CHILDHOOD CANCER SURVIVOR STUDY ANALYSIS CONCEPT PROPOSAL

STUDY TITLE: Infertility and the use of fertility treatments in female survivors of childhood cancer.

WORKING GROUP
Chronic Disease

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Investigators

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BACKGROUND AND RATIONALE:

When considering the long term sequelae of cancer therapy, infertility surfaces as a primary concern, particularly, among female survivors (Zeltzer, 1993). Cancer survivors have a decrease in ovarian reserve compared to controls, even if they are having regular menstrual cycles. Acute ovarian failure is uncommon in children except for high risk protocols such as those used for bone marrow transplant when ovarian failure is reported to be as high as 80% (Meirow and Nugent, 2001). Therefore, this leaves a large percentage of survivors at risk for infertility due to decreased ovarian reserve.

In one study of childhood cancer survivors, 92% of survivors progressed through puberty and had menarche within the normal range, however, sonographic and endocrine changes suggestive of impaired ovarian function were seen. Those at highest risk for diminished ovarian reserve were those who had ovaries in the irradiation field or who received alkylating chemotherapy (Larsen, 2003). Furthermore, previous reports from the Childhood Cancer Survivor Study demonstrate the risk of non-surgical premature menopause was 13 fold higher for cancer survivors than sibling controls with a cumulative incidence of 8% by age 40. Risk factors for premature menopause included age, diagnosis of Hodgkin lymphoma, and exposure to increasing doses of alkylating agents and radiation to the ovaries (Sklar, 2006).

In addition to early menopause, cancer survivors are less likely to have ever been pregnant when compared to their siblings. Green et al reported a relative risk of pregnancy of 0.81 compared to siblings. Again, increasing dosage of radiation to the ovaries and uterus, increasing dose of hypothalamic/pituitary, as well as increase alkylating exposure were risk factors for having never been pregnant. Ovarian/uterine radiation exposure of 5-10 Gy had a

relative risk of pregnancy of 0.56 (95% CI, 0.37 to 0.85) and exposure of greater than 10 Gy had a relative risk of pregnancy of 0.18 (95% CI, 0.13 to 0.26). Hypothalamic/pituitary doses of greater than 30 Gy had a relative risk of pregnancy of 0.61 (95% CI, 0.44 to 0.83). Summed AAD score of three or four was associated with risk of pregnancy of 0.72 (95% CI, 0.58 to 0.90) and 0.65 (95% CI, 0.45 to 0.96) respectively (Green, 2009). Additional studies support an increased risk of childlessness among female cancer survivors compared to the general population (Magelssen, 2008).

Although prior studies demonstrate definite fertility impairment, they do not provide an estimate of the true risk of infertility in childhood cancer survivors for several reasons. Firstly, using likelihood of pregnancy as a measure of fertility does not take into account individual desires for childbearing and attempts at pregnancy. Furthermore, time to pregnancy and the use of infertility treatments is not captured by measuring pregnancy alone. In this study, we aim to quantify infertility in the survivor cohort compared to the sibling cohort. Measures of fertility/infertility will include time to pregnancy, frequency of infertility (defined as greater than 1 year of pregnancy attempts without success), and the use of infertility treatments such as medication or in vitro fertilization.

There are several reasons why quantifying the risk of infertility based on type of cancer therapy among female cancer survivors is important. As previously mentioned, puberty and menstrual cyclicity are not sensitive in identifying women with diminished ovarian reserve. In a study of 182 adults with a mean age of cancer diagnosis of 5.8 years- 27% of survivors had a serum level of anti-müllerian hormone (AMH) of less than the 10th percentile of normal. (AMH is an emerging marker of ovarian reserve). A subset of women in this study also had other markers of ovarian reserved measured (FSH and Inhibin B) and FSH was shown to be in the normal range. This is concerning, given that FSH and menstrual cyclicty are the most commonly used markers of ovarian reserve in cancer survivors. Furthermore 44% of cancer survivors had levels of AMH less than a level thought to be predictive of successful pregnancy after assisted reproduction. (Lie Fong, 2009).

In those at risk for infertility due to diminished ovarian reserve, fertility preservation options exist. The current options for fertility preservation in young people are dynamic, with standard of care for fertility preservation in adult women being embryo cryopreservation after IVF prior to cancer therapy. Oocyte cryopreservation is another option for postpubertal women without a partner, and success of this method for fertility preservation has increased steadily to acceptable pregnancy rates over the last several years (Porcu, 2004; Borini, 2006; Parmegiani L, 2009). To date, fertility preservation in the very young consists of removal of ovarian tissue for cryopreservation and reimplantation at a later date after completion of therapy. Although live births have been reported from ovarian tissue freezing, this is still in early development (Donnez, 2004). Options for fertility preservation exist but are costly and in some cases experimental; it is necessary to determine those patients whose cancer therapy puts them at a substantial risk of infertility.

SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

The purpose of this study is to describe the prevalence of infertility and the use of infertility therapy among survivors of childhood cancer and to compare the risk of infertility for survivors

compared to sibling. In addition, the relative risks of infertility among various diagnostic, treatment and demographic groups will be evaluated.

Hypotheses:
1) Survivors of childhood cancer will have a greater risk of infertility compared to siblings.
2) Survivors receiving alkylating agents of increasing doses, increasing dosage of radiation to the ovaries/uterus, or increasing doses of radiation to the pituitary will have a higher risk of infertility than those who did not receive this therapy.
3) Survivors who did achieve pregnancy will have a longer time to pregnancy and will utilize infertility services more frequently than siblings.

ANALYSIS FRAMEWORK:

(A) Outcomes of interest

1. To describe the prevalence of infertility and the use of infertility treatment in female cancer survivors:

a. Prevalence of infertility in survivor and sibling cohorts, calculated two ways:

Method 1: Inclusive definition including women with ovarian insufficiency/failure (women who may have self-defined as infertile without trying for one year or more due to premature ovarian failure.)

questionnaire= baseline ≥18 years

Sum of those women reporting trying for > 1 year (M5 Y)
+ those who do not report trying but never had a menstrual period (M5 N/E16 No)
+ those who do report having ever had a menstrual period, but none in the last five years (M5 N/E16 Y/E17 N and age reported at LMP ≥5 years less than age at baseline.)

Method 2: Clinical infertility (tried to get pregnant for at least one year without success)
This method will be used for subsequent analyses involving infertility RR between demographic and treatment groups.

questionnaire= baseline ≥18 years

Prevalence of infertility M.5. (Y)

b. Prevalence of use of infertility treatment:

questionnaire= baseline ≥18 years
M.6., M.7., M.8 (Y)

2. To calculate the relative risk of infertility female survivors compared to siblings.

a. questionnaire: baseline ≥18 years survivor; question M.5.(Y) compared to baseline ≥ 18 years sibling; question M.5.(Y)

Poisson regression models will be used to evaluate univariate and adjusted relative risks. Adjustments will be made for age at baseline and other exploratory variables listed in section C. (1).

3. To identify treatment, disease, and demographic characteristics which increase the risk of infertility among survivors.

Treatment: Individual questions M.5-M.9. Describe the prevalence and the relative risk (with first group listed as the reference group unless otherwise indicated) in the following treatment groups:

a. Cyclophosphamide equivalent dose (in grams) [this replaces summed AAD score] (0, 1-10, 11-20, 21-30, >30)
b. Ovary/uterine radiation exposure (No RT, Dose 1-5 Gy, Dose 5.1-10 Gy, Dose 10.1-20 Gy, Dose >20 Gy)
c. Hypothalamic/pituitary radiation groups (No RT, Dose 1-20 Gy, Dose 20.1-30 Gy, Dose >30 Gy)
d. Specific chemotherapy exposures: (none, CCNU, Cisplatin, Cyclophosphamide, Cytosine arabinoside, Doxorubicin, Nitrogen mustard, Procarbazine, Vinblastine, VM26, VP16)
e. Bone marrow transplant (no, yes)
f. Relapse (no, yes)
g. Second malignancy prior to completion of baseline ≥18 years questionnaire (no, yes)
h. Diagnosis (Leukemia, Hodgkin Lymphoma, NHL, Bone cancer, Soft tissue sarcoma, CNS, neuroblastoma, kidney)

Demographic: Individual questions M.5-M.9. Describe the prevalence and the relative risk in the following demographic groups:

a. Age at diagnosis (0-4, 5-9, 10-14, ≥15)
b. Educational level (no high school or GED, high school or GED, some college without a bachelor's degree, bachelor's degree or higher)
c. Marital status (never married, currently married, formerly married)
d. Smoking (Never smoked, current smoker, former smoker)
e. Alcohol use (None, moderate drinkers [1-6 drinks per week], heavy drinkers [≥7 drinks per week]). *Baseline asks this question in drinks/month so will need to convert (N.6)*
f. Ethnicity (non-Hispanic white, Hispanic, non-Hispanic black, other)
g. Age at baseline (<20, 20-24, 25-29 (referent), 30-34, 35-39)
h. BMI (<18.5, 18.5-24.9, 25-29.9, ≥30)

Prevalence of infertility will also be tabulated for survivors and siblings by demographic groups. The prevalence of infertility among survivors will be tabulated by disease and treatment characteristics. Univariate analyses will be performed to assess diagnosis, treatment and demographic factors. Multivariable models (e.g., logistic regression or Poisson regression) will be used to evaluate relative risks adjusting for demographic variables, such as age at baseline questionnaire, race/ethnicity, and diagnosis and treatment variables. Multivariable models may include factors strongly associated with infertility risk upon univariate analysis. In addition, factors that are known to be associated with infertility risk may be included even if univariate analysis does not demonstrate a statistically significant association.

