Breast Cancer in Childhood Cancer Survivors: The Impact of Screening on Morbidity

WORKING GROUP: This report will be written within the Cancer Control Working Group with oversight from the Second Malignant Neoplasms Working Group. Proposed investigators include:

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BACKGROUND AND RATIONALE

Women exposed to chest radiation for a childhood malignancy have a significantly elevated risk of breast cancer at a young age, as it is estimated 13-20% of these women will develop breast cancer by the age of 45 years.[1] The risk appears to increase about 8 years following the radiation exposure and does not appear to plateau. Breast cancer characteristics in childhood cancer survivors generally are similar to that of the general population, as 77-85% of the pathologic findings for breast cancer is invasive ductal carcinoma. However, in many cases, due to previous cancer exposures, breast cancer treatments are limited (i.e. anthracycline and radiation dose limits). Limited outcomes in this population suggest that early stage at diagnosis results in improved survival. In 2003, the Children's Oncology Group developed their surveillance guidelines for long-term follow-up of childhood cancer survivors, which included recommendations for yearly mammography starting at age 25 or 8 years after radiation exposure (whichever occurred later).[2] These guidelines were subsequently updated in 2010 to include yearly MRI as well as mammography, which reflect consistent recommendations to the American Cancer Society.[1,3,4]

Studies examining the impact of surveillance on morbidity in women exposed to chest radiation are limited, as the size of the population limits a prospective studied powered to answer this question. The Childhood Cancer Survivor Study has the largest identified series of women (N=208) who have developed breast cancer after exposure to chest radiation for a childhood cancer. We propose to recontact these women, and in the cases where the woman is deceased, recontact her proxy. Through this recontact, we plan to query women about their breast cancer surveillance practices, including barriers and facilitators to these practices, their breast cancer-

related outcomes (i.e., stage at diagnosis, pathology, treatment, and vital status), and ultimately, examine whether women's health care and surveillance practices prior to their breast cancer diagnoses impacted their breast cancer outcomes.

Dr. Henderson was awarded a NCI K07 award (NIH K07CA134935: awarded 2008-2012) entitled, "Health Beliefs and Behaviors: Cohort Studies in Childhood Cancer Survivors," co-mentored by Dr. Kevin Oeffinger and endorsed by Dr. Les Robison. This grant supported in-depth interviews of 25 women who developed breast cancer after childhood cancer at the University of Chicago and Memorial Sloan Kettering Cancer. The preliminary findings of this qualitative work informed the development of the instrument we used to survey the women with breast cancer (or their proxies) in the cohort. (See Appendix for survey instruments).

SPECIFIC AIMS:
Aim 1: To determine the association of breast cancer surveillance practices and stage of breast cancer diagnosis in women who developed breast cancer after chest radiation.

Aim 2: To determine the facilitators and barriers to breast cancer surveillance among women who ultimately developed breast cancer.

Aim 3: To describe the detailed clinical and pathological characteristics of the breast cancer cases in women exposed to chest radiation.

STUDY DESIGN:
The proposed study is being conducted as an ancillary study through the Childhood Cancer Survivor Study (CCSS). It is a telephone and web-based survey study of all the women who developed breast cancer in the cohort (with contact of identified proxies in the event the survivor is deceased.)

The inclusion criteria are:
a. CCSS participant
b. Long-term survivor ($\geq$ 5 years) of a cancer diagnosed before the age of 21 years
c. Previous treatment with chest (chest, mantle, spinal, lung or mediastinal) radiation therapy
d. Developed invasive breast cancer or ductal carcinoma in-situ (DCIS) at least 5 years following primary cancer diagnosis

As briefly described previously, a total of 208 female survivors with a history of chest radiation exposure reported developing at least one DCIS or invasive breast cancer.

A. Study Questionnaire
A telephone- and web-based survey has been developed (please see attached). Recognizing the sensitive nature of this study including potential guilt in delay in diagnosis, as well as medico-legal aspects, the survey avoids any implied standard of care. There are seven domains of questions:
- Pre-breast cancer surveillance
- Barriers and facilitators to breast cancer surveillance

- Health beliefs and late effects knowledge
- Family and estrogen-related risk for breast cancer development
- Initial method of breast cancer diagnosis (self breast examination, clinical breast examination, screening mammogram or MRI, or other)
- Breast cancer diagnosis experience and treatment (including physicians and institutions where patient was screened and treated – including primary care physicians, oncologists, surgeons, radiologists, radiation oncologists, etc.)
- Stages and outcomes of breast cancer therapy
- Measure of health care beliefs.

Included with the questionnaire, is a medical record release such that the investigators may obtain the medical records for each survivors regarding their breast cancer diagnosis and treatment, including all screening mammograms and breast biopsy pathology.

The questionnaire was developed in collaboration with Kevin Oeffinger, Chaya Moskowitz (for her work developing a breast cancer risk calculator in this population), Greg Armstrong and the CCSS coordination center team, and evaluated for clarity and content by the research team, with special attention to the sensitive nature of this population and study.

B. Data Collection

i. Administering the Study Questionnaire and Data Collection Protocol

All survey administration and data collection is being completed by the CCSS Coordinating Center at St. Jude Research Hospital. Potential participants have been drawn from the estimated 208 women with breast cancer in the CCSS who previously agreed to be contacted for studies and will be mailed an introduction letter describing the study. Within 2 weeks of mailing the introduction letter, the potential participant have been contacted by the CCSS Coordinating Center. In the event the potential subject is deceased, a family proxy (parent/spouse/partner) identified and consented upon entry into the CCSS have been contacted.

