CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

1. Title: Second primary breast cancers among childhood cancer survivors: joint effects of treatment and host factors

2. Working Group and Investigators: This proposed publication will be within the Second Malignancies Working Group (Joseph Neglia, chair).

Proposed investigators include:

Peter Inskip (lead)	inskippe@mail.nih.gov	National Cancer Institute
Sara Schonfeld	schonfes@mail.nih.gov	National Cancer Institute
Amy Berrington de Gonzalez	berringtona@mail.nih.gov	National Cancer Institute
Joseph Neglia	jneglia@tc.umn.edu	University of Minnesota
Marilyn Stovall	mstovall@mail.mdanderson.org	M.D. Anderson Cancer Center
Susan Smith	sasmith@mdanderson.org	M.D. Anderson Cancer Center
John Whitton	jwhitton@fhcrc.org	Fred Hutchinson Cancer Research Center
Wendy Leisenring	wleisenr@fhcrc.org	Fred Hutchinson Cancer Research Center
Sarah Donaldson	sarah2@ stanford.edu	Stanford University
Ann Mertens	ann.mertens@choa.org	Emory University
Sue Hammond	sue.hammond@nationwidechildrens.org	Ohio State School of Medicine
Kevin Oeffinger	oeffingk@mskcc.org	Memorial Sloan Kettering
Chaya Moskowitz	moscowc1@MSKCC.ORG	Memorial Sloan Kettering
Lisa Kenney	Lisa_Kenney@DFCI.harvard.edu	Dana Farber Cancer Institute
Lisa Diller	lisa_diller@dfci.harvard.edu	Dana Farber Cancer Institute
Smita Bhatia	SBhatia@coh.org	City of Hope Cancer Center
Anna Meadows	meadows@email.chop.edu	Univ. Pennsylvania School of Medicine
Leslie Robison	Les.Robison@STJUDE.org	St. Jude Children's Research Hospital

3. Background and Rationale:

Previous studies have demonstrated a markedly increased risk of breast cancer following radiotherapy to the chest at a young age (1-9), with excess risk persisting for more than 25 years (9). Data are consistent with a linear dose-response relation for breast doses up to 40 Gy. A recent report from the Childhood Cancer Survivor Study (CCSS) indicated an 11-fold increased risk at 40 Gy relative to zero dose (7). The estimated cumulative absolute risk of breast cancer for a female treated with ≥40 Gy of chest irradiation for Hodgkin lymphoma at age 25 years is 29% by age 55 years (10).

Less clear are factors that may modify the dose-response relation. Particularly as the survivors mature into middle age and postmenopausal years when breast cancer incidence rates are expected to increase, it is important to understand whether radiation-related risks add to, or multiply, risk associated with other established breast cancer risk factors (e.g., reproductive and hormonal factors, family history of breast cancer) and to understand the temporal patterns of these radiation-induced breast tumors. The CCSS cohort is now entering the age range where some of these questions can be explored. The number of second breast cancers has increased to the point that it is possible to

evaluate the joint effects of treatment and host factors and more precisely quantify the excess risk from radiation by temporal factors, including age at diagnosis, attained age, and calendar year of diagnosis.

Endogenous ovarian hormones (estrogen and progesterone) and exogenous sources of these hormones are well established in breast cancer etiology (11). There is some evidence that hormones modify the radiation-related risk of breast cancer. Among atomic bomb survivors, early age at first birth and multiparity significantly reduced the excess risk from radiation (12). A case-control study of Hodgkin lymphoma survivors suggested that breast cancer risk from radiation may be greater among parous women compared with nulliparous women (13). In studies of childhood and young adult cancer survivors, females who received high doses of radiation (> 5 Gy) to the ovaries had a significantly lower radiation-related risk of breast cancer compared with females who received lower dose to the ovaries (6, 7). Ovarian function is suppressed at high doses, and it is hypothesized that radiation-damaged and potentially tumorigenic cells in the breast may be less likely to develop into frank tumors in the absence of the stimulatory effect of ovarian hormones (6, 7). Based on these observations, it is hypothesized that other hormone-related and reproductive factors (e.g., parity, ages at menarche and menopause, exogenous hormone use, pubertal status at time of radiation treatment), may modify the radiation dose-response but the data are inconclusive (5, 6, 13). Previous case-control studies with detailed treatment and risk factor data were based on ≤120 breast cancer cases and thus had limited power to evaluate effect modification.

Etiologic heterogeneity within breast cancers is increasingly recognized, particularly differences between estrogen receptor (ER) positive and negative tumors (14, 15). Previous studies of childhood cancer survivors have not quantified the dose-response from radiation separately for ER+ and ER- breast tumors although there is some suggestion that breast cancers following Hodgkin lymphoma are more likely to be ER- than breast cancers in the general population (16, 17). The overall dose-response from radiation and modification by other treatment or host factors has not been characterized for ER+ and ER- tumors separately. In addition to ER status, it is of interest to characterize factors (treatment and host related) associated with stage at breast cancer diagnosis and histology, to the extent that this information is available.

