03-06

CHILDHOOD CANCER SURVIVAL STUDY
CONCEPT PROPOSAL

SUBMITTED: May 2003

I- **Title:** Risk of a Carcinoma as a Second Primary Neoplasm in Survivors of Childhood Cancer: a Report from the Childhood Cancer Survivor Study

II- **Working Group and Investigators:** Second Tumor Working Group. Proposed investigators will include:

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III- **Background and Rationale:**

As the survival rates for childhood cancer have improved over the past few decades, second malignant neoplasms (SMNs) have emerged as a growing concern. As reported by Mertens et al., SMNs accounted for 12.7% of late mortality in the current CCSS cohort. Exposure to radiation therapy, history of therapy with certain chemotherapeutic agents, and genetic factors have been shown to be associated with a higher risk of SMNs. The types of SMNs that occur vary with the childhood cancer diagnosis, the type of therapy received, and the time from initial treatment.

An interesting phenomenon in young survivors of childhood cancer is the occurrence of second malignancies which are more characteristic of primary carcinomas in older adults. Several small series have reported the occurrence of carcinomas of the lung, GI tract, bladder, kidney and cervix, which occurred after treatment for diverse types of childhood cancers. Although an association between renal cell carcinoma as a second malignancy following neuroblastoma

has been suggested, the etiology of these adult-type carcinomas in young adult survivors of childhood malignancies has not yet been properly defined.

The second malignancies to be evaluated in this report are distinguished by the fact that they are all the reported carcinomas, with the exclusion of breast cancer, thyroid cancer, skin carcinomas and carcinomas in-situ. Due to the many compelling issues unique to breast cancer, carcinomas of the breast will be examined in analyses separate from this proposal. Similarly, thyroid cancer will be excluded from this analysis as the development of secondary thyroid carcinomas is well-defined and has been the subject of many other reports. Finally, basal cell carcinoma, squamous cell carcinoma and carcinoma in-situ will also be excluded from this analysis as these malignancies are not recorded in the Surveillance, Epidemiology and End Results (SEER) registry. In summary, the carcinomas eligible for inclusion in this analysis are those identified by the ICDO-2 morphology codes 8010-8570 and 9100-9110, excluding 8050-8080 (squamous cell neoplasms occurring in skin sites), 8090-8110 (basal cell neoplasms), 8330-8350 (thyroid neoplasms) and 8500-8540 (breast neoplasms).

Malignancies of carcinoma morphology are known to occur in older adults. The peak incidence for the occurrence of the majority of these carcinomas in the general population is the sixth and seventh decades of life. They are highly unusual in patients less than 40 years of age. In the current CCSS cohort, 68 cases of adult-type carcinomas (excluding breast cancer, thyroid cancer, carcinomas in-situ, and skin cancers) have been reported and confirmed, not including follow-up data. Once available, the cases identified from the follow-up questionnaire will be included in the final manuscript. The CCSS provides a valuable resource to quantify the risk of these SMNs among childhood cancer survivors and to identify contributing patient and treatment risk factors. Understanding the risk of these carcinomas in the childhood cancer survivor population could also have future implications for early detection and prevention of these conditions.

In this report, we describe the risk of the carcinomas, as defined above, as second malignant neoplasms in young adult survivors of childhood cancer using the large cohort of CCSS participants. We also seek to identify patient and treatment characteristics that are associated with increased risk of developing a carcinoma.

IV- Specific Aims/Objectives/Research Hypotheses:

A. Primary Aim: Describe the risk of pathologically confirmed adult-type carcinomas (excluding breast, thyroid and skin cancers) in young adult survivors of childhood malignancies.

B. Objectives:

1. Calculate the standardized incidence ratio, excess absolute risk and cumulative incidence of adult-type carcinomas in childhood cancer survivors
2. Describe the patient and treatment characteristics associated with an increased risk of developing an adult-type carcinoma

C. Hypotheses:

1. There is an increased incidence of certain carcinomas in survivors of childhood malignancies when compared to the general population
2. Childhood cancer survivors will be at increased risk for developing a carcinoma if they have the following characteristics:
   - Younger age at diagnosis
   - History of radiation therapy exposure
   - History of greater cumulative alkylator dosage
   - Family history of cancer

V- Preliminary Data:

Sixty-eight individuals in the CCSS cohort have so far been verified to have a carcinoma (as described above) as a second malignancy. The following table lists those carcinomas and their counts by site.

