Effects of radioactive iodine treatment on cardiovascular disease in thyroid cancer patients: a nationwide cohort study

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Background: Radioactive iodine (RAI) treatment is a standard treatment in differentiated thyroid cancer (TC). However, its adverse effects on cardiovascular diseases (CVDs) have not been clearly elucidated.

Methods: In this retrospective cohort study based on the Korean National Health Insurance Service-National Health Screening Cohort (2002–2015), we analyzed 4,845 patients with TC with a median follow-up of 66 months. We evaluated and compared the risk of CVD between patients treated with and without RAI therapy. The primary CVD outcome was defined as a composite of ischemic stroke (IS), ischemic heart disease (IHD), hemorrhagic stroke (HS), or heart failure (HF).

Results: Overall, 2,533 patients (52.3%) received RAI treatment with a median cumulative dosage of 103 mCi [interquartile range (IQR), 40–162 mCi]. The incidence of the primary CVD outcome in patients who did not receive RAI therapy and those who did was 17.32 [95% confidence interval (CI), 15.07–19.90] and 13.96 (95% CI, 12.17–16.01) per 1,000 person-years, respectively, indicating an adjusted hazard ratio (HR) of 0.87 (95% CI, 0.71–1.07) after multivariate adjustments for variable confounding factors. The risks of IS (HR, 0.83; 95% CI, 0.51–1.34), IHD (HR, 0.90; 95% CI, 0.71–1.13), HS (HR 1.01; 95% CI, 0.49–2.09), and HF (HR 0.89; 95% CI, 0.49–1.63) were comparable between the patients who received RAI therapy and those who did not. There was no cumulative dose-dependent risk for CVD in TC patients who received RAI treatment.

Conclusions: RAI treatment is a prevalent and crucial treatment for TC, and has been used in more than half of TC patients in Korea from 2004 to 2015. This study found no significant between-group difference for the CVD risk in patients with TC who received RAI treatment and those who did not, giving further evidence to allay concerns related to the adverse effects of RAI.

Keywords: Thyroid neoplasms; radioactive iodine treatment (RAI treatment); cardiovascular disease (CVD)

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Introduction

Thyroid cancer (TC) is the most common malignancy of the endocrine system and has a rapidly increasing global incidence (1-4). Despite this, the American Cancer Society reported that the 5-year relative survival rate in TC between 2008 and 2014 was 98% (5). A large number of living survivors, especially those with papillary thyroid cancer (PTC), the most common TC, inevitably face issues of overdiagnosis and overtreatment (6-8). Additionally, treatment-related adverse outcomes, including

cardiovascular disease (CVD) due to levothyroxine replacement therapy (9,10) or second primary cancer due to radioactive iodine (RAI) therapy (11,12), have been reported as patients with TC have good survival with low disease-specific mortality.

The conventional treatment of differentiated thyroid cancer (DTC) is composed of initial thyroidectomy, followed by thyroid-stimulating hormone (TSH) suppression therapy and adjuvant radioactive iodine (RAI) therapy. RAI therapy using iodine-131 (^{131}I) is a well-established treatment that can be administered to reduce disease recurrence after thyroidectomy in patients with DTC and aggressive histopathologic features or distant metastasis (13,14). Although RAI therapy is generally safe and effective, there are several adverse effects to be mentioned, for example, sialadenitis, gastrointestinal discomfort, second primary malignancy and infertility. Particularly, in previous studies, patients receiving RAI therapy for hyperthyroidism or toxic adenoma showed an increased risk of cerebrovascular diseases (15-17). In la Cour *et al.*'s study (18), the calculated radiation dose to the carotid artery after RAI therapy for benign thyroid disease was high enough to facilitate endothelial dysfunction and lead to atherosclerosis. However, several years later, la Cour *et al.* reported that RAI therapy had no or minimal effects on the atherosclerotic burden of the carotid arteries (19). These inconsistent results can be explained by the differences in the sample size, RAI dosage, underlying thyroid disease, and duration of follow-up; they further highlight the importance of concluding the debate concerning RAI treatment and CVD risk. Moreover, previous studies have primarily focused on stroke and cerebrovascular diseases in benign thyroid disease patients, who receive a relatively low cumulative RAI dosage. Another study, albeit with a small number of patients and short-term follow-up, investigated the adverse effects of severe hypothyroid state, induced by the withdrawal of thyroid hormone replacement therapy before RAI therapy, on the metabolic parameters, suggesting an increased risk of CVD in patients with RAI therapy (20).

