Subsequent thyroid cancer risk among childhood cancer survivors: characterizing the joint effects of radiation dose, chemotherapy and other risk factors in the Childhood Cancer Survivor Study

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Background:

Survivors of childhood cancer have substantially elevated risk of thyroid cancer compared to the general population,[1] with the majority of subsequent thyroid cancers occurring among survivors exposed to radiation therapy (RT).[2] Several prior studies in the CCSS and other cohorts have extensively characterized the dose-response relationship between thyroid radiation exposure and subsequent thyroid cancer risk.

In 2005 Sigurdson et al. published the first large study examining the risk of subsequent thyroid cancer over the range of clinical radiotherapy doses to define the dose-response relationship.[3] In a CCSS nested case control study comprised of 69 cases and 265 matched controls, they found that risk increased with increasing radiation dose up to 20-29 Gy, followed by a decline in the dose-response above 30 Gy, consistent with a cell-killing effect at high RT doses. Risks were highest in survivors diagnosed with childhood cancer prior to age 10 versus 10 years or older. Chemotherapy was not associated with thyroid cancer risk and did not modify the RT association. A subsequent publication from the same case control study in 2006 focused on examining the dose response relationship at high RT doses and applied models based on radiobiology to find convincing evidence for a true downturn in risk at RT doses exceeding 20 Gy.[4]

A 2010 publication by Bhatti et al. described a cohort analysis in CCSS with 119 subsequent thyroid cancer cases among 12,547 survivors diagnosed with childhood cancer between 1970-1986.[5] In that analysis, thyroid cancer risk increased linearly with RT dose up to approximately 20 Gy, with a peak relative risk (RR) of 14.6 (95% CI, 6.8-31.5) for those exposed to 20 Gy versus no RT. The best-fitting excess relative risk (ERR) model was a linear-exponential quadratic model to allow for a linear dose response at low doses with a downturn at doses above 20 Gy. Age at exposure modified the linear dose term (i.e. in the lower RT dose range), with a decreased RT effect up to 20 Gy for those diagnosed and treated at older ages. Significant effect modification was not observed for the high dose exponential quadratic term.

Having established the non-linear dose response relationship for RT and thyroid cancer risk, the next CCSS analysis used the same cohort with 119 cases to evaluate chemotherapy-related risk and possible joint effects of RT and chemotherapy.[6] Treatment with alkylating agents was associated with 2.4-fold increased thyroid cancer risk (95% CI, 1.3-4.5), but only among survivors with thyroid RT doses of 20 Gy or less. There was evidence of a dose response for alkylating agents among this group, and risk associated with alkylating agents decreased with increasing RT dose. Although results suggested an association between anthracycline exposure and thyroid cancer risk in those with no or low RT doses, there was no evidence of dose response.

The two most recent analyses of subsequent thyroid cancer risk pooled CCSS data on survivors diagnosed from 1970-1986 with data from other studies of thyroid cancer patients exposed to radiation in childhood. A 2012 study by Veiga et al pooled data from two cohort studies of childhood cancer survivors (CCSS and the France/UK CCSS) and two case control studies (nested within the Late Effects Study Group and Nordic Countries CCSS), yielding a total of 187 thyroid cancer cases.[7] Similar to prior studies, they reported an approximately linear increase in thyroid cancer risk with increasing RT dose up to 10 Gy, after which the dose response leveled off between 10-30 Gy, then declined at doses >30 Gy. Both the ERR and EAR (excess absolute risk) associated with RT were higher at younger ages of childhood cancer diagnosis and treatment. In models adjusted for RT dose, positive associations were

found for exposure to alkylating agents, anthracyclines, or bleomycin, but these chemotherapy exposures were not associated with thyroid cancer risk among survivors exposed to >20 Gy thyroid RT. Chemotherapy associations generally diminished with increasing RT dose, and likewise RT associations were lower in survivors exposed to these chemotherapies.

