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Topic: Second Malignant Neoplasms

Lead CCSS Investigator: Joe Neglia
Collaborators: Yasui, Hammond, Friedman, Donaldson, Meadows, Stovall, Mertens, Robison
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CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

Title
Second Malignant Neoplasms Following Childhood Cancer: A report from the Childhood Cancer Survivor Study

Working Group and Investigators
This publication will be written within the Second Malignancy Working Group, with input from the Epidemiology/Biostatistics Working Group. Proposed investigators include:

Debra Friedman  friedman@kermit.oncol.chop.edu  215-590-2013

Background & Rationale
Cure rates for childhood cancer approach 70% and continue to improve. This results in a large cohort of childhood cancer survivors at risk for late effects of their disease and its therapy. One of the most significant late effects is the development of a second malignant neoplasm (SMN). Among all cancer survivors, with the exception of those with heritable retinoblastoma, those with Hodgkin’s disease have the greatest prevalence of SMN’s. However, other groups of survivors are still at significant risk. Studies have reported an excess of second malignancies after Hodgkin’s disease with an overall 15 year cumulative incidence of about 7%. Within this cohort of SMN’s, breast cancer is rising rapidly. This is most likely due at least in part to the therapy they have received. However, between 1970 and 1989, this therapy has changed and it is therefore important to see how patterns of SMN have evolved as well. The CCSS population represents the largest cohort of childhood cancer survivors, treated in the most recent age of cancer therapy. In this group, we seek to examine the incidence and spectrum of SMN’s. With identification of the most common primary and second malignancies, a companion paper will be submitted that will focus on specific risk factor analyses.
Specific Aims/Objectives/Research Hypotheses

This publication is intended to examine the epidemiology of SMN’s following childhood cancer in a descriptive manner. The objectives are as follows:

- Describe the cohort
- Describe the methodology for identification and verification of SMN’s
- Quantify the cumulative incidence of SMN following childhood cancer
- Document the association between specific primary and secondary malignancies
- Identify the most common primary malignancies associated with SMN’s
- Identify the most common second malignancies following childhood cancer
- Document SMN’s by both site and histology
- Examine latency periods with respect to site/histology of SMN
- Identify new associations between risk for SMN and demographic factors such as age, race, and gender
- Propose a higher risk group for SMN based on above for a detailed risk factor analysis to be submitted as a companion paper. (See concept proposal from L. Diller)
- Propose a higher risk group for SMN for participation in secondary cancer prevention programs

Analysis Framework

(a) Outcome of interest: Development of SMN following childhood cancer

(b) Subject Population: All cases registered in CCSS

(c) Explanatory variables: initial diagnosis, stage of primary malignancy, age at dg, age at last contact or at dg of SMN, follow-up time since diagnosis, race, gender, recurrence, type of treatment, radiation dose, radiation field, chemotherapy doses, and if applicable: site of SMN, histology of SMN, age at dg of SMN, latency time from primary malignancy, outcome of SMN.

(d) Specific tables:
   1) Characteristics of cases in CCSS vs. those in the SMN cases:
      vital statistics (% alive)
      gender (%M; %F)
      age at dg (median and range)
      follow-up (median and range)
Stage
race (% C, AA, H, Asian, other)
recurrent disease (%)
type of treatment: chemotherapy, radiation, splenectomy, combined chemo &
radiation, combined chemo and splenectomy, combined radiation &
splenectomy, all three modalities.
Radiation doses
Radiation fields
Chemotherapy protocols
Alkylating agent scores
For the SMN cases only:
age at dg of SMN (median with range)
mean follow-up time with SD (median with range)
site and histology of SMN
treatment for SMN
outcome of SMN

3) Cumulative Incidence and Standardized incidence ratios by
type of SMN:

- All
- leukemia
- sarcoma
- breast cancer
- thyroid
- NHL
- other solid tumors
- melanoma

4) Relative Risk for SMN by treatment exposure and type of SMN

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<tr>
<th></th>
<th>Chemotherapy alone</th>
<th>Radiation Alone</th>
<th>Chemotherapy + Radiation</th>
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<td>Sarcomas</td>
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<td>Other solid tumors</td>
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5) Standardized risk ratios for SMN’s according to length of f/u interval by SMN type

- All
- leukemia
- sarcoma
- breast cancer
- thyroid
- NHL
- other solid tumors
- melanoma
6) Kaplan-Meier Survival Curve for Patients with SMN’s

7) Association between primary malignancy and secondary malignancy – cumulative incidence and SIR (using SEER data)

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<th>MDS/AML</th>
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