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JNCI J Natl Cancer Inst (2016) 108(2): djv314

doi:10.1093/jnci/djv314
First published online November 3, 2015
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Use of Radioactive Iodine for Thyroid Cancer and Risk for Second Primary Malignancy: A Nationwide Population-Based Study

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Abstract

Background: Radioactive iodine (RAI) is widely used for the treatment of thyroid cancers. However, information on associations between RAI dose and second primary malignancy (SPM) is lacking.

Methods: Patients without antecedent cancer age 20 years or older and newly diagnosed with thyroid cancer were recruited from the Taiwan National Health Insurance database between 1997 and 2010. Standardized incidence ratios (SIRs) for the cancers were calculated to compare the incidence of thyroid cancer with the general population. The association between RAI dosage and cancer development was estimated using time-dependent Cox regression analysis. All statistical tests were two-sided.

Results: A total of 692 cases of SPM were identified among 20 235 patients with thyroid cancer. Regarding the latter, 79.7% of the patients were women, the median age was 46 years, and the follow-up period included 134 178 person-years. The SIR for any SPM was 1.41 (95% confidence interval [CI] = 1.31 to 1.52). A statistically significantly higher SIR was observed in leukemia (2.74), non-Hodgkin's lymphoma (2.38), prostate (2.30), lung and mediastinum (1.93), pancreas (1.83), kidney (1.81), breast (1.48), and colon-rectum (1.31) cancers. Cumulative RAI dose (per 30 mCi increase) conferred a strong risk for SPM (adjusted hazard ratio [aHR] = 1.01, 95% CI = 1.01 to 1.02, $P < .001$) and leukemia (aHR = 1.03, 95% CI = 1.02 to 1.04, $P < .001$) occurrences. A cumulative RAI dose greater than 150 mCi possessed a statistically significant risk for all cancer combined (aHR = 1.30) and leukemia (aHR = 6.03).

Conclusions: An increased risk of SPM was observed for thyroid cancer patients, especially with cumulative RAI doses over 150 mCi.

Thyroid cancer is the most prevalent endocrine malignancy diagnosed, and the incidence of this disease has been increasing over the past three decades worldwide (1–3). The average annual increase in the rate of incidence for thyroid cancer has been 6.6% per year since 1998 (4). With appropriate treatment, patients with thyroid cancer have a favorable prognosis, with the 10-year survival rate estimated to be greater than 90% (5–7). However, favorable survival, coupled with the young age of most thyroid cancer patients, leads to an increased risk for subsequent cancer.

Received: October 23, 2014; **Revised:** March 19, 2015; **Accepted:** October 1, 2015

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Increased risk of SPM in thyroid cancer patients has been reported in several cancer registry and epidemiologic studies (8–13). It is hypothesized that increased SPM risk may be related to a genetic predisposition to malignancy or disease-specific treatments. Regarding the latter, radioactive iodine (RAI) is a commonly used treatment. Iodine-131 is a unique RAI that targets thyroid tissue and is widely used to eliminate occult residual tumors in order to reduce the risk of recurrence. RAI is also used to treat persistent disease and to ablate any normal thyroid remnant, thereby facilitating further surveillance by serum thyroglobulin or radioiodine whole-body scintigraphy (14). A meta-analysis (15) of two studies (16,17) found that the only statistically significant SPM that could be attributed to the use of RAI was leukemia while other studies revealed an increased risk of hematologic malignancies (16–18), as well as cancer of the salivary gland (17,18), colorectum (17,19), and soft tissue sarcoma (17).

There are various guidelines regarding indications and dosage for RAI therapy that have been used. However, there is clinical variation in choosing the dose of RAI. For example, the empiric fixed high dosing strategy, with dosage usually at 100 to 200 mCi, was often used in some institutions (20,21). On the other hand, the administration of a low fixed dose or dosimetric method strategy to patients with low to intermediate risk could prevent dose-dependent side effects such as sialadenitis and oral complications such as xerostomia and stomatitis, as well as caries formation (20,22). It is hypothesized that an analysis of dosage in relation to RAI-related adverse events, especially cancer risk, would facilitate the standardization of RAI doses. Therefore, the goal of this study was to investigate the risk of SPM among thyroid cancer patients, as well as the association between RAI dosage and cancer development, using a nationwide population-based dataset.