Certain alkylating agents (e.g., cyclophosphamide, procarbazine, mechlorethamine) may also suppress ovarian function, and there have been reports of lower breast cancer risk following these treatments (5, 6). Conversely, a recent paper from the CCSS based on cases diagnosed through 2000 pointed to possible increased risks associated with prior treatment with doxorubicin, dactinomycin and bischloroethylnitrosourea (BCNU) (7). Questions remain about the main effects, as well as interactions with radiation dose, of different chemotherapy formulations on the risk of breast cancer.

It is well established that irradiation at a young age carries a higher risk than irradiation in middle or older age, but the variation in risk in young children through puberty and adolescence is less clear (18). It is of interest to examine whether the radiation dose-response varies by age at treatment for initial childhood cancer as well as other temporal factors, such as calendar year of- and time since treatment for the initial childhood cancer and attained age.

This concept proposes an extension of the previous case-control study conducted within the CCSS cohort (7). The previous study focused on quantifying the radiation dose-response relationship for breast cancer and was not well-powered to study interactions. The current proposal will focus on potential modification of the radiation risk by traditional breast cancer risk factors, chemotherapy, as well as age, calendar-time and tumor characteristics. We will also examine the radiation risk by ER status if the data permit. We estimate that there are now 250 breast cancer cases, approximately twice the number included in our previous report (7), and thus a more robust sample in which to analyze interactions between radiation and other factors. The analysis will combine the cases in (7) with cases diagnosed subsequently.

There would be little overlap with a study proposed by another team of investigators, in which the primary aim concerns cumulative incidence of breast cancer. The proposed study will conduct detailed radiation dosimetry which is not anticipated for the cumulative incidence study. Also, our proposed study would utilize a case-control design and thus be unable to address cumulative incidence.

4. **Specific Aims/Objectives/Research Hypotheses**: The primary objectives are to:

(a) Assess modification of radiation-related breast cancer risk by 1) reproductive and hormonal factors (pubertal status at treatment for childhood cancer, ages at menarche and menopause, attained menopausal status, gravidity, parity, exogenous hormone use); and 2) other established breast cancer risk factors (body mass index (BMI), alcohol consumption, and family history of breast or ovarian cancer)

(b) Quantify ER+ and ER- breast cancer risks separately in relation to radiation dose to the breast and ovary. We recognize that the feasibility of this aim will depend on the availability of estrogen receptor status for a sufficient number of patients with a second breast cancer

(c) Evaluate breast cancer risk with respect to prior chemotherapy, particularly anthracyclines and alkylating agents such as cyclophosphamide, and evaluate possible effect modification between radiation and chemotherapy on breast cancer risk

(d) Assess modification of radiation-related effects with respect to age at irradiation, time since irradiation, calendar year of irradiation and attained age

5. Analysis Framework

(a) *Outcome of interest*: Breast cancer as second or subsequent primary cancer. Both invasive and *in situ* cancers will be included.

(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 (19, 20). 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 (19). Only females would be included in the present study, with follow-up through that included in the 2007 frozen data set.

We estimate that there are 250 breast cancer cases, approximately twice the number included in our previous report (7). Four controls will be selected for each case, matched on age at diagnosis of first cancer and duration of survival (follow-up) (± 2 years). We will not match on type of first primary cancer, but will handle this covariate in the analysis instead. Previous 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. If none of the four selected controls had the same type of first cancer as the case, we will select a supplemental control who will only be included in secondary analyses restricted to controls with the same type of first cancer as the case. This is the same scheme as was used in the earlier study.

(c) *Radiation dosimetry*: Collaborating medical physicists at M.D Anderson Hospital will use radiotherapy records together with all other available relevant medical records to estimate dose to the site of the tumor in the case and the corresponding location in the matched controls. Dose to the ovaries will be estimated as well. Precise location of the cancer within the breast will be unknown for some women, and this information will have to be tracked down; however, dose reconstruction can be performed for the case-control sets with known location in the meantime. Radiation doses from the previous case-control study will be incorporated into the present analysis.

Age at menarche will be used to estimate Tanner stage of breast development and breast size at the time of radiotherapy. .

(d) *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, radiation dose to the ovaries, types and cumulative doses of chemotherapy agents, type of first 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 and ovarian cancer, menstrual and reproductive history, exogenous hormone use, oophorectomy, body mass index, and alcohol consumption. Information on tumor characteristics including estrogen receptor status for breast cancer cases will be sought from pathology reports or other available sources.

The baseline questionnaire (1992-1994) will serve as the primary source of information on non-treatment related factors (e.g., hormonal and reproductive factors) but additional information may be taken from follow-up questionnaires. The temporal association between exposures of interest and breast cancer can be determined from relevant dates or ages of exposures as indicated on the questionnaire.

