Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Cancer and Mortality Risks of Graves' Disease in South Korea Based on National Data from 2010 to 2019

Young Ju Choi[1], Kyungdo Han[2], Won Kyoung Cho[3], Min Ho Jung[1], Byung-Kyu Suh[4]

[1]Department of Pediatrics, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Department of Statistics and Actuarial Science, College of Natural Sciences, Soongsil University, Seoul, Republic of Korea; [3]Department of Pediatrics, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [4]Department of Pediatrics, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Correspondence: Won Kyoung Cho, Department of Pediatrics, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 93, Jungbu-daero, Paldal-gu, Suwon-si, Gyeonggi-do, 16247, Republic of Korea, Tel +82-31-249-8869, Fax +82-2-783-2589, Email wendy626@catholic.ac.kr

Purpose: This study aimed to investigate Graves' disease (GD) associated cancer and mortality risk using a Korean population-based study.

Patients and Methods: We included 6435 patients with GD using the Korean National Health Insurance Service–National Sample Cohort database from 2010 to 2019. Data concerning such patients were compared in a 1:5 ratio with age- and sex-matched non-GD group (n=32,175). Eighteen subdivided types of cancer and cancers-in-total were analyzed. In addition to the mortality analysis, subgroup analyses were performed according to age and sex.

Results: After adjustment, the hazard ratio (HR) of the GD group for cancer-in-total was 1.07 (95% confidence interval [CI], 0.91–1.27), showing no difference when compared to the non-GD group. However, among different types of cancer, the thyroid cancer risk of the GD group was higher than that of the non-GD group (HR=1.70; 95% CI, 1.20–2.39). When subdivided by age and sex, the thyroid cancer risk of the GD group in males aged 20–39 years was higher than that of the non-GD group (HR=7.00; 95% CI, 1.48–33.12). The mortality risk of the GD group was not different from that of the non-GD group (HR=0.86; 95% CI, 0.70–1.05).

Conclusion: In South Korea, patients with GD had a higher risk of thyroid cancer than the non-GD group. In particular, males aged 20–39 years with GD were more likely to have thyroid cancer than the non-GD group.

Keywords: Graves disease, neoplasms, mortality, Republic of Korea

Introduction

Autoimmune thyroid disorders, including Graves' disease (GD), are organ-specific autoimmune disorders.[1] GD is the most common cause of hyperthyroidism.[2] The main mechanism of GD involves the binding of the thyroid-stimulating hormone (TSH) receptor stimulation antibody (TRAb) in the thyroid cell membrane to the TSH receptor, instead of TSH, to stimulate the growth and function of thyroid cells, resulting to hyperthyroidism.[3] Patients with GD may present with emotional disorders, such as hyperactivity and concentration loss, accompanied by clinical symptoms of increased appetite, weight loss, tachycardia, and increased sweating. In addition, GD is characterized by diffuse goiter of the thyroid gland, and thrill or bruit may be felt in the thyroid gland.[4]

According to a nationwide population-based cohort study on the prevalence and annual incidence of thyroid disease in Korea, the prevalence of patient with hyperthyroidism receiving treatment was 2.76 per 1000 population in 2015. The annual incidence of patients newly diagnosed with hyperthyroidism who were undergoing treatment was 0.55/1000 population in 2015.[5] In a meta-analysis of the incidence and prevalence of thyroid dysfunction in Europe, the incidence of hyperthyroidism was reported at 0.51/1000 population per year.[6] The duration of medical treatment is prolonged owing to continuous thyroid autoimmunity and autoantibody stimulation, and the remission rate with medical treatment

Received: 30 January 2023
Accepted: 18 April 2023
Published: 2 May 2023

varies from 20% up to 70% in individual studies. Conversely, radioactive iodine therapy and surgery treatment have a resolution chance of more than 90%.[7–9]

Cancer development in patients with GD is possibly attributed to GD autoimmunity or abnormal host immune system tolerance.[10] However, the mechanisms underlying GD and cancer pathogenesis remain unclear. Previous studies have investigated the incidence of various cancers in patients with GD using a nationwide cohort. In Taiwan, the hazard ratios (HRs) for developing breast and thyroid cancers are 1.5- and 10.4-fold, respectively, in patients with GD. In particular, within the first 3 years of GD diagnosis, the risk of thyroid cancer is 16 times higher in patients with GD than in patients without GD.[11] In a Swedish population-based cohort study of hospitalized patients with GD, the risk of thyroid, parathyroid, mouth, and breast cancers was high within a short period of time, whereas colon cancer, melanoma, and non-Hodgkin's lymphoma had a low risk.[12] Additionally, in previous studies that identified the incidence of thyroid cancer in patients diagnosed with GD, the incidence varied from 2.3% to 21.1%.[13]

Although the medical cost burden of thyroid disease has been increasing over the past decade,[14] there remain no research data investigating the risk of various cancers and death in patients with GD using a large-scale nationwide cohort in South Korea. These epidemiological data can predict the prognosis of patients with GD and will be helpful in future studies on the oncogenesis of autoimmune diseases. Given the disparities in previous studies, this study aimed to evaluate the risks of various cancers, including thyroid cancer, and mortality risk in patients with GD using the data from the Korea National Health Insurance Service (NHIS)–National Sample Cohort (NSC).

Materials and Methods

Data Source

In 1989, the South Korean government launched the NHIS, which contains population insurance, maintains records of personal health information, and provides almost 100% coverage of the total population. In 2014, the NHIS covered 97.2% (n=50,316,384) of the population, and the Medical Aid system covered the remaining 2.8% (n=1,440,762).[15] Formed by the NHIS, the National Health Information Database (NHID), which stores data of more than 50 million people based on records from healthcare providers, is linked to the national databases using unique personal identification numbers. The NHID is a public database on healthcare utilization, health screening, sociodemographic variables, and mortality for the entire population of South Korea.[16]

The NHIS–NSC is a population-based cohort established by the NHIS. The sample size of the NHIS–NSC database is approximately 1 million, including 2% of randomly selected Koreans who have been eligible for at least 1 year as of December 2006. This cohort consists of a nationally representative random sample of 1,020,005 individuals, generated by the NHIS, using a systematic, stratified random sampling method from all 46,605,433 individuals from 2006. This cohort was followed up for 13 years until 2019, unless individuals was disqualified due to death or emigration. To maintain the age structure over time, approximately 9000 newborns have been added to the dataset annually since 2006. The NHIS–NSC data also provide medical records of individuals, including diagnosis codes, prescription details, and health screening results, between 2006 and 2019.[17]

The NHIS–NSC database (NHIS-2022-2-324) was used to obtain information on patients with GD from 2010 to 2019. This study was approved by the Institutional Review Board (IRB) of the Catholic University of Korea (IRB Number: SC22ZASE0159). In this retrospective study, informed consent was not obtained because of the use of a database in which personal identification was removed.