Methods

Data Sources

Data was obtained from the National Health Insurance (NHI) database that is managed by the National Health Research Institute in Taiwan. The NHI program began in 1995 and is a mandatory universal health insurance policy that offers comprehensive medical care coverage for up to 99% of all Taiwanese residents (23). This care includes outpatient, inpatient, emergency, dental, and traditional Chinese medicine services. Numerous NHI research databases (NHIRDs), including enrollment files, claims data, and the registry for drug prescriptions, were integrated with the NHI database of catastrophic illness, thereby providing comprehensive utilization and enrollment information for all patients with severe disease who have received copayment exemption under the NHI program. However, all information that could potentially identify an individual patient is encrypted. Because the NHI dataset consists of de-identified secondary data for research purposes, this study was exempt from full review by the institutional review board.

Study Population and Postdiagnosis Follow-up

Data for patients newly diagnosed with thyroid cancer between January 1, 1997, and December 31, 2010, were retrieved from the Registry of Catastrophic Illness according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 193. Patients diagnosed with thyroid cancer prior to January 1, 1997, were not enrolled to assure that the thyroid cancer was newly diagnosed and the antecedent malignancies could be traced accurately. Patients were also excluded if they were: 1) younger than age 20 years at the time of diagnosis—the criterion suggested by the institutional review board and with consideration of different prevalent cancer types and cancer risk in the population; or 2) had a history of malignancies; or 3) within one year of a thyroid cancer diagnosis, had died, were lost to follow-up, or developed cancer.

After a diagnosis of thyroid cancer, the postdiagnosis follow-up in general clinical practice in Taiwan was basically in accordance with NCCN or ESMO guidelines (24,25), which included a blood test (TSH ± free T3 and/or T4, Tg ± Tg antibodies) plus neck ultrasound every three months (for at least five years). Radioiodine imaging would be dependent on clinical doubtful symptoms/signs.

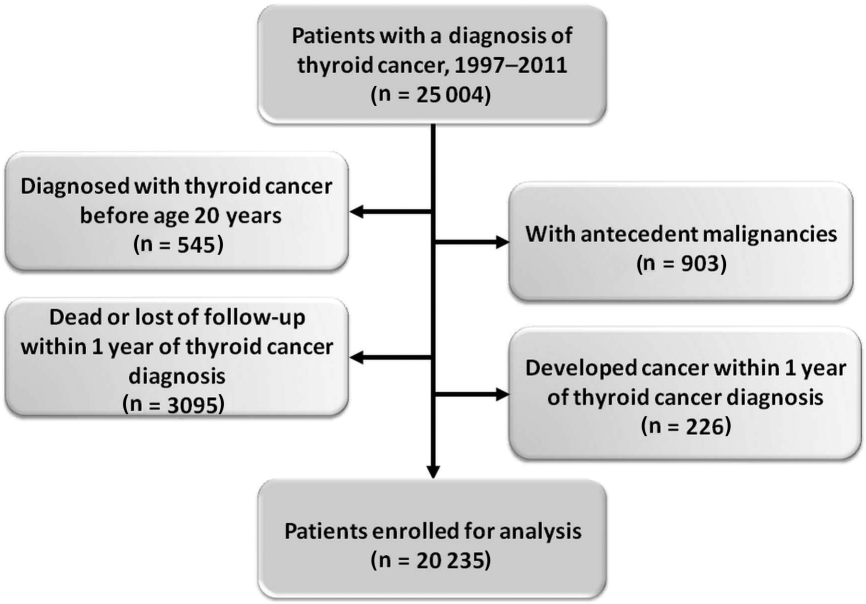

Figure 1. CONSORT flow diagram showing patient selection criteria and the number of patients associated with each criterion.

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Diagnosis of Cancer and Records for Comorbidities, Radioactive Iodine Therapy, and Radiotherapy

A diagnosis of cancer, either thyroid cancer or any of the subsequent malignancies, was made according to the certification of "catastrophic illness" (ie ICD-9-CM 140–208). Accordingly, histological confirmation of malignancy with or without associated laboratory and imaging studies was provided for peer review. The so-called "catastrophic illness" system exempts copayment under the NHI program. All patients with the certification of catastrophic illness could get appropriate outpatient follow-up with $NT 100 dollars (approximately $US 3.2 dollars) each time to seek medical advice and clinical workup.

Comorbidity data were also retrieved according to ICD-9-CM, and these involved diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, liver cirrhosis, autoimmune diseases, and dyslipidemia. For each patient, the severities of their comorbidities were individually scored, then the Charlson comorbidity index (CCI), and the sum of these scores at the time of the thyroid cancer diagnosis were recorded (26). The CCI is a scoring system that was originally developed as a prognostic indicator for patients with a variety of medical conditions; it was commonly used to measure each patient's comorbid conditions.

