Analysis Concept Proposal

1. Study Title

Updated Analysis of Non-Surgical Premature Menopause in the Childhood Cancer Survivor Study

2. Working Group and Investigators

CCSS Working Group:
Chronic Disease

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3. Background and Rationale

Contemporary combined modality therapy has resulted in a five year relative survival rate of 80% in children and adolescents diagnosed with cancer.[1] With improved survival rates however comes a greater recognition of the long term complications of treatment,[2] including premature menopause (the onset of menopause prior to the age of 40).[3] Premature menopause has obvious implications for reproductive capacity but it also impacts quality of life and psychosexual functioning[4] and increases the risk for developing osteoporosis and cardiovascular disease.[5] The ability to lead full reproductive lives has been identified as

important to young cancer survivors and their families.[6] With an estimate that one in 570 young adults in prime reproductive years (20-40 years of age) is a survivor of childhood cancer,[7] issues of reproductive health represent a significant public health concern in this population.

The gonadotoxic profile of alkylating agents, such as cyclophosphamide, busulfan, and ifosfamide, have been well described.[5, 8-12] The mechanism of action related to gonadotoxicity from chemotherapeutic agents is direct toxicity to the ovarian follicles, resulting in diminished ovarian reserve.[13] Retrospective studies have shown increasing age at treatment, type of disease and increasing cumulative doses of alkylating agents to be associated with increasing risk of ovarian failure.[14-16] In particular, post menstrual adolescents appear to be at greater risk from gonadotoxicity due to relatively smaller follicular pool present at the start of therapy compared to pre-pubertal girls.[15] Pelvic radiation therapy is also known to cause follicular destruction followed by reproductive dysfunction and this also demonstrates a dose dependent effect.[5, 11, 17, 18] Cross sectional studies of survivors of pediatric cancers have shown that, years after treatment, primordial and antral follicles are diminished compared to controls, even in patients who are not menopausal and who continue to menstruate.[19-21] Cranial radiation can also diminish fertility exerting a central effect on the hypothalamic-pituitary axis, causing a dysregulation of normal ovulation through hormonal control without impacting ovarian reserve. Subjects with cessation of menses due to central causes are generally not included in the definition of “premature menopause” as the underlying pathophysiology is different and because these individuals are amenable to corrective therapies (e.g., LH/HCG/FSH or GnRH stimulation) that can restore both ovarian function and fertility, in contrast to women with premature menopause due to direct ovarian damage.

Analysis of the CCSS 2000 questionnaire data clearly demonstrated that survivors of childhood cancer are at increased risk of premature menopause due to direct effects of chemotherapy and radiation on the ovaries.[5, 12] As a result of treatment, non-surgical premature menopause (NSPM) was 13 times higher among survivors than among sibling controls. Independent risk factors included attained age, exposure to increasing doses of alkylating agents, increasing dose of radiation to the ovaries and a diagnosis of Hodgkin Lymphoma.[5] However, this initial analysis in 2000 was based on only 65 cases of NSPM and significant findings were associated

with wide confidence intervals. Moreover, while a dose response was noted for NSPM and ovarian RT, this was only observed in survivors with diagnoses other than Hodgkin Lymphoma. The latter finding likely reflects a type 2 error due to small numbers of cases. The follow-up questionnaire from 2007 offers the opportunity to re-examine the rates of NSPM with longer follow-up and to provide a more reliable incidence rate. A preliminary examination of the data indicates there will be approximately 105 confirmed NSPM cases; the exact number will not be known until the cases have been reviewed in detail. With this increased number of cases and the increase in person years assessed, it will be possible to better define the risk factors associated with NSPM, including assessing the impact of individual agents, the role of other agents and whether there is a dose response effect of ovarian RT in survivors of Hodgkin Lymphoma. In addition, we anticipate that we will be better able to assess fertility in those destined to develop NSPM as well as to further clarify which individuals are at lower risk for the development of NSPM. All of these more robust analyses will strengthen and elaborate on the conclusions from the initial analysis

4. Specific Aims /Research hypotheses

Specific Aim 1: Compare the cumulative incidence of NSPM in the survivor population as assessed by the 2000 and 2007 CCSS questionnaire to sibling controls.
Hypothesis: Relative risk for NSPM will be higher in the survivor population than for sibling controls. We will improve the power in the current analysis compared to the analysis of the 2000 questionnaire alone, improving the reliability of our estimate.

Table 1. Impact on Power of additional cases.

Number of additional (/total) cases in the new analysis	Power (OR=2.0, risk factor: 50% Y, 50% N)
65 / 2819 (initial analysis)	0.885
90 / 2941	0.961
105 / 2941	0.979
120 / 2941	0.989

Specific Aim 2: Identify treatment, disease and demographic characteristics that predict risk of NSPM identified by the 2007 follow-up.
Hypothesis: Risk factors for NSPM will include attained age, time from diagnosis, exposure to increasing doses of radiation to the ovaries, increasing alkylating agent score and a diagnosis of Hodgkin Lymphoma.

Exploratory Aim 1: Identify rates of pregnancy and live births preceding diagnosis of NSPM.
Hypothesis: Within the survivor population, survivors reporting NSPM will have lower rates for pregnancy and live births than those that do not report NSPM, at the same ages.

