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Cancer Risk in Graves Disease with Radioactive ^{131}I Treatment: A Nationwide Cohort Study

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Radioactive ^{131}I (RAI) therapy has potential effects for the treatment of Graves disease (GD). However, whether RAI therapy for GD increases cancer risk remains controversial in medicine and public health. We aimed to investigate whether the risk of cancer increases in patients with GD receiving RAI therapy compared with those who did not. **Methods:** We used the Korean National Health Insurance Service's National Health Information Database from 2004 to 2020 and defined GD as prescribing antithyroid drugs, RAI, or thyroidectomy as a treatment for GD (*International Classification of Diseases,* 10th revision, E05 group). We investigated the hazard ratios (HRs) of overall and site-specific cancers associated with RAI in patients with GD. Subsequent cancer was defined as a primary malignancy treated at least 1 y after RAI therapy. **Results:** In total, 10,737 patients with GD who received RAI therapy (7,193 women, 67.0%; mean age, 43.7 ± 13.4 y) were matched to 53,003 patients with GD who had never received RAI treatment (35,471 women, 66.9%; mean age, 43.8 ± 13.2 y) in a 1:4–5 ratio by age, sex, and health checkup data. The median follow-up duration was 8.7 y (interquartile range, 5.2–12.1 y), and the median cumulative RAI dose was 555 MBq (interquartile range, 370–630 MBq) in the RAI therapy group. During 2004–2020, the overall subsequent cancer rates were 5.66 and 5.84 per 1,000 person-years in the RAI and non-RAI groups, respectively, with an unadjusted HR of 0.97 (95% CI, 0.88–1.06); this remained at 0.96 (95% CI, 0.83–1.10) after adjustment for multiple clinical confounding factors. For cancer subtypes, the risk of leukemia was significantly increased, with an HR of 2.39 (95% CI, 1.17–4.91). However, a loss of statistical significance was observed after adjusting for confounding factors, which may be attributed to the limited number of absolute events. Moreover, cancer-specific mortality was not different between the RAI and the non-RAI groups, with an adjusted HR of 0.99 (95% CI, 0.66–1.47). **Conclusion:** This study identified that the overall cancer risk in patients with GD who received RAI therapy compared with those who did not was not significant in Korea. Further long-term studies are needed to determine the risks and advantages of RAI therapy in patients with GD.

Key Words: Graves disease; radioactive ^{131}I therapy; cancer risk

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Graves disease (GD) is an autoimmune condition that occurs because of excessive production of thyroid hormones by the thyroid-stimulating autoantibodies, the most common form of hyperthyroidism (*1*,*2*). The prevalence of GD ranges from 0.1% to 2.9% worldwide and was approximately 2.76 cases per 1,000 population in Korea in 2015 (*1*,*3*–*5*). Conventional antithyroid drugs, radioactive ^{131}I (RAI) therapy, and surgical thyroidectomy are the main treatment modalities for GD. Although regional differences with regard to the diagnosis and management of GD are apparent (*6*), RAI has been strongly recommended as the initial treatment option by National Institute for Health and Care Excellence guidelines (*7*). In addition, it has been recommended for patients who prefer this approach by the European Thyroid Association and the American Thyroid Association, with moderate-quality evidence (*3*,*8*,*9*). However, long-term GD survivors who have undergone RAI therapy inevitably face related adverse effects, especially RAI-associated cancer risks, with discordant results. Metso et al. (*10*). analyzed 2,793 patients treated with RAI for hyperthyroidism between 1954 and 2022 using the Finnish Cancer Registry and the Population Registry Center. They identified that cancer incidence among patients who received RAI therapy was significantly higher than that in the control group with a rate ratio of 1.25, especially for cancer related to the stomach, kidney, and breast. However, in a recent metaanalysis, the overall pooled cancer risk after exposure to RAI therapy compared with the risk in the nonexposure group was not significant. Meanwhile, a linear association was observed between RAI dose and cancer mortality, underscoring the need for meticulous monitoring for increased cancer-related mortality at higher levels of the administered dose (*11*).

We conducted, to our knowledge, the largest retrospective nationwide GD cohort study in Korea to date, focusing on the association between RAI therapy and cancer risk in the context of GD. Our study, which included a substantial sample size and had minimal loss to follow-up, investigated the dose–response relationship and identified differences according to the specific cancer subtypes. Moreover, we considered various confounding factors that could have affected the results, including smoking, alcohol consumption, body mass index (BMI), and other comorbidities. In addition, we investigated overall and cancer-specific mortality in patients with GD who received RAI therapy compared with those who did not.

