ABSTRACT

Title of Thesis: RACIAL/ETHNIC VARIABILITY IN THE EFFECT OF RADIATION ON SECOND PRIMARY THYROID CANCER IN CHILDREN: ANALYSIS USING SURVEILLANCE EPIDEMIOLOGY AND END RESULTS DATA

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Increases in pediatric thyroid cancer incidence could be partly due to previous clinical intervention. This retrospective cohort study used 1973-2012 data from the Surveillance Epidemiology and End Results program to assess the association between previous radiation therapy exposure in development of second primary thyroid cancer (SPTC) among 0-19-year-old children. Statistical analysis included the calculation of summary statistics and univariable and multivariable logistic regression analysis. Relative to no previous radiation therapy exposure, cases exposed to radiation had 2.46 times the odds of developing SPTC (95% CI: 1.39-4.34). After adjustment for sex and age at diagnosis, Hispanic children who received radiation therapy for a first primary malignancy had 3.51 times the odds of developing SPTC compared to Hispanic children who had not received radiation therapy, [AOR=3.51, 99% CI: 0.69-17.70, p=0.04]. These findings support the development of age-specific guidelines for the use of radiation based interventions among children with and without cancer.

RACIAL/ETHNIC VARIABILITY IN THE EFFECT OF RADIATION ON SECOND PRIMARY THYROID CANCER IN CHILDREN: ANALYSIS USING SURVEILLANCE EPIDEMIOLOGY AND END RESULTS DATA

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I. Introduction

Cancer is the second leading cause of mortality among children in the United States and incidence rates for common childhood cancers have been increasing slightly since the 1980's (1). However, pediatric thyroid cancer, a historically rare childhood malignancy that develops on the thyroid gland among those less than 20 years of age, has been increasing in incidence over the past few decades at an alarming rate (1-3). Epidemiologic data from the National Cancer Institute's (NCI) Surveillance Epidemiology and End Results (SEER) program have shown that the incidence rate for pediatric thyroid cancer has increased from 0.48 per 100,000 in 1975 to 1.15 per 100,000 in 2012 (4). Furthermore, the incidence rate of pediatric thyroid cancer has been increasing at approximately 1.1% per year and the reasoning for its increase is unknown (5-7).

Pediatric thyroid cancer has not only become more common as a first primary cancer type but it is also becoming more common as a second primary cancer type (8-10). Second primary cancer is when an individual with a history of cancer develops a new malignancy that is not through metastasis, or spread of, the first primary cancer (9, 11). Very little information is available on the distribution of thyroid cancer by cancer sequence (i.e., primary cancer, first primary cancer, second primary cancer, etc.) within the pediatric population; which supports the need for additional descriptive epidemiologic research in this area. The number of second primary thyroid cases is on the rise possibly due to this gland's high sensitivity to radiation in childhood (8-10). Radiation is often given in both low and high dosage amounts for diagnostic and therapeutic purposes in

childhood (10). Although multiple exposures to radiation within a child's life have become common (e.g., dental x-rays, computed tomography (CT) scans), they can cause a buildup in radiation dosage that can put a child at risk for malignancy; especially if they endured previous radiation-based cancer therapies (10). Treatment-related second primary cancer among children is a great concern within the medical community since the high dosage of radiation received for the first cancer can elevate the child's risk of developing cancer later in life (10). Further studies are needed in order to investigate the role that radiation based therapeutic and diagnostic therapies have on the development of second primary thyroid cancer among the pediatric population within the United States.

II. Research Question/Specific Aims

I. *Objectives*

The main objective of this study was to investigate the association between previous radiation therapy exposure and the development of second primary thyroid cancer among the pediatric population. Additionally, descriptive epidemiologic information was provided for pediatric thyroid cancer by cancer sequence number and potential risk factors for second primary thyroid cancer among children were assessed.

II. *Importance*

Currently, cancer is the leading cause of disease-specific mortality among the pediatric population in the United States; however, more research is needed to identify any demographic and geographic differences that may exist among the various childhood cancer types (12). Pediatric thyroid cancer, historically, was not commonly researched given its rare incidence and good prognosis (5). The incidence rate of pediatric thyroid cancer cases, however, has since changed in the U.S. and has been increasing

dramatically over the past few decades (5-7). Given this, there is a dire need for more research to be conducted in this area in order to investigate the demographic, geographic and potential risk factors of this condition. This study aimed to address this gap within the pediatric cancer research literature by assessing the proportion of pediatric thyroid cancer among various population subgroups by sequence number and by assessing potential risk factors for this condition given previous radiation therapy exposure.

III. *Specific Aim*

The specific aim of this study was to assess the association between previous radiation therapy exposure and the development of second primary thyroid cancer, while also considering other potential risk factors, such as geographic locale, age at diagnosis, insurance status, race/ethnicity and sex, in this association.

IV. Hypothesis

The null hypothesis that we aimed to reject consisted of the following:

Hypothesis (Φ) 1: There is no association between previous radiation therapy exposure and second primary thyroid cancer among 0-19-year-old children.

Alternate Hypothesis (I) 1: There is an association between previous radiation therapy exposure and second primary thyroid cancer among 0-19-year-old children.

