01-04

# CHILDHOOD CANCER SURVIVOR STUDY
## Analysis Concept Proposal

I. **Title:** Treatment-related breast cancer in the CCSS cohort

I. **Working Group and Investigators:** This proposed publication will be within the Second Malignancies Working Group (Anna Meadows, chair).

Proposed investigators include:


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I. **Background and Rationale:** Dramatic gains in the treatment of childhood cancer were achieved in the 1960s and 1970s, and a large majority of patients now can be cured (Meadows and Hobbie 1986). This success has not come without a cost, as the treatments that have proven to be so effective at prolonging life also increase the risk of second cancers years later. Increases in the risk of acute, nonlymphocytic leukemia were appreciated early on, as therapy-induced leukemias begin to appear within a few years of treatment. Longer follow-up was required to detect excess risk for solid tumors. Risks for solid cancers still are not fully understood due, in part, to the relative youth of most of the populations studied. Long-term survivors of childhood cancer have begun to reach the ages at which background incidence rates for many common cancers increase sharply. It is important to quantify the treatment-related risks for these common cancers. Even modest relative increases in risk could involve substantial absolute risks. More frequent screening or closer surveillance may be indicated for persons at increased risk.

Studies of secondary breast cancer following treatment for Hodgkin's disease or other cancers of childhood or adolescence indicate large relative increases in risk following thoracic radiotherapy (Hancock et al. 1993; Bhatia et al. 1996; van Leeuwen et al. 1994, 2000; Aisenberg et al. 1997; Metayer et al. 2000). Excess risk persists for more than 25 years following treatment for Hodgkin's disease in childhood (Metayer et al. 2000). The relative risk (RR) of radiation-related breast cancer is inversely related to age at exposure for persons treated as adolescents or adults (Hancock et al. 1993; Bhatia et al. 1996; van Leeuwen et al. 2000; Swerdlow

et al 2000). In one study, the RR was higher among patients treated for Hodgkin's between the ages of 10 and 16 y than for those younger than 10, which is consistent with the hypothesis that radiation risks are higher when the breast tissue is undergoing rapid cell proliferation (Bhatia et al. 1996). However, such a pattern was not seen among atomic bomb survivors (Thompson et al. 1994), and requires further evaluation. To this point, data do not indicate a strong causal effect of chemotherapy, but the evidence is limited, particularly for long follow-up intervals. Some agents may be protective, due to induction of a premature menopause or other effects on ovarian function (Swerdlow et al. 2000). Further information is needed concerning possible joint effects of radiotherapy and chemotherapy. Such analyses require detailed information on doses.

Limitations of the studies cited above include small sample size, absence of detailed dosimetry, and absence of information on factors that might modify radiation-related cancer risk. The Childhood Cancer Survivor Study (CCSS) cohort provides the opportunity to improve on each of these fronts. As of December 2001, nearly 100 breast cancers had been identified among 5-year survivors of childhood cancer. This number is larger than in any study published to date. Radiation treatment records for the first cancer were photocopied and are available to the collaborating medical physicist (Marilyn Stovall). Chemotherapy data (cumulative doses and routes of administration for 28 agents) have been abstracted from medical records. Information about possible breast cancer risk factors was collected by questionnaire. These data can be used both to control for confounding and assess possible modification of treatment effects. In sum, the experience of the CCSS population represents an important potential source of information concerning risk of therapy-related breast cancer among long-term survivors of childhood cancer.

**I. Specific Aims/Objectives/Research Hypotheses**: The primary objectives are to describe the risk of breast cancer in relation to radiation dose to the breast among members of the CCSS, and clarify factors that modify this risk. We expect risk to increase with increasing dose at lower doses, with possible flattening at very high doses. To help achieve this objective, we will attempt to locate the breast cancer within the breast as precisely as possible, at least as to quadrant. The potential modifying effects of age at irradiation and time since irradiation will be evaluated. We also will consider effects of chemotherapy (CT) but expect any carcinogenic effects of CT to be small relative to those of thoracic radiotherapy. Indeed, some forms of CT might be protective. Joint effects of RT and CT, and RT and known breast cancer risk factors will be examined.

