05-04

Childhood Cancer Survivor Study

Analysis Concept Proposal

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Title: The risk of disease recurrence and second malignancies following pregnancy in female survivors of childhood cancer.

Working Group: Reproduction

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Background and Rationale

The overall survival rate of childhood cancer – defined as a malignant neoplasm diagnosed before the age of 21 years - has improved during the last three decades. It is now greater than 70%, and continues to improve[1]. Consequently, as the population of childhood cancer survivors entering adulthood increases steadily, the late effects after treatment are of increasing importance[2, 3]. Endocrine complications are the most prevalent late effects observed in these patients, and issues regarding gonadal function and future fertility are of particular concern to young adult survivors. Fortunately, the majority of prepubertal girls and adolescent females receiving standard chemotherapy and radiotherapy retain or recover their ovarian function and are able to become pregnant[4]. However, very little is known about the impact of pregnancy on the risk of disease recurrence or of developing a second malignant neoplasm (SMN) in female survivors of childhood cancer.

Pregnancy is a complex endocrine condition that results in changes in estrogen and progesterone levels, while also altering immunologic competence. In the recent past, breast cancer survivors were advised not to get pregnant[5]. At the time, there was a belief that hormonal changes during pregnancy might induce tumor growth in residual breast cancer cells that remained after treatment. In addition, some studies reported a lower survival rate for women who were pregnant at the time they were diagnosed with breast cancer.[6-8] However, more recent literature has demonstrated that pregnancy following chemotherapy and/or radiotherapy did not impact adversely the prognosis of breast cancer patients[11-16], lymphoma patients[17], and thyroid cancer patients[18]. Other studies have demonstrated that pregnancy may have a protective, or even an inhibitory effect, on both the incidence and development of some human and animal tumors[19, 20].

For survivors of childhood cancer the existing literature focuses mainly on the fertility rate, pregnancy outcome and the health of offspring[21-23]. Overall, the results are reassuring; in their recent study of the CCSS cohort, Green et al. did not find adverse pregnancy outcomes for female survivors treated with most chemotherapeutic agents[22]. Other reports demonstrated neither increased risk of genetic disease nor non-hereditary cancer among offspring of childhood cancer survivor, compared with the risk in offspring of sibling controls [24,25]. To the best of our knowledge, however, the impact of pregnancy on the health of female survivors of childhood cancer has not been investigated. Specifically, whether or not pregnancy in female survivors of childhood cancer alters the risk of recurrence of their primary malignancy or of their developing a SMN has not been investigated. In the current study, we aim to address this deficiency by assessing the risk of disease recurrence and SMN in female childhood cancer survivors who have become pregnant after successfully completing their cancer treatment.

Specific Aims:

In this population of female survivors of childhood cancer:

1. Identify whether pregnancy increases the risk for disease recurrence and/or development of a second malignant neoplasm.

2. Determine which, if any, patient characteristics, treatment exposures or pregnancy related outcomes (e.g., miscarriage, preterm delivery), correlate with the risk of disease recurrence or development of a SMN following a first pregnancy.

Hypotheses:

- Becoming pregnant does not increase the risk of disease recurrence or of developing SMN in survivors of childhood cancer.
- The risk factors for developing recurrence of the primary malignancy or developing SMN after pregnancy will be the same as those described for non-pregnant female survivors.
- Pregnancy outcome (e.g., miscarriage, live birth) does not increase the risk of disease recurrence or developing SMN.

Analysis Framework:

1. Outcomes of interest: (Baseline questionnaire items)

a. Disease recurrence
b. Second malignant neoplasms (SMN)

2. Subject population:

a. **Cases**: All female survivors registered in CCSS with a documented pregnancy.
b. **Controls:** All female survivors registered in CCSS with no documented pregnancy.

