

Proposal No: 00-02  
Topic: Pulmonary Complications

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Lead CCSS Investigator: Ann Mertens

Collaborators: Sklar

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Priority Rating: 2.0

CHILDHOOD CANCER SURVIVOR STUDY  
Analysis Concept Proposal

June 14, 2000

1. **Title:** Pulmonary Complications in Survivors of Childhood and Adolescent Cancer

2. **Working Group and Investigators:** This proposed publication will be within the Chronic Disease Working Group. Proposed investigators (name/e-mail/fax) will include:

Ann Mertens

mertens@epi.umn.edu

612-624-0315

3. **Background and Rationale:** With current improvements in therapies during the past 30 years, survival for many diagnostic groups has increased dramatically; the overall five year survival in 1998 was 80% for children and adolescents diagnosed before the age of 20. Several studies have shown that pulmonary function in survivors of childhood cancer, can be compromised by certain types of anticancer therapy. Adverse effects have been detected after both radiation therapy and chemotherapy, leading to pneumonitis and subsequent fibrosis, as well as other obstructive changes.

The lung is one of the most radiation sensitive structures in the body. The predominant symptoms of radiation induced lung disease are dyspnea and a persistent dry cough. Studies of children treated with radiation at an early age, found a significant reduction in both lung volume and in dynamic compliance over time, as well as restrictive ventilatory impairment and thoracic hypoplasia. Other studies have indicated that pulmonary radiation causes pneumonitis and subsequent fibrosis. A recent study of Hodgkins disease cases who received radiation to the lung has shown an increase in the risk of lung cancer, with the risk continuing to increase with time from diagnosis.

Pulmonary toxicity has been shown to occur with exposure to both bleomycin and nitrosoureas, such as BCNU. The most common lung injury seen is pulmonary fibrosis. Studies have indicated that lung fibrosis due to bleomycin or BCNU chemotherapy in childhood may remain asymptomatic, or become symptomatic at any time. Increased deaths due to pulmonary toxicity have also been demonstrated with exposure to these agents.

By studying pulmonary conditions 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 pulmonary complications, (2) which patients require special attention in follow-up, and (3) what interventions may be considered to reduce excess pulmonary compromise 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 pulmonary conditions and complications. We have two objectives: (1) to describe the risk of pulmonary complications in a large cohort of childhood cancer survivors by survivors' characteristics (clinical and demographic) and time, and (2) to compare the rates of pulmonary conditions with the US population and assess excess risk by survivors characteristics (clinical and demographic).

Hypothesis:

i. Self-reported pulmonary complications will be higher in subjects who have received specific chemotherapy: bleomycin, CCNU (Iomustine), and BCNU (carmustine). Increased risks within these subjects will depend on diagnosis, age at diagnosis, time since diagnosis, and sex. Specifically, the risk is high among survivors of Hodgkin disease, females, younger age at diagnosis, longer time since diagnosis, and higher doses of chemotherapy.

ii. Self-reported pulmonary complications will be higher in subjects who have received radiation, specifically to the chest or the spine area. Increased risks within these subjects will depend on diagnosis, age at diagnosis, time since diagnosis, and sex. Specifically, the risk is high among survivors of Hodgkin disease, females, younger age at diagnosis, longer time since diagnosis, and interactions with bleomycin or BCNU.

iii. Survivors will have a significant excess risk of pulmonary cause-specific mortality, relative to the US population, associated with the type of childhood cancer and exposure to specific treatment modalities.

iv. Survivors will have a significant excess risk of lung cancer, relative to the US population, associated with the type of childhood cancer and exposure to specific treatment modalities.

