CHILDHOOD CANCER SURVIVOR STUDY
ANALYSIS CONCEPT PROPOSAL

1. Study title: Subsequent neoplasms among survivors of childhood cancer not previously treated with radiation

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:

Subsequent neoplasms (SNs), including subsequent malignant neoplasms (SMNs), non-melanoma skin cancers (NMSCs) and benign meningiomas, following a childhood cancer diagnosis are associated with significant morbidity and mortality. Large cohorts of childhood cancer survivors have been utilized to describe the incidence of SNs, as well as associated risk factors. Therapeutic radiation has consistently been the greatest risk factor for development of SNs. Recent data from the Childhood Cancer Survivor Study (CCSS) have shown that use of therapeutic radiation among childhood cancer patients steadily decreased from the 1970s to the 1990s [1, 2]. Within this same timeframe, an increasing proportion of survivors received alkylating agents, anthracyclines, epipodophyllotoxins, and platinum agents (Turcotte LM, submitted manuscript). Within earlier treatment eras, there were few patients treated with chemotherapy without radiation (~17% in 1970s vs. 53% in 1990s) (Turcotte LM, submitted manuscript). The overall cumulative incidence of SNs and risk for SMNs has decreased with advancing treatment decades, which appears to be at least partially attributable to decreases in therapeutic radiation exposure (Turcotte LM, submitted manuscript). However, there remains a group of survivors experiencing SNs who were not treated with radiation, and this represents a group of survivors that is less well understood.

The associations between alkylator therapy and epipodophyllotoxins and subsequent leukemias have been well described [3, 4]. Among survivors of testicular nonseminomas, treated with chemotherapy only, there was significantly increased risk for developing subsequent solid tumors, including cancers of the kidney, thyroid, and soft tissue, although associations with specific chemotherapeutic agents were not reported [5]. Previous studies from the CCSS have identified associations between chemotherapeutic agents and SNs. In two analyses of survivors

experiencing secondary sarcomas, anthracyclines exposure was identified as a risk factor [6, 7] and the earlier of the two analyses identified alkylator exposure as a risk factor as well [7]. Although the most important risk factor for gastrointestinal (GI) SMNs was radiation therapy, survivors not treated with radiation were still at increased risk for GI SMNs, and multivariable models revealed high-dose procarbazine and platinum exposure as risk factors [8]. A case-control study of secondary colorectal carcinoma completed at St. Jude Children's Research Hospital identified a significant association with alkylator exposure, although nearly all patients were treated with radiation therapy [9]. Cisplatin exposure has been associated, independent of radiation therapy, with subsequent renal carcinoma in survivors of childhood cancer [10]. Among survivors of non-Hodgkin lymphoma, cytarabine exposure was associated with a significantly increased risk of solid SMNs [11]. Bassal et al. examined subsequent carcinomas, excluding breast, thyroid and NMSCs, in survivors and found that 33% of the carcinoma cases developed in body regions not previously exposed to radiation therapy and that 73% of those cases had been exposed to previous alkylating agents [12]. A recent CCSS report specifically considered breast cancer risk among survivors not exposed to previous radiation therapy and found that both alkylating agent and anthracyclines exposure were associated with increased risk for breast cancer [13]; however, this type of analysis has not yet been performed for other types of SMNs. Additionally, there are data to support a possible modifying effect of alkylating agents when combined with radiation therapy on breast cancer risk, as well as a protective effect when given without radiation therapy, with risk decreasing with increasing numbers of cycles [14]. Although we have observed a decrease in risk for SMNs that appears to be attributable to decreased therapeutic radiation, the risk for SMN remains greater than what is expected within the general population (Turcotte LM, submitted manuscript). Despite multiple identified associations between chemotherapeutic agents and SMNs, these findings have been somewhat inconsistent and these associations require further study as more patients are receiving chemotherapy alone, particularly as the types and doses of chemotherapy agents have changed over recent treatment eras.

