsequent neoplasms).

	Second Neoplasm																	
	Total SN	ALL	AML	Other Leuk	HL	NHL	Other Lymphoma	Glial	Medullo/PNET	Meningioma	Other CNS	Breast	Bone	STS	Thyroid	Other solid tumor	Melanoma	NMSC
Primary Diagnosis																		
ALL																		
AML																		
Other leuk																		
Astrocytoma																		
Medullo/PNET																		
Other CNS																		
HL																		
NHL																		
Kidney																		
NBL																		
STS																		
Ewings																		
Osteosarc																		
Other bone																		
Total																		

Table 3: Observed and Expected Numbers and SIRs of Subsequent Malignant Neoplasms, for overall cohort and by decade of diagnosis

	Overall Cohort				1970-79				1980-89				1990-99			
SMN	**O**	**E**	**O/E (95 % CI)**	**Median time to occurrence, y**	**O**	**E**	**O/E (95 % CI)**	**Median time to occurrence, y**	**O**	**E**	**O/E (95 % CI)**	**Median time to occurrence, y**	**O**	**E**	**O/E (95 % CI)**	**Median time to occurrence, y**
All																
Leukemia																
ALL																
AML																
Other																
Lymphoma																
CNS																
Glial																
Medullo/PNET																
Breast																
Bone																
STS																
Thyroid																
Melanoma																
All others																

Table 4: SIR, cumulative incidence at 15 years and AER for SMN, for each childhood cancer diagnosis, by decade of diagnosis

	1970-79			1980-89			1990-99		
Childhood cancer diagnosis	**SIR (95% CI)**	**CI at 15 years**	**AER/1000 person-years**	**SIR (95% CI)**	**CI at 15 years**	**AER/1000 person-years**	**SIR (95% CI)**	**CI at 15 years**	**AER/1000 person-years**
All diagnoses									
Hodgkin lymphoma									
NHL									
Soft tissue sarcoma									
Neuroblastoma									
Kidney tumor									
ALL									
AML									
Other leukemia									
Bone cancer									
CNS tumor									

Table 5: Multivariable table

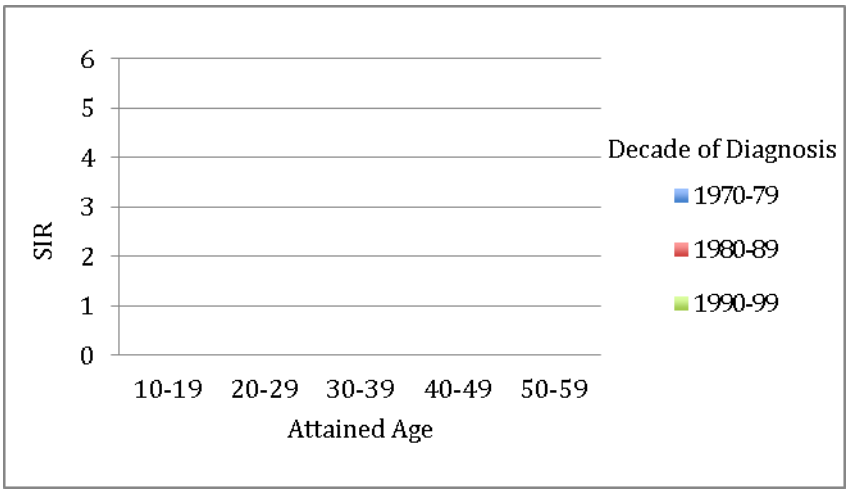
	Any SN		SMN		Meningioma		NMSC	
Variable	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
Sex								
Male								
Female								
Age at diagnosis of first cancer								
0-4								
5-9								
10-14								
≥ 15								
Treatment Initiation decade								
1970-79								
1980-89								
1990-99								
Radiation therapy								
yes								
no								
Splenectomy								
yes								
no								
Type of first cancer								
Leukemia								
HL								
CNS								
STS								
Renal								
Osteosarcoma								

Other Bone								
NHL								
NBL								
Alkylator score								
1								
2								
3								
Anthracycline exposure								
None								
1-100mg/m2								
101-300mg/m2								
≥301								
Epipodophyllotoxin exposure								
None								
1-1000mg/m2								
1001-4000mg/m2								
≥4001mg/m2								
Platinum exposure								
None								
1-400mg/m2								
401-750mg/m2								
≥751mg/m2								

Figures A-C: Cumulative incidence of second neoplasms, with years from initial cancer diagnosis as the x-axis time scale

A. Overall cohort, with curves for Any SN, SMN, NMSC and meningioma
B. Radiation and Non-radiation exposed curves, for Any SN, SMN, NMSC and meningioma
C. Individual curves for each primary cancer diagnosis, with breakdown by treatment decade

Figure D. SIRs for SMN, by attained age and decade of diagnosis.



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