06-04

CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

Title: Updated late mortality rates and cause of death in CCSS

Working Group and Investigators: This proposed publication will be within the Epidemiology/Biostatistics Working Group. Proposed investigators will include:

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Background and Rationale: With current improvements in therapies, survival has increased dramatically in most types of cancer seen in children, with an increase in the probability of five year survival is currently over 80%. Several studies have shown an excess in the mortality rates in survivors of childhood cancer, and it has been suggested that this excess risk may be even higher in individuals who have received multi-modal therapy.

In our previous analysis of late mortality, we found that while recurrent disease remains a major contributor to late mortality in five year survivors of childhood cancer, significant excesses in mortality risk associated with treatment-related complications existed up to 25 years following the initial cancer diagnosis. In this analysis we will be able to include an additional 8 years of follow-up. This allows us 11-27 years follow-up from the 5th year anniversary of cancer diagnosis for each CCSS case. Also, because of the increased number of deaths and longer-follow-up, we will be able to perform more detailed analysis.

Specific Aims/ Objectives/Research Hypotheses: This analysis is designed to investigate the long-term effects of cancer and its associated therapies on mortality rates and on the specific cause of death.
Hypothesis I: Survivors will have a significant excess risk of cause-specific mortality associated with the type of childhood cancer and exposure to specific treatment modalities. Specifically:
a) Recurrence will be the leading cause of death in survivors of childhood cancer, and the risk will decrease from time of original diagnosis;
b) Risk of death due to causes other than recurrence will be higher in survivors than in the general population, and will be mediated by treatment and cancer related psychosocial sequelae.

Analysis Framework:
This analysis will update the mortality rates and the specific causes of death in all eligible cohort members (n=20,507). In the previous analysis there were 2030 deaths; in the current analysis, there are 2556 deaths before Dec 31, 2002.

Standardized mortality ratios (SMR) will be calculated using age- and sex-specific rates from U.S. Mortality Statistics, National Center for Health Statistics for all causes of death.

Information on the underlying cause of death was obtained from death certificates on cases who resided in the United States. As in the previous analysis, cause of death has been determined from the death certificates, and will be categorized as follows:

- cancer recurrence
- treatment related complications during remission of primary diagnosis
    - SMN
    - cardiac
    - pulmonary
    - infection
    - other
- other causes, not treatment-related
    - unintentional injury
    - AIDS
    - suicide
    - other causes

All-cause and cause-specific mortality rates and SMNs will be analyzed using Poisson regression models.

a. Outcomes of interest: alive/dead status

Other variables of interest:

- Demographics/cancer characteristics: gender, race, age at diagnosis, mean age at follow-up, mean duration of follow-up, diagnosis type, type of treatment (see below).
- For cases who have died: date of death, cause of death

b. Subject population:

1) Characteristics of all CCSS cases by alive/dead status
2) Mortality data on cases who have died

c. Specific tables:

1) Characteristics of all CCSS cases by alive/dead status:
    - sex
    - age at diagnosis
    - survival after diagnosis (years)
    - diagnosis (using 14 categories described in Methods paper)
    - type of treatment
        - chemotherapy Y/N
            - look separately at alkylating agents, anthracyclines, epipophyllotoxin, bleomycin
        - radiation Y/N
            - look separately at cranial radiation, chest radiation
        - chemotherapy + radiation Y/N

2) Number of deaths and rates by:
    - overall
    - diagnosis type

- sex
- survival after diagnosis (years)
- type of treatment
- our assigned cause of death categories (recurrences, treatment related, and other)
- 72 cause of death categories assigned by National Death Index

3) Comparison of CCSS death rates to US population rates (matched by age, sex, and calendar period) for:
- overall
- diagnosis type
- sex
- survival after diagnosis (years)
- type of treatment
- our assigned cause of death categories (recurrences, treatment related, and other)

4) Cumulative mortality on anniversary dates from 5 years post-diagnosis, modeled by diagnosis, treatment, and patient characteristics
- at 5, 10, 15, 20 year anniversaries from 5-year post diagnosis

5) Comparison of cause of death rates in cohort to US population rates for:
- all cases
- treatment related COD (separated out by SMN, cardiac, pulmonary, infections, other)
- non-treatment related COD (separated out by accidents, HIV, suicides, other)

6) Kaplan Meier survival curves for:
- overall
- diagnosis type
- sex
- type of treatment
- our assigned cause of death categories (recurrences, treatment related, and other)

7) We will also evaluate the rate of mortality rate over time, to see if in accelerates or decelerates with time from diagnosis.

Special Consideration: Analysis will be performed at the University of Alberta by Qi Liu, under the supervision of Yutaka Yasui