In view of this, it is a salient point of our study to compare the cardiovascular events between patients with TC who received RAI treatment and those who did not using real-world data based on the Korean National Health Insurance-Health Screening Cohort (NHIS-HEALS, 2002-2015). We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-5222).

Methods

Data source and study population

The Korean NHIS is the sole mandatory public medical insurance system managed by the South Korean government and covers all citizens of South Korea. The NHIS recently released the second version of the NHIS-HEALS database (2002–2015), which included information from 512,568 randomly selected South Koreans aged 40–79 years who were eligible for the National Health Screening Program. The longitudinal information of the participants' demographic, medical, and pharmaceutical records based on the International Classification of Disease, 10th revision (ICD-10) were accessed, and data on the medical procedures, hospitalization, biochemical laboratory results (such as fasting glucose and lipid profiles), blood pressure, and drug prescriptions were recorded. The detailed cohort protocol has been published previously (21-23).

This study originally included 7,894 patients newly diagnosed with TC of all types (ICD-10 C73) between January 1, 2004 to December 31, 2015. We excluded patients who met the following criteria: (I) patients who did not undergo thyroidectomy after TC diagnosis or had already undergone thyroidectomy 6 months before the diagnosis, (II) those with prior diagnosis of other malignancies (C00–C97, except C73), (III) those with a history of levothyroxine or RAI treatment, or (IV) those with incomplete information regarding levothyroxine or RAI treatments. A total of 4,845 patients with TC who underwent thyroidectomy after diagnosis and had no history of other malignancies and levothyroxine prescription or RAI treatment were finally evaluated. *Figure 1* illustrates the schematic design of this study. All the 4,845 cases were analyzed without additional data handing since there was no missing data.

This study was approved by the Institutional Review Board of the Korea University Anam Hospital (IRB number: ED16255). Informed consent was not required because this study was based on the NHIS database, which includes fully anonymized and de-identified data. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study definition and outcomes

To minimize false-positive detection, which the national insurance claims database inevitably includes, we defined the primary CVD outcome only as a composite of ischemic stroke

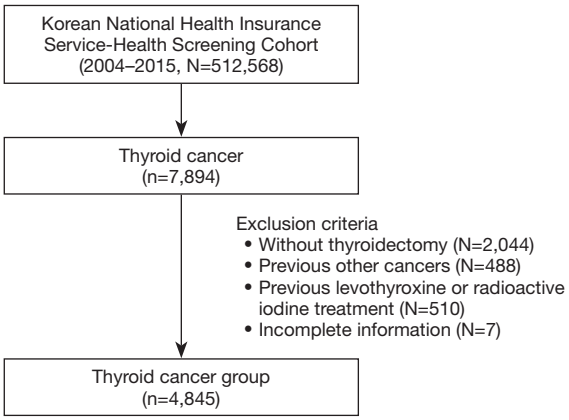

Figure 1 Flowchart of the study design.

(IS), ischemic heart disease (IHD), hemorrhagic stroke (HS), or heart failure (HF), which account for most, but not all, CVD events, and we supplemented the ICD-10 codes of the primary CVD outcomes with hospitalization history. Based on the ICD-10 codes, IHD was defined as hospitalization for I20–I25; IS was defined as hospitalization for I63; HS was defined as hospitalization for I60–I62 or I64; cerebrovascular disease was defined as hospitalization for I60–I69; and HF was defined as hospitalization for I42–I43 or I50. We performed a subgroup analysis of the following specific CVD outcomes: IHD; IS; HS; cerebrovascular disease composed of IS, HS; and HF. We further used specific criteria for reducing false-positive diagnoses of previous diseases. Hypertension was defined as codes I10–I15 with concurrent hypertension medication prescription or codes I10–I15 with systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg. Diabetes mellitus (DM) was defined as codes E10–E14 with concurrent diabetes medication prescription or fasting glucose level ≥126 mg/dL, and dyslipidemia was defined as code E78 with total cholesterol level >240 mg/dL. Previous CVD history was defined as at least one event of IHD, IS, or HS before the index date. Socioeconomic status (SES) at baseline was categorized into three groups based on the income level of an individual: lower, 30%; middle, 40%; and upper, 30%.

