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The Risk of Second Cancers After Diagnosis of Primary Thyroid Cancer Is Elevated in Thyroid Microcarcinomas

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Background: Thyroid cancers have increased dramatically over the past few decades. Comorbidities may be important, and previous studies have indicated elevated second cancer risk after initial primary thyroid cancers. This study examined the risk of second cancers after development of a thyroid cancer, primary utilizing the Surveillance, Epidemiology, and End Results (SEER) program database.
Methods: The cohort consisted of men and women diagnosed with first primary thyroid cancer who were reported to a SEER database in 1973–2008 ($n = 52{,}103$). Standardized incidence ratios (SIR) were calculated for all secondary cancers. Confidence intervals and p-values are at 0.05 significance alpha level and are two-sided based on Poisson exact methods.
Results: In this cohort, 4457 individuals developed second cancers. The risk of developing second cancers after a primary thyroid cancer varied from 10% to 150% depending on different cancer types. Cancers in all sites, breast, skin, prostate, kidney, brain, salivary gland, second thyroid, lymphoma, myeloma, and leukemia were elevated. The magnitude of the risk varied by histology, tumor size, calendar year of first primary thyroid cancer diagnosis, and the treatment of the primary thyroid cancer. The risk of a second cancer was elevated in patients whose first primary thyroid carcinomas were small, or were diagnosed after 1994, or in whom some form of radiation treatment was administered.
Conclusions: This large population-based analysis of second cancers among thyroid cancer patients suggests that there was an increase of second cancers in all sites, and the most commonly elevated second cancers were the salivary gland and kidney. Additionally, the increase in second cancers in patients with recently diagnosed thyroid microcarcinomas (< 10 mm) suggests that aggressive radiation treatment of the first primary thyroid cancer, the environment, and genetic susceptibility, may increase the risk of a second cancer.

Introduction

Thyroid cancer has increased dramatically over the past few decades in the United States (1). According to the Surveillance, Epidemiology, and End Results (SEER) report, thyroid cancer has the fastest reported increase in age-adjusted annual incidence rate compared to other cancers. During the past few years, the rate has increased from $3.4/10^5$ in 1994 to $6.5/10^5$ in 2008 in males, and increased from $8.7/10^5$ in 1994 to $19.4/10^5$ in 2008 in females (2). While a portion of this increase can be attributed to better detection methods, it does not account for all of the increase (3). Because thyroid cancer is highly curable with a five-year survival rate >95%, monitoring treatment outcomes and side effects are important (2).

Several studies have reported a consensus increase in the risk of second primary cancers among thyroid cancer primary patients. A European study suggested that second cancers were elevated 27% compared to general population cancer rates, and that treatment may play a role in future second cancer risk (4). In a pooled analysis of 13 registries, a UK group discovered a 31% increase (5). One study utilizing SEER data through 2000 reported a 42% increased risk of developing second cancers in thyroid cancer patients. Another study with SEER data through 2002 reported a 9% increase in second primary cancers (6). However, none of these studies examined the second cancer risk by size of the primary thyroid cancer. Diagnoses of thyroid cancers of small size have increased with time (1), but it has been unclear whether

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this increase is due to better detection methods or an actual increase in thyroid cancers (7).

Using the current SEER database, we systemically examined the risk of second cancers after primary thyroid cancers that were diagnosed in the United States between 1973 and 2008. This was done to determine if characteristics such as histology, tumor size, time of diagnosis, and treatment influenced the risk of a second cancer.

Methods and Materials

Source population

The baseline cohort for this analysis consisted of individuals diagnosed with a primary thyroid cancer and identified by site code ICD-0-3: C739, reported to a SEER 9 database between 1973 and 2008 ($n = 52{,}103$). Individuals were followed up through death or the end of the study period (December 31, 2008). Men and women of all ages and U.S. Office of Management and Budget race/ethnicity codes (OMB codes) were included in this analysis. Any second cancers within the first two months after initial thyroid cancer were excluded from the second cancer group unless otherwise stated. A total of 4457 patients developed a second cancer after their diagnosis of a primary thyroid cancer. Additionally, several stratified analyses were conducted by various characteristics of the first thyroid cancer, which included analyses by histologic subtype of the thyroid cancer (papillary: M8050, M8052, M8260, M8340–M8344, M8450; follicular: M8290, M8330–M8332, M8335; medullary: M8345, M8346, M8510; anaplastic: M8021), tumor size (data available for 1988–2008, 0–10 mm, 11–20 mm, 21–50 mm, >51 mm), year of diagnosis of the thyroid cancer, and the status of radiation treatment of for that cancer (no radiation, isotopes only, beam radiation, radiation not otherwise specified).