4. To compare the time to first pregnancy in those achieving pregnancy (survivor cohort vs. sibling cohort and amongst survivor groups in Figure 1.b.)

a. questionnaire= Pregnancy; question A.3. (number of months to pregnancy) in survivors and survivors compared to siblings.
b. questionnaire= Pregnancy; question A.3 proportion of survivors >12 months to conception compared to proportion of siblings > 12 months to conception (relative risk).

Include first pregnancy only

Time to first pregnancy in months will be summarized for survivors and for siblings and amongst survivor groups (see Figure 1.b.) using descriptive statistics. To compare survivors and siblings, times may be dichotomized using a Cox regression model or times will be dichotomized using a cut-point (e.g., <12 mo vs. ≥12 mo) and logistic regression models will be used to determine relative risk. Adjustments will include age at baseline questionnaire.

5. To determine the frequency and relative risk of the use of infertility treatment among cancer survivors and compare this utilization to siblings in those achieving pregnancy (data from first pregnancy only).

A. questionnaire= Pregnancy; questions A4a, A5a, A6 prevalence in survivors and survivors compared to siblings (relative risk).

a. Utilization of medical provider to address infertility in survivors and controls. A4a

b. Use of medication to aid in getting pregnancy in survivors and controls A.5a.

c. Use of IVF in survivors vs. sibling controls in those who became pregnant. A6

The use of infertility treatment prior to a first pregnancy will be tabulated for survivors and for siblings. Use of infertility treatment will be tabulated by type (A4a: seeing a doctor because of

difficulties, A5a: medications to aid in getting pregnant, A6: pregnancy resulting from in-vitro fertilization) and overall (use of any of the three types).

(B) Subject population:

1. Female survivors that completed the baseline ≥18 years old questionnaire M.5.
2. Female sibling controls that completed the baseline ≥18 years old questionnaire M.5
3. Female survivors who completed the pregnancy questionnaire (data from 1st pregnancy only). This is to be used in the pregnancy analyses only (see section A4 and A5 above).
4. Female siblings who completed the pregnancy questionnaire (data from 1st pregnancy only). This is to be used in the pregnancy analyses only (see section A4 and A5 above).
5. Exclude survivors and siblings who were < 18 or ≥40 years old at completion of the baseline questionnaire.

(C) Exploratory variables:

1. Prevalence of infertility and relative risk of infertility survivor vs. sibling
   - Age at baseline (<20, 20-24, 25-29, 30-34, 35-39)
   - Age at diagnosis (0-4, 5-9, 10-14, ≥15)
   - Educational level (no high school or GED, high school or GED, some college but no bachelor's degree, bachelor's degree or higher)
   - Ethnicity (non-Hispanic white, Hispanic, non-Hispanic black, other)
   - Smoking (Never smoked, current smoker, former smoker)
   - Alcohol use (None, moderate drinkers [1-6 drinks per week], heavy drinkers [≥7 drinks per week])
   - Marital status (never married, currently married, formerly married)
   - BMI (<18.5, 18.5-24.9, 25-29.9, ≥30)

2. Treatment and disease characteristics relative risk of infertility (multivariate model with adjustments for the variables listed above in #1)

   Treatment: Individual questions M.5-M.9. Describe the prevalence and the relative risk in the following treatment groups:

   a. Cyclophosphamide equivalent dose (in grams) [this replaces summed AAD score] (0, 1-10, 11-20, 21-30, >30)
   b. Ovary/uterine radiation groups (No RT, Dose 1-5 Gy, Dose 5.1-10 Gy, Dose 10.1-20 Gy, Dose >20 Gy)
   c. Hypothalamic/pituitary radiation groups (No RT, Dose 1-20 Gy, Dose 20.1-30 Gy, Dose >30 Gy)
   d. History of the following chemotherapies compared to those not receiving this agent (CCNU, Cisplatin, Cyclophosphamide, Cytosine arabinoside, Doxorubicin, Nitrogen mustard, Procarbazine, Vinblastine, VM26, VP16)
   e. History of bone marrow transplant compared to those without transplant
   f. History of relapse compared to those without a history of relapse
   g. History of second malignancy prior to completion of baseline ≥18 years questionnaire compared to those without this history.