The study has been described to subjects interested in participating and oral informed consent has been obtained. Subsequently, the telephone interview or web-based survey is conducted. Upon completion of the survey, the participant is informed that an envelope will be mailed by 2-day express mail. The following forms are included with a pre-stamped, pre-addressed envelope to return the completed, signed forms:

- Health Insurance Portability and Accountability Act (HIPAA) release form
- Medical record release form for imaging studies
- Medical record release form for medical records, with a pre-addressed, pre-stamped envelope to return the completed questionnaire and forms

ii. Medical Record Abstraction

Medical records regarding the breast cancer diagnosis and treatment will be abstracted. This process will be led by Drs. Henderson and Oeffinger. We will obtain summary data on initial breast cancer diagnosis, including stage and TNM status, detailed breast cancer pathology (i.e., hormone receptor status, HER-2, etc.), treatment, and available outcomes including remission, relapse and vital status. We will also develop a mammogram repository of identified breast cancers in pre-menopausal, radiation exposed women for future study.

C. Statistical Analysis

Descriptive statistics will be evaluated using standard methods. Depending on the number of subjects within categories defined by method of detection, we will either dichotomize or treat the method of detection outcome as categorical. We will carry out univariate logistic or polytomous logistic (as appropriate) regression analyses to evaluate the associations between methods of detection with the following: age at breast cancer diagnosis (< 40 vs. ≥40 years), TNM and stage. The following potential confounding factors will be evaluated along with the above risk factors of interest in multivariable analyses: race, primary diagnosis, age at primary diagnosis, and primary cancer treatment variables (radiation and chemotherapy as defined above).

Mortality information will be collected through the National Death Index, as supported by the CCSS. Statistical analysis of mortality will be primarily descriptive and will include survival estimates for this population as a whole, divided by stage of breast cancer and divided by type of breast cancer detection. Time from diagnosis of breast cancer to death or date of last follow-up will be utilized to calculate survival estimates (see **Figure 1a and 1b** below). Where possible, Cox proportional hazards models will be fit to evaluate the independent effects of the above covariates on the hazards of death.

D. Descriptive Analysis

We will describe identified barriers and facilitators to risk-based health care and surveillance prior to breast cancer diagnosis in this population.

E. Tables

Table 1: Characteristics of Women with Breast Cancer in CCSS

Characteristic	N	%
Primary cancer diagnosis Leukemia CNS Hodgkin disease Non-Hodgkin lymphoma Wilms' tumor Neuroblastoma Bone tumor Sarcoma		
Race/Ethnicity White Native American Asian Black Hispanic Other		
Alkylating agent score 0 1 2 3		
Anthracycline score 0		

1 2 3		
Treatment era 1970 – 1975 1976 – 1979 1980 – 1986		
Age at Primary Diagnosis		
Pelvic RT exposure Yes No Unknown		
Family history of BC Yes No		
Family history of Ovarian Cancer Yes No		
Vital Status Alive Deceased Unknown		

Table 2. Breast cancer diagnosis, stage and outcomes

	N (%)
Breast cancer pathology	
Breast cancer stage	
Age at breast cancer dx Less 40 years 40 or more years	
Method of first diagnosis Screening mammogram and/or MRI Survivor felt a lump Physician felt a lump Other	
Stage at diagnosis DCIS Stage I Stage II Stage III Stage IV	
TNM Status	
ER status Positve Negative Unknown	
PR status Positive Negative Unknown	
HER 2 Status	

Positive Negative Unknown	
Location Upper outer quadrant Upper inner quadrant Lower outer quadrant Lower inner quadrant	
Bilateral Yes No	
If deceased, due to BC Yes No	

Table 3: Risk of BC Age, Stage and TNM By Method of Diagnosis

	Surveillance Detection **N (%) OR (95% CI)**	**Physician Detection** **N (%) OR (95% CI)**	**Patient Detection** **N (%) OR (95% CI)**
Age at Breast Ca **< 40 years** **≥ 40 years**			
Stage at diagnosis DCIS Stage I Stage II Stage III Stage IV			
TNM status			

Figure 1: 1a: Overall survival curves of BC participants; 1b: Survival curves based on method of diagnosis – screening vs. physician exam vs. patient detection vs. Other

STRENGTHS AND LIMITATIONS

This study is informed by rigorous and in-depth qualitative pilot studies at two institutions, University of Chicago and Memorial Sloan Kettering Cancer Center. In utilizing the CCSS, this study utilizes the largest population of such cancer survivors (women who developed breast cancer following chest radiation for a pediatric cancer) to date.

Ultimately, this study will address the question of the rates and effectiveness of risk-based surveillance in women previously exposed to chest radiation. It will significantly impact the care of childhood cancer survivors as follows:

- **If early detection is associated with improved outcomes, standards for health insurance coverage in these high-risk women can be established.**
- **The data can be used to develop primary care screening guidelines for this population based on the outcomes in this population, not adapted from other high-risk populations.**

There are notable limitations to this study. First, the CCSS is not population-based, thus, selection bias needs to be considered when generalizing the findings. The overall CCSS population, as well as the women in this study, includes very few minority patients. Understanding the needs of minority and low-income patients will require the development of additional, diverse study cohorts.

The study is a retrospective, descriptive study. The breast cancer history will be obtained through retrospective review of medical records as well as self-report, thereby introducing recall and other biases.

REFERENCES

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