The Risk of Second Primary Malignancies up to Three Decades after the Treatment of Differentiated Thyroid Cancer

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Background: The 10-yr survival rate of patients with differentiated thyroid cancer exceeds 90%. These patients may be at elevated risk for secondary cancers.

Methods: The risk of nonthyroid second primary malignancies after differentiated thyroid cancer was determined in 30,278 patients diagnosed between 1973 and 2002 from centers participating in the National Cancer Institute's Surveillance, Epidemiology, and End Results program. Median follow-up was 103 months (range, 2–359 months). Risk was further assessed for the addition of radioisotope therapy, gender, latency to development of secondary cancer, and age at thyroid cancer diagnosis.

Results: There were 2158 patients who developed a total of 2338 nonthyroid second primary malignancies, significantly more than that expected in the general population [observed/expected (O/E) = 1.09; 95% confidence interval (CI), 1.05–1.14; $P < 0.05$; absolute excess risk per 10,000 person-years (AER) = 6.39]. A significantly greater risk of second primary malignancies over that expected in the general population was for patients treated with radioisotopes (O/E = 1.20; 95% CI, 1.07–1.33; AER = 11.8) as well as for unirradiated patients (O/E = 1.05; 95% CI, 1.00–1.10; AER = 3.53). However, the increased risk was greater for the irradiated *vs.* the unirradiated cohort (relative risk = 1.16; 95% CI, 1.05–1.27; $P < 0.05$). Gender did not affect risk. The greatest risk of second primary cancers occurred within 5 yr of diagnosis and was elevated for younger patients.

Conclusions: The overall risk of second primary malignancies is increased for thyroid cancer survivors and varies by radioisotope therapy, latency, and age at diagnosis. **(*J Clin Endocrinol Metab* 93: 504–515, 2008)**

An estimated 25,000 people in the United States are diagnosed with a primary thyroid malignancy every year, and approximately 1,500 of those patients will die of their disease (1). Although thyroid cancer accounts for only approximately 1.5% of cancers diagnosed in the United States, the age-adjusted incidence of thyroid cancer has been steadily rising (2). Women are three times more likely than men to develop thyroid cancer, with a peak incidence seen in people 40–50 yr old (2). Exposure to radiation is a well-established risk factor, and some of the increase may be due to the former practice of treating some benign childhood conditions of the head and neck with radiotherapy (3–5).

The differentiated papillary and follicular histologies account for approximately 90% of cases and have a 10-yr overall survival exceeding 90% (6). Definitive therapy for these differentiated cancers is complete or partial surgical thyroidectomy, with adjuvant radioiodine ablation/therapy used for residual, unresectable, and/or metastatic disease (7–9). Radioiodine use in thyroid

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Abbreviations: AER, Absolute excess risk per 10,000 person-years; CI, confidence interval; CNS, central nervous system; O/E, observed-to-expected ratio; PY, person-years; RR, relative risk; SEER, Surveillance, Epidemiology, and End Results; SIR, standardized incidence ratio.

TABLE 1. Demographics

	Median	Range or %
Age at diagnosis (yr)	42	4–100
Latency period to secondary cancer (yr)	8.1	0.2–29.7
Follow-up time (yr)	8.6	0.2–29.7
Study population (n)		
Male	7,219	23.8%
Female	23,059	76.2%
Total	30,278	
No. developed secondary malignancy	2,158	7.1%
Histologies (n)		
Papillary	26,517	88.0%
Follicular	3,761	12.0%
Radiation (n)		
No radiation	18,029	59.5%
Radioisotope therapy	10,257	33.9%
Other[a]	1992	6.6%

[a] Includes combination radioisotope-external beam therapy, external beam therapy alone, brachytherapy, and otherwise uncategorized radiotherapy.

cancer treatment has caused concern about the potential for development of secondary malignancies. Numerous malignancies are thought to be radiogenic, which have been identified by studies involving environmental, medical, and occupational exposures and most notably in Japanese survivors of nuclear warfare (10–14). The most prominent among these cancers are leukemia, thyroid, breast, lung, and skin cancers, contrasted with some more radioresistant organs such as the prostate and the central nervous system (15).

Because most survivors of differentiated thyroid cancer have a long life expectancy, it is important to understand how differences in clinical, pathological, and treatment characteristics alter their risk profiles for developing second primary cancers. In this study, we determined how these factors affected the incidence of second primary malignancy in a large U.S. population database over a period of up to three decades.

Patients and Methods

The study population was assembled using records from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. The SEER program database includes records from patients starting in 1973. A 98% case ascertainment is mandated from 14 population-based registries and three supplemental registries representing approximately 26% of the U.S. population (16). The SEER registries contain information on patient demographics, tumor site, histology, date and source of diagnosis, date of death, and treatment. Each year quality and completeness studies are conducted in SEER areas to ensure high quality data.

The SEER program statistical analysis software package (SEER*Stat, version 6.2.3) was used to identify patients diagnosed with a primary thyroid malignancy of follicular or papillary type from 1973–2002 (the histological subtypes included in analysis were ICD codes 8330, 8331, 8335, 8340–8344, 8260, and 8050). Patients with other thyroid cancer histologies or whose thyroid malignancy was not their first primary cancer were excluded from analysis. Second primary cancers diagnosed within 2 months of the thyroid cancer diagnosis and secondary thyroid cancers were also excluded. The time to development of second primary malignancies was calculated from the date of diagnosis of differentiated thyroid cancer.

From 1973–1987, the SEER registries encoded radioisotope therapy as other radiation. Registrars were also instructed to encode radioactive interstitial implants (brachytherapy) in the other category during that time period. External beam radiation was encoded as its own distinct entity. For our statistical analysis, we considered patients treated from 1973–1987 encoded as other as patients who received radioisotope therapy, because it was unlikely that papillary or follicular thyroid cancer would be treated with brachytherapy. From 1988 onward, radioisotope therapy was specifically encoded. In addition, thyroid ablative radioisotope doses used before the mid-1980s were higher than more modern practices (9, 17, 18). For these reasons, additional analyses with radioisotope therapy as a cohort were performed for the period 1988 onward to provide more statistical certainty.

The SEER*Stat MP-SIR (Multiple Primary-Standardized Incidence Ratio) tool was used to calculate standardized incidence ratios (SIRs) and excess risk for second primary malignancies by comparing these patients' subsequent cancer profile to the number of cancers that would be expected based on incidence rates for the general U.S. population.

Statistics

The risk of second primary cancers was estimated by compiling person-years (PY) of observation according to age, sex, and calendar-year periods from 2 months after the date of thyroid cancer diagnosis to the date of death, date of last follow-up evaluation, date of diagnosis of second primary cancer, or the end of the study (December 31, 2002), whichever occurred first. Cancer incidence rates specific for 5-yr age groups, gender, and calendar-year intervals were multiplied by the accumulated PY at risk to estimate the number of cancer cases expected. The observed and expected numbers of second cancers were then summed, with the SIR expressed as the ratio of observed-to-expected (O/E) cases. The absolute excess risk per 10,000 PY (AER) was determined by subtracting the expected number from the observed number of second cancers and then dividing the difference by the number of PY at risk. The number of excess second cancers was expressed per 10,000 PY. Risks of second cancers were stratified by sex, age group at thyroid cancer diagnosis, time since diagnosis (latency), and treatment (radiotherapy *vs.* no radiotherapy). The statistical analysis, including the tests for heterogeneity and linear trend as well as the regression modeling, were conducted using the Poisson modeling method of Breslow *et al.* (19). This approach is based on the fact that for grouped data, proportional hazards modeling with known baseline hazard is formally equivalent to a Poisson regression.

