CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

Study Title: Age of Menopause in Childhood Cancer Survivors and the Association with Cardiovascular Events and Bone Health

Working Group and Investigators: This proposed analysis will be within the Chronic Disease Working Group with secondary oversight by the Epidemiology/Biostatistics Working Group. Proposed investigators will include:

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Terminology clarification:
Menopause: The permanent cessation of menses and end of reproductive window, pregnancy is no longer possible. For this study, we will use the criteria of sustained cessation of menses for ≥6 months. This is a time point.

For the purposes of this analysis, we seek to identify menopause, which is referred to as “premature” if it occurs prior to the age of 40 and “early” which occurs before the age of 45.

Females exposed to cranial or CNS-directed radiation are at risk for central hypogonadism due to hypothalamic or pituitary injury. These individuals may present with amenorrhea or ‘early menopause’ due to secondary ovarian dysfunction. Given this mechanism, these individuals will be analyzed separately to avoid misclassification of POI.

Background and Rationale:

Females are born with a finite supply of follicles that naturally decline with age. Menopause occurs when the non-renewable follicle number falls below a critical threshold, menses cease and pregnancy is no longer possible.[1] Data from studies performed in the 1990s and 2000s show that most women in the US experience menopause between age 40 and 58 with a mean age at menopause of approximately 52 years.[2–6] Approximately 10% of women experience “early” menopause, that is menopause before age 45 years and 1% before age 40, referred to as premature menopause indicating either early cessation of reproductive function or culmination of accelerated reproductive aging throughout the premenopausal years.[5–7]

Women who experience menopause at a younger age may have a shorter total duration of premenopausal estrogen exposure than women with later menopause. Premature and early menopause have been associated with increased rates of cardiovascular diseases, with more significant cardiovascular disease occurring the earlier that menopause occurs.[8–14] An analysis from the Women's Health Initiative demonstrated that in post-menopausal women, shorter total reproductive duration was associated with higher risk of incident heart failure.[15] Based on these studies the American College of Cardiology/American Heart Association has updated their primary prevention and cholesterol guideline to include a history of premature menopause in cardiovascular risk assessments and to guide statin prescription for asymptomatic women in midlife at intermediate risk of atherosclerotic cardiovascular disease.[16] Early menopause is cited as an additional individual risk factor in those individuals who are at borderline risk.[17,18] [17,18] Both nonsurgical and surgical premature menopause has also been associated with increased risk for osteoporosis, psychosexual dysfunction, mood disorders, and cognitive decline.[8,14,16,19] Additionally, 2024 guidelines developed by European Society for Human Reproduction and Embryology recommend hormone therapy for women with POI until the usual age of menopause for primary prevention of cardiovascular disease regardless of estrogen deficiency symptoms or not as well as to maintain bone density and prevent osteoporosis.[14] For this proposal, we will focus on the relationship between early menopause and cardiovascular and bone health.

When analyzing the relationship between age of menopause and the risk of atherosclerotic cardiovascular disease and bone health in survivors of childhood cancer and their siblings, it is essential to account for various covariates that may impact these outcomes. Several factors have been identified as important covariates in this context, including tobacco use, age, race/ethnicity, obesity, hypertension, diabetes, dyslipidemia, hormonal therapy, and pregnancy history.

1. Tobacco Use: Tobacco use is a significant risk factor for both cardiovascular disease and bone health.[20] Smoking has been linked to an increased risk of ischemic heart disease, as it promotes the development of atherosclerosis and impairs cardiovascular function. Moreover, smoking can contribute to decreased bone mineral density, leading to a higher risk of fractures.
2. Age: Women who experience early menopause (before the age of 45) have been found to have an increased risk of cardiovascular disease and osteoporosis-related fractures.[16,19,21,22] Additionally, age influences the prevalence of other risk factors such as obesity, hypertension, and diabetes, which can impact both menopause age and subsequent health outcomes.
3. Race/Ethnicity: Race and ethnicity play a significant role in determining health disparities and susceptibility to certain diseases. Different racial and ethnic groups may have varying rates of menopause and different risks of developing ischemic heart disease and fractures.[23]
4. Obesity: Obesity is a well-established risk factor for cardiovascular disease and bone fractures.[24,25] Excess weight can contribute to the development of hypertension, dyslipidemia, and diabetes, all of which are associated with an increased risk of ischemic heart disease.
5. Hypertension, Diabetes, and Dyslipidemia: These three conditions—hypertension, diabetes, and dyslipidemia—are known risk factors for cardiovascular disease.[26] They can lead to the development of atherosclerosis, which increases the likelihood of ischemic heart disease. Additionally, hypertension and dyslipidemia have been associated with an increased risk of fractures.
6. Hormonal Therapy: It is important to consider hormonal therapy as a covariate in this analysis. Estrogen replacement therapy has been associated with changes in cardiovascular risk and bone health.[22,27]
7. Pregnancy History: Pregnancy history, including factors such as the number of pregnancies, can affect menopause age and subsequent health outcomes. Women who have had multiple pregnancies tend to

experience menopause at a later age. Additionally, these factors may have independent effects on cardiovascular health and bone mineral density.[28,29]