We defined follow-up duration as the time between the date of TC claim to the earliest date of incident-specific CVD outcome or the last date of data collection in this cohort (December 31, 2015).

Statistical analysis

Categorical data are presented as frequencies and percentages. Continuous data are presented as mean and standard deviation (SD) for normally distributed variables and median and interquartile range (IQR) for non-normally distributed variables. The Kaplan-Meier analysis followed by a log-rank test was used to examine difference of cumulative incidence between RAI and non-RAI treatments for all CVD outcomes. Adjusted effect of RAI treatment on CVD outcomes was evaluated using a multivariable Cox's PH regression model, whose effect was presented in terms of hazard ratio (HR) and its 95% confidence interval (CI). Variables adjusted for were age, sex, body mass index, socioeconomical status, smoking, alcohol consumption, levothyroxine dosage, and previous history of hypertension, DM, dyslipidemia, and CVD. All reported p-values were two-sided, and a P value <0.05 was considered significant. Statistical analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA) and R Statistical Software v3.3.3 (Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of the study population

This study included 4,845 patients with TC (3,794 women and 1,051 men) with a median age of 56 years (IQR, 51–62) (*Table 1*). Of them, 2,533 (52.3%) patients had undergone thyroidectomy and RAI treatment. The median follow-up was 58 (IQR, 34–91) and 72 (IQR, 45–101) months in the non-RAI and RAI treatment groups, respectively. Almost all patients in the RAI group underwent total or subtotal thyroidectomy (98.8%), and the median cumulative RAI dose was 103 mCi (IQR, 40–162 mCi). Levothyroxine treatment for at least 90 days was prescribed in 100% and 88.2% patients in the RAI and non-RAI groups, respectively. The median levothyroxine dose prescribed in the RAI and non-RAI groups was 107.7 (IQR, 86.5–148.6) mcg/day and 100.0 (IQR, 77.7–122.1) mcg/day, respectively. Previous histories of hypertension (43.8% *vs.* 43.4%), DM (10.7% *vs.* 10.3%), dyslipidemia (8.8% *vs.* 8.5%), upper SES levels (51.7% *vs.* 52.3%), and CVD (7.6% *vs.* 7.1%) were comparable, with no statistical significance between the non-RAI and RAI groups. However, the proportion of patients who had never consumed alcohol was significantly lower (68.4% *vs.* 71.4%) and the BMI was slightly lower (23.9 *vs.* 24.3 kg/m^2) in the non-RAI treatment group compared to the RAI group. In summary, the patients who received RAI treatment were younger, were composed of more males, and received total or subtotal thyroidectomy with longer follow-up than those who

Table 1 Baseline demographics of the study population

Characteristics	Total TC (n=4,845)	No RAI (n=2,312)	RAI (n=2,533)	P value
Age, median (years, IQR)	56 [51–62]	56 [52–62]	55 [51–61]	<0.001
Female, n (%)	3,794 (78.3)	1,848 (79.3)	1,946 (76.8)	0.009
Follow-up, median (months, IQR)	66 [40–96]	58 [34–91]	72 [45–101]	<0.001
Thyroidectomy, n (%)				<0.001
Total + subtotal thyroidectomy	4,116 (85.0)	1,613 (69.8)	2,503 (98.8)	
Hemithyroidectomy	729 (15.0)	699 (30.2)	30 (1.2)	
Levothyroxine treatment (≥90 days), n (%)	4,573 (94.4)	2,040 (88.2)	2,533 (100.0)	<0.001
Levothyroxine prescription period (days, IQR)	2,210 [1,295–3,330]	1,769 [963–2,838]	2,559 [1,599–3,692]	<0.001
Levothyroxine median dosage (IQR)	100.2 (82.8–138.0)	100.0 (77.7–122.1)	107.7 (86.5–148.6)	<0.001
Median cumulative RAI dosage, median (mCi, IQR)	103 (40–162)	–	103 (40–162)	–
Cumulative RAI dosage (mCi, %)		–		–
<100	1,045 (41.3)	–	1,045 (41.3)	
≥100 & <200	1,106 (43.7)	–	1,106 (43.7)	
≥200	382 (15.0)	–	382 (15.0)	
BMI, median (kg/m^2, IQR)	24.1 (22.3–26.0)	23.9 (22.1–25.8)	24.3 (22.5–26.2)	<0.001
SES, n (%)				0.580
Upper (30%)	2,519 (52.0)	1,195 (51.7)	1,324 (52.3)	
Mid (40%)	1,456 (30.0)	688 (29.8)	7638 (30.3)	
Lower (30%)	870 (18.0)	429 (18.5)	441 (17.4)	
Smoking, n (%)				0.217
Never	4,129 (85.2)	1,992 (86.2)	2,37 (84.4)	
Ex-smoker	341 (7.1)	150 (6.5)	191 (7.5)	
Current	283 (5.8)	128 (5.5)	155 (6.1)	
Unknown	92 (1.9)	42 (1.8)	50 (2.0)	–
Alcohol consumption, n (%)				0.014
Never	3,390 (70.00)	1,581 (68.4)	1,809 (71.4)	
≤2 times a week	1,145 (23.6)	590 (25.5)	555 (21.9)	
≥3 times a week	257 (5.3)	118 (5.1)	139 (5.5)	
Unknown	53 (1.1)	23 (1.0)	30 (1.2)	
Hypertension, n (%)	2,112 (43.6)	1,012 (43.8)	1,100 (43.4)	0.809
DM, n (%)	509 (10.5)	248 (10.7)	261 (10.3)	0.632
Dyslipidemia, n (%)	318 (8.6)	203 (8.8)	215 (8.5)	0.714
Cardiovascular disease, n (%)	355 (7.3)	175 (7.6)	180 (7.1)	0.537

