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Article

Linear association between radioactive iodine dose and second primary malignancy risk in thyroid cancer

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Abstract

Background: We aimed to investigate whether the risk of second primary malignancy (SPM) in patients with thyroid cancer (TC) receiving radioactive iodine (RAI) therapy rises in a cumulative, dose-dependent manner compared with those not undergoing RAI.

Methods: Using the Korean National Health Insurance Service National Health Information Database (2002-2019), we investigated hazard ratios of SPM associated with RAI in TC. SPM was defined as a second primary malignancy diagnosed at least 1 year after TC diagnosis.

Results: Of 217 777 patients with TC (177 385 women and 40 392 men; mean [SD] age, 47.2 [11.6] years), 100 448 (46.1%) received RAI therapy. The median (IQR) follow-up duration was 7.7 (5.5-10.3) years, and the median (IQR) cumulative RAI dose was 3.7 (1.9-5.6) GBq. From 2004 to 2019, SPM incidence rates were 7.30 and 6.56 per 1000 person-years in the RAI and non-RAI groups, respectively, with an unadjusted hazard ratio of 1.09 (95% confidence interval = 1.05 to 1.13); this rate remained at 1.08 (95% confidence interval = 1.04 to 1.13) after adjustment for multiple clinical confounding factors. Notably, SPM risk increased significantly, from 3.7 GBq with full adjustments, and a strong linear association between cumulative RAI dose and SPM was observed in the restricted cubic spline analysis. Regarding cancer subtypes, myeloid leukemia and salivary gland, trachea, lung and bronchus, uterus, and prostate cancers were the most significantly elevated risks in patients who underwent RAI therapy.

Conclusions: This study identified that SPM risk increased linearly in a dose-dependent manner in patients with TC undergoing RAI therapy compared with those not undergoing RAI therapy.

Thyroid cancer (TC) is the most common endocrine malignancy, and its incidence is increasing rapidly (1-3). Conventional surgical thyroidectomy and adjuvant radioactive iodine (RAI) therapy are the main treatment modalities for follicular cell-derived TC (4). Although it is apparent that RAI treatment improves the prognosis of intermediate- and high-risk differentiated TC (4), numerous long-term TC survivors with low disease-specific mortality inevitably underlie treatment-related adverse effects, especially RAI-associated second primary malignancy (SPM), with discordant results (5-9). Molenaar et al. (6) analyzed the Surveillance, Epidemiology, and End Results (SEER) registries through 2017 and identified that patients with well-differentiated TC treated with RAI had an increased early risk of developing acute myeloid leukemia (AML) and chronic myeloid leukemia (CML). Another nationwide population study from Korea (8) reported that RAI therapy was strongly associated with the development of leukemia if the cumulative RAI dose exceeded 3.7 GBq. These studies had large sample sizes but focused only on the hematologic malignancy. Recent studies using the Korean nationwide population-based database demonstrated that RAI therapy was associated with SPM in children and young adults (aged from birth to 29 years) (10) and identified that RAI doses greater than 3.7 GBq were a significant risk factor for SPM in patients with TC older than 18 years of age (11). Several studies have investigated the relationship between SPM risk and dose response to RAI with discordant results (6,7,10). A major issue of most previous studies is that RAI was analyzed as a binary variable (yes vs no), raising the question of whether a linear relationship exists between the continuous dosage of RAI and SPM risk.

Therefore, we conducted what is, to the best of our knowledge, the largest retrospective nationwide TC cohort study in Korea to elucidate the dose-response relationship between RAI therapy and SPM in patients with TC and the differences according to the specific types of SPM. Moreover, we investigated the SPM risk in patients undergoing low (≤1.1 GBq) to moderate (<1.1 to ≤3.7 GBq) cumulative-dose RAI therapy—the crux of the recent matter—as well as higher-dose (>3.7 GBq) RAI therapy.

Methods

Data source and study population

We investigated SPM risk in patients with TC using the Korean National Health Insurance Service (NHIS) National Health Information Database (NHID), which is a compulsory medical insurance system covering all citizens of South Korea (N = 51 344 938). The database includes longitudinal information

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about individuals' demographic, medical, and pharmaceutical data based on the *International Statistical Classification of Diseases, Tenth Revision (ICD-10)*. In addition, the database was merged with death records that listed the specific causes of death by *ICD-10* code and was managed by the Korean National Statistical Office. A more detailed cohort protocol has been published previously (12,13).

We initially included 469 856 patients with new diagnosis of any type of TC (*ICD-10* C73) registered from January 1, 2004, to June 30, 2017. A total of 217 777 patients with TC were finally analyzed, after excluding patients who met the following criteria: 1) did not undergo any surgical treatment, including total thyroidectomy, subtotal thyroidectomy, or hemithyroidectomy, after the TC diagnosis or who had undergone thyroidectomy 6 months before diagnosis; 2) had a diagnosis of other malignant neoplasms (*ICD-10* C00-C97, except C73) before or within 1 year of TC diagnosis; 3) had a history of levothyroxine prescription or RAI treatment or radiation treatment before TC diagnosis; 4) were younger than 19 years of age; or 5) died or were lost to follow-up within 1 year of TC diagnosis (Figure 1).