An updated pooled analysis in 2016 included the same four childhood cancer survivor studies but added additional studies with childhood radiation exposure from either treatment of benign diseases (seven studies) or survival of the atomic bombs detonated in Japan (one study).[8] In a pooled analysis with 1070 cases and 5.3 million person-years of follow-up, they confirmed the non-linear RT dose response relationship, with a linear increase in risk up to 10 Gy, a plateau between 10-30 Gy, and a downturn in the dose-response at doses > 30 Gy. Inclusion of the non-childhood cancer survivor studies enabled detailed analyses at low RT doses, and a significant linear trend of increasing risk with RT dose was evident even at doses ≤0.10 Gy. Radiation effects were again found to be stronger at younger ages at exposure, with the fitted relative risk at 10 Gy (versus no RT) estimated to be 51.9 for those exposed prior to age 1 year, 24.2 for those exposed at ages 5-9, and 9.4 for those exposed at ages 15-19. Adjusted for radiation dose, chemotherapy exposure was associated with a four-fold increased thyroid cancer risk, and formal evaluation of the joint relationship between RT dose and chemotherapy exposure demonstrated that an additive, or nonsynergistic, joint association was consistent with the data. The diversity of studies included in the pooled analysis precluded precise evaluations of chemotherapy, such as examination of specific drug classes or agents.

Finally, a retrospective cohort analysis of 4,338 children treated for cancer in France and the United Kingdom examined associations of thyroid RT dose and other risk factors with thyroid cancer risk.[9] They identified 55 subsequent thyroid cancers with a mean follow-up of 27 years, representing a 20-fold increased incidence compared to that expected based on general population rates. The non-linear radiation dose response for thyroid cancer risk in this study was similar to those observed in other studies, and although there was no significant association with chemotherapy as a whole or classes of chemotherapy, exposure to nitrosoureas (a specific type of alkylating agent) was associated with 6.6-fold increased thyroid cancer risk (95% CI, 2.5-15.7). Surgical or radiological (>20 Gy to the spleen) splenectomy was associated with thyroid cancer risk but did not modify the radiation dose response. The study also reported a significant interaction between radiation exposure to the pituitary gland and thyroid radiation on subsequent thyroid cancer risk, with no association between thyroid RT and cancer risk among those with pituitary RT exposure. Among a subset of patients who returned a questionnaire, there was suggestive evidence that the RT dose response may have been higher in survivors with a body mass index > 25 kg/m^2.

Rationale:

Large, pooled studies have extensively characterized the RT dose response and established the importance of age at exposure on the impact of RT, but these studies have been limited in their ability to quantitatively examine chemotherapy utilizing specific agents and doses. The CCSS study led by Veiga et al. demonstrated the utility of having detailed chemotherapy data but included a relatively small number of thyroid cancer cases (N=119). We therefore propose to extend prior investigations by incorporating the CCSS expansion cohort and additional follow-up time, providing a total of 427 cases (360% increase; numbers from 2023 CCSS Investigator Meeting Book) from CCSS alone, yielding the

largest analysis to date with detailed RT and chemotherapy data for all participants. Improving understanding of the joint effects of RT, chemotherapy, and age as well as other potential risk factors (e.g. splenectomy, obesity) would provide insight into thyroid carcinogenesis and inform survivorship care guidelines, which currently recommend annual physical exams for all individuals who received head/brain, neck, spine, or total body radiotherapy exposures but do not have recommendations based on chemotherapy or other treatment exposures, patient factors such as age, or other potential cancer risk factors.[10]

We have downloaded the majority of the necessary data for this project from dbGaP, however, we are requesting access to several variables that are not currently available in the dbGaP datasets. Specifically, more precise dates (minimally including month, but also day if possible) of birth, diagnosis, subsequent neoplasm, death, and last follow-up are needed to construct person-year tables for dose-response analyses in Epicure to enable flexible modeling of the radiation dose response, including a linear component. Additionally, we would also like to conduct the analyses using the thyroid doses for those cohort members with available data, rather than the body-region neck dose which is posted to dbGaP.

