Title: Breast Cancer Risk in the Modern Treatment Era: A Report from the Childhood Cancer Survivor Study

Working Group: Second Malignancy Working Group

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Background and Rationale:

In childhood cancer survivors treated in the 1970's and 1980's, breast cancer is the most frequent subsequent malignant neoplasm (SMN), after non-melanoma skin cancers.[1-4] Much of our knowledge of this important outcome derives from the original Childhood Cancer Survivor Study (CCSS) cohort, which includes children diagnosed during 1970-1986 and represents the largest known series of women with breast cancer after childhood cancer. The work in the CCSS has been complemented by studies in Dutch Childhood Cancer Cohorts as well as the British Childhood Cancer Survivor Study.[5,6] Exposure to chest radiation in Hodgkin lymphoma survivors of this era accounts for the majority of breast cancers in childhood cancer survivors.[1,3,7,8] Most recently, we showed that in women exposed to chest radiation in the CCSS the cumulative incidence of breast cancer among Hodgkin lymphoma survivors was 30% by age 50 (95% CI, 20.7-34).[9] A previous CCSS publication documented the linear risk-dose relationship for breast radiation, with risk modified by exposure to radiation dose to the ovaries.[7] Subsequently, we have also found that volumetric assessment of radiation exposure is important with lower doses of radiation (median 14 Gy, range 2 to 20 Gy) to a large

volume of breast tissue (whole lung field) being associated with a high risk of breast cancer (SIR=43.6; 95% confidence interval [CI], 27.2 to 70.3) as did survivors treated with high doses of delivered radiation (median 40 Gy) to the mantle field (SIR=24.2; 95% CI, 20.7 to 28.3).[10] However, many women exposed to chest radiation in this era were treated with mantle field radiation, limiting our ability to draw definitive conclusions about breast cancer risk for women treated with lower prescribed doses of radiation with more modern techniques and approaches.

Both during and subsequent to the era of the initial CCSS cohort, childhood cancer therapies have been modified. Specifically for Hodgkin lymphoma, both chemotherapeutic backbones and radiation regimens have evolved. Radiation therapy now includes lower doses (earlier eras: approximately 35-45 Gy vs current: approximately 10-25 Gy) and includes reductions in the volumes of the developing breast tissue exposed [i.e. extended, mantle field radiation versus involved field radiation (IFRT)].[11-13] There have been several studies, including our recent analysis of the CCSS, which suggest that there is a significantly lower risk of breast cancer in women treated with reduced radiation fields.[10,14,15] O'Brien and colleagues followed 35 female Hodgkin lymphoma survivors treated with MOPP or ABVP/MOPP chemotherapy plus 10-25.5 Gy IFRT and 6 women developed breast cancer after 20 years of follow up (SIR=72.3, 95% CI 26.5-157.3).[16] Other studies examining risk of SMNs in survivors of Hodgkin lymphoma treated with combined modalities and low dose radiation suffer from short follow-up time (median, 8 to 13 years).[17-19]

Moreover, recent work has begun to elucidate that childhood cancer survivors who never were exposed to chest radiation have an elevated risk of developing breast cancer as compared to the general population.[20] We analyzed 47 women who developed breast cancer among 3,768 women in the original CCSS cohort never exposed to chest radiation. A four-fold increased breast cancer risk (standardized incidence ratio [SIR] = 4.0; 95% CI, 3.0 to 5.3) was observed when compared with the general population. Risk was highest among sarcoma and leukemia survivors (SIR = 5.3; 95% CI, 3.6 to 7.8 and SIR = 4.1; 95% CI, 2.4 to 6.9, respectively). By the age of 45 years, the cumulative incidence of breast cancer in sarcoma and leukemia survivors was 5.8% (95% CI, 3.7 to 8.4) and 6.3% (95% CI, 3.0 to 11.3), respectively. Alkylators and anthracyclines were associated with an increased breast cancer risk in a dose-dependent manner (P values from test for trend were both <0.01).