SIR and AER are two complementary measures of the incidence of an event of interest (in this case second primary cancer) in a subpopulation compared with the entire population. Both are based on comparing the observed number of events in the subpopulation O with the

TABLE 2. SIRs and AER for secondary malignancies after a primary thyroid cancer

	All persons			
	Persons = 30,278		PY at risk = 310,258	
Secondary tumors	Observed	Excess risk[a]	O/E	95% CI
All sites[b]	2338	6.39	*1.09*[c]	1.05–1.14
All solid tumors[b]	2078	4.98	*1.08*[c]	1.03–1.13
CNS	41	0.48	*1.58*[c]	1.13–2.14
Eye and orbit, nonmelanoma	0	−0.01	0	0.00–8.74
Head and neck[b]	50	−0.57	*0.74*[c]	0.55–0.97
Thymus, adrenal gland, and other endocrine	3	0.02	1.3	0.26–3.81
Lung and mediastinum	250	−1.39	*0.85*[c]	0.75–0.96
Breast	600	3.53	*1.22*[c]	1.13–1.32
Female breast	597	3.47	*1.22*[c]	1.12–1.32
Male breast	3	0.05	2.16	0.43–6.32
Digestive system	379	−0.78	0.94	0.85–1.04
Esophagus	6	−0.36	*0.35*[c]	0.13–0.76
Stomach	42	0.17	1.14	0.82–1.55
Small intestine	8	0.03	1.12	0.48–2.20
Colon and rectum	246	−0.09	0.99	0.87–1.12
Anus	4	−0.06	0.67	0.18–1.71
Liver, gallbladder, and biliary	27	−0.15	0.85	0.56–1.24
Pancreas	41	−0.29	0.82	0.59–1.11
Gynecological malignancies	177	−0.63	0.9	0.77–1.04
Prostate	284	2.32	*1.34*[c]	1.19–1.51
Testis	5	0.03	1.23	0.40–2.86
Penis	1	0	1.02	0.01–5.66
Urinary bladder	60	−0.6	*0.76*[c]	0.58–0.98
Kidney and renal pelvis	110	2.07	*2.4*[c]	1.97–2.89
Ureter	2	−0.01	0.83	0.09–3.00
All lymphatic and hematopoietic diseases	199	1.23	*1.24*[c]	1.07–1.42
Hodgkin lymphoma	16	0.22	*1.75*[c]	1.00–2.85
Non-Hodgkin lymphoma	76	−0.11	0.96	0.75–1.20
Myeloma	39	0.48	*1.63*[c]	1.16–2.22
Leukemia	68	0.64	*1.41*[c]	1.10–1.79
Mesothelioma	5	0.03	1.27	0.41–2.97
Kaposi sarcoma	0	−0.15	*0*[c]	0.00–0.81
Miscellaneous	52	0.08	1.05	0.78–1.38
Melanoma	89	0.42	1.17	0.94–1.44
Sarcoma	19	0.2	1.47	0.89–2.30
Salivary gland	14	0.29	*2.72*[c]	*1.48–4.56*
Head/neck excluding thyroid and salivary	36	−0.86	*0.58*[c]	0.4–0.8

Values in *italics* represent $P < 0.05$ for SIR *vs.* general U.S. population.

[a] Excess risk is number of cases per 10,000 PY.

[b] Excludes secondary thyroid cancer diagnoses.

[c] $P < 0.05$.

number of events E expected if the risk profile of the subpopulation were identical to that of the full population. Because, as a person ages, his or her risk of an event typically changes (due to both attained age and attained calendar year), the calculation of the expected number of events is adjusted for these variables. Additionally, fixed characteristics affecting event rates, such as gender and race, are incorporated in the calculation of the expected number of events. These adjustments make subpopulations of different structures comparable, for example, longer follow-up in one group. SIR and AER differ in the way they combine O and E; SIR measures the fold difference between the observed and expected number of events (SIR = O/E), whereas AER measures the actual number of excess events normalized to the number of PY observed [AER = (O − E)/PY). Thus, SIR measures the relative risk (RR) of the event on an individual level and does not depend on the frequency of the event in the population, whereas AER measures the population impact, where small increases in the relative risk of a common event affects more people than a large increase in a rare event. It should be noted that the length of follow-up does not affect either measure; the number of observed events O increases, but so do the number of expected events E and the number of person-years PY.

We have also used case-level analysis to examine the effect of latency and age at diagnosis on second primary cancers without categorizing. In this analysis, we considered any nonthyroid second primaries diagnosed at least 2 months after the primary thyroid cancer as an event. We have used SEER*Stat to obtain population rates of nonthyroid cancers by race, gender, and 5-yr age and calendar-year periods. The follow-up period of each case was broken into intervals in which the age group and year group did not change. The expected number of events during each such period was estimated as the length of the interval multiplied by the corresponding risk of cancer. The observed number of events (equal to 0 if the patient survived the interval without an event and 1 if the interval ended with a cancer

TABLE 3. The effect of gender on development of secondary malignancies

	Females				Males			
	Persons = 23,059		PY at risk = 237,376		Persons = 7,219		PY at risk = 72,882	
Secondary tumors	Observed	Excess risk[a]	O/E	95% CI	Observed	Excess risk[a]	O/E	95% CI
All sites[b]	1572	5.59	*1.09*[c]	1.04–1.15	766	8.98	*1.09*[c]	1.02–1.17
All solid tumors[b]	1393	4.04	*1.07*[c]	1.02–1.13	685	8.07	*1.09*[c]	1.01–1.18
CNS	29	0.5	*1.69*[c]	1.13–2.43	12	0.42	1.35	0.70–2.35
Eye and orbit, nonmelanoma	0	−0.01	0	0.00–16.96	0	−0.03	0	0–18.04
Head and neck[b]	28	−0.21	0.85	0.56–1.23	22	−1.74	*0.63*[c]	0.40–0.96
Thymus, adrenal gland, and other endocrine	2	0.02	1.23	0.14–4.44	1	0.04	1.48	0.02–8.26
Lung and mediastinum	145	−1.34	*0.82*[c]	0.69–0.97	105	−1.58	0.9	0.74–1.09
Breast	597	4.54	*1.22*[c]	1.12–1.32	3	0.22	2.16	0.43–6.32
Female breast	597	4.54	*1.22*[c]	1.12–1.32	0	0	0	0–0
Male breast	0	0	0	0–0	3	0.22	2.16	0.43–6.32
Digestive system	250	−0.46	0.96	0.84–1.08	129	−1.85	0.91	0.76–1.08
Esophagus	2	−0.22	0.28	0.03–1.00	4	−0.81	0.4	0.11–1.03
Stomach	21	0.02	1.02	0.63–1.56	21	0.67	1.3	0.80–1.99
Small intestine	6	0.05	1.26	0.46–2.74	2	−0.05	0.84	0.09–3.03
Colon and rectum	165	−0.04	0.99	0.85–1.16	81	−0.28	0.98	0.77–1.21
Anus	3	−0.07	0.64	0.13–1.86	1	−0.04	0.77	0.01–4.27
Liver, gallbladder, and biliary	18	−0.05	0.93	0.55–1.47	9	−0.46	0.73	0.33–1.38
Pancreas	30	−0.16	0.89	0.60–1.27	11	−0.71	0.68	0.34–1.22
Gynecological malignancies	177	−0.83	0.9	0.77–1.04	0	0	0	0–0
Prostate	0	0	0	0–0	284	9.89	*1.34*[c]	1.19–1.51
Testis	0	0	0	0–0	5	0.13	1.23	0.40–2.86
Penis	0	0	0	0–0	1	0	1.02	0.01–5.66
Urinary bladder	27	−0.24	0.82	0.54–1.20	33	−1.77	0.72	0.49–1.01
Kidney and renal pelvis	66	1.68	*2.52*[c]	1.95–3.21	44	3.34	*2.24*[c]	1.63–3.01
Ureter	1	−0.01	0.78	0.01–4.33	1	−0.02	0.89	0.01–4.96
All lymphatic and hematopoietic diseases	135	1.31	*1.3*[c]	1.09–1.54	64	0.99	1.13	0.87–1.44
Hodgkin lymphoma	12	0.24	1.91	0.99–3.34	4	0.16	1.41	0.38–3.60
Non-Hodgkin lymphoma	55	0.11	1.05	0.79–1.37	21	−0.83	0.78	0.48–1.19
Myeloma	25	0.4	*1.61*[c]	1.04–2.37	14	0.76	1.66	0.91–2.79
Leukemia	43	0.56	*1.45*[c]	1.05–1.95	25	0.9	1.36	0.88–2.00
Mesothelioma	2	0.03	1.42	0.16–5.13	3	0.07	1.19	0.24–3.48
Kaposi sarcoma	0	−0.02	0	0–9.59	0	−0.57	*0*[c]	0–0.88
Miscellaneous	38	0.16	1.11	0.79–1.53	14	−0.19	0.91	0.50–1.53
Melanoma	57	0.28	1.13	0.86–1.47	32	0.86	1.24	0.85–1.75
Sarcoma	12	0.14	1.38	0.71–2.41	7	0.38	1.66	0.67–3.42
Salivary gland	8	0.2	*2.42*[c]	1.04–4.77	6	0.57	*3.25*[c]	1.19–7.08
Head/neck excluding thyroid and salivary	20	−0.41	0.67	0.41–1.04	16	−2.31	*0.49*[c]	0.28–0.79

Values in *italics* represent $P < 0.05$ for SIR *vs.* general U.S. population.