Definition of Patients with GD

GD was defined based on the tenth revision of the International Classification of Diseases (ICD-10) code E05, with patients with GD receiving treatment, including ATDs (propylthiouracil, methimazole, and carbimazole), thyroid surgery (codes P4551–4554), or radioactive iodine ablation (code HD071). ATDs are first-time prescription drugs. Patients who received antithyroid medication for less than 60 days were excluded.

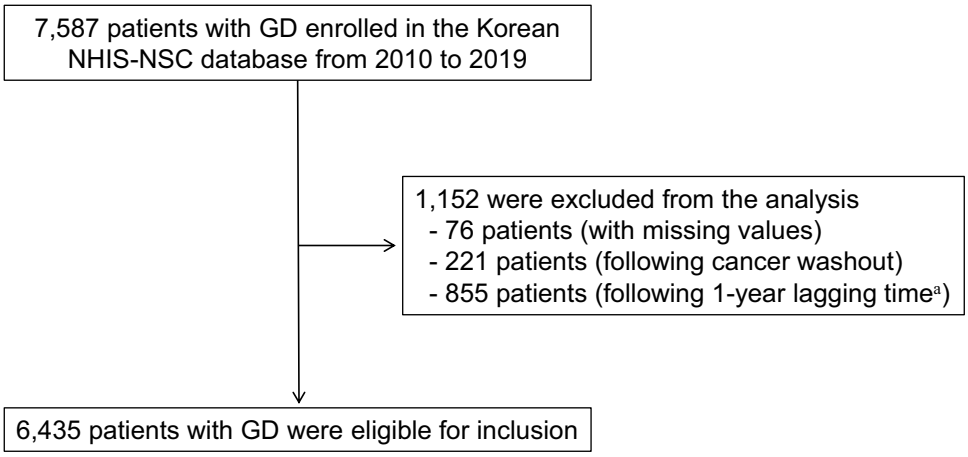

Figure 1 Flow Diagram of the Study Population.
Note: [a]Cancer occurrence or death within the first year of follow-up.
Abbreviations: GD, Graves' disease; NHIS–NSC; National Health Insurance Service–National Sample Cohort.

Study Population

Retrospective cohort data were extracted from 2010 to 2019 based on data collected during the process of claiming healthcare services using the Korean NHIS–NSC data. To exclude individuals with a previous history of cancer, a washout period of 4 years was applied. Moreover, within a 1-year lag time after diagnosis of GD, individuals diagnosed with various cancers or have died were excluded.

According to the NHIS–NSC database, of the 7587 patients diagnosed with GD between 2010 and 2019, 76 patients had missing values (n=7511). Further screening of participants with cancer (221) and those who were within the 1-year lagging period (855), a total of 6435 patients with GD were finally included in our study (Figure 1). To investigate the cancer and mortality risks of GD, the data of patients with GD were compared with those of the non-GD group consisting of 1:5 age- and sex-matched 32,175 individuals. The non-GD group were selected randomly from the NHIS–NSC database between 2010 and 2019.

Outcome Variables

Factors associated with cancer and mortality risks, including household income, residential characteristics, and the presence of metabolic comorbidities were investigated in both the GD and non-GD groups. The comorbidities including diabetes mellitus (DM), hypertension (HTN), and dyslipidemia were defined based on diagnosis via ICD-10 codes and medication prescription. We defined DM as the ICD-10 codes E11–E14 excluding code E10 (type 1 diabetes). The incidence rate (IR) and hazard ratio (HR) for 18 different cancer types on the ICD-10 codes, namely stomach cancer (ICD-10, C16), colorectal cancer (C18–20), liver cancer (C22), pancreatic cancer (C25), lung cancer (C33–34), thyroid cancer (C73), oral cancer (C00–14), esophageal cancer (C15), biliary cancer (C24), laryngeal cancer (C32), renal cancer (C64), bladder cancer (C67), nervous system cancer (C70–72), Hodgkin's disease (C81), lymphoma (C82–86), multiple myeloma (C90), leukemia (C91–95), and skin (C43), were estimated for both groups. The HR for death was calculated by comparing the mortality rate (MR) between the two groups. Adjusted HRs were calculated concerning factors including age, sex, income status, DM, HTN, and dyslipidemia that could affect cancer incidence and death. Sub-analyses of the GD and non-GD groups were performed according to age (0–19-, 20–39-, and ≥40-years-olds) and sex. Breast, corpus, and uterine cancer in females, and prostate cancer in males were excluded because they were classified as sensitive diseases for which detailed data are not presented when analyzing the Korean national sample cohort.

Statistical Analyses

Age, which is a continuous variable, was analyzed using *t*-test and expressed as mean ± standard deviation. The categorical variables were expressed as the number of cases (N) and percentage (%), and differences in categorical

variables between the two groups were analyzed using the chi-squared test. The IRs in both groups were calculated by dividing the incidence of different cancers by the total follow-up period from 2010 to 2019. The MRs of both groups were calculated by dividing the incidence of death by the total follow-up period from 2010 to 2019. The HR and 95% confidence interval (CI) were calculated using the Cox proportional hazard model. Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Sociodemographic Characteristics of the Non-GD and GD Groups

In total, 6435 patients with GD and 32,175 individuals in a 1:5 ratio age- and sex-matched non-GD group were analyzed (Table 1). The mean age of the two groups was 45.26 years. After stratifying by age, the 0–19, 20–39, and ≥40-year-old groups accounted for 5.27%, 32.41%, and 62.32% in the two groups, respectively. The percentage of females was 71.19% in total, which was higher than that of males. Household income (low), residential characteristics (urban), and metabolic comorbidities were analyzed as variables that could influence cancer incidence and mortality. Low household income (18.66% among non-GD group vs 17.89% among GD group), and residential characteristics (46.47% vs 45.35%) of the GD group were not different from those of the non-GD group. The GD group were more likely to suffer from metabolic comorbidities, including DM (5.91% vs 9.37%), HTN (16.44% vs 29.17%), and dyslipidemia (11.77% vs 15.07%).