Statistical analysis

The number of observed second cancers was determined from the SEER database. Expected cancers were calculated based on the 2000 U.S. standard population distribution. Standardized incidence ratios (SIRs) were calculated by dividing the number of observed cancers by expected cancers. Confidence intervals (CIs) and *p*-values were at 0.05 significance alpha levels and were two-sided based on Poisson exact methods. To avoid statistically unstable estimates, SIRs and CIs were not presented where the number of observed cancers was less than five. All analyses were conducted with the National Cancer Institute's (NCI) statistical program SEER*Stat version 7.0.4 (8) utilizing the MP-SIR (multiple primary standardized incidence ratio) tool.

Results

In this cohort, 4457 individuals developed a second cancer after having thyroid cancer (Table 1). Of these, 2939 were female (65.94%) and 1518 were male (34.06%). The group was predominantly white (85.24%) according to OMB codes. The majority of initial thyroid cancers were diagnosed prior to the age of 40 (37.50%) and the majority of these diagnoses occurred in 1994 or later (61.69%). As expected, the majority of the initial thyroid cancers were papillary (83.66%). A plurality of the initial thyroid cancers were small (0–10 mm) in size (21.80%). More second cancers were diagnosed between ages 50 and 59 years (24.34%) than in any other age group, and the majority were in patients who had their first primary diagnosed either between 1973 and 1983 (36.17%) or between 1984 and 1993 (30.85%).

Table 1. Characteristics of Patients with a First Primary Thyroid Cancer and a Second Primary Cancer, SEER 1973–2008

	First primary		*Second primary*	
	N *(52,103)*	%	n *(4457)*	%
Sex				
Male	12,875	24.71%	1518	34.06%
Female	39,228	75.29%	2939	65.94%
Race/ethnicity				
Black	2932	5.63%	272	6.10%
White	43,045	82.62%	3799	85.24%
Other	5717	10.97%	384	8.62%
Unknown	409	0.78%	2	0.04%
Age at diagnosis (years)				
<40	19,539	37.50%	794	17.81%
40–49	11,653	22.37%	959	21.52%
50–59	9408	18.06%	1085	24.34%
60–69	6211	11.92%	1009	22.64%
70+	5292	10.16%	610	13.69%
Year of diagnosis				
1973–1983	8978	17.23%	1612	36.17%
1984–1993	10,983	21.08%	1375	30.85%
1994–2003	17,745	34.06%	1192	26.74%
2004–2008	14,397	27.63%	278	6.24%
Histology				
Papillary	41,989	83.66%	—	—
Follicular	6438	12.83%	—	—
Medullary	1314	2.62%	—	—
Anaplastic/other	450	0.90%	—	—
Tumor size				
0–10 mm	11,356	21.80%	672	15.08%
11–20 mm	9981	19.16%	501	11.24%
21–50 mm	11,018	21.15%	624	14.00%
>51 mm	6737	12.93%	493	11.06%
N/A	13,011	24.97%	2167	48.62%
Radiation treatment				
None	29,376	58.39%	2814	63.35%
Beam radiation	2019	4.01%	201	4.52%
Isotopes	16,602	33.00%	934	21.03%
Radiation, NOS	130	0.26%	423	9.52%
Other	2182	4.34%	70	1.58%

N/A, not available; NOS, not otherwise specified.

The risk of developing a second cancer was elevated among both males (13%) and females (7%; Table 2). Second salivary cancers after the initial thyroid cancer were elevated by 211% (SIR 3.11 [CI 2.12–4.42]), kidney cancer by 130% (SIR 2.30 [CI 2.00–2.64]), thyroid cancer by 65% (SIR 1.65 [CI 1.39–1.94]), myeloma by 57% (SIR 1.57 [CI 1.23–1.96]), leukemia by 40% (SIR 1.40 [CI 1.17–1.66]), brain cancer by 38% (SIR 1.38 [CI 1.06–1.76]), melanoma of the skin by 28% (SIR 1.28 [CI 1.10–1.46]), prostate cancer by 22% (SIR 1.22 [CI 1.11–1.33]), lymphoma by 16% (SIR 1.16 [CI 1.01–1.33]), and breast cancer by 13% (SIR 1.13 [CI 1.06–1.20]). The results were similarly elevated when analyses were stratified by sex.