TC, thyroid cancer; RAI, radioactive iodine; IQR, interquartile range; DM, diabetes mellitus; CVD, cardiovascular disease; CI, confidence interval.

Table 2 Incidence rate per 1,000 person-years and hazard ratio of specific cardiovascular diseases in patients with thyroid cancer who received RAI treatment compared to those who did not

Outcomes	Events (n)	Incidence rate (per 1,000 person-years)	Unadjusted		Adjusted*	
			HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular disease						
No RAI (n=2,312)	199 (8.6)	17.32 (15.07–19.90)	1 (reference)		1 (reference)	
RAI (n=2,533)	204 (8.1)	13.96 (12.17–16.01)	0.85 (0.70–1.03)	0.098	0.87 (0.71–1.07)	0.188
IS						
No RAI	38 (1.6)	3.12 (2.27–4.29)	1 (reference)		1 (reference)	
RAI	36 (1.4)	2.34 (1.69–3.24)	0.77 (0.49–1.22)	0.266	0.83 (0.51–1.34)	0.448
IHD						
No RAI	154 (6.7)	13.21 (11.28–15.47)	1 (reference)		1 (reference)	
RAI	162 (6.4)	10.96 (9.4–12.78)	0.87 (0.70–1.09)	0.230	0.90 (0.71–1.13)	0.368
HS						
No RAI	14 (0.6)	1.14 (0.68–1.93)	1 (reference)		1 (reference)	
RAI	18 (0.7)	1.16 (0.73–1.84)	1.02 (0.51–2.05))	0.959	1.01 (0.49–2.09)	0.978
Cerebrovascular disease						
No RAI	97 (4.2)	8.08 (6.62–9.86)	1 (reference)		1 (reference)	
RAI	103 (4.1)	6.78 (5.59–8.23)	0.86 (0.65–1.14)	0.300	0.88 (0.66–1.17)	0.379
HF						
No RAI	22 (1.0)	1.8 (1.18–2.73)	1 (reference)		1 (reference)	
RAI	25 (1.0)	1.62 (1.09–2.40)	0.93 (0.53–1.65)	0.807	0.89 (0.49–1.63)	0.714

*, adjusted for age, sex, body mass index, socioeconomical status, smoking, alcohol consumption, levothyroxine dosage, and previous history of hypertension, diabetes mellitus, dyslipidemia, and cardiovascular disease. RAI, radioactive iodine; IS, ischemic stroke; IHD, ischemic heart disease; HS, hemorrhagic stroke; HF, heart failure; CI, confidence interval.

did not receive RAI treatment. However, previous histories of HTN, DM, dyslipidemia, and major CVD, which were important risk factors of CVD outcomes, were comparable between the two groups.