Cancer Risks of the Patients with GD Compared with Age- and Sex-Matched Non-GD Group

During the observation period, the total numbers of cancer were 164 and 758, and the IRs of cancers in total were 5.60 and 5.18 per 1000 persons in the GD and non-GD groups, respectively (Table 2). After adjusting for age, sex, low

Table 1 Baseline Characteristics of the Non-GD and GD Groups

	Non-GD (n=32,175)	GD (n=6435)
	N (%)	N (%)
Mean age, year	45.26 ± 15.73	45.26 ± 15.74
Age group, year		
<20	1695 (5.27)	339 (5.27)
20–39	10,430 (32.41)	2086 (32.41)
≥40	20,050 (62.32)	4010 (62.32)
Sex		
Male	9270 (28.81)	1854 (28.81)
Female	22,905 (71.19)	4581 (71.19)
Low Income (20%)	6005 (18.66)	1151 (17.89)
Location (Urban)	14,953 (46.47)	2918 (45.35)
Metabolic comorbidity		
DM	1901 (5.91)	603 (9.37)
HTN	5288 (16.44)	1877 (29.17)
DYS	3786 (11.77)	970 (15.07)

Note: Data are presented as mean age ± standard deviation or number (%).
Abbreviations: DM, diabetes mellitus; DYS, dyslipidemia; GD, Graves' disease; HTN, hypertension; N, number.

Table 2 The Cancers Risk of Patients with GD Compared with Age- and Sex-Matched Non-GD Group in Total

Cancer	Group	N	Event	Duration (Person-Years)	IR (per 1000 Persons)	Model 1 HR (95% CI)[a]	Model 2 HR (95% CI)[b]
Thyroid	Non-GD	32175	139	147,802.92	0.94	1 (Ref.)	1 (Ref.)
	GD	6435	44	29,572.66	1.49	1.58 (1.13–2.22)	1.70 (1.20–2.39)
Stomach	Non-GD	32175	80	148,045.75	0.54	1	1
	GD	6435	15	29,672.35	0.51	0.93 (0.54–1.62)	0.91 (0.52–1.59)
Colorectal	Non-GD	32175	92	148,052.84	0.62	1	1
	GD	6435	17	29,655.95	0.57	0.92 (0.55–1.54)	0.88 (0.52–1.49)
Liver	Non-GD	32175	55	148,197.17	0.37	1	1
	GD	6435	8	29,696.83	0.27	0.72 (0.34–1.51)	0.65 (0.31–1.36)
Pancreatic	Non-GD	32175	34	148,220.91	0.23	1	1
	GD	6435	6	29,703.87	0.20	0.87 (0.37–2.08)	0.74 (0.31–1.79)
Lung	Non-GD	32175	68	148,187.46	0.46	1	1
	GD	6435	11	29,701.07	0.37	0.80 (0.42–1.51)	0.88 (0.46–1.67)
Oral	Non-GD	32175	12	148,240.77	0.08	1	1
	GD	6435	5	29,695.6	0.17	2.06 (0.73–5.86)	1.70 (0.59–4.88)
Esophagus	Non-GD	32175	6	148,269.36	0.04	1	1
	GD	6435	2	29,709.39	0.07	1.62 (0.33–8.05)	1.55 (0.31–7.79)
Biliary	Non-GD	32175	22	148,238.88	0.15	1	1
	GD	6435	3	29,705.09	0.10	0.67 (0.20–2.24)	0.64 (0.19–2.16)
Renal	Non-GD	32175	26	148,212.95	0.18	1	1
	GD	6435	5	29,701.89	0.17	0.96 (0.37–2.50)	0.80 (0.30–2.10)
Lymphoma	Non-GD	32175	15	148,251.5	0.10	1	1
	GD	6435	5	29,701.45	0.17	1.65 (0.60–4.54)	1.47 (0.53–4.09)
Multiple myeloma	Non-GD	32175	5	148,262.95	0.03	1	1
	GD	6435	3	29,706.04	0.10	2.96 (0.71–12.40)	2.34 (0.54–10.14)
Leukemia	Non-GD	32175	15	148,252.37	0.10	1	1
	GD	6435	2	29,710.02	0.07	0.66 (0.15–2.90)	0.60 (0.14–2.68)
Skin	Non-GD	32175	15	148,247.2	0.10	1	1
	GD	6435	7	29,697.31	0.24	2.32 (0.95–5.70)	2.33 (0.94–5.80)
Cancers in total[c]	Non-GD	32175	758	146,362.65	5.18	1	1
	GD	6435	164	29,259.7	5.60	1.08 (0.91–1.28)	1.07 (0.91–1.27)

Notes: [a]Hazard ratios were calculated after adjusting for age, sex, income, and location; [b]hazard ratios were calculated after adjusting for age, sex, income, location, DM, HTN, and DYS; [c]eighteen site-specific cancers considered on the ICD-10 codes.

Abbreviations: CI, confidence interval; DM, diabetes mellitus; DYS, dyslipidemia; GD, Graves' disease; HR, hazard ratio; HTN, hypertension; IR, incidence rate; N, number.

household income, residence, and metabolic comorbidities, the HR of the GD group for cancers in total was 1.07 (95% CI, 0.91–1.27), showing no difference when compared to the non-GD group. In addition, IR and HR for cancers in total were analyzed by sex. In males, the IRs were 5.13 and 5.15 per 1000 persons in the GD and non-GD groups, respectively, and the adjusted HR was 0.96 (95% CI, 0.69–1.34) (Table 3). In females, the IRs were 5.79 and 5.19 per 1000 persons in the GD and non-GD groups, respectively, and the adjusted HR was 1.12 (95% CI, 0.92–1.37) (Table 4).