Table 2. Standardized Incidence Ratios of Second Cancer Risk in Thyroid Cancer Patients, Overall and by Sex

	Overall		*Female*		*Male*	
Sites	n	*SIR [CI]*	n	*SIR [CI]*	n	*SIR [CI]*
All sites	4457	1.09 [1.06–1.12]	2939	1.07 [1.03–1.11]	1518	1.13 [1.07–1.18]
Oral cavity and pharynx	84	0.95 [0.76–1.18]	44	0.96 [0.70–1.28]	40	0.95 [0.68–1.30]
Salivary	31	3.11 [2.12–4.42]	12	3.30 [1.71–5.77]	19	3.00 [1.81–4.69]
Digestive system	720	0.94 [0.88–1.02]	466	0.94 [0.86–1.03]	254	0.95 [0.84–1.07]
Esophagus	22	0.66 [0.41–1.00]	7	0.51 [0.21–1.06]	15	0.76 [0.42–1.25]
Stomach	72	1.10 [0.86–1.38]	40	1.08 [0.77–1.47]	32	1.12 [0.77–1.58]
Small intestine	19	1.24 [0.75–1.94]	11	1.09 [0.54–1.95]	8	1.54 [0.66–3.03]
Colon, rectum, and anus	461	0.99 [0.90–1.08]	308	0.98 [0.87–1.10]	153	1.01 [0.85–1.18]
Liver, gallbladder, intrahep bile duct, and other biliary	57	0.85 [0.64–1.10]	34	0.85 [0.59–1.19]	23	0.84 [0.53–1.26]
Liver	31	0.86 [0.58–1.22]	15	0.86 [0.48–1.42]	16	0.86 [0.49–1.39]
Pancreas	83	0.82 [0.66–1.02]	61	0.89 [0.68–1.15]	22	0.68 [0.43–1.03]
Respiratory system	531	0.89 [0.82–0.97]	329	0.90 [0.81–1.00]	202	0.88 [0.76–1.01]
Lung and bronchus	504	0.90 [0.83–0.98]	315	0.90 [0.80–1.00]	189	0.91 [0.78–1.05]
Skin excluding basal and squamous	218	1.28 [1.12–1.46]	131	1.19 [0.99–1.41]	87	1.46 [1.17–1.80]
Melanoma of the skin	200	1.28 [1.10–1.46]	119	1.17 [0.97–1.40]	81	1.47 [1.17–1.83]
Other non-epithelial skin	18	1.36 [0.81–2.15]	12	1.43 [0.74–2.49]	6	1.24 [0.46–2.71]
Breast	1041	1.13 [1.06–1.20]	1037	1.13 [1.06–1.20]	4	—
Female genital system	339	0.93 [0.84–1.04]	339	0.93 [0.84–1.04]	0	—
Cervix uteri	38	0.71 [0.50–0.97]	38	0.71 [0.50–0.97]	0	—
Corpus and uterus, NOS	177	0.95 [0.82–1.11]	177	0.95 [0.82–1.11]	0	—
Ovary	106	1.07 [0.88–1.30]	106	1.07 [0.88–1.30]	0	—
Prostate	511	1.22 [1.11–1.33]	0	—	511	1.22 [1.11–1.33]
Testis	9	1.31 [0.60–2.49]	0	—	9	1.31 [0.60–2.49]