Anthropometric and biochemical laboratory information, including alcohol consumption, smoking status, body weight, height, systolic and diastolic blood pressure, fasting blood glucose, and lipid profile, were obtained by the National Health Screening Program database for 166 309 of the total patients with TC. We used smoking status, which is an important and universal carcinogen for every cancer, as a dichotomous parameter. i) Never-smokers were defined as those who had never smoked at least 100 cigarettes in their entire life; ii) ex-smokers were defined as those who had smoked at least 100 cigarettes in their entire life but who have quit smoking; iii) current smokers were defined as those who have smoked at least 100 cigarettes in their entire life and are still smoking. We used the most recent information before TC diagnosis, with a median (IQR) difference of 5.7 (1.3-14.1) months. Underlying comorbidities of hypertension, diabetes mellitus, and dyslipidemia were defined using the following criteria; hypertension was defined as blood pressure of at least 140/90 mm Hg or use of antihypertensive agents under the *ICD-10* codes for hypertension (I10-I15); diabetes was defined as a fasting blood glucose level of at least 126 mg/dL or current use of glucose-lowering agents under the *ICD-10* codes for diabetes mellitus (E10-E14); and dyslipidemia was defined as total cholesterol above 240 mg/dL or current use of lipid-lowering agents under the *ICD-10* code for dyslipidemia (E78).

This study was approved by the institutional review board of Korea University Anam Hospital (No. 2020AN0310). Informed consent was not required because this study was based on the NHIS database, which was fully anonymized and de-identified for analysis.

Outcome definition

To minimize detection bias, SPM was defined as second primary malignancy diagnosed at least 1 year after TC diagnosis and having the same *ICD-10* cancer code at least twice. The recurrence of TC and a secondary malignant neoplasm of other primary cancer implying metastatic malignancy (*ICD-10* C77–C80) were excluded. To evaluate the site specificity of the SPM, we divided SPMs as follows: head and neck cancer (C00-C14), digestive cancer (C15-26), respiratory and intrathoracic cancer (C30-C39), breast cancer (C50), genitourinary cancer (C51-C58, C60-C63, and C64-C68), lymphoid and hematopoietic cancer (C81-C96), bone and articular cartilage cancer (C40-C41), skin cancer (C43-C44), mesothelial and soft tissue cancer (C45-C49), brain and eye cancer (C69-C72), endocrine cancer (C74-C75), and unknown and not otherwise specified (all of C00-C97 except for the above-mentioned diagnosis, C73, and C77-C80). Follow-up duration was defined as the time from the date of a TC claim to the date of the first SPM claim or the date of last data collection in this cohort (December 31, 2019).

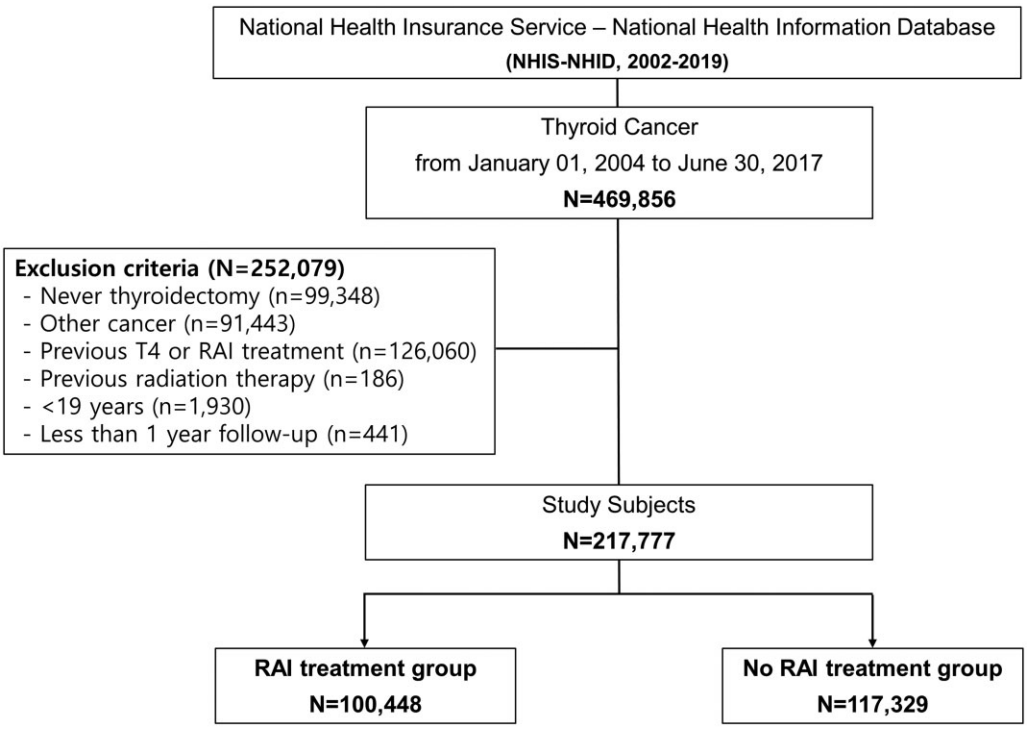

Figure 1. Schematic study design. RAI = radioactive iodine; T4 = thyroxine.