Each of the 18 subdivided cancers was analyzed. After adjusting for age, sex, low household income, residence, and metabolic comorbidities, the HR of the GD group for thyroid cancer was 1.70 (95% CI, 1.20–2.39), showing a difference when compared to the non-GD group (Table 2). In males, after adjusting for age, sex, low household income, and residence, the HR of the GD group

Table 3 The Cancers Risk of Patients with GD Compared with Age- and Sex-Matched Non-GD Group in Male

Cancer	Group	N	Event	Duration (Person-Years)	IR (per 1000 Persons)	Model 1 HR (95% CI)[a]	Model 2 HR (95% CI)[b]
Thyroid	Non-GD	9270	10	41,376.53	0.24	1 (Ref.)	1 (Ref.)
	GD	1854	6	8275.53	0.73	2.98 (1.08–8.19)	2.69 (0.95–7.68)
Stomach	Non-GD	9270	39	41,314.66	0.94	1	1
	GD	1854	5	8282.41	0.60	0.63 (0.25–1.60)	0.59 (0.23–1.51)
Colorectal	Non-GD	9270	34	41,317.69	0.82	1	1
	GD	1854	5	8288.29	0.60	0.72 (0.28–1.84)	0.69 (0.27–1.77)
Liver	Non-GD	9270	27	41,351.07	0.65	1	1
	GD	1854	4	8291.96	0.48	0.74 (0.26–2.11)	0.70 (0.24–2.00)
Pancreatic	Non-GD	9270	11	41,386.66	0.27	1	1
	GD	1854	3	8296.44	0.36	1.35 (0.38–4.83)	1.07 (0.29–3.95)
Lung	Non-GD	9270	39	41,366.2	0.94	1	1
	GD	1854	7	8289.15	0.84	0.88 (0.39–1.97)	0.96 (0.43–2.16)
Oral	Non-GD	9270	7	41,387.16	0.17	1	1
	GD	1854	3	8288.43	0.36	2.05 (0.53–7.94)	1.52 (0.38–6.03)
Esophagus	Non-GD	9270	5	41,398.54	0.12	1	1
	GD	1854	1	8297.03	0.12	0.96 (0.11–8.19)	0.99 (0.12–8.57)
Biliary	Non-GD	9270	7	41,386.32	0.17	1	1
	GD	1854	1	8295.99	0.12	0.71 (0.09–5.77)	0.76 (0.09–6.24)
Renal	Non-GD	9270	9	41,387.95	0.22	1	1
	GD	1854	1	8298.85	0.12	0.57 (0.07–4.50)	0.51 (0.06–4.12)
Lymphoma	Non-GD	9270	6	41,397.37	0.14	1	1
	GD	1854	3	8294.79	0.36	2.47 (0.61–9.87)	2.13 (0.52–8.67)
Multiple myeloma	Non-GD	9270	1	41,402.34	0.02	1	1
	GD	1854	1	8295.32	0.12	4.70 (0.29–75.17)	4.16 (0.26–66.61)
Leukemia	Non-GD	9270	2	41,400.78	0.05	1	1
	GD	1854	1	8296.62	0.12	2.33 (0.21–25.74)	2.04 (0.17–24.10)
Skin	Non-GD	9270	3	41,395.8	0.07	1	1
	GD	1854	3	8292.46	0.36	4.86 (0.98–24.06)	5.31 (1.05–26.82)
Cancers in total[c]	Non-GD	9270	211	40,978.9	5.15	1	1
	GD	1854	42	8190.13	5.13	0.98 (0.71–1.37)	0.96 (0.69–1.34)

Notes: [a]Hazard ratios were calculated after adjusting for age, sex, income, and location; [b]hazard ratios were calculated after adjusting for age, sex, income, location, DM, HTN, and DYS; [c]eighteen site-specific cancers considered on the ICD-10 codes.

Abbreviations: CI, confidence interval; DM, diabetes mellitus; DYS, dyslipidemia; GD, Graves' disease; HR, hazard ratio; HTN, hypertension; IR, incidence rate; N, number.

for thyroid cancer was 2.98 (95% CI, 1.08–8.19) (Table 3). In females, the adjusted HR of the GD group for thyroid cancer was 1.60 (95% CI, 1.11–2.31) (Table 4). The HR for skin cancer in males showed a remarkable result in the GD group (adjusted HR=5.31; 95% CI, 1.05–26.82). No other types of cancer showed notable results in the GD group (Tables 2–4).

Thyroid Cancer Risks of Patients with GD According to Age

The IR and HR for thyroid cancer were analyzed according to age (0–19, 20–39, and ≥40 year-olds) (Table 5). At the age of 0–19 years, there was no thyroid cancer in the GD group during the observation period. In total, the adjusted HR of the GD group at the age of 20–39 years was 2.05 (95% CI, 1.20–3.51), showing a difference when compared to the non-GD group. However, the adjusted HR of the GD group aged ≥40 years was 1.44 (95% CI, 0.91–2.26), showing no difference

Table 4 The Cancers Risk of Patients with GD Compared with Age- and Sex-Matched Non-GD Group in Female

