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Topic: Non-Treatment Risk Factors for Breast Cancer

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Childhood Cancer Survivor Study

Analysis concept proposal-REVISED

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Title: Non-treatment related risk factors for breast cancer after childhood cancer

Working group: Secondary Malignancy

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Background and rationale: Studies have reported an excess of second malignancies in survivors of childhood cancer with a 15-year cumulative incidence of 5%. The most commonly noted secondary cancers reported thus far in childhood cancer survivors include leukemias, breast cancer, NHL, and thyroid cancers. The risk factors for secondary cancers cited in prior literature include exposure to radiation therapy, exposure to combined modality therapy, exposure to alkylating agents, and young age at diagnosis. Other less clearly associated risk factors may include family history, and lifestyle.

The increased risk of breast cancer in female survivors of childhood cancer that has been described in the literature is particularly alarming. The Late Effects Study Group recently reported that women treated for Hodgkin's disease during childhood had a 75 fold increased risk for breast cancer and a cumulative probability of breast cancer at age 40 of approximately 30%. Treatment-related risk factors, such as radiation therapy has been well documented. However, risk factors for breast cancer described for the general population have not been examined in the childhood cancer survivor cohort. In large cohort studies of the general population the following factors have been described as risk factors for breast cancer: early age at menarche, age at first live birth, family history of breast cancer, prolonged use of oral contraceptives before first pregnancy, history of breast biopsy, and behaviors such as alcohol use and smoking.

The self-report questionnaire used by the CCSS may be helpful in elucidating the interaction between population risk factors and treatment risk factors for breast cancer.

Specific aims:

1. To perform a risk factor analysis for the development of secondary breast cancer after childhood cancer in the CCSS cohort, controlling for treatment. To assess the effects of recognized population based risk factors for breast cancer including family cancer history,

estrogen exposure, and behaviors on the development of breast cancer in female survivors in the CCSS cohort.

2. To describe the clinical features, pathology, and outcome of the breast cancer cases in the CCSS cohort compared to published data on breast cancer cases in the general population.

Hypothesis:

Childhood cancer survivors who develop secondary breast cancer are more likely to have recognized risk factors for breast cancer than childhood cancer survivors who do not develop secondary breast cancer.

Analysis framework:

a. Outcome of interest: Confirmed breast cancer diagnosis at time of submission of patient questionnaire.

b. Subject population: Cases are all female survivors with secondary breast cancer in the CCSS cohort and controls are (aged-matched?) female survivors without breast cancer in the CCSS cohort.

c. Dependent variables: Variables that reflect estrogen exposure (including parity, menstrual history, and exogenous estrogens), first degree relative's family cancer history, history of breast biopsies, and behaviors such as smoking and alcohol use.

d. Independent variables: Primary cancer, age at dx of first cancer, years of follow up, age at breast cancer diagnosis, race, recurrence of primary cancer, stage of primary cancer, other malignancies, type of therapy (XRT, chemo, XRT/chemo), radiation field, alkylating agent chemotherapy dose, anthracycline chemotherapy dose, splenectomy, thyroid disease as a marker of other radiation induced organ toxicity.

d. Additional Data: Pathology reports for all breast cancer cases in the survivors.

e. Plan for data analysis: After examination of the relationship between the individual risk factors, a multivariate analysis will be performed. It is likely that this model will attempt to answer the question – "do any of the non-treatment related risk factors identified influence the effect of treatment-related risk factors?".

Specific tables:

Table 1: Description of female survivors with breast cancer

[This table is intended to describe the cohort of interest]

Number of cases
Primary Disease (list and number of each)
Age at first CA diagnosis (median, range)
Age at diagnosis of breast cancer (median, range)
Years from first cancer to breast cancer (median, range)
History of other confirmed cancers (list and number of each)

Table 2: Analysis of disease and treatment-related risk factors

[The intent of this table is to both show what was presented in the Neglia paper, and to explore the relationship between radiation field and breast cancer. This analysis would be comparing patients with breast cancer to females without breast cancer in the cohort.]

	Survivors with Breast Cancer	Survivors without BrCa
Diagnosis		
HD		
Bone tumor		
etc		
Age at diagnosis		
Time since diagnosis		
Treatment		
Radiation therapy (%y)		
Chemotherapy(%y)		
Chemotherapy +radiation(%y)		
Radiation Field (%y)		
Chest		
Spinal		
Abdominal		
Head/neck		
Upper extremity		
Lower extremity		
TBI		
Alkylating agents(%y)		
Anthracyclines(%y)		
Epipodophyllotoxins(%y)		
Platinum agents(%y)		
BMT(%y)		
Splenectomy(%y)		

Table 3. Population based risk factors in survivors with and without confirmed breast cancers

[This table will be looking for population-based risk factors which might impact on risk of treatment related breast cancers; this should be controlled for chest rads and age]

STRONGEST POPULATION BASED RISK FACTORS (Estrogen exposure, terminal differentiation of breast tissue, family history, history of breast biopsy not related to immediate diagnosis of breast cancer):

Female survivors with BrCA Female survivors without BrCa

Ever Pregnant (L.9)
Age at first pregnancy (L.11) [only if <age at breast cancer diagnosis]
Number live births (L.11)
Age at first live birth(L.11) [only if <age at breast cancer diagnosis] (Note: the population-based increased risk is categorized as age >30 vs < 30; age <20 very protective)
Ever menarche (E.16)
Age at menarche (E.16) (Note the population-based increased risk is categorized as age <12 vs >12)
Age at menopause (E.17)
Primary ovarian failure (yes to question E.11)– ≤ ۴۵
History of Breast Biopsy [yes to L18, if > 2 years prior to age at breast cancer diagnosis]
Mother, sister or daughter with history of Breast Cancer
Mother, sister or daughter with history of Ovarian Cancer
"Low estrogen exposure" (created variable) (%Y)
If patient has been exposed to TBI, Pelvic radiation, an oopherectomy, or AA dose ≥ 20gm/m2, then "Low estrogen exposure"= yes

WEAKER POPULATION BASED RISK FACTORS

Smoker (%Y) [If M.1 =yes and M.1a<age at breast cancer diagnosis]
Alcohol use (%Y) [If M.3=yes and M.3a < age at breast cancer diagnosis]
Diet (not available in questionnaire)
Exercise (not available in questionnaire)

RISK FACTORS NOT SEEN IN GENERAL POPULATION, BUT MAY BE OPERATIVE IN CHILDHOOD CANCER SURVIVORS (this analysis needs discussion with genetics working group members)

Parent, sibling or offspring with history of other malignancies
- Sarcoma
- CNS
- Leukemia
- Other

Family History of multiple cancers [>1 cancer in first degree relatives]

Table 4. Clinical and pathologic features of breast cancer cases
[we will use this data and compare to published rates of "community" breast cancers; this data would be obtained from path reports and additional medical record tracking, to be carried out by the investigators]

Stage
Histology
Laterality
Estrogen receptor +
Node +
Tumor size

Item 5. Additional exploratory analyses:

We hypothesize that there is a group of childhood cancer survivors predisposed to develop radiation-induced toxicities such as SMNs and thyroid disease.

Is a history of thyroid disease (yes to E. 1,2,3,4) and or other SMNs a predictor of breast cancer in women who received chest radiation?