Childhood Cancer Survivor Study
Analysis Concept Proposal

Title: Multiple Subsequent Neoplasms

Working Group and Investigators:

This proposed publication will be within the Second Malignancy Working Group

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Background and Rationale:

Survivors of childhood cancer are at significant risk for the development of subsequent neoplasms (SNs) the cumulative incidence of which continues to increase many years after primary diagnosis and treatment.(1-3) The original publication of the CCSS subsequent malignant neoplasms (SMN) experience identified 314 SMNs in 298 individuals. The cumulative incidence of development of a SMN was 3.2% at 20 years. The most frequent SMNs were breast (n=60) and thyroid (n=43). In multivariate models adjusted for radiation exposure, the development of SMNs was independently associated with female sex, cancer at a young age, a diagnosis of Hodgkin's disease or soft-tissue sarcoma, and exposure to alkylating agents.(1) An analysis that will update this experience is currently underway.

Based upon the most recent CCSS data set, the participants in the CCSS cohort have reported, and CCSS investigators have now validated a total of 2362 subsequent neoplasms in 1188 participants (Table A). (Note: these numbers exclude SNs in the first 5 years after primary diagnosis). To date, few cohorts have had sufficient size or length of follow-up to properly characterize survivors with multiple SNs. However, considering that SNs are the most common cause of cancer death after recurrence of primary disease, identification and description of a sub-population with multiple SNs and determination of predisposing factors associated with the development of multiple SNs (disease-related, treatment-related and demographic characteristics) may help predict which survivors are at high risk for this important late-effect.

Table A. Distribution of SNs in the CCSS Cohort										
# of SNs	1	2	3	4	5	6	7	8	9	10 or more
# of participants	856	158	60	26	17	11	9	7	6	38
Excluding NMSC	665	64	3							

In the general population, the development of non-melanoma skin cancer (NMSC), including basal cell and squamous cell carcinomas, has been associated with an increased risk of subsequent cancer.(4-13) NMSCs are by far the most common form of human malignancy, and while they are typically not life threatening, they may serve as a marker to identify persons at increased risk for more invasive malignancies.(4) Radiotherapy exposure among children treated for childhood cancer is also associated with the increased risk for developing NMSCs as well as other SNs, but no study to date studied the predictive nature of the development of NMSC with future development of more invasive neoplasms in a population of cancer survivors treated with RT. Therefore, we propose to describe the patterns and characteristics of participants with multiple SNs, identify treatment-, disease-, and demographic characteristics that predict the risk of more than one neoplasm, and determine if the development of NMSC is associated with an increased risk of development of a SN.

Specific Aims:

1. To describe patterns of subsequent neoplasms among survivors who have developed more than one neoplasm, including rates with 95% CIs for developing subsequent neoplasms among populations exposed and unexposed to RT. Multiple SNs will demonstrate patterns that are suggestive of the underlying etiology:

a) Aggregation of cancers typical of familial syndromes (Li-Fraumeni etc.) that are due to the presence of high-penetrance, low-prevalence genes – can be identified by Family History

b) Aggregation of specific SNs that do not belong to the above category – that are most likely due to the interaction of genotoxic exposure with low-penetrance, but high-susceptibility genes, will be identified.

2. Identify treatment-, disease-, and demographic characteristics and presence of high-risk families that predict the risk of more than one neoplasm.

a) Radiation exposure will be associated with an increased risk of multiple SNs.

b) Females will have an increased risk of multiple SNs compared to males.

c) Among survivors not exposed to radiation; risk of developing multiple second malignancies will be greater among diagnostic groups associated with genetic predisposition (i.e. sarcomas).

d) Individuals with a family history consistent with familial cancer syndromes (Li Fraumeni, Fanconi's etc.) will have a higher risk of multiple SN.

3. Determine if histology and time to onset of the first SN are associated with risk of additional SNs.

a) Among radiation-exposed survivors, risk for development of non-cutaneous malignancies will be greater among individuals with non-melanoma skin cancer.

b) Independent of treatment and original diagnosis, shorter latency period between diagnosis of original cancer and first SN will be associated with a greater risk of developing additional SNs, and with a higher likelihood of belonging to a high-risk familial syndrome.