The date and dose (in mCi units) of RAI applied at each treatment and follow-up were retrieved from the registry of drug prescriptions. The date of external beam radiotherapy (EBRT), if any, was also retrieved. However, information regarding radiation dose and sites of irradiation were not available from the NHIRD.

Statistical Analyses

The main dependent variable was development of SPM. The risk of SPM among the study cohort was determined using a standardized incidence ratio (SIR) (27). This ratio was calculated by dividing the observed number of cancer occurrences by the expected number of cancer occurrences. The latter was calculated by multiplying the national incidence rate of cancers according to sex, calendar year, and patient age in five-year intervals by the corresponding stratum-specific person-time accrued for the cohort. The overall incidence rate and the incidence rate for each specified cancer among the general population were obtained from the Taiwan National Cancer Registry. The 95% confidence intervals (CIs) for the SIRs were estimated based on the assumption that the observed number of cancers followed a Poisson probability distribution. SIRs were also determined according to sex and age group (ie, 20–39, 40–59, 60–79, and ≥80 years). Another subgroup analysis included a stratification by duration because a diagnosis was obtained in order to avoid surveillance bias and to evaluate a possible latent effect. SIRs for each cancer type were also estimated.

Univariate and multivariable Cox proportional hazard models were applied to identify predictors of SPM development among the patients with thyroid cancer with age as the time scale (28). The calculated hazard ratios were adjusted for patient age, sex, and CCI. By analyzing the association between RAI and cancer risk, the cumulative dosage of RAI was analyzed within a two-year latent period (29) and also as a time-dependent covariate to avoid immortal time bias (30,31). In addition, to explore potential dose-effect relationships, Cox regression analyses were performed to estimate the risk of cancer at cumulative RAI dose levels according to the following quartiles: 1–30 mCi, 30–100 mCi, 100–150 mCi, and greater than 150 mCi (with 30, 100, and 150 representing the first, second, and third quartiles, respectively). A comparison between the risk for patients with low vs high cumulative doses of RAI was also performed using 30 mCi increments. Extraction and computation of data were performed using the Perl programming language (version 5.12.2). Microsoft SQL Server 2012 (Microsoft Corp., Redmond, WA) was used for data linkage, processing, and sampling. All statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC). Statistical significance was defined as a P value of less than .05, and all statistical tests were two-sided.

Table 1. Characteristics of patients with thyroid cancer in Taiwan, 1997–2010 (follow-up more than 1 y)*

Characteristics	Total	Men	Women
No. of patients	20 235	4116	16 119
Person-years at risk	134 178	25 489	108 689
Median follow-up (IQR), y	5.91 (3.10–9.92)	5.33 (2.83–9.23)	6.10 (3.16–10.11)
Median age (IQR), y	46 (36–56)	48 (37–58)	45 (36–55)
Age at diagnosis, y			
20–39	6782	1231	5551
40–59	9826	1955	7871
60–79	3359	852	2507
≥80	268	78	190

* IQR = interquartile range.

Table 2. The profile of radioactive iodine therapy for patients with thyroid cancer in Taiwan, 1997–2010 (follow-up more than 1 y)*

Therapy characteristics	Total	Men	Women
No. of patients receiving RAI therapy with any dose, n	11 799	2433	9366
No. of RAI treatment, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)
Each RAI dose in mCi, median (IQR)	75 (30–100)	90 (30–120)	70 (30–100)
Accumulated RAI dose in mCi, median (IQR)	100 (30–150)	100 (50–200)	100 (30–150)
Also received external beam radiotherapy, n (%)	260 (2.2)	98 (4.0)	162 (1.7)
Also received chemotherapy, n (%)	222 (1.9)	41 (1.7)	181 (1.9)
No. of patients receiving RAI therapy with dose >100 mCi, n	4782	1193	3589
Also received external beam radiotherapy, n (%)	194 (4.1)	84 (7.0)	110 (3.1)
Also received chemotherapy, n (%)	96 (2.0)	25 (2.1)	71 (1.9)

* IQR = interquartile range; RAI = radioactive iodine.