Cancer	Group	N	Event	Duration (Person-Years)	IR (per 1000 Persons)	Model 1 HR (95% CI)[a]	Model 2 HR (95% CI)[b]
Thyroid	Non-GD GD	22905 4581	129 38	106,426.39 21,297.13	1.21 1.78	1 (Ref.) 1.47 (1.02–2.11)	1 (Ref.) 1.60 (1.11–2.31)
Stomach	Non-GD GD	22905 4581	547 122	105,383.75 21,069.57	5.19 5.79	1 1.21 (0.61–2.42)	1 1.24 (0.62–2.50)
Colorectal	Non-GD GD	22905 4581	41 10	106,731.1 21,389.94	0.38 0.47	1 1.03 (0.55–1.92)	1 1.01 (0.54–1.88)
Liver	Non-GD GD	22905 4581	58 12	106,735.15 21,367.67	0.54 0.56	1 0.70 (0.25–2.00)	1 0.59 (0.21–1.70)
Pancreatic	Non-GD GD	22905 4581	28 4	106,846.1 21,404.87	0.26 0.19	1 0.64 (0.19–2.13)	1 0.55 (0.17–1.86)
Lung	Non-GD GD	22905 4581	23 3	106,834.25 21,407.43	0.22 0.14	1 0.68 (0.24–1.93)	1 0.75 (0.26–2.16)
Oral	Non-GD GD	22905 4581	5 2	106,853.61 21,407.17	0.05 0.09	1 1.94 (0.38–10.01)	1 1.65 (0.31–8.70)
Esophagus	Non-GD GD	22905 4581	1 1	106,870.82 21,412.36	0.009 0.05	1 4.98 (0.31–79.56)	1 3.89 (0.23–64.83)
Biliary	Non-GD GD	22905 4581	15 2	106,852.56 21,409.1	0.14 0.09	1 0.65 (0.15–2.86)	1 0.59 (0.13–2.60)
Renal	Non-GD GD	22905 4581	17 4	106,825 21,403.04	0.16 0.19	1 1.17 (0.40–3.49)	1 0.95 (0.32–2.86)
Lymphoma	Non-GD GD	22905 4581	9 2	106,854.13 21,406.65	0.08 0.09	1 1.1 (0.24–5.09)	1 0.98 (0.21–4.64)
Multiple myeloma	Non-GD GD	22905 4581	4 2	106,860.61 21,410.72	0.04 0.09	1 2.42 (0.44–13.20)	1 1.88 (0.33–10.79)
Leukemia	Non-GD GD	22905 4581	13 1	106,851.59 21,413.39	0.12 0.05	1 0.38 (0.05–2.93)	1 0.36 (0.05–2.80)
Skin	Non-GD GD	22905 4581	12 4	106,851.41 21,404.85	0.11 0.19	1 1.67 (0.54–5.19)	1 1.62 (0.51–5.12)
Cancers in total[c]	Non-GD GD	22905 4581	547 122	105,383.75 21,069.57	5.19 5.79	1 1.11 (0.92–1.36)	1 1.12 (0.92–1.37)

Notes: [a]Hazard ratios were calculated after adjusting for age, sex, income, and location; [b]hazard ratios were calculated after adjusting for age, sex, income, location, DM, HTN, and DYS; [c]eighteen site-specific cancers considered on the ICD-10 codes.

Abbreviations: CI, confidence interval; DM, diabetes mellitus; DYS, dyslipidemia; GD, Graves' disease; HR, hazard ratio; HTN, hypertension; IR, incidence rate; N, number.

when compared to the non-GD group. When subdivided by sex, the thyroid cancer risk of the GD group among males aged 20–39 years was higher than that of the non-GD group (adjusted HR=7.00; 95% CI, 1.48–33.12). However, in males aged ≥40 years, the adjusted HR was 0.67 (95% CI, 0.08–5.50).

Mortality Risks of Patients with GD Compared with Age- and Sex-Matched Non-GD Group

During the observation period, 116 deaths occurred in the GD group (Table 6). Most of the deaths were observed in the aged ≥40 years (94.8%), and more than half were females (59.4%). In total, the MRs of the GD and non-GD

Table 5 The Thyroid Cancer Risk of Patients with GD According to Age Groups

Age Group, Year	Group	N	Thyroid Cancer	Duration (Person-Years)	IR (per 1000 Persons)	HR (95% CI)[a]
Total						
0–19	Non-GD	1695	1	8532.75	0.12	1 (Ref.)
	GD	339	0	1704.41	0	NC
20–39	Non-GD	10430	50	50,327.4	0.99	1
	GD	2086	20	10,036.02	1.99	2.05 (1.20–3.51)
≥40	Non-GD	20050	88	88,942.77	0.99	1
	GD	4010	24	17,832.23	1.35	1.44 (0.91–2.26)
Male						
0–19	Non-GD	440	0	2182.04	0	1
	GD	88	0	437.29	0	NC
20–39	Non-GD	2975	3	13,720.48	0.22	1
	GD	595	5	2723.38	1.84	7.00 (1.48–33.12)
≥40	Non-GD	5855	7	25,474.01	0.28	1
	GD	1171	1	5114.85	0.20	0.67 (0.08–5.50)
Female						
0–19	Non-GD	1255	1	6350.7	0.16	1
	GD	251	0	1267.12	0	NC
20–39	Non-GD	7455	47	36,606.93	1.28	1
	GD	1491	15	7312.63	2.05	1.74 (0.96–3.13)
≥40	Non-GD	14195	81	63,468.76	1.28	1
	GD	2839	23	12,717.38	1.81	1.51 (0.95–2.41)

Note: [a]Hazard ratios were calculated after adjusting for age, sex, income, location, DM, HTN, and DYS.
Abbreviations: CI, confidence interval; DM, diabetes mellitus; DYS, dyslipidemia; GD, Graves' disease; HR, hazard ratio; HTN, hypertension; IR, incidence rate; N, number; NC, noncount.

Table 6 The Mortality Risk of Patients with GD Compared with Age- and Sex-Matched Non-GD Group

	Group	N	Death	Duration (Person-Years)	MR (per 1000 Persons)	HR (95% CI)[a]
Death	Non-GD	32175	631	148,276.08	4.26	1 (Ref.)
	GD	6435	116	29,712.45	3.90	0.86 (0.70–1.05)
Death by age groups						
0–19	Non-GD	1695	1	8534.32	0.12	1
	GD	339	1	1704.41	0.59	5.48 (0.34–87.62)
20–39	Non-GD	10430	21	50,482.9	0.42	1
	GD	2086	5	10,098.97	0.50	1.28 (0.47–3.46)
≥40	Non-GD	20050	609	89,258.87	6.82	1
	GD	4010	110	17,909.07	6.14	0.84 (0.68–1.03)

Note: [a]Hazard ratios were calculated after adjusting for age, sex, income, location, DM, HTN, and DYS.
Abbreviations: CI, confidence interval; DM, Diabetes mellitus; DYS, dyslipidemia; GD, Graves' disease; HR, hazard ratio; HTN, hypertension; MR, mortality rate.

groups were 3.90 and 4.26 per 1000 persons, respectively. However, there was no difference (adjusted HR=0.86; 95% CI, 0.70–1.05) between the two groups. After stratification by age, the MR of the GD and non-GD groups in aged ≥40 years were 6.14 and 6.82 per 1000 persons, with no difference between the two groups (adjusted HR=0.84; 95% CI, 0.68–1.03).