## 5. Analysis Framework:

a. Outcome of interest: responses on Section G of baseline questionnaire (G.1-G.13), exercise causes severe chest pains, shortness of breath, or irregular heartbeat (F.17), bronchoscopy since therapy stopped (I.19), other lung surgery (I.20), lung transplant (I.24), cancer of lung (K.2, K.6), death due to pulmonary complications.

b. Subject population: all CCSS cases

c. Explanatory variables: sex, age at diagnosis (see d.1), age at follow-up, time since diagnosis, diagnosis type, type of treatment (see d.1), radiation to the chest/spine (yes/no), dose of radiation, specific chemotherapeutic agents that have been implicated in pulmonary disease: bleomycin, CCNU, BCNU, busulfan, cyclophosphamide, chlorambucil, melphalan, methotrexate, Ara-C, procarbazine (yes/no), doses of specific chemotherapy agents listed.

Possible risk factor variables that will also need to be taken into consideration are: history of smoking (N.1), physical activity (N.9), limitations to activities (to determine difficulty with exercise) (N.14), and pre-existing lung disease (positive answer in Section G for any age of occurrence before diagnosis),

d. Specific tables:

1) Characteristics of all CCSS cases by yes/no answers to specific questions in section G: pleurisy (G.5), abnormal chest wall (G.7), chronic cough (G.8), ever used oxygen (G.9), lung fibrosis (G.12). Characteristics will include:

- sex
- age at diagnosis (0-4, 5-9, 10-14, 15+)
- mean age at follow-up (standard deviation)
- mean time since diagnosis (standard deviation)
- diagnosis type
- race (white, black, Hispanic, Am Indian, Asian, other)
- type of treatment
  - chemotherapy only
  - radiation only
  - surgery only

- chemotherapy+surgery
- chemotherapy+radiation
- radiation+chemotherapy
- chemotherapy+radiation+surgery
- dose of radiation to chest/spine (1-2399, 2400-4799, 4800-5399, >5400)
- doses of selected chemotherapy agents listed above

2) Standardized incidence ratios (observed/expected) of pulmonary complications calculated using the following comparisons: a) questions in section G will be age-, sex-standardized to the National Health Interview Survey rates; b) lung cancer rates will be compared to age-, sex- standardized to the SEER rates; c) deaths due to pulmonary complications will be compared to age-, sex- standardized the National Center for Health Statistics rates. Calculated rates will also be evaluated by:

- diagnosis type
- sex
- time since diagnosis
- type of treatment
- dose of radiation to chest/spine
- selected chemotherapy agents

3) Multivariate analysis tables will be constructed to describe the risk for each pulmonary complication (stated in 5a) by diagnosis type, sex, time since diagnosis, radiation exposure, and selected chemotherapy agents.

4) Cumulative incidence curves will be generated for pulmonary complications (stated in 5a) by age at occurrence and time since diagnosis. For those with sufficient sample size and statistical importance, curves will also be generated by treatment exposure.

**6. Special Consideration:** Sue Duvall is a biostatistician at the University of Minnesota, and is currently involved with the CCSS cardiac outcomes proposal. Sue has experience with the CCSS datasets, and will also be responsible for the analysis of this proposal.

One limitations to this analysis is the fact that answers to pulmonary complications listed in section G are self report, and will likely only reflect symptomatic cases. By describing those who are symptomatic, results may be useful in identifying possible asymptomatic cases that should be evaluated for possible complications.

**MEMORANDUM**

**DATE:** June 14, 2000  
**TO:** Anna Meadows, M.D. and Les Robison, Ph.D.  
**FROM:** Ann Mertens, Ph.D.  
**SUBJECT:** CCSS Analysis Concept Proposal

I am enclosing an analysis concept proposal that I am submitting through the Chronic Disease Working Group, titled 'Pulmonary Complications in Survivors of Childhood and Adolescent Cancer'.

I have included as authors individuals who have expressed interest in looking at pulmonary complications in this cohort. I have also included on this proposal, Sue Duval, Ph.D. who is a biostatistician at the University of Minnesota. She is currently working with us on the cardiac outcomes proposal and will also be responsible for the analysis on this proposal.

This proposal has been reviewed and approved by the Chronic Disease Working Group. If you have any questions or comments about this, please let me know.

Thank you.