4. Specific aims:
   4.1. Estimate the cumulative incidence and cumulative burden of subsequent neoplasms (SN) and calculate the standardized incidence ratios (SIRs) for subsequent malignant neoplasms (SMN), based on the following group definitions: a) treated with chemotherapy but not radiotherapy, b) treated with radiotherapy and chemotherapy, c) treated with radiotherapy and no chemotherapy, and d) not treated with chemotherapy or radiotherapy, for their primary childhood malignancy.
   Hypothesis: Individuals treated with chemotherapy only will have a lower cumulative incidence of SNs and lower SIRs for SMNs compared to CCSS participants treated with radiation or combined modality therapy for their childhood malignancy; however, they will experience an increased risk for SMNs compared to individuals not exposed to chemotherapy or radiotherapy and compared to the age- and sex-matched U.S. population.

   4.2. Identify chemotherapeutic exposures associated with SMN (all malignant diagnoses combined) and individual SMN diagnosis risk, based on:
      4.2.1. class of chemotherapeutic agent (alkylating agent, platinum agent, epipodophyllotoxin, anthracycline)

4.2.2. cumulative dose of chemotherapeutic agent delivered
4.2.3. combinations of chemotherapeutic agents
4.2.4. latency between chemotherapy exposure and SMN diagnosis

Hypothesis: High cumulative doses of alkylating agent and platinum exposure will be associated with increased rate risk for developing SMN. We will see changes in SMN rates as the cumulative doses of chemotherapies change.

4.3. Describe specific SN/SMN patterns and risk factors based on therapeutic and clinical factors, in radiation non-exposed vs. exposed survivors.

Hypothesis: We will observe a unique pattern of SMNs, consisting of a larger proportion of hematologic, gastrointestinal and renal malignancies and melanomas in chemotherapy-only survivors compared to CCSS participants treated with radiation or combined modality therapy for their childhood malignancy.

4.4. ***Exploratory Aim:*** Determine if changes in specific chemotherapeutic exposures over time have altered relative rates of SNs, SMNs, or meningiomas in survivors.

Hypothesis: We will observe reductions in rates of SNs, SMNs or meningiomas over time associated with alkylating agent exposure (cyclophosphamide equivalent dose or individual alkylating agent) or with anthracycline (overall or individuals agent) exposures because the cumulative dosing of these groups have decreased over time.

5. Analysis framework: This analysis will include survivors enrolled in the CCSS cohort (1970-1999) who were a) treated with chemotherapy but not radiotherapy (N=7,495), b) treated with radiotherapy and chemotherapy (N=10,586), c) treated with radiation and no chemotherapy (N=1,959), and d) not treated with chemotherapy or radiotherapy (N=2,115) Individuals with unknown treatment exposure will be excluded from this analysis. Subsequent neoplasm data will be identified from the most recently frozen data set. We will analyze and present the following data:

5.1. Descriptive characteristics of the cohort:

5.1.1. Age at diagnosis, sex, race, childhood malignancy, attained age, time from initial diagnosis, decade of diagnosis (1970s, 80s, 90s)

5.1.2. Environmental/lifestyle exposures: smoking status (yes [ever smoked]/no), alcohol use (yes/no/average drinks per week)

5.1.3. Therapeutic exposures

5.1.3.1. Splenectomy (yes/no)

5.1.3.2. Surgery (yes/no)

5.1.3.3. Therapeutic radiation

5.1.3.3.1. Yes/No

5.1.3.3.2. Maximum dose to exposed body part

5.1.3.4. Chemotherapy agent class and cumulative doses

5.1.3.4.1. Alkylating agents (yes/no/cumulative dose, reported as cyclophosphamide equivalent dose [15])

5.1.3.4.2. Anthracyclines (yes/no/cumulative dose)

5.1.3.4.3. Epipodophyllotoxins (yes/no/cumulative dose)

5.1.3.4.4. Platinums (yes/no/cumulative dose)

We will also comprehensively report individual chemotherapeutic agents and cumulative exposures for agents.