SEER Code	Site Categories	Counts
C00.0-C14.0	Lip, oral cavity & pharynx	20
C15.0-C26.0	Digestive organs excluding Colon and Rectum	8
C18.0-C20.0	Colon and Rectum	8
C34.0	Lung and bronchus	5
C51.0-C58.0	Female genital organs	3
C60.0-C63.0	Male genital organs	2
C64.0	Kidney	11
C65.0-C68.0	Urinary tract excluding Kidney	4
	Others*	7
Total		**68**

* Includes ICDO-2 codes C41.0, C47.9, C74.0, C77.0, C76.2, C80.9, which represent the following sites and counts: bones of skull and face and assoc'd joints (1), peripheral nerves and ANS (1), adrenal gland (1), lymph nodes (2), abdomen NOS (1), and unknown site (1).

VI- Analysis Framework:

A. Outcomes of interest:
The primary outcome of interest is the development of a secondary carcinoma (excluding breast cancer, thyroid cancer, carcinoma in-situ and basal or squamous cell carcinoma) as defined by the ICDO-2 morphology codes described above in the young adult survivors of childhood malignancies.

B. Study population:
The entire CCSS cohort

C. Predictor variables to be analyzed:
Patient and treatment characteristics which are associated with an increased risk of developing a second malignancy:

1. Case diagnosis
2. Age at diagnosis
3. Gender
4. Race
5. Time elapsed since diagnosis
6. History of higher cumulative alkylator therapy to be examined two ways:
    i. Cumulative doses of the 3 most prevalent alkylator agents in the CCSS database, analyzed as a categorical variable defined by quartiles of the dose distributions
    ii. Alkylator score (the calculation of the alkylator score has been described elsewhere: Tucker MA, D'Angio GJ, Boice JD et al. Bone sarcomas linked to radiotherapy and chemotherapy in children N Engl J Med 317: 588-93, 1987)
7. History of radiation and site
   For those having received radiation, site will be based on 5 regions as previously constructed by the data center: head and neck, chest, abdomen, pelvis, extremities. Radiation doses to those sites will be stratified according to the rough categories: no direct radiation to site of interest, 1-999cGy, 1000-2499cGy, 2500-3499cGy, 3500-4499cGy, 4500-5499cGy, >5500cGy which is data that is currently available.
8. Family history of cancer in first degree relatives (yes/no)

D. Analysis:

1. We will describe in detail the attributes of the patients who developed a second carcinoma including primary diagnosis, sex, age at diagnosis, elapsed time to developing the carcinoma, and treatment exposures.
2. We will calculate the standardized incidence ratio and excess absolute risk of carcinomas in young adult survivors of childhood malignancies in the CCSS cohort, overall, and stratified by patient and treatment characteristics (listed above) compared to age- and gender-specific Surveillance, Epidemiology and End Results (SEER) incidence data.

3. We will calculate the cumulative incidence of carcinomas in this population.

E. Classification schema:
The second carcinomas will be classified according to site based on SEER categories as well as morphology based on their ICDO-2 numerical listing. The following tables describe the proposed classification schema both by site and by morphology:

SEER Code	Site Categories	Counts
C00.0-C14.0	Lip, oral cavity & pharynx	20
C15.0-C26.0	Digestive tract excluding Colon and Rectum	8
C18.0-C20.0	Colon and Rectum	8
C34.0	Lung and bronchus	5
C51.0-C58.0	Female genital organs	3
C60.0-C63.0	Male genital organs	2
C64.0	Kidney	11
C65.0-C68.0	Urinary tract excluding Kidney	4
OTHERS		
C41.0	Bones of skull and face and assoc'd joints	1
C47.9	Peripheral nerves and ANS	1
C74.0	Adrenal gland	1
C77.0	Lymph nodes	2
C76.2	Abdomen NOS	1
C80.9	Unknown site	1
Total		**68**

ICDO-2 morphology code	Morphology of second malignant neoplasm according to ICDO-2 code
8010-8040	Epithelial neoplasm NOS
8120-8130	Transitional cell papillomas and carcinomas
8140-8380*	Adenomas and adenocarcinomas*
8312.3	Renal cell carcinoma