This hypothesis was assessed using crude as well as adjusted measures of association. Additionally, racial/ethnic variation in the association between previous radiation therapy exposure and second primary thyroid cancer was assessed in both stratified and multivariable analytic models.

III. Background

The thyroid gland is a vital organ of the body responsible for creating thyroid hormones, which help to control a person's metabolism and are key growth factors in children (13, 14). This butterfly shaped gland, located in the front of the neck, consists of two main types of cells; which include the follicular and parafollicular cells (14). Follicular cells use iodine in the blood to create the thyroid hormones needed for metabolism and healthy neurologic development in children (14, 15). Parafollicular cells create calcitonin which is a hormone that regulates calcium in the body; an important mineral for the growth and development of children (14). The rapid division of the thyroid cells in childhood compared to adulthood has been shown to increase the likelihood of carcinogenesis (23).

Typically, the first indicator that a child may have a possible malignancy in the thyroid is the presence of symptoms similar to other thyroid diseases, such as hypothyroidism, or an accidental discovery through head or neck imaging (16, 17). As a result, children generally have a more advanced stage of thyroid cancer upon diagnosis; with approximately 80% of cases experiencing lymph node metastases and 20% experiencing pulmonary metastases (6, 16, 17). The usually aggressive nature of thyroid cancer in children often warrants an equally aggressive approach in therapy with treatment options including thyroidectomy with radioiodine remnant ablation (RAI); which would destroy any remaining thyroid cells left in the body after surgery (16).

Although overall prognosis after this type of treatment has been favorable in children, postoperative complications and late-effects of RAI continue to be an issue (16). Children diagnosed with thyroid cancer still face a lifetime of regular monitoring for reoccurrence

or metastases with the possibility for reoperation or multiple courses of radioactive iodine treatments (6). Currently, age specific clinical guidelines in the management of thyroid cancer do not exist and recommendations for care vary (18). This presents an enormous issue for the quality of life of these young cancer patients and their caregivers who are now tasked with making major life decisions in their treatment options that could potentially impact their future fertility, body image, sexuality, education, and career plans (5). Additionally, as these cancer patients age and increase in independence, accessible medical care and follow up will need to be maintained as they navigate the transition from pediatric to adult care. Given the surmounting evidence of the physical, mental and emotional impact that a diagnosis of thyroid cancer can have on a child, it is vitally important that this cancer type be fully investigated in order to assess potential age-specific risk factors.

Given the current literature, pediatric thyroid cancer has now become the most common solid tumor malignancy among 15-19 year old adolescents and is the second most common solid tumor malignancy among girls within this same age group (5). Adolescents have ten times the incidence of thyroid cancer, compared to younger age groups, with a female to male ratio of five to one that is not seen among younger children (18). Variability in tumor subtype also exists by sex, with a female to male ratio of 1 to 3 for papillary and follicular cell types (19). However, this sex ratio is not seen within all tumor subtypes of pediatric thyroid cancer. The pediatric medullary carcinoma subtype, for example, does not show this difference in sex. Possible explanations for the observed sex differences in papillary and follicular cell types, include increased estrogen levels among female cases (19). Racial variability also exists in the incidence of thyroid cancer

where white children have two times the risk for developing this malignancy in comparison to black children (20). White female children have been seen to have higher incidence rates of thyroid cancer compared to males and other racial groups; however, a possible explanation for the observed racial difference in incidence includes poorer cancer survival among non-Hispanic black children, Hispanic children and male children for the first primary cancer type (2, 20, 21).

Due to improvements in treatment, children diagnosed with cancer are now surviving for longer periods of time. As a result, these young individuals are at increased risk for developing a variety of treatment related diseases or conditions; namely therapy related second primary malignancies (22). Epidemiologic data has suggested that ionizing radiation in particular is associated with increasing predisposition to pediatric thyroid cancer. In addition to this, children who had an external exposure to active iodine for enlarged thymus glands, were demonstrated to develop papillary-follicular thyroid carcinoma after a latency of an estimated ten years (23). This demonstrates the long-term effect of different therapeutics and diagnostics among those who were diagnosed with a first primary childhood malignancy. The thyroid gland is a very radiosensitive area of the body especially in childhood and the incidence of thyroid cancer as a second primary cancer type is increasing (24). Adolescents have a 10-fold greater incidence than younger children and there is a female: male preponderance (5:1) during adolescence that is not seen in younger children (17). Children under the age of five, however, have the greatest sensitivity to certain therapies and are thus at a higher risk for developing treatment-related second primary thyroid cancer later in life (18).

I. Gaps in Research

There is a lack of descriptive and epidemiologic information on pediatric thyroid cancer on individuals under the age of 20, and a lack of information on the distribution of thyroid cancer by sequence within this population. Risk factors for pediatric thyroid cancer are not well understood within the scientific community, and histopathological subtypes, and the prognostic variability associated with the different cell subtypes, have not been fully researched (7). Research that has investigated epidemiologic risk factors for thyroid carcinoma have primarily been focused on the adult population. Hormones, somatic events, inherited susceptibility, and exposure to ionizing radiation are adult risk factors for thyroid cancer that are similarly implicated among those with pediatric thyroid carcinoma. Epidemiologic risk factors that have not been fully established in pediatric thyroid carcinogenesis include illegal drug use, smoking, diet, alcohol consumption, hormone levels, weight, comorbidities, parental occupational exposures, diagnostics and therapeutics (21, 25). Epidemiologic data on temporal incidence trends are also needed to investigate the occurrence of pediatric thyroid carcinoma in individuals under the age of 20 by sex, race/ethnicity, geographic locale, and age at diagnosis (26).

