Childhood Cancer Survivor Study
Analysis concept proposal

Study title: Cause-Specific Mortality among Childhood Cancer Survivors with a Subsequent Thyroid Cancer

Working group: Second Malignancy (Primary), Cancer Control (Secondary)

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Background and Significance

Thyroid nodules are a common finding in radiation-exposed childhood cancer survivors.[1-4] The risk of thyroid cancer is also increased in this population. An elevated risk of thyroid cancer has been reported at doses as low as 0.1 Gy and the elevated risk likely persists for life. [5] Kovalchik et al reported 124 cases of confirmed thyroid cancer in the original CCSS cohort of 12,150 childhood cancer survivors.[6] Extending this work, Bhatti et al reported a standardized incidence ratio of 14 for incident thyroid cancer for the original cohort.[7] The relative risk for survivors exposed to radiotherapy compared to survivors not treated with radiotherapy ranges from 3.4 to 5.5.[7-9] The dose-response relationship is bell-shaped with an increase in risk until 20-29 Gy and then the risk plateaus and decreases (Figure 1).[10-12]

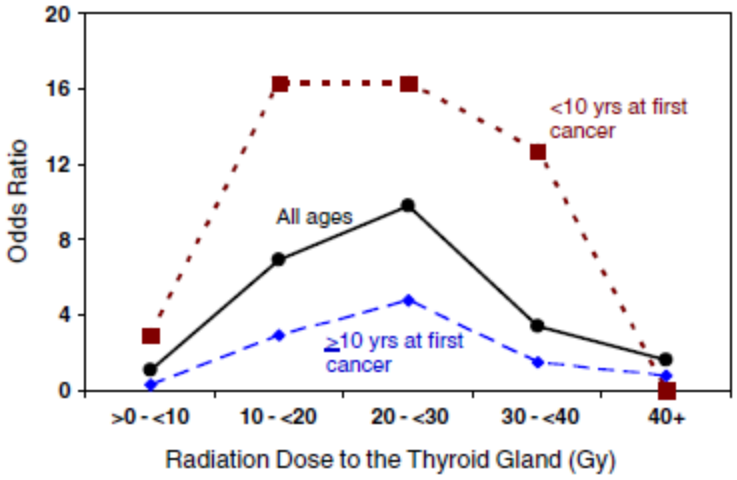


Figure 1: adapted from Sigurdson AJ, 2005[11,12]

Thyroid cancer can be detected either by palpation of a nodule on physical exam or by demonstration of a nodule on imaging. The best imaging modality for the thyroid is ultrasound.[13] Ultrasound screening for thyroid cancer in the general population is not recommended since most cases of incidentally found small thyroid cancer are indolent and will usually not cause morbidity or mortality.[13,14] Current Children's Oncology Group (COG) guidelines recommend annual thyroid physical examination and ultrasound with FNA of palpable nodules in survivors exposed to radiation to the neck. These guidelines do not advocate routine ultrasound examinations. The recently published American Thyroid Association guidelines on management of pediatric thyroid nodules also recommend routine physical examination without ultrasound screening in childhood cancer survivors.[15] However, there have been publications advocating routine ultrasound screening in radiation exposed cancer survivors.[3,4,16-18] The American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association (AACE/AME/ETA) guidelines, published in 2010, classify radiation-exposed individuals as a high risk category for thyroid cancer and therefore recommend screening ultrasound, even if palpation is negative.[13] Most of these publications base their recommendations on the high prevalence of thyroid cancer in this population, regardless of the excellent prognosis of thyroid cancer, even when detected in more advanced stages.

As mentioned above, thyroid cancer has an excellent prognosis; the 5-year overall survival rate for thyroid cancer in the U.S. is 98% based on SEER data.[19] As in the general population, the histology of radiation-related thyroid cancer is most commonly papillary carcinoma and less frequently follicular carcinoma.[20] Some studies have reported an excellent prognosis in these patients - comparable to the general population.[21-27] Most of these studies have followed a relatively limited number of survivors with subsequent thyroid cancer. In contrast to this, Goldfarb and Freyer compared mortality of secondary thyroid cancer in adolescents and young adults to mortality of primary thyroid cancer using the National Cancer Database (NCDB) and reported higher mortality in secondary thyroid cancer (RR=6.63, CI 4.97-8.86).[28] However, only all-cause mortality was captured, not thyroid cancer-specific mortality. It is likely that competing causes of death, such as cardiovascular disease, confounds this observation. Therefore, robust data regarding thyroid cancer-related mortality in childhood cancer survivors is lacking.