Specific Aims:

Aim 1. To quantify the magnitude and shape of the dose-response relationship for thyroid cancer risk after childhood cancer associated with radiation dose to the thyroid and specific chemotherapeutic agents.

Hypothesis 1: Updated analysis with increased thyroid case numbers will confirm the established non-linear dose response for RT and thyroid cancer risk in more recently treated survivors.

Hypothesis 2: Thyroid cancer risk will be increased with increasing doses of alkylating agents and anthracyclines.

Aim 2. To examine whether treatment-related thyroid cancer risks estimated in Aim 1 (RT or specific chemotherapy agents) modify one another, and also are modified by patient characteristics (age at exposure, sex, attained age, first primary childhood cancer type), other treatment exposures (splenectomy, RT dose to the pituitary gland), or other thyroid cancer risk factors (body mass index, physical activity, other endocrinopathies). Based on the literature, the primary focus of this aim is to assess the joint effects of RT, chemotherapy, and age at exposure. Investigation of other potential effect modifiers will be exploratory.

Hypothesis 1: Chemotherapy associations identified in Aim 1 will be modified by RT dose, with associations stronger at lower RT doses; no significant associations with chemotherapy will be identified among survivors with high thyroid RT doses (>20 Gy).

Hypothesis 2: Associations between both RT and specific chemotherapy exposures and thyroid cancer risk will be stronger among survivors with younger age at exposure, but for chemotherapy this interaction will only be evident among those with low thyroid RT exposure. Based on previous studies of thyroid cancer among childhood cancer survivors, sex will not be a significant modifier of treatment-related associations, and risk will remain elevated with increasing attained age.

Hypothesis 3: Other treatment exposures (splenectomy, pituitary RT) will be associated with thyroid cancer risk, and the association between thyroid RT and thyroid cancer risk will be more pronounced among patients with low/no pituitary RT exposure.

Hypothesis 4: Treatment-related thyroid cancer risks will be more pronounced among survivors with a BMI indicative of obesity (BMI ≥30 kg/m^2).

Aim 3. To quantify the joint effects of RT dose, chemotherapy doses, and age at exposure on thyroid cancer risk, and to determine cumulative incidence estimates among strata determined by these three important risk factors and any others identified in Aim 2.

Hypothesis 1: The cumulative incidence of thyroid cancer will differ substantially across strata defined by combinations of RT dose, chemo exposure, and age at diagnosis, or other modifying factors as identified in Aim 2.

Analytic Plan:

1. **Outcome(s) of interest:** The outcome of interest is subsequent primary thyroid cancer, overall and by subtype including papillary, follicular, other (non-medullary) and NOS based on ICD-O-3 morphology and topography codes. Exploratory analyses by histologic subtype will be conducted if sample size allows, and by tumor size pending data availability from another ongoing project.

2. **Subject population:** The study population will include patients in the original and expansion cohort (i.e., patients diagnosed with a first primary childhood cancer during 1970-1999). Patients missing age or year of first primary cancer diagnosis as well those patients with a reported SN at an age < age at first primary cancer will be excluded.

3. **Exploratory variables:** All variables, except BMI captured in follow-up questionnaires, are available from medical record abstraction or baseline survey.

   RT and chemotherapy data for treatments received within 5 years of childhood cancer diagnosis: RT (yes/no/unknown); RT thyroid dose; RT body region neck dose (to be used a proxy for thyroid dose for those participants without available thyroid dose); RT pituitary gland dose; and chemotherapy (dose for each type).

   Demographics: Sex; race and ethnicity; first primary cancer type; cohort (original, expansion).