CVD risks in patients with TC according to RAI treatment

Table 2 summarizes the incidence and risks of composite CVD outcome and specific CVDs between the RAI and non-RAI groups. Between 2004 and 2015, the incidence of composite CVD (per 100 person-years) in the non-RAI and RAI treatment groups was 17.32 and 13.96, respectively, with an unadjusted HR of 0.85 (95% CI, 0.70–1.03), which remained at 0.87 (95% CI, 0.71–1.07) after adjustments for age, sex, BMI, SES, smoking, alcohol consumption, levothyroxine dosage, and histories of hypertension, DM, dyslipidemia, and CVD. The risks of IS (adjusted HR, 0.83; 95% CI, 0.51–1.34), IHD (adjusted HR, 0.90; 95% CI, 0.71–1.13), HS (adjusted HR, 1.01; 95% CI, 0.49–2.09), cerebrovascular disease (adjusted HR, 0.88; 95% CI, 0.66–1.17), and HF (adjusted HR, 0.89; 95% CI, 0.49–1.63) were not significantly different between the two groups. The Kaplan-Meier curves for the incidence of composite CVD outcome and each specific CVDs in patients with and without RAI treatment are shown in *Figure 2*.

We analyzed whether the cumulative RAI dosage was associated with CVD outcomes in patients with TC (*Table 3*). We divided the patients into the following three groups according to the cumulative RAI dosage: no RAI, <100, and ≥100 mCi. After adjustments for age, sex, BMI, SES, smoking, alcohol consumption, levothyroxine dosage, and histories of hypertension, DM, dyslipidemia, and CVD,

