Childhood Cancer Survivor Study
Analysis Concept Proposal
November 12, 2010

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1. **Title:** Radiation dose and benign thyroid conditions in the Childhood Cancer Survivor Study: analysis of radiation dose-response and its modifiers.

2. **Investigators:** These proposed publications will be within the Chronic Diseases Working Group. Proposed investigators will include:

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3. **Background and Rationale**

Cancer of the thyroid gland exhibits an unusual dose-response pattern after radiation exposure for treatment of a childhood malignancy. In contrast to the linear radiation dose-response relation observed across a wide range of dose for other solid tumors, we have found that the risk is curvilinear, with the risk peaking around 20 Gy and then decreasing at higher doses (Sigurdson et al, 2005; Ronckers et al, 2006; Bhatti et al, in press). The risk relationship appears consistent with cell killing at high doses, and any effect of chemotherapy on thyroid cancer risk can only be seen when the radiation dose is less than 20 Gy where, presumably, cell sparing predominates over cell killing (Veiga et al, submitted). In the most recent analysis of thyroid cancer in relation to radiation dose, age at exposure was found to modify the ERR linear dose term whereas sex and time since exposure modified the EAR linear dose term (Bhatti et al, in press). Only with the increased number of cases

and using the entire cohort was statistical power adequate to discern more complex relationships. However, we have not examined thyroid dysfunction with the same approach for evaluating radiation-related risk as we have done for thyroid cancer. While several reports from the CCSS have examined thyroid dysfunction, these have focused on specific subsets of childhood malignancies such as ALL (Chow et al, 2009) or Hodgkin lymphoma (Sklar et al, 2000), rather than the entire cohort, and no CCSS reports have, to our knowledge, quantitatively assessed the dose-response relation between radiation treatment and benign thyroid conditions. Risk of benign thyroid diseases among childhood cancer survivors treated with chemotherapy also has been investigated, with mixed results. An increased risk of hypothyroidism among survivors treated with chemotherapy alone has been reported in one study (Madanat et al, 2007), but no increase in risk was found in other several studies (Chow et al, 2009, Sklar et al, 2000; Nygaard et al, 1988 and Van Santen et al, 2003).

In contrast to thyroid cancer, findings regarding effects of radiation on benign (non-malignant) thyroid diseases, including hypothyroidism, hyperthyroidism, and thyroid nodules have been much less consistent. While there is evidence that irradiation at high doses could be associated with increased risk of benign thyroid conditions (reviewed in Brent, 2010), the magnitude and condition-specific shape of the dose-response relationships and the chemotherapy-related risk remain uncertain. Also, much less is known about factors that could potentially modify the dose-response relationship, specifically, gender, age at exposure, chemotherapy, and time since exposure. The possible effect of irradiation of the pituitary and hypothalamus, as well as of the thyroid, also deserves more investigation. Chow et al (2009) attempted to examine the effect of radiation to the thyroid and to the hypothalamic-pituitary area in ALL patients treated with cranial or craniospinal radiotherapy. Results suggested that cranial radiotherapy alone is insufficient to induce reportable hypothyroidism, whether central or primary in origin, whereas, craniospinal radiotherapy is associated with a higher amount of thyroid gland exposure and strongly associated with subsequent hypothyroidism. Nevertheless, in this

study, it was difficult to separate out any treatment effects on the hypothalamic-pituitary area from direct effects on the thyroid, as ALL patients who received thyroid gland radiation also received cranial radiotherapy. We propose to examine this effect in the overall CCSS cohort including other types of first cancer.

In summary, we propose a cohort analysis of benign thyroid conditions that were not explored in the original cancer incidence reports and may not have been addressed quantitatively by other CCSS investigators. Specifically, we propose extended analysis of the occurrence of benign thyroid conditions in relation to thyroid and pituitary radiation dose and to address the importance of other factors such as chemotherapy, age at diagnosis, sex, and time since exposure.

Despite the quantitative approach, this paper will be targeted to clinicians. We would prefer a general medical journal over an oncology specialty journal to be able to not only reach the pediatric oncologists who initially treat the childhood cancer patients, but also clinicians who are involved in medical care of long-term survivors.