MATERIALS AND METHODS

Data Source

We investigated the association between cancer risk and RAI treatment in patients with GD using data from the Korean National Health Insurance Service's National Health Information Database (NHIS-2022-1-208), a comprehensive medical insurance system covering all citizens of South Korea (n = 52,870,968 in 2020). The database

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contains longitudinal information on individual demographic, pharmaceutical, and health-screening data, as well as mortality and medical records based on the *International Classification of Diseases,* 10th revision (ICD-10). In addition, the database includes specific cause-of-death data based on ICD-10 codes and is managed by the Korean National Statistical Office. A more detailed cohort protocol was previously published by other institutions and authors (*12*), as well as by our group (*13*).

This study was approved by the Institutional Review Board of Korea University Anam Hospital (2021AN0339). Informed consent was not required because this study was based on data from the Korean National Health Insurance Service database, which was fully anonymized and deidentified for analysis.

Study Population

We identified 641,203 patients who were prescribed antithyroid drugs, RAI, or thyroidectomy as treatment for hyperthyroidism (in the ICD-10 E05 group, E05.0–E05.5, E05.8, and E05.9) between January 1, 2002, and June 30, 2020. In total, 465,683 patients with GD were included in the GD cohort after applying the exclusion criteria, such as age less than 18 y, GD diagnosis in 2002–2003, previous diagnosis of thyroid cancer (ICD-10 C73), prior RAI treatment or thyroidectomy, or follow-up duration of less than 6 mo. Patients in the GD cohort were divided into 2 groups based on their history of RAI treatment for GD during the follow-up period after inclusion in the cohort. The index date of the patients who received RAI treatment was defined as the date of first RAI treatment. To avoid the immortal time bias related to the timing of RAI treatment after GD diagnosis, we applied a matching procedure similar to the risk-set sampling method. At each time point of RAI treatment, we identified a set of patients who had never received RAI treatment and were followed up. We randomly selected 4–5 patients in this set by matching the cohort entry year, sex, age, and availability of health checkup data with those of patients who had received RAI treatment. The index date of patients who had never received RAI treatment was matched with that of patients who had received RAI treatment. Finally, we included 10,737 patients who had received RAI treatment (RAI group) and 53,003 patients who had never received RAI treatment (non-RAI group), after excluding those who had previously undergone radiation therapy before the index date, had been diagnosed with cancer up to 1 y after the index date, or were followed up for fewer than 18 mo from the index date (Supplemental Figs. 1 and 2 [supplemental materials are available at http://jnm.snmjournals.org]).

Exposure and Covariates

RAI treatment for GD was defined as the prescription of a single dose of at least 185 MBq. The cumulative RAI treatment dose for each patient in the RAI group was calculated by summing the individual RAI treatment doses received throughout the follow-up period. Patients in the RAI group were stratified into tertile groups based on their cumulative doses: 185–370, 371–555, and at least 556 MBq.

The definitions of underlying comorbidities of hypertension, diabetes mellitus (DM), and dyslipidemia are described in Supplemental Table 1. Anthropometric and biochemical laboratory information, including alcohol consumption, smoking, BMI, systolic and diastolic blood pressure, fasting plasma glucose, and total cholesterol, were obtained from the National Health Screening Program database for 38,834 of the total study patients (6,535 in the RAI group and 32,299 in the non-RAI group). We used the most recent information before the index date, with a median difference of 7.4 mo (interquartile range [IQR], 0.03–20.6 mo). Smoking, which is an important and universal carcinogen for every cancer, was used as a dichotomous parameter. Individuals who smoked fewer than 100 cigarettes in their entire life were categorized as nonsmokers, those who smoked at least 100 cigarettes but were not currently smoking were categorized as ex-smokers, and those who smoked at least 100 cigarettes in their entire life and were still smoking were categorized as current smokers.