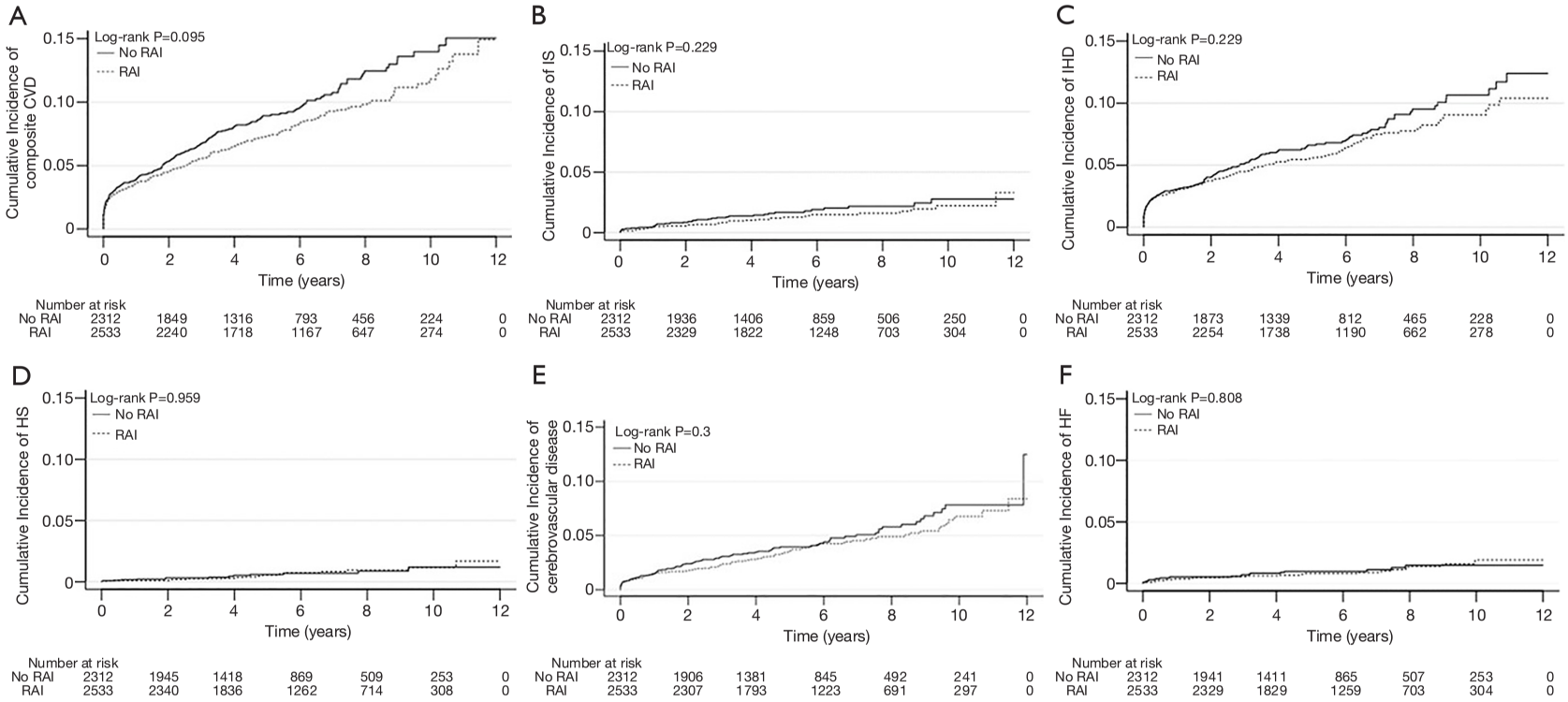

Figure 2 Cumulative incidence of (A) composite CVD, (B) ischemic stroke, (C) ischemic heart disease, (D) hemorrhagic stroke, (E) cerebrovascular disease, and (F) heart failure in patients with thyroid cancer who received RAI treatment and those who did not. CVD, cardiovascular disease; RAI, radioactive iodine.

Table 3 Incidence rate per 1,000 person-years and radioactive iodine dose-dependent hazard ratio of specific cardiovascular diseases in patients with thyroid cancer who received RAI treatment compared to those who did not

Outcomes	Events (n)	Incidence rate (per 1,000 person-years)	Unadjusted		Adjusted*	
			HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular disease						
No RAI (n=2,312)	199 (8.6)	17.32 (15.07–19.90)	1 (reference)		1 (reference)	
Cumulative RAI dose <100 mCi (n=1,045)	91 (8.7)	14.71 (11.98–18.07)	0.90 (0.70–1.15)	0.407	0.91 (0.70–1.18)	0.452
Cumulative RAI dose ≥100 mCi (n=1,488)	113 (7.6)	13.41 (11.15–16.12)	0.81 (0.64–1.02)	0.074	0.85 (0.67–1.08)	0.173
IS						
No RAI	38 (1.6)	3.12 (2.27–4.29)	1 (reference)		1 (reference)	
Cumulative RAI dose <100 mCi	17 (1.6)	2.6 (1.62–4.18)	0.87 (0.49–1.54)	0.622	0.92 (0.51–1.69)	0.798
Cumulative RAI dose ≥100 mCi	19 (1.3)	2.14 (1.37–3.36)	0.70 (0.41–1.22)	0.211	0.77 (0.44–1.35)	0.357
IHD						
No RAI	154 (6.67)	13.21 (11.28–15.47)	1 (reference)		1 (reference)	
Cumulative RAI dose <100 mCi	67 (6.4)	10.67 (8.4–13.56)	0.86 (0.64–1.14)	0.292	0.86 (0.64–1.16)	0.329
Cumulative RAI dose≥100 mCi	95 (6.4)	11.17 (9.14–13.66)	0.89 (0.69–1.14)	0.351	0.93 (0.71–1.20)	0.560
HS						
No RAI	14 (0.6)	1.14 (0.68–1.93)	1 (reference)		1 (reference)	
Cumulative RAI dose <100 mCi	13 (1.2)	1.98 (1.15–3.41)	1.74 (0.82–3.70)	0.152	1.67 (0.76–3.68)	0.203
Cumulative RAI dose ≥100 mCi	5 (0.3)	0.56 (0.23–1.34)	0.49 (0.18–1.36)	0.172	0.52 (0.18–1.45)	0.210
Cerebrovascular disease						
No RAI	97 (4.2)	8.08 (6.62–9.86)	1 (reference)		1 (reference)	
Cumulative RAI dose <100 mCi	53 (5.1)	8.26 (6.31–10.82)	1.06 (0.76–1.48)	0.744	1.05 (0.74–1.50)	0.778
Cumulative RAI dose ≥100 mCi	50 (3.4)	5.7 (4.32–7.52)	0.72 (0.51–1.02)	0.063	0.76 (0.53–1.07)	0.116
HF						
No RAI	22 (1.0)	1.8 (1.18–2.73)	1 (reference)		1 (reference)	
Cumulative RAI dose <100 mCi	12 (1.2)	1.83 (1.04–3.22)	1.06 (0.52–2.14)	0.871	0.97 (0.46–2.04)	0.935
Cumulative RAI dose ≥100 mCi	13 (0.9)	1.46 (0.85–2.52)	0.84 (0.42–1.66)	0.613	0.84 (0.42–1.69)	0.624

