Childhood Cancer Survivor Study
Analysis Concept Proposal # 07-01

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1. Title: Incidence of cataract in relation of radiation dose in survivors of childhood and adolescent cancer

2. Proposed working group and investigators: Chronic diseases

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3. Background and rationale

The lens of the eye is relatively radiosensitive, and cataract formation has long been documented as a major ocular complication associated with ionizing radiation[1]. However, the lowest cataractogenic dose and the dose-response relationship of cataracts in humans are not well established. Studies of cataract occurrence 19 years after the atomic bombings in Hiroshima indicated that based on linear extrapolation, the threshold-dose point estimate for radiation-induced cataract was approximately 2.0 Sv [2-4]. However, recent reanalysis of cataract prevalence among the atomic-bomb survivors provided no evidence for a threshold level in dose response[5].

The significant association between exposure to low dose radiation and elevated risk for formation of cataract in the atomic bomb survivors agrees with several previous studies, such as a cohort with chronic exposure to low-dose-rate radiation from Cobalt[60] contaminated steel in their residences[6], studies of children exposed to low doses from the Chernobyl accident[7], commercial airline pilots[8], and astronauts[9].

The Childhood Cancer Survivor Study provides a unique opportunity to study and quantify the association between exposure to ionizing radiation and cataract due to the following reasons:

(a) A wide range of radiation exposure: The CCSS cohort includes a wide range of radiation dose including pediatric cancer survivors who were treated with external beam radiotherapy to the head and neck, cancer patients who were irradiated to body parts remote from the lens of the eye, and cancer patients who never received radiotherapy.

(b) Young age at exposure to ionizing radiation: The lens is highly radiosensitive during childhood, while it is undergoing growth and proliferation. In one study[10], all children with haematological

malignancies who received total body irradiation of 10 Gy in one session before bone marrow transplantation developed lens opacification, and only 25% had unaffected visual acuity after 3 years. Increased risk for early development of cataract was also observed in children after radiotherapy for skin hemangiomas.[11] In the CCSS, 68% of the survivors received radiotherapy before the age of 21 years.

(c) Long follow up period: The length of the latency period between exposure to ionizing radiation and the formation of cataract is not entirely clear and may range from six months to 35 years. The CCSS allows a relatively long follow-up period from exposure to radiotherapy (1970-1986) to the time of the follow-up questionnaire (starting from August, 1994).

(d) Large sample size: Previous studies on the risk of cataract in pediatric cancer survivors[10 12-15] had limited sample size (n<500) and study power. The CCSS cohort includes a much large number (approx. 68%) of exposed individuals, with 300 persons diagnosed with cataract to date.

(e) Radiation dosimetry: A previous CCSS study[16] has documented the availability of radiotherapy records to determine maximum total brain dose and brain regions exposed. A similar quantification process will be used to estimate doses to the lens of the eye.

4. Study aims and hypotheses

The goal of this analysis is to describe the incidence of cataract in the overall CCSS cohort and to investigate the association between the risk for cataract and the dose of ionizing radiation to the lens of the eye. Specifically, we plan to address the following questions:

(a) Are pediatric cancer survivors at increased risk of cataract formation following radiation.
Hypothesis: Childhood cancer survivors who underwent radiotherapy are at increased risk for cataract compared to other cancer survivors or sibling controls.

(b) What is the dose-response relationship between dose to the lens to the eyes and risk of cataract, and is there a dose below which no or very little increase in the risk is observed?
Hypothesis: The relationship between the dose of ionizing radiation to the lens of the eye and the risk of cataract is linear with no or minimal threshold level.

(c) Does age at radiotherapy alter the dose-response relationship?
Hypothesis: Age at radiotherapy is inversely associated with the risk of cataract.

(d) What is the latency period between radiotherapy and the occurrence of cataract in pediatric cancer survivors and does it depend on dose?
Hypothesis: According to previous observations, we expect that the shortest latency period between irradiation and the first diagnosis of cataract is several months. Since exposure to higher doses may increase the probability for cataract, shorter time period between exposure and the occurrence of first cataract does not necessarily mean shorter latency. Thus, we speculate that the proportion of all cataracts diagnosed within the first five years after exposure will be significantly larger among patients exposed to high doses than among individuals exposed to low doses.

5. Analysis framework

We propose a study to retrospectively follow all persons eligible for the CCSS cohort until the first diagnosis of cataract, or the date of the follow-up questionnaire, whichever occurred first. Using Cox regression analyses we will investigate the relationship between the risk of cataract and the dose of ionizing radiation to the lens of the eye from radiotherapy. Since CCSS is limited for 5-years survivors, we will analyze the incidence and the risk of cataract during the first five years separately.

