

Proposal No: 98-01
Topic: Late Mortality

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98-01

CHILDHOOD CANCER SURVIVOR STUDY Analysis Concept Proposal

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1. **Title:** Mortality Rates and Causes of Death in Survivors of Childhood and Adolescent Cancer
2. **Working Group and Investigators:** This proposed publication will be within the Epidemiology/Biostatistics Working Group. Proposed investigators (name/e-mail/fax) will include:

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3. **Background and Rationale:** With current improvements in the treatment of children and adolescents for cancer, survival has increased dramatically, with an overall increase in the probability of five year survival of over 65% in 1986. Several studies have shown an excess in the mortality rates in survivors of childhood cancer, and it has been suggested that this excess risk depends on therapeutic modalities, and is higher in individuals who have received multi-modal therapies. Increased mortality rates are primarily due to recurrences of the primary diagnosis, but they may also be increased for other causes of death, when compared to the US population. By studying mortality rates by therapeutic modalities as well as clinical and demographic variables, we will be able to gain insights regarding 1) which therapeutic modalities are associated with higher mortality, 2) which patients require special attention in follow-up, and 3) what interventions may be considered to reduce excess mortality among childhood cancer survivors.
4. **Specific Aims/Objectives/Research Hypotheses:** This publication is designed to investigate the long-term effects of cancer and its associated therapies on mortality rates and on the specific cause of death. We have two objectives: (1) to describe mortality risk in a large cohort of childhood cancer survivors by survivors' characteristics (clinical and demographic) and time, and (2) to compare cause-specific mortality rates with the US population and assess excess risk by survivors characteristics (clinical and demographic) and time.

Hypotheses:

1. Mortality risk from all causes of death will depend on diagnosis, age at diagnosis, time since diagnosis, sex, and exposure to specific treatment modalities. Specifically, the risk is high among survivors of HD, younger age at diagnosis, shorter time since diagnosis, male, multi-modal therapies, higher dose of radiation, and higher doses of chemotherapy drugs.
2. Survivors will have a significant excess risk of cause-specific mortality, relative to the US population, associated with the type of childhood cancer and exposure to specific treatment modalities.
 - 2.a Recurrence of cancer will be the leading cause of death in survivors of childhood cancer, and the risk will increase with HD, younger age at diagnosis, shorter time since diagnosis, male, multi-modal therapies, higher dose of radiation, and doses of chemotherapy drugs.
 - 2.b Individuals who have a recurrence (especially within the first five years) will have higher mortality rates.
 - 2.c Risk of death due to causes other than recurrence will be higher in survivors than in the general population. Specifically, risk of death from a second neoplasm (ICD=140-208), infectious disease (ICD=001-139), diseases of circulatory system (ICD9=390-459), accidents (ICD9=E800-949) and suicide (ICD9=E950-959) will be higher among the survivors. This will be mediated by treatment and cancer related psychosocial factors (smoking, educational attainment).

5. Analysis Framework:

- a. Outcome of interest: alive/dead status of each CCSS subject (date and cause of death if died) as of December 31, 1996.
- b. Subject population: all CCSS cases (whose vital status is known)
- c. Explanatory variables: sex, age at diagnosis (see d.1), age at follow-up, time since diagnosis, diagnosis type, race (see d.1), recurrence(see d.1), type of treatment (see d.1), dose of radiation, doses of chemotherapy drugs, smoking (see d.1), educational attainment (see d.1).

Note that effects of radiation or chemotherapy drugs may be modified by age at diagnosis and/or sex.

d. Specific tables:

1) Characteristics of all CCSS cases by alive/dead status:

Alive N= -- (90%) Dead N= -- (10%)

- sex male N= -- (87%) male N= -- (13%)
 female N= -- (93%) female N= -- (7%)
- age at dx (0, 1-3, 4-6, 7-9, 10-2, 13-15, 16-18, 19-21)
- mean age at follow-up/death (standard deviation)
- mean time since diagnosis (standard deviation)
- diagnosis type (8 type categories)
- race (white, black, Hispanic, Am Indian, Asian, other)
- smoking (current smoker: N.1 and N.1a)
- educational attainment (O.1)
- recurrence (none, <= 5 years from dx, > 5 years from dx)
- type of treatment
 - chemotherapy only
 - radiation only
 - surgery only
 - chemotherapy+surgery
 - chemotherapy+radiation
 - radiation+chemotherapy
 - chemotherapy+radiation+surgery
- dose of radiation (1-999, 1000-2499, 2500-3499, 3500-4499, >4500 cGy)
- use of each chemotherapy drug (yes/no)
- dose of each chemotherapy drug (the 28 major drugs)

2) Mortality rates and standardized mortality ratio (age-sex-calendar-period standardized to the US population) by:

- diagnosis type
- sex
- time since dx
- smoking (current smoker: N.1 and N.1a)
- educational attainment (O.1)
 - type of treatment
 - dose of radiation
 - dose of each chemotherapy drug (the 28 major drugs)
- recurrence

3) Repeat 2) with cause-specific mortality rates, namely, mortality from a second neoplasm (ICD=140-208), infectious disease (ICD=001-139), diseases of circulatory system (ICD9=390-459), accidents (ICD9=E800-949) and suicide (ICD9=E950-959).

6. Special Consideration: Causes of death will be determined from the death certificates by specific rules, to be established by Neglia and Mertens. The rules will categorize deaths into the following 3 groups:

- cancer recurrence
- treatment related complications during remission of primary diagnosis (include infectious disease (ICD=001-139) and diseases of circulatory system (ICD9=390-459))
- other causes
 - new cancer during remission of first cancer
 - accidents, unintentional injury (ICD9=E800-949)
 - suicide (ICD9=E950-959)
 - other causes

If any cause of death that is not specified above shows a high frequency, it will be investigated as a separate category.