   Age and date variables: Age at first primary cancer; age at SN; age at death or last follow-up; date of first primary diagnosis; date of birth; date of each subsequent cancer (excluding NMSC); date of first questionnaire; date of last questionnaire; and date of death. For each date variable, we request month, day and year but we can proceed with month and year if day cannot be provided.

   Non-thyroid subsequent malignancies: We request all available subsequent malignancy data (date of diagnosis, type) so that we can create a time-dependent covariate for intervening malignancies during follow-up.

Additional variables:

BMI calculated from reported height and weight at baseline (from all available time points). We note that the association between BMI and treatment is complicated, particularly as cranial RT in particular can affect BMI. We will consider BMI at different time points in our analysis of effect modification and potentially treat BMI as a time-dependent variable when adjusting for this variable.

Splenectomy (yes/no/unknown)

Other endocrinopathies (ever/never, age at first diagnosis) including diabetes mellitus, hyperthyroidism, hypothyroidism, and thyroid nodules. We recognized that it will be challenging to distinguish whether these are risk factors vs an indication of early thyroid cancer. If we include these in our models, we will explore different lag periods between diagnosis of endocrinopathies and thyroid cancer. Consistent with previous CCSS publications on hypothyroidism and hyperthyroidism, we also request thyroid-related medications for the purpose of classifying these conditions.

4. Statistical analysis:

For all analyses, participants will be followed starting 5 years following childhood cancer diagnosis until earliest of subsequent thyroid cancer, death, or last questionnaire completed. Descriptive statistics will be presented for patient, disease, and treatment factors.

We propose conducting two broad types of analyses. First, we will model the association between RT and chemotherapy and thyroid cancer risk and formally assess effect modification using Poisson models to estimate the excess relative risk (ERR) models fitted in Epicure. Guided by these results, we will then estimate the cumulative incidence of developing a second primary thyroid cancer for different subgroups of patients.

ERR models: We will fit multivariable Poisson regression models to model the ERR of thyroid cancer as a function of RT (thyroid and neck) radiation dose and chemotherapy (overall and by type). We will adjust the baseline for attained age, sex, and calendar year of diagnosis. We will examine whether it is appropriate to further adjust for first primary cancer diagnosis type, given the potential collinearity with treatment, and other factors such as BMI. Analyses of all subsequent thyroid cancer (i.e., not restricted to second primary) will further adjust for intervening malignancies in a time dependent fashion.

For RT (thyroid and neck) and chemotherapy (overall and by type), the shape of the dose response curve will be assessed by comparing linear and non-linear (e.g., quadratic, linear-exponential, linear-exponential quadratic) ERR models. Nested models will be compared using likelihood ratio test (LRT) statistics. Non-nested models can be compared with AIC values (lower indicating better model fit). We will report relative risks (RR) for dose categories in addition to modeling ERRs as a function of continuous dose.

Additional potential effect modifiers to be investigated in exploratory analyses include sex, BMI, splenectomy, pituitary dose, endocrinopathies, and first primary childhood cancer type. In addition to formally assessing effect modification by testing the significance of interaction terms, we will report stratified model results (e.g., ERR and RR estimates of thyroid dose stratified by chemotherapy dose categories).

Cumulative incidence: We will estimate the cumulative incidence of developing subsequent primary thyroid cancer, accounting for competing risks of death for joint categories of thyroid RT dose, chemotherapy, age at first primary diagnosis, and potentially other factors found to modify the association between treatment and thyroid cancer risk. Cumulative incidence models will provide insights into how these factors together impact absolute risk.

5. Sample tables:

Initial shell tables that we would propose to generate are attached. The final presentation will depend on the results and journal selection (e.g., more technical modeling tables may go into supplementary tables).