4. Hypotheses

- Risk of hypothyroidism, hyperthyroidism and thyroid nodules increases linearly with thyroid radiation dose. Risk is higher in females than males and decreases with time since exposure.
- Sex, time since exposure, age at exposure, chemotherapy and pituitary radiation dose do not modify the risk of thyroid conditions related to thyroid radiation dose.
- Radiation dose to the hypothalamic-pituitary axis can also induce hypothyroidism, but the effect is much lower than for direct radiation to the thyroid gland.
- An effect of chemotherapy on risk of thyroid conditions can only be observed among patients not exposed to radiotherapy or those who received lower thyroid radiation dose.

5. Study objectives

1. Cohort-based estimates of absolute risk of benign thyroid conditions including self-reported hypothyroidism, hyperthyroidism, and thyroid nodules in relation to thyroid dose overall and relative risk for groups defined by gender, age at exposure, chemotherapy, and time since exposure.
2. Determine the shape of the dose-response for hypothyroidism, hyperthyroidism and thyroid nodules in relation to thyroid radiation dose and potential risk modifiers (gender, age at exposure, time since exposure, pituitary radiation dose and chemotherapy).
3. Determine differences between effects of direct radiation to thyroid and to the hypothalamic-pituitary axis.
4. Determine risk of benign thyroid conditions with respect to chemotherapy by thyroid radiation dose subgroups.

6. Study population

The latest frozen CCSS data set that includes cancer survivors who responded to the baseline questionnaire and the 2007 follow-up questionnaire is planned to be used as the basis for these analyses. Siblings will not be included.

7. Definition of Outcomes of interest

Outcomes of interest are benign thyroid conditions, including hypothyroidism, hyperthyroidism and thyroid nodules. We will take into account information about thyroid conditions in the baseline and 2007 follow-up questionnaires in which participants were asked whether they had been diagnosed with an underactive or overactive thyroid gland, if they ever developed a thyroid nodule, if their thyroid gland had been removed, whether they had subsequently developed any other malignancies, and their age at first occurrence for any of these outcomes. Participants also were asked to list any prescribed thyroid medications they consistently used in the prior 2 years. Participants could answer ‘‘yes,’’ ‘‘no,’’ or ‘‘not sure’’ to any question.

Hypothyroidism - we will consider the outcome to have occurred if a patient answered ‘‘yes,’’ to an underactive thyroid gland (questions E.2 and F.2 of the baseline and 2007 follow-up questionnaires, respectively).

Hyperthyroidism - outcome will be considered to have occurred if a patient answered ‘‘yes,’’ to an overactive thyroid gland (questions E.1 and F.1 of the baseline and 2007 follow-up questionnaires, respectively).

Thyroid nodules - outcome will be considered to have occurred if a patient answered ‘‘yes’’ to thyroid nodules (questions E.3 and F.3 of the baseline and 2007 follow-up questionnaires, respectively) and answered ‘‘no’’ to thyroid cancer as a subsequent cancer following the original diagnosis.

Participants who answered ‘‘not sure’’ to any question will be considered unaffected. In order to do a sensitivity analysis, we will compare results for all patients who reported hypothyroidism with results for those who also reported they took medications for hypothyroidism (in addition to reporting hypothyroidism).

Participants who reported thyroid conditions before the first cancer treatment and with missing information on thyroid conditions will be excluded, as will patients who did not report an age when the thyroid condition was diagnosed. As thyroid conditions are unlikely to be life-threatening, follow-up will start on date of first cancer diagnosis and not 5 years after first malignancy treatment as in many others adverse outcomes studied in CCSS. In addition, a sensitivity analysis excluding patients who developed any of the thyroid conditions within 5 years will be performed.

Follow-up will be truncated at the earliest of the following events: a) second cancer; b) death; c) date of last follow-up d) date of hyperthyroidism development in the hypothyroidism analysis and vice versa in the analysis of hyperthyroidism and, e) thyroid removal (for hypothyroidism and hyperthyroidism analysis). Thyroid removal will be considered to have occurred if a patient answered ‘‘yes’’ for surgical procedures related to removal of the thyroid gland and also reported age at its occurrence (question I.15 and J.17 of the baseline and 2007 follow-up questionnaire, respectively).

Explanatory variables: The exposure of main interest is radiation dose to the thyroid and pituitary gland, which is available for the cohort as provided by Marilyn Stovall and her team and already used by us. In addition to radiation dose, other explanatory variables include: chemotherapy (yes/no), chemotherapy classes of drugs (alkylating agents, anthracyclines agents and bleomycin (yes/no), and type of first cancer. Potential confounders include: gender, age at exposure, type of first cancer and attained age.