(d) *Analytic methods*: PECAN, a program for fitting conditional logistic regression models (21), and SAS version 9.1. 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. Product terms will be used to assess effect modification by treatment and host-related factors.

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 as available. Intervening cancers will be enumerated.

(e) *Examples of specific tables and figures*: Sample tables capturing each aim are presented below but we anticipate preparing two manuscripts (manuscript 1: aims a, b; manuscript 2: aims c, d).

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

Table 2: Odds ratios by radiation dose to the breast for all breast cancers and by ER status (if sufficient numbers of cases have ER status). Up to four dose categories will be selected based on the dose distribution among controls. Excess odds ratio (EOR) per Gy overall and by radiation dose to the ovary (<5 Gy / ≥ 5 Gy) will also be presented.

Table 3: Odds ratios for the main effects of breast cancer risk factors (factors listed in Aim 1)

Table 4: Excess odds ratios for breast cancer per Gy by breast cancer risk factors (factors listed in Aim 1)

Table 5: Odds ratios for the main effects of different chemotherapy formulations

Table 6: Excess odds ratios for breast cancer per Gy by chemotherapy formulations

Table 7: Excess odds ratios for breast cancer per Gy by age at exposure, calendar year of exposure, time since exposure, and attained age.

Figures (possible): Radiation dose-response relationship for second breast cancer, including observed ORs and fitted relationships by one or two factors that modify the dose-response.

6. References

1. Swerdlow AJ, Barber JA, Hudson GV, Cunningham D, Gupta RK, Hancock BW, et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. J Clin Oncol. 2000 Feb;18(3):498-509.
2. Kenney LB, Yasui Y, Inskip PD, Hammond S, Neglia JP, Mertens AC, et al. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. Ann Intern Med. 2004 Oct 19;141(8):590-7.
3. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst. 1993 Jan 6;85(1):25-31.

4. Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med. 1996 Mar 21;334(12):745-51.
5. van Leeuwen FE, Klokman WJ, Stovall M, Dahler EC, van't Veer MB, Noordijk EM, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst. 2003 Jul 2;95(13):971-80.
6. Travis LB, Hill DA, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA. 2003 Jul 23;290(4):465-75.
7. Inskip PD, Robison LL, Stovall M, Smith SA, Hammond S, Mertens AC, et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. J Clin Oncol. 2009 Aug 20;27(24):3901-7.
8. Friedman DL, Whitton J, Leisenring W, Mertens AC, Hammond S, Stovall M, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2010 Jul 21;102(14):1083-95.
9. Metayer C, Lynch CF, Clarke EA, Glimelius B, Storm H, Pukkala E, et al. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. J Clin Oncol. 2000 Jun;18(12):2435-43.
10. Travis LB, Hill D, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. J Natl Cancer Inst. 2005 Oct 5;97(19):1428-37.
11. Henderson BE, Feigelson HS. Hormonal carcinogenesis. Carcinogenesis. 2000 Mar;21(3):427-33.
12. Land CE, Hayakawa N, Machado SG, Yamada Y, Pike MC, Akiba S, et al. A case-control interview study of breast cancer among Japanese A-bomb survivors. II. Interactions with radiation dose. Cancer Causes Control. 1994 Mar;5(2):167-76.
13. Hill DA, Gilbert E, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al. Breast cancer risk following radiotherapy for Hodgkin lymphoma: modification by other risk factors. Blood. 2005 Nov 15;106(10):3358-65.
14. Yang XR, Chang-Claude J, Goode EL, Couch FJ, Nevanlinna H, Milne RL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. J Natl Cancer Inst. 2011 Feb 2;103(3):250-63.
15. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomarkers Prev. 2004 Oct;13(10):1558-68.
16. Elkin EB, Klem ML, Gonzales AM, Ishill NM, Hodgson D, Ng AK, et al. Characteristics and Outcomes of Breast Cancer in Women With and Without a History of Radiation for Hodgkin's Lymphoma: A Multi-Institutional, Matched Cohort Study. J Clin Oncol. 2011 Jun 20;29(18):2466-73.
17. Dores GM, Anderson WF, Beane Freeman LE, Fraumeni JF, Jr., Curtis RE. Risk of breast cancer according to clinicopathologic features among long-term survivors of Hodgkin's lymphoma treated with radiotherapy. Br J Cancer. 2010 Sep 28;103(7):1081-4.
18. Ronckers CM, Erdmann CA, Land CE. Radiation and breast cancer: a review of current evidence. Breast Cancer Res. 2005;7(1):21-32.

19. Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J Natl Cancer Inst. 2001 Apr 18;93(8):618-29.
20. Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SS, Green DM, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. Med Pediatr Oncol. 2002 Apr;38(4):229-39.
21. Preston D LJ, Pierce D, McConney M, editor. EPICURE user's guide. Seattle, WA: HiroSoft International Corporation; 1993.