

Title: Breast Cancer in Survivors Not Exposed to Chest Radiation: A Report from the Childhood Cancer Survivor Study

Working Group: This report will be written within the Second Malignancy Working Group with oversight from the Genetics Working Group. Proposed investigators include:

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1. Background and Rationale

Breast cancer is the most frequent subsequent malignant neoplasm (SMN) in childhood cancer survivors, after non-melanoma skin cancers.¹⁻⁴ Breast cancer occurs in a relatively young age in this population and the cumulative incidence increases with age.¹ Exposure to chest radiation in Hodgkin lymphoma survivors accounts for the majority of breast cancers in childhood cancer survivors. However, breast cancer has also been diagnosed in survivors of non-Hodgkin lymphoma, leukemia, Wilms tumor, neuroblastoma, bone cancer and soft tissue sarcoma. While many of these survivors were exposed to chest radiation, there appears to be a growing number of survivors who are developing breast cancer at a young age and yet have not been exposed to chest radiation. In order to identify these women for early surveillance and prevention strategies, it is important to examine the risk factors (primary cancer, treatment exposures and genetics) associated with their development.

Kenney and colleagues previously reported on breast cancer in the Childhood Cancer Survivor Study (CCSS). In this 2004 study, with a median follow-up time of approaching 20 years, 20 cases of breast cancer were identified in women not exposed to chest radiation for their childhood cancer out of a total of 95 women with breast cancer. Standardized incidence ratios of 6.7 and 7.6 were reported in survivors of bone and soft-tissue sarcoma not exposed to chest radiation, respectively.¹ In a recent update of SMN in the CCSS cohort, Friedman and colleagues reported 176 survivors who had been diagnosed with breast cancer after a median follow-up of approximately 23 years.² This report did not report a standardized incidence ratio analysis or risk factor analysis restricted to women not exposed to chest radiotherapy.

In the current 2007 CCSS frozen data set, we have identified 58 women with breast cancer who did not receive chest radiation for their primary cancer. Given this substantial increase in cases in

the cohort with less than 5 years difference in median follow-time, we plan to update the analysis done by Kenney and colleagues focused only on the women who were treated without chest radiation. An understanding of this population, will improve our ability to identify high risk survivors such that appropriate surveillance and risk prevention strategies can be developed and implemented.

SPECIFIC AIMS:

Aim 1: To describe the cumulative incidence, standardized incidence ratio and absolute excess risk of breast cancer in women not exposed to chest radiation for a pediatric malignancy.

Aim 2: To describe the risk factors (treatment related, familial and behavioral) associated with the development of breast cancer tract among female childhood cancer survivors not exposed to chest radiation.

Aim 3: To describe the clinical and pathological characteristics of the breast cancer cases in women not exposed to chest radiation.

ANALYSIS FRAMEWORK:

- 1. Outcome of Interest:** Breast cancer at any point following the pediatric malignancy. We will include women diagnosed with ductal carcinoma in-situ and invasive breast cancer in our definition of breast cancer.
- 2. Population:** Females in CCSS cohort who were not exposed to chest radiation for their pediatric malignancy. We include the following fields of radiation in our definition of chest radiation: mantle, mediastinum, whole lung, spinal (craniospinal), total body irradiation, axilla other chest/lung/rib fields.
- 3. Predictor variables to be analyzed**
 - a. Primary cancer diagnosis
 - b. Age at primary cancer diagnosis
 - c. Years of follow-up
 - d. Race
 - e. Chemotherapy
 - i. Type (alkylating agents, platinum compounds, anti-metabolites, anthracyclines, anti-tumor antibiotics, corticosteroids, plant alkaloids, epipodophyllotoxins)
 - ii. Dose (dose where available)
 - f. History of Pelvic Radiation (Yes/No)
 - g. History of other SMN
- 4. Variables for descriptive analysis**
 - a. Family History of cancer (Baseline survey P2-P6):
 - i. Breast cancer (Yes/No)
 - ii. Ovarian cancer (Yes/No)

- iii. Sarcoma (Yes/No)
- iv. Leukemia (Yes/No)
- v. CNS cancer (Yes/No)
- b. SES
- c. Use of birth control pill in the last 2 years (baseline survey B2)
- d. Estrogen and progesterone use (baseline survey B3)
- e. Menstrual periods (baseline survey E16, 17, 18 and F/U #1 survey 19)
- f. Pregnancy history

5. Analysis

- a. Cumulative incidence of breast cancer in women not exposed to chest radiation will be evaluated from entry into the cohort (5 years post diagnosis), treating death as a competing event.
- b. We will determine age-adjusted standardized incidence ratios (SIR) and absolute excess risk (AER) for subsequent breast cancers in women not exposed to chest radiation. SIRs of observed to expected breast cancer cases will be calculated using expected numbers obtained from age-, sex-, and calendar year-specific rates from the Surveillance, Epidemiology, and End Results (SEER) Program as the reference population. AER will be estimated by subtracting the expected number of breast cancer cases from the observed number, dividing the difference by person-years of follow-up and multiplying by 1000.
- c. To the extent possible, we will evaluate the association between the above mentioned risk factors (i.e. demographic, cancer related, treatment) and the risk of developing breast cancer in women not exposed to chest radiation in the CCSS cohort using Cox proportional hazards regression models. Due to the small number of events, the primary focus will be on evaluating the impact of cancer therapies (e.g. pelvic radiation, specific chemotherapies), with additional predictor variables included in sequential models to identify the most important effect modifiers/confounders.
- d. To the extent possible based on the CCSS data, we will summarize the data regarding family history of cancer in association with the development of a SMN. Since family history was last assessed on the Baseline Questionnaire, the potential time lapse makes it difficult to include this variable as a risk factor in regression models.
- e. We will include in the manuscript descriptive data including SES, use of birth control pill in the last 2 years (baseline survey B2), estrogen and progesterone use (baseline survey B3), menstrual periods (baseline survey E16, 17, 18 and F/U #1 survey 19), and pregnancy history. Given this data is cross sectional or may have changed since the baseline survey, it is difficult to include in a time-to-event analysis and so we are including it in the study as descriptive.