II. *Relevance to Specific Aims*

Thyroid malignancy, historically, was a rarity among children but is currently increasing in incidence as both a first primary cancer and second primary cancer type (2). Epidemiologic data has also implicated radiation as a potential risk factor for increasing the predisposition of thyroid cancer among children under the age of 20. The specific aim of this study was to assess the association between previous radiation therapy exposure, geographic locale, age at diagnosis, insurance status, race/ethnicity and sex in

the development of second primary thyroid cancer by providing the proportion of cases who developed the condition and by conducting a regression analysis. We theorized that previous radiation therapy exposure may play a role in the development of second primary thyroid cancer among children.

IV. Research Design and Methods

I. Overall Study Design

This study utilized a retrospective cohort study design. With approval of the University of Maryland-College Park Institutional Review Board (IRB) committee, we examined the proportion of first primary and second primary thyroid cancer among children registered in the SEER database between the years of 1973 to 2012. The odds for the development of second primary thyroid cancer given previous radiation therapy exposure was stratified by race/ethnicity while controlling for sex and age at diagnosis.

II. Description of Cases and Criteria for Selection

A secondary data analysis was conducted using the 1973 to 2012 SEER dataset which includes Hurricane Katrina impacted Louisiana cases. In order to be included in this study, a case had to be registered in the National Cancer Institute SEER cancer registry database between the years 1973 and 2012. The case must also have been under the age of 20 when diagnosed with cancer. Information related to the case's age at diagnosis, sex, race/ethnicity, insurance type, previous radiation therapy exposure, geographic locale, cancer sequence number and cancer type was pulled from the SEER dataset and included in this analysis. Any participant with missing information on cancer sequence and unknown previous radiation therapy exposure in this dataset was excluded from the final analysis of the study (n=395, 16.9%).

III. Sampling, power and sample size estimations

This study involved the analysis of pre-existing data (secondary data analysis). Because the sample size was already set, power estimation was conducted in order to determine our ability to detect significant differences with respect to second primary thyroid cancer. To estimate the statistical power, alpha (Type 1 error tolerance) was set at 5% for univariable analysis as well as for the Type 1 error in the multivariable model. This level was determined based off of the Bonferroni recommendation where Type 1 error tolerance level was divided by the number of variables, namely 0.05/2 to obtain the significance level. The effect size (delta) was set at a clinically acceptable level of 0.1 [10% difference]. With this specification, we obtained sufficient power [89.4%] to determine a minimum difference of 10% in previous radiation therapy exposure to be statistically stable [significance at 5%]. Similarly, utilizing the same procedure in calculating statistical power for the univariable analysis, the multivariable analysis, using 1% Type 1 error, was determined to have sufficient power at 80%.

IV. *Data Source*

The Surveillance Epidemiology and End Results (SEER) Cancer Registry database is operated by the National Cancer Institute and was first established in 1973 as a result of the National Cancer Act of 1971 (27, 28). Cancer registries are strategically located in 20 geographic areas and are required to routinely collect information on all incident cancer cases who reside in the SEER geographic locales (27, 28). Data collected for this database include a patient's sociodemographic information, such as race, ethnicity, age at diagnosis, tumor stage and grade, tumor type, tumor markers, surgery, therapy type, vital status and cause-specific mortality (28). The data collected from the SEER cancer

registries represent approximately 28% of the United States population and are demographically representative in comparison to national data (28).

In order to maintain quality data, the NCI has employed SEER Quality Improvement Teams at each of the cancer registry sites (27). These teams work to ensure that there is standardized medical coding and summary writing by the individuals who collect and code patient data at each cancer registry. They also ensure consistency and accuracy in coding through educating and training SEER cancer registry sites (27). Finally, in order to ensure quality, coding rules and descriptions are listed in the databases that are created in order to allow for proper inference of information from those who may use the database (27).

V. Dependent Variable Definition

The outcome variable in this study was second primary thyroid cancer. Second primary thyroid cancer was measured on a binary scale implying absence or presence of the diagnosis coded as 0 and 1. This variable was not recoded, and as a response variable, was entered into the model as a binary scale variable for the purpose of the analysis.

