02-13

Childhood Cancer Survivor Study

Analysis Concept Proposal (rev 07 Nov 02)

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1. Title: Low Birth Weight Among Offspring of Childhood Cancer Survivors Treated with Radiation

2. Working Group and Investigators. This proposed publication will be within the Reproductive Working Group. Proposed investigators will include, among others,

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3. Background and Rationale:

Rationale. The proposed concept is an extension and enhancement of the low birth weight component of previous concept 98-02 entitled "Pregnancy Outcomes of Survivors of Cancer Diagnosed During Childhood and Adolescence" with a focus on the potential effect of radiation exposure to gonads among male and female survivors and to pelvis and brain among female survivors. Associations will be sought among preterm and fullterm births. This proposed concept will enable a first look at the pregnancy data sets that will be analyzed quantitatively with regard to radiation dose as described in another concept entitled "Genetic and Reproductive Effects of Radiation and Chemotherapy on Survivors of Childhood and Adolescent Cancer".

The present CCSS survivor cohort is large and includes patients with diverse treatment exposures, and will allow an accurate estimation of the possible effects of treatment on birth weight of live born children. Contact and recruitment of eligible participants began in August of 1994. Survivors 18 years of age or older were contacted directly, while parents were contacted for survivors under 18 years of age. Subjects, or their parents, were asked to complete a 24-page questionnaire, provide consent for release of medical records and for future contact to update the health history and to consider participation in other research projects, such as the study of adverse pregnancy outcomes. Those who reported a pregnancy were sent a Pregnancy Questionnaire which included questions on birth weight and factors associated with each pregnancy (Robison et al. Med Pediatr Oncol 38:229-239, 2002).

Among the 12,459 sexually active survivors of childhood cancer, 2,978 reported 6,017 pregnancies. Medical records of all members of the cohort are available to obtain chemotherapeutic agents administered, and the dates and details of administration of all radiation therapy. Radiotherapy records were sent to MD Anderson Cancer Center in Houston. Reporting of birth weight has been found to be reliable in previous studies (Olsen JE, et al. Am J Epidemiol 145:58-67, 1997), and the proposed concept will evaluate whether a reduction of birth weight (<2500 g) might be associated with radiation exposure to the gonads among male and female survivors and, among females, radiation exposure to the brain (hypothalamus and pituitary) and radiation exposure to the pelvis (uterus). Chemotherapeutic exposures

will also be evaluated, characterizing possible differences between alkylating and non-alkylating agents. For the proposed analysis, radiation dose will be crudely characterized (gonads in radiation field, near, distant, shielded), and exact doses determined for only a small sample of study subjects. However, reasonable levels of dose ranges (high, medium, low, none) should be sufficient to conduct dose-response analyses.

The analysis would be coordinated by John Boice at IEI, i.e., outside Seattle, using local resources and no funds will be required from CCSS. The analysis will be coordinated with Dan Green to minimize any potential overlap with analyses for concept 98-02 which have already been completed and submitted for publication. The concept is submitted in cooperation with the Pregnancy Outcomes Working Group.

4. Specific Aims/Objectives/Research Hypotheses

Hypothesis:

Among male and female survivors of childhood cancer, prior radiotherapy results in low birth weight of offspring.

Specific Aims:

(1) to learn whether prior radiotherapy to the gonads of male and female survivors results in low birth weight of offspring;
(2) to learn whether prior radiotherapy to the cranium of female survivors (i.e., exposure to the pituitary and hypothalamus) results in low birth weight of offspring;
(3) to learn whether prior radiotherapy to the pelvis of female survivors (i.e., exposure to the uterus) results in low birth weight of offspring;
(4) to learn whether prior radiotherapy among male and female survivors results in preterm deliveries;
(5) to learn whether birth weights of the offspring of childhood cancer survivors differ from the birth weights of the offspring of the siblings of childhood cancer survivors;
(6) and to evaluate and control for the possible effects of prior chemotherapy (alkylating agents and non-alkylating agents separately) among male and female survivors on birth weight (and preterm deliveries) of offspring.

The object of this concept will be to evaluate whether radiation to the testes of males and the ovaries of females can result in mutational damage that is manifested by preterm deliveries and low birth weight (among full term births). Such genetic effects of radiation were evaluated among the Japanese atomic bomb survivors and the findings were generally negative. However, the gonadal doses associated with radiotherapy for childhood cancer are much higher as described in the next section.

The potential effect of pituitary and hypothalamic irradiation of female survivors of childhood cancer will provide information on whether very high doses might disrupt the hormonal mileau to such an extent that low birth weight children are born.

Radiotherapy to the uterus has been associated with low birth weight, likely due to structural damage resulting in intrauterine growth retardation. Such effects will be characterized among female survivors.

Finally, the role of chemotherapy, both direct or as a confounder, will be characterized. To the extent possible, alkylating and non-alkylating agents will be considered separately.

5. Analysis Framework

All the data necessary to conduct the proposed analysis have already been collected. There are two sources of pregnancy information: the baseline questionnaire and the pregnancy questionnaire. The completeness and consistency of the reporting between these two questionnaires will be evaluated. With regard to radiation dosimetry, the currently available parameters will be used to characterize radiation exposure to gonads of male and female survivors and to uterus, pituitary and hypothalamus of female survivors.