h. Diagnoses: Leukemia, Hodgkin Lymphoma, NHL, Bone cancer, Soft tissue sarcoma, CNS, neuroblastoma, kidney (Wilms)

Demographic: Individual questions M.5-M.9. Describe the prevalence and the relative risk in the following treatment groups:

a. Age at diagnosis (0-4, 5-9, 10-14, ≥15)
b. Educational level (no high school or GED, high school or GED, some college but no bachelor's degree, bachelor's degree or higher)
c. Marital status (never married, currently married, formerly married)
d. Smoking (Never smoked, current smoker, former smoker)
e. Alcohol use (None, moderate drinkers [1-6 drinks per week], heavy drinkers [≥7 drinks per week])
f. Ethnicity (non-Hispanic white, Hispanic, non-Hispanic black, other)
g. Age at baseline (<20, 20-24, 25-29, 30-34, 35-39)
h. BMI (<18.5, 18.5-24.9, 25-29.9, ≥30)

3. Time to pregnancy and the use of fertility treatments in those achieving pregnancy (1st pregnancy data only) in survivors and siblings and relative risk of use of fertility treatment survivor vs. sibling and amongst survivor treatment groups (see Figure 1.b.).

- Age at baseline (<20, 20-24, 25-29, 30-34, 35-39)
- Age at diagnosis (0-4, 5-9, 10-14, ≥15)
- Educational level (no high school or GED, high school or GED, some college but no bachelor's degree, bachelor's degree or higher)
- Ethnicity (non-Hispanic white, Hispanic, non-Hispanic black, other)
- Smoking (Never smoked, current smoker, former smoker)
- Alcohol use (None, moderate drinkers [1-6 drinks per week], heavy drinkers [≥7 drinks per week])
- Marital status (never married, currently married, formerly married)
- BMI (<18.5, 18.5-24.9, 25-29.9, ≥30)
- Treatment groups in survivors (any pelvic or abdominal radiation, any alkylating therapy, any cranial radiation, treatment did not include any of the previous therapy)

Table 1: Demographic and treatment characteristics of female survivors of childhood cancer and of siblings.

Characteristic	Survivors		Siblings		P
	#	%	#	%	
Age at baseline					
<20					
20-24					
25-29					
30-34					
35-39					
Age at diagnosis					
0-4					
5-9					
10-14					
≥15					
Marital status					
never married					
currently married					
formerly married					
Educational level					
no high school or GED					
high school or GED					
some college, no bachelor's degree					
bachelor's degree or higher					
Ethnicity					
non-Hispanic white					
Hispanic					
non-Hispanic black					
other					
Smoking					
Never smoked					
current smoker					
former smoker					
Alcohol use					
None					
Moderate (1-6 drinks/wk)					
Heavy (≥7 drinks/wk)					

BMI		
<18.5		
18.5-24.9		
25-29.9		
≥30		
Primary diagnosis	NA	NA
Leukemia		
Hodgkin Lymphoma		
NHL		
Bone cancer		
Soft tissue sarcoma		
CNS		
Neuroblastoma		
Kidney (Wilm's)		
Radiation dose	NA	NA
Ovarian uterine		
No RT		
1-5 Gy		
5.1-10 Gy		
10.1-20 Gy		
>20 Gy		
Hypothalamic/pituitary dose	NA	NA
No RT		
1-20 Gy		
20.1-30		
>30 Gy		
Cyclophosphamide Equvalent dose (grams)	NA	NA
0		
1-10		
11-20		
21-30		
≥30		
CCNU	NA	NA
Yes		
no		
Cisplatin	NA	NA
Yes		
no		
Cyclophosphamide	NA	NA

Yes no		
Cytosine arabinoside Yes No	NA	NA
Doxorubicin Yes No	NA	NA
Nitrogen mustard Yes No	NA	NA
Procarbazine Yes Bo	NA	NA
Vinblastine Yes No	NA	NA
VM26 Yes No	NA	NA
VP16 Yes No	NA	NA
History of BMT Yes No	NA	NA
History of relapse Yes No	NA	NA
History of 2nd malignancy (prior to baseline >18 years) Yes No	NA	Na

Table 2: Relative risk of infertility in female survivors of childhood cancer compared to siblings.