Table 1. Selected patient, disease and treatment characteristics of XX,XXX 5-year childhood cancer survivors

	Subsequent thyroid cancer during follow-up				Total	
	No		Yes			
	N	%	N	%	N	%
Cohort						
Original						
Expansion						
Sex						
Male						
Female						
First primary cancer type						
Leukemia						
CNS						
HL						
NHL						
Kidney (Wilms)						
Neuroblastoma						
Soft tissue sarcoma						
Age at first primary cancer						
Median (IQR)						
<5 y						
5-9 y						
10-14 y						
15- 20 y						
Year of first primary cancer						
1970-1979						
1980-1989						
1990-1999						
BMI (baseline questionnaire)						
Median (IQR)						
<18.5 kg/m^2						
18.5-24.9 kg/m2						
25-29 kg/m2						
30+ kg/m2						
Missing						
Thyroid radiation dose (Gy)						
0						
>0 -<1						
1-<10						
10-<20						
20-<30						
30-<40						
40+						
Missing						
Neck radiation dose (Gy)						
0						
>0 -<1						
1-<10						
10-<20						
20-<30						
30-<40						
40+						
Missing						
Chemotherapy						
No						
Yes						
Unknown						
Anthracycline dose within 5 years of first primary						
0						
Cat1						
Cat2						
Cat…						
Missing						
Alkylating agent CED within 5 years of first primary						
0						
Cat1						
Cat2						
Cat…						
Missing						
Platinum dose within 5 years of first primary						
0						
Cat1						
Cat2						
Cat…						
Missing						
Pituitary radiation dose						
None						
<x						
x+						
Unknown dose						
Splenectomy						
No/unknown						
Yes						

Note: Categories for chemotherapy types to be determined based on cohort distribution. Cutpoint for pituitary dose to be determined after evaluating the thyroid cancer dose-response relationship

Table 2. Excess relative risk models for subsequent thyroid cancer

		Dose terms			Model fit statistics				
Thyroid dose									
Model	Equation	β1	β2	β3	Deviance	AIC	LRT stat	DF diff from comparison	P-value LRT
Linear (vs no dose)	$\alpha[1 + \beta 1d]$						vs no dose		
Quadratic (vs no dose)	$\alpha[1 + \beta 1d2]$						vs no dose		
Linear-quadratic (vs linear)	$\alpha[1 + \beta 1d + \beta 2d2]$						vs linear		
Linear-exponential linear (vs linear)	$\alpha[1 + \beta 1d \times \exp(\beta 2d)]$						vs linear		
Linear-exponential quadratic (vs linear)	$\alpha[1 + \beta 1d \times \exp(\beta 2d2)]$						vs linear		
Linear-quadratic exponential linear (vs linear)	$\alpha[1 + \beta 1d \times \exp(\beta 2d) + \beta 2d2]$						vs linear		
Anthracycline dose									
Model		β1	β2	β3	Deviance	AIC	LRT stat	DF diff from comparison	P-value LRT
Linear (vs no dose)	$\alpha[1 + \beta 1d]$						vs no dose		
Quadratic (vs no dose)	$\alpha[1 + \beta 1d2]$						vs no dose		
Linear-quadratic (vs linear)	$\alpha[1 + \beta 1d + \beta 2d2]$						vs linear		
Linear-exponential linear (vs linear)	$\alpha[1 + \beta 1d \times \exp(\beta 2d)]$						vs linear		
Linear-exponential quadratic (vs linear)	$\alpha[1 + \beta 1d \times \exp(\beta 2d2)]$						vs linear		
Linear-quadratic exponential linear (vs linear)	$\alpha[1 + \beta 1d \times \exp(\beta 2d) + \beta 2d2]$						vs linear		
Alkylating agent score									
Model		β1	β2	β3	Deviance	AIC	LRT stat	DF diff from comparison	P-value LRT
Linear (vs no dose)	$\alpha[1 + \beta 1d]$						vs no dose		
Quadratic (vs no dose)	$\alpha[1 + \beta 1d2]$						vs no dose		
Linear-quadratic (vs linear)	$\alpha[1 + \beta 1d + \beta 2d2]$						vs linear		
Linear-exponential linear (vs linear)	$\alpha[1 + \beta 1d \times \exp(\beta 2d)]$						vs linear		
Linear-exponential quadratic (vs linear)	$\alpha[1 + \beta 1d \times \exp(\beta 2d2)]$						vs linear		
Linear-quadratic exponential linear (vs linear)	$\alpha[1 + \beta 1d \times \exp(\beta 2d) + \beta 2d2]$						vs linear		
Platinum dose									
Model		β1	β2	β3	Deviance	AIC	LRT stat	DF diff from comparison	P-value LRT
Linear (vs no dose)	$\alpha[1 + \beta 1d]$						vs no dose		
Quadratic (vs no dose)	$\alpha[1 + \beta 1d2]$						vs no dose		
Linear-quadratic (vs linear)	$\alpha[1 + \beta 1d + \beta 2d2]$						vs linear		
Linear-exponential linear (vs linear)	$\alpha[1 + \beta 1d \times \exp(\beta 2d)]$						vs linear		
Linear-exponential quadratic (vs linear)	$\alpha[1 + \beta 1d \times \exp(\beta 2d2)]$						vs linear		
Linear-quadratic exponential linear (vs linear)	$\alpha[1 + \beta 1d \times \exp(\beta 2d) + \beta 2d2]$						vs linear		