*, adjusted for age, sex, body mass index, socioeconomical status, smoking, alcohol consumption, levothyroxine dosage, and previous history of hypertension, diabetes mellitus, dyslipidemia, and cardiovascular disease. RAI, radioactive iodine; IS, ischemic stroke; IHD, ischemic heart disease; HS, hemorrhagic stroke; HF, heart failure; CI, confidence interval.

the HR for the incidence of composite CVD was 0.91 (95% CI, 0.70–1.18) for cumulative RAI dosage <100 mCi, and 0.85 (95% CI, 0.67–1.08) for cumulative RAI dosage ≥100 mCi compared with no RAI. The risks of incident IS, IHD, HS, cerebrovascular disease, and HF were not significantly different with a higher cumulative RAI dosage. In addition, we analyzed the effect of the cumulative RAI dosage with CVD outcomes only in patients who received RAI therapy (*Table S1*). Higher cumulative RAI dosages did not significantly increase the risks of composite CVD outcomes.

Discussion

Over the past several decades, RAI therapy has been largely

used as an essential treatment modality in DTC as it allows for accurate postoperative staging and postsurgical follow-up while yielding better clinical outcomes (13,14). However, the adverse effects of RAI treatment have been much debated, and the RAI therapy-related CVD adverse effects, in particular, have yet to be fully elucidated. To this end, we used a large nationwide cohort database to compare patients who received RAI therapy with those who did not, and found that the risks of composite CVD were not significantly increased in TC patients with RAI therapy.

Previously, la Cour *et al.* (16) reported an increased risk of cerebrovascular events by comparing >4,000 hyperthyroid and 1,022 euthyroid patients treated with RAI for benign thyroid disorders with 20,540 age- and sex-matched controls over a median follow-up of 11.5 years. In multivariate analyses after adjustments, the HR for cerebrovascular events was 1.17 (95% CI, 1.07–1.28) in hyperthyroid patients and 1.21 (95% CI, 1.02–1.44) in euthyroid patients. It should be noted, however, that the actual values of thyroid stimulating hormone (TSH), which are important discriminative factors between RAI-treated patients and controls for cerebrovascular events, were not included in this study, and the median total dosage of RAI therapy (approximately 11 mCi) was relatively low compared to that used in other studies of patients with TC (9,24). We also postulate baseline patient age, extent of residual thyroid tissue as well as differences in underlying disease contribute discrepancy between two studies. Another recent nationwide cohort study with a 10-year follow-up from Taiwan (24) reported an HR of 0.89 (95% CI, 0.60–1.33) after adjustments for age, sex, and comorbidities, suggesting that ^{131}I treatment for TC did not increase the risk of stroke. These discrepancies are likely due to the studies' different underlying thyroid diseases, population parameters, and design; therefore, the inconsistent findings concerning higher cerebrovascular disease risk at lower cumulative RAI dosage and no increase risk at higher cumulative RAI dosage requires standardized international studies to acquire definite conclusions.

Unlike previous research, which focused on cerebrovascular diseases, especially IS, our study analyzed the specific CVDs, such as IHD and HF. Ryödi *et al.* (25) recently reported that hyperthyroid patients treated with RAI remained at higher CVD risk, particularly for HF, compared with patients treated with thyroidectomy. Furthermore, there have been few studies that have focused on coronary artery disease and HF induced by RAI treatment even with higher cumulative RAI dosage. Although more evidence is required, our findings demonstrated that a higher cumulative dosage did not significantly increase the risk of IHD and HF.

In the further analysis, old age and previous histories of HTN and major CVD, which have been well established as risk factors of CVD, were identified as independent risk factors of CVD (*Table S2*). Interestingly, the levothyroxine median dosage and type of surgery were not related with CVD risk in the patients with thyroid cancer.