[a] Excess risk is number of cases per 10,000 PY.

[b] Excludes secondary thyroid cancer diagnoses.

[c] $P < 0.05$.

diagnosis) was modeled using Poisson regression offset by the logarithm of the expected number of events. Because log(SIR) = log(O) − log(E), this approach actually models log(SIR). Gender, race, and treatment group were entered as categorical predictors (including radiotherapy as an independent predictor), and age at diagnosis and latency at the end of the interval were modeled via a restricted cubic spline. An examination of the fitted splines showed that age at diagnosis could be modeled as a linear effect.

The effect of external beam radiation therapy for treatment of thyroid cancer on the development of second primary malignancies was analyzed for cohorts based on age at diagnosis, gender, and the latency period in 5-yr intervals to the development of second cancers.

Results

Overall risk of developing second primary cancers

The demographics of the study population are shown in Table 1. A total of 30,278 patients were evaluable. Of these patients, 2158 patients (7.1%) developed a total of 2338 nonthyroid second primary malignancies, significantly more than that expected in the general population [O/E = 1.09; 95% confidence interval (CI), 1.05–1.14; $P < 0.05$; AER = 6.39] (Table 2). There was a significantly increased risk for cancers of the central nervous system (CNS), breast, prostate, kidney, Hodgkin lymphoma,

TABLE 4. The effect of age at diagnosis in development of secondary malignancies

	Under 25				25–49 yr			
	Persons 2,896		PY at risk 36,773		Persons 17,104		PY at risk 185,166	
Secondary tumors	Observed	Excess risk[a]	O/E	95% CI	Observed	Excess risk[a]	O/E	95% CI
All sites[b]	36	1.08	1.12	0.79–1.56	876	7.33	*1.18*[c]	1.11–1.26
All solid tumors[b]	29	0.46	1.06	0.71–1.53	785	6.05	*1.17*[c]	1.09–1.25
CNS	1	−0.03	0.89	0.01–4.94	31	1.06	*2.75*[c]	1.87–3.90
Eye and orbit, nonmelanoma	0	0	0	0–293.54	0	−0.01	0	0–27.87
Head and neck[b]	5	1.15	*6.34*[c]	2.04–14.79	19	−0.27	0.79	0.47–1.23
Thymus, adrenal gland, and other endocrine	0	−0.02	0	0–41.60	1	0	0.92	0.01–5.10
Lung and mediastinum	0	−0.29	0	0–3.45	66	−0.81	0.81	0.63–1.04
Breast	11	0.42	1.16	0.58–2.08	310	4	*1.31*[c]	1.17–1.47
Female breast	11	0.42	1.16	0.58–2.08	308	3.91	*1.31*[c]	1.17–1.46
Male breast	0	0	0	0–519.48	2	0.09	4.99	0.56–18.03
Digestive system	2	−0.1	0.85	0.10–3.06	105	0.23	1.04	0.85–1.26
Esophagus	0	−0.02	0	0–60.65	1	−0.19	0.23	0–1.26
Stomach	0	−0.06	0	0–15.74	13	0.24	1.51	0.80–2.58
Small intestine	0	−0.02	0	0–42.53	2	−0.03	0.81	0.09–2.91
Colon and rectum	2	0.17	1.44	0.16–5.22	69	0.45	1.14	0.88–1.44
Anus	0	−0.03	0	0–35.92	1	−0.08	0.4	0.01–2.23
Liver, gallbladder, and biliary	0	−0.06	0	0–17.99	8	−0.02	0.95	0.41–1.88
Pancreas	0	−0.05	0	0–18.51	10	−0.09	0.86	0.41–1.57
Gynecological malignancies	6	0.24	1.18	0.43–2.56	75	−0.73	0.85	0.67–1.06
Prostate	0	−0.04	0	0–23.06	41	−0.03	0.99	0.71–1.34
Testis	1	0.07	1.33	0.02–7.38	2	−0.05	0.68	0.08–2.46
Penis	0	0	0	0–674.09	1	0.04	3.85	0.05–21.42
Urinary bladder	0	−0.1	0	0–9.60	19	0.03	1.03	0.62–1.61
Kidney and renal pelvis	0	−0.13	0	0–7.63	50	1.84	*3.13*[c]	2.32–4.13
Ureter	0	0	0	0–906.31	1	0.03	2.39	0.03–13.31
All lymphatic and hematopoietic diseases	7	0.78	1.69	0.68–3.48	73	1.07	*1.37*[c]	1.08–1.73
Hodgkin lymphoma	4	0.67	2.59	0.70–6.63	10	0.28	2.07	0.99–3.8
Non-Hodgkin lymphoma	0	−0.42	0	0–2.35	33	0.28	1.19	0.82–1.62
Myeloma	1	0.24	9.78	0.13–54.41	7	0.04	1.13	0.45–2.32
Leukemia	2	0.29	2.12	0.24–7.65	23	0.47	*1.61*[c]	1.02–2.41
Mesothelioma	0	−0.01	0	0–137.17	2	0.06	2.06	0.23–7.43
Kaposi sarcoma	0	−0.14	0	0–7.18	0	−0.18	0	0–1.12
Miscellaneous	0	−0.09	0	0–11.37	13	0.07	1.12	0.59–1.91
Melanoma	2	−0.61	0.47	0.05–1.70	51	0.6	1.28	0.95–1.68
Sarcoma	1	0.08	1.4	0.02–7.78	10	0.23	1.75	0.84–3.22
Salivary gland	1	0.23	5.86	0.08–32.61	7	0.26	*3.33*[c]	1.33–6.86
Head/neck excluding thyroid and salivary	4	0.92	*6.47*[c]	1.74–16.57	12	−0.54	*0.55*[c]	0.28–0.95

Values in *italics* represent $P < 0.05$ for standardized incidence ratio *vs.* general U.S. population.

[a] Excess risk is number of cases per 10,000 person years.

[b] Excludes secondary thyroid cancer diagnoses.

[c] $P < 0.05$.

leukemia, myeloma, and salivary gland as well as a significantly decreased risk for cancers of the head and neck (excluding thyroid and salivary gland), lung, esophagus, and bladder.

Gender

The ratio of female to male patients was 3.13 (23,059 and 7,219 males, respectively); a distribution consistent with prior reports (2). Both genders had equivalent overall risk of developing second primary cancers (RR = 1.00; 95% CI, 0.92–1.09). For specific cancers, males had an increased risk of developing secondary prostate, kidney, and salivary gland cancers and a decreased risk for other head and neck cancers. Females had increased risk for secondary leukemia, myeloma, breast, kidney, salivary gland, and CNS cancers and a decreased risk for lung and mediastinum (Table 3).

Age at diagnosis

Significantly increased overall risk of second primary cancers was observed in the cohort of patients diagnosed from ages 25–49 yr but not in cohorts of patients 0–24, 50–74, or 75 yr and older (Table 4). However, the risk for several specific cancer sites was elevated in the other age cohorts.

Latency to development of second primary cancer

Overall risk of second primary cancers was significantly elevated within the first 10 yr after thyroid cancer diagnosis (yr 0–5: O/E = 1.18; 95%, CI 1.10–1.27; AER = 9.71; yr 6–10: O/E = 1.10; 95% CI, 1.01–1.19; AER = 6.5) but not for longer latency periods.

Interaction of age at diagnosis and latency to development of second primary cancer

A more detailed case-level regression analysis revealed gender, race, and treatment group did not appear to affect the SIR ($P = 0.31$, $P = 0.33$, and $P = 0.58$, respectively). Decreased age at diagnosis resulted in higher SIR; for each decade of age (relative to any comparatively prior decade), SIR is 1.14-fold higher (95% CI, 1.11–1.18; $P < 0.0001$). The effect of latency