VI. *Description of Variables*

The variables of interest in this study included geographic locale (which included the 20 different regions assessed through the SEER cancer registry locations), radiation therapy (such as beam radiation, radioactive isotopes, other radiation, etc.) and previous radiation exposure (which consisted of previous radiation therapy treatment for the first primary cancer). In addition to this, age at diagnosis, sex, insurance status and race/ethnicity were included as variables of interest for this study.

i. Race/Ethnicity

Race/ethnicity was an independent variable that was used to examine the distribution of second primary thyroid cancer as well as first primary thyroid cancer. This variable was a nominal variable and was created by combining the two separate, nominal variables, race and ethnicity, from SEER. The race/ethnicity variable was coded as 1=Non-Hispanic White, 2=Non-Hispanic Black, 3=Non-Hispanic Asian American, 4=Non-Hispanic Other Race and 5=Hispanic. As an independent variable, race/ethnicity was used to determine whether there were racial/ethnic differences in the proportion of first primary thyroid cancer and second primary thyroid cancer, or differences in the association between previous radiation therapy exposure and the development of second primary thyroid cancer.

ii. Sex

In SEER, sex is described as male and female. In this study, sex was measured using a nominal scale (0=male, 1=female). This variable was entered into the analysis as a nominal variable and was not recoded. As an independent variable, sex was used to determine whether there were sex differences in the frequency of first primary thyroid cancer and second primary thyroid cancer; or differences in the association between previous radiation therapy exposure and the development of second primary thyroid cancer. Additionally, as a clinically relevant variable, sex was entered into the multivariable logistic regression analysis to adjust for the confounding effect of sex while observing the association between previous radiation therapy exposure and second primary thyroid malignancy.

iii. Previous Radiation Therapy Exposure

The previous radiation therapy exposure variable was coded as 0=none and 1=previous radiation therapy exposure. This previous radiation therapy exposure variable related to the second primary thyroid cancer as the main predictor and independent variable. For the purpose of the logistic regression model, this variable was entered in a binary scale, implying those who received previous treatment of radiation for their first primary cancer equal 1 and those who did not, or refused radiation treatment, equal 0.

iv. Age at Diagnosis

In SEER, age at diagnosis is measured in an ordinal scale and is categorized as 00 years, 1-4 years, 5-9 years, 10-14 years and 15-19 years. Age at diagnosis was treated as an ordinal variable and was recoded to 1=0-4 years, 2=5-9 years, 3=10-14 years and 4=15-19 years. This variable was used in the stratification, tabulation and regression analysis of this study. Given that age is a clinically relevant variable, it was entered into the multivariable model to adjust for the relationship between previous radiation therapy exposure and the development of second primary thyroid cancer.

v. Insurance

In SEER, insurance is measured on a nominal scale and was categorized as insured, insured/no specifics, any Medicaid, uninsured, insurance status unknown, or blank(s). This variable was used only in the descriptive analysis of this study given the large amount of missing information for this variable for those with second primary cancers (n=785, 32.6%).

VII. Data Analysis

Descriptive statistics were used to examine the proportion of pediatric cancer in the population registered in the SEER database between 1973 and 2012, characterized by only those with primary malignancies, first primary thyroid cancer and second primary thyroid cancer. Age at diagnosis, race/ethnicity, insurance status, geographic locale, radiation therapy and previous radiation therapy exposure were examined in order to investigate the proportion of cases among each group.

Inferential statistics were also applied in order to investigate the association between previous radiation therapy exposure and the development of second primary thyroid cancer, and whether a significant difference exists between various age at diagnosis, sex, racial/ethnic or geographic locale groups. The univariable logistic regression analysis and the multivariable logistic regression analysis were both used in this portion of the data analysis. For the univariable logistic regression model, the 95% confidence interval level was used. The 99% confidence interval level was used for the multivariable logistic regression model since it is possible for the Type 1 error to be inflated due to the multiple comparisons of the independent variables in the multivariable logistic regression model. . Additionally, the decision to set the confidence interval at 99% in this analysis is consistent with the Bonferroni correction method whereby you divide 0.05 by the number of independent variables in the multivariable logistic regression model. Prior to conducting the logistic regression analysis, however, effect measure modification and confounding effects were tested for each of the independent variables in relation to second primary thyroid cancer and previous radiation therapy exposure. All of the

variables of interest were found to be confounders, and race/ethnicity was found to be an effect measure modifier.

i. Effect measure modifier: Assessment and Explanation

Effect measure modification in the association between second primary thyroid cancer and previous radiation therapy exposure was assessed first before testing for confounding by observing the difference in the strength of association between two variables, given a third variable. Biologically, an effect measure modifier is a third or extraneous variable that should be described. Effect measure modification was assessed by performing stratified analysis using Mantel-Haenszel models.

ii. Confounding: Assessment and Adjustment

Sex, race/ethnicity, geographic locale and age at diagnosis were assessed for potential confounding of the association between second primary thyroid cancer and previous radiation therapy exposure. We used a univariable logistic regression model to examine the relationship of the independent variables with second primary thyroid cancer as well as with previous radiation therapy exposure. Additionally, we used Mantel-Haenszel stratification analysis to assess the difference in the odds ratio given the presence of these independent variables in the stratified analysis. In order for a variable to be considered as a confounder and to be controlled for in the relationship between second primary thyroid cancer and previous radiation therapy exposure, a 10% difference in the odds ratio within the stratified analysis would need to be observed. Likewise, in the univariable regression model, if the statistical significance was less than or equal to 25% Type 1 Error tolerance, a variable was considered as a confounder and was adjusted in the multivariable model.

iii. Hypothesis-driven Analysis

A multivariable logistic regression model was used to examine the non-confounding effect of the previous radiation therapy exposure on the odds of developing second primary thyroid cancer. Additionally, to examine racial/ethnic differences in this association, a decomposition analysis was used. We forward loaded and backward eliminated all variables in the univariable model that were significant at 25% Type 1 error or had biological and clinical relevance, such as age at diagnosis and sex. This process allowed us to build a model that balanced the distribution of the confounding variables between those diagnosed with and without second primary thyroid cancer.

