

Childhood Cancer Survivor Study Analysis Concept Proposal

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Title: Abnormal Timing of Menarche in Survivors of Childhood Central Nervous System Tumors

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Chronic Disease Working Group

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Background and Rationale

The onset of puberty and menarche is a complicated process the timing of which is regulated by the hypothalamic-pituitary (H-P) axis. In girls, the first signs of puberty are breast development (thelarche) and a growth spurt at an average age of 10 years¹. This is followed by the development of pubic hair and within two years the beginning of menses (menarche). The average age of menarche is 12.8 years. Females beginning menses prior to age 10 are considered early and those beginning after age 16 are considered late.

Damage to the H-P axis can alter the regulation and timing of puberty and menarche in addition to the other hormone systems regulated by the H-P axis such as growth hormone, thyroid hormone, prolactin, cortisol, and vasopressin. Children with central nervous system tumors in proximity to the H-P axis or who have a surgical resection or radiation therapy in this region are at particular risk for injury². Growth hormone deficiency is the most common deficiency after hypothalamic injury, however central hypothyroidism and alterations in pubertal timing are common as well³.

Under normal conditions the anterior pituitary secretes luteinizing hormone (LH) and follicle stimulating hormone (FSH) in a pulsatile manner based on the episodic release of gonadotropin-releasing hormone (GnRH) from the hypothalamus. This GnRH stimulus is actively inhibited between 6 months of age and the onset of puberty. Central precocious puberty appears to result when GnRH secretion is disinhibited².

The strongest evidence that cranial radiation causes early menarche comes from extensive acute lymphoblastic leukemia literature in which cranial radiation in doses between 18-24 Gy was used for CNS prophylaxis of disease. Early case series

demonstrated earlier menarche, tendency toward earlier sexual development, and lower final height in girls⁴⁻⁷. Girls who received 18 Gy prior to age 8 were at particular risk for early menarche suggesting that the young immature H-P axis may be more sensitive to radiation effects. Notably when girls received 24 Gy of craniospinal radiation the opposite effect occurred; menarche was delayed⁸. Additional studies have suggested that girls are particularly sensitive to the effect of radiation and are more likely than boys when exposed to radiation to begin puberty at an earlier age^{9,10}. Oberfeld and others have speculated that this sexual dichotomy may be due to the increased obesity seen in girls treated for ALL leading to premature puberty¹¹⁻¹⁴.

There have been fewer studies addressing the issue of altered timing of menarche in female survivors of CNS tumors. However, it appears that while lower doses of cranial radiation (18-40 Gy) increase the incidence of early puberty, higher doses (> 40 Gy) are more likely to be associated with gonadotropin deficiency¹⁵⁻¹⁷. In patients who receive craniospinal radiation, scatter to the ovaries may put females at risk for primary hypogonadism and thus delayed or absent menarche.

We, therefore propose a retrospective cohort study to evaluate the incidence of abnormal timing of menarche in survivors of childhood CNS tumors. Using the large sample provided by the CCSS cohort will allow the most powerful investigation of this question to date.

Primary Aim:

- To determine the incidence of 1) early (< 10 years old) and 2) delayed (> 16 years old) menarche in 5 year survivors of childhood central nervous system (CNS) tumors.

Secondary Aims:

- To assess in detail the relationship between dose of CNS irradiation to the H-P axis and risk of early or delayed menarche
- To assess in detail the relationship between dose of craniospinal irradiation and risk of delayed menarche
- To identify other risk factors for early and delayed menarche including age at radiation, chemotherapeutic agents, and tumor type
- To compare/correlate the incidence of early and delayed menarche to other markers of hypothalamic injury (central hypothyroidism, growth hormone deficiency)
- To determine the impact of early menarche on final height in survivors of childhood CNS tumors

Hypotheses:

- Early menarche will have increased incidence in survivors of childhood CNS tumors who receive moderate doses of radiation to the hypothalamus/suprasellar/chiasmatic regions in comparison to participants who do not receive radiation
- Delayed menarche due to primary hypogonadism will occur more often in survivors of childhood CNS tumors who received spinal radiation and high doses of alkylating agents as compared to participants who do not receive spinal radiation
- Shorter final height will occur more often in survivors who experience premature menarche than in those with normal menarchal timing, controlling for the effects of craniospinal radiation

Analysis Framework:

(a) Population

- **Cases:** Female five-year survivors of childhood CNS tumors who were diagnosed prior to the onset of menarche and completed (or proxy completed) both the baseline and first follow-up questionnaire

Exclusions: follow-up in this time-to-event analysis will be truncated at SMN or recurrence or death (competing risk event).

- **Controls:** Female siblings of survivors of CNS tumors for overall incidence. For analyses of dose response and other possible risk factors, participants who did meet inclusion criteria but did not receive radiation will serve as controls.

(b) Outcomes of Interest

- **Menarche:** age at menarche (follow-up #1, Q. 19a) among women who had a natural menstrual period, assessment of post-menarchal regularity (follow-up #1, Q. 19c). Early menarche for this study will be defined as age <10 and delayed menarche will be age > 16 years old at time of first menses.