Outcomes

To minimize detection bias, the occurrence of new incident cancer was defined as the diagnosis of a malignancy in which the same ICD-10 cancer code was claimed at least twice, occurring at least 1 y after the index date. To evaluate site specificity of the malignancy, we classified malignancies as follows: head and neck cancer (C00–C14), digestive cancer (C15–C26), 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), thyroid cancer (C73), other endocrine cancer (C74–C75), and unknown or not otherwise specified (all from C00 to C97, except for the previously mentioned diagnoses). Each patient was followed up from the index date until the earliest date of the first cancer claim, date of death, or date of the last data collection in the cohort (December 31, 2020). The median follow-up time was determined by calculating the median value of the follow-up time distribution observed for each patient.

Statistical Analysis

Continuous data are presented as mean ± SD for normally distributed variables and as medians and IQRs for nonnormally distributed variables. Categoric data are presented as frequencies and percentages. Baseline characteristics were compared by calculating the absolute standardized difference (ASD) between the 2 groups (*14*). All incidence rates are expressed as the number of cases per 1,000 person-years. The incidence rate of each malignancy was calculated as the number of participants with each malignancy divided by the total person-time. The cumulative incidence rate of total malignancy was estimated using the Kaplan–Meier curve and graphically presented. To evaluate the relative risk of malignancy in the RAI group compared with that in the non-RAI group, we used the Cox proportional hazards regression model with a robust sandwich covariance matrix estimate to account for age- and sex-matched data. We performed 2 models using confounding variables that differ in ASD and those that can affect cancer risk. Model A was applied to the entire group of patients with GD, and adjustments were made only for hypertension, DM, dyslipidemia, modified Charlson comorbidity index (mCCI), and treatment for GD at baseline. Model B, which additionally integrated health checkup data related to cancer, including smoking, alcohol consumption, BMI, systolic blood pressure, total cholesterol, and fasting plasma glucose, was analyzed using subjects with no missing data on the additional adjusted variables. The proportional hazard assumption was checked using a test for independence between the scaled Schoenfeld residuals and time. The risk of malignancy related to RAI treatment is presented as the hazard ratio (HR) and corresponding 95% CI. Missing data were not imputed, and all analyses were based on available data. All reported P values were 2-sided, and statistical significance was set at a P value of less than 0.05. All statistical analyses were performed using SAS Enterprise Guide version 7.1 (SAS Institute Inc.) and R software version 4.1 (R Foundation for Statistical Computing).

RESULTS

Baseline Characteristics

Of the 10,737 patients in the RAI group and 53,003 matched patients in the non-RAI group, 7,193 (67%) and 35,471 (66.9%) were women (ASD, 0.001) and the mean age was 43.7 ± 13.4 and

43.8 ± 13.2 y, respectively (ASD, 0.009; Table 1). The median time from GD diagnosis to RAI treatment for the RAI group was 2.2 y (IQR, 0.4–4.6 y); that from GD diagnosis to the defined index date for the non-RAI group was also 2.2 y (IQR, 0.4–4.6 y; ASD, 0.031; Supplemental Table 2). The median follow-up duration was 8.7 y (IQR, 5.2–12.1 y) and 8.5 y (IQR, 5.5–11.8 y) in the RAI and non-RAI groups, respectively (ASD, 0.012). In the RAI group, the median cumulative RAI dose during the follow-up period was 555 MBq (IQR, 370–630 MBq; range, 185–7,474 MBq). Antithyroid drugs before the index date were prescribed to 8,602 (80.1%) patients in the RAI group and 52,148 (98.4%) patients in the non-RAI group (ASD, 0.617); 30 (0.3%) and 1,121 (2.1%) patients underwent thyroidectomy before the index date in the RAI and non-RAI groups, respectively (ASD, 0.169). The number of patients with an mCCI of at least 3 was 5,509 (51.3%) in the RAI group and 24,641 (46.5%) in non-RAI group. Socioeconomic status, BMI, alcohol consumption, smoking, and the proportion of patients with underlying comorbidities, including hypertension, DM, and dyslipidemia, were comparable between the RAI and the non-RAI groups.