8. Analysis Frame-work

For each thyroid condition outcome, data will be arranged in a multidimensional table with each cell providing case counts and person-years of follow-up for categorized demographic, diagnostic and treatment-related variables. These include categories of thyroid radiation dose, sex, year of birth, age at childhood cancer diagnosis, type of childhood cancer, and a number of dichotomous variables (yes/no) for treatment with various chemotherapeutic agents. The DATAB module of Epicure (Hirosoft International Corporation, Seattle, WA) will be used to construct the person-year table.

The excess relative risk (ERR) and excess absolute risk (EAR) for each thyroid condition will be assessed using Poisson regression models in which risk will be allowed to increase with increasing dose. Likelihood ratio tests (LRT) will be used to evaluate nested models to determine the most parsimonious models that best fit the data. If the dose-response function is linear in dose alone, the model is the linear excess relative risk (ERR) model, $r(x,d)=r0(x)\ (1 + \beta d)$, where β is the parameter which measures the unit increase in excess relative risk per Gy (ERR/Gy). Deviations from this linear model will be evaluated by fitting a linear quadratic model, $r(x,d) = r0(x)\ (1 + \beta d + \theta d2)$ and also a linear-exponential dose-response, $r(x,d) = r0(x)\ (1 + \beta d)\ e-\theta d2$, where θ is a parameter which measures the nonlinear deviation of the dose-response relationship. A test of nonlinearity in the dose-response relationship will be carried out using a score test of the null hypothesis $\theta=0$.

We will also evaluate potential modifiers of the linear term of the dose-response model using likelihood ratio tests. We will assess the effect of categories of sex, age at exposure, time since exposure, type of first cancer, chemotherapy and pituitary radiation dose as modifying factors of the ERR function.

Corresponding P-values and 95% confidence intervals (CI) will be also calculated. All statistical tests will be two-sided with statistical significance at $P \leq 0.05$. The AMFIT module of Epicure (Hirosoft International Corporation, Seattle, WA) will be used for these analyses.

We will perform separate analyses for the overall cohort and for sub-cohorts defined by pre-defined categories of thyroid radiation dose to evaluate the effect of chemotherapy as previously proposed and described by Veiga et al (submitted).

We will present the cumulative risk of each thyroid condition in the cohort relative to radiation dose, type of treatment and type of first cancer. Cumulative incidence of thyroid conditions by time since treatment during the follow-up period and accounting for death from any cause as a competing risk event (Gooley, 1999) will be computed using Stata software (Stata, release 10.1, College Station, TX).

9. Other Considerations

NCI investigators will conduct the analysis in consultation with the statisticians at the co-ordinating center. Gila Neta (NCI) will be the primary analyst with oversight by Lene Veiga, Alina Brenner, and Peter Inskip. NCI has a long experience in conducting radiation-risk modeling and in analyzing CCSS data specifically.

References

Bhatti P, Veiga LHS., Ronckers CM, Sigurdson AJ et al: Radiotherapy for childhood cancer and risk of thyroid cancer in a large cohort study: An update from the Childhood Cancer Survivor Study. Radiation Research (in press).

Brent GA. Environmetal exposures and autoimmune thyroid disease. Thyroid 20:755-761, 2010.

Chow EJ, Friedman, D L, Stovall M, Yasui Y et al: Risk of thyroid dysfunction and subsequent thyroid cancer among survivors of acute lymphoblastic leukemia: A report from the Childhood Cancer Survivor Study. Pediatr Blood Cancer 2009;53:432–437

Gooley TA, Leisenring W, Crowley J, et al: Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 18:695-706, 1999

Hancock SL, Cox R and McDougall R: Thyroid diseases after treatment of Hodgkin´s disease. N Engl J Med. 1991:29;325(9):599-605.

Madanat LM, Lahteenmaki PM, Alin J, et al. The natural history of thyroid function abnormalities after treatment for childhood cancer. Eur J Cancer 2007;43:1161–1170

Nygaard R, Bjerve KS, Kolmannskog S, et al. Thyroid function in children after cytostatic treatment for acute leukemia. Pediatr Hematol Oncol 1988;5:35–38

Ronckers CM, Sigurdson AJ, Stovall M, et al: Thyroid cancer in childhood cancer survivors: a detailed evaluation of radiation dose response and its modifiers. Radiat Res 166:618-28, 2006

Sigurdson AJ, Ronckers CM, Mertens AC, et al: Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. Lancet 365:2014-23, 2005

Sklar C, Whitton J, Mertens A, Stovall M, Green D, Marina N, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab. 2000;85:3227–32.