Ongoing studies in CCSS include a breast cancer risk-prediction model development (led by Chaya Moskowitz) as well as a case-control study of the joint effects of treatment and host factors on the development of second primary breast cancers (led by Amy Berrington de González, NCI). While Dr. Moskowitz's study uses the original cohort to develop the model and the expanded cohort to validate it, it is focused exclusively on women treated with chest radiation and there are no plans to combine data from the two cohorts and look at temporal trends. . In addition, although Dr. Berrington de Gonzalez's case-control study of joint effects of treatment and host factors on the development of second primary breast cancers will be examining the interaction of radiation and other treatment related risk factors (similar to this proposal), it uses information on the dose of radiation as estimated by dosimetry, it does not look at cumulative incidence and temporal trends, and it will be limited to breast cancers in the original CCSS Cohort.

We now propose to expand CCSS investigation of breast cancer risk over time by conducting an analysis in the full CCSS cohort, including survivors diagnosed during

1970-1999. Examination of breast cancers in the expanded CCSS cohort provides a unique opportunity to better examine the interactions between primary cancer, radiation (including low dose exposures) and chemotherapy exposures as well as other clinical risk factors, given the larger number of women – both exposed and not exposed to chest radiation. Prior studies have been limited in their sample size and therefore, power, to examine interactions between multiple risk factors. The proposed study is novel in that, in addition to describing cumulative incidence of the expanded cohort, it will examine the temporal impact of changes in therapy on the risk of breast cancer. This analysis represents an important update of breast cancer in CCSS and will have significant impact in our understanding of breast cancer risk and breast cancer risk factors in childhood cancer survivors, and will inform our surveillance guidelines for female childhood cancer survivors at high risk for breast cancer.[8,21]

Specific Aims:

1. To describe the cumulative incidence, standardized incidence ratio (SIR) and absolute excess risk (AER) of breast cancer in female childhood cancer survivors diagnosed with their primary cancer between 1970 and 2000 and explore trends across time (by decade) for the whole cohort and for subgroups defined primary childhood cancer diagnosis and exposure to chest radiotherapy.

We hypothesize that lower volumes of chest radiotherapy used in modern treatment era protocols, results in decreased breast cancer rates and risk.

We hypothesize that breast cancer rates and risk in leukemia and sarcoma survivors treated without chest radiation are stable across treatment eras.

2. To evaluate the association of a breast cancer diagnosis with patient and treatment-related risk factors and their potential interactions among childhood cancer survivors diagnosed with their primary cancer between 1970 and 2000.

We hypothesize that we will observe interactions between radiation risk groups and 1) chemotherapy exposures (eg. alkylators and anthracyclines) and 2) childhood cancer diagnoses.

We hypothesize that we will observe an association with decreasing breast cancer risk associated with changing treatment exposures over time.

We hypothesize that survivors of leukemia and sarcoma will have increased risk of breast cancer with increasing exposures to anthracyclines and/or alkylators but different trends will be observed among survivors of other childhood cancers.

3. To describe the clinical and pathological features among women who developed breast cancer in the CCSS cohort.

We hypothesize that we will observe large numbers of women with bilateral breast cancer.

Analysis Framework:

1. **Outcome of interest:** confirmed diagnosis of invasive breast cancer or DCIS
2. **Population:** all females CCSS cohort
3. **Predictor variables to be analyzed:**