VIII. Human subjects

This study involved secondary data analysis of the National Cancer Institute SEER cancer registry dataset. Permission to use this dataset was obtained from NCI prior to the development of this thesis, which states clearly the agreement between the data user and the NCI including the logistics for citation and publication. This dataset does not include personal identifiers, and no additional informed consent was required. Prior approval was obtained from the University of Maryland College Park Institutional Review Board before these data were analyzed.

IX. *Results*

During 1973-2012, there were 85,648 malignancies registered in the SEER database, which consisted of all cancer cases diagnosed in childhood and each subsequent cancer diagnosis thereafter for the same individual. Table 1 presents the characteristics of the study sample by primary malignancy and by primary thyroid cancer. More than half of primary malignancies were male (n=44,397, 54.2%). In contrast, the majority of the

patients with primary thyroid cancer were female (n=2,569,81.4%). One-third of primary cancer cases were diagnosed before the age of 5 (n=26,265, 32.1%) whereas the majority of primary thyroid cancer cases were 15-19 years of age at the time of diagnosis (n=2,362, 74.8%). Non-Hispanic Whites represented the highest proportion of single primary malignancy (n=47,980, 58.6%) as well as primary thyroid cancer (n=2,026, 64.2%). Hispanics had the second highest proportion of primary malignancy (n=18,367, 22.4%) as well as primary thyroid cancer (n=637, 20.2%). The majority of primary cancer cases (n=57,587, 70.3%) did not receive radiation based therapy; whereas 56% of primary thyroid cancer cases did receive radiation based therapy (n=1,768). One out of four primary cancer cases received beam radiation (n=20,829, 25.4%) whereas the majority of primary thyroid cancer cases received radioisotopes radiation therapy (n=1,477, 46.8%).

Table 1. Study Characteristics of Children with Primary Cancer versus Primary Thyroid Cancer, SEER 1973-2012

	Primary Cancer		Primary Thyroid Cancer	
	n=81,914	%	n=3,157	%
Sex				
Male	44,397	54.20	588	18.63
Female	37,517	45.80	2569	81.37
Age at diagnosis				
0-4	26,265	32.06	20	0.63
5-9	14,187	17.32	139	4.40
10-14	15,739	19.21	636	20.15
15-19	25,723	31.4	2,362	74.82
Race/Ethnicity				
Non-Hispanic White	47,980	58.57	2026	64.17
Non-Hispanic Black	8,365	10.21	154	7.60
Non-Hispanic Asian American	4,688	5.72	236	7.48
Non-Hispanic Other Race	2,514	3.07	104	3.29
Hispanic	18,367	22.42	637	20.18
Geographic Locale				
Northeast	11,333	14.49	496	16.33
Midwest	7,176	9.18	247	8.13
South	8,827	11.29	327	10.77
West	43,970	56.22	1684	55.45
Not in SEER 17	1,794	2.29	76	2.50
Blank(s)	5,109	6.53	207	6.82
Insurance				
Private Insured	11,836	15.00	786	24.89
Insured/No specifics	2,485	3.15	121	3.83
Any Medicaid	7,577	9.60	251	7.95
Uninsured	547	0.69	25	0.79
Insurance status unknown	780	0.99	29	0.92
Blank(s)	55,647	70.55	1,945	61.61
Radiation therapy				
None	57,587	70.30	1389	43.99
Beam Radiation	20,829	25.43	55	1.74
Radioisotopes	1,509	1.84	1477	46.78
Radioactive Implants	110	0.13	35	1.11
Radiation NOS	273	0.33	9	0.29
Other Radiation	122	0.15	115	3.64
Combination Beam with isotopes or Implants	129	0.16	18	0.57
Recommend but Unknown	732	0.89	37	1.17
Unknown	500	0.61	14	0.44
Refused	123	0.15	8	0.25

Note:
Geographic locale based on U.S. Census 2010 Geographic Regions
Racial/ethnic categories based on the Office of Management and Budget standards.

Table 2 highlights the cases diagnosed with first primary thyroid cancer (FPTC) and cases with second primary thyroid cancer (SPTC). The majority of first primary thyroid cancer (n=81, 89.0%) and SPTC (n=31, 64%) cases were females. Most FPTC (n=69, 75.8%) and SPTC (n=34, 69.3%) cases occurred among those 15-19 years of age at diagnosis, Non-Hispanic White (n=68, 74.7%; n=30, 61.2%), and from the west region of the U.S. (n=43, 48.8%; n=26, 56.5%). Fifty-five percent (n=27) of SPTC cases had previous exposure to radiation therapy.