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Results

Characteristics of the Study Population and RAI Therapy

A total of 25 004 patients with thyroid cancer were identified in the Catastrophic Illness Registry of the NHIRD. Of these, 545 patients were diagnosed before age of 20 years, 903 patients had antecedent malignancies, 3095 were dead or lost to follow-up within one year of thyroid cancer diagnosis (82.5% of whom were diagnosed less than one year prior to the end of study), and 226 developed cancer within the first year of their thyroid cancer diagnosis. After excluding these patients, the final cohort consisted of 20 235 patients (Figure 1), 79.7% of which were women. This cohort was observed for 134 178 person-years from 1997 to 2011, and the median follow-up period was 5.91 years (interquartile range [IQR] = 3.10–9.92). The median age at diagnosis was 46 (IQR = 36–56) years. Among them, a total of 11 799 patients (58.3%) received RAI therapy, with median single and cumulated RAI dose at 75 (IQR = 30–100) and 100 (IQR = 30–150) mCi, respectively. Demographic data for the cohort are listed in Table 1 and the detail profile of RAI therapy in Table 2. A total of 11 799 (58.3%) patients had ever received one or more RAI treatments, with the median accumulative RAI dose of 100 mCi. Among these patients there were 4782 (40.5%) patients, including 1193 (24.9%) men and 3589 (75.1%) women, who ever received a single RAI dose greater than 100 mCi. The percentage of patients receiving EBRT among those ever receiving a single RAI dose of greater than 100 mCi was nearly twice that of those receiving RAI with any dose (4.1% and 2.2%, respectively). Because very few patients also received EBRT (n = 260, 2.2%) or chemotherapy (n = 222, 1.9%), we also performed the analysis that excluded patients receiving EBRT or chemotherapy to eliminate the potential confounding effect.

Overall Cancer Data

During the observation period, 692 cancers were detected. Compared with the general population, patients with thyroid cancer exhibited a statistically significantly higher cancer risk, with an SIR estimate of 1.41 (95% CI = 1.31 to 1.52, $P < .001$) for all cancer combined. For men vs women, the SIR was 1.31 (95% CI = 1.12 to 1.52, $P = .001$) and 1.44 (95% CI = 1.32 to 1.57, $P < .001$), respectively. A subanalysis according to age at diagnosis revealed that the SIR was highest for patients age 20 to 39 years (SIR = 2.04, 95% CI = 1.54 to 2.65), and the SIR gradually decreased with age (40–59 y: SIR = 1.40, 95% CI = 1.25 to 1.56; 60–79 y: SIR = 1.38, 95% CI = 1.22 to 1.55; and ≥80 y: SIR = 1.13, 95% CI = 0.80 to 1.56). This tendency was observed for both men and women (Table 3). A subgroup analysis according to the duration of thyroid cancer also showed that SIR increased when there was a longer interval between SPM and thyroid cancer (ie, 1.33, duration 1–5 y, to 1.49, duration ≥ 5 y). SIR and 95% confidence interval values for these subgroup analyses are summarized in Table 3.

Specific Cancer Types

The highest significant SIR for SPM that was observed for thyroid cancer patients was associated with leukemia (SIR = 2.74, 95% CI = 1.65 to 4.28), followed by non-Hodgkin's lymphoma (SIR = 2.38, 95% CI = 1.55 to 3.48), prostate (SIR = 2.30, 95% CI = 1.49 to 3.40), lung and mediastinum (SIR = 1.93, 95% CI = 1.58 to 2.35), pancreas (SIR = 1.83, 95% CI = 1.02 to 3.02), kidney (SIR = 1.81, 95% CI = 1.15 to 2.72), breast (SIR = 1.48, 95% CI = 1.25 to 1.72), and

Table 3. Standardized incidence ratios according to sex, age at diagnosis, and duration of thyroid cancer*

Characteristics	Total			Men			Women		
	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)
All cancer combined	692	491.53	1.41 (1.31 to 1.52)	165	126.18	1.31 (1.12 to 1.52)	527	365.35	1.44 (1.32 to 1.57)
Age at diagnosis, y									
20–39	56	27.45	2.04 (1.54 to 2.65)	9	4.00	2.25 (1.03 to 4.27)	47	23.45	2.00 (1.47 to 2.67)
40–59	312	223.06	1.40 (1.25 to 1.56)	58	42.85	1.35 (1.03 to 1.75)	254	180.21	1.41 (1.24 to 1.59)
60–79	286	207.52	1.38 (1.22 to 1.55)	88	67.49	1.30 (1.05 to 1.61)	198	140.03	1.41 (1.22 to 1.63)
≥80	38	33.50	1.13 (0.80 to 1.56)	10	11.83	0.85 (0.41 to 1.55)	28	21.66	1.29 (0.86 to 1.87)
Duration of thyroid cancer									
1–5	329	247.72	1.33 (1.19 to 1.48)	89	66.68	1.33 (1.07 to 1.64)	240	181.04	1.33 (1.16 to 1.50)
≥5	363	243.81	1.49 (1.34 to 1.65)	76	59.50	1.28 (1.01 to 1.60)	287	184.31	1.56 (1.38 to 1.75)

* CI = confidence interval; SIR = standardized incidence ratio.