Table 1. Baseline characteristics of patients with thyroid cancer undergoing radioactive iodine treatment

	Patients with TC N = 217 777		RAI n = 100 448		No RAI n = 117 329		SMD
Age, mean (SD), y	47.2	(11.6)	47.1	(11.6)	47.2	(11.5)	0.004
Female, No. (%)	177 385	(81.5)	80 597	(80.2)	96 788	(82.5)	0.058
Total thyroidectomy, No. (%)	166 704	(76.5)	97 693	(97.3)	69 011	(58.8)	1.048
Levothyroxine, No. (%)	203 141	(93.3)	100 448	(100.0)	102 693	(87.5)	0.534
RAI cumulative dose, median (IQR), GBq	–		3.7 (1.9-5.6)		–		–
0	117 329	(52.9)	–		117 329	(100.0)	
≤1.1	20 331	(9.3)	20 331	(20.2)	–		
>1.1 to ≤3.7	32 402	(14.9)	32 402	(32.3)	–		
>3.7 to ≤7.4	35 313	(16.2)	35 313	(35.2)	–		
>7.4 to ≤11.1	8540	(3.9)	8540	(8.5)			
>11.1	3862	(1.8)	3862	(3.8)	–		
Radiation therapy, No. (%)	1569	(0.7)	1006	(1.0)	563	(0.5)	0.061
Follow-up duration, median (IQR), y	7.7 (5.5-10.3)		8.2 (6.1-10.7)		7.2 (4.9-9.6)		0.311
BMI, mean (SD)[a]	24.0	(3.4)	24.0	(3.4)	23.8	(3.4)	0.097
Socioeconomic status, No. (%)[a]							0.027
Low (lower 30%)	44 757	(20.6)	20 737	(20.6)	24 020	(20.5)	
Middle (middle 40%)	76 249	(35.0)	35 228	(35.1)	41 021	(35.0)	
Upper (upper 30%)	96 771	(44.4)	44 483	(44.3)	52 288	(44.6)	
Smoking status, No. (%)[a]							0.036
Unknown	51 360	(23.6)	25 703	(25.6)	25 657	(21.9)	
Never	138 942	(63.8)	61 948	(61.7)	76 994	(65.6)	
Ex-smoker	12 810	(5.9)	5933	(5.9)	6877	(5.9)	
Current	14 665	(6.7)	6864	(6.8)	7801	(6.6)	
Alcohol consumption, No. (%)[a]							0.044
Unknown	51 132	(23.5)	25 590	(25.5)	25 542	(21.8)	
Never	112 226	(51.5)	50 603	(50.4)	61 623	(52.5)	
≤2 times/wk	44 494	(20.4)	19 878	(19.8)	24 616	(21.0)	
≥3 times/wk	9925	(4.6)	4377	(4.4)	5548	(4.7)	
Comorbidities,[a] No. (%)							
Hypertension	66 414	(30.5)	31 757	(31.6)	34 657	(29.5)	0.045
Diabetes	14 605	(6.7)	6981	(6.9)	7624	(6.5)	0.018
Dyslipidemia	50 222	(23.1)	23 009	(22.9)	27 213	(23.2)	0.007
Systolic blood pressure, mean (SD), mm Hg[a]	121.0	(15.1)	121.0	(15.1)	120.5	(15.0)	0.086
Diastolic blood pressure, mean (SD), mm Hg[a]	75.6	(10.2)	75.6	(10.2)	75.2	(10.1)	0.085
Total cholesterol, mean (SD), mg/dL[a]	194.8	(40.0)	194.8	(40.0)	194.7	(40.0)	0.009
Fasting glucose, mean (SD), mg/dL[a]	96.2	(21.3)	96.2	(21.3)	96.0	(20.6)	0.026

[a] Data on these characteristics were from the National Health Information Database for 166 309 of the total patients with thyroid cancer (TC). IQR = interquartile range; BMI = body mass index; RAI = radioactive iodine; SMD = standardized mean difference.