Veiga, LHS, Bhatti Bhatti, P, Ronckers CM, Sigurdson AJ et al: Chemotherapy and the risk of thyroid cancer after a childhood malignancy in Childhood Cancer Survivor Study. NEJM (submitted)

van Santen HM, Vulsma T, Dijkgraaf MG, et al. No damaging effect of chemotherapy in addition to radiotherapy on the thyroid axis in young adult survivors of childhood cancer. J Clin Endocrinol Metab 2003;88:3657–3663.

Examples of tables and figures

Table 1. General characteristics of study subjects in the CCSS cohort study with benign thyroid conditions.

	Hypothyroidism	Hyperthyroidism	Thyroid nodules	Overall
Number of cases (% of total)				
Mean thyroid gland dose, Gy				
Mean pituitary gland dose, Gy				
Mean age at first cancer (range in years)				
Mean follow-up, in years (range)				
Mean number of years since exposure (range)				
Mean age at diagnosis of thyroid condition (range)				
Number of females (%)				
Number who had chemotherapy, (%)				
Type of first cancer (%)				
Leukemia				
Bone cancer				
Central nervous system cancer				
Hodgkin lymphoma				
Kidney cancer (Wilms tumor)				
Neuroblastoma				
Non-Hodgkin lymphoma				
Soft tissue sarcoma				
Radiotherapy exposure (%)				
None, chemotherapy only				
Cranial<20 Gy, no spinal radiotherapy				
Cranial≥20 Gy, no spinal radiotherapy				
Cranial<20 Gy, any spinal radiotherapy				
Cranial≥20 Gy, any spinal radiotherapy				

Table 2 – Risk of thyroid conditions by selected variables

	Hypothyroidism			Hyperthyroidism			Thyroid nodules		
	PYR	Cases	RR[a] (95%CI)	PYR	Cases	RR[a] (95%CI)	PYR	Cases	RR[a] (95%CI)
Gender									
Male									
Female									
P-value[b]									
Age at first cancer									
<1									
1-<5									
5- <10									
10 - <15									
>15									
P-value[c]									
Time since first cancer									
<15									
15-20									
<20									
P-value[c]									
Attained age									
<20									
20-29									
>30									
P-value[c]									
Type of primary cancer									
Leukemia									
Hodgkin lymphoma									
Others									
P-value[c]									
Radiotherapy exposure									
None, chemotherapy only									
Cranial, no spinal radiotherapy									
Cranial, any spinal radiotherapy									
P-value[c]									

[a]RR adjusted for potential confounders and also for thyroid radiation dose.
[b]P-value for heterogeneity
[c]P-value for trend

Table 3 - Risk of benign thyroid conditions according to radiation dose to the thyroid and pituitary glands.

Characteristic	Categories	PYR	Hypothyroidism[a] Mean radiation dose (Gy)	Cases	RR(95% CI)	P-value[b]
Thyroid radiation dose (Gy)	0					
	>0-<5					
	5-<10					
	10-<15					
	15-<20					
	20-<25					
	25-<30					
	30-<35					
	35-<40					
	≥40					
Pituitary gland radiation dose (Gy)	0					
	>0-<5					
	5-<10					
	10-<15					
	15-<20					
	20-<25					
	25-<30					
	30-<35					
	35-<40					
	≥40					
			Hyperthyroidism[c]			
Thyroid radiation dose (Gy)	0					
	>0-<5					
	5-<10					
	10-<15					
	15-<20					
	20-<25					
	25-<30					
	30-<35					
	35-<40					
	≥40					
			Benign thyroid nodules[c]			
Thyroid radiation dose (Gy)	0					
	>0-<5					
	5-<10					
	10-<15					

	15-<20
	20-<25
	25-<30
	30-<35
	35-<40
	≥40

[a]RR adjusted for potential confounders and also for thyroid radiation dose or radiation dose to the pituitary gland accordingly.
[b]P-value for trend.
[c]RR adjusted for potential confounders.