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colon-rectum (SIR = 1.31, 95% CI = 1.06 to 1.61) cancers. The 95% confidence interval values for each significant SIR according to specific cancer type in total, male, and female populations are presented in Table 4. The SIRs for specific cancer types among the preponderance of subjects, those age 40 to 59 years, who constituted 48.6% (n = 9826) of the entire population, were also calculated (Supplementary Table 1, available online); the results showed that this preponderant patient population remained representative.

Predictors of Risk for All Cancer Combined and Leukemia

As shown in Table 5, multivariable analysis identified cumulative RAI dose (per 30 mCi increase) (aHR = 1.01, 95% CI = 1.01 to 1.02, $P < .001$) and EBRT (aHR = 1.80, 95% CI = 1.20 to 2.70, $P = .005$) as predictive factors for all cancer combined. Cumulative RAI dose (per 30 mCi increase) served as a strong predictive factor for leukemia (aHR = 1.03, 95% CI = 1.02 to 1.04, $P < .001$). The results remained true when the potential confounding effects of EBRT and/or chemotherapy were eliminated (Supplementary Table 2, available online). In addition, the predictive role of cumulative RAI dose (per 30 mCi increase) for leukemia retained statistical significance in patients receiving a single RAI dose greater than 100 rather than 100 mCi or less (Supplementary Table 3, A and B, available online).

The Effect of Cumulative RAI

As shown in Table 6, cumulative RAI was found to serve as a risk factor for leukemia (aHR per 30 mCi increase, 1.03, 95% CI = 1.02 to 1.04, $P < .001$) and lung-mediastinum cancers (aHR for per 30 mCi increase = 1.02, 95% CI = 1.00 to 1.04, $P = .045$). Cumulative RAI was also a protective factor for non-Hodgkin's lymphoma (aHR for per 100 mCi increase = 0.77, 95% CI = 0.62 to 0.96, $P = .012$). When the cumulative doses of RAI were categorized into quartiles, it was observed that the highest quartile (>150 mCi) was associated with a statistically significant effect for all cancer combined (aHR = 1.30, 95% CI = 1.03 to 1.65, $P = .036$) and for leukemia (aHR = 6.03, 95% CI = 1.89 to 19.25, $P = .002$). When we excluded patients receiving EBRT and/or chemotherapy, the aHR of cumulative RAI (per 30 mCi increase) for leukemia (1.03) and lung-mediastinum cancers (1.03) stayed statistically significant, as well as the aHR of highest RAI quartile (>150 mCi) for all cancers combined (1.52) and leukemia (5.33) (Supplementary Table 4, available online).

Discussion

To our knowledge, this is the first population-based study to evaluate the risk for SPM among patients with thyroid cancer and also the dose-response relationship between RAI and leukemia in an Asian population. The main findings include: 1) a statistically significant increase in SPM risk was associated with