Statistical analysis

Continuous data are presented as mean (SD) for normally distributed variables and as median (IQR) for non-normally distributed variables. Categorical data are presented as frequencies and percentages. The incidence rate of each SPM was calculated as the number of patients with any SPM in the SPM category divided by total person-time; the incidence of SPM-related mortality was calculated as the number of deaths from cancers other than TC divided by total person-time. To evaluate the relationship between the RAI treatment and time to occurrence of SPM or death, we used the Cox proportional hazards regression model that included age; sex; body mass index (BMI); socioeconomical status; smoking; alcohol consumption; and previous history of hypertension, diabetes, and dyslipidemia as covariates. The risk of each SPM related to RAI treatment was presented as hazard ratio (HR) and corresponding 95% confidence interval (CI). To examine the flexible association between the cumulative doses of RAI, we performed a restricted cubic spline interpolation, allowing for 5 knots to estimate the hazard ratio and 95% confidence interval of the cumulative RAI dose compared with a reference value of 0 GBq. The number needed to harm (NNH) refers to the average number of patients who need to be exposed to RAI therapy to cause an average of 1 patient to develop SPM who would not have been harmed otherwise. The NNH was calculated based on cumulative event proportions and the reciprocal of the difference in the risks of SPM between the RAI and no RAI treatment groups (14). All analyses were based on available data, and we did not include any missing data in the analysis. All reported *P* values were 2-sided, and statistical significance was set at less than .05. All statistical analyses were performed using the SAS Enterprise Guide, version 7.1 (SAS Institute Inc, Gary, NC, USA) and R, version 4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Of the 217 777 patients with TC (177 385 women and 40 392 men; mean [SD] age = 47.2 [11.6] years), 100 448 (46.1%) received RAI therapy (Table 1). The median (IQR) follow-up duration was 8.2 (6.1-10.7) and 7.2 (4.9-9.6) years in the RAI and non-RAI treatment groups, respectively (standardized mean difference = 0.311). Overall, 166 704 patients (76.5%) underwent initial total thyroidectomy (97 693 [97.3%] and 69 011 [58.8%] in the RAI and non-

Table 2. Hazard ratios for second primary malignancy in patients with thyroid cancer undergoing radioactive iodine therapy

SPM	No. of events	Incidence rate per 1000 person-years	Unadjusted		Adjusted[a]	
			HR (95% CI)	P	HR (95% CI)	P
TC with no RAI therapy (n = 117 329)	5772	6.56	1 (Referent)	–	1 (Referent)	–
TC with RAI therapy (n = 100 448)	6148	7.30	1.09 (1.05 to 1.13)	<.001	1.08 (1.04 to 1.13)	<.001
Cumulative RAI dose, GBq						
≤1.1 (n = 20 331)	1285	7.39	1.11 (1.04 to 1.18)	.001	1.06 (0.98 to 1.13)	.121
>1.1 to ≤3.7 (n = 32 402)	1654	6.70	1.02 (0.96 to 1.08)	.535	1.00 (0.94 to 1.07)	.965
>3.7 to ≤7.4 (n = 35 313)	2152	7.23	1.09 (1.04 to 1.15)	.001	1.09 (1.03 to 1.16)	.002
>7.4 to ≤11.1 (n = 8540)	681	7.93	1.13 (1.04 to 1.23)	.003	1.18 (1.07 to 1.31)	.001
>11.1 (n = 3862)	376	9.88	1.41 (1.27 to 1.56)	<.001	1.58 (1.39 to 1.80)	<.001
Cumulative RAI dose (per 3.7 GBq)	–	–	1.06 (1.04 to 1.08)	<.001	1.08 (1.06 to 1.10)	<.001

[a] Adjusted for age; sex; body mass index; socioeconomical status; smoking status; alcohol consumption; and previous history of hypertension, diabetes, or dyslipidemia. CI = confidence interval; HR = hazard ratio; RAI = radioactive iodine; SPM = second primary malignancy; TC = thyroid cancer.

RAI groups, respectively). Levothyroxine supplementation, defined as continuing to take levothyroxine for at least 90 days after thyroidectomy, was noted in 100% (100 448 of 100 448) and 87.5% (102 693 of 117 329) of patients in the RAI and non-RAI groups, respectively. The median (IQR) cumulative RAI dose was 3.7 (1.9-5.6) GBq. Overall, 96 771 patients with TC (44.4%) had higher socioeconomic status. BMI; alcohol consumption; smoking status; and the proportion of patients with underlying comorbidities, including hypertension, diabetes, and dyslipidemia were comparable between the RAI and non-RAI therapy groups.

SPM risks in TC according to RAI therapy

From 2004 to 2019, the number of SPM events numbered 6148 in the RAI therapy group and 5772 in the non-RAI group, with incidence rates of 7.30 and 6.56 per 1000 person-years in the RAI and non-RAI groups, respectively. The unadjusted hazard ratio for SPM was 1.09 (95% CI: 1.05 to 1.13), and remained at 1.08 (95% CI: 1.04 to 1.13) after adjusting for age; sex; BMI; socioeconomic status; smoking; alcohol consumption; comorbidities of hypertension, diabetes, and dyslipidemia (Table 2). The median (IQR) time to SPM was 52.3 (31.2-83.6) months in the RAI group and 59.2 (34.9-91.6) months in the non-RAI group. The time to SPM with a cumulative RAI dose of greater than 11.1 GBq was significantly shorter than that with no RAI dose (Supplementary Figure 1, available online). The risk of SPM was most evident after 10 years from the diagnosis of TC, with 90% of cases of SPM occurring after this point (Supplementary Table 1, available online). We further analyzed the risk of SPM according to the age at diagnosis of TC, and the adjusted hazard ratios of patients with TC younger than 40 years of age and 60 years of age or older were 1.17 (95% CI = 1.02 to 1.34) and 1.11 (95% CI = 1.03 to 1.20), which demonstrated statistical significance, but there was no *P* value for interaction across ages at diagnosis (Supplementary Table 2, available online). The adjusted hazard ratios of SPM were 1.06 (95% CI = 0.98 to 1.13) and 1.00 (95% CI = 0.94 to 1.07) in the low-cumulative-dose (≤1.1 GBq) and the moderate-cumulative-dose (>1.1 GBq and ≤3.7 GBq) groups, respectively (Table 2). The Cox proportional hazards regression model with RCS demonstrated that there was an independent linear association between the cumulative RAI dose and risk of SPM, with statistical significance from 3.7 GBq after adjustment for the confounding variables (Figure 2, A). The actual calculated NNH was 1361, and the median (IQR) follow-up time was 7.7 (5.7-10.2) years after RAI therapy, which is a limitation because the NNH can change based on the follow-up duration.