It is noteworthy that when screening this population, 25% to 70% of radiation-exposed survivors have thyroid nodules on an ultrasound (Figure 2).[1-4] Ultrasound screening can detect nodules as small as 1-2 mm, leading to an increase in detection of smaller thyroid cancers. For example, in the U.S. in the last three decades the incidence of thyroid cancer in the general population has tripled – mostly due to detection of smaller cancers.[29] While the incidence of diagnosed thyroid cancer has rapidly increased, the number of deaths from thyroid cancer has remained constant. Further evidence for the indolence of most thyroid cancer comes from autopsy studies demonstrating a strikingly high prevalence of thyroid cancer – up to 35% in some areas around the world.[30] Stratifying the risk of a nodule as thyroid cancer based upon sonographic features is sometimes difficult and not specific.[31] Therefore, screening would lead to a steep increase in the number of performed biopsies. Due to the indolent nature of thyroid cancer, this would not necessarily result in a mortality benefit. Thus, there is potential for overdiagnosis, defined as a screen-detected cancer that would not have led to symptomatic thyroid cancer if undetected by screening, and consequent overtreatment. Childhood survivors undergo many screening tests and as a result are, at times, under substantial mental and financial stress. It is prudent that we undertake only the most necessary and beneficial screening tests to minimize the burden of testing and potential harm.

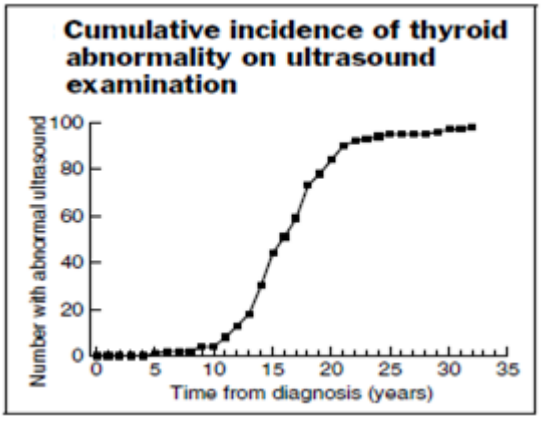


Figure 2: Adapted from Somerville *et al*[3].

The purpose of this study is to examine thyroid cancer-specific mortality rates and survival rates for thyroid cancer in childhood cancer survivors. Our hypothesis is that thyroid cancer does not contribute substantially to mortality rates in this population. The results of this study will further inform screening guidelines.

Specific aims

Aim 1: Estimate standardized mortality ratio (SMR) for thyroid cancer specific deaths observed among survivors of childhood cancer in two ways: (1) comparing the all-eligible CCSS survivors with the general population; and (2) comparing the CCSS survivors who have developed a thyroid subsequent malignant neoplasm (SMN) with the subjects of the general population who have developed a primary thyroid cancer. We will use age-, sex-, race-, and calendar-year-specific mortality rates for thyroid cancer in the general U.S. population (expected) in (1) and age-, sex-, race-, and calendar-year-specific mortality rates AFTER thyroid cancer in the U.S. SEER population (expected) in (2).

Hypothesis: Thyroid cancer-specific mortality in childhood cancer survivors will be comparable to rates among persons in the general U.S. population, overall and after thyroid cancer.

Aim 2: Assess the impact of thyroid SMN incidence on the subsequent mortality rate for CCSS survivors.

Hypothesis: Thyroid SMN will not significantly impact mortality rates.

Aim 3: Stratify by healthcare usage/medical screening utilization assessed at the CCSS baseline and assess both thyroid SMN incidence and mortality (Aims 1 and 2).

Hypothesis: Healthcare usage/medical screening utilization is associated with higher incidence of thyroid SMN incidence but not mortality.

Supplementary to Aim 3: We will compare the size distribution of thyroid tumors in the CCSS and SEER (age/sex matched) and assess whether the thyroid tumors in the CCSS are more likely to be screen detected or palpated.