TABLE 4. *Continued*

50–74 yr				Over 75 yr			
Persons 9,014		PY at risk 82,275		Persons 1,264		PY at risk 6,043	
Observed	Excess risk[a]	O/E	95% CI	Observed	Excess risk[a]	O/E	95% CI
1,287	6.69	1.04	0.99–1.10	139	5.77	1.03	0.86–1.21
1,139	4.01	1.03	0.97–1.09	125	13.05	1.07	0.89–1.27
9	−0.44	0.71	0.33–1.35	0	−1.62	0	0–3.74
0	−0.03	0	0–16.00	0	−0.08	0	0–79.44
24	−1.9	*0.61*[c]	0.39–0.90	2	−1.96	0.63	0.07–2.27
2	0.12	1.9	0.21–6.86	0	−0.11	0	0–54.44
171	−2.88	0.88	0.75–1.02	13	−5.64	0.79	0.42–1.35
258	3.96	*1.14*[c]	1.01–1.29	21	2.02	1.06	0.66–1.62
257	3.95	*1.14*[c]	1.01–1.29	21	2.18	1.07	0.66–1.63
1	0.01	1.13	0.01–6.29	0	−0.16	0	0–38.80
231	−3.59	0.89	0.78–1.01	41	2.27	1.03	0.74–1.40
4	−0.9	*0.35*[c]	0.09–0.09	1	−0.31	0.84	0.01–4.69
24	0.03	1.01	0.65–1.51	5	1.45	1.21	0.39–2.83
6	0.23	1.45	0.53–3.16	0	−0.75	0	0–8.11
147	−1.76	0.91	0.77–1.07	28	4.52	1.11	0.74–1.60
3	−0.01	0.97	0.20–2.84	0	−0.53	0	0–11.43
18	−0.26	0.89	0.53–1.41	1	−3.12	0.35	0–1.93
26	−0.86	0.79	0.51–1.15	5	0.07	1.01	0.33–2.35
90	−0.61	0.95	0.76–1.16	6	−3.34	0.75	0.27–1.63
216	7.41	*1.39*[c]	1.21–1.59	27	19.62	*1.78*[c]	1.17–2.59
2	0.2	5.3	0.60–19.15	0	−0.02	0	0–281.01
0	−0.08	0	0–5.79	0	−0.14	0	0–43.61
35	−2.14	*0.67*[c]	0.46–0.93	6	−1.97	0.83	0.30–1.82
56	3.54	*2.08*[c]	1.57–2.71	4	2.5	1.61	0.43–4.12
1	−0.09	0.57	0.01–3.19	0	−0.4	0	0–15.07
109	2.14	1.19	0.98–1.44	10	−3.26	0.84	0.40–1.54
1	−0.18	0.4	0.01–2.21	1	1.29	4.51	0.06–25.08
39	−0.7	0.87	0.62–1.19	4	−2.19	0.75	0.20–1.92
28	1.5	*1.79*[c]	1.19–2.58	3	1.64	1.49	0.30–4.36
41	1.52	*1.44*[c]	1.03–1.95	2	−4	0.45	0.05–1.64
3	0.05	1.14	0.23–3.34	0	−0.51	0	0–11.98
0	−0.08	0	0–5.77	0	−0.21	0	0–29.36
35	0.42	1.11	0.77–1.54	4	−3.25	0.67	0.18–1.72
33	0.45	1.13	0.77–1.58	3	0.72	1.17	0.23–3.42
6	0.02	1.03	0.38–2.25	2	2.19	2.95	0.33–10.63
5	0.3	1.95	0.63–4.56	1	1.13	3.14	0.04–17.46
19	−2.2	*0.51*[c]	0.31–0.80	1	−3.09	0.35	0–1.94

is more complicated and is shown in Fig. 1. The SIR is greatly increased immediately after initial diagnosis and treatment; however, this excess risk decreases rapidly and by approximately 5 yr after diagnosis, the effect levels out (at a level dependent on the age at diagnosis). Cancers that show statistically elevated excess risk and represent the largest numbers of newly diagnosed second primaries within 5 yr of diagnosis include breast, prostate, and lymphatic and hematopoietic malignancies.

Risk of developing second primary cancers with radioisotope therapy

For the entire study period (1973–2002), patients receiving radioisotope therapy were at increased risk of developing nonthyroid second primary cancers (O/E = 1.21; 95% CI, 1.12–1.30; AER = 13.3) over the general population as well as the nonirradiated survivors (O/E = 1.05; 95% CI, 1.00–1.10; AER = 3.53), although the nonirradiated group had a risk more similar to the endemic rate. The RR was significantly greater for the irradiated patients than for the nonirradiated patients (RR = 1.16; 95% CI, 1.05–1.27; $P < 0.002$). When isolating the analysis period from 1988–2002, increased risk was observed in both the isotope-irradiated (O/E = 1.20, 95% CI 1.08–1.34, AER=12.01) and nonirradiated (O/E = 1.12; 95% CI, 1.02–1.23; AER = 7.86) cohorts, but the RR became statistically indistinguishable (RR = 1.08; 95% CI, 0.93–1.24; $P = 0.31$) overall (Table 5).

An additional analysis was undertaken using a latency exclusion period for secondary cancers of 36 months as opposed to 2

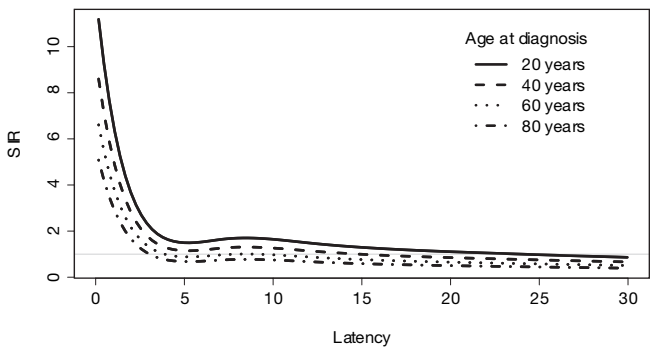

FIG. 1. Fitted estimates of SIR of all nonthyroid malignancies by latency and age at diagnosis (gender, race, and treatment group do not appreciably alter the SIR). The four curves represent fits for four different diagnosis ages (20, 40, 60, and 80 yr old). The *thin horizontal line* represents a SIR equal to 1.

TABLE 5. The effect of radiotherapy in development of secondary malignancies, 2-month latency exclusion

	1988–2002							
	No radiotherapy				Radioisotopes			
	Persons 9,901		PY at risk 60,289		Persons 8,159		PY at risk 46,666	
Secondary tumors	Observed	Excess risk[a]	O/E	95% CI	Observed	Excess risk[a]	O/E	95% CI
All sites[b]	448	7.86	*1.12*[c]	1.02–1.23	331	12.01	*1.2*[c]	1.08–1.34
All solid tumors[b]	396	5.88	1.1	0.99–1.21	285	8.06	*1.15*[c]	1.02–1.29
CNS	10	0.86	2.08	1–3.83	7	0.75	2.01	0.81–4.15
Eye and orbit, nonmelanoma	0	−0.01	0	0–47.89	0	−0.01	0	0–66.31
Head and neck[b]	7	−0.75	0.61	0.24–1.25	3	−1.14	0.36	0.07–1.05
Thymus, adrenal gland and other endocrine	1	0.09	2.27	0.03–12.61	0	−0.07	0	0–11.26
Lung and mediastinum	34	−3.13	*0.64*[c]	0.45–0.9	40	0.92	1.12	0.8–1.52
Breast	126	4.71	*1.29*[c]	1.08–1.54	76	2.79	1.21	0.95–1.51
Female breast	125	4.59	*1.28*[c]	1.07–1.53	76	2.84	1.21	0.95–1.52
Male breast	1	0.12	3.91	0.05–21.75	0	−0.04	0	0–17.83
Digestive system	63	−1.38	0.88	0.68–1.13	51	0.55	1.05	0.78–1.38
Esophagus	1	−0.34	0.33	0–1.81	2	−0.04	0.92	0.1–3.3
Stomach	7	0.16	1.16	0.47–2.39	12	1.65	*2.79*[c]	1.44–4.87
Small intestine	2	0.09	1.4	0.16–5.06	1	0.01	1.04	0.01–5.76
Colon and rectum	38	−0.92	0.87	0.62–1.2	27	−0.45	0.93	0.61–1.35
Anus	1	−0.04	0.82	0.01–4.56	2	0.25	2.44	0.27–8.81
Liver, gallbladder, and biliary	4	−0.3	0.69	0.18–1.76	2	−0.48	0.47	0.05–1.7
Pancreas	10	0.17	1.11	0.53–2.05	3	−0.64	0.5	0.1–1.47
Gynecological malignancies	39	0.41	1.07	0.76–1.46	24	0.06	1.01	0.65–1.5
Prostate	60	3.17	*1.47*[c]	1.12–1.89	45	2.8	*1.41*[c]	1.03–1.88
Testis	0	−0.12	0	0–4.9	1	0.04	1.26	0.02–7.01
Penis	0	−0.03	0	0–22.13	1	0.19	7.45	0.1–41.47
Urinary bladder	15	0.14	1.06	0.59–1.75	6	−0.87	0.6	0.22–1.3
Kidney and renal pelvis	16	1.18	*1.8*[c]	1.03–2.93	11	1.02	1.76	0.88–3.14
Ureter	0	−0.07	0	0–9.1	0	−0.06	0	0–13.1
All lymphatic and hematopoietic diseases	42	1.94	1.39	1–1.87	38	3.62	*1.8*[c]	1.27–2.47
Hodgkin lymphoma	6	0.7	*3.38*[c]	1.24–7.36	2	0.13	1.42	0.16–5.13
Non-Hodgkin lymphoma	16	0.11	1.04	0.6–1.69	11	0.05	1.02	0.51–1.83
Myeloma	11	1.09	*2.47*[c]	1.23–4.42	6	0.66	2.04	0.75–4.45
Leukemia	9	0.04	1.03	0.47–1.95	19	2.78	*3.14*[c]	1.89–4.91
Mesothelioma	1	0.05	1.41	0.02–7.85	1	0.1	1.95	0.03–10.85
Kaposi sarcoma	0	−0.11	0	0–5.37	0	−0.13	0	0–6.03
Miscellaneous	8	−0.09	0.94	0.4–1.85	7	0.32	1.27	0.51–2.62
Melanoma	22	1	1.38	0.86–2.09	17	1.15	1.46	0.85–2.34
Sarcoma	2	−0.09	0.79	0.09–2.84	2	0.03	1.08	0.12–3.9
Salivary gland	0	−0.16	0	0–3.75	2	0.28	2.84	0.32–10.24
Head/neck excluding thyroid and salivary	7	−0.59	0.66	0.27–1.37	1	−1.42	*0.13*[c]	0–0.73