(a) Outcomes of interest:
- Self-reported incident cataract
- Self-reported cataract extraction surgery.

(b) Study population:
The study will be based on the experience of the CCSS cohort of five-year survivors of childhood cancer (exclusive of retinoblastoma) diagnosed at any of 25 institutions in the U.S. or Canada between January 1, 1970 and December 31, 1986. The study population will include all patients who answered (either directly or by surrogate) the baseline Long-term Follow-up Study questionnaire. ~~Individuals who reported being legally blind in one or two eyes will be excluded from study.~~

*(c) Dosimetry: M*edical records, treatment diagrams, and photographs taken in the treatment position will be reviewed to make the determination of the dose to the lens of the eyes and use of eye blocks to protect the lens. This will be done in collaboration with Marilyn Stovall, Susan Smith, and Rita Weathers from M.D. Anderson. Additional information on a few basic parameters (e.g., age, type of first cancer, tumor dose, area of treatment, etc) will be included into an estimated exposure level to the lens of the eye.

(d) Explanatory variables: The following variables will be included when analyzing the data;
- Exposure variables: History of radiotherapy treatment: body part irradiated (e.g. head, chest, spine, total-body), and radiation dose to the lens (as continuous and categorized variable), chemotherapeutic agents, and steroids.
- Potential modifiers of radiation effect: Age at diagnosis of first cancer, attained age, gender. We will also examine the use of various chemotherapeutic agents which increase the skin sensitivity to radiation, such as actinomycin D, adriamycin, bleomycin, 5-fluorouracil, methotrexate.
- Potential confounders and modifiers: personal characteristics (race, marital status, highest education level, income), history of chemotherapy treatment (general categories of chemotherapy treatments, dose, administration method, co-treatments such as glucocorticoids), health behaviors prior to cataract diagnosis (cigarette smoking, alcohol consumption), type of primary cancer and recurrence of cancer, health problems (diabetes, high blood pressure, BMI, general health status).

(e) Specific tables:
-Characteristics of CCSS population and proportions diagnosed with cataract by age, age at diagnosis, primary cancer, type of treatment: chemotherapy and/or radiotherapy, use of steroids (Table 1).
-Crude, age-and-gender-adjusted, and fully-adjusted relative risk for cataract according to radiation dose to the lens of the eye secondary to radiation treatment for the first cancer (Table 2).
-Survival curves for cataract according to: primary cancer cause, cancer treatment (e.g. use of steroids), and dose to the lens of the eyes (figure 1).

-Excess relative risk curve for cataract according to dose to the lens of the eyes using continuous and categorized dose levels (figure 2).
- Similar tables and figure will be prepared with cataract extraction as the outcome variable.

(f) Analytic methods:

For the current cohort study, multivariate analyses will be performed using PEANUTS (EPICURE©, Hirosoft, Seattle, WA), a program for fitting Cox proportional hazard models[17]. It uses individual data and performs Cox regression in terms of a partial likelihood that is conditional on age at occurrence of cataract. Excess relative and absolute risks will be modeled using AMFIT (EPICURE©, Hirosoft, Seattle, WA).

6) Special considerations

(a) Personnel: Analysis will be performed at the Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics Division at the National Cancer Institute, by Dr. Gabriel Chodick. Dr. Chodick has recently conducted studies on the incidence of cataract among US radiologic technologists and retinoblastoma survivors. He will work under the close supervision of Peter Inskip, Alice Sigurdson, and Ruth Kleinerman.

(b) Potential Information bias: Cancer survivors who received radiotherapy to the head or neck may undergo more screening tests and thus may have a higher chance of having cataract and lens opacities diagnosed in comparison to patients who did not have radiotherapy to the face or neck body regions. This potential differential surveillance bias may increase the observed risk for cataract among brain cancer or ALL patients receiving cranial radiotherapy. To overcome this potential bias, we will use several strategies:
- Stratify the analyses according to type of first cancer.
- Use cataract extraction surgeries as an outcome. Cataract surgeries are performed only when vision is impaired, thus diminishing the risk of differential chance of detection.
- Use another ophthalmologic illness as a negative control. Since this outcome is independent of radiation dose, testing its association with radiotherapy doses may indicate information bias.
- The study population is restricted to 5-year survivors, reducing the potential for detection bias due to more frequent eye examinations in patients who received radiotherapy to the head.

(c) Study power: the estimated number of cataract cases among the CCSS cohort is approximately 300 (Sklar, personal communication). This number of cases allows 90% power to detect a HR for exposure to radiotherapy of 1.5 with statistical significance of 5%.