8430	Mucoepidermoid neoplasms
8440-8490	Cystic, mucinous and serous neoplasms
8550	Acinar cell neoplasms
9100	Trophoblastic neoplasms

* Excluding renal cell carcinoma

VII- Tables:

Table I: Characteristics of CCSS Participants

1. Sex:
   - male N= (%)
   - female N= (%)

2. Age at diagnosis of primary malignancy
   - less than 1 year N= (%)
   - 1-3 years N=(%)
   - 4-7 years N= (%)
   - 8-10 years N= (%)
   - 11-14 years N= (%)
   - 15-20 years N= (%)

3. Primary diagnosis
   - leukemia N= (%)
   - brain/CNS tumor N= (%)
   - Hodgkin's N= (%)
   - Non-Hodgkin's N= (%)
   - kidney N= (%)
   - neuroblastoma N= (%)
   - soft tissue sarcoma N= (%)
   - bone tumor N= (%)

4. Age at entry into CCSS
   - < 20 years N= (%)
   - 20-29 years N=(%)
   - 30-39 years N= (%)
   - > 40 years N= (%)

5. Therapy received for primary malignancy
   - Chemotherapy only N= (%)
   - Radiation only N= (%)
   - Surgery only N= (%)

- Chemotherapy + Radiation N= (%)
- Chemotherapy + Surgery N= (%)
- Chemotherapy + Radiation + Surgery N= (%)

6. Chemotherapy
   - Alkylating agent
     - Yes N= (%)
     - No N= (%)

7. Additional risk factors…

Table II: Characteristics of Patients with Second Malignant Neoplasms Stratified by Second Malignancy

1. Sex (%M, %F)
2. Age at Diagnosis of primary malignancy (mean ± SD)
3. Primary malignancy
3. Age at diagnosis of second malignancy (mean ± SD)
4. Elapsed time between malignancies (mean ± SD)
5. Radiation (%yes/ %no)
6. Alkylator Score
7. Malignancies reported in first degree relatives (%yes/ %no)

Table III: Comparison of Risk Indices by Site

SEER Code	Site of second malignant neoplasm according to SEER categories	Observed/ expected ratio (95% CI)	Cumulative incidence of SMN at 20 years, %	Absolute excess risk/1000 person-years of follow-up
C00.0-C14.0	Lip, oral cavity & pharynx			
C15.0-C26.0	Digestive organs excluding colon and rectum			
C18.0-C20.0	Colon and Rectum			
C34.0	Lung and bronchus			
C51.0-C58.0	Female genital organs			
C60.0-C63.0	Male genital organs			
C64.0	Kidney			
C65.0-C68.0	Urinary tract excluding Kidney			
C41.0	Bones of skull and face and assoc'd joints			
C47.9	Peripheral nerves and ANS			
C74.0	Adrenal gland			
C77.0	Lymph nodes			
C76.2	Abdomen NOS			
C80.9	Unknown site			
	Overall			

Table IV: Comparison of Risk Indices by Morphology

ICDO-2 morphology code	Morphology of second malignant neoplasm according to ICDO-2 code	Observed/ expected ratio (95% CI)	Cumulative incidence of SMN at 20 years, %	Absolute excess risk/1000 person-years of follow-up
8010-8040	Epithelial neoplasm NOS			
8120-8130	Transitional cell papillomas and carcinomas			
8140-8380*	Adenomas and adenocarcinomas*			
8312.3	Renal cell carcinoma			
8430	Mucoepidermoid neoplasms			
8440-8490	Cystic, mucinous and serous neoplasms			
8550	Acinar cell neoplasms			
9100	Trophoblastic neoplasms			
	Overall			

* Excluding 8312.3 renal cell carcinomas, which are evaluated separately.

Table V: Comparison of Risk Indices by Childhood Cancer Diagnosis

Childhood Cancer Diagnosis	Observed/expected ratio (95% CI)	Cumulative incidence of SMN at 20 years, %	Absolute excess risk/1000 person-years of follow-up

VIII- Other considerations:

Dr. Mylène Bassal will take the leadership role in executing this project as part of the research requirements of her Pediatric Hematology/Oncology fellowship and Certificate program in Clinical Science at the University of Colorado. The data analysis will be conducted by the CCSS Statistical Center. Drs. Nina Kadan-Lottick and Brian Greffe, in addition to the other co-investigators, will mentor Dr. Bassal in this endeavor.