5.2. Cumulative incidence and cumulative burden curves of SNs:
- 5.2.1. All subsequent neoplasms combined
- 5.2.2. SMNs (overall and individual types)
- 5.2.3. NMSCs
- 5.2.4. Benign meningiomas

For each of the subsequent neoplasm outcome definitions (SMN, NMSC, and meningioma), cumulative incidence and cumulative burden [16] will be reported, beginning at 5 years following initial childhood cancer diagnosis, 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, for example: by primary diagnosis, chemotherapeutic exposure or combinations of chemotherapeutic exposures. We will identify the chemotherapy agents associated with the greatest number of SN events and will then identify drug combinations for further analysis. Permutation-based p-values will be calculated for comparisons of cumulative incidence and cumulative burden at given time points.

5.3. Standardized incidence ratios (SIRs) and absolute excess risk (AER) for SMNs: risk for SMNs (ICD-O, 5^{th} digit =3) will be calculated, using age, sex, race/ethnicity and calendar year U.S. cancer rates from SEER to evaluate the expected number of events. SIRs will be reported by primary childhood cancer diagnosis, type of SMN, and chemotherapy agent exposure.

5.4. Compare SIRs for individual SMNs in groups a-d, as described above, to determine radiation-related and chemotherapy-related SMNs.

5.5. Evaluate for interactions between chemotherapeutic agents and radiation therapy.

5.6. Multivariable piecewise exponential analysis will be performed to look at the impact of demographic factors (age at primary diagnosis, attained age, sex, and 5-year treatment era as a continuous variable), splenectomy, and specific chemotherapeutic exposures (type, cumulative dose, possibly combinations) on rates of SN (overall and by outcomes definitions: SMN, NMSC, and meningioma). The associations between individual chemotherapeutic agents and common chemotherapy combinations and SN outcomes will be assessed initially with univariate analyses and those where $p<0.1$ will be considered in the multivariable model.

5.7. Based on the above model, we will remove the chemotherapeutic exposures and check how the relative rate per 5-year treatment era changes. We anticipate that if the relative rates are attenuated with the adjustment for chemotherapeutic exposures, changes in chemotherapy would be at least partially responsible for changes in SN rates over time. Based on initial models, we may look more closely at specific agents or combinations of agents in this same context.

6. Tables and figures:

Table. Cohort characteristics.

	Overall N=	Survivors exposed to chemo/no radiation N=	Survivors exposed to radiation+ chemo N=	Survivors exposed to radiation/no chemo N=	Survivors not exposed to chemo or radiation N=
Mean age at primary diagnosis, years					
Sex Male Female					
Race White Black Hispanic Other Unknown					
Primary diagnosis Acute lymphoblastic leukemia Acute myeloid leukemia CNS cancer Hodgkin lymphoma Non-Hodgkin lymphoma Wilms tumor Neuroblastoma Rhabdomyosarcoma Osteosarcoma Ewing sarcoma					
Therapeutic exposures Could put either groups of agents (anthracyclines, epipodophyllotoxins, alkylators, platinums) or individual agents; will want to include cumulative dose levels in this table					
History of splenectomy					
Vital status Alive Deceased					
Subsequent neoplasm Subsequent malignant neoplasms Benign meningiomas Non-melanoma skin cancers					
Number of person-years since cohort entry					
Mean years of follow up from diagnosis, years					

Table. Detailed chemotherapeutic exposures.

Chemotherapy agent	# exposed	Mean/Median/Dose Range
Agent #1	N	
Agent #2…		

Table. Multivariable analysis of subsequent neoplasm, overall and by subtypes in chemo exposed (no radiation) patients.