TABLE 1
Baseline Characteristics of Patients with GD According to RAI Treatment

Characteristic	RAI	Non-RAI	ASD
Total	10,737	53,003	
Age (y)	43.7 ± 13.4	43.8 ± 13.2	0.009
Women	7,193 (67.0)	35,471 (66.9)	0.001
Socioeconomic status			0.043
Low (first tertile)	2,845 (26.5)	13,401 (25.3)	
Middle (second tertile)	3,515 (32.7)	18,425 (34.8)	
High (third tertile)	4,377 (40.8)	21,177 (39.9)	
Treatment for GD at baseline			
Thyroidectomy	30 (0.3)	1,121 (2.1)	0.169
Antithyroid drugs	8,602 (80.1)	52,148 (98.4)	0.617
Comorbidities			
Hypertension	2,985 (27.8)	13,240 (25.0)	0.064
DM	1,059 (9.9)	4,800 (9.1)	0.028
Dyslipidemia	1,751 (16.3)	9,978 (18.8)	0.066
mCCI*	3 (1–3)	2 (1–3)	0.115
0	1,650 (15.4)	9,183 (17.3)	0.083
1	1,575 (14.7)	8,656 (16.3)	
2	2,003 (18.7)	10,523 (19.9)	
≥3	5,509 (51.3)	24,641 (46.5)	
Health checkup data†			
Missing	4,202 (39.1)	20,704 (39.1)	<0.001
BMI (kg/m^2)	23.2 ± 3.2	23.4 ± 3.3	0.051
Systolic blood pressure (mm Hg)	122.2 ± 14.8	121.4 ± 14.7	0.056
Diastolic blood pressure (mm Hg)	75.3 ± 9.9	75.3 ± 9.8	0.005
Total cholesterol (mg/dL)	180.6 ± 41.3	186.9 ± 39.4	0.158
Fasting plasma glucose (mg/dL)	97.8 ± 21.5	97.3 ± 22.4	0.025
Smoking status			0.088
Nonsmoker	4,375 (67.0)	22,918 (71.0)	
Ex-smoker	814 (12.5)	3,600 (11.1)	
Current smoker	1,346 (20.6)	5,781 (17.9)	
Alcohol consumption			0.041
No	4,118 (63.0)	20,002 (61.9)	
≤2 times per week	2,006 (30.7)	10,169 (31.5)	
≥3 times per week	411 (6.3)	2,128 (6.6)	

*mCCI is median with IQR in parentheses.
†Health checkup data were analyzed only in 38,834 patients, 6,535 in RAI group and 32,299 in non-RAI group.
Data are number with percentage in parentheses or mean ± SD.

Malignancy Risks and Cancer-Related Mortality in GD According to RAI Therapy

From 2004 to 2019, the number of newly diagnosed malignancy events was 530 in the RAI group and 2,679 in the non-RAI group, with incidence rates of 5.66 and 5.84 per 1,000 person-years, respectively. With regard to the risk of malignancy, the unadjusted HR comparing the RAI group with the non-RAI group was 0.97 (95% CI, 0.88–1.06; $P = 0.455$) and the HR was 0.96 (95% CI, 0.83–1.10; $P = 0.553$) after adjusting for socioeconomic status; comorbidities of hypertension, DM, and dyslipidemia; mCCI; treatment for GD at baseline; BMI; systolic blood pressure; total cholesterol; fasting plasma glucose; smoking status; and alcohol consumption (Table 2; Fig. 1A). The adjusted HRs of malignancy were 0.89 (95% CI, 0.73–1.09; $P = 0.259$), 0.97 (95% CI, 0.79–1.20; $P = 0.807$), and 1.03 (95% CI, 0.83–1.28; $P = 0.802$) in the first (185–370 MBq), second (371–555 MBq), and third (≥556 MBq) tertile cumulative dose groups, respectively (Table 2). With regard to the cancer subtype, the incidence rate of leukemia was 0.12 and 0.05 in the RAI and non-RAI groups, respectively (Supplemental Table 3). The unadjusted HR for leukemia was 2.39 (95% CI, 1.17–4.91; $P = 0.017$) and remained at 2.23 (95% CI, 1.03–4.83; $P = 0.043$) after adjusting for socioeconomic status; comorbidities of hypertension, DM, and dyslipidemia; mCCI; and treatment for GD at baseline. However, when further adjusted for BMI, systolic blood pressure, total cholesterol, fasting plasma glucose, smoking status, and alcohol consumption, the risk of leukemia associated with RAI treatment was no longer statistically significant (HR, 2.06; 95% CI, 0.74–5.77; $P = 0.169$). Head and neck cancer (HR, 1.31; 95% CI, 0.38–3.30; $P = 0.830$); digestive cancer (HR, 0.84; 95% CI, 0.64–1.09; $P = 0.189$), especially gastric cancer (HR, 0.94; 95% CI, 0.59–1.49; $P = 0.790$); breast cancer (HR, 1.19; 95% CI, 0.83–1.70; $P = 0.340$); and thyroid cancer (HR, 0.92; 95% CI, 0.68–1.26; $P = 0.612$) did not significantly increase in the RAI group from the non-RAI group after adjustments of confounding factors (Supplemental Table 3; Supplemental Fig. 3). However, among urinary tract cancers, the HR for bladder cancer was 2.09 (95% CI, 0.98–4.45; $P = 0.056$) after adjusting for all confounding factors (Supplemental Fig. 3). The cancer risks associated with RAI therapy were not increased according to the latency periods, with no statistical significance of the temporal differences (Supplemental Table 4).