A subset of childhood cancer survivors (CCS) are at increased risk of accelerated ovarian germ cell depletion from treatment that manifests as premature menopause and associated reproductive sequelae.[30–32] Risk factors associated with premature menopause in CCS, when compared with sibling controls, include exposure to increasing doses of radiation to the ovaries, increasing cumulative dose of alkylating agents, procarbazine, stem cell transplant, and a diagnosis of Hodgkin lymphoma.[30–33] Prior studies have shown that Norwegian women who underwent unilateral oophorectomy entered menopause about one year earlier than those with intact ovaries, though additional impacts on CCS remain unexplored.[34] While premature menopause has been studied, the mean age of menopause among CCS and the prevalence of early menopause remain largely unknown. A French study found that women with a history of childhood cancer entered menopause at a median age of 44—eight years earlier than the general population.[31]

In addition to ovarian toxicity, one-third of CCS face severe or life-threatening medical complications from treatment 30 years after diagnosis, with early mortality from cardiovascular disease being a leading cause of non-relapse mortality.[35–38] It is not currently understood whether earlier age at menopause in CCS is associated with increased prevalence of atherosclerotic cardiovascular disease and diminished bone health (fractures and osteopenia). However, studies from the St. Jude Lifetime Cohort have shown that low bone mineral density and frailty were concurrently associated with premature ovarian insufficiency.[32] CCSS questionnaires have asked participants about age at menarche, current menstrual status, age at last menstrual period, type of menopause (surgical or nonsurgical), as well as cardiac outcomes.

In the proposed analyses we aim to describe the median age at menopause (a novel analysis) in addition to the prevalence and incidence of early (novel analysis) and premature menopause (updated analysis given aging population) in CCS. We will also investigate whether premature or early menopause is and independent association between age at menopause and development of atherosclerotic cardiovascular disease given the known association in the general population.

SPECIFIC AIMS/OBJECTIVES/REARCH HYPOTHESES:

Aim 1.0: Describe the distribution of age at menopause in childhood cancer survivors and siblings, including the prevalence of premature menopause and early menopause.

Aim 1.1 Describe the distribution of age at menopause by treatment exposures (i.e., to ovarian and cranial radiotherapy, alkylating agent, and unilateral oophorectomy).

Hypotheses: Overall, CCS will have a lower mean age of menopause compared to siblings and lower than the national mean of 52. The prevalence of premature menopause will be similar to prior publications (around 10%). An additional subset of subjects in the cohort will report early menopause. CCS with exposures to radiation involving the ovaries, higher doses of alkylating agents, hematopoietic stem cell transplant, and/or unilateral oophorectomy will have an earlier age at menopause compared to survivors who have not.

Aim 2: Evaluate the association of age at menopause with the development of atherosclerotic cardiovascular disease (coronary artery disease and ischemic stroke) in childhood cancer survivors compared to siblings after adjusting for tobacco exposure, attained age, race/ethnicity, obesity, hypertension, diabetes, dyslipidemia, use of hormonal therapy, pregnancy history and cancer directed therapy exposure.

> *Hypothesis: CCS who enter menopause at an earlier age will have an increased rate of* coronary artery disease, ischemic stroke*, compared to survivors and siblings who enter menopause later after controlling for radiation and anthracycline exposure. Additionally, premature or early menopause will be an additional independent risk factor for ischemic heart disease.*

Analysis Framework:

Study Population:

Inclusion Criteria:

1. female
2. older than the age of 18 at the time of the 2017 questionnaire
3. completed the 2000 and/or 2007 and/or 2014 and/or 2019 survey follow-up questionnaire

Exclusion Criteria:

1. other diagnoses associated with ovarian dysfunction (e.g. Turner's)

Exposures of Interest:

Aim 1:

- Cancer Treatment
  - Chemotherapy
    - chemotherapy, yes/no
    - alkylating agent dose CED g/m^2
    - Platinum agents (carboplatin/cisplatin) mg/m^2
  - Hematopoietic stem cell transplant
  - Radiation therapy
    - cardiac radiation, yes/no
    - ovarian radiation, yes/no
    - cardiac radiation dose, Gy
    - ovarian radiation dose, Gy
    - cranial radiation dose, Gy
  - Unilateral oophorectomy

Aim 2:

- Age at menopause.

