Title Incidence of breast cancer among women treated with chest radiation therapy for a pediatric malignancy

Working Group and Investigators

This proposed publication will be within the Second Malignancy Working Group.

Proposed investigators:

Kevin Oeffinger	oeffingk@mskcc.org
Chaya Moskowitz	moskowc1@mskcc.org
Joanne Chou	chouj@mskcc.org
Matt Matasar	matasarm@mskcc.org
Tara Henderson	thenderson@peds.bsd.uchicago.edu
Lisa Diller	Lisa_Diller@dfci.harvard.edu
Smita Bhatia	SBhatia@coh.org
Lisa Kenney	Lisa_Kenney@dfci.harvard.edu
Melissa Hudson	Melissa.Hudson@stjude.org
Louis Constine	louis_constine@urmc.rochester.edu
Marilyn Stovall	mstovall@mdanderson.org
Wendy Leisenring	wleisenr@fhcrc.org
John Whitton	jwhitton@fhcrc.org
Les Robison	Les.Robison@STJUDE.ORG
Joseph Neglia	jneglia@umn.edu

Background and Rationale

Women who were treated with radiotherapy to the chest for a pediatric malignancy have a substantially increased risk of breast cancer after their primary cancer has been cured.[1-5] While the risk of breast cancer increases as the dose of chest radiation increases, even female cancer survivors treated with low to moderate doses of chest radiation have a high risk of breast cancer compared with women who were not treated with chest radiation.[2] Breast cancer has been diagnosed at a relatively young age in this population (< 25 years of age) with the cumulative incidence of breast cancer increasing with age.[3] Although survivors of Hodgkin lymphoma comprise a majority of these breast cancer cases, breast cancer has also been diagnosed in irradiated survivors of other pediatric malignancies including non-Hodgkin lymphoma, leukemia, Wilms tumor, neuroblastoma, bone cancer, and soft tissue sarcoma.

Prior publications reporting on the CCSS cohort have quantified the risk of breast cancer. In 2004, using data from 2002 where survivors had a median follow-up of approximately 19 years, Kenney *et al*. found 73 women with breast cancer subsequent to receiving chest radiation for their primary childhood cancer.[3] This analysis resulted in a standardized incidence ratio of 24.7. Including all female survivors in the cohort regardless of their exposure to radiation, there were 95 women with breast cancer at that time. In a recent update of subsequent neoplasms in the CCSS cohort, Friedman and colleagues found 176 survivors who had been diagnosed with breast cancer based on a median follow-up of approximately 23 years.[6] They did not report the

standardized incidence ratio restricted to women who had been previously treated with radiation to the chest. Since the Friedman study, there has been a further increase in the number of women with breast cancer following chest radiation (Updated SMN Dataset).

Given the over 2-fold increase in the number of CCSS women diagnosed with breast cancer following chest radiation with a difference in the median follow-up of around seven years, we aim to revisit and update the analysis done by Kenney *et al*, focusing only on women who were treated with chest radiation. The goals of this analysis are to extend the estimate of the cumulative incidence of breast cancer following chest radiation for women now in their fifth decade of life (current published estimates are for women 45 years of age) and to determine if risk plateaus with age (we hypothesize that it does not).

Of note, there are two related and current studies led by investigators within this working group. First, Tara Henderson, as part of her K07 grant, will be collecting information regarding the mode of breast cancer detection in the cases. The proposed analysis will consolidate what we already have collected regarding stage of disease at diagnosis and inform Tara on what information is missing for her analysis. Second, Chaya Moskowitz, with support from the NCI (R01CA136783), is developing a model to predict absolute risk of breast cancer among women treated with chest radiation. Additional variables that will be tested in the development of the model include dose/volume/field of chest radiation, ovarian toxic therapy, estrogen replacement, and traditional risk factors of breast cancer.