Table 2. Study Characteristics of Children with First Primary Thyroid Cancer versus Second Primary Thyroid Cancer, SEER 1973-2012

	First Primary Thyroid Cancer		Second Primary Thyroid Cancer	
	n=91	%	n=49	%
Gender				
Male	10	10.99	18	36.73
Female	81	89.01	31	64.58
Age at Diagnosis in years				
0-4	0	0.00	0	0.00
5-9	4	4.40	2	4.08
10-14	18	19.78	13	26.53
15-19	69	75.82	34	69.39
Race/Ethnicity				
Non-Hispanic White	68	74.73	30	61.22
Non-Hispanic Black	5	5.49	1	2.04
Non-Hispanic Asian American	6	6.59	4	8.16
Non-Hispanic Other Race	2	2.20	1	2.04
Hispanic	10	10.98	13	26.53
Geographic Locale				
Northeast	12	13.64	7	15.22
Midwest	10	11.36	6	13.04
South	8	9.09	3	6.52
West	43	48.86	26	56.52
Not in SEER 17	4	4.54	2	4.35
Blank(s)	11	12.50	2	4.35
Insurance				
Insured	10	10.99	12	24.49
Insured/No specifics	0	0.00	0	0.00
Any Medicaid	1	1.10	11	22.45
Uninsured	0	0.00	1	2.04
Insurance status unknown	0	0.00	0	0.00
Blank(s)	80	87.91	25	51.02
Previous Radiation Exposure				
No	-	-	22	44.89
Yes	-	-	27	55.10

Notes:
Geographic locale based on U.S. Census 2010 Geographic Regions
Racial/ethnic categories based on the Office of Management and Budget population standards.

Table 3 illustrates the association between SPTC and previous radiation therapy exposure, sex, race/ethnicity, age at diagnosis, insurance status and geographic locale. Non-Hispanic Asian Americans had 10% increased odds (OR=1.10; 95% CI: 0.37-3.25) and Hispanics had 11% increased odds (OR=1.11; 95% CI: 0.56-2.18) in comparison to

Non-Hispanic White. Relative to boys, girls previously exposed to radiation therapy were 91% more likely to be diagnosed with SPTC (OR=1.91; 95% CI: 1.05-3.47).

Table 3. Unconditional Univariable Logistic Regression Models for the Association between Second Primary Thyroid Cancer in Children and Study Variables, SEER 1973-2012

	OR	95% CI
Sex		
Male	1.00	Referent
Female	1.91	1.05-3.47
Age at Diagnosis in years		
0-4	-	-
5-9	0.70	0.36-1.35
10-14	0.13	0.03-0.58
15-19	1.00	Referent
Race/Ethnicity		
Non-Hispanic White	1.00	Referent
Non-Hispanic Black	0.17	0.02-1.33
Non-Hispanic Asian American	1.10	0.37-3.25
Non-Hispanic Other Race	0.58	0.07-4.44
Hispanic	1.11	0.56-2.18
Geographic Locale		
Northeast	1.00	Referent
Midwest	1.20	0.38-3.74
South	0.51	0.12-2.03
West	0.75	0.31-1.79
Not SEER 17	1.29	0.25-6.68
Blank(s)	0.58	0.11-2.91

Notes:
OR=odds ratio and CI=confidence interval
Geographic locale based on U.S. Census 2010 Geographic Regions
Racial/ethnic categories based on the Office of Management and Budget standards.

Relative to no previous radiation exposure, cases exposed to radiation had 2.46 times the odds of developing SPTC (95% CI: 1.39-4.34). Table 4 shows the race/ethnicity specific strata for the association between previous radiation therapy exposure and SPTC. Hispanic children who had received radiation therapy had 3.85 times the odds of developing SPTC than Hispanic children who had not receive radiation therapy (95% CI: 0.83-17.71, p=0.02).

Table 4. Unadjusted Logistic Regression Model of Previous Exposure to Radiation and Second Primary Thyroid Cancer Stratified by Race,1973-2012 SEER data

	OR	95 % CI	p
Race/Ethnicity			
Non-Hispanic White	2.03	0.76-5.37	0.06
Non-Hispanic Black	-	-	-
Non-Hispanic Asian American	2.68	0.18-39.35	0.34
Non-Hispanic Other Race	-	-	-
Hispanic	3.85	0.83-17.71	0.02

Notes:
OR=odds ratio, CI=confidence interval, p=p value
Geographic Locale based on U.S. Census 2010 Geographic Regions
Racial categories based on the Office of Management and Budget population breakdown.
Insufficient data for Non-Hispanic Black and Non-Hispanic Other Race to produce a point estimate
Despite a statistically significant p value for Hispanic children, the reduced sample size from the excluded cases resulted in a wide confidence interval that crosses 1.

Table 5 shows the adjusted model for the association between SPTC and previous radiation therapy received by race/ethnicity. After adjustment for sex and age at diagnosis, the association between previous radiation therapy exposure and SPTC persisted among Hispanics. Hispanic children who received radiation therapy for primary malignancy had 3.51 times the odds of developing SPTC in comparison to Hispanic children who had not received radiation therapy, [Adjusted Odds Ratio (AOR)=3.51, 99% CI: 0.69-17.70, p=0.04].