Analysis will be conducted to learn whether therapeutic exposures are related to preterm births. Among full-term births, low-birth weight will be evaluated, including categories of very low birth weight <2000 g. Both male and female survivors will be evaluated with respect to gonadal exposure and birth weight of their offspring.

The analysis will be multivariate and account for the possible independent effects of radiation dose to gonads, and among females to pelvis and brain, as well as mutagenic chemotherapy. Potential confounding factors will also be characterized and accounted for to the extent possible, including alcohol, cigarette smoking, hypertension, recreational drugs, prescribed drugs, diabetes and other self-reported exposures during the pregnancy. It is realized, however, that the small numbers of these potential confounders may preclude detailed analyses. Birth order, maternal age and other factors will also be characterized and accounted for to the extent possible in the analysis.

To the extent possible, birth weight among siblings of the survivors of childhood cancer will also be evaluated and compared. Evaluation of birth weight by cancer diagnosis of the survivor will be made. The effect of age at treatment, calendar year of treatment, and the interval between treatment and pregnancy will be evaluated to the extent feasible.

Attached are examples of specific tables to be considered for the final draft.

6. Special Considerations (and possible future initiatives)

This analysis concept will allow an in depth look at the various pregnancy data sets and thus will help in the future evaluations of other adverse pregnancy outcomes (congenital malformations, stillbirths, neonatal deaths, and others) in relation to radiation dose that are incorporated under a previous concept. Further, there will be a quality control component to evaluate carefully any differences between the responses to the baseline questionnaire and the pregnancy questionnaire. Characteristics of nonrespondents to the pregnancy questionnaire (perhaps, for example, nonresponders are those who had elective abortions) will be considered. Additional pregnancies, identified during the next questionnaire contact with survivors (2000), might also be incorporated into any future evaluation.

The analysis will be coordinated at the International Epidemiology Institute (IEI) and funds have been secured already for this effort. If any dosimetry costs are incurred, they will be covered under an existing agreement between IEI and the MD Anderson Cancer Center. Throughout the evaluation, close coordination is envisioned with Dan Green to assure that any overlap in efforts is minimized.

Table 1. Descriptive characteristics of the pregnancies of the male and female childhood cancer survivors and their siblings.

Covariate	Females		Males	
	Survivors (N=)	Siblings (N=)	Survivors (N=)	Siblings (N=)
	N %	N %	N %	N %
Maternal age				
< 15				
15-19				
20-24				
25-29				
30-34				
≥ 35				
Birth order				
1				
2				
3				
4				
5				
6				
Infant sex				
Male				
Female				
Use of assisted reproductive technology[a]				
Yes				
No				
Maternal high blood pressure during pregnancy				
Yes				
No				
Maternal toxemia during pregnancy				
Yes				
No				

Table 1. (cont.)

Covariate	Females		Males	
	Survivors (N=)	**Siblings** (N=)	**Survivors** (N=)	**Siblings** (N=)
	N %	N %	N %	N %
Maternal diabetes during pregnancy				
Yes				
No				
Maternal smoking of cigarettes during pregnancy				
Yes				
No				
Maternal drinking of alcohol during pregnancy				
Yes				
No				
Maternal use of recreational drugs during pregnancy				
Yes				
No				
Maternal use of vitamin supplements during pregnancy				
Yes				
No				

[a] Reported use of either maternal fertility drugs, in vitro fertilization, or use of some other technology to assist in getting pregnant.

Table 2. Infant birthweight and duration of gestation for the liveborns of male and female childhood cancer survivors and their siblings.

	Females		Males	
	Survivors (N =)	**Siblings** (N =)	**Survivors** (N =)	**Siblings** (N =)
	N %	N %	N %	N %
Birthweight (grams)				
< 1500				
1500 – 1999				
2000 – 2499				
2500 – 2999				
3000 – 3499				
3500 – 3999				
≥ 4000				
Low birthweight[a]				
Non low birthweight[a]				
Duration of gestation				
Preterm[b]				
Fullterm[b]				
Among preterm[b] births				
Low birthweight[a]				
Non low birthweight[a]				
Among fullterm[b] births				
Low birthweight[a]				
Non low birthweight[a]				

[a] Low birthweight is defined as birthweight less than 2500 grams
[b] Preterm = < 37 weeks gestation; Fullterm = ≥ 37 weeks gestation

Table 3. Risk of preterm birth and low birthweight among the liveborns of male and female childhood cancer survivors, by treatment type.