(d) Subtype of cataract: Cataract may be classified according to anatomic location into nuclear, posterior subcapsular (PSC) cataract, or mixed types. Previous studies on the risk for age-related cataract associated with ionizing radiation exposure showed a stronger association for PSC and cortical cataracts than for nuclear cataract. Type of cataract is not available for the current study. However, nuclear cataracts occur at older ages (above 60) [18,19] and the maximum age in the cohort is 55 years, so nuclear cataracts are likely to be uncommon.

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Table 1 (hypothetical) Characteristics of study population and proportion diagnosed with cataract

		No. (%)	Proportion diagnosed with cataract (%)
Age at interview	mean ± SD		
Sex	Women		
	Men		
Education	Did not complete high school		
	High-school graduate		
	Some college or higher education		
Race	Non-Hispanic white		
	Other group		
Household income	$20,000/yr		
	≥$20,000/yr		
Cancer diagnosis	Leukemia		
	Central nervous system tumor		
	Hodgkin's disease		
	Non-Hodgkin's lymphoma		
	Wilms' tumor		
	Neuroblastoma		
	Sarcoma		
	Bone tumor		
	Other		
Radiation therapy	Face or neck irradiation		
	Other head irradiation		
	Chest irradiation		
	Abdominal or pelvic irradiation		
	No radiotherapy		
	Missing or unknown treatment		
Age at face or neck irradiation	<5y		
	5-14y		
	15-24y		
	>24y		
	Irradiation to other body parts		
	No irradiation		
Chemotherapy	Alkylating agent		
	Anthracycline		
	Other chemotherapy		
	No chemotherapy		
Use of steroids	No		
	Yes		

Table 2 (hypothetical) Hazard ratios (HR) and 95% confidence intervals (CI) for cataract, according to selected personal characteristics and medical conditions prior to cataract diagnosis

Covariate		Univariate analysis		Multivariate analysis*	
		HR	95% CI	HR	95% CI
Age at interview (years)	<10				
	10-19				
	20-29				
	30-39				
	>39				
Sex	Men				
	Women				
Education	Did not complete high school				
	High-school graduate				
	Some college or higher				
Body Mass Index (kg/m^2)	<20				
	20-25				
	25-30				
	>30				
Cigarette smoking (pack-years)	Never				
	<5				
	5-10				
	10-15				
	>15				
Alcohol consumption (drinks per week)	<1				
	Never				
	1-2				
	3-6				
	7-10				
	>10				
Hypertension	No				
	Yes, not requiring medication				
	Yes, requiring medication				
CVA or MI	No				
	Yes, CVA only				
	Yes, MI only				
	Yes, CVA and MI				
Diabetes Mellitus	No				
	Yes, controlled with diet				
	Yes, controlled with hypoglycemic medication				
	Yes, controlled with insulin				

* Hazard ratios will be estimated from a single Cox Proportional Hazards multiple regression model that included all the variables in Table 2 using time of follow-up as the time covariate

Table 3 (hypothetical) Hazard ratio (HR) for cataract, according to variables related to cancer treatment

		Univariate analysis		Multivariate analysis*	
		HR	**95% CI**	**HR**	**95% CI**
Cancer diagnosis	Leukemia				
	CNS				
	Hodgkin's disease				
	NHL				
	Wilms' tumor				
	Neuroblastoma				
	Sarcoma				
	Bone tumor				
	Other				
Chemotherapy	Any chemotherapy				
	Alkylating agent				
	Anthracycline				
Age at face or neck irradiation	<5y				
	5-14y				
	15-24y				
	>24y				
	Irradiation to other parts				
	No irradiation				
Radiation therapy	Face or neck				
	Other head				
	Chest				
	Abdominal/pelvic				
	No radiotherapy				
	Unknown treatment				
Use of steroids	No				
	Yes				
Dose to the lens of the eye (Gy)	<0.1				
	0.1-0.5				
	0.5-1				
	1-2				
	2-5				
	5-9				
	10-19				
	>20				

* Adjusted for variable found significant in Table 2 and all other variables in Table 3.