Urinary system	345	1.32 [1.18–1.46]	173	1.38 [1.18–1.60]	172	1.26 [1.08–1.47]
Urinary bladder	114	0.74 [0.61–0.89]	44	0.69 [0.50–0.93]	70	0.77 [0.60–0.97]
Kidney and renal pelvis	224	2.24 [1.96–2.55]	128	2.20 [1.83–2.61]	96	2.30 [1.86–2.81]
Renal pelvis, ureter, and other urinary organs	18	1.22 [0.72–1.92]	7	0.84 [0.34–1.73]	11	1.71 [0.85–3.05]
Kidney	213	2.30 [2.00–2.64]	122	2.27 [1.89–2.71]	91	2.35 [1.89–2.88]
Renal pelvis	11	1.46 [0.73–2.61]	6	1.33 [0.49–2.90]	5	1.65 [0.54–3.85]
Eye and orbit	7	1.10 [0.44–2.26]	7	1.66 [0.67–3.42]	0	—
Brain and other nervous system	70	1.45 [1.13–1.83]	47	1.47 [1.08–1.95]	23	1.40 [0.89–2.1]
Brain	63	1.38 [1.06–1.76]	42	1.40 [1.01–1.89]	21	1.34 [0.83–2.04]
Cranial nerves other nervous system	7	2.55 [1.03–5.26]	5	2.46 [0.80–5.75]	2	2.81 [0.34–10.15]
Endocrine system	152	1.69 [1.43–1.98]	118	1.49 [1.24–1.79]	34	3.04 [2.10–4.25]
Thyroid	141	1.65 [1.39–1.94]	113	1.49 [1.23–1.79]	28	2.85 [1.90–4.12]
Thymus, adrenal gland, and other endocrine	11	2.37 [1.18–4.24]	5	1.53 [0.50–3.56]	6	4.38 [1.61–9.52]
Thymus	4	—	2	—	2	—
Adrenal gland	5	2.94 [0.95–6.86]	3	—	2	—
All lymphatic and hematopoietic diseases	415	1.29 [1.17–1.42]	267	1.28 [1.13–1.45]	148	1.31 [1.11–1.54]
Lymphoma	206	1.16 [1.01–1.33]	138	1.17 [0.98–1.39]	68	1.14 [0.89–1.45]
Hodgkin lymphoma	21	1.30 [0.8–1.98]	16	1.43 [0.82–2.33]	5	0.99 [0.32–2.31]
Non-Hodgkin lymphoma	185	1.15 [0.99–1.33]	122	1.14 [0.95–1.37]	63	1.16 [0.89–1.48]
Myeloma	75	1.57 [1.23–1.96]	46	1.48 [1.09–1.98]	29	1.72 [1.15–2.47]
Leukemia	134	1.40 [1.17–1.66]	83	1.40 [1.12–1.74]	51	1.39 [1.04–1.83]
Lymphocytic leukemia	57	1.26 [0.96–1.63]	33	1.25 [0.86–1.75]	24	1.28 [0.82–1.90]
Non-lymphocytic leukemia	77	1.52 [1.20–1.90]	50	1.52 [1.13–2.01]	27	1.51 [1.00–2.20]
Other leukemia	9	1.38 [0.63–2.62]	5	1.18 [0.38–2.74]	4	—
Miscellaneous	93	1.08 [0.87–1.32]	63	1.06 [0.82–1.36]	30	1.11 [0.75–1.59]