Discussion

In this study, we investigated the cancer and mortality risks in patients with GD during a 10-year observation period in Korea. Patients with GD had a higher risk of developing thyroid cancer than the non-GD group. Concomitantly, there was a notable risk of thyroid cancer in young males with GD aged 20–39 years. Few significant results were noted for other types of cancer. During the observation period, patients with GD did not show higher MR than that in the non-GD group.

GD can occur at any age, but its peak age is at 40–60 years. The prevalence of GD is higher in females than in males. In this study, more than half of the patients with GD were females, and patients aged ≥40 years accounted for 70% of all patients, similar to the epidemiology of GD.[1,18] The risks of HTN, DM, and dyslipidemia increase in thyroid diseases, including GD.[19–22] We showed that the rates of these metabolic diseases were higher in the GD than in the non-GD group. Moreover, they can increase the risks of cancers, including thyroid cancer;[23,24] therefore, HTN, DM, and dyslipidemia were selected as confounding factors and adjusted during statistical analyses.

A national or population-based cohort study of thyroid disorders and associated cancer risk has been conducted in several countries. In Denmark, there was an association between patients with benign thyroid disease and cancers of kidney, bladder, and thyroid.[25] Hyperthyroidism, including GD, was positively associated with thyroid cancer risk in a Danish nationwide study.[26] In a US population-based case study, the risk of papillary thyroid cancer increased in females with TSH levels below the normal range.[27] In a Taiwanese national cohort study, the overall cancer and thyroid cancer risks increased in patients with hyperthyroidism. Furthermore, the longer the duration of hyperthyroidism, the higher the risk of cancer.[28] In another study, there were high risks of thyroid and breast cancers in patients with GD than in patients without GD.[11] In an analysis of Korean national data, the incidence of thyroid diseases, such as thyroid nodules, hypothyroidism, hyperthyroidism, and thyroid cancer, increased and peaked in 2012, decreased until 2015, and remained stable thereafter.[5,29] Thyroid cancer mortality in Korea increased from the 1980s to 2004 and then decreased continuously until 2015.[30] In Korea, the prevalence of thyroid cancer in patients with GD was 3.3% based on a prospective single-center study,[31] and 1.7% for those who underwent thyroidectomy according a recent multicenter retrospective study.[32]

Although sex-specific cancers were excluded from this study, a significant association between thyroid disorders and breast cancer using Taiwanese national population data was found in females with hyperthyroidism aged <55 years and in females with hypothyroidism.[33] A meta-analysis reported that hyperthyroidism, thyroid cancer, and autoimmune thyroiditis increased risk of breast cancer; conversely, hypothyroidism lowered the risk of breast cancer.[34] High thyroid hormone levels have an estrogenic effect, which can promote breast cancer through breast cell proliferation.[35,36]

In general, there are hypotheses regarding the association between thyroid dysfunction and carcinogenesis that causes subsequent types of cancer. The binding of TRAb to TSH receptors may promote tumorigenesis and angiogenesis. TRAb upregulates various growth factors and enhances tumor invasiveness in the thyroid gland.[37] The autoimmunity of GD affects the risk of cancer, or abnormal host immune system resistance further increases the risk of cancer.[10] However, the pathogenesis remains complex and uncertain.

There is a sex disparity in the occurrence of thyroid cancer, which is approximately three times more common in females than in males.[38] Few studies have examined the association between thyroid diseases and thyroid cancer in males, and a US population-based cohort study revealed a high risk of thyroid cancer in males with benign thyroid diseases.[39] In this study, male patients with GD, especially young adult males aged 20–39 years, had a higher risk of thyroid cancer than non-GD group. The underlying mechanisms responsible for an increased ratio of thyroid cancers in the younger male GD group are not well understood; however, much attention has been focused on genetic differences and early-onset autoimmune thyroid disease (AITD) may be more strongly affected by genetic factors than late-onset AITD.[40–42]

There are studies on the increase in mortality associated with thyroid diseases. In an 11-year observational cohort study of inpatients with GD in Denmark, the overall MR of patients with GD increased, especially due to cardiovascular diseases.[43] In an analysis of cause-specific mortality in patients with hyperthyroidism and hypothyroidism, the MR from breast cancer increased in females with hyperthyroidism aged >60 years, and there was also an increased risk of death

from ovarian cancer, albeit in a small number of cases.[44] In addition, there was an increase in the MR caused by suicide in patients with thyroid diseases, including Hashimoto's thyroiditis and GD.[45,46] In this study, although the risk of thyroid cancer was higher in patients with GD, the MR of patients with GD was not different from that of the non-GD group. Since it was a short observation period to evaluate mortality, a long-term study is required in the future, and an analysis of the main causes of death in patients with GD is also needed.

This study has some limitations. First, the clinical information was insufficient because the study cohort was a retrospective cohort based on the NHID. Over- or underdiagnoses were unavoidable because the diagnosis should be based on ICD codes. As this was a registry-based study, there were no data on the causes of death. Second, it was not possible to limit all disturbance factors affecting cancer incidence and death. Age and sex were matched, and household income, residential characteristics, and metabolic comorbidities were adjusted. However, other confounding factors that were not discussed in this study may have been missed. Third, sensitive cancers in females and males, such as breast, corpus, and prostate cancers, were excluded. Based on the significant results of breast cancer in previous studies, future studies including sensitive cancers are required to investigate their relevance in Korea. In addition, the differences in cancer risk according to the treatment of Graves' disease were not analyzed. Finally, the biological mechanism of cancer development in GD could not be determined in this study. These limitations must be addressed to understand the etiopathogenesis, morbidity, and mortality in patients with GD.