	SN		SMN		Meningioma		NMSC	
Variable	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**
Sex								
Male								
Female								
Age at diagnosis								
0-4								
5-9								
10-14								
15+								
Per 5 year treatment era								
History of splenectomy (yes/no)								
Yes								
No								
Cyclophosphamide equivalent dose (mg/m^2)								
None								
1-3999								
4000-7999								
8000+								
Anthracycline (mg/m^2)								
None								
0-100								
101-300								
>300								
Epipodophyllotoxin (mg/m^2)								
None								
1-1000								
1001-4000								
>4000								
Platinum (mg/m^2)								
None								
1-400								
401-750								
>750								

*In addition to the above variables in the model, attained age was adjusted for in the model for each outcome using cubic splines.

Abbreviations: CI, confidence interval; NMSC, non-melanoma skin cancer; RR, relative rate; SMN, subsequent malignant neoplasm; SN, subsequent neoplasm.

***Could include more detailed chemotherapy info within this analysis, as well as more detailed SMN subtypes depending on the frequency.

Table. Cumulative incidence at 15 years, SIR, and AER per 1000 person years for subsequent malignant neoplasms, for each childhood cancer diagnosis (can compare these measures in chemo-only vs. radiation exposed patients).

Childhood cancer diagnosis	**Observed**	**Expected**	**SIR (95% CI)**	**AER(95% CI)**	**Cumulative Incidence (95% CI)**
All diagnoses					
Hodgkin lymphoma					
Non-Hodgkin lymphoma					
Rhabdomyosarcoma					
Neuroblastoma					
Wilms tumor					
ALL					
AML					
Other leukemia					
Bone cancer					
Ewing					
Osteosarcoma					
CNS cancer					

Abbreviations: AER, absolute excess risk; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; CI, confidence interval; CNS, central nervous system; SIR, standardized incidence ratio.

Table. Subsequent neoplasm diagnoses by primary childhood cancer diagnosis.

Subsequent neoplasm / Primary DX	All SNs	Leukemia			Lymphoma			CNS				Solid organ				Other cancer	Skin	
		ALL	AML	Other	HL	NHL	Other	Glial	Medullo PNET	Meningioma (benign and malignant)	Other	Breast	Bone	STS	Thyroid		Melanoma	NMSC
ALL																		
AML																		
Other leukemia																		
Astrocytoma																		
Medullo/PNET																		
Other CNS																		
HL																		
NHL																		
Wilms																		
NBL																		
Rhabdomyosarcoma																		
Ewing sarcoma																		
Osteosarcoma																		
Other bone																		
TOTAL																		

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; CNS, central nervous system; HL, Hodgkin lymphoma; Medullo, medulloblastoma; NHL, Non-Hodgkin lymphoma; NMSC, non-melanoma skin cancer; PNET, primitive neuroectodermal tumor; SN, subsequent neoplasm; STS soft tissue sarcoma.

Table. Observed and expected SMNs, SIRs, and median time to occurrence

	Overall Cohort			
SMN	O	E	SIR (95% CI)	Median time to Occurrence (range), y
All				
Leukemia				
ALL				
AML				
Other				
Lymphoma				
CNS				
Glial				
Medulloblastoma				
Breast				
Bone				
Osteosarcoma				
Ewing sarcoma				
Other bone				
Rhabdomyosarcoma				
Thyroid				
Melanoma				
All Others				

Table. Relative rates of overall and subsequent neoplasm subtypes, per 5-year treatment era, without and with adjustment for individual treatment exposures. (could do this type of model for individual types of SMNs if we see specific associations)

	SN		SMN		Meningioma		NMSC	
Models	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**
Full model								
Remove:								
Splenectomy								
Chemo agent #1								
Chemo agent #2								
Chemo agent #3								
Chemo combinations, etc								

Figures.

1. Cumulative incidence and cumulative burden curves for SNs (overall), SMNs (overall), NMSCs and meningiomas, with curves for patient groups a-d listed above.
2. Will also want to create curves for specific SMN types and curves looking at different cumulative doses of chemo exposure or at different combinations of chemotherapy agents that appear to be associated with increase in SNs.
3. If applicable, based on data, compare cumulative incidence/burden curves for SNs, SMNs, NMSCs and meningiomas, for patients with the same primary diagnosis, treated with chemo only vs. chemo+radiation.

References:

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