Outcome(s) of Interest:

Aim 1:

- Age of menopause in childhood cancer survivors and siblings. (First reported age at menopause)

Aim 2

- Atherosclerotic cardiovascular disease based on the chronic conditions dataset
  - coronary artery disease (grade 3+)
  - stroke (grade 4+)

Adjustment Variables:

- Health Behaviors: Tobacco (Ever smoker)
- Demographic: Attained Age, Race/Ethnicity
- Medical Conditions: Ever Obese, Ever hypertension, Ever diabetes, Ever dyslipidemia; for hypertension, diabetes, and dyslipidemia, limited to chronic health conditions grade 2+ (requiring medications)
- Medications: Ever use of hormonal therapy (estrogen)
- Reproductive: Pregnancy history and number of births prior to event
- Cancer Treatment: Chemotherapy, Radiation therapy, Surgery (specifically unilateral oophorectomy)
- Physical Activity (metabolic equivalent task [MET], most recent reported)

Statistical Methods:

Aim 1.0. We will use descriptive statistics to describe the median age at menopause and report median, quartiles, and range in CCS and siblings. For Aims 1 and 2, we will analyze CCS who received CNS radiation as a separate subgroup. The number and proportion of survivors and siblings who never have menarche will be reported separately. For CCS and siblings who have menarche, we will describe cumulative incidence of menopause according to attained age.

Aim 1.1. We will compare age at menopause in CCS by treatment exposure including chemotherapy (chemotherapy, yes/no; alkylating agent dose in CED, g/m^2; procarbazine, g/m^2; hematopoietic stem cell transplant, yes/no), radiation therapy (radiation, yes/no; ovarian radiation dose, Gy), surgery (specifically unilateral oophorectomy) and with siblings using Fine and Gray's model using death and SMN as the competing risk events, adjusting for attained age, pregnancy history, number of births and ever use of hormonal therapy.

Additionally, age at menopause in CCS who have had a unilateral oophorectomy will be reported and its comparisons will be made between this population and those without unilateral oophorectomy and siblings. Fine and Gray's model with death and SMN as the competing risk events will be used, adjusting for attained age, pregnancy history, number of births and ever use of hormonal therapy as well as treatment exposure including chemotherapy (chemotherapy, yes/no; alkylating agent dose, CED mg/m^2; procarbazine, g/m^2; hematopoietic stem cell transplant, yes/no), and radiation therapy (radiation, yes/no; ovarian radiation dose, Gy).

Aim 2. We will analyze all incident atherosclerotic cardiovascular disease (coronary artery disease and stroke). Using time-dependent covariates of "early menopause" and "normal menopause", we will examine whether women with early menopause had higher risk of incident atherosclerotic cardiovascular disease at a younger age than those with later menopause and siblings, HRs and 95% CIs will be adjusted for attained age during follow up, race/ethnicity, time-dependent covariates of obesity, smoking, and hormone therapy use. Since age at menarche and parity are also potential confounders, the models will additionally adjust for these covariates as well as treatment exposures. We will also take in to consideration patients who have cardiovascular disease prior to age at menopause and determine how best deal with these data based.

We are aware there are potential concerns with self-reported menopause including participants reporting different ages of onset. Therefore, we will plan to use the age of menopause at the first time it is reported. We

are also aware that there are other confounding variables such as duration of hormonal exposure that may confound these results however this issue also arises in general population analyses as well.

Example Tables

Table 1: Basic Demographic Data and Characteristic

Characteristic	Survivors		Siblings
	No CNS Radiation	CNS Radiation	
Race/Ethnicity			
Age at cancer diagnosis			N/A
Age at last follow-up			
Tobacco (Ever smoker)			
Obese			
Hypertension			
Diabetes			
Dyslipidemia			
Hormonal therapy (estrogen)			
Number of pregnancies			
Number of live births			
Oophorectomy			
Chemotherapy			N/A
Alkylator Exposure			N/A
Hematopoietic Cell Transplant			N/A
Total Body Irradiation			N/A
Ovarian Radiation			N/A
Cardiac Radiation			N/A

Table 2: Descriptive statistics at menopause for childhood cancer survivors.

	Survivors		Siblings
	No CNS Radiation	CNS Radiation	
Median age at menopause (median, quartiles, range)			
Cumulative Incidence of Menopause according to attained age			

Table 3: Hazard model for age at menopause in childhood cancer survivors by treatment exposure compared with siblings using Fine and Gray's model.

Treatment Exposure	Exposure Detail	Survivors (No CNS Radiation) HR (95% CI)	Siblings
Chemotherapy	Chemotherapy (y/n) Alkylating agent dose (CED mg/m2) Platinum Agents (mg/m2)		
Hematopoietic stem cell transplant			
Radiation Therapy	Radiation (y/n) Ovarian radiation Total Body Irradiation (TBI)		
Surgery	Unilateral Oophorectomy		

*Death and SMN as the competing risk events

**Pregnancy history, number of births and ever use of hormonal therapy.

CED = Cyclophosphamide Equivalent Dose

TBI = Total body irradiation

Table 4: Incident atherosclerotic cardiovascular disease (coronary artery disease and stroke) in childhood cancer survivors and siblings with “early menopause” and “normal menopause”.

	Survivors (No CNS Radiation)		Siblings	
	Early Menopause HR (95% CI)	Normal Menopause HR (95% CI)	Early Menopause HR (95% CI)	Normal Menopause HR (95% CI)
Coronary artery disease				
Stroke				
Composite atherosclerotic cardiovascular disease (coronary artery disease + stroke)				

*Adjusted for attained age during follow up, race/ethnicity, time-dependent covariates of obesity, smoking, and hormone therapy use. age at menarche and parity.

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