CHILDHOOD CANCER SURVIVOR STUDY
ANALYSIS CONCEPT PROPOSAL

1. **Study Title**: Risk of Breast Cancer Following Spinal Irradiation for a Pediatric Malignancy

2. **Working Group and Investigators**: This proposed publication will be within the Second Malignancy Working Group. Proposed investigators will include:

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3. **Background and Rationale:**

While breast cancer is not commonly thought to be a late sequela of a pediatric leukemia or central nervous system (CNS) tumor, there are no studies of which we are aware that address whether there is an increased risk of breast cancer following one particular treatment that is used for both of these two cancers, spinal radiation. Multiple papers assessing the occurrence of second neoplasms in leukemia and CNS tumor survivors report very few instances of breast cancer despite studying thousands of patients with varying lengths of follow-up (up to a median follow-up of 18.7 years).[1-7] In a recent report from the British CCSS,[8] the standardized incidence ratio (SIR) for breast cancer among leukemia survivors was 2.0 (95% CI, 1.0 to 4.2) with an absolute excess risk (AER) per 10,000 person-years of 0.4 (95% CI, -0.2 to 1.1). For CNS tumor survivors, the SIR and AER were 0.8 (95% CI, 0.4-1.4) and -0.4 (-1.1 to 0.4), respectively. However, this study did not report outcomes by radiation exposure, and as with the other studies, did not present in detail sufficient to permit evaluation of whether these breast cancers are occurring specifically in those survivors who were treated with spinal radiation. Although theoretical calculations have suggested a possible notable risk of breast cancer in females treated with conventional photon therapy to the spine for a pediatric malignancy[9], it is unclear whether there is supporting evidence to be found in epidemiological cohorts.

In light of this gap in the literature, we propose an exploratory analysis to describe the CCSS experience with breast cancer in female survivors who were treated with spinal

radiation. Our goal is not to compare childhood cancer survivors who were exposed to spinal radiation to childhood cancer survivors who were not exposed to spinal radiation, but rather to compare those survivors who were treated with spinal radiation to the general population. We recognize that the CCSS sub-population in which we are interested is small as is the incidence of breast cancer cases in these survivors. While we have yet to complete review of the radiation records to finalize the total number of women we will include as having been treated with spinal radiation, we expect this number will be close to 370. While this is a relatively small number, it is by far the largest number of women who were treated with spinal radiation as children to be studied as adults for breast cancer occurrences. Because of the very small number of breast cancer cases we expect (3 cases), we are very limited in the analyses we can do. For instance, we will not be able to determine the relationship between radiation dose and breast cancer. Our intention is to conduct a purely descriptive analysis which simply highlights the small number of women with breast cancer and characterize these women, their treatments, and their breast cancers.

4. Specific Aims/Objectives/Research Hypotheses:

Aim 1: To evaluate the risk of breast cancer in women who were treated with spinal irradiation for a pediatric malignancy in the absence of chest radiation

Hypothesis: Survivors treated with spinal radiation will have a higher incidence of breast cancer than the general population.

Aim 2: To describe the women who did develop breast cancer, characteristics of their breast cancer, and the treatments they received for their pediatric malignancy

5. Analysis Framework:

a. Subject population: Female survivors of a leukemia or CNS tumor who were treated with spinal radiation. We will exclude women who were treated with other fields of radiation near breast tissue, particularly those survivors treated with radiation to high abdominal fields and total body irradiation.

b. 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.

c. Exploratory variables of interest: (1) Childhood cancer diagnosis (2) dose of spinal radiation contained in the medical record (We have abstracted this information from the radiation treatment summary of the patients' medical records.)

d. Statistical analysis:

Aim 1: We will quantify the risk of breast cancer with standardized incidence ratios (SIRs) and corresponding 95% confidence intervals using age- and calendar-year-specific incidence rates of invasive and in situ carcinoma from the Surveillance, Epidemiology, and End Results (SEER) program as the reference population. For obtaining the crude rates of breast cancer from SEER for use in calculating the expected number of breast cancers, we will use the SEER 9-registry data, choosing from the selection criteria for “Behavior recode for analysis” to include both the “malignant” and “in situ” options and deselecting the check box for “Select only Malignant Behavior” (default option in SEER*Stat is for this to be checked on). Only the first primary breast cancer diagnosis will be included. CCSS participants will be considered at risk of breast cancer starting at five years after the diagnosis of their childhood cancer until either a diagnosis of breast cancer, death, or December 30, 2008. December 30, 2008 is used as an administrative cutoff because this is the cutoff for the most recent release of SEER data. We are unable to calculate the expected rates of breast cancer needed for the SIRs beyond 2008.

An SIR will be estimated using all CCSS participants who belong to our target population and then separate SIRs will be estimated for leukemia survivors and CNS tumor survivors. The median dose of spinal radiation will be estimated separately for leukemia and CNS tumor survivors.

Aim 2: No statistical analysis will be done. We will simply present characteristics as shown in Table 3 below.

6. Tables and Figures:

Table1. Characteristics of leukemia and CNS tumor survivors treated with spinal radiation

	Total		Leukemia survivors*		CNS tumor survivors**	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**
Age at diagnosis of primary cancer, years						
0-4						
5-11						
12 and older						
Year of diagnosis of primary cancer						
1970-1974						
1975-1979						
1980-1986						
Dose of spinal radiation, cGy						
Less than 1899						
1900-2499						
2500-3599						
3600+						
Race						
White, non-Hispanic						
Minorities						
Unknown						
Vital Status						
Alive						
Deceased						
Age at analysis, years* **						
Under 25						
25-39						
40+						

*Diagnoses of leukemia survivors consist of acute lymphoblastic leukemia (n=), acute myeloid leukemia (n=), and other leukemia (n=)

**Diagnoses of CNS tumor survivors consist of medulloblastoma or primitive neuroectodermal tumor (n=), astrocytoma (n=), and other CNS tumor (n=)

***Defined as the age at breast cancer diagnosis, death, or December 30, 2008.

Table 2. Standardized incidence ratio of breast cancer among 5-year survivors of leukemia and CNS tumors treated with spinal radiation relative to the general population

Diagnosis	**N**	**Dose*, cGy**	**Person years**	**Observed (N)**	**Expected (N)**	**SIR**	**(95% CI)**
Total							
Leukemia							
CNS tumor							

*Median dose of spinal radiation

Table 3. Characteristics of women diagnosed with breast cancer

	Survivor 1	Survivor 2	Survivor 3
Primary diagnosis			
Age at primary diagnosis, years			
Spinal radiation dose, cGy			
Age at breast cancer diagnosis, years			
Breast cancer histology			
Location of breast cancer			
Laterality			
Quadrant			
Family history of breast cancer in first-degree relative			

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