a. Previous diagnosis
b. Age at primary cancer
c. Years of follow up
d. Race
e. History of radiation therapy (Yes/No)
f. History of chest radiation
    i. Yes/no
    ii. Maximum tumor dose (Max TD) to the chest body region
    iii. Delivered radiation field to the chest (mantle, mediastinal/IFRT, TBI, whole lung, high abdominal fields, other)
g. History of pelvic radiation therapy (Yes/No)
    i. Ovary dose <5Gy and ≥5Gy
h. Chemotherapy
    i. Type (alkylators, heavy metals (platinum based drugs), Anti-metabolites, Anthracyclines, Anti-Tumor Antibiotics (bleomycin), corticosteroids, enzymes, plant alkaloids, epipophyllotoxins
    ii. Dose
i. Family history of breast cancer (Yes/No) (Only limited information available but may use descriptively)
j. Family history of non-breast cancer (Yes/No) (Only limited information available but may use descriptively)
k. Autologous hematopoietic stem cell transplant (Yes/No)
l. Allogeneic hematopoietic stem cell transplant (Yes/No)
m. Age at menarche
n. Age at menopause
o. Exposure to exogenous estrogenand/or progestin
p. Treatment era: 1970's/1980's/1990's
q. Breast cancer stage
r. ER receptor status
s. PR receptor status
t. HER2 status

4. Analysis

Aim 1: We will estimate age-, gender- and calendar-year-adjusted standardized incidence ratios (SIRs) and absolute excess risks (AERs) for secondary breast cancers among childhood cancer survivors, obtaining general population estimates from SEER. Cumulative incidence of secondary breast cancers will be evaluated with age as the time scale using methods for left truncated data and treating death as a competing risk event.

In addition to presenting results for the whole cohort, we will evaluate and present results separately for subgroups defined by whether or not participants were treated with chest radiotherapy, by primary childhood cancer diagnosis (Hodgkin lymphoma, leukemia and sarcoma), and by the breast cancer hormone receptor status (at the very least ER+, but depending on the quality of the data also defined by PR-status and HER2-status). Within the whole cohort and for each subgroup separately, SIRs and AERs will be estimated for age at diagnosis, attained age, treatment era (10-year intervals) and the treatment- and hormone-

related factors listed in the Analysis Framework section. Note that based on Aim 2 analyses, we will also display SIRs and AERs using categories of treatment (or combinations of treatment) generated based on those models. In addition, if we have a sufficient number of DCIS cases, we will present the DCIS results separately from invasive cases.

Aim 2: For these analyses, we plan to represent chest radiation exposure as a single variable incorporating exposure yes/no together with the chest radiation field and prescribed dose. We plan for this variable to have 4 categories, no chest radiation, lower-risk exposure (including women not treated with a chest field but who have had scatter radiation to the chest), intermediate-risk exposure, and high-risk exposure. To help identify the parameters that would define the categories of this variable, we will use a classification and regression tree (CART) analysis. CART cycles through the input variables to the model to split the data into tree "branches" based on the combinations of factors that result in maximal separation of risk between groups, following predefined criteria including maximum number of desired groups. In this CART analysis, we will model breast cancer risk as a function of chest radiation field and prescribed dose. We expect that CART will define a combination of these two variables that classifies women into low, medium, and high risk subgroups (e.g. women with posterior chest fields might be low risk, women with high doses of involved field radiation and women with low doses of mantle field radiation might be medium risk, and women with high doses of mantle field radiation might be high risk). We show an example at the end of this concept proposal of the output of a very preliminary CART analysis run with the original cohort data. Note that this is not meant to be the final analysis, but just to give a somewhat hypothetical example of what we might see and to demonstrate the potential for meaningful results from a CART analysis of this data. For the actual analysis, we will run CART on the full dataset using cross-validation to minimize the bias that arises from attempting to define and evaluate an optimal classification scheme on the same data.

Adjusted relative rates (RRs) and 95% confidence intervals will be estimated from multivariable piecewise-exponential models. Reference absolute rates per 1000 person-years will be calculated modeling treatment era, the chest radiation exposure variable, and other key predictors such as treatment modalities and hormone exposure. We will evaluate interactions between treatment era and primary childhood cancer diagnosis and treatment exposures.