SIR, standardized incidence ratio; CI, 95% confidenci interval.

For individuals whom data on tumor size were available (52%), the risk of second cancers was elevated for most tumor sizes (Table 3). Breast, prostate, kidney, and thyroid cancers, as well as melanoma, were elevated in both small and large size initial thyroid cancer, but skin, brain, and salivary cancers, as well as leukemia, were elevated only in when the initial thyroid cancer was >10 mm. The greatest elevation for second cancers among initial small thyroid cancers (<10 mm) was kidney cancer (SIR 3.24 [CI 2.26–4.22]), and the greatest increase among initial large thyroid cancers (>51 mm) was a second thyroid cancer (SIR 3.49 [CI 2.23–5.19]).

The risk of second cancer for those who received radiation treatment for their initial thyroid cancer was elevated between 19% and 38%, but was not elevated for individuals who did not receive any radiation treatment for their initial thyroid cancer (Table 3). The risk of second cancer was most

Table 3. Standardized Incidence Ratios of Selected Second Cancer Risk in Thyroid Cancer Patients by Tumor Size and Treatment

	Tumor size							
	0–10 mm		*11–20 mm*		*21–50 mm*		*>51 mm*	
Site	n	*SIR [CI]*	n	*SIR [CI]*	n	*SIR [CI]*	n	*SIR [CI]*
All sites	672	1.27 [1.17–1.37]	501	1.10 [1.00–1.20]	624	1.07 [0.98–1.15]	493	1.31 [1.19–1.42]
Salivary	8	0.87 [0.27–1.47]	4	—	6	4.05 [0.81–7.30]	4	—
Kidney	42	3.24 [2.26–4.22]	18	1.63 [0.88–2.39]	26	1.80 [1.11–2.5]	24	2.58 [1.55–3.61]
Breast	174	1.28 [1.09–1.47]	123	1.04 [0.85–1.22]	129	1.05 [0.87–1.23]	89	1.28 [1.01–1.55]
Prostate	68	1.44 [1.09–1.78]	51	1.29 [0.94–1.65]	91	1.27 [1.01–1.53]	63	1.17 [0.88–1.46]
Melanoma of the skin	31	1.32 [0.85–1.78]	39	1.81 [1.24–2.37]	33	1.32 [0.87–1.77]	19	1.26 [0.7–1.83]
Non-Hodgkin lymphoma	23	1.08 [0.64–1.53]	18	0.98 [0.53–1.44]	31	1.29 [0.84–1.75]	24	1.56 [0.94–2.19]
Thyroid	29	1.21 [0.81–1.74]	43	1.63 [1.18–2.2]	45	1.59 [1.16–2.12]	24	3.49 [2.23–5.19]
Leukemia	17	1.46 [0.77–2.15]	19	1.89 [1.04–2.74]	29	2.08 [1.32–2.84]	14	1.52 [0.72–2.31]
Myeloma	13	2.20 [1–3.4]	13	2.65 [1.21–4.1]	6	0.87 [0.17–1.56]	10	2.12 [0.81–3.43]
Brain	8	1.35 [0.42–2.29]	15	2.80 [1.38–4.22]	6	0.91 [0.18–1.64]	4	—

	Radiation treatment							
	None		*Isotopes*		*Beam radiation*		*Radiation, NOS*	
Site	n	*SIR [CI]*	n	*SIR [CI]*	n	*SIR [CI]*	n	*SIR [CI]*
All sites	2814	1.02 [0.98–1.06]	934	1.25 [1.17–1.33]	201	1.39 [1.19–1.58]	423	1.2 [1.09–1.32]
Salivary	18	2.72 [1.61–4.30]	11	5.70 [2.85–10.21]	2	—	0	—
Kidney	129	2.12 [1.77–2.52]	44	2.35 [1.7–3.15]	14	4.26 [2.03–6.48]	23	3.02 [1.79–4.26]
Breast	717	1.13 [1.05–1.21]	193	1.14 [0.98–1.31]	27	1.02 [0.64–1.41]	86	1.17 [0.92–1.42]
Prostate	302	1.15 [1.03–1.29]	117	1.36 [1.13–1.63]	24	1.17 [0.7–1.64]	50	1.22 [0.88–1.56]
Melanoma of the skin	122	1.20 [1.00–1.43]	54	1.57 [1.18–2.05]	3	—	18	1.45 [0.78–2.12]
Non-Hodgkin lymphoma	107	0.99 [0.81–1.2]	44	1.44 [1.05–1.93]	9	1.62 [0.56–2.67]	22	1.63 [0.95–2.32]
Thyroid	115	2.15 [1.78–2.58]	18	0.84 [0.5–1.33]	2	—	3	—
Leukemia	74	1.14 [0.89–1.43]	41	2.39 [1.71–3.24]	6	1.70 [0.34–3.06]	11	1.35 [0.55–2.15]
Myeloma	50	1.53 [1.14–2.02]	15	1.79 [1–2.95]	1	—	7	1.73 [0.45–3.02]
Brain	44	1.44 [1.05–1.94]	13	1.49 [0.8–2.56]	0	—	5	1.27 [0.16–2.38]

elevated for those who received directed beam radiation for their initial thyroid cancer (SIR 1.39 [CI 1.19–1.58]). Kidney cancer was the most elevated second cancer, particularly among patients who received beam radiation for their initial thyroid cancer (SIR 4.26 [CI 2.03–6.48]) and radiation not otherwise specified for their initial thyroid cancer (SIR 3.02 [CI 1.79–4.26]).

The risk of second primary cancers was varied somewhat by histologic subtype of the initial thyroid cancer (Table 4). Breast, prostate, skin, and brain cancers, as well as leukemia and myeloma, were elevated for patients whose initial thyroid cancer was a papillary subtype by histology. Kidney cancer was elevated for all histologic subtypes of the initial thyroid cancer except for initial medullary thyroid carcinoma. Salivary cancer was elevated in patients whose initial thyroid cancer was papillary thyroid carcinoma. Second thyroid cancers were elevated among patients whose initial thyroid carcinoma was papillary, or follicular, or medullary thyroid carcinoma.