	Surgery only (referent)	Radiation, no chemotherapy[a]		Chemotherapy and radiation[a]		Chemotherapy, no radiation[a]	
	N (%)	N (%)	OR (95%CI)	N (%)	OR (95%CI)	N (%)	OR (95%CI)
FEMALES	(N=)	(N=)		(N=)		(N=)	
Preterm[b]							
Fullterm[b]							
Unknown gestational age							
Low birthweight[c]							
Non-low birthweight[c]							
Unknown birthweight							
Among preterm births[b]							
Low birthweight[c]							
Non-low birthweight[c]							
Unknown birthweight							
Among fullterm births[b]							
Low birthweight[c]							
Non-low birthweight[c]							
Unknown birthweight							
MALES	(N=)	(N=)		(N=)		(N=)	
Preterm[b]							
Fullterm[b]							
Unknown gestational age							
Low birthweight[c]							
Non-low birthweight[c]							
Unknown birthweight							
Among preterm births[b]							
Low birthweight[c]							
Non-low birthweight[c]							
Unknown birthweight							

Table 3. (cont.)

	Surgery only		Radiation, no chemotherapy[a]		Chemotherapy and radiation[a]		Chemotherapy, no radiation[a]	
	N (%)	OR	N (%)	OR (95%CI)	N (%)	OR (95%CI)	N (%)	OR (95%CI)
Among fullterm births[b]								
Low birthweight[c]								
Non-low birthweight[c]								
Unknown birthweight								

[a] Does not exclude survivors who underwent surgery
[b] Fullterm = ≥ 37 weeks gestation; Preterm = < 37 weeks gestation
[c] Low birthweight is defined as less than 2500 grams

Table 4. Risk of preterm birth among the liveborns of male and female childhood cancer survivors and their siblings, by radiation treatment type.

	Fullterm birth[a]	Preterm birth[a]	OR (95%CI) for preterm birth
FEMALES			
Siblings			
Survivors - Brain irradiated			
Yes (without pelvis irradiated)			
No			
Unknown			
Survivors - Pelvis irradiated			
Yes			
No			
Unknown			
Survivors - Gonads in the pelvic field			
Yes			
Near			
Shielded			
No			
Unknown			
MALES			
Siblings			
Survivors - Brain irradiated			
Yes (without pelvis irradiated)			
No			
Unknown			
Survivors - Pelvis irradiated			
Yes			
No			
Unknown			
Survivors - Gonads in the pelvic field			
Yes			
Near			
Shielded			
No			
Unknown			

[a] Fullterm = ≥ 37 weeks gestation; Preterm = < 37 weeks gestation

Table 5. Risk of low birthweight[a] among the liveborns of female childhood cancer survivors and their siblings, by radiation treatment type.

	Low birthweight[a]		Non low birthweight		OR (95%CI) for low birthweight
	N	(%)	N	(%)	
ALL GESTATIONAL AGES					
Siblings					
Survivors - Brain irradiated					
Yes (without pelvis irradiated)					
No					
Unknown					
Survivors - Pelvis irradiated					
Yes					
No					
Unknown					
Survivors - Gonads in the pelvic field					
Yes					
Near					
Shielded					
No					
Unknown					
PRETERM [b]					
Siblings					
Survivors - Brain irradiated					
Yes (without pelvis irradiated)					
No					
Unknown					
Survivors - Pelvis irradiated					
Yes					
No					
Unknown					
Survivors - Gonads in the pelvic field					
Yes					
Near					
Shielded					
No					
Unknown					

Table 5. (cont.)

	Low birthweight		Non low birthweight		OR (95%CI) for low birthweight
	N	(%)	N	(%)	
FULLTERM [b]					
Siblings					
Survivors - Brain irradiated					
Yes (without pelvis irradiated)					
No					
Unknown					
Survivors - Pelvis irradiated					
Yes					
No					
Unknown					
Survivors - Gonads in the pelvic field					
Yes					
Near					
Shielded					
No					
Unknown					

[a] Low birthweight is defined as less than 2500 grams
[b] Fullterm = $\geq$ 37 weeks gestation; Preterm = < 37 weeks gestation

Table 6. Risk of low birthweight[a] among the liveborns of male childhood cancer survivors and their siblings, by radiation treatment type.

	Low birthweight[a]		Non low birthweight		OR (95%CI) for low birthweight
	N	(%)	N	(%)	
ALL GESTATIONAL AGES					
Siblings					
Survivors - Brain irradiated					
Yes (without pelvis irradiated)					
No					
Unknown					
Survivors - Pelvis irradiated					
Yes					
No					
Unknown					
Survivors - Gonads in the pelvic field					
Yes					
Near					
Shielded					
No					
Unknown					
PRETERM[b]					
Siblings					
Survivors - Brain irradiated					
Yes (without pelvis irradiated)					
No					
Unknown					
Survivors - Pelvis irradiated					
Yes					
No					
Unknown					
Survivors - Gonads in the pelvic field					
Yes					
Near					
Shielded					
No					
Unknown					

Table 6. (cont.)

	Low birthweight[a] N	(%)	Non low birthweight N	(%)	OR (95%CI) for low birthweight
FULLTERM [b]					
Siblings					
Survivors - Brain irradiated					
Yes (without pelvis irradiated)					
No					
Unknown					
Survivors - Pelvis irradiated					
Yes					
No					
Unknown					
Survivors - Gonads in the pelvic field					
Yes					
Near					
Shielded					
No					
Unknown					

[a] Low birthweight is defined as less than 2500 grams
[b] Fullterm = ≥ 37 weeks gestation; Preterm = < 37 weeks gestation