Values in *italics* represent $P < 0.05$ for standardized incidence ratio *vs.* general U.S. population.

[a] Excess risk is number of cases per 10,000 person years.

[b] Excludes secondary thyroid cancer diagnoses.

[c] $P < 0.05$.

months (Table 6). In this scenario, the risk of developing nonthyroid second primary cancers was elevated over that of the general population for those receiving radioisotope therapy (O/E = 1.22; 95% CI, 1.11–1.34; AER = 14.9). The nonirradiated cohort had a risk similar to the endemic rate (O/E = 1.03; 95% CI, 0.97–1.08; AER = 1.97). Even with the 3-yr latency exclusion period, the risk of hematological malignancies was significantly elevated in the radioisotope cohort (O/E = 1.73; 95% CI, 1.29–2.29; AER = 3.75) but not for the nonirradiated cohort (O/E = 1.02; 95% CI, 0.83–1.24; AER = 0.11).

Discussion

Second or higher-order malignancies account for approximately 16% of incident cancers in the United States (2). Several U.S. and European studies have described an increased association of second primary malignancies after diagnosis of thyroid cancer (20–29). With 30,278 patients and up to nearly 30 yr of follow-up, our results represent the largest U.S. population-based study of second primary malignancies in thyroid cancer survivors and the longest period of follow-up reported. A similar SEER-based analysis by Ronckers *et al.* (26) was recently performed, but their analysis included undifferentiated medullary cancers and assessed the risk of radioisotope exposure only after 1988. We chose to exclude medullary histologies because of lower survival rates and association with multiple endocrine neoplasias that could confound the diagnosis of nonfamilial second primary tumors (30, 31). In addition, we feel justified in recoding the 2098 persons who received other radiotherapy between 1973 and 1987 as radioisotope therapy for this analysis because SEER registrars were instructed to encode only radioisotope and interstitial implants as other radiation. During that time period, radio-

TABLE 5. *Continued*

1973–2002							
No radiotherapy				Radioisotopes			
Persons 18,029		PY at risk 210,960		Persons 10,257		PY at risk 81,530	
Observed	Excess risk[a]	O/E	95% CI	Observed	Excess risk[a]	O/E	95% CI
1,573	3.53	1.05	1.00–1.10	618	13.3	*1.21*[c]	1.12–1.31
1,412	3.1	1.05	0.99–1.10	533	9.13	*1.16*	1.07–1.27
28	0.47	*1.55*	1.03–2.24	12	0.69	1.89	0.97–3.3
0	−0.01	0	0–12.71	0	−0.01	0	0–35.72
37	−0.47	0.79	0.55–1.09	7	−1.15	*0.43*	0.17–0.88
3	0.07	1.9	0.38–5.55	0	−0.07	0	0–6.26
158	−2.26	*0.77*[c]	0.65–0.90	77	0.98	1.12	0.88–1.39
435	3.9	*1.23*[c]	1.12–1.35	135	2.89	*1.21*[c]	1.02–1.43
433	3.85	*1.23*[c]	1.12–1.35	134	2.82	*1.21*[c]	1.01–1.43
2	0.05	2.23	0.25–8.04	1	0.08	2.59	0.03–14.42
249	−1.69	*0.87*[c]	0.77–0.99	101	0.98	1.09	0.88–1.32
3	−0.42	*0.26*[c]	0.05–0.75	2	−0.27	0.47	0.05–1.71
24	−0.07	0.94	0.60–1.40	16	0.89	*1.83*[c]	1.04–2.97
5	0	1	0.32–2.34	2	0.03	1.16	0.13–4.19
169	−0.37	0.96	0.82–1.11	59	0.34	1.05	0.8–1.35
1	−0.15	0.24	0–1.31	3	0.19	2.11	0.42–6.16
17	−0.22	0.78	0.46–1.25	8	0.01	1.01	0.44–1.99
27	−0.4	0.76	0.50–1.11	9	−0.29	0.79	0.36–1.51
128	−0.68	0.9	0.75–1.07	41	−0.3	0.94	0.68–1.28
180	2.09	*1.32*[c]	1.14–1.53	82	2.71	*1.37*[c]	1.09–1.7
4	0.07	1.61	0.43–4.11	1	−0.04	0.76	0.01–4.22
0	−0.03	0	0–5.69	1	0.09	3.79	0.05–21.1
42	−0.58	0.78	0.56–1.05	12	−0.88	0.62	0.32–1.09
71	1.87	*2.24*[c]	1.75–2.83	28	2.05	*2.47*[c]	1.64–3.57
2	0.01	1.18	0.13–4.28	0	−0.07	0	0–6.6
124	0.56	1.11	0.92–1.32	67	3.49	*1.74*[c]	1.36–2.21
11	0.23	1.79	0.89–3.21	5	0.31	2.05	0.66–4.78
49	−0.3	0.89	0.66–1.17	24	0.58	1.24	0.8–1.85
28	0.52	*1.65*[c]	1.10–2.39	10	0.55	1.81	0.86–3.32
36	0.1	1.07	0.75–1.48	28	2.05	*2.48*[c]	1.65–3.58
4	0.06	1.5	0.40–3.84	1	0	1.01	0.01–5.6
0	−0.14	0	0–1.23	0	−0.16	0	0–2.89
30	−0.26	0.84	0.57–1.20	17	0.76	1.57	0.91–2.51
56	0.2	1.08	0.82–1.4	29	1.14	1.47	0.99–2.11
12	0.15	1.35	0.70–2.36	6	0.34	1.84	0.67–4.-1
11	0.35	*3.09*[c]	1.54–5.53	2	0.09	1.57	0.18–5.66
26	−0.82	*0.6*[c]	0.39–0.88	5	−1.24	*0.33*[c]	0.11–0.77

isotope therapy was already a standard of care, whereas interstitial implant therapy would have been unusual. A recent study by Sandeep *et al.* (28) including 39,002 patients from 13 population-based cancer registries in Europe, Canada, Australia, and Singapore was recently reported. Their findings were similar to ours, with notable exceptions described below.

Our analysis confirmed some previous reports of increased incidence of breast cancer in thyroid cancer survivors. The risk was significantly elevated only for women ages 25–75 yr at diagnosis and only within 10 yr of thyroid cancer diagnosis. Other authors have postulated that the increased incidence could be due to radioisotope therapy (32, 33). Radioiodine is known to be excreted in breast milk by the sodium iodide symporter, which is also expressed in salivary gland tissue and the stomach (34–37). Nevertheless, it is unlikely that many women in our study were lactating at the time of radioiodine administration, and this information is not included in the SEER database. In our analysis, both the nonirradiated and irradiated patients had significantly elevated risk for breast cancer, but the relative risk was statistically indistinguishable between the groups. This suggests that the increased risk of breast cancer is likely due to other factors.