ANALYSIS FRAMEWORK

Outcomes of interest

1. All-cause mortality.
2. Thyroid-cancer-specific mortality.

Subject Population

The study population will include all participating survivors from the original and expansion CCSS cohort with and without a thyroid SMN. The analysis will be limited to survivors who have consented for medical record abstraction only for analyses that require treatment information. **Exploratory variables**

1. Primary cancer diagnosis
2. Age at primary cancer diagnosis
3. Age at thyroid cancer diagnosis
4. Histology of thyroid cancer (pathology reports will be reviewed)
5. Size of thyroid cancer (pathology reports will be reviewed)
6. Subsequent malignant neoplasms, not including thyroid cancer
7. Gender
8. Race or ethnic group
9. Estimated thyroid radiation dose
10. Age at radiation
11. Chemotherapy (anthracyclines, alkylating agents, bleomycin – yes/no)
12. Grade 3-4 chronic condition (yes/no)
13. Last contact date
14. Vital status
15. Age at death
16. Cause of death

Statistical Analysis

We will use the most recent update of NDI data for death ascertainment in the CCSS subjects (~12/31/2012). Standard epidemiological methods and statistical inference based on Poisson probability models for SMRs/rates will be employed. Specifically, we will obtain age-sex-calendar-year-race-specific thyroid cancer mortality rates from the CDC portal as previously done by CCSS investigators and use them as the reference. SMRs for thyroid cancer death as well as 95% confidence intervals will be calculated for the CCSS cohort overall and stratified by each of the following variables: diagnosis-era and childhood cancer type. The above analysis for Aim 1 (1) will include all eligible survivors. Then we will run a similar comparison comparing the CCSS survivors who have developed a thyroid SMN with the subjects of the general population who has developed a primary thyroid cancer. We will use age-, sex-, race-, and calendar-year-specific mortality rates for thyroid cancer in the general U.S. population (expected) in (1) and age-, sex-, race-, and calendar-year-specific mortality rates AFTER thyroid cancer in the U.S. SEER population (expected) in (2).

In addition, limiting the analysis to CCSS participants (i.e., completed the CCSS baseline questionnaire) of the original cohort, we will stratify the SMR analysis by healthcare/screening utilization assessed within two years prior to thyroid cancer diagnosis using baseline, 2003 and 2007 surveys (Aim 3).

Following the above descriptive analysis, we will assess the impact of developing thyroid SMN on the overall mortality more analytically using a regression model. Using the previously developed CCSS mortality model (Armstrong et al mortality analysis), we will add a time-dependent covariate of developing thyroid SMN and assess whether it has any impact on overall mortality over and beyond the covariates that have been known to affect the mortality in this survivor cohort – including sex, age at diagnosis and attained age (Aim 2). We will then examine the effect of adding on reporting of a grade 3-4 condition and primary cancer diagnosis to the model to see if this explains any differences in mortality.

We will consider adding specific treatment exposures such as neck radiation and anthracyclines for their effect on mortality differences. This will be performed for the CCSS cohort overall.

We will explore potential for screening bias (Aim 3). For the original cohort, we will examine healthcare utilization reported in the survey (baseline, 2003, 2007) within two years prior to the diagnosis of the thyroid SMN. We will assess any medical care, cancer center visit, and risk-based care (cancer-related care). Of note, the percentage of general internists and family physicians that are familiar with screening guidelines for secondary cancer for childhood cancer survivors is low.[32,33] This suggests that screening outside of the cancer center is uncommon. Thus, a visit at a cancer center may be a proxy for screening for thyroid cancer. This allows us to compare the incidence of thyroid cancer between survivors seen and those not seen at a cancer center before thyroid cancer diagnosis. The expansion cohort has only received a single questionnaire, therefore we cannot ascertain if the individual with thyroid cancer had been seen at a cancer center prior to diagnosis.

Secondly, size of cancer can serve as a proxy for ultrasound screening. Nodules less than 1.5 cm are usually not palpable.[34] Therefore, we will compare the size distribution of thyroid tumors in the CCSS and SEER (age- and sex- matched) and assess whether the thyroid tumors in the CCSS are more likely to be ultrasound detected or palpated. This will be conducted for the overall cohort and will be stratified by diagnosis-era; childhood cancer type; and healthcare/screening utilization (as described above).