Thus, our proposed concept analysis is focused on one specific aim:

Specific Aim

1. To evaluate the risk of breast cancer in women who were treated with radiotherapy to the chest for a pediatric malignancy by estimating the standardized incidence ratio relative to an age- and era-matched US general population, the absolute excess risk, and the cumulative incidence of breast cancer by attained age. These quantities will be estimated for
    a. All women in the CCSS cohort who received chest radiation
    b. Subgroups defined by the primary childhood cancer diagnosis:
        i. Hodgkin lymphoma
        ii. All other diagnoses grouped together
    c. Subgroups defined by the maximal dose of chest radiation received
        i. 1-9 Gy
        ii. 10-19 Gy
        iii. 20-29 Gy
        iv. 30-39 Gy
        v. 40 + Gy

Analysis Framework

1. Outcome of interest: The outcome of interest is the development of breast cancer at any point subsequent to five years after the pediatric malignancy. We will include ductal

carcinoma in-situ (DCIS) and invasive breast cancer in our definition of breast cancer. Each of the analyses described in this proposal will be carried out first grouping DCIS and invasive breast cancer together and then restricted to only the invasive breast cancer cases.

2. Sample: All women in the CCSS cohort who were treated with radiation to the chest. We include the following fields of radiation in our definition of chest radiation: mantle, mediastinum, whole lung, spinal (craniospinal), and total body irradiation.

Statistical Methods

The cohort consisting of all women who received radiation to the chest will be described. The descriptive variables that will be assessed are listed in Table 1 below. Women who were diagnosed with breast cancer will be characterized using additional variables as listed in Table 2 below.

The standardized incidence ratio (SIR) 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.

Absolute excess risk 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.

The cumulative incidence of breast cancer by attained age will be calculated treating death as a competing risk.[7] If there are cases of breast cancer prior to five years from diagnosis of the primary breast cancer, they will be excluded from the analysis.

Table 1. Description of the chest radiation-exposed cohort

	Total	Breast cancer	No breast cancer
Primary cancer, n (%)			
Hodgkin lymphoma			
Bone sarcoma			
Soft tissue sarcoma			
Non-Hodgkin lymphoma			
Wilms tumor			
Leukemia (ALL and AML)			
CNS tumors			
Neuroblastoma			
Race, n (%)			
White, non-Hispanic			
Black, non-Hispanic			
Hispanic			
Other			
Unknown			
Median age at diagnosis of primary cancer, years			
Therapy for primary cancer, n (%)			
Alkylating agent therapy			
Pelvic radiation therapy			
Ovarian failure*, n (%)			
Median age at last follow-up, years (range)			
Median duration of follow-up, years (range)			
Vital Status, n (%)			
Alive at last point of contact			
Deceased at last point of contact			

* Surgical menopause, acute ovarian failure, premature menopause

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*	

* Denominator excludes women with bilateral mastectomy

Table 3a. Observed and expected numbers of breast cancers by primary diagnosis

Primary Diagnosis	Observed	Expected	SIR (95% CI)	AER (95% CI)	AER, by age at primary cancer diagnosis	
					Age range, years	AER
All diagnoses					0-20	
					0-14	
					15-19	
Hodgkin lymphoma						
Other cancers						

Table 3b. Observed and expected numbers of breast cancers by chest radiation dose

Dose of chest radiation	Observed	Expected	SIR (95% CI)	AER (95% CI)	AER, by age at primary cancer diagnosis	
					Age range, years*	AER
1-9					0-20	
					0-14	
					15-19	
10-19					0-20	
					0-14	
					15-19	
20-29					0-20	
					0-14	
					15-19	
30-39					0-20	
					0-14	
					15-19	
40+					0-20	
					0-14	
					15-19	

*Where data is sufficient to determine estimates with reasonable confidence intervals.

Figure 1. Cumulative incidence of breast cancer in the CCSS cohort and the general U.S. population.