## I. Analysis Framework

(a) *Outcome of interest*: Breast cancer as second or subsequent primary cancer

(b) *Study population*: The study will be based on the experience of the CCSS cohort of five-year survivors of childhood cancer (exclusive of retinoblastoma)

diagnosed at any of 25 institutions in the U.S. and Canada between January 1, 1970 and December 31, 1986 (Neglia et al. 2001). The qualifying childhood cancer was diagnosed before the age of 21 years and confirmed microscopically. As of January 1, 2000, 13,581 of 20,245 eligible patients had been located and agreed to participate in the study, including 7,277 males and 6,304 females (Neglia et al. 2001). The median interval from diagnosis of first cancer to enrollment was 15.4 years.

Eligible cases are persons with a second or subsequent invasive primary breast cancer diagnosed before the earlier of December 31, 2001 and date of return of follow-up survey. Data for the 2001 follow-up are still being processed. As of summer 2000, 71 breast cancer cases had been identified, all among females. The average year of initial cancer diagnosis was 1975 (range, 1970-85); the average age at diagnosis of the first primary cancer among the cases was 15.5 y (range, 6.0 - 20.0 y), and the average age at diagnosis of secondary breast cancer was 32 y (range, 20-46 y). Hodgkin's disease was the initial cancer for 14% of the cohort, but for more than 70% of the survivors diagnosed with a secondary breast cancer. When results of the 2001 follow-up surveys become available, we expect the number of breast cancer cases to increase substantially, possibly to 100 or more.

Four controls will be selected for each case, matched on gender, age at diagnosis of first cancer and duration of survival (follow-up) ($\pm$ 2 years). We will not match on type of first primary cancer, but will handle this covariate in the analysis instead. Simulated sampling of controls with and without matching on initial cancer indicated that matching on first cancer would produce large numbers of matched sets concordant for history of thoracic radiotherapy, with possible serious loss of study efficiency.

(c) *Explanatory variables*: Variables to be considered include local radiation dose to the presumed site of origin of the breast tumor for the case and matched controls from all cancer treatments, radiation dose to the ovaries, types and cumulative doses of chemotherapy agents, type of first primary cancer, age at diagnosis of first cancer, time since diagnosis of first cancer, attained age, year of diagnosis of initial cancer, race, family history of breast or ovarian cancer, menstrual and reproductive history, exogenous hormone use, oophorectomy, osteoporosis, alcohol consumption, body mass index, and physical activity. For girls younger than 13 years at the time of diagnosis of the first cancer, all potential breast cancer precursor cells will be assumed to be concentrated within a small volume in vicinity of the nipple for the purposes of radiation dosimetry.

(d) *Analytic methods*: PECAN, a program for fitting conditional logistic regression models (Lubin 1981; Preston et al. 1993), will be used to estimate odds ratios (ORs), perform likelihood ratio tests and calculate 95% confidence intervals (CIs). Linear and curvilinear dose-response models will be fitted. The possibility of an effect of type of first cancer, independent of treatment, will be addressed in two ways: first, through the use of indicator variables for type of initial cancer and, second by

restriction to controls with the same type of first cancer as the case. Product terms will be used to assess possible effect modification.

Separate analyses will be conducted for breast cancer as the second cancer (only) and for breast cancer as the second or subsequent cancer. For the former, cases and controls with a cancer other than breast as the second cancer will be excluded. For the latter, treatments for intervening cancer, prior to the breast cancer, will be taken into account.

(e) *Examples of specific tables and figures*:

Table 1: Descriptive characteristics of cases and controls (matching variables, type of initial cancer, year of diagnosis of initial cancer, time since initial diagnosis, and broad categories of treatment (e.g., RT to chest, RT to other part of body, any CT, type of CT, surgery only).

Table 2: (Dose-response): OR for breast cancer by radiation dose. Up to four categories will be selected based on the dose distribution among controls. Risks also will be evaluated with respect to dose of the more common types of CT, possibly grouped by class of agent.

Table 3: (Time-response): Results of analyses for possible modification of radiation effect by age at exposure, time since exposure and attained age.

Table 4: Joint effects of RT and CT (dose-specific).

Table 5: Possible modification of radiation effect by known reproductive risk factors. Statistical power will be low for these analyses. If results do not warrant a table, they will be described in the text instead.

Figure 1 (possible): Radiation dose-response relationship for second breast cancer, including observed ORs and fitted relationships.

## I. References

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