- **Other Hypothalamic Dysfunction:** hypothyroidism (Q.E2), Growth hormone deficiency and history of growth hormone supplementation (Q. E8, E9 – either of these = yes)

- **Final Height:** Height obtained at the age of 20 years or later on either the baseline or follow-up survey #2.

(c) Variables

Exposure variables:

- CNS radiation dosimetry to pituitary (H-P Axis)
- Radiation dosimetry to craniospinal axis

Potential confounders:

- Age at radiation (categorize as 0-8 years or >8 years)
- Tumor type
- history of surgical resection
- BMI
- Ethnicity
- Year of Menarche (secular trend toward younger age of menarche)
- Chemotherapy (general, yes/no)
 - alkylating agents (yes/no, or use of “alkylator score”)

(d) Analytical plan;

Descriptive analysis:

- Incidence of early/delayed menarche in cases and controls
- Distribution of CNS tumor by diagnosis
- Distribution of CNS tumors by treatment category (no treatment, cranial radiation only, spinal radiation only, chemotherapy only, chemotherapy + cranial radiation, chemotherapy + spinal radiation, Cranial + spinal radiation)
- Distribution of participants across dose ranges of radiation to pituitary region
- Distribution of patients across radiation dose ranges to craniospinal region
- Incidence of growth hormone deficiency and hypothyroidism
- Distribution of age for CNS tumors
- Distribution of BMI prior to menarche
- Incidence of short stature

Univariate analysis:

- Hazard Ratio of early/delayed menarche by CNS tumor diagnosis
- Hazard Ratio of early/delayed menarche by treatment category (no treatment, cranial radiation only, spinal radiation only, chemotherapy only, chemotherapy + cranial radiation, chemotherapy + spinal radiation, Cranial + spinal radiation)
- Hazard Ratio of early/delayed menarche by radiation dose to pituitary
- Hazard Ratio of early/delayed menarche by dose to relevant locations
- Hazard Ratio of early/delayed menarche by: age at time of radiation, BMI at time of radiation, ethnicity

- Correlations of early/delayed menarche with growth hormone deficiency and hypothyroidism
- Odds of short stature by premature menarche status
- Correlation of short stature and premature menarche
- Cumulative Incidence curves for time to menarche with above variables. Relapse, SMN and death will be treated as competing risk events.

Multivariate analysis:

Cox regression on time to menarche will be used with the above variables. Two outcomes will be evaluated in this model. The first will be time to early menarche (< 10 years of age). All eligible subjects will be included and follow-up time will be to menarche or age 10, whichever comes first. In the second analysis, time to late menarche (> 16 years of age) will be the outcome of interest. For this analysis, subjects will be censored at menarche that occurs prior to 16 years of age. For both the early and late menarche analyses, relapse, SMN and death occurring prior to menarche will be treated as competing risk events and for the Cox model, follow-up will be censored at those event times. Otherwise, follow-up will be censored at the time of FU1 response.

Assumptions of the Cox proportional hazards model will be evaluated. If they are not met and it is deemed necessary, polytomous logistic regression will be carried out instead.

Multivariate logistic regression will be used to analyse the correlations of early/delayed menarche with growth hormone deficiency and hypothyroidism

Tables and Figures:

Table 1: Characteristics of Female survivors of CNS tumors and Sibling Controls

Characteristic	Survivors (n=)	Siblings (n=)
Age at study entry, years		
Median		
Range		
Year of Birth, %		
Pre-1960		
1960-1969		
1970-1979		
1980-1986		
Ethnicity		
Caucasian, non Hispanic		
Black, non-Hispanic		

Hispanic/Latino		
Asian/Native American/Pac. Islander		
Other		
Year at Diagnosis, years		
Median		
Treatment Exposure, %		
No Treatment		
Any Surgery		
Cranial radiation only (focal and whole brain)		
Craniospinal radiation only		
Cranial + Craniospinal radiation, no chemo		
Chemotherapy only		
Chemo + any radiation		
Dose to Pituitary		
None		
0-2400 cGy		
2400-3600 cGy		
3600-5000 cGy		
> 5000 cGy		
Dose to Craniospinal Axis		
None		
0-2400 cGy		
2400-3600 cGy		
>3600 cGy		

Table 2: Odds ratios of abnormal Menarche by treatment related exposure

Exposure Group	Early Menarche			Late Menarche		
	n (%)	OR	95% CI	n (%)	OR	95% CI
Pituitary Dose						
None						
0-2400 cGy						
2400-3600 cGy						
3600-5000cGy						
>5000 cGy						
Craniospinal Dose						
None						
02400 cGy						
2400-3600 cGy						

>3600 cGy						
	Controlling for chemo and surgical exposure in Logistic Regression*					

*** Other factors may need to be included as confounders – we will need to evaluate in the modeling phase.**

**Figure 1: Cumulative Incidence Time to Menarche Curve
-no treatment vs. Any cranial radiation vs. any craniospinal radiation**

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