Table 4. Standardized incidence ratios for specific cancer types*

	Total			Men			Women		
Site of cancers	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)
All cancer combined	692	491.53	1.41 (1.31 to 1.52)	165	126.18	1.31 (1.12 to 1.52)	527	365.35	1.44 (1.32 to 1.57)
Head and neck	38	32.57	1.17 (0.83 to 1.60)	14	20.54	0.68 (0.37 to 1.14)	24	12.04	1.99 (1.28 to 2.97)
Digestive system	188	165.06	1.14 (0.98 to 1.31)	61	57.31	1.06 (0.81 to 1.37)	127	107.75	1.18 (0.98 to 1.40)
Esophagus	7	6.26	1.12 (0.45 to 2.31)	5	4.96	1.01 (0.33 to 2.35)	2	1.30	1.54 (0.19 to 5.57)
Stomach	21	20.86	1.01 (0.62 to 1.54)	4	6.88	0.58 (0.16 to 1.49)	17	13.98	1.22 (0.71 to 1.95)
Colon and rectum	93	70.80	1.31 (1.06 to 1.61)	18	19.50	0.92 (0.55 to 1.46)	75	51.30	1.46 (1.15 to 1.83)
Liver and biliary tract	52	58.95	0.88 (0.66 to 1.16)	29	23.64	1.23 (0.82 to 1.76)	23	35.31	0.65 (0.41 to 0.98)
Pancreas	15	8.20	1.83 (1.02 to 3.02)	5	2.32	2.15 (0.70 to 5.02)	10	5.87	1.70 (0.82 to 3.13)
Lung and mediastinum	102	52.77	1.93 (1.58 to 2.35)	27	17.68	1.53 (1.01 to 2.22)	75	35.09	2.14 (1.68 to 2.68)
Bone and soft tissue	4	4.06	0.98 (0.27 to 2.52)	2	1.09	1.83 (0.22 to 6.61)	2	2.97	0.67 (0.08 to 2.43)
Skin	12	8.80	1.36 (0.70 to 2.38)	3	2.23	1.35 (0.28 to 3.93)	9	6.58	1.37 (0.63 to 2.60)
Breast	158	107.06	1.48 (1.25 to 1.72)	0	0.13	0.00 (0.00 to 27.76)	158	106.93	1.48 (1.26 to 1.73)
Genitourinary system	122	90.34	1.35 (1.12 to 1.61)	40	19.22	2.08 (1.49 to 2.83)	82	71.12	1.15 (0.92 to 1.43)
Cervix	21	25.53	0.82 (0.51 to 1.26)	N/A	N/A	N/A	21	25.53	0.82 (0.51 to 1.26)
Uterus	17	16.12	1.05 (0.61 to 1.69)	N/A	N/A	N/A	17	16.12	1.05 (0.61 to 1.69)
Ovary	20	12.78	1.56 (0.96 to 2.42)	N/A	N/A	N/A	20	12.78	1.56 (0.96 to 2.42)
Prostate	25	10.85	2.30 (1.49 to 3.40)	25	10.85	2.30 (1.49 to 3.40)	N/A	N/A	N/A
Bladder	16	12.36	1.29 (0.74 to 2.10)	8	5.18	1.54 (0.67 to 3.04)	8	7.18	1.11 (0.48 to 2.19)
Kidney	23	12.70	1.81 (1.15 to 2.72)	7	3.19	2.19 (0.88 to 4.52)	16	9.51	1.68 (0.96 to 2.73)
Hematologic system	50	21.06	2.37 (1.76 to 3.13)	16	5.68	2.81 (1.61 to 4.57)	34	15.37	2.21 (1.53 to 3.09)
Non-Hodgkin's lymphoma	26	10.94	2.38 (1.55 to 3.48)	7	2.84	2.47 (0.99 to 5.08)	19	8.10	2.34 (1.41 to 3.66)
Hodgkin's Disease	0	0.47	0.00 (0.00 to 7.80)	0	0.14	0.00 (0.00 to 26.47)	0	0.33	0.00 (0.00 to 11.06)
Multiple myeloma	5	2.70	1.85 (0.60 to 4.32)	1	0.76	1.31 (0.03 to 7.31)	4	1.94	2.06 (0.56 to 5.28)
Leukemia	19	6.94	2.74 (1.65 to 4.28)	8	1.94	4.12 (1.78 to 8.11)	11	5.00	2.20 (1.10 to 3.94)
All others	18	9.79	1.84 (1.09 to 2.91)	2	2.30	0.87 (0.11 to 3.15)	16	7.49	2.13 (1.22 to 3.47)

* CI = confidence interval; N/A = not applicable; SIR = standardized incidence ratio.

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leukemia, non-Hodgkin's lymphoma, prostate, lung and mediastinum, pancreas, kidney, breast, and colon-rectum cancers; 2) the increased risk of leukemia was found to be associated with the cumulative dosage of RAI; and 3) cumulative RAI was the only statistically significant factor for leukemia, and a clear dose-response relationship was identified.

In Taiwan, radioactive compounds are highly regulated by the Atomic Energy Council, Executive Yuan. Therefore, RAI for medical purposes is synthesized with 1 mCi as the minimal calculated unit and each 1 mCi used per individual is recorded in detail. An advantage of the NHIRD database is that precise doses (per 1 mCi as the minimal unit) and dates of RAI treatments could be tracked, thereby facilitating its effect as a time-dependent covariate. Additional advantages of the present study include the enrollment of more recently treated patients (ie, 1997–2010) and the availability of comprehensive coding for each patient to include all comorbidities.