The risk of second cancer was significantly elevated for patients who had their initial thyroid cancer diagnosed between 1994 and 2008 (Table 4). The most recent time period (2004–2008) had the highest elevation in risk (SIR 1.45 [CI 1.28–1.62]) followed by 1994–2003 (SIR 1.21 [CI 1.14–1.28]). Certain cancers such as breast, prostate, kidney, brain, and salivary cancers, as well as myeloma, were also elevated among patients whose initial thyroid cancer was diagnosed before 1994.

Discussion

This study shows is that patients with thyroid cancer had an increased risk of developing a second cancer in all sites examined including salivary gland, kidney, prostate, skin, breast, brain, myeloma, leukemia, and non-Hodgkin lymphoma, compared to the general population. This was noted particularly for recently diagnosed initial thyroid cancers and radiation treated initial thyroid cancers. Both small and large initial thyroid cancers were associated with an increased risk of developing second cancers.

It has been suggested that recent increases in the diagnoses or thyroid cancer is due to better detection of small nodules and is not a true increase in incidence of thyroid cancer (1). The results presented in this study, however, suggest that the most recently diagnosed and all sizes of thyroid cancers increase the

Table 4. Standardized Incidence Ratios of Selected Second Cancer Risk in Thyroid Cancer Patients by Histology and Year of Diagnosis

	Histologic subtypes							
	Papillary		*Follicular*		*Medullary*		*Anaplastic*	
Site	n	*SIR [CI]*	n	*SIR [CI]*	n	*SIR [CI]*	n	*SIR [CI]*
All sites	3405	1.09 [1.06–1.13]	764	1.06 [0.99–1.14]	117	0.9 [0.74–1.06]	11	1.93 [0.96–3.44]
Salivary	29	3.78 [2.53–5.43]	2	—	0	—	0	—
Kidney	161	2.26 [1.93–2.64]	37	2.35 [1.65–3.24]	1	—	2	—
Breast	835	1.14 [1.06–1.22]	153	1.07 [0.91–1.25]	28	1.16 [0.77–1.68]	0	—
Prostate	385	1.26 [1.14–1.39]	99	1.18 [0.96–1.43]	13	0.81 [0.43–1.38]	1	—
Melanoma of the skin	164	1.31 [1.12–1.53]	24	1.03 [0.66–1.53]	8	1.84 [0.79–3.62]	1	—
Non-Hodgkin lymphoma	138	1.12 [0.94–1.32]	27	0.97 [0.64–1.41]	10	1.95 [0.94–3.59]	0	—
Thyroid	104	1.46 [1.19–1.77]	25	2.31 [1.5–3.42]	8	4.44 [1.92–8.74]	0	—
Leukemia	106	1.48 [1.21–1.78]	22	1.25 [0.78–1.89]	1	—	2	—
Myeloma	58	1.63 [1.24–2.11]	13	1.42 [0.76–2.44]	2	—	0	—
Brain	52	1.46 [1.09–1.92]	9	1.21 [0.55–2.29]	1	—	0	—
	Year of diagnosis							
	1973–1983		*1984–1993*		*1994–2003*		*2004–2008*	
Site	N	*SIR [CI]*	N	*SIR [CI]*	N	*SIR [CI]*	N	*SIR [CI]*
All sites	1612	1.02 [0.97–1.07]	1375	1.03 [0.97–1.08]	1192	1.21 [1.14–1.28]	278	1.45 [1.28–1.62]
Salivary	10	2.68 [1.28–4.93]	4	—	11	4.37 [2.18–7.83]	6	12.08 [4.43–26.29]
Kidney	77	2.37 [1.87–2.96]	61	2.07 [1.58–2.65]	58	2.33 [1.77–3.01]	17	3.13 [1.83–5.02]
Breast	394	1.13 [1.02–1.25]	318	1.06 [0.95–1.18]	280	1.21 [1.08–1.37]	49	1.09 [0.81–1.45]
Prostate	163	1.09 [0.93–1.27]	182	1.28 [1.1–1.48]	141	1.32 [1.11–1.56]	25	1.21 [0.78–1.78]
Melanoma of the skin	56	1.09 [0.82–1.41]	64	1.27 [0.98–1.63]	61	1.34 [1.03–1.73]	19	1.95 [1.18–3.05]
Non-Hodgkin lymphoma	62	1.03 [0.79–1.32]	57	1.08 [0.82–1.4]	58	1.44 [1.09–1.86]	8	1.02 [0.44–2]
Thyroid	29	1.21 [0.81–1.74]	43	1.63 [1.18–2.2]	45	1.59 [1.16–2.12]	24	3.49 [2.23–5.19]
Leukemia	41	1.08 [0.78–1.47]	35	1.13 [0.79–1.57]	50	2.2 [1.63–2.9]	8	1.88 [0.81–3.7]
Myeloma	23	1.22 [0.77–1.83]	25	1.61 [1.04–2.38]	21	1.85 [1.14–2.83]	6	2.73 [1–5.93]
Brain	24	1.37 [0.87–2.03]	24	1.64 [1.05–2.43]	13	1.16 [0.62–1.98]	2	—