Tables/Figures

Table 1. Characteristics of the non-chest irradiated sub-cohort

<u>Characteristic</u>	<u>Total</u>	<u>Breast Cancer (N: %)</u>	<u>No Breast Cancer (N: %)</u>
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)			
Current Age			
Mean (SD)			
Median (Range)			
Primary Diagnosis			
Leukemia			
Brain/CNS Tumor			
Hodgkin disease			
Non-Hodgkin Lymphoma			
Kidney Tumor			
Neuroblastoma			
Soft Tissue Sarcoma			
Bone Tumor			
Chemotherapy for Primary Malignancy			
Alkylators			
Heavy Metals (Platinum based drugs)			
Anti-Metabolites			
Anthracyclines			
Plant Alkaloids			
EPIPPODOPHYLLOTOXINS			
Pelvic Radiation Therapy for Primary Malignancy			
Yes			
No			
Family History of any cancer			
Yes			

No			
Family History of Breast Cancer or Ovarian Cancer			
Yes			
No			
Family History of Sarcoma			
Yes			
No			
Stem Cell Transplant for Primary Malignancy			
Yes			
No			
Other Second Malignant Neoplasm			
Yes			
No			
Treatment Era			
1970-1974			
1975-1979			
1980-1986			
Vital Status			
Alive			
Deceased			

Table 2. Characteristics of breast cancer cases

Characteristic	
Median age at diagnosis of breast cancer, years (range)	
Age at diagnosis of breast cancer, n (%)	
20-24 years	
25-29 years	
30-34 years	
35-39 years	
40-44 years	
45-50 years	
50+	
Median time from primary cancer to breast cancer, years (range)	
Laterality of breast cancer, n (%)	
Left	
Right	

Bilateral	
Stage of breast cancer, n (%)	
Ductal carcinoma in situ	
Stage I	
Stage II	
Stage III	
Stage IV	
Unknown	
Pathologic features of invasive breast cancer, n (%)	
Invasive ductal carcinoma	
Lobular carcinoma	
Mixed ductal or lobular carcinoma	
Poorly differentiated carcinoma	
Malignant phylloides tumor	
Breast angiosarcoma	
Malignant fibrosarcoma	
Estrogen receptor status of invasive breast cancer, n (%)	
Positive	
Negative	
Unknown	
Bilateral	
Synchronous	
Metachronous	
Cause of Death of Breast Cancer Participants	
Primary Cancer	
Breast Cancer	
Other SMN	
Late Effects Toxicities	
Other	
Unknown	

Figure 1 Cumulative Incidence Curve (vs cumulative incidence in general population)

Table 3. Standardized Incidence Ratios and Absolute Excess Risks for Development of Breast Cancer in Women Not Exposed to Chest Radiation

Primary Diagnosis	Observed	Expected	SIR (95% CI)	AER (95% CI)	AER, by age at primary cancer diagnosis	
					Age range, years	AER
All diagnoses						
Age at Primary Dx (years)					0-20	
					0-14	
					15-19	
Primary Cancer Dx						
Leukemia						
NHL						
Neuroblastoma						
CNS/Brain Tumor						
HL						
Bone Tumor						
Kidney Tumor						
STS						
First Degree Relative with Breast Cancer						
First Degree Relative with Sarcoma						

Table 4. Risk Factors for the Development of Breast Cancer in Women Not Exposed to Chest Radiation: Univariate Analysis

Variable	Relative Risk (95% CI)	P Value
Sex		
Race		
White		
Black		
Hispanic		
Other		
Age at Primary Diagnosis		
Current age		
Primary Cancer Diagnosis		
Pelvic Radiation Therapy		
Chemotherapy (Yes/No)		
Alkylator score		
Antimetabolite (yes/no)		
Anthracycline dose tertile		
Epipodophyllotoxins		
Treatment Era		
1970-1974		
1975-1979		
1980-1986		

Table 5. Multivariate Rate Ratios for the Development of Breast Cancer in Women Not Exposed to Chest Radiation

<u>Variable</u>	<u>RR (95% CI)</u>	<u>P Value</u>

REFERENCES

1. Kenney LB, Yasui Y, Inskip PD, et al. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Intern Med* 2004;141:590-7.
2. Friedman DL, Whitton J, Leisenring W, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2010;102:1083-95.
3. Bhatia S, Yasui Y, Robison LL, et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. *J Clin Oncol* 2003;21:4386-94.
4. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA* 2003;290:465-75.