Analysis Framework:

1. Outcomes of interest: The primary outcome of interest is the development of multiple SNs defined as ≥2 SNs occurring since the time of primary diagnosis. Subsequent neoplasms will include three subsets, exclusive of one another: 1) subsequent malignant neoplasms (SMN), which included all neoplasms with an ICD 0 behavior code of "3", excluding non-melanoma skin cancers; 2) non-malignant meningioma; and 3) non-melanoma skin cancers (NMSC). For the analysis of Aim 2, we will conduct a time-to-event analysis for the outcome "multiple SMN", defined at the time the subject develops their second SMN. For the analysis of Aim 3, the outcome "multiple SMNs" will be evaluated using time-to-event analysis, with first or second SMN constituting the endpoint, depending on the hypothesis.

2. Population: Assessment of Aims 1 & 2 will require utilization of the entire CCSS participating population. The populations for Aim 3 will be limited to CCSS participants exposed to RT (Hypothesis A) and to participants who experienced at least one SMN (Hypothesis B).

3. Explanatory Variables:

-Primary diagnosis
-Age at diagnosis
-Sex
-Treatment era
-RT exposure (binomial: yes/no)
-Family history of cancer
-Epipodophyllotoxin exposure (mg/m2)
-Alkylating agent score
-Smoking status
-Educational level
-Income
-Access to healthcare (# visits in last 2 years)

-Sun exposure
-Skin type

D. Analysis Plan:

Aim 1: We will present descriptive analysis of patterns of subsequent neoplasms among survivors who have developed more than one neoplasm including:

-Participants with multiple SNs, % of total number of SNs, and % of total cohort

-Distribution of SN outcomes (any SN, single SN, multiple SN, etc) according to demographic- and cancer/treatment-related factors

-Participants who's first SN was NMSC (basal cell or Squamous cell)

-Participants who had a first SN that was NMSC and subsequently developed a SN of any type (including NMSC)

-Participants who had a first SN that was NMSC and subsequently developed a SN other than NMSC

-Participants with multiple SN who have a first degree relative with cancer

In addition, rates and 95% CIs for developing subsequent neoplasms among populations exposed and unexposed to RT, and conditional on number of prior malignancies. History of cancer among a first degree relative will be evaluated for risk of SN among individuals not exposed to RT. These will be calculated using Poisson regression methods for evaluating rates. Alternatively, we may present cumulative incidence curves of time to a subsequent malignancy, conditional on different prior numbers of malignancies (from the time of the last prior malignancy).

For Aims 2 and 3, multivariable Cox regression analyses will be utilized with age as the time scale so that current age will be adjusted for explicitly in the models. For each hypothesis, different outcomes and time frames will be utilized, as appropriate to the question at hand.

Aim 2: The outcome variable will be age at second SN, and will be analyzed in Cox regression to estimate the hazard ratio of developing multiple SNs, and to estimate the hazard ratio for of developing $\geq$5 SNs, for hypothesized risk factors based on participant characteristics (Soft tissue sarcoma vs. other diagnoses, females vs. males) and therapeutic exposures (radiation yes/no,). Subjects will enter the analysis risk set at the age at which they reach 5 years post-diagnosis, and will contribute to the analysis until the age of second SN, death or end of follow-up. Analysis will be stratified based on RT exposure.

Aim 3:

Aim 3a: Among RT exposed survivors, the outcome variable will be defined as time to the first non-cutaneous SN and the key risk factor of interest will be the time-dependent covariate of occurrence of NMSC. Subjects will enter the analysis risk set at the age at which they are 5 years post-diagnosis contribute to analyses until the age at which they reach their first non-cutaneous SN, death or end of follow-up. We hypothesize that a first diagnosis of NMSC will be associated with an increased risk of developing a subsequent non-cutaneous malignant neoplasm. Adjustment of the final model will need to be considered for important potential confounders and effect modifiers including: age at diagnosis, sex, smoking status, education, and sun exposure. Additional analyses looking separately at basal and squamous cell NMSC as risk factors will also be considered.