risk of second cancers. Current American Thyroid Association (ATA) guidelines include recommendations for fine needle aspiration (FNA) evaluation of small nodules, particularly in high-risk individuals (9). Our data show an increasing trend in risk of second cancer, particularly for salivary and kidney cancers and myeloma, across time periods, with the most recent years having the largest increase in second cancers. Even if recent diagnoses were limited to small-sized thyroid tumors that previously went undetected, their presence still increased the risk of second cancers, suggesting the detection of these small first tumors is not necessarily trivial.

Increased risk of cancer among small thyroid tumors could be due to aggressive treatment involving radiation exposure. Currently, suggested treatment for microcarcinomas is total thyroidectomy (9). However, many patients may receive ^{131}I (10). In the future, consideration of a patient's individual tumor genome (including *BRAF* genotype, etc.) may help develop a cohesive treatment plan (11). Currently, in rare cases or where staging of the thyroid tumor is stage IV, directed beam radiation therapy may follow (12). Radiation (radioisotopes included) is known to elevate cancer risk (13). Studies of second cancer risk in thyroid cancer patients treated with radioiodine have suggested an increased risk of second malignancy. Studies by Hall *et al.* (14), Rubino *et al.* (4), and Sawka *et al.* (15) reported that patients who received radioiodine had elevated second cancers, but a study by Chuang *et al.* did not note an overall increase in second cancers (16). External beam radiation irradiates areas of the body outside of the immediate target area, and many second cancers have been found close to the treated target organ (17). External beam radiation is often given to individuals in conjunction with radioisotopes if a tumor has a high chance of relapse, potentially exposing patients to multiple rounds of radiation (18). In our study, some individuals who received beam radiation for their initial thyroid cancer also received isotopes, which possibly accounted for the large increase in second thyroid and kidney cancers among those who received beam radiation. Overall, there was no observation of increased risk of second cancers in non-radiation treated patients in this study, although several cancers (*i.e.*, kidney, salivary, prostate, and myeloma) that were elevated by radiation treatment were also elevated in non-treated cases as well. That observation suggests other factors aside from treatment may influence second cancer risk (*e.g.*, genetic susceptibility). Additionally, the most

recently detected thyroid cancers had the highest risk of second cancer in this study, a period in which detection of small thyroid cancers increased and were treated similarly to large carcinomas. Aggressive treatment for microcarcinomas that were detected more recently might explain an elevation in the risk of a second cancer. In addition, this study shows a significant increase in second cancer of all sites combined among patients who received radiation treatments, although the reporting of radiation treatment in SEER has increased in completeness over the years. However, to remain consistent with older data, simplified data were utilized for this study.

The results of this study are consistent with others (4–6,19,20), and this study suggests an increase in the number of several cancers. All studies noted an increase in salivary, breast, and kidney cancers (4–6,19,20); three noted an increase in prostate, brain, and leukemias (5,6,19); two an increase in lymphomas (5,6); and one an increase in melanoma (6). Skin cancer risk, in particular, melanoma, which was elevated in just two studies (4,5), was only elevated in the most recently diagnosed patients and in patients who received isotope treatment and who had a tumor size of 11–20 mm. This result suggests that this may be a result of recent treatment for small nodules.