Regarding cancer subtype, the increased risk of SPM was most evident in head and neck cancer (incidence rate per 1000 person-years for no RAI and RAI = 0.13 vs 0.28; HR = 2.18, 95% CI = 1.67 to 2.84; Figures 2, B and 3), respiratory and intrathoracic cancer (incidence rate per 1000 person-years for no RAI and RAI = 0.71 vs 0.89; HR = 1.20, 95% CI = 1.06 to 1.36; Figure 2, C and 3), male genital (incidence rate per 1000 person-years for no RAI and RAI = 0.26 vs 0.35; HR = 1.27, 95% CI = 1.04 to 1.53; Figure 2, D and 3), and leukemia (incidence rate per 1000 person-years for no RAI and RAI = 0.09 vs 0.19; HR = 2.38, 95% CI = 1.72 to 3.28; Figure 2, E and 3). Figure 3 shows the hazard ratios for SPM for more specific cancer subtypes. Among head and neck cancers, the hazard ratios for SPM were highest in salivary gland cancer (incidence rate per 1000 person-years for no RAI and RAI = 0.03 vs 0.11; HR = 3.89, 95% CI = 2.28 to 6.62; Supplementary Figure 2, A, available online). The hazard ratios for trachea, lung and bronchus (incidence rate per 1000 person-years for no RAI and RAI = 0.60 vs 0.78; HR = 1.24, 95% CI = 1.09 to 1.42; Supplementary Figure 2, B, available online) among the respiratory and intrathoracic cancer was statistically significant. For female genital cancer, the risk of uterus cancer increased (incidence rate per 1000 person-years for no RAI and RAI = 0.19 vs 0.23; HR = 1.28, 95% CI = 1.01 to 1.63; Supplementary Figure 2, C, available online). For male genital cancer, the risk of prostate cancer increased (incidence rate per 1000 person-years for no RAI and RAI = 0.26 vs 0.34; HR = 1.26, 95% CI = 1.04 to 1.53; Supplementary Figure 2, D, available online) with statistical significance. The risk of AML (incidence rate per 1000 person-years for no RAI and RAI = 0.04 vs 0.08; HR = 2.21, 95% CI = 1.36 to 3.59; Supplementary Figure 2, E, available online) and CML (incidence rate per 1000 person-years for no RAI and RAI = 0.02 vs 0.07; HR = 4.82, 95% CI = 2.27 to 10.23; Supplementary Figure 2, F, available online) increased statistically significantly. We observed statistically significant linear trends in overall SPM as the cumulative RAI dose increased, and most of the cancer subtypes showed a statistically significant increase, excluding uterus cancers.

Discussion

There is mounting evidence that RAI treatment, widely conducted in intermediate- and high-risk differentiated TC (DTCs), helps improve prognosis (4,15-18). Concerns about the adverse effects of RAI treatment, however—particularly for SPM—have been raised in recent years in the face of the increasing number of long-term survivors and discordant results (5,6,8,19). In this