With the addition of the expansion cohort, more breast cancer cases and the novel reduction of chest radiation therapy variables to a single multi-level risk factor, we will have the ability to examine interaction terms that have been suggested, but not confirmed by previous analyses. For example, we will be able to further examine possible differential effects of anthracyclines by RT risk level and by childhood cancer diagnosis.

We will also explore multivariable modeling of the SIRs and use Poisson regression to look at adjusted SIRs and potential interactions.

Finally, we may explore risk factors separately by ER- or PR-status depending upon the extent of missingness in hormone receptor status.

Aim 3: The clinical characteristics of the breast cancers in CCSS (listed in Table 2) will be descriptively summarized with summary statistics such as frequencies, means, medians, and ranges.

Tables and Figures

Table 1 Characteristics of the CCSS cohort, including separately for survivors who have and have not developed a secondary breast cancer

Characteristic	Patients with secondary BC (N; %)	Cohort Members without secondary BC (N; %)
Median age at last follow-up, years (Range)		
Median duration of follow-up, years (Range)		
Race White Black Other Unknown		
Age at Primary Diagnosis, years Mean (SD) Median (Range)		
Attained Age Mean (SD) Median (Range)		
Primary Diagnosis Leukemia Brain/CNS Tumor Hodgkin disease Non-Hodgkin Lymphoma Kidney Tumor Neuroblastoma Soft Tissue Sarcoma Bone Tumor		
Radiation Therapy Yes No		
Chemotherapy for Primary Malignancy Alkylators Heavy Metals (Platinum based drugs) Anti-Metabolites Anthracyclines Plant Alkaloids Epipodophyllotoxins		
Chest Radiation Therapy for Primary Malignancy Yes No		
Primary field of Chest irradiation, dose in Gy Mantle (median, range)		

Mediastinal (median, range) Whole lung (median, range) Total body (median, range) Abdominal (median, range) Posterior chest (median, range) Other one-sided anterior (median, range)		
Pelvic radiation Yes No		
Age at menarche, years <11 11-13 14+		
Age at menopause, years <20 20-40 40+		
Hematopoietic stem cell transplant Yes No		
Family History of any cancer Yes No		
Family History of BC Yes No		
Other Second Malignant Neoplasm Yes No		
Treatment Eras 1970's 1980's 1990's		
Vital Status Alive Deceased		

Table 2 Secondary BC Clinical Characteristics

Clinical Characteristic	N (%)
Median Time from primary diagnosis to diagnosis of BC, years (Range)	
Age at diagnosis of BC, years Quartiles to be determined	
Bilateral breast cancer -Metachronous -Synchronous	
Radiation Exposure for Treatment of Primary Cancer BC in radiation field BC distant from radiation field No radiation from primary cancer Unknown primary radiation data	
Cause of Death of BC Participants Primary Cancer Secondary BC Late Effects Toxicities Other Unknown	
BC Stage at Diagnosis I II III IV Unknown	
Site of BC Left UOQ Left UIQ Left LOQ Left LIQ Right UOQ Right UIQ Right LOQ Right LIQ Bilateral	
BC Receptor Status ER + PR+ HER-2 Unknown	
Family History of any cancer Yes No	
Family History of BC Yes No	

Figure 1a: Cumulative Incidence Curve of BC in the CCSS cohort (original and expanded cohorts combined vs cumulative incidence in general population)

Figure 1b: Cumulative incidence of breast cancer in women exposed to chest radiation vs women never exposed to chest radiation

Figure 1c: Cumulative incidence of breast cancer in women exposed to pelvic radiation versus never exposed to pelvic radiation.

