CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

1. **Title**: Outcome after second malignant neoplasm in adult survivors of pediatric malignancy.

2. **Working Group and Investigators**: Second Malignancy Committee
    Proposed investigators:
        Rob Goldsby
        Raj Nagarajan
        Anna Meadows
        Jim Gurney
        Joe Neglia
        Yan Liu
        Les Robison
        (Others to be determined)

3. **Background and Rationale:**

The remarkable improvement in the ability to treat children with cancer is one of the true modern medical triumphs. Childhood cancer was almost incurable 50 years ago. Now, with current multidisciplinary therapy more than 70% of children with cancer survive beyond 5 years after therapy. With the increasing numbers of people surviving childhood cancer, there is an increasing awareness and recognition of long-term sequelae. One of the most worrisome complications following cancer therapy is second malignant neoplasms (SMNs). Recent studies have shown that SMNs are on the rise, but little data exists regarding the outcome of these patients.

The CCSS cohort includes over 12,000 adult survivors of pediatric malignancies (surviving 5 or more years after their diagnosis). Over 1000 SMNs have been identified in the study population. While this cohort will have under-representation of post-therapy related leukemia, as they tend to occur early after therapy, it does include a substantial number of solid tumors. There have been more than 400 cases of skin cancer, over 100 cases of breast cancer, greater than 70 cases of secondary sarcomas and at least 70 CNS tumors (excluding meningiomas). The number of SMNs has been increasing as the time from the original cancer diagnosis increases.

We propose a study to assess survival after development of SMN in adult survivors of pediatric malignancies identified in the CCSS cohort. Analysis of survival post SMN diagnosis may provide additional information concerning prognosis, the need for follow-up and screening. This study may provide insight for future data collection regarding second malignant neoplasms.

4. Specific Aims/Research Hypotheses:

Aims:
    1) Determine the length of survival after the development of secondary malignancies that occur more than 5 years after the primary diagnosis.
    2) Analyze the length of survival for each specific SMN (i.e., breast, thyroid, sarcoma, CNS)

Hypothesis:

    1. Patients with a second malignant neoplasm will have a shorter survival compared to patients with a similar diagnosis as a primary cancer.

    2. The use of XRT for the treatment of the primary cancer will predispose the survivor to develop an SMN.

3. Those treated with XRT for their primary malignancy will have a poorer survival compared to those treated without XRT.

4. Shorter duration between primary cancer and SMN portends a worse survival.

5. **Analysis Framework:**

a. Outcomes of interest:

    I.   Survival time after diagnosis of SMN (overall and by each type of SMN). The data from the most recent National Death Index search will also be used to help establish deaths.

    II.   Analysis will also be done adjusting for sex, age at diagnosis of SMN, time from prior diagnosis or original diagnosis.

    III.   Additional analysis to see if treatments for original diagnosis was predictive of survival

b. Subject population: All CCSS cases that developed SMN.

    I.   There are 1039 patients with SMN within the CCSS.

    Breakdown of SMN by diagnosis:

    Skin cancers = 404

        Basal cell carcinomas = 350

        Melanoma =26

        Squamous cell carcinoma = 28

    Breast cancer = 148

    Thyroid = 82

    Sarcomas = 70

    CNS = 79
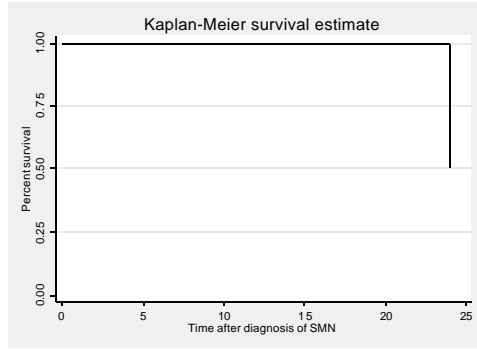
    Meningiomas = 89

    Leukemia/lymphoma = 60

    Others = 196

    II.   Explanatory Variables: Original diagnosis, treatment of original diagnosis (radiation, alkylator score, adriamycin dose, splenectomy y/n), age at SMN, gender, age at original and time since original diagnosis.
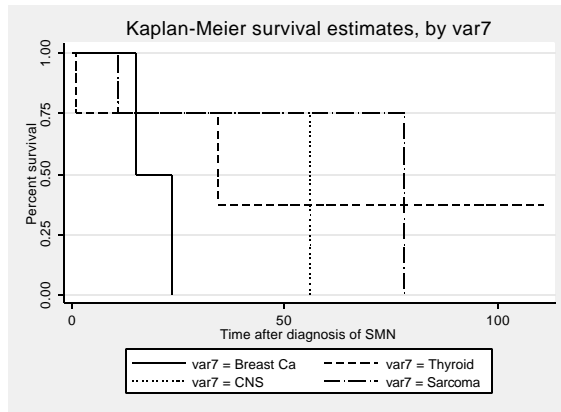
c. Specific Tables and Figures:

    I.   Patient characteristics: sex, race, ethnicity, diagnosis, site of primary tumor, age at original diagnosis, age at SMN.

    II.   Outcome: Kaplan Meier survival curve Overall – Using the updated National Death Index

Kaplan-Meier survival estimate

a.

III.   Kaplan Meier survival curve by SMN type.

Kaplan-Meier survival estimates, by var7

var7 = Breast Ca   var7 = Thyroid
var7 = CNS   var7 = Sarcoma

a.

IV.   Kapln -Meier curves for SMN survival according to the primary neoplasm

V.   SEER data comparison

a.   Compare survival time of the CCSS to that of SEER based on original and subsequent histologies

Limitations: Limited data regarding the stage of disease at diagnosis of the SMN and the therapy utilized make interpretation of the results somewhat limited.   However, this study will give some indication regarding the outcome after diagnosis of a second malignant neoplasm and may lay the basis for future data collection. The diagnosis of second malignant neoplasm is based on self-reporting and this may bias the results. Small numbers may make sub-group analyses less reliable.