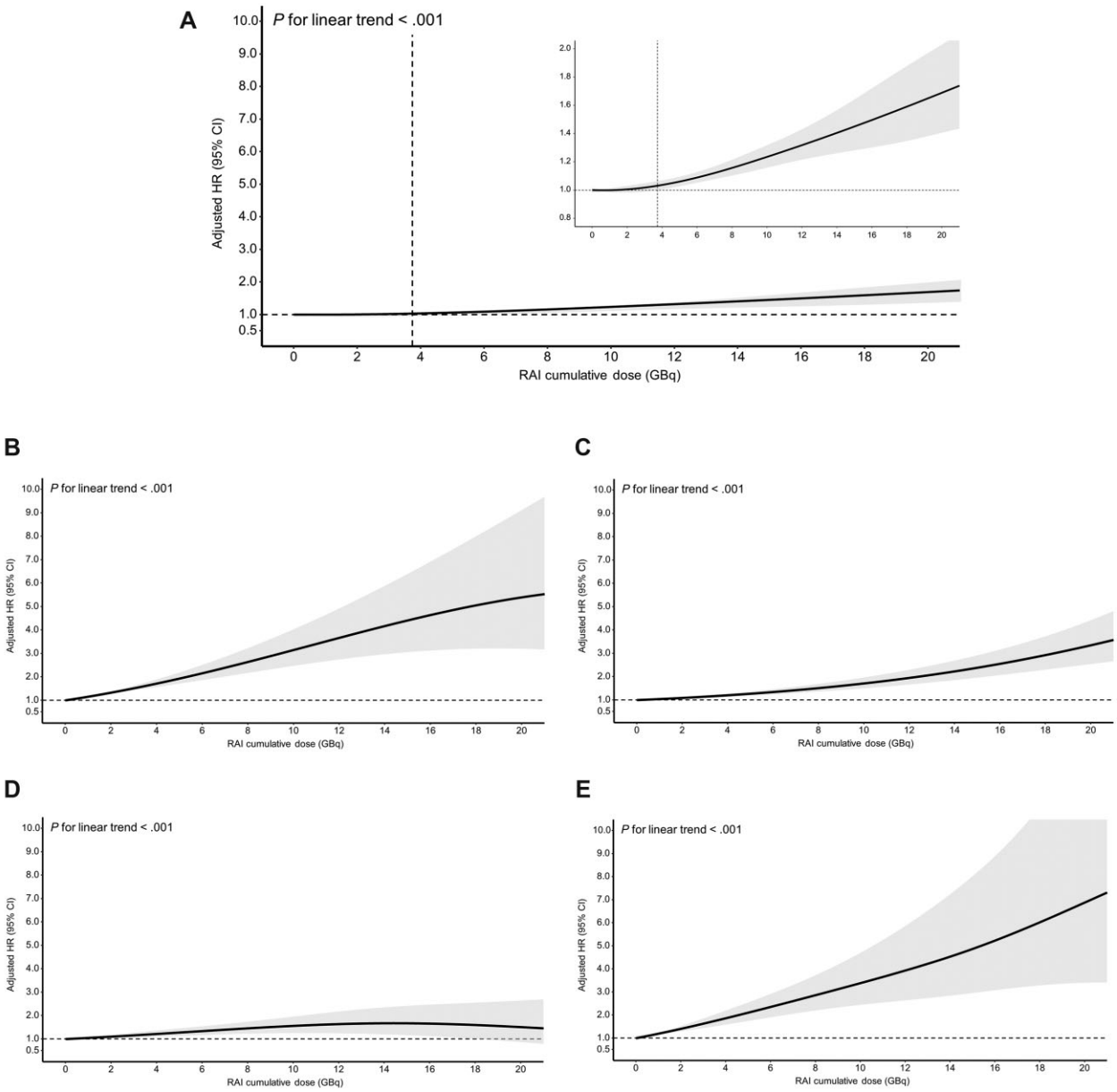

Figure 2. Restricted cubic spline models for risk of second primary malignancy and cumulative dose of radioactive iodine (RAI) therapy: (**A**) all cancer, (**B**) head and neck cancer, (**C**) respiratory and intrathoracic cancer, (**D**) male genital, and (**E**) leukemia. The model was adjusted for the following confounding factors: age; sex; body mass index; socioeconomic status; smoking status; alcohol consumption; previous history of hypertension, diabetes, or dyslipidemia. CI = confidence interval; HR = hazard ratio.

context, our results demonstrated that overall SPM risk increases in a dose-dependent manner in patients with TC who have undergone RAI therapy compared with those who have not, based on the largest nationwide TC cohort in Korea. Moreover, a robust increase was observed in several SPM subtypes, including salivary gland, lung, uterus, and prostate cancer; AML; and CML.

Recent studies conducted in Korea that use data from hospital-based medical records demonstrate discordant results (20,21). Kim et al. demonstrated that there was no significant difference in the risk of SPM between 5374 patients with TC who underwent RAI therapy and 5374 propensity-matched patients with TC who did not undergo RAI therapy at 4 hospitals in Korea (20). Another study on the Korean population that included 3106 patients with TC at 7 tertiary hospitals in Korea performed by Hong et al. demonstrated that the rate only of hematologic cancers, not solid cancers, increased in patients with TC who underwent RAI therapy compared with those who did not undergo RAI therapy (21).

Yu et al. (22) performed a meta-analysis of 17 studies published before March 2018 and reported a pooled risk ratio of subsequent malignant neoplasms after RAI of 1.16 (95% CI = 0.97 to 1.39) after adjusting for confounders; the hazard ratio they reported is comparable to the adjusted hazard ratio in our study (adjusted HR = 1.07). This study, however, did not include recent large studies and those with RAI dose-response results. Another study from Pasqual et al. (23) reported that RAI treatment for childhood and young-adulthood DTC was associated with increased risks of solid cancer as well as leukemia based on 9 US SEER cancer registries (1975-2017), with a median follow-up of 15 years. Our results are in line with those of this long-term study in that RAI therapy