Table 5. Adjusted Logistic Regression Model of Previous Exposure to Radiation and Second Primary Thyroid Cancer Stratified by Race,1973-2012 SEER data

	AOR	99 % CI	p
Race/Ethnicity			
Non-Hispanic White	1.94	0.72-5.24	0.08
Non-Hispanic Black	-	-	-
Non-Hispanic Asian American	1.81	0.11-29.20	0.58
Non-Hispanic Other Race	-	-	-
Hispanic	3.51	0.69-17.70	0.04

Notes:
AOR=adjusted odds ratio, CI=confidence interval, p=p value
Geographic locale based on U.S. Census 2010 Geographic Regions
Racial/ethnic categories based on the Office of Management and Budget standards.
Adjusted for sex and age at diagnosis
Insufficient data for Non-Hispanic Black and Non-Hispanic Other Race to produce a point estimate
Despite a statistically significant p value for Hispanic children, the reduced sample size from the excluded cases resulted in a wide confidence interval that crosses 1.
Insurance and geographic locale, although confounders, were not included in the model due to the large amount of unknown information within the dataset for the time period of interest.

V. Discussion

Using SEER data from 1973-2012, we assessed the association between previous radiation therapy exposure and the odds of developing second primary thyroid cancer (SPTC) among children 0-19 years old. Additionally, we determined with appropriate modeling whether the observed relationship varied by race/ethnicity. This investigation has a few relevant findings. First, although imprecise, there was a sizeable effect size found in the association between previous radiation therapy exposure on the development of SPTC in children. Second, SPTC was associated with sex and age at diagnosis but not geographic locale. Third, the association between previous radiation therapy exposure and the SPTC development in children varied by race/ethnicity.

This study demonstrates an association between previous radiation therapy received for first primary malignancy and the odds of developing SPTC among children. This finding is supported by previous literature which has demonstrated that radiation results in cellular mutation, thus increasing the risk of abnormal cellular proliferation (26). For the past 40 years, studies have shown an association between radiation and the development of cancer in adulthood (29); however the association between radiation and the development of pediatric cancer, or more specifically pediatric thyroid cancer, has not been investigated as thoroughly. Our study attempted to fill this gap by investigating the impact that radiation based therapeutics and diagnostics have on the development of second primary cancers. Whereas SEER data have been used to assess the odds of second primary malignancies, we are unaware of any study that has investigated the role of radiation therapy received and the development of SPTC in children. We surmise that our study represents the largest sample that has clearly implicated with a sizeable magnitude

(OR=2.46) the risk of development of SPTC given previous exposure to radiation. Overall, our findings are supported by similar studies of adults (2, 5).

We have demonstrated that SPTC is associated with the sex of the child and age at diagnosis of the malignancy. Based on our data, development of SPTC among girls showed increased odds when compared to boys. Previous studies in adults have clearly illustrated similar patterns with respect to sex and cancer incidence including thyroid (2, 5). The primary function of the thyroid is to regulate metabolism, and females have been shown to have impaired thyroid regulation relative to males (30). This observation, from either a metabolic perspective or infectious perspective, may introduce or initiate DNA damage that results in ultimate abnormal cellular proliferation (31, 32). The observed increased odds of thyroid cancer in girls may be due to survival advantage of girls following the diagnosis for the first primary malignancy. Previous studies have shown increased odds among girls of primary thyroid cancer as well as survival advantage of girls with other malignancies, namely leukemia (31).

Age at diagnosis has been shown to influence cancer diagnosis and survival in children (16-18). Among those who had SPTC, 69.3% of cases were 15-19 years of age at the time of diagnosis. This finding is consistent with previous studies given that cancer often has a long induction period (18). However, since the focus of this study was examine only those who developed second primary thyroid cancer before the age of 20, a significant portion of potential SPTC cases could have been excluded from this study. Although most childhood malignancies are diagnosed among younger age groups, pediatric thyroid cancer in particular is mainly diagnosed among older age groups. Given this, children diagnosed with a first primary cancer at the later ages of childhood could

have ended up developing second primary thyroid cancer as an adult. Future studies should examine development of SPTC by time since exposure or age at first primary cancer.

The observation of race/ethnicity as an effect measure modifier in the association between previous radiation therapy exposure and SPTC is a new finding given that we are unaware of any other data or studies that demonstrate this observed association. Despite the novelty of our findings, the SEER program provides limited data on factors that could possibly explain these racial/ethnic variances. For example, data on family history of cancer, parental exposure in occupational and environmental settings, smoking, vitamin ingestion, diet, and socioeconomic status (SES) could have provided further explanation to the observed racial/ethnic variances in the association between previous radiation therapy exposure and SPTC in children. In addition to this, retrospective information on previous malignancies the case may have endured, such as first primary cancer type, histological subtype of the first primary cancer type or previous radiation therapy type that was received, could have explained why certain racial/ethnic groups seem to experience a greater effect in this association. Although the majority of pediatric cancers are treated with external radiation, the type of radiation therapy used varies by cancer type. Hispanic children have a higher incidence of certain solid tumor primary malignancies (e.g., germ cell tumors, retinoblastoma) which can impact the type of previous radiation therapy received and subsequent risk of developing treatment-related malignancies. (33).