Figure 1d: Cumulative incidence of breast cancer by treatment era in Hodgkin lymphoma survivors vs other childhood cancers (1970-1986 vs 1987-2000)

Figure 1e: Cumulative incidence of breast cancer by radiation and chemotherapeutic exposures and potential interactions (will depend upon sample size)

Table 3 Standardized Incidence Ratios and Excess Absolute Risks for Development of BC in Expanded CCSS Cohort

a. Entire cohort

	Person Years	Observed Cases	Expected Cases	SIR (95% CI)	EAR (95% CI)
Total					
Age at Primary Diagnosis (years)					
Time since primary diagnosis to BC					
History of Chest Radiation Therapy Yes No Unknown					
Chest RT Strata None Low risk Medium risk High risk					
Pelvic radiation Yes No Unknown					
Primary Cancer Diagnosis Leukemia Non-Hodgkin Lymphoma Neuroblastoma CNS/Brain Tumor Hodgkin Lymphoma Bone Tumor Kidney Tumor Soft Tissue Sarcoma					

Alkylators Yes No CED, mg/m2 0 1-5,999 6,000-17,999 > 18,000					
Anthracyclines Yes No Cumulative dose categories 0 mg/m^2 1-249 mg/m^2 > 250 mg/m^2					
Age at menarche <11 11-13 14+					
Age at menopause < 20 years 20-40 years 40+ years					

b-d. Hodgkin lymphoma/Sarcoma/Leukemia survivors (one table for each diagnosis)

	Person Years	Observed Cases	Expected Cases	SIR (95% CI)	EAR (95% CI)
Total					
Age at Primary Diagnosis (years)					
Time since primary diagnosis to BC					

History of Chest Radiation Therapy Yes No Unknown					
Chest RT Strata None Low risk Medium risk High risk					
Pelvic radiation Yes No Unknown					
Alkylators Yes No CED, mg/m2 0 1-5,999 6,000-17,999 > 18,000					
Anthracyclines Yes No Cumulative dose categories 0 mg/m^2 1-249 mg/m^2 > 250 mg/m^2					
Age at menarche <11 11-13 14+					

Age at menopause < 20 years 20-40 years 40+ years					

e. Women exposed to Chest Radiation

	Person Years	Observed Cases	Expected Cases	SIR (95% CI)	EAR (95% CI)
Total					
Age at Primary Diagnosis (years)					
Time since primary diagnosis to BC					
Primary Cancer Diagnosis Leukemia Non-Hodgkin Lymphoma Neuroblastoma CNS/Brain Tumor Hodgkin Lymphoma Bone Tumor Kidney Tumor Soft Tissue Sarcoma					
Treatment Era 1970-1986 1987-1999					
Age at menarche, years <11 11-12 13-14 15+					
Chest RT within 1 year of menarche No Yes					
Age at menopause, years <20 20-40 40+					

f. Women Never Exposed to Chest RT

	Person Years	Observed Cases	Expected Cases	SIR (95% CI)	EAR (95% CI)
Total					
Age at Primary Diagnosis (years)					

Time since primary diagnosis to BC					
Primary Cancer Diagnosis Leukemia Non-Hodgkin Lymphoma Neuroblastoma CNS/Brain Tumor Hodgkin Lymphoma Bone Tumor Kidney Tumor Soft Tissue Sarcoma					
Treatment Era 1970-1980 1981-2000					
Age at menarche, years <11 11-12 13-14 15+					
Age at menopause <20 20-40 40+					