The increased diagnosis of prevalent cancers (breast and prostate) within 5 yr of diagnosis of thyroid cancer may be evidence of surveillance bias in our data. Patients who have been diagnosed with a previous malignancy may be more likely to seek routine and follow-up health care resulting in a perceived increase in second primary cancers. To address this issue, we performed an additional analysis using a latency exclusion period of 3 yr as opposed to 2 months, because radiogenic malignancies are thought to have a latency rate of several years before clinical presentation. In this scenario, we still identified an elevated risk of both hematological and solid second malignancies in the irradiated cohort but did not see an overall elevated risk in the nonirradiated group. With some studies reporting reciprocal associations of thyroid with breast, prostate, kidney, and salivary gland cancers (26, 28), we cannot exclude an environmental or genetic mechanism (38) responsible for this correlation. One of the primary molecular changes in papillary, but not follicular, thyroid cancer is mutation of the RET protooncogene (16), which has also been linked to leukemia, prostate cancer, and breast cancer (39–42). In addition, a missense variant (I157T) of the CHEK2 protein, which participates in DNA repair, is asso-

TABLE 6. The effect of radiotherapy in development of secondary malignancies, 36-month latency exclusion

	1988–2002							
	No radiotherapy				Radioisotopes			
	Persons 5,413		PY at risk 24,312		Persons 4,248		PY at risk 17,497	
Secondary tumors	Observed	Excess risk[a]	O/E	95% CI	Observed	Excess risk[a]	O/E	95% CI
All sites[b]	191	2.81	1.04	0.9–1.2	145	15.69	*1.23*[c]	1.04–1.45
All solid tumors[b]	170	1.76	1.03	0.88–1.19	125	10.97	1.18	0.98–1.41
CNS	6	1.6	*2.85*[c]	1.04–6.2	1	−0.24	0.71	0.01–3.93
Eye and orbit, nonmelanoma	0	−0.01	0	0–104.76	0	−0.01	0	0–156.45
Head and neck, excluding thyroid	2	−1.29	0.39	0.04–1.41	1	−1.39	0.29	0–1.62
Thymus, adrenal gland, and other endocrine	0	−0.08	0	0–18.73	0	−0.08	0	0–27.24
Lung and mediastinum	13	−4.74	*0.53*[c]	0.28–0.91	17	0.94	1.11	0.64–1.77
Breast	59	5.91	*1.32*[c]	1.01–1.71	34	3.85	1.25	0.86–1.74
Female breast	59	5.96	*1.33*[c]	1.01–1.71	34	3.9	1.25	0.87–1.75
Male breast	0	−0.05	0	0–30.5	0	−0.05	0	0–41.81
Digestive system	28	−2.22	0.84	0.56–1.21	25	2.26	1.19	0.77–1.75
Esophagus	0	−0.59	0	0–2.56	1	0.03	1.06	0.01–5.92
Stomach	3	0.1	1.09	0.22–3.18	7	2.96	*3.85*[c]	1.54–7.92
Small intestine	0	−0.28	0	0–5.44	1	0.33	2.36	0.03–13.15
Colon and rectum	19	−0.55	0.93	0.56–1.46	9	−2.07	0.71	0.33–1.35
Anus	0	−0.24	0	0–6.42	1	0.37	2.77	0.04–15.43
Liver, gallbladder, and biliary	1	-0.73	0.36	0–2.01	2	0.08	1.08	0.12–3.88
Pancreas	5	0.31	1.18	0.38–2.74	2	−0.36	0.76	0.09–2.75
Gynecological malignancies	13	−1.4	0.79	0.42–1.35	11	0.54	1.09	0.55–1.96
Prostate	22	1.31	1.17	0.73–1.77	18	2.63	1.34	0.8–2.12
Testis	0	−0.11	0	0–13.39	0	−0.16	0	0–13.33
Penis	0	−0.03	0	0–46.81	0	−0.03	0	0–63.29
Urinary bladder	8	0.52	1.19	0.51–2.34	3	−0.8	0.68	0.14–1.99
Kidney and renal pelvis	7	1.17	1.68	0.67–3.46	5	1.3	1.84	0.59–4.29
Ureter	0	−0.08	0	0–19.3	0	−0.07	0	0–30.17
All lymphatic and hematopoietic diseases	16	0.86	1.15	0.66–1.87	16	4.01	*1.78*[c]	1.02–2.89
Hodgkin lymphoma	1	0.13	1.47	0.02–8.16	2	0.86	3.98	0.45–14.36
Non-Hodgkin lymphoma	5	−0.87	0.7	0.23–1.64	5	0.22	1.08	0.35–2.53
Myeloma	5	1.2	2.4	0.77–5.6	1	−0.16	0.78	0.01–4.34
Leukemia	5	0.4	1.24	0.4–2.89	8	3.1	*3.1*[c]	1.34–6.11
Mesothelioma	1	0.27	3.01	0.04–16.76	1	0.45	4.56	0.06–25.38
Kaposi sarcoma	0	−0.08	0	0–19.14	0	−0.09	0	0–22.94
Miscellaneous	4	0.03	1.02	0.27–2.61	3	0.36	1.27	0.26–3.71
Melanoma	11	1.55	1.52	0.76–2.72	7	1.21	1.43	0.57–2.95
Sarcoma	0	−0.47	0	0–3.24	2	0.71	2.62	0.29–9.45
Salivary gland	0	−0.18	0	0–8.2	1	0.4	3.35	0.04–18.67
Head/neck excluding thyroid and salivary	2	−1.1	0.43	0.05–1.54	0	−1.79	0	0–1.17

Values in *italics* represent $P < 0.05$ for standardized incidence ratio *vs.* general U.S. population. CNS, Central nervous system.

[a] Excess risk is number of cases per 10,000 person years.

[b] Excludes secondary thyroid cancer diagnoses.

[c] $P < 0.05$.

ciated with an increased risk of thyroid, breast, prostate, kidney, and colon cancers (43–45). How these molecular changes may have affected our study population is unknown and beyond the scope of the current work.

Our study also confirmed previous reports of increased risk of prostate cancer. Prostate cancer was the only cancer we analyzed that had statistically increased incidence for patients diagnosed with thyroid cancer after age 75. This could be due to shared molecular-genetic susceptibilities or the potential for surveillance bias, both discussed above. Unfortunately, the SEER database does not track this type of information and is beyond the scope of this work.

Because radioiodine is excreted both fecally and renally, we evaluated these body sites for a radiation effect. Previous studies reported a significantly increased incidence of kidney cancer (29, 46), colorectal cancer (28, 47, 48), and bladder cancer (32, 49) in patients who received radioisotopes. Our analysis did show an increased risk of kidney cancer, but this increased risk was statistically equivalent in both the irradiated and nonirradiated cohorts. We found no increased risk of gastrointestinal malignancies in our study population, with the notable exception of a statistically increased risk for stomach cancer in the radioisotope cohort. The stomach is both strongly avid for ^{131}I (as measured by nuclear medicine scans) and has some of the greatest expression of the sodium iodide symporter of all body tissues tested (35).

Salivary glands are also known to concentrate and excrete ^{131}I. Interestingly, in our study, this risk was significantly increased in the nonirradiated patients only. The interpretation of this finding is challenging. Again, one may surmise that the environmental and genetic factors leading to a thyroid cancer are similar to those resulting in salivary tumors. For example, both thyroid and salivary malignancies are known to be induced by radiation (9, 32, 50). However, if it were true that medical or