5. Analysis Framework

A. Outcome of Interest: Relative Risk of Non-Surgical Premature Menopause

B. Eligibility

Patients/Cases

Inclusion Criteria:

1. female
2. older than the age of 18 at the time of the 2007 questionnaire
3. completed the 2000 and/or the 2007 survey follow-up questionnaire

Exclusion Criteria:

1. other diagnosis associated with ovarian dysfunction (e.g. Turner's)
2. ceased spontaneous menstruation within the first five years following cancer diagnosis
3. received more than 30Gy RT to the brain and/or had a primary tumor in the region of the hypothalamus-pituitary gland
4. questionnaire completed by someone other than the participant
5. developed a second malignancy before the onset of menopause
6. incomplete or unavailable radiation data
7. undergone bilateral oophorectomy and/ or hysterectomy

Sibling Controls

Eligibility:

1. females older than the age of 18
2. achieved spontaneous menarche

C: Dependent Variable: Incidence of Non Surgical Premature Menopause

Definition: Prior to the age of 40, no spontaneous menses for at least 6 months, exclusive of pregnancy, and use of hormonal medications. Age at premature menopause will be defined as age at most recent menstrual period.

2000 Questionnaire:

Question 8: pregnancy

Question 19: Menstrual History

2007 Questionnaire :

Questions: F13, F14, F15, F16: Menstrual History

Questions Q1, 2: Pregnancy History

D. Exploratory Variables:

1. Current Age
2. Age at Diagnosis
3. Time from Diagnosis
4. Diagnosis
5. Alkylator Dose Exposure
6. Chemotherapy Exposure
7. Radiation Exposure
8. Pregnancy (yes/no plus age at event)
9. Live Births (yes/no plus age at event)
10. Smoking history

Statistical Analysis

Descriptive analyses, including univariable summaries of survivors and siblings, with NSPM and without NSPM, will be evaluated, and comparisons made using standard methods. Number of subjects developing NSPM prior to entry to the cohort (5 years after diagnosis) will be reported descriptively, though this number is expected to be small. For analyses of prospective NSPM, person-years at risk of NSPM will be calculated as the number of years between either menarche or entry to CCSS cohort (whichever comes last) and the most recent menstrual period. Poisson regression models will be used to compare risk of NSPM for survivors vs. siblings, adjusted for attained age, smoking and BMI. Similar models will be used for evaluation of risk factors among the survivor group. For the comparison between survivors and siblings, a GEE model will be utilized with robust variance estimates, to account for within-family correlation. Key risk factors to be examined in the within-survivor models are listed above and will first be evaluated in univariate models for NSPM. Factors associated in univariate analysis with $p<0.10$ will be incorporated in multivariable models and factors included in a final model determined based on minimizing Akaike information criteria.

Cumulative incidence curves, treating death as a competing risk event, will be evaluated for premature menopause, to illustrate the incidence of NSPM with increasing age in both survivors and siblings, and within groups defined by identified risk factors from regression analyses. Note that these curves will need to begin at age 26, the latest age at which a subject enters the cohort (5 years after age 21), and will be among subjects who have not yet reached premature menopause. If a sufficient number of cases occur within a broad enough range of ages, we will also consider estimating conditional cumulative incidence curves, among subjects without NSPM at a given age, representing the risk of developing NSPM later.

For the exploratory aim, to examine whether rates of pregnancy and live births are lower among women who will eventually develop NSPM, we will compare pregnancy rates between those with and without NSPM. For this, all pregnancies and live births reported will be utilized between study entry or menarche, (whichever comes last), and the first of NSPM, or age 40. Poisson regression will be used to calculate adjusted age-specific rates (within 5 year age bands) for pregnancy per 1000 person-years at risk. Rates will be compared between subjects who

develop NSPM and those who don't based using parameters from the Poisson model, adjusted for current age, race/ethnicity, income, level of education, marital status/living as married.

All statistical tests will be two-sided and considered significant if $p<0.05$.

Examples of Tables and Figures

Tables

1. Characteristics of survivors with and without nonsurgical premature menopause

Variable	Total (n= X)	NSPM (n =X)	No NSPM (n=X)	p
Mean Age at Diagnosis, (range), y				
Mean age at Menarche, (range), y				
Mean Age at Study, (range), y				
Diagnosis, n (%)				
Leukemia				
Hodgkin Lymphoma				
Non Hodgkin Lymphoma				
Bone Tumors				
Kidney tumors				
Sarcomas				
Neuroblastoma				
Brain Tumors				
Treatment n (%)				
Surgery Only				
Chemotherapy Only				
Radiation Only				
Chemotherapy + Radiation				
Surgery + Chemotherapy				
Surgery + Radiation				
Surgery + Chemotherapy + Radiation				
Alkylating Agents				

Alkylating Agent Score				
0				
1				
2				
3				
Abdominopelvic RT				
Radiation to ovaries, cGy				
No RT				
1-99				
100-999				
≥ 1,000				
Stem Cell Transplant				

2. Risk factors for non-surgical premature menopause among survivors

Variable	RR	95% CI	P-value
Attained age (years)			
21-25			
26-30			
31-35			
36-40			
Diagnosis			
Hodgkin Lymphoma			
Other			
Alkylating Agent Score			
0			
1			
2			
3			
Abdominopelvic RT			
No			
Yes			
Radiation to ovaries, cGy			
No RT			
1-99			
100-999			
≥ 1,000			
Stem Cell Transplant			
Smoking History			
Never Smoker			
Ever Smoker			
BMI			
≤ 24.9			
25-29.9			
≥30			

3. Age-specific pregnancy rates per 1000 person-years for survivors with non-surgical premature menopause vs survivors without.

	Ages 21-25	Ages 26-30	Ages 31-35	Ages 36-40	All Ages (21-40)
NSPM					
Non-NSMP					
P-value					

4. Age-specific live birth rates per 1000 person-years for survivors with non-surgical premature menopause vs. survivors without.

	Ages 21-25	Ages 26-30	Ages 31-35	Ages 36-40	All Ages (21-40)
NSPM					
Non-NSMP					
P-value					

Figure 1. Cumulative incidence curve of non-surgical premature menopause in survivors vs. sibling controls

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