Table 3 provides the risk of overall and malignancy-related morality. The HRs for all-cause and cancer-related mortality were 0.85 (95% CI, 0.67–1.08; $P = 0.188$) and 0.99 (95% CI, 0.66–1.47; $P = 0.947$), respectively, after adjusting for socioeconomic status; comorbidities of hypertension, DM, and dyslipidemia; mCCI; treatment for GD at baseline; BMI; systolic blood pressure; total cholesterol; fasting plasma glucose; smoking status; and alcohol consumption (Figs. 1B and 1C).

DISCUSSION

RAI treatment, which has been widely administered in patients with GD for more than 7 decades, has shown mounting evidence of its role in achieving complete remission. Although the adverse effects of RAI treatment, such as sialadenitis and exacerbation of Graves ophthalmopathy, are well known and tolerably controlled, concerns with regard to cancer risk have been continuously raised in recent years. Our results used the largest nationwide GD cohort in Korea, to our knowledge, and demonstrated that the overall cancer risk did not increase in patients with GD who had undergone

TABLE 2
Risk of New-Onset Malignancy in Patients with GD who Received RAI Treatment

Group	*n*	Events	Unadjusted		Adjusted*		Events	Adjusted†	
			HR	*P*	HR	*P*		HR	*P*
GD with no RAI therapy	53,003	2,679 (5.84)	1		1		1,588 (6.31)	1	
GD with RAI therapy	10,737	530 (5.66)	0.97 (0.88–1.06)	0.455	0.93 (0.83–1.04)	0.181	312 (6.08)	0.96 (0.83–1.10)	0.553
Cumulative RAI dose (MBq)									
First tertile, 185–370	3,932	224 (5.85)	0.97 (0.85–1.11)	0.672	0.89 (0.76–1.03)	0.122	126 (6.09)	0.89 (0.73–1.09)	0.259
Second tertile, 371–555	3,783	166 (5.55)	0.97 (0.83–1.13)	0.666	0.98 (0.83–1.15)	0.782	98 (5.73)	0.97 (0.79–1.20)	0.807
Third tertile, ≥556	3,022	140 (5.52)	0.96 (0.81–1.13)	0.600	0.93 (0.78–1.11)	0.424	88 (6.50)	1.03 (0.83–1.28)	0.802
Cumulative RAI dose per 370 MBq			0.98 (0.93–1.02)	0.347	0.97 (0.92–1.02)	0.185		1.00 (0.93–1.06)	0.901

*Adjusted for socioeconomic status, hypertension, DM, dyslipidemia, mCCI, and treatment for GD at baseline.
†Adjusted for socioeconomic status, hypertension, DM, dyslipidemia, mCCI, treatment for GD at baseline, BMI, systolic blood pressure, total cholesterol, fasting plasma glucose, smoking status, and alcohol consumption. These results were analyzed only in 38,834 patients, 6,535 in RAI group and 32,299 in non-RAI group, with available baseline health checkup data.
Event data are number with incidence rate per 1,000 person-years in parentheses. HR is followed by 95% CI in parentheses.