Table 4 (hypothetical) Odds ratio (OR) for cataract and 95CI% according to variables related to cancer treatment among cataract cases and matched controls

		Cataract	Controls	OR	95CI%
Cancer diagnosis	Leukemia				
	CNS				
	Hodgkin's disease				
	NHL				
	Wilms' tumor				
	Neuroblastoma				
	Sarcoma				
	Bone tumor				
	Other				
Chemotherapy	Any chemotherapy				
	Alkylating agent				
	Anthracycline				
Age at face or neck irradiation	<5y				
	5-14y				
	15-24y				
	>24y				
	Irradiation to other parts				
	No irradiation				
Radiation therapy	Face or neck				
	Other head				
	Chest				
	Abdominal/pelvic				
	No radiotherapy				
	Unknown treatment				
Use of steroids	No				
	Yes				
Dose to the lens of the eye (Gy)	<0.1				
	0.1-0.5				
	0.5-1				
	1-2				
	2-5				
	5-9				
	10-19				
	>20				

Figure 1 (hypothetical) Cumulative incidence of cataract among childhood cancer survivors, according to radiotherapy dose to the lens of the eye

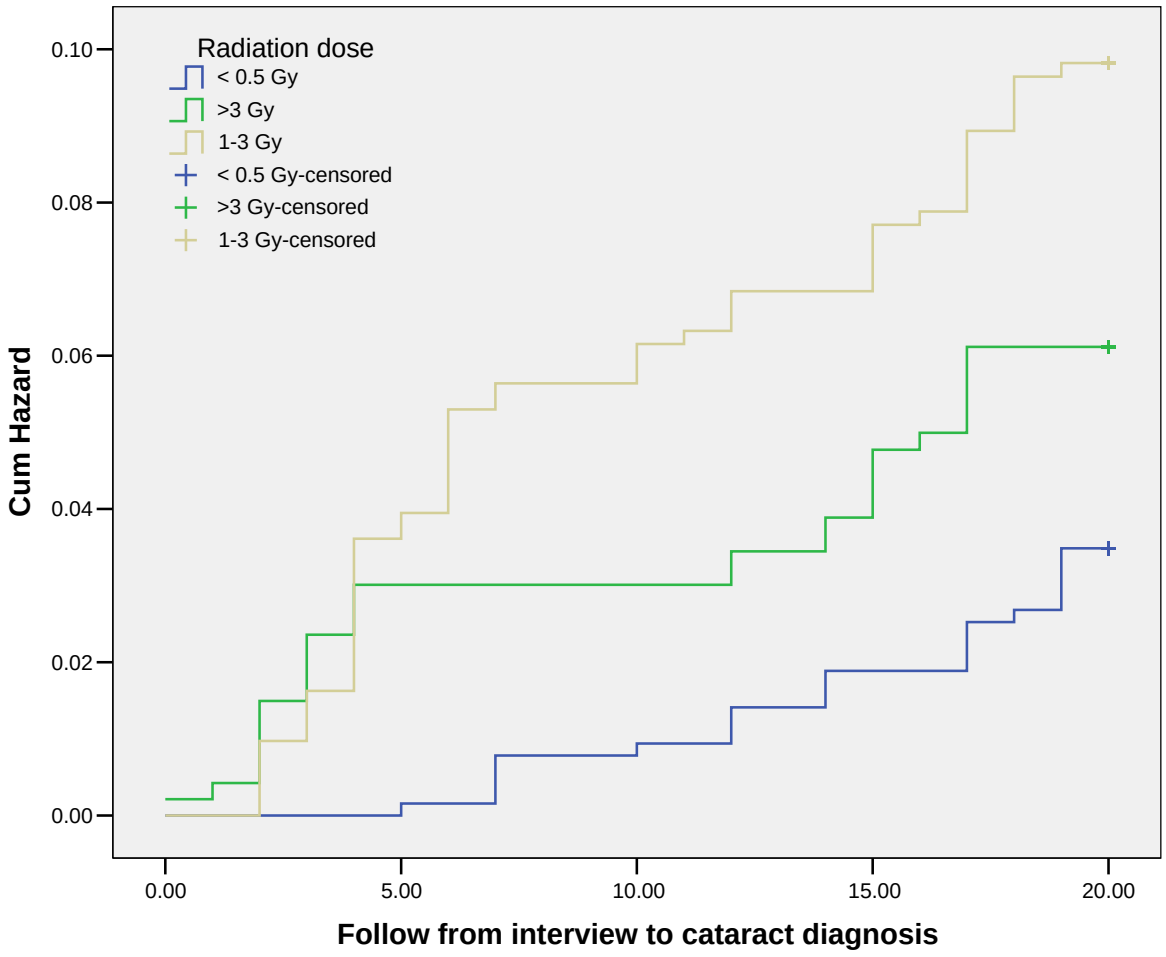

Figure 2 (hypothetical) Excess relative risk for cataract according to dose of ionizing radiation to the lens of the eye. The plots display the best-fitting linear ERR model* together with ERR estimates for 6 dose categories and 95%CI