Aim 3b: Among patients who experienced at least one SN, we will examine the outcome variable of at least one subsequent SN, again using multivariable Cox regression. Subjects begin follow-up for this analysis at the age at which they develop the first SN and are followed to the age at which they develop a subsequent SN, death or end of follow up. The primary risk factor of interest is the time from primary diagnosis to development of the first SN. This will be examined as a continuous covariate initially, as well as a categorical variable (divided in quartiles),

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Table 1. Frequency of Demographic & Treatment Patterns with SMN Development						
	Entire Cohort N (%)	**Any SMN N (%)**	**Single SMN N (%)**	**Multiple SMNs N (%)**	**2nd or 3rd SMN N (%)**	**4th + SMN N(%)**
Total						
Sex						
Male						
Female						
Age at diagnosis						
<1						
1-4						
5-9						
10+						
Current age (mean)						
Treatment Era						
1970-74						
1975-1979						
1980-86						
Childhood cancer diagnosis						
Leukemia						
CNS tumor						
Hodgkin disease						
Non-Hodgkin lymphoma						
Renal tumor						
Neuroblastoma						
Soft-tissue sarcoma						
Bone cancer						
Treatment of primary dx						
RT only						
Chemo only						
Surgery only						
RT + Chemo						
RT + Surgery						
RT + Chemo + Surgery						
Chemo + Surgery						
Radiation exposure						
Any						
None						
Yrs Primary to Secondary						
< X yrs						
>= X yrs						

Alkylating score						
0						
1-2						
3-4						
≥5						
Epipodophyllotoxin score						
None						
1-1000						
1001-4000						
≥4000						
Smoking status						
Never						
Former						
Current						
Education						
<high school						
High school						
>high school						
Income						
<20,000/year						
>20,000/year						
Type of Secondary Neoplasm						
Breast						
Bone						
Thyroid						
Soft Tissue Sarcoma						
CNS						
Leukemia						
Lymphoma						
Melanoma						
NMSC						
Other						
Family History of Cancer in First Degree Relative						
Yes						
No						

Table 2. Multivariate Analysis of risk factors for multiple malignancies (HR and 95% CI)			
	Any SMN	**Multiple SMNs**	**≥5SMNs**
Sex			
Male			
Female			
Age at diagnosis			
<1			
1-4			
5-9			
10+			
Current age (mean and SD)			
Current age (median, range)			
Treatment Era			
1970-74			
1975-1979			
1980-86			
Childhood cancer diagnosis			
Leukemia			
CNS tumor			
Hodgkin disease			
Non-Hodgkin lymphoma			
Renal tumor			
Neuroblastoma			
Soft-tissue sarcoma			
Osteosarcoma			
Ewing sarcoma			
Other			
Treatment of primary dx			
RT only			
Chemo only			
Surgery only			
RT + Chemo			
RT + Surgery			
RT+ Chemo + Surgery			
Chemo + Surgery			
Radiation exposure			
Any			
None			
Alkylating score			
0			
1-2			
3-4			
≥5			

Epipodophyllotoxin score			
None			
1-1000			
1001-4000			
≥4000			
Smoking status			
Never			
Former			
Current			
Education			
<high school			
High school			
>high school			
Income			
<20,000/year			
>20,000/year			
Type of Secondary Neoplasm			
Breast			
Bone			
Thyroid			
Soft Tissue Sarcoma			
CNS			
Leukemia			
Lymphoma			
Melanoma			
NMSC			
Other			
Type of Secondary Neoplasm			
p53 associated cancers			
non-p53 associated cancers			
Family History of Cancer			
Cancer in first degree			
No Cancer in first degree			
Years Primary to Secondary			
<10			
10+			

Table 3. Rate of Subsequent Neoplasm

Non-RT Population		
	Rate of Subsequent Neoplasm (rate per 1000 person years)	
	Rate	95% CI
5 yrs from primary		
Any SN		
Sarcoma		
Non-sarcoma		
From secondary		
Any SN		
Sarcoma		
Non-sarcoma		
From third		
Any SN		
Sarcoma		
Non-sarcoma		
From fourth +		
Any SN		
Sarcoma		
Non-sarcoma		

Table 4. Rate of Subsequent Neoplasm

RT Population		
	Rate of Subsequent Neoplasm (rate per 1000 person years)	
	Rate	95% CI
5 yrs from primary		
Any SN		
Sarcoma		
Non-sarcoma		
From secondary		
Any SN		
Sarcoma		
Non-sarcoma		
From third		
Any SN		
Sarcoma		
Non-sarcoma		
From fourth +		
Any SN		
Sarcoma		
Non-sarcoma		