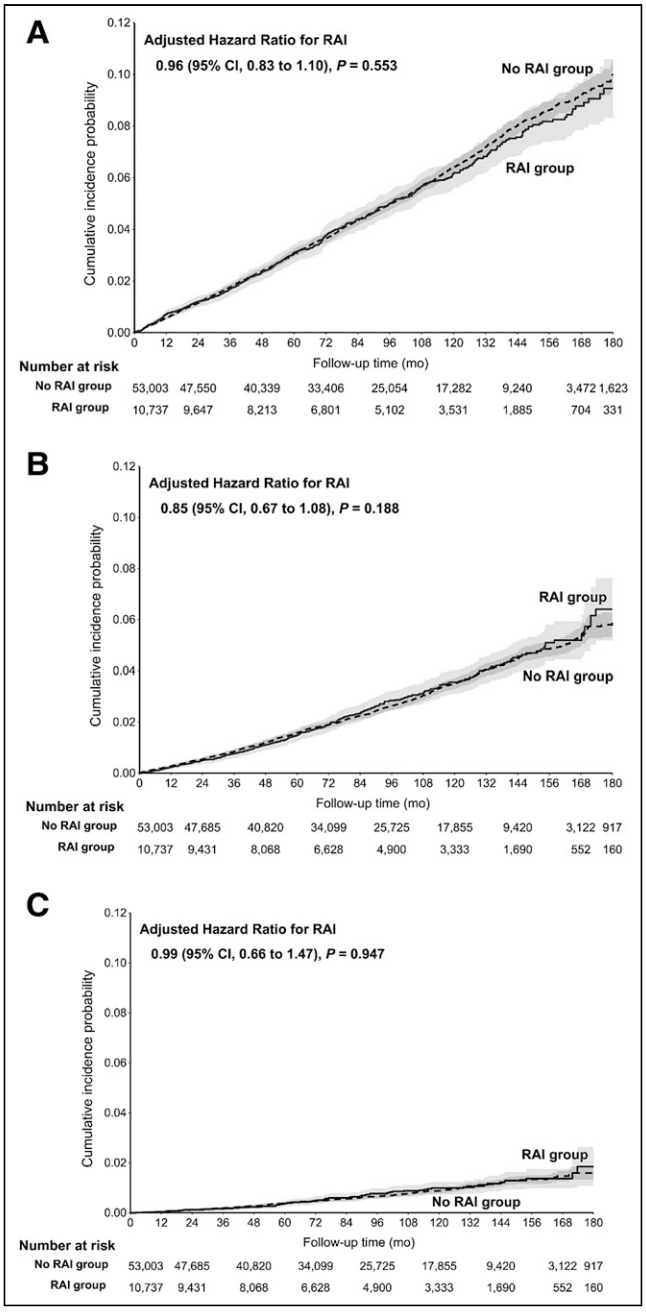

FIGURE 1. Cumulative incidence rate for new-onset malignancy (A), all-cause mortality (B), and cancer-related mortality (C) in GD patients according to RAI treatment.

RAI therapy from the risk in those who had not. In addition, we found that a higher cumulative RAI dose was not associated with cancer risk and that cancer-specific mortality did not increase in patients receiving RAI therapy.

The most recent metaanalysis by Shim et al. (*11*), including 12 observational studies and 479,452 participants, showed that RAI therapy was not associated with a significant increase in overall cancer risk or site-specific cancer incidence or mortality, except for thyroid cancer. These results are consistent with ours, except for thyroid cancer. Unlike previous observational studies that were criticized for the limited adjustment of confounding factors, such as smoking, alcohol consumption, and underlying diseases (*15*), our large nationwide cohort study included all possible related factors. We also compared the cancer risks of patients who received RAI therapy with age- and sex-matched patients with GD who did not receive RAI therapy, rather than the general population, leading to more reliable results. More long-term follow-up studies are warranted; however, results from previous studies (*11*,*16*,*17*) and ours suggest that the cancer risk associated with RAI therapy at low cumulative doses is not significantly increased.

The administered dosage is a critical factor in the relationship between RAI therapy and cancer risk. Kitahara et al. (*18*) reported that higher absorbed doses in organs were associated with an increased risk of solid cancer death. Another study by the same research group demonstrated that in patients receiving RAI treatment, solid cancer mortality was positively correlated with the total administered dose (*19*). In contrast, Gronich et al. (*17*) used data from Israel's largest health service and reported no association between RAI therapy and subsequent cancer risk compared with treatment with thionamides. However, there was a lack of RAI dose-related data.

Previous studies have shown that thyroid cancer mortality increased by more than 2-fold after RAI therapy for hyperthyroidism (*11*,*20*,*21*), which is inconsistent with the results of our study. High-dose radiation exposure of the thyroid gland may be one of the possible reasons. However, the pitfall of previous studies was that they analyzed the standardized mortality rate compared with that of the general population; thus, whether hyperthyroidism or RAI therapy is the main reason for the increased thyroid cancer risk is unclear.