Nevertheless, this is the first large-scale nationwide population-based retrospective cohort study to investigate cancer and mortality risks associated with GD based on a national sample cohort from 2010 to 2019. This can represent the national status because long-term follow-up with a maximum of 10 years was performed using a 2% sample cohort representing the entire population of Korea. In conclusion, we report an increased risk of thyroid cancer in patients with GD, particularly in young males aged 20–39 years. No association was observed in terms of the occurrence of other types of cancer in patients with GD; however, further studies are required to determine the mechanism underlying this result. In addition, based on this study, large-scale long-term studies using total national population data are required to understand the long-term complications and prognosis of GD.

Data Sharing Statement

All files for the analysis of the present study are available at the national health insurance sharing service webpage (https://nhiss.nhis.or.kr).

Ethical Statement

This study was approved by the Institutional Review Board (IRB) of the Catholic University of Korea (IRB approval Number: SC22ZASE0159).

Acknowledgments

The authors wish to acknowledge the financial support of the Institute of Clinical Medicine Research at Yeouido St. Mary's Hospital, Catholic University of Korea.

Funding

This research was supported by a grant from the Institute of Clinical Medicine Research at Yeouido St. Mary's Hospital, Catholic University of Korea.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune thyroid disorders. *Autoimmun Rev*. 2015;14(2):174–180. doi:10.1016/j.autrev.2014.10.016
2. Smith TJ, Hegedüs L. Graves' disease. *N Engl J Med*. 2016;375(16):1552–1565. doi:10.1056/NEJMra1510030

3. Davies TF, Andersen S, Latif R, et al. Graves' disease. *Nat Rev Dis Primers*. 2020;6(1):52. doi:10.1038/s41572-020-0184-y
4. Hanley P, Lord K, Bauer AJ. Thyroid disorders in children and adolescents: a review. *JAMA Pediatr*. 2016;170(10):1008–1019. doi:10.1001/jamapediatrics.2016.0486
5. Kwon H, Jung J, Han KD, et al. Prevalence and annual incidence of thyroid disease in Korea from 2006 to 2015: a nationwide population-based cohort study. *Endocrinol Metab*. 2018;33(2):260–267. doi:10.3803/EnM.2018.33.2.260
6. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *J Clin Endocrinol Metab*. 2014;99(3):923–931. doi:10.1210/jc.2013-2409
7. Mohlin E, Filipsson Nyström H, Eliasson M. Long-term prognosis after medical treatment of Graves' disease in a northern Swedish population 2000–2010. *Eur J Endocrinol*. 2014;170(3):419–427. doi:10.1530/EJE-13-0811
8. Brito JP, Payne S, Singh Ospina N, et al. Patterns of use, efficacy, and safety of treatment options for patients with Graves' disease: a nationwide population-based study. *Thyroid*. 2020;30(3):357–364. doi:10.1089/thy.2019.0132
9. Burch HB, Cooper DS. Antithyroid drug therapy: 70 years later. *Eur J Endocrinol*. 2018;179(5):R261–R274. doi:10.1530/EJE-18-0678
10. Ferrari SM, Fallahi P, Elia G, et al. Thyroid autoimmune disorders and cancer. *Semin Cancer Biol*. 2020;64:135–146. doi:10.1016/j.semcancer.2019.05.019
11. Chen Y-K, Lin C-L, Chang Y-J, et al. Cancer risk in patients with Graves' disease: a nationwide cohort study. *Thyroid*. 2013;23(7):879–884. doi:10.1089/thy.2012.0568
12. Shu X, Ji J, Li X, Sundquist J, Sundquist K, Hemminki K. Cancer risk in patients hospitalised for Graves' disease: a population-based cohort study in Sweden. *Br J Cancer*. 2010;102(9):1397–1399. doi:10.1038/sj.bjc.6605624
13. Kwon H, Moon B-I. Prognosis of papillary thyroid cancer in patients with Graves' disease: a propensity score-matched analysis. *World J Surg Oncol*. 2020;18(1):266. doi:10.1186/s12957-020-02044-x
14. Hyun K-R, Kang S, Lee S. Cost-of-illness trends associated with thyroid disease in Korea. *Endocrinol Metab*. 2014;29(3):257–269. doi:10.3803/EnM.2014.29.3.257
15. Song SO, Jung CH, Song YD, et al. Background and data configuration process of a nationwide population-based study using the Korean national health insurance system. *Diabetes Metab J*. 2014;38(5):395–403. doi:10.4093/dmj.2014.38.5.395
16. Sang CS, Kim YY, Khang YH, et al. Data resource profile: the national health information database of the National Health Insurance Service in South Korea. *Int J Epidemiol*. 2017;46(3):799–800. doi:10.1093/ije/dyw253
17. Lee J, Lee JS, Park S-H, Shin SA, Kim K. Cohort profile: the national health insurance service–national sample cohort (NHIS-NSC), South Korea. *Int J Epidemiol*. 2017;46(2):e15. doi:10.1093/ije/dyv319
18. Tunbridge WM, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol*. 1977;7(6):481–493. doi:10.1111/j.1365-2265.1977.tb01340.x
19. Berta E, Lengyel I, Halmi S, et al. Hypertension in thyroid disorders. *Front Endocrinol*. 2019;10:482. doi:10.3389/fendo.2019.00482
20. Wang C. The relationship between type 2 diabetes mellitus and related thyroid diseases. *J Diabetes Res*. 2013;2013:390534. doi:10.1155/2013/390534
21. Peppa M, Betsi G, Dimitriadis G. Lipid abnormalities and cardiometabolic risk in patients with overt and subclinical thyroid disease. *J Lipids*. 2011;2011:575840. doi:10.1155/2011/575840
22. Brandt F, Thvilum M, Almind D, et al. Morbidity before and after the diagnosis of hyperthyroidism: a nationwide register-based study. *PLoS One*. 2013;8(6):e66711. doi:10.1371/journal.pone.0066711
23. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care*. 2012;35(11):2402–2411. doi:10.2337/dc12-0336
24. Park J-H, Choi M, Kim J-H, et al. Metabolic syndrome and the risk of thyroid cancer: a nationwide population-based cohort study. *Thyroid*. 2020;30(10):1496–1504. doi:10.1089/thy.2019.0699
25. Mellemgaard A, From G, Jørgensen T, Johansen C, Olsen JH, Perrild H. Cancer risk in individuals with benign thyroid disorders. *Thyroid*. 1998;8(9):751–754. doi:10.1089/thy.1998.8.751
26. Kitahara CM, Rmendiné FD, Jørgensen JOL, Cronin-Fenton D, Sørensen HT. Benign thyroid diseases and risk of thyroid cancer: a nationwide cohort study. *J Clin Endocrinol Metab*. 2018;103(6):2216–2224. doi:10.1210/jc.2017-02599
27. Huang H, Rusiecki J, Zhao N, et al. Thyroid-stimulating hormone, thyroid hormones, and risk of papillary thyroid cancer: a nested case-control study. *Cancer Epidemiol Biomarkers Prev*. 2017;26(8):1209–1218. doi:10.1158/1055-9965.EPI-16-0845
28. Yeh N-C, Chou C-W, Weng S-F, et al. Hyperthyroidism and thyroid cancer risk: a population-based cohort study. *Exp Clin Endocrinol Diabetes*. 2013;121(7):402–406. doi:10.1055/s-0033-1341474
29. Choi YM, Lee J, Kwak MK, et al. Recent changes in the incidence of thyroid cancer in Korea between 2005 and 2018: analysis of Korean National Data. *Endocrinol Metab*. 2022;37(5):791–799. doi:10.3803/EnM.2022.1533
30. Choi YM, Kim WG, Kwon H, et al. Changes in standardized mortality rates from thyroid cancer in Korea between 1985 and 2015: analysis of Korean national data. *Cancer*. 2017;123(24):4808–4814. doi:10.1002/cncr.30943
31. Kim WB, Han SM, Kim TY, et al. Ultrasonographic screening for detection of thyroid cancer in patients with Graves' disease. *Clin Endocrinol*. 2004;60(6):719–725. doi:10.1111/j.1365-2265.2004.02043.x
32. Yoon JH, Jin M, Kim M, et al. Clinical characteristics and prognosis of coexisting thyroid cancer in patients with Graves' disease: a retrospective multicenter study. *Endocrinol Metab*. 2021;36(6):1268–1276. doi:10.3803/EnM.2021.1227
33. Weng C-H, Chen Y-H, Lin C-H, Luo X, Lin T-H. Thyroid disorders and breast cancer risk in Asian population: a nationwide population-based case–control study in Taiwan. *BMJ Open*. 2018;8(3):e020194. doi:10.1136/bmjopen-2017-020194
34. Chen S, Wu F, Hai R, et al. Thyroid disease is associated with an increased risk of breast cancer: a systematic review and meta-analysis. *Gland Surg*. 2021;10(1):336–346. doi:10.21037/gs-20-878
35. Dinda S, Sanchez A, Moudgil V. Estrogen-like effects of thyroid hormone on the regulation of tumor suppressor proteins, p53 and retinoblastoma, in breast cancer cells. *Oncogene*. 2002;21(5):761–768. doi:10.1038/sj.onc.1205136
36. Conde I, Paniagua R, Zamora J, et al. Influence of thyroid hormone receptors on breast cancer cell proliferation. *Ann Oncol*. 2006;17(1):60–64. doi:10.1093/annonc/mdj040