Table 4 - Risk of benign thyroid conditions with respect to chemotherapy by thyroid radiation dose subgroups

Treatment	Overall			Radiation, thyroid dose ≤ 20 Gy			Radiation, thyroid dose ≤ 10 Gy			No radiation (thyroid dose=0 Gy)		
	PYR	Cases	RR[a] (95% CI)	PYR	Cases	RR[b] (95% CI)	PYR	Cases	RR[b] (95% CI)	PYR	Cases	RR[c] (95% CI)
Hypothyroidism												
Chemotherapy												
No												
Yes												
P-value												
Alkylating agents												
No												
Yes												
P-value												
Anthracyclines												
No												
Yes												
P-value												
Bleomycin												
No												
Yes												
P-value												
Hyperthyroidism												
Chemotherapy												
No												
Yes												
P-value												
Alkylating agents												
No												
Yes												
P-value												
Anthracyclines												
No												
Yes												
P-value												
Bleomycin												
No												
Yes												
P-value												
Benign thyroid nodules												
Chemotherapy												
No												

Yes	
P-value	
Alkylating agents	
No	
Yes	
P-value	
Anthracyclines	
No	
Yes	
P-value	
Bleomycin	
No	
Yes	
P-value	

[a] RR adjusted for potential confounders and categorical thyroid radiation dose. For hypothyroidism, the RR also is adjusted for radiation dose to the pituitary gland.
[b] RR adjusted for potential confounders and thyroid radiation dose as continuous variable within the sub-cohorts of radiation dose. For hypothyroidism, the RR also is adjusted for radiation dose to the pituitary gland.
[c] RR adjusted for potential confounders.

Table 5 – ERR and EAR for benign thyroid conditions in the CCSS

Thyroid conditions	Excess Relative Risk		Excess Absolute Risk	
	ERR/Gy (95%CI)	P-value[a]	EAR/Gy per 10^4 PYR (95%CI)	P-value[a]
Hypothyroidism				
Hyperthyroidism				
Thyroid nodules				

[a]P-value for non-linearity

Table 6 – Effect modification of the excess relative risk of thyroid conditions

Potential effect modifier	Linear term (ERR/Gy) (95% CI)[a]
Sex	
Male	
Female	
P-LRT[b]	
Pituitary gland radiation dose (Gy)	
0-<5	
5-<10	
10-<20	
20-<30	
30-<40	
+40	
P-LRT[b]	
Ptrend[c]	
Type of first cancer	
Leukemia	
Hodgkin Lymphoma	
Other	
P-LRT[b]	
Age at radiation exposure, yrs	
<5	
5-9	
10-14	
≥15	
P-LRT[b]	
P trend[c]	
Time since radiation exposure, yrs	
5-14	
15-19	
20-24	
≥25	
P-LRT[b]	
P trend[c]	
Chemotherapy	

No
Yes

P-LRT[b]

[a] 95 % confidence interval based on the likelihood ratio profile of the parameter estimates

[b] Likelihood ratio test comparing models with and without effect modification terms

[c] Likelihood ratio test using the underlying continuous variable

Figure 1- Fitted ERR and EAR dose-response models for: a) hypothyroidism; b) hyperthyroidism; and c) thyroid nodules

Figure 2: Cumulative incidence of thyroid conditions in the CCSS cohort by gender, type of treatment and type of first cancer for: a) hypothyroidism; b) hyperthyroidism and c) nodules.

Appendix

Preliminary figures

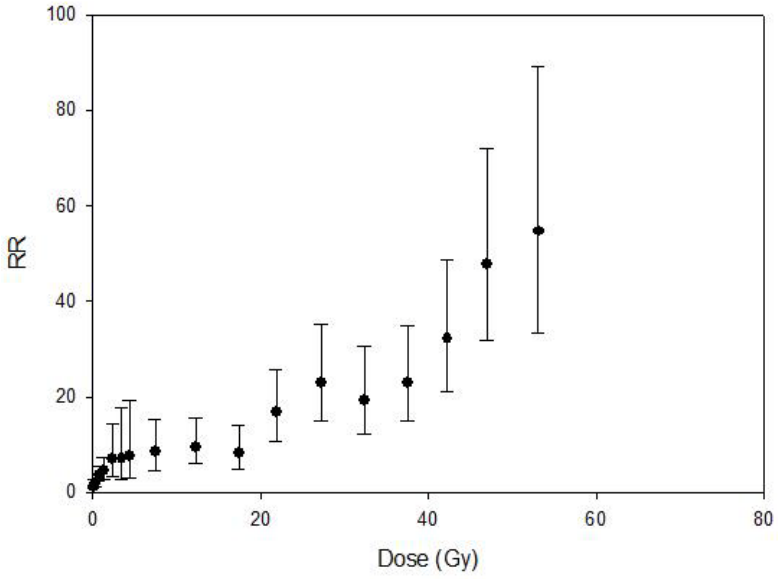

Figure 1 – Thyroid radiation dose-response for hypothyroidism