	Survivor		Sibling[1]	
Group	N (%)	RR(95% CI)	N (%)	RR(95% CI)
Infertility present[2]				1.0
Visit to a doctor For infertility				1.0
Doctor found a Reason for infertility				1.0
Medication to help you Get pregnant				1.0
Any infertility treatment				1.0
Ever became pregnant				1.0

[1]Sibling group is referent when calculating relative risks
[2]Infertility defined as trying to 1 year to get pregnant without success (M5=Y)

Table 3: Relative risk of infertility by demographic, disease and treatment characteristics in survivors of childhood cancer.

Characteristic	n	%	RR (95% CI)
Age at diagnosis			
0-4			
5-9			
10-14			
≥15 (referent)			
Age at baseline			
<20			
20-24			
25-29 (referent)			
30-34			
35-39			
Educational level			
no high school or GED (referent)			
high school or GED			
some college, no bachelor's degree			
bachelor's degree or higher			
Ethnicity			
non-Hispanic white (referent)			
Hispanic			
non-Hispanic black			
other			
Smoking			
Never smoked (referent)			
current smoker			
former smoker			
Alcohol use			
None (referent)			
Moderate (1-6 drinks/wk)			
Heavy (≥7 drinks/wk)			
Marital status			
never married (referent)			
currently married			
formerly married			
BMI			

<18.5
18.5-24.9 (referent)
25-29.9
≥30

Primary diagnosis
Leukemia (referent)
Hodgkin Lymphoma
NHL
Bone cancer
Soft tissue sarcoma
CNS
Neuroblastoma
Kidney (Wilms)

Radiation dose
Ovarian uterine
No RT (referent)
1-5 Gy
5.1-10 Gy
10.1-20 Gy
>20 Gy

Hypothalamic/pituitary dose
No RT (referent)
1-20 Gy
20.1-30
>30 Gy

Cyclophosphamide equivalent dose
0 g (referent)
1-10 g
11-20 g
21-30 g
≥30 g

CCNU
No (referent)
Yes

Cisplatin
No (referent)
Yes

Cyclophosphamide

No (referent)
Yes

Cytosine arabinoside
No (referent)
Yes

Doxorubicin
No (referent)
Yes

Nitrogen mustard
No (referent)
Yes

Procarbazine
No (referent)
Yes

Vinblastine
No (referent)
Yes

VM26
No (referent)
Yes

VP16
No (referent)
Yes

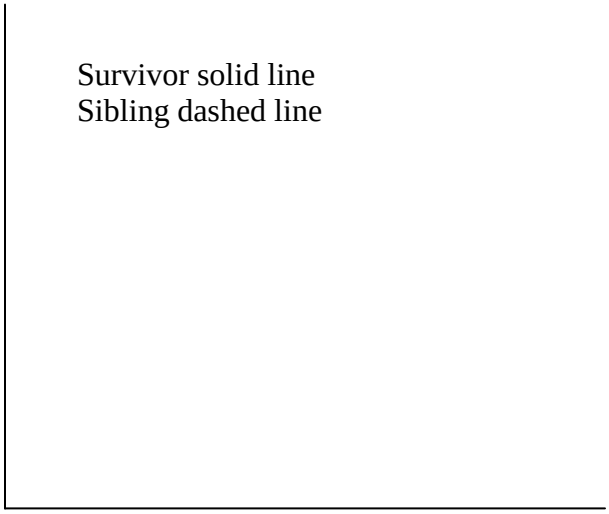
History of BMT
No (referent)
Yes

History of relapse
No (referent)
Yes

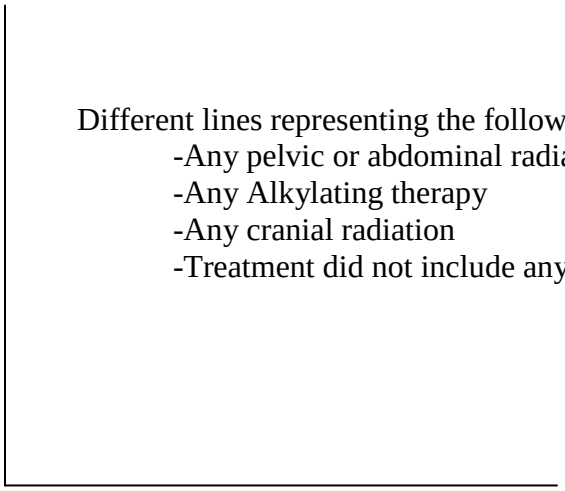
History of 2nd malignancy
(prior to baseline ≥18 years)
No (referent)
Yes

Figure 1: Time to first pregnancy among childhood cancer survivors and siblings for those that reported a pregnancy. (for this % refers to the percentage of those reporting a first pregnancy that were pregnant by that month, will equal 100% at the end)

a.



b.



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