TABLE 6. *Continued*

1973–2002							
No Radiotherapy				Radioisotopes			
Persons 14,841		PY at risk 164,783		Persons 7,624		PY at risk 56,437	
Observed	Excess risk[a]	O/E	95% CI	Observed	Excess risk[a]	O/E	95% CI
1,292	1.97	1.03	0.97–1.08	467	14.89	*1.22*[c]	1.11–1.34
1,165	2.01	1.03	0.97–1.09	403	10.31	*1.17*[c]	1.06–1.29
25	0.61	*1.68*[c]	1.09–2.48	6	0.24	1.29	0.47–2.82
0	−0.01	0	0–15.27	0	−0.01	0	0–48.03
31	−0.47	0.8	0.54–1.13	7	−0.9	0.58	0.23–1.19
2	0.04	1.53	0.17–5.54	0	−0.08	0	0–8.52
132	−2.57	*0.76*[c]	0.63–0.9	62	1.73	1.19	0.91–1.52
355	3.56	*1.2*[c]	1.08–1.33	95	2.04	1.14	0.92–1.39
353	3.49	*1.19*[c]	1.07–1.33	94	1.92	1.13	0.91–1.38
2	0.08	2.65	0.3–9.57	1	0.13	3.43	0.04–19.11
211	−1.74	0.88	0.77–1.01	79	1.55	1.12	0.89–1.4
2	−0.48	*0.2*[c]	0.02–0.73	1	−0.39	0.31	0–1.75
19	−0.13	0.9	0.54–1.4	11	0.79	1.68	0.84–3
2	−0.14	0.47	0.05–1.7	2	0.12	1.53	0.17–5.53
146	−0.17	0.98	0.83–1.15	47	0.81	1.11	0.81–1.47
1	−0.16	0.28	0–1.56	2	0.16	1.87	0.21–6.75
14	−0.27	0.76	0.42–1.27	6	0	1	0.36–2.17
25	−0.3	0.84	0.54–1.23	8	−0.11	0.93	0.4–1.83
102	−0.94	0.87	0.71–1.05	31	−0.2	0.96	0.66–1.37
150	2.04	*1.29*[c]	1.09–1.51	63	3	*1.37*[c]	1.05–1.75
2	0.01	1.07	0.12–3.87	1	0.02	1.14	0.01–6.36
0	−0.03	0	0–6.87	0	−0.04	0	0–18.54
36	−0.6	0.79	0.55–1.09	11	−0.64	0.75	0.38–1.35
58	1.89	*2.16*[c]	1.64–2.8	22	2.38	*2.57*[c]	1.61–3.9
2	0.04	1.41	0.16–5.08	0	−0.07	0	0–8.73
96	0.11	1.02	0.83–1.24	50	3.75	*1.73*[c]	1.29–2.29
4	−0.04	0.85	0.23–2.18	5	0.59	3.03	0.98–7.08
38	−0.54	0.81	0.57–1.11	20	0.97	1.38	0.84–2.13
21	0.4	1.46	0.91–2.24	6	0.32	1.43	0.52–3.1
33	0.28	1.17	0.8–1.64	19	1.87	*2.25*[c]	1.35–3.51
4	0.11	1.77	0.48–4.53	1	0.04	1.33	0.02–7.37
0	−0.15	0	0–1.53	0	−0.15	0	0–4.28
26	−0.23	0.87	0.57–1.28	13	0.86	1.6	0.85–2.73
42	−0.06	0.98	0.7–1.32	20	0.98	1.38	0.84–2.13
11	0.22	1.51	0.75–2.7	5	0.46	2.1	0.68–4.91
10	0.43	*3.39*[c]	1.62–6.24	2	0.19	2.12	0.24–7.65
21	−0.9	*0.59*[c]	0.36–0.9	5	−1.09	0.45	0.14–1.05

occupational radiation was causing the thyroid and salivary gland tumors, we might expect to see this risk proportionally shared over both the irradiated and nonirradiated cohorts, which we did not. Upon closer review, the excess risk was observed in cases diagnosed between 1973 and 1988, with no excess risk noted for the later time period. This might be attributed to the earlier practice of head and neck irradiation for benign conditions that is a known risk factor for radiogenic malignancies such as thyroid cancer. However, Mehta *et al.* (4) suggest that these particular malignancies have been dramatically declining since 1970. Our result may simply reflect statistical noise in the setting of multiple subgroup testing.

We observed a decreased risk of smoking-related cancers such as bladder, lung, and nonthyroid head and neck cancers than what was expected in the general population. This decrease could be attributable to smoking cessation among survivors of thyroid cancer, because lifestyle modification in cancer survivors has been documented (51). Alternatively, our study population may represent people less likely to smoke than the general U.S. population. Unfortunately, smoking habits are not encoded by SEER registrars. Sandeep *et al.* (28) did not observe this decrease and in fact reported an increase in pharyngeal second primaries. This may be explained by different exposures in Sandeep's study population compared with the U.S. population.

The most frequently reported cancer associated with radioisotope therapy is leukemia (26, 28, 32, 47–49, 52). Our study confirmed a statistically significant increase of leukemia in patients receiving radioisotope therapy compared with patients who received no radiation therapy (1973–2002: RR = 2.33; 95% CI, 1.38–3.79; $P < 0.001$; 1988–2002: RR = 3.05; 95% CI, 1.48–8.3; $P = 0.004$), with greater numbers diagnosed within 10 yr after primary diagnosis. Leukemia, like thyroid cancer, is known to be associated with radiation and chemotherapy and usually occurs within 10 yr of treatment for other cancers (14, 53, 54). The described association of thyroid cancer with leukemia cannot be entirely attributed to treatment, because a reciprocal relationship has been reported (26, 28), indicating other factors separate from treatment effects.

The strengths of our study include the use of a large, high-quality, population database representing diverse sites in the

United States and the longest period of follow-up of any study of second primary tumors after thyroid cancer diagnosis. Limitations include the many sources of bias inherent in retrospective studies, particularly surveillance bias that would detect more secondary malignancies in patients with follow-up after thyroid cancer and misclassification bias, as well as the small numbers of relatively rare second primaries and the inability to standardize histology review of malignancies. Some clinical and pathological data known to be of prognostic significance are not available in the SEER database. Specifically lacking is information regarding details about dose and number of courses of radioiodine administration making the investigation of a dose-effect relationship impossible. In addition, the SEER database does not record history of treatment failure or time of relapse. Therefore, we were unable to adjust for these factors in our analyses.

In summary, the overall risk of second primary malignancies is slightly increased for thyroid cancer survivors over that of the general U.S. population. These risks are modified by age at diagnosis, radioisotope use, and latency period. Cancer-specific screening for common second primary cancers, (*e.g.* leukemia, breast, and prostate) is recommended during follow-up for thyroid cancer survivors. Additional studies investigating molecular-genetic and environmental factors may aid in the identification of specific groups at the greatest risk of developing second primary cancers in the future.