Overall, a second occurence of thyroid cancer was elevated by 69% in this study, and less than half of those cancers ($n = 69$) occurred within the first five years, suggesting the possibility of a second primary rather than recurrence of the initial thyroid cancer. Papillary thyroid cancer can recur several decades later and be multicentric, leading to detection of persistent disease. However, the most significant increase was in medullary thyroid cancer only, suggesting these patients were part of multiple endocrine neoplasia type 2 (MEN2) kindreds. However, after excluding all second thyroid cancers, the data were reanalyzed and the results remained largely the same.

As a public health concern, genetic and environmental factors could have played a role in the increased risk of thyroid cancer and subsequent cancers. Several common inherited single nucleotide polymorphisms (SNPs) were associated with increased risk of thyroid tumorigenesis, including *FOXE1* and *NKX2-1* (21); *VDR*, *XRCC1*, *ADPRT*, *WDR3*, *SPAG1*, *GDAP2*, and $P2X_7R_i$ (22). The *FOXE1* risk allele was associated with low T4 and thyrotropin (TSH) and high triiodothyronine (T3) serum concentrations, and the *NKX2-1* risk allele was associated with low TSH. Mutation of the *RET* gene and a missense variant (I157T) of the CHEK2 protein were associated with an increased risk of breast, colon, kidney, prostate, and thyroid cancer (23,24). Thyroid cancer and prostate cancer are also associated with the co-expression of *hK2* (25), *P2X7* (26), and *hTR* (27) genes. Common gene variants in *VHL* (28), *MET* (29), and *SDH* (30) increase the risk of kidney cancer and thyroid cancer. Kidney cancer is now considered to be a metabolic syndrome disorder (31) that is linked with hypothyroidism (32). A strong risk factor for thyroid cancers are thyroid diseases (33–35). Hyperthyroid function is associated with prostate cancer risk (36), and hypothyroid function is associated with kidney cancer risk (32). Radioiodine, a common treatment for thyroid cancer, is excreted through the urine and taken up in the salivary glands, causing acute and long-term effects, including second primary malignancies (37); an elevation of salivary gland cancer was observed in this study. Moreover, some chemicals such as polychlorinated biphenyls, dioxins, flame retardants, and pesticides cause endocrine disruption (38), altering T3, T4, and TSH homeostasis. There has been a significant increase in the quantity of these chemicals in the environment over the past 15 years (39), suggesting a potential environmental chemical role in thyroid health. Although there is a lack of evidence to support their direct association with thyroid and other cancers, these compounds have been speculated to play a role in carcinogenesis (40–42) and could be playing a role in the increase in thyroid cancer in recent years.

The primary strength of this study is the use of a large, standardized, well-established, and thorough population database representing a variety of locations throughout the United States. The SEER program has run since 1973, and contains rich information to perform the analyses. This study adds six years of additional follow-up compared to the most recent study (6). However, as with many registry-based studies of cancer, surveillance bias could be a concern, as previous cancer patients tend to be under enhanced surveillance and are more likely to be diagnosed with a second malignancy. To address this issue, we analyzed the data by latency period and found that the risk of second cancer was elevated up to 10 years after first primary diagnosis, suggesting that surveillance bias is unlikely a sole explanation of the observed associations. Potential misclassification bias is another concern. There may be some heterogeneity during the review of information. However, any significant bias present is likely to be non-differential, as many years and sites report and aggregate these data, making any systemic errors unlikely. Also, stratification by some variables made interpretation of the results statistically unstable (*e.g.*, anaplastic histologic subtype, since many patients die soon after diagnosis/treatment), making the results difficult to interpret. For size analyses, data were not captured prior to 1988. As such, the generalizability of these results may only be applicable to recently diagnosed tumors.

In summary, these large population-based tumor registry data in the United States suggest an increased risk of second cancers in all sites. In particular, the salivary gland and kidney cancers were elevated in patients with thyroid cancer as first primary malignancy. Cancers of the brain, skin, prostate, and breast, and leukemia, myeloma, and non-Hodgkin lymphoma were also elevated. The findings of the risk in patients with either small or large-sized tumors suggest newly detected thyroid cancers of all sizes may be of importance to monitor for potential second cancers, especially where aggressive radiation-based treatments, environment, and genetic susceptibility may increase risk.

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Author Disclosure Statement

Authors have nothing to disclose.

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