3. Explanatory variables:

3. **Outcome variables:** see above
4. **Exposure variables:**
    - Exposure to any chemotherapy
    - Exposure to alkylating agents

- Exposure to any radiation therapy

5. Potential confounders and effect modifiers:

- Diagnosis
- Age at diagnosis of primary cancer
- Age at pregnancy
- Time interval between diagnosis and pregnancy
- History of prior (before pregnancy) recurrence
- History of prior (before pregnancy) SMN

4. Analyses:

The analysis will be based on two counts of person-years: female survivors who have been pregnant first will be placed in the "before pregnancy" group until their pregnancy date, when they will be placed in the "after pregnancy" group unless their second cancer occurred first. Female survivors who have never been pregnant will be placed only in the "before pregnancy" group. A Cox regression model with time-dependent covariates will be used to determine the odds ratios of developing disease recurrence and SMN following a first pregnancy. In order to correct for older ages in the "after pregnancy" group, we will also include in the regression other possible explanatory variables such as age and/or time since diagnosis. In addition, other control variables such as chemotherapy, radiotherapy, and pregnancy-related outcomes will be included in the regression.

Alternatively, if the proportional-hazards assumptions of the Cox model are not met, a Poisson regression model (using GEE to adjust for some participants being in both groups) could be used.

Tables:

First identify:

1. A total # of all female survivors:
2. # of all female survivors with pregnancy: Baseline#M4/9 & Follow up 1#N1/2 & Follow up2 #8#19 c-d
3. # of all female survivors with **no** pregnancy: Baseline#M4/9&Follow up 1#N1/2 & Follow up2 #8#19 c-d

Table 1. Characteristics of female survivors

Variables	Cases reporting Pregnancy (n=)	Cases reporting no pregnancy (n=)
Mean age at primary disease diagnosis		
Diagnoses		
Leukemia		
CNS tumors		
Hodgkin's lymphoma		
Non- Hodgkin's lymphoma		
Wilms Tumor		
Neuroblastoma		
Soft tissue sarcoma		
Bone cancer		
Chemotherapy		
Yes		
No		
Radiotherapy		
Yes		
No		

***Table 2. Risk factors for disease recurrence in female survivors**

Variables	All cases (n)	Cases with pregnancies (n)	No. of Recurrences		OR
			Before Pregnancy	After Pregnancy	
Mean age at primary disease diagnosis					
Mean age at diagnosis of disease recurrence					
Diagnoses					
Leukemia					
CNS tumors					
Hodgkin's lymphoma					
Non- Hodgkin's lymphoma					
Wilms Tumor					
Neuroblastoma					
Soft tissue sarcoma					
Bone cancer					
Chemotherapy					
No					
Yes					
Radiotherapy					
No					
Yes					

*** Risk factors for recurrence taken from Sklar et al., JCEM 2002 (26).**

***Table 3. Risk factors for SMN in female survivors**

Variables	All cases (n)	Cases with pregnancies (n)	No. of SMN		OR
			Before Pregnancy	After Pregnancy	
Mean age at primary disease diagnosis					
Mean age at diagnosis of SMN					
Primary Diagnoses					
Leukemia					
CNS tumors					
Hodgkin's lymphoma (HL)					
Non- Hodgkin's lymphoma (NHL)					
Wilms Tumor					
Neuroblastoma (NBL)					
Soft tissue sarcoma (STS)					
Bone cancer (BC)					
Chemotherapy					
No					
Yes					
Alkylating agent					
No					
Yes					
GH Treatment					
No					
Yes					
Radiotherapy					
No					
Yes					

*** Risk factors for SMN taken from Sklar et al., JCEM 2002 (26).**

***Table 4. The impact of pregnancy outcome on disease recurrence and SMN**

	No. of Disease Recurrence			No. of SMN		
Pregnancy Outcome	Before Pregnancy	After Pregnancy	OR	Before Pregnancy	After Pregnancy	OR
Miscarriage/abortion						
Live birth						
Still birth						

***Classification taken from Green et al., 2002 (22).**

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