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References

1. **Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ** 2005 Cancer statistics, 2005. CA Cancer J Clin 55:10–30
2. **Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Feuer EJ, Edwards BK, eds,** SEER Cancer Statistics Review, 1975–2002, based on November 2004 SEER data submission, posted to the SEER web site 2005. Bethesda, MD: National Cancer Institute
3. **Mack WJ, Preston-Martin S,** Epidemiology of thyroid cancer. In: Fagin JA, ed. Thyroid cancer. Vol 2. Boston: Kluwer Academic Publishers; 1998:1–25
4. **Mehta MP, Goetowski PG, Kinsella TJ** 1989 Radiation induced thyroid neoplasms 1920 to 1987: a vanishing problem? Int J Radiat Oncol Biol Phys 16:1471–1475
5. **Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, Schneider AB, Tucker MA, Boice Jr JD** 1995 Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 141:259–277
6. **Gilliland FD, Hunt WC, Morris DM, Key CR** 1997 Prognostic factors for thyroid carcinoma. A population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973–1991. Cancer 79:564–573
7. **Blankenship DR, Chin E, Terris DJ** 2005 Contemporary management of thyroid cancer. Am J Otolaryngol 26:249–260
8. 2005 Thyroid Cancer Clinical Practice Guidelines in Oncology. JNCCN 3:404.
9. **Schlumberger MJ** 1998 Papillary and follicular thyroid carcinoma. N Engl J Med 338:297–306
10. **Kendall GM, Muirhead CR, Darby SC, Doll R, Arnold L, O'Hagan JA** 2004 Epidemiological studies of UK test veterans. I. General description. J Radiol Prot 24:199–217
11. **Muirhead CR, Kendall GM, Darby SC, Doll R, Haylock RG, O'Hagan JA, Berridge GL, Phillipson MA, Hunter N** 2004 Epidemiological studies of UK test veterans. II. Mortality and cancer incidence. J Radiol Prot 24:219–241
12. **Yoshinaga S, Mabuchi K, Sigurdson AJ, Doody MM, Ron E** 2004 Cancer risks among radiologists and radiologic technologists: review of epidemiologic studies. Radiology 233:313–321
13. **Schleipman AR** 2005 Occupational radiation exposure: population studies. Radiol Technol 76:185–191
14. **Little JB** 1993 Cellular, molecular, and carcinogenic effects of radiation. Hematol Oncol Clin North Am 7:337–352
15. **Wakeford R** 2004 The cancer epidemiology of radiation. Oncogene 23:6404–6428
16. **Jhiang SM** 2000 The RET proto-oncogene in human cancers. Oncogene 19: 5590–5597
17. **Beierwaltes WH, Rabbani R, Dmuchowski C, Lloyd RV, Eyre P, Mallette S** 1984 An analysis of "ablation of thyroid remnants" with I-131 in 511 patients from 1947–1984: experience at University of Michigan. J Nucl Med 25:1287–1293
18. **Koral KF, Adler RS, Carey JE, Beierwaltes WH** 1986 Iodine-131 treatment of thyroid cancer: absorbed dose calculated from post-therapy scans. J Nucl Med 27:1207–1211
19. **Breslow NE, Lubin JH, Marek P, Langholz B** 1983 Multiplicative models and cohort analysis. J Am Stat Assoc 78:1–12
20. **Adjadj E, Rubino C, Shamsaldim A, Le MG, Schlumberger M, de Vathaire F** 2003 The risk of multiple primary breast and thyroid carcinomas. Cancer 98:1309–1317
21. **Akslen LA, Glattre E** 1992 Second malignancies in thyroid cancer patients: a population-based survey of 3658 cases from Norway. Eur J Cancer 28:491–495
22. **Chen AY, Levy L, Goepfert H, Brown BW, Spitz MR, Vassilopoulou-Sellin R** 2001 The development of breast carcinoma in women with thyroid carcinoma. Cancer 92:225–231
23. **Hall P, Holm LE, Lundell G** 1990 Second primary tumors following thyroid cancer. A Swedish record-linkage study. Acta Oncol 29:869–873
24. **Hemminki K, Jiang Y** 2001 Second primary neoplasms after 19281 endocrine gland tumours: aetiological links? Eur J Cancer 37:1886–1894
25. **Li CI, Rossing MA, Voigt LF, Daling JR** 2000 Multiple primary breast and thyroid cancers: role of age at diagnosis and cancer treatments (United States). Cancer Causes Control 11:805–811
26. **Ronckers CM, McCarron P, Ron E** 2005 Thyroid cancer and multiple primary tumors in the SEER cancer registries. Int J Cancer 117:281–288
27. **Verkooijen RB, Smit JW, Romijn JA, Stokkel MP** 2006 The incidence of second primary tumors in thyroid cancer patients is increased, but not related to treatment of thyroid cancer. Eur J Endocrinol 155:801–806
28. **Sandeep TC, Strachan MW, Reynolds RM, Brewster DH, Scelo G, Pukkala E, Hemminki K, Anderson A, Tracey E, Friis S, McBride ML, Kee-Seng C, Pompe-Kirn V, Kliewer EV, Tonita JM, Jonasson JG, Martos C, Boffetta P, Brennan P** 2006 Second primary cancers in thyroid cancer patients: a multinational record linkage study. J Clin Endocrinol Metab 91:1819–1825
29. **Canchola AJ, Horn-Ross PL, Purdie DM** 2006 Risk of second primary malignancies in women with papillary thyroid cancer. Am J Epidemiol 163:521–527
30. **Liska J, Altanerova V, Galbavy S, Stvrtina S, Brtko J** 2005 Thyroid tumors: histological classification and genetic factors involved in the development of thyroid cancer. Endocr Regul 39:73–83
31. **Saad MF, Ordonez NG, Rashid RK, Guido JJ, Hill Jr CS, Hickey RC, Samaan NA** 1984 Medullary carcinoma of the thyroid. A study of the clinical features and prognostic factors in 161 patients. Medicine (Baltimore) 63:319–342
32. **Edmonds CJ, Smith T** 1986 The long-term hazards of the treatment of thyroid cancer with radioiodine. Br J Radiol 59:45–51
33. **Vassilopoulou-Sellin R, Palmer L, Taylor S, Cooksley CS** 1999 Incidence of breast carcinoma in women with thyroid carcinoma. Cancer 85:696–705
34. 1998 Radiation dose from radiopharmaceuticals: a report of a task group of committee 2 of the ICRP. Ann ICRP 28:1–126
35. **Bruno R, Giannasio P, Ronga G, Baudin E, Travagli JP, Russo D, Filetti S, Schlumberger M** 2004 Sodium iodide symporter expression and radioiodine distribution in extrathyroidal tissues. J Endocrinol Invest 27:1010–1014
36. **Robinson PS, Barker P, Campbell A, Henson P, Surveyor I, Young PR** 1994 Iodine-131 in breast milk following therapy for thyroid carcinoma. J Nucl Med 35:1797–1801
37. **Spitzweg C, Morris JC** 2002 The sodium iodide symporter: its pathophysiological and therapeutic implications. Clin Endocrinol (Oxf) 57:559–574
38. **Hemminki K, Boffetta P** 2004 Multiple primary cancers as clues to environmental and heritable causes of cancer and mechanisms of carcinogenesis. IARC Sci Publ 157:289–297

39. **Jarzab B, Wloch J, Wiench M** 2001 Molecular changes in thyroid neoplasia. Folia Histochem Cytobiol 39(Suppl 2):26–27
40. **Dawson DM, Lawrence EG, MacLennan GT, Amini SB, Kung HJ, Robinson D, Resnick MI, Kursh ED, Pretlow TP, Pretlow TG** 1998 Altered expression of RET proto-oncogene product in prostatic intraepithelial neoplasia and prostate cancer. J Natl Cancer Inst 90:519–523
41. **Meric F, Lee WP, Sahin A, Zhang H, Kung HJ, Hung MC** 2002 Expression profile of tyrosine kinases in breast cancer. Clin Cancer Res 8:361–367
42. **Kroll TG** 2004 Molecular events in follicular thyroid tumors. Cancer Treat Res 122:85–105
43. **Cybulski C, Gorski B, Huzarski T, Masojc B, Mierzejewski M, Debniak T, Teodorczyk U, Byrski T, Gronwald J, Matyjasik J, Zlowocka E, Lenner M, Grabowska E, Nej K, Castaneda J, Medrek K, Szymanska A, Szymanska J, Kurzawski G, Suchy J, Oszurek O, Witek A, Narod SA, Lubinski J** 2004 CHEK2 is a multiorgan cancer susceptibility gene. Am J Hum Genet 75:1131–1135
44. **Cybulski C, Wokolorczyk D, Huzarski T, Byrski T, Gronwald J, Gorski B, Debniak T, Masojc B, Jakubowska A, Gliniewicz B, Sikorski A, Stawicka M, Godlewski D, Kwias Z, Antczak A, Krajka K, Lauer W, Sosnowski M, Sikorska-Radek P, Bar K, Klijer R, Zdrojowy R, Malkiewicz B, Borkowski A, Borkowski T, Szwiec M, Narod SA, Lubinski J** 2006 A large germline deletion in the Chek2 kinase gene is associated with an increased risk of prostate cancer. J Med Genet 43:863–866
45. **Cybulski C, Wokolorczyk D, Huzarski T, Byrski T, Gronwald J, Gorski B, Debniak T, Masojc B, Jakubowska A, van de Wetering T, Narod SA, Lubinski J** 2006 A deletion in CHEK2 of 5,395 bp predisposes to breast cancer in Poland. Breast Cancer Res Treat 102:119–122
46. **Hall P, Holm LE, Lundell G, Bjelkengren G, Larsson LG, Lindberg S, Tennvall J, Wicklund H, Boice Jr JD** 1991 Cancer risks in thyroid cancer patients. Br J Cancer 64:159–163
47. **de Vathaire F, Schlumberger M, Delisle MJ, Francese C, Challeton C, de la Genardiere E, Meunier F, Parmentier C, Hill C, Sancho-Garnier H** 1997 Leukaemias and cancers following iodine-131 administration for thyroid cancer. Br J Cancer 75:734–739
48. **Rubino C, de Vathaire F, Dottorini ME, Hall P, Schvartz C, Couette JE, Dondon MG, Abbas MT, Langlois C, Schlumberger M** 2003 Second primary malignancies in thyroid cancer patients. Br J Cancer 89:1638–1644
49. **Glanzmann C** 1992 Subsequent malignancies in patients treated with 131-iodine for thyroid cancer. Strahlenther Onkol 168:337–343
50. **Schneider AB, Lubin J, Ron E, Abrahams C, Stovall M, Goel A, Shore-Freedman E, Gierlowski TC** 1998 Salivary gland tumors after childhood radiation treatment for benign conditions of the head and neck: dose-response relationships. Radiat Res 149:625–630
51. **Blanchard CM, Denniston MM, Baker F, Ainsworth SR, Courneya KS, Hann DM, Gesme DH, Reding D, Flynn T, Kennedy JS** 2003 Do adults change their lifestyle behaviors after a cancer diagnosis? Am J Health Behav 27:246–256
52. **Roldan Schilling V, Fernandez Abellan P, Dominguez Escribano JR, Rivas Gonzalez C, Mut Barbera E, Calatayud Cendra R** 1998 Acute leukemias after treatment with radioiodine for thyroid cancer. Haematologica 83:767–768
53. **Levine EG, Bloomfield CD** 1992 Leukemias and myelodysplastic syndromes secondary to drug, radiation, and environmental exposure. Semin Oncol 19:47–84
54. **Leone G, Mele L, Pulsoni A, Equitani F, Pagano L** 1999 The incidence of secondary leukemias. Haematologica 84:937–945