The impact of RAI on the subsequent development of leukemia has previously been reported in case reports, small case series, and some epidemiologic studies (15,16,18). However, a dose-response relationship between cumulative RAI dose and leukemia is a novel finding of the present study. The results of the present study are also consistent with those of a European cohort study conducted by Rubino et al. (17), where an increased risk of leukemia was observed with an increasing cumulative RAI dose. In that study, an excess absolute risk of 0.8 for leukemia per GBq (27 mCi) of RAI was found per 100 000 person-years of follow-up (17). In contrast, a dose-response effect of RAI was not observed for leukemia in a study conducted by Hall et al. using a Swedish cohort (32). This result may be explained by the fact that most of the patients enrolled had benign diseases and received a lower dose of RAI (77% for diagnostic procedure with a mean activity 1.9 MBq [0.05 mCi] and 21% for treating hyperthyroidism with a mean activity 505 MBq [13.6 mCi]). Taken together, these data suggest that for patients with benign disease, the leukemogenic effect of RAI may be minimal or nonexistent at low doses of RAI. Data from the present report not only showed a positive association of increased leukemia risk along with RAI dosage (per 30 mCi increase in cumulative dose) with an adjusted hazard ratio of 1.03 (95% CI = 1.02 to 1.04) but also further emphasized a strongly statistically increased leukemia risk for cumulative RAI dosage greater than 150 mCi (aHR = 6.03, 95% CI = 1.89 to 19.25). The wide range of 95% confidence intervals for the hazard ratios of leukemia at higher dose levels implies small event numbers. In general, RAI is commonly administered at a dose of 30 to 100 mCi, and this is considered a dose that does not increase the risk of SPM.

Table 5. Analysis of risk factors for all cancer combined and leukemia occurrences

	All cancer combined	Leukemia
Variables	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Cumulative RAI dose*	1.01 (1.01 to 1.02)†	1.03 (1.02 to 1.04)†
Sex (male)	1.16 (0.98 to 1.34)	2.90 (1.09 to 7.74)‡
External beam radiotherapy	1.80 (1.20 to 2.70)§	2.53 (0.33 to 19.61)

* Per 30 mCi increase. CI = confidence interval; HR = hazard ratio; RAI = radioactive iodine.
† $P < .001$.
‡ $P < .05$.
§ $P < .01$.

Table 6. Hazard ratios of cumulative radioactive iodine dose for all cancer combined and specific cancer types

			Adjusted HR according to dose level (95% CI) †‡			
Variables	Crude HR (95% CI)*	Adjusted HR (95% CI) *†	1–30 mCi	30–100 mCi	100–150 mCi	>150 mCi
All cancer combined	1.01 (1.00 to 1.02)§	1.01 (1.00 to 1.02)	0.97 (0.76 to 1.23)	0.96 (0.77 to 1.19)	1.02 (0.77 to 1.34)	1.30 (1.03 to 1.65)§
Leukemia	1.03 (1.02 to 1.04)‖	1.03 (1.02 to 1.04)‖	0.48 (0.05 to 4.51)	1.10 (0.25 to 4.86)	0.71 (0.08 to 6.45)	6.03 (1.89 to 19.25)¶
Female breast	0.99 (0.96 to 1.02)	0.99 (0.96 to 1.02)	1.21 (0.76 to 1.93)	0.93 (0.59 to 1.48)	1.15 (0.65 to 2.02)	1.09 (0.63 to 1.90)
Pancreas	1.00 (0.95 to 1.06)	1.00 (0.93 to 1.07)	0.66 (0.08 to 5.76)	2.40 (0.62 to 9.25)	0.83 (0.09 to 7.81)	1.52 (0.27 to 8.64)
Colon-rectum	1.01 (0.99 to 1.03)	1.01 (0.99 to 1.03)	1.25 (0.69 to 2.27)	0.69 (0.36 to 1.32)	0.93 (0.44 to 1.98)	1.25 (0.66 to 2.38)
Prostate	1.01 (0.98 to 1.04)	1.01 (0.97 to 1.05)	1.20 (0.30 to 4.72)	0.71 (0.19 to 2.69)	1.03 (0.27 to 3.83)	1.69 (0.63 to 4.49)
Non-Hodgkin's lymphoma	0.77 (0.61 to 0.96)§	0.77 (0.62 to 0.96)§	0.65 (0.17 to 2.16)	0.71 (0.25 to 2.04)	0.29 (0.04 to 2.20)	N/A#
Kidney	1.01 (1.00 to 1.03)	1.01 (0.99 to 1.04)	1.46 (0.35 to 6.08)	2.35 (0.75 to 7.31)	0.63 (0.07 to 5.36)	1.42 (0.37 to 5.42)
Lung-mediastinum	1.02 (1.00 to 1.04)§	1.02 (1.00 to 1.04)§	0.68 (0.30 to 1.56)	1.41 (0.79 to 2.49)	1.12 (0.52 to 2.38)	1.49 (0.78 to 2.83)