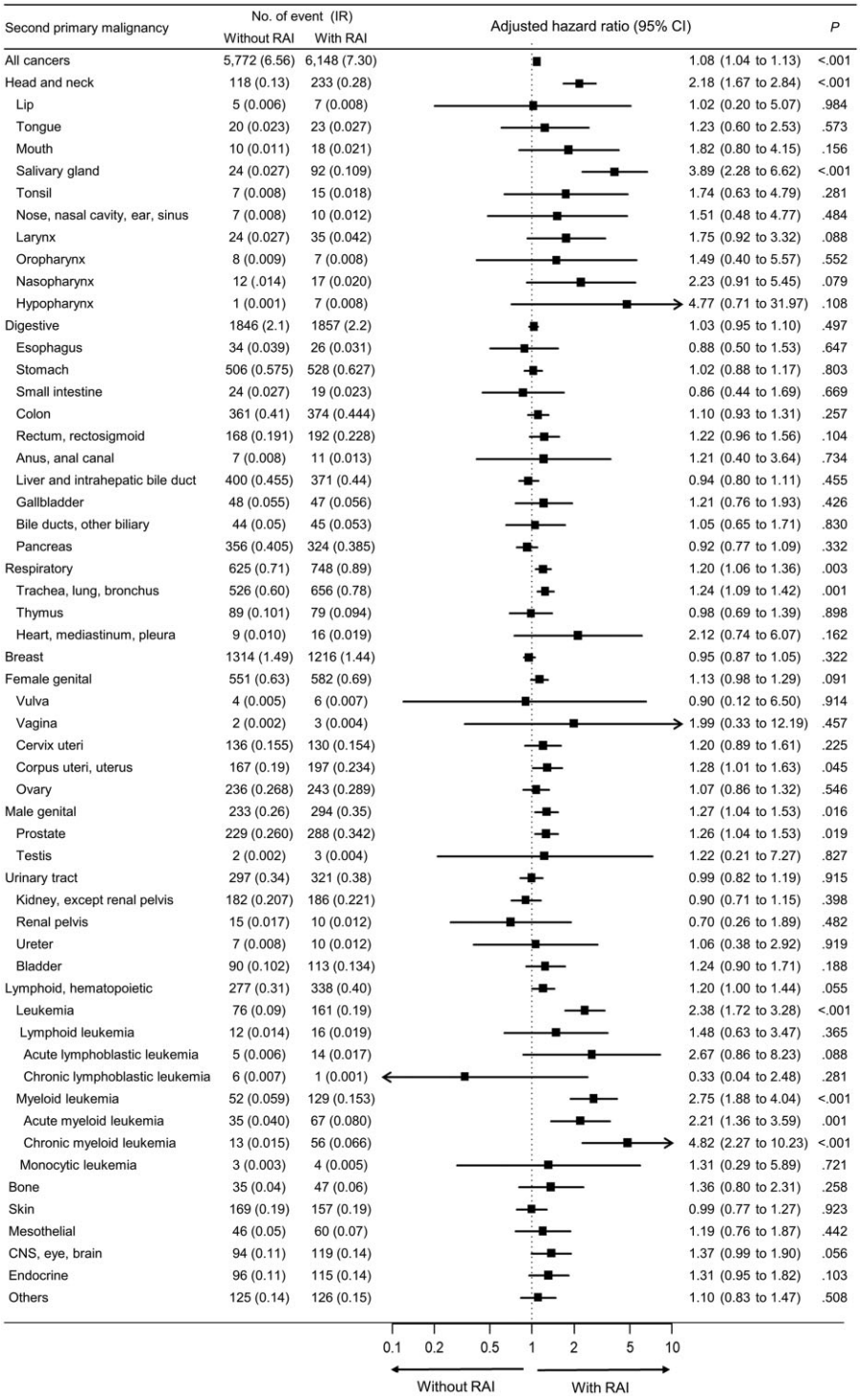

Figure 3. Forest plot showing hazard ratios for second primary malignancy in patients with thyroid cancer according to the specific cancer subtype. The model was adjusted for the following confounding factors: age; sex; body mass index; socioeconomic status; smoking status; alcohol consumption; previous history of hypertension, diabetes, or dyslipidemia. CI = confidence interval; CNS = central nerve system; IR = incidence rate per 1000 person-years; RAI = radioactive iodine.

increases the risk of solid cancer in addition to leukemia, but our study was discriminatory in that only adult patients with TC were included; in addition, the increased risk of head, neck, and lung cancer carried a corresponding significant increase in SPM risk, albeit with relatively short-term follow-up periods.

The risk of breast cancer, one of the most controversial topics, was not significantly increased in patients with TC who underwent RAI therapy compared with those who did not, a result that is consistent with the results of some previous reports (22,24) but inconsistent with the results of other reports (10). These discrepancies are derived from the age at exposure to RAI, which is a potential risk modifier for the association between RAI therapy and breast cancer. Additional long-term studies and subgroup analyses according to the age at exposure to RAI in this

population are needed to better elucidate the outcomes regarding this issue.