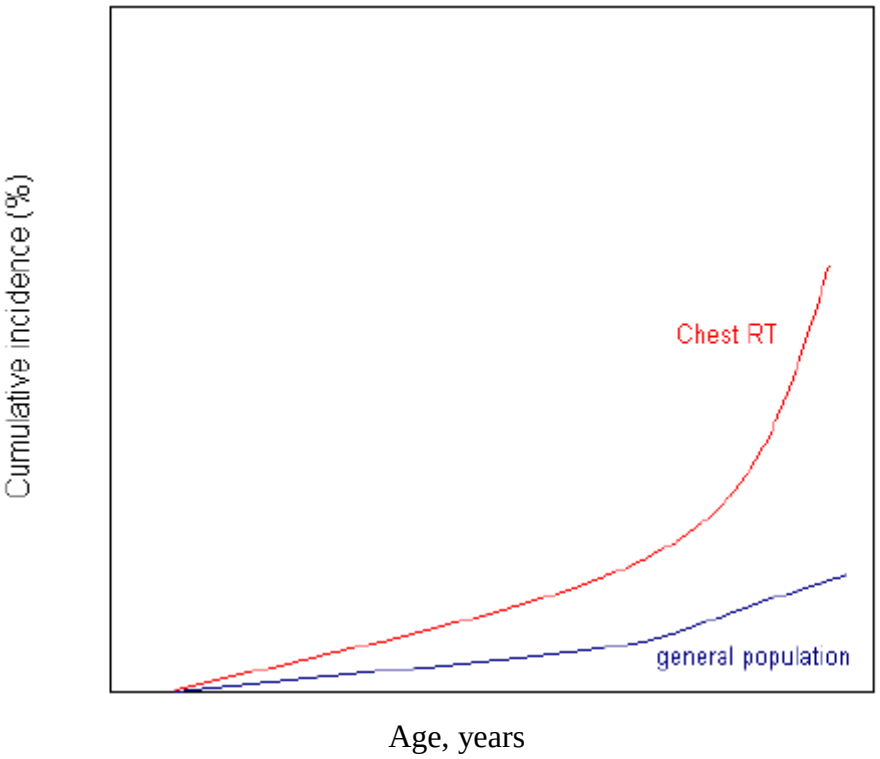
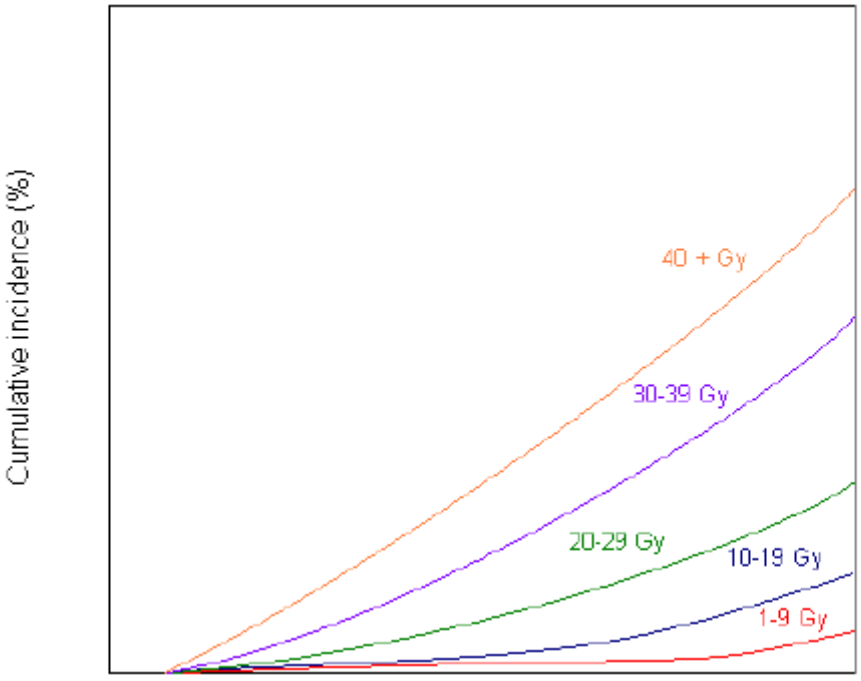


Figure 2. Cumulative incidence by maximal dose of chest radiation



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