* Per 30 mCi increase in cumulative dose. CI = confidence interval; HR = hazard ratio; N/A = not applicable.
† Adjusted for age, sex, and RT dose level.
‡ Reference: radioactive iodine dose = 0.
§ $P < .05$.
‖ $P < .001$.
¶ $P < .01$.
# No cases in this category.

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Weinberg et al. hypothesized that any RAI dose causes sublethal damage to the bone marrow, and this can lead to chromosomal aberrations and, eventually, malignant transformation (33). Support for this hypothesis was subsequently obtained (34,35). Although individual susceptibility is probably a contributing factor, the results of the present study suggest that a dose-response effect also exists between RAI and the subsequent onset of leukemia. This is an important consideration when evaluating the potential benefit vs harm of an RAI treatment plan for thyroid cancer patients.

Typically, a latency is observed between the development and diagnosis of cancer. For example, the leukemogenic effect of radiation has been reported to be approximately two years or more (29). The tumorigenic effect in solid organs is even longer (36). Patients with newly diagnosed thyroid cancer may undergo a series of physical examinations, and this increases the potential for finding other physical problems, including another cancer. Therefore, it was hypothesized that a diagnosis of SPM within one year of a thyroid cancer diagnosis may be because of surveillance bias (37). Correspondingly, the SIR for the first year of follow-up was 2.78 (95% CI = 2.43 to 3.16), and it was 4.20 for the first six months of follow-up (95% CI = 3.60 to 4.87). Thus, these results indicate that surveillance bias did exist, and therefore, Tables 3 and 4 only present the SIRs after one year of follow-up.

There are several limitations associated with the present study. First, a number of potential confounders, including occupational and environmental radiation exposure (other than RAI or radiotherapy), tobacco use, alcohol use, obesity, and a family history of malignancy, were not included in the information provided by the NHIRD. Therefore, we could not adjust for these factors. Second, the pathological type (such as medullary or anaplastic subtypes) and stage of each thyroid cancer were not available in the NHI dataset, thereby preventing a subanalysis of different types and disease extent of thyroid cancer. However, we have applied several analytic techniques in the study design and data analysis (use of standardized incidence ratio, restrict population not receiving radiotherapy and chemotherapy, and risk adjustment for specified variables) to avoid bias; lack of some clinical information may not overturn the main conclusion of the relationship between increased leukemia and all cancer risk along with RAI dosage. Third, the effects of radiation may last for more than forty years according to studies of atomic bomb survivors (38). Although the maximal follow-up period for the present study was approximately 10 years, it might still be too short to fully evaluate the effect of radiation carcinogenesis.

In conclusion, this nationwide population-based study demonstrated that thyroid cancer survivors are at risk for developing a SPM. Our data also showed a positive association of increased leukemia risk along with RAI dosage, as well as a statistically significantly increased risk of all cancer combined and leukemia at a cumulative RAI dosage of greater than 150 mCi. Overall, it is recommended that fewer patients receive high doses of RAI for the treatment of thyroid cancer; a low fixed dose or dosimetric method would be more favorable strategies. For those whose disease burden necessitates a higher RAI dose, we suggest a more thorough survey to investigate clinically suspicious symptoms of SPM.

Funding

This study is supported in part by a grant from Taipei Veterans General Hospital (V103B-022 and V103E10-001) and the Taiwan Clinical Oncology Research Foundation. The supporting sources had no role in the study design or conduct, or in the decision to submit for publication.

Notes

The study is based on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance (BNHI), Department of Health, Executive Yuan, Taiwan, and managed by National Health Research Institutes (NHRI), Taiwan. We express our particular gratitude to the government organization BNHI and the nonprofit foundation NHRI.

The authors have no conflicts of interest to declare.

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