37. Staniforth JUL, Erdirimanne S, Eslick GD. Thyroid carcinoma in Graves' disease: a meta-analysis. *Int J Surg*. 2016;27:118–125. doi:10.1016/j.ijsu.2015.11.027
38. Rahbari R, Zhang L, Kebebew E. Thyroid cancer gender disparity. *Future Oncol*. 2010;6(11):1771–1779. doi:10.2217/fon.10.127
39. Balasubramaniam S, Ron E, Gridley G, Schneider AB, Brenner AV. Association between benign thyroid and endocrine disorders and subsequent risk of thyroid cancer among 4.5 million US male veterans. *J Clin Endocrinol Metab*. 2012;97(8):2661–2669. doi:10.1210/jc.2011-2996
40. Webb R, Kelly JA, Somers EC, et al. Early disease onset is predicted by a higher genetic risk for lupus and is associated with a more severe phenotype in lupus patients. *Ann Rheum Dis*. 2011;70(1):151–156. doi:10.1136/ard.2010.141697
41. Dai R, Ahmed SA. Sexual dimorphism of miRNA expression: a new perspective in understanding the sex bias of autoimmune diseases. *Ther Clin Risk Manag*. 2014;10:151–163. doi:10.2147/TCRM.S33517
42. Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. *Hum Reprod Update*. 2005;11(4):411–423. doi:10.1093/humupd/dmi008
43. Brandt F, Thvilum M, Almind D, et al. Graves' disease and toxic nodular goiter are both associated with increased mortality but differ with respect to the cause of death: a Danish population-based register study. *Thyroid*. 2013;23(4):408–413. doi:10.1089/thy.2012.0500
44. Journy NMY, Bernier M-O, Doody MM, Alexander BH, Linet MS, Kitahara CM. Hyperthyroidism, hypothyroidism, and cause-specific mortality in a large cohort of women. *Thyroid*. 2017;27(8):1001–1010. doi:10.1089/thy.2017.0063
45. Ferløv-Schwensen C, Brix TH, Hegedüs L. Death by suicide in Graves' disease and Graves' orbitopathy: a nationwide Danish register study. *Thyroid*. 2017;27(12):1475–1480. doi:10.1089/thy.2017.0365
46. Heiberg Brix T, Ferløv-Schwensen C, Thvilum M, Hegedüs L. Death by unnatural causes, mainly suicide, is increased in patients with Hashimoto's thyroiditis. A nationwide Danish register study. *Endocrine*. 2019;65(3):616–622. doi:10.1007/s12020-019-01946-5