g. Women Diagnosed with ER+ Breast Cancer

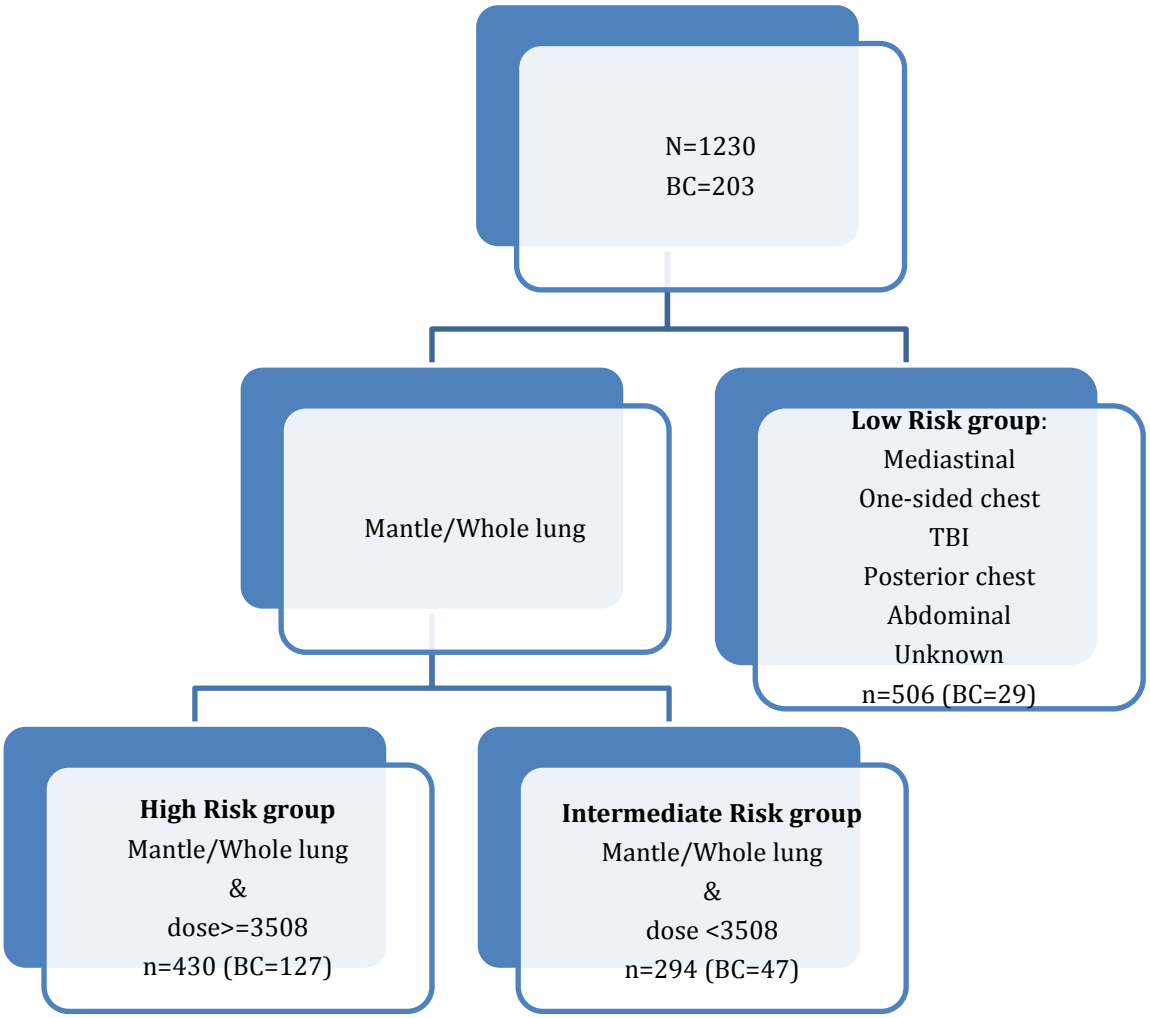
	Person Years	Observed Cases	Expected Cases	SIR (95% CI)	EAR (95% CI)
Total					
Age at Primary Diagnosis (years)					
Time since primary diagnosis to BC					
Primary Cancer Diagnosis Leukemia Non-Hodgkin Lymphoma Neuroblastoma CNS/Brain Tumor Hodgkin Lymphoma Bone Tumor Kidney Tumor Soft Tissue Sarcoma					
Treatment Era 1970-1980 1981-2000					
Age at menarche, years <11 11-12 13-14 15+					
Age at menopause					

<20 20-40 40+					

Table 5: Multivariable risk factor analysis for development of BC

Variable	RR (95% CI)	*P* Value

Example of a CART analysis. Classification and regression tree example run using only the primary chest radiation field and delivered dose.



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