The most important aspect of our study is that the rate of salivary gland and myeloid leukemia increased robustly, even with a low to moderate RAI dose in patients with TC undergoing RAI therapy compared with those not undergoing therapy (Supplementary Figure 2, available online). Although it is widely known that leukemia, particularly AML and CML, is radiation induced and that the latency period is relatively short compared with that of other solid cancers, few studies to date have shown that the risk increases in a continuous dose-dependent manner. Moreover, the SPM-related mortality risk rose significantly, with a hazard ratio of 1.19 (95% CI = 1.04 to 1.37) in patients with RAI compared with those not on RAI therapy (Supplementary Table 3, available online), reinforcing the importance of long-term management for SPM after TC treatment. TC-related mortality (Supplementary Table 3, available online) is defined as TC being the primary cause of death on the death certificates managed by the Korea National Statistical Office. Patients receiving RAI therapy had an increased risk of TC-related mortality, suggesting that they were more likely to have an advanced stage of TC than those not receiving RAI therapy.

With the recognition of the increased risk of SPM in patients with TC undergoing RAI therapy, interpretation of our results is challenging. The fully adjusted hazard ratio for overall SPM was 1.07, which is a marginal range, even if it is statistically significant. Moreover, the NNH of 1361 has the limitation of not including patients with SPM that developed during a long-term follow-up period beyond our study period, but it implies that 1 case of SPM occurred in every 1361 patients with TC who were treated with RAI therapy.

The primary strengths of the present study include its population-based design, sufficient sample size, accurate detection of RAI treatment, and minimal loss to follow-up. Moreover, we included various confounding factors for the risk of SPM, especially smoking status; alcohol consumption; BMI; and comorbidities, such as hypertension, diabetes, and dyslipidemia, which do not affect the results. Another strength of our study is that it incorporates the all-cause mortality as well as SPM-related mortality, using the death records by the Korean National Statistical Office. Nevertheless, this study has several limitations to be addressed. The NHIS-NHID contains no information regarding clinicopathologic characteristics, such as pathological subtype and stage, connoting that poorly differentiated TC, anaplastic TC, and medullary TC may also be present in the 217 777 patients with TC in our study. Previous studies, however, have reported that the vast majority of TC cases in Korea are DTC, particularly papillary TC, accounting for up to 97% of total TC patients (25-27). The TC stage and pathological risk factors, however, have a more substantial impact on the risk of SPM because the patients with an advanced stage of cancer and poor pathologic factors received a higher RAI dose and may also have higher carcinogenic stresses that can affect other organs as well as the thyroid. Another major limitation of this study is the lack of biochemical laboratory results for thyroid-stimulating hormone and thyroglobulin antigen and antibody. Therefore, we could not investigate the extent of thyroid-stimulating hormone suppression therapy or TC recurrence risk. Moreover, we could not precisely define local recurrence, regional recurrence, and distant metastasis, which may be a competing risk for SPM, although we excluded secondary malignant neoplasms from the original site. It is also possible that the 1-year exclusion criterion for SPM after the diagnosis of TC was not sufficient for defining the occurrence of SPM to determine the association between RAI dose and the occurrence of SPM, although nearly 85% of the patients with TC who underwent RAI therapy completed the therapy within 1 year of the diagnosis. The relatively short follow-up time, which does not completely cover the natural course of overall TC treatment and occurrence of SPM, is a potential caveat for overlooking the late occurrence of SPM. Molenaar et al. (6), however, reported that a median follow-up of 6.5 years after DTC diagnosis is adequate for second hematologic malignancy risk assessments because of the short latency period for SPM. Finally, overdiagnosis for salivary gland and lung cancer resulting from frequent image evaluation during the follow-up and distant metastasis of advanced TC may have been misdiagnosed as SPM, especially for head and neck, lung, and bone cancer. A more careful interpretation is needed to reach concrete conclusions regarding the increased risk of solid cancer.

In summary, it is apparent that the risk of overall SPM increases in patients with TC undergoing RAI therapy compared with those not undergoing RAI therapy in a dose-dependent manner according to a nationwide database in Korea. Although there is good evidence that RAI therapy reduces disease progression in patients with TC, a recent randomized study demonstrated no beneficial effects of RAI therapy in low-risk patients with TC (28). Moreover, RAI therapy has major side effects, including salivary gland damage and a risk of SPM; therefore, personalized and precise attention should be paid to determine the risks and benefits of RAI therapy among TC survivors with excellent prognoses. Although long-term studies will need to be conducted in the future, our study encourages physicians not to consider RAI therapy in patients with low-risk TC, given the increasing evidence of a lack of a benefit, and to use the least effective dose to maximize the therapeutic effects of RAI therapy and minimize the adverse effects of SPM. RAI also warrants surveillance schemes to appropriately monitor SPM occurrence.

Data Availability

The data that support the findings of this study are available from the cohort committees and national registers of the cohorts and countries involved (the Korean National Health Insurance Service, https://nhiss.nhis.or.kr). Restrictions apply to the availability of these data, which were used under license for this study.

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Conflicts of interest

All authors declare no potential conflicts of interest.

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Author contributions

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