Notes: AIC: Akaike Information Criterion; LRT: likelihood ratio test; DF: degrees of freedom

α: Baseline model

The purpose of these models is to evaluate the best fit to describe the dose-response relationship between a treatment and second thyroid cancer.

Table 3. Examination of effect modification

	Linear term (ERRGy) (95% CI)			
Characteristic	Thyroid radiation dose	Anthracyline dose	Alkylating agent score	Platinum dose
Age at first primary cancer				
<10				
10-20				
*P (LRT) heterogeneity**				
Sex				
Male				
Female				
P (LRT) heterogeneity				
Thyroid dose (Gy)				
0				
<10				
10+				
P (LRT) heterogeneity				
BMI				
<30				
30+				
P (LRT) heterogeneity				
Splenectomy				
Yes				
No				
P (LRT) heterogeneity				
Pituitary dose				
0				
<10				
10+				
P (LRT) heterogeneity				

Based on comparison of the model with dose only vs dose*effect modifier (modeled categorically). Additionally, we may test for effect modification by comparing model with dose only (e.g., $\alpha[1 + \beta 1d]$) to one with the potential effect modifier treated as a continuous variable modifying the linear term ($\alpha[1 + \beta 1d \times \exp(\beta 2var)]$.

Table 4. Relative risks of subsequent thyroid cancer by treatment of first primary cancer, overall and by subgroups

	Total			Age <10 at first primary diagnosis			Age 10-20 at first primary cancer			Males			Females			BMI <25			BMI 25<30			BMI 30+			Splenectomy			No Splenectomy			Pituary dose < x			Pituary dose >= x		
	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)	Cases	RR	(95% CI)
Thyroid radiation dose (Gy)																																			
0																																			
>0 -<1																																			
1-<10																																			
10-<20																																			
20-<30																																			
30-<40																																			
40+																																			
Missing																																			
Anthracycline dose within 5 years of first primary																																			
0																																			
Cat1																																			
Cat2																																			
Cat…																																			
Missing																																			
Alkylating agent CED within 5 years of first primary																																			
0																																			
Cat1																																			
Cat2																																			
Cat…																																			
Missing																																			
Platinum dose within 5 years of first primary																																			
0																																			
Cat1																																			
Cat2																																			
Cat…																																			

Table 5. Cumulative incidence of developing a subsequent primary thyroid cancer

	Cumulative incidence (95% confidence interval)		
	5 years	10 years	15 years
Subgroup 1			
Subgroup 2			
Subgroup 3			
Subgroup 4			
Subgroup…			

To be presented as cumulative incidence curves

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