Socioeconomic status (SES) has been implicated as a potential risk factor in the development of childhood malignancies (e.g., lymphoid leukemia) and this variable may

act as a proxy for access to care. (34). In addition, parental occupational exposure (i.e., metal, automotive, radiation related industries, agriculture) as well as environmental exposures associated with pollutants may explain predisposition to excess cancer incidence in children including SPTC among those with low SES.

VI. Study Strengths and Limitations

There were several strengths to this study. The SEER dataset is nationally representative of approximately 28% of the U.S. population and consists of data from cancer registry sites strategically located in 20 different geographic areas (27, 28). The large sample size of this study allowed for sufficient power for the analysis. The large sample size also allowed the use of advanced statistical methods (i.e., multivariable regression analysis) in this study given the satisfactory cancer counts seen in each of the subcategories in this dataset. The SEER database also has certain quality standards in place that minimize the misclassification of variables, in particular gender, age and race (27, 28). This is accomplished through the SEER Quality Improvement Teams located at each of the cancer registry sites who work to ensure that there is standardized medical coding and summary writing by the individuals who collect and code patient data at each cancer registry (27). Finally, the study design allowed us to investigate an outcome with a long induction period. By using a retrospective cohort study design, we avoided a potentially lengthy follow up period seen in most prospective study designs that investigate cancer. Also, given SEER data's accessibility, and our low research costs, our study was relatively inexpensive.

Since this study was based on a secondary data analyses, we were limited in the availability of data on potential confounders. Complete information on insurance status,

tumor grade, histological subtype, environmental and parental exposures, and other potential confounders were not available on the dataset, or of insufficient quality (e.g., high percentage of missing data) to use for our analysis. For example, all pediatric second primary thyroid cancer cases in the SEER dataset for 1973-2012 were localized at the time of diagnosis and do not reflect those who would later develop metastasis. As seen in current literature, a large proportion of children with pediatric thyroid cancer eventually end up developing metastasis (6, 16, 17), and by not having this information, we are unable to control for this difference in the sample. SEER data, despite its accuracy and reliability do not have sufficient variables to assess individual and community risk factors. Collection of data on exposures and individual health behaviors, such as diet, environmental and parental exposures may enhance this dataset for further understanding regarding the role played by potential carcinogens in the development of SPTC. Due to the unavailability of these potential confounders or risk factors in the association between previous radiation therapy exposure and SPTC, our results may be influenced by residual confounding. However, we do not assume that the observed association is driven solely by these unmeasured confounders in our study given the biologic plausibility of ionizing radiation and cellular mutation including DNA instability and damage.

Racial/ethnic variability in the observed association between the previous radiation therapy exposure and SPTC may be further explained by SES, family history, parental occupation, as well as host factors. However, given that the sub-group analysis was underpowered despite sufficient power for the main association, caution should be taken when interpreting and inferring the results of this analysis (35). The wide confidence interval that was observed for Hispanics containing one, despite the statistically

significant p-value (Table 4), could be explained by the relatively small numbers of cancer cases in the analysis, and the fact that the statistical software package STATA uses different tests to estimate the p value (likelihood ratio) and confidence intervals (Wald statistic) (35). Finally, there may be potential misclassification of the exposure and the outcome variables resulting in information bias; however, given the National Cancer Institutes' quality standards and practices, the possibility for misclassification is low and would be most likely non-differential.

VII. Public Health Significance

Pediatric cancer remains the leading cause of disease related death among children in the United States (1). Despite improvements in the 5 year related survival rate for pediatric cancer, the incidence of second primary cancers continues to increase. The increase in incidence may be due in part to improvement in diagnostics as well as the influence of certain risk factors which are not completely understood. Lack of understanding of the causes of pediatric cancer remains a challenge for public health professionals and requires public health action in mounting a defense against this disease. In order to address this need, further research is required in order to improve pediatric cancer treatment through management decisions based on evidence involving quality control, planning, training, and evaluation of effectiveness of treatment programs and intervention.

This study has the potential to guide our understanding of the role played by therapeutics and diagnostics in children and the long term adverse effect they have on the development of second primary thyroid cancer. By using the National Cancer Institute's SEER data, we are able to assess risk factors for second primary thyroid cancer in

children with a nationally, representative sample and with adequate power. As a result, this study provides reliable and valuable information for public health decision making regarding pediatric thyroid cancer prevention and education. This study can contribute to the evidence base for future public health policy development, specifically relating to the regulation of the use of ionizing radiation as well as radioactive imaging, including CT scans, in diagnostics and therapeutics in children. Such policies could eventually lead to a reduction in second primary thyroid cancer among children.

VIII. Conclusion

In summary, previous radiation therapy received for first primary malignancy is associated with increased risk of SPTC in children. Additionally, the association between SPTC and previous radiation therapy exposure indicates racial/ethnic heterogeneity. These findings, although imprecise, are suggestive of the need to develop age-specific guidelines for the use of radiation based therapeutics and diagnostics in children with and without cancer. These findings also support the need to develop guidelines for the management and treatment of first primary malignancies in children in order to reduce the incidence of subsequent treatment-related malignancies. Finally, given the limitations of this preliminary study, additional research should be conducted focusing on this particular association and our findings should be replicated by others.

IX. References

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