Table 1: Demographics and Treatment Characteristics of Survivors with Thyroid SMN and CCSS cohort

	Thyroid SMN N=	All CCSS survivors without Thyroid SMN N=
Primary diagnosis		
Leukemia		
Lymphoma		
CNS tumor		
Sarcoma		
Other cancers		
Age at primary diagnosis		
0-1 years		
2-4		
5-10		
11-18		
Gender		
Female		
Male		
Radiation to neck		
Yes		
No		
Radiation dose		
0-199 cGy		
200-999		
1000-1999		
2000-2999		
3000-3999		
>4000		
Chemotherapy		
Alkylating agents		
Yes		
No		
Anthracyclines		
Yes		
No		
Bleomycin		
Yes		
No		
Other agents		
Yes		
No		
Grade 3-4 chronic condition		
Yes		
No		
Length of follow-up (person years)		
Survival status		
Alive		
Dead		

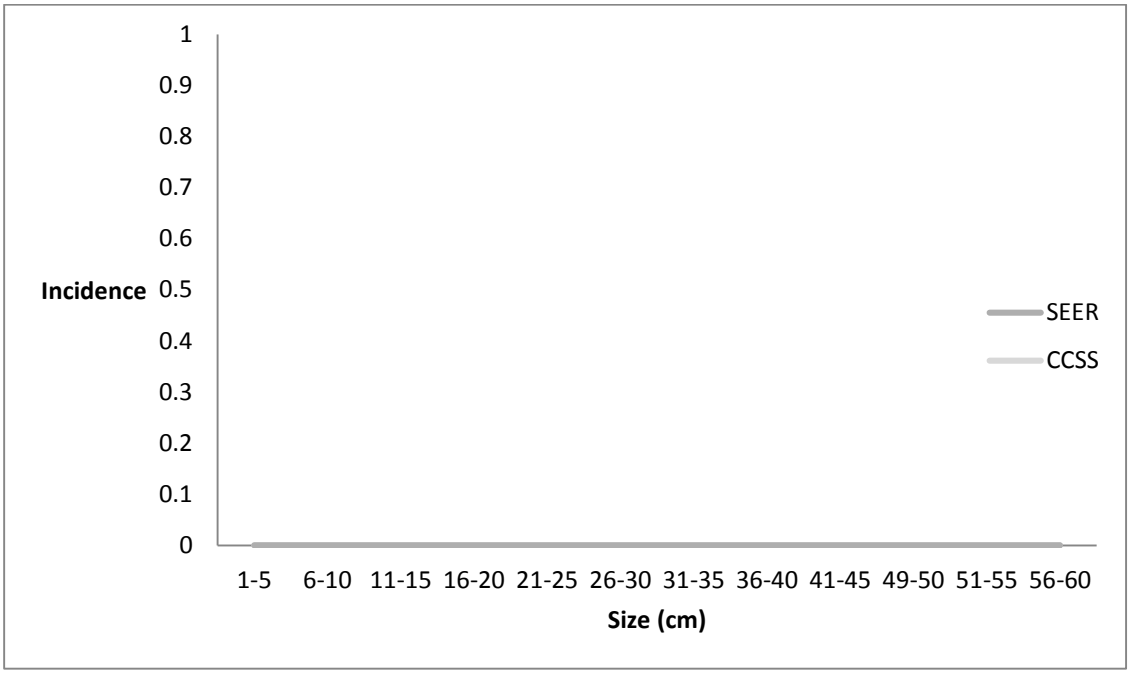
Table 2: Standardized Mortality Ratio (SMR) for Thyroid Cancer Related Mortality

	Thyroid cancer related mortality		
	Observed, n	**Expected, n**	**SMR**
All CCSS survivors			
All thyroid cancer survivors			
Age at thyroid cancer 0-18 19-40 >40			
Sex Female Male			

Table 3: Characteristics of Thyroid SMN

	Thyroid SMN in CCSS	Thyroid cancer in SEER
Age at thyroid cancer diagnosis		
0-19		
20-29		
30-39		
40-49		
≥50		
Latency between primary diagnosis and thyroid cancer (yrs)		
0-5		N/A
6-10		N/A
>10		N/A
Subtype of thyroid cancer		
Papillary		
Follicular		
Anaplastic		
Medullary		
Unknown		
Size of tumor		
1-5		
6-10		
11-15		
16-20		
21-25		
26-30		
31-35		
36-40		
41-45		
49-50		
51-55		
56-60		

Figure 1: Distribution of thyroid cancer size comparing CCSS thyroid SMN and SEER thyroid cancer



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