Results with regard to myeloid leukemia require careful interpretation. The HR adjusted for socioeconomic status, hypertension, DM, dyslipidemia, mCCI, and treatment for GD at baseline was 2.23 with statistical significance, which was lost after additional adjustment for alcohol consumption, smoking, BMI, and underlying comorbidities. Low statistical power arising from a small number of events may have contributed to the statistically nonsignificant result for leukemia risk. Thus, it cannot be concluded that there is no increased risk of leukemia in the RAI group from the risk in the non-RAI group. Leukemia is widely known as a radiation-sensitive cancer with a relatively short latency period (*22*,*23*), requiring a larger and more exact dosimetry analysis.

The primary strengths of the present study include the substantial sample size, population-based design, accurate detection of RAI treatment, and minimal loss to follow-up. Moreover, we analyzed cancer risks, including various confounding factors, especially smoking, alcohol consumption, BMI, and other comorbidities, such as hypertension, dyslipidemia, DM, and mCCI, that could have affected the results. Another strength of our study is that it integrates cancer-related mortality data using death records from the Korean National Statistical Office. However, this study has several limitations. In the Korean National Health Insurance Service's National Health Information Database, information with regard to biochemical laboratory results for thyroid function tests and antibodies was not available, resulting in false-positive detection of GD, including multinodular toxic goiter or transient thyrotoxicosis. Therefore, we strictly applied the diagnostic criteria of GD to minimize this bias, combining at least 6-mo follow-up periods and antithyroid drug use with the ICD-10 code for the definition of GD. Another major limitation of this study is the relatively short follow-up period, which did not completely cover the natural course of overall GD treatment and the occurrence of subsequent cancer.

TABLE 3
Comparison of Risk for Overall and Malignancy-Related Mortalities in Patients with GD who Received RAI Therapy and Those who Did Not

		Unadjusted		Adjusted*			Adjusted†	
Group	Deaths	HR	*P*	HR	*P*	Deaths	HR	*P*
All-cause mortality								
Non-RAI	1,385 (2.94)	1		1		661 (2.56)	1	
RAI	288 (3.00)	1.02 (0.91–1.15)	0.727	0.94 (0.79–1.10)	0.426	137 (2.61)	0.85 (0.67–1.08)	0.188
Cancer mortality								
Non-RAI	352 (0.75)	1		1		204 (0.79)	1	
RAI	75 (0.78)	1.06 (0.83–1.36)	0.651	1.04 (0.78–1.40)	0.797	44 (0.84)	0.99 (0.66–1.47)	0.947

*Adjusted for socioeconomic status, hypertension, DM, dyslipidemia, mCCI, and treatment for GD at baseline.
†Adjusted for socioeconomic status, hypertension, DM, dyslipidemia, mCCI, treatment for GD at baseline, BMI, systolic blood pressure, total cholesterol, fasting plasma glucose, smoking status, and alcohol consumption. These results were analyzed only in 38,834 patients, 6,535 in RAI group and 32,299 in non-RAI group, with available baseline health checkup data.
Death data are number with incidence rate per 1,000 person-years in parentheses. HR is followed by 95% CI in parentheses.

More careful interpretation and long-term studies are needed to reach definitive conclusions with regard to the risk of solid cancers. Lastly, genetic predisposition as a factor for cancer risk was not considered in this analysis, which may have diminished the clinical implications of the research findings.

CONCLUSION

We used a nationwide database to assess the risks of cancer and cancer-related mortality in patients with GD who underwent RAI therapy compared with those who did not receive RAI treatment. Overall cancer risks were not significantly different between patients with GD who received RAI therapy and those who did not. Although long-term studies are needed, our results provide evidence for the safety of RAI therapy in the context of cancer risk in patients with GD.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Is the risk of malignancy increased in patients with GD receiving RAI therapy compared with those who did not?

PERTINENT FINDINGS: In this population-based retrospective cohort study of 63,740 patients with GD in Korea, the risk of malignancy did not increase in patients who received RAI therapy from the risk in those who did not.

IMPLICATIONS FOR PATIENT CARE: This study offered population-based, large-cohort evidence on the safety of RAI-associated cancer risk and related mortality in patients with GD.

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