Some limitations of this study should also be addressed. First, the relatively short follow-up might have masked the latent adverse effects of RAI therapy that occur 5 or 10 years after exposure, and more careful interpretation is required before reaching definite conclusions because of possible false-negative effects. Another major limitation of this study is the lack of clinicopathological information, such as the tumor stage, pathological subtype, and thyroid-stimulating hormone (TSH) levels, which can affect the treatment course and prognosis in TC. Recently, TSH levels have been reported to be associated with CVD events and CVD-related mortality (9,10,26); therefore, the effects of long-term TSH suppression therapy on CVD risks in patients with TC might have been overlooked. Third, our results cannot be generalized to patients aged <40 and ≥80 years because the NHIS-HEALS cohort only includes patients aged 40–79 years. However, a previous report has demonstrated that the incidence of newly diagnosed TC markedly increases after the age of 45 years (27), and a majority of CVD outcomes usually occur in this population (9,28). Lastly, as a common caveat of claims data, the primary outcomes were based on ICD-10 codes. To reduce the false-positive detection bias, we defined specific primary outcomes along with hospitalization history for each CVD ICD-10 code.

In this large nation-wide cohort study, we demonstrated that the risk of IS, IHD, HS, and HF was not significantly increased in patients with TC who received RAI treatment compared with those who did not, and that the cumulative RAI dosage was not associated with increased CVD risks in patients with TC. These results, together with those of previous studies, provide invulnerable evidence regarding the long-term effects of RAI therapy in patients with TC.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Review Board of the Korea University Anam Hospital (IRB number: ED16255). Informed consent was not required because this study was based on the NHIS database, which includes fully anonymized and de-identified data. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Incidence rate per 1,000 person-years and radioactive iodine dose-dependent hazard ratio of cardiovascular disease only in patients with thyroid cancer who received RAI treatment

Outcomes	Events (n)	Incidence rate (per 1,000 person-years)	Unadjusted		Adjusted*	
			HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular disease						
Cumulative RAI dose <100 mCi (n=1,045)	91 (8.7)	14.71 (11.98–18.07)	1 (reference)		1 (reference)	
Cumulative RAI dose ≥100 mCi (n=1,488)	113 (7.6)	13.41 (11.15–16.12)	0.90 (0.68–1.19)	0.459	0.94 (0.71–1.25)	0.673
Cardiovascular disease						
Cumulative RAI dose <100 mCi (n=1,045)	91 (8.7)	14.71 (11.98-18.07)	1 (reference)		1 (reference)	
100 mCi ≤ cumulative RAI dose <200 mCi (n=1,106)	86 (7.8)	15.19 (12.29–18.76)	0.99 (0.74–1.33)	0.936	1.01 (0.74–1.36)	0.965
Cumulative RAI dose ≥200 mCi (n=382)	27 (7.1)	9.77 (6.70–14.24)	0.71 (0.46–1.08)	0.111	0.78 (0.51–1.21)	0.270

*, adjusted for age, sex, body mass index, socioeconomical status, smoking, alcohol consumption, levothyroxine dosage, and previous history of hypertension, diabetes mellitus, dyslipidemia, and cardiovascular disease. RAI, radioactive iodine.

Table S2 Factors associated with cardiovascular disease in patients with thyroid cancer

Variables	Primary CVD outcome	
	Adjusted HR* (95% CI)	P value
Age, 10 years	1.59 (1.41–1.81)	<0.001
Sex		
Male	1 (reference)	–
Female	0.84 (0.620–1.13)	0.252
Type of surgery		
Hemithyroidectomy	1 (reference)	–
Total + subtotal thyroidectomy	0.84 (0.62–1.13)	0.239
Levothyroxine median dose, 100 μg/day	1.07 (0.86–1.33)	0.548
BMI (kg/m^2)		
<18.5	1 (reference)	–
<23	0.85 (0.37–1.95)	0.694
≥23	1.28 (0.57–2.91)	0.550
SES		
Upper (30%)	1 (reference)	–
Mid (40%)	1.01 (0.80–1.23)	0.944
Lower (30%)	1.08 (0.83–1.41)	0.576
Smoking		
Never	1 (reference)	–
Ex-smoker	0.77 (0.481–1.234)	0.278
Current	1.311 (0.840–2.044)	0.233
Alcohol consumption		
Never	1 (reference)	–
<2 times a week	1.07 (0.82–1.40)	0.623
≥3 times a week	0.81 (0.49–1.34)	0.416
Hypertension	1.90 (1.49–2.41)	<0.001
Diabetes mellitus	1.14 (0.88–1.49)	0.315
Dyslipidemia	0.98 (0.71–1.36)	0.902
CVD	6.12 (4.87–7.69)	<0.0001

*, analyzed by multivariable Cox proportional hazards regression analysis.