Thyroid

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Association between eight autoimmune diseases and thyroid cancer: A Nationwide Cohort Study

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ABSTRACT

Background: It has often been reported that thyroid-specific autoimmune diseases, such as Hashimoto's thyroiditis and Graves' disease, could increase the risk of thyroid cancer, but the association between other autoimmune diseases beyond thyroid and thyroid cancer has not been well investigated. This study aimed to examine the risk of thyroid cancer in patients with 8 autoimmune diseases compared with those without autoimmune diseases.

Methods: This nationwide retrospective matched cohort study was conducted to investigate the relationship of 8 autoimmune diseases (Hashimoto's thyroiditis, Graves' disease, type 1 diabetes mellitus, Sjogren's disease, inflammatory bowel disease, vitiligo, systemic lupus erythematosus, rheumatoid arthritis) with the risk of incident thyroid cancer using the National Health Insurance Service- National Sample Cohort. The Cox-proportional hazard model was used to estimate the adjusted hazard ratio (HR) and 95% confidence intervals (95% CI) for thyroid cancer in relation to each of autoimmune disease compared with control group without autoimmune disease.

Results: During the average follow-up of 9.49 years, 138 thyroid cancer cases were newly developed in control group and 268 cases were occurred in group with 8 autoimmune diseases. For all of study participants, the risk of thyroid cancer was significantly increased in patients with Hashimoto's thyroiditis (HR=2.10 [1.57 – 2.81]), Graves' disease (HR=2.67 [1.99 – 3.62]), inflammatory bowel disease (HR=2.06 [1.50 – 2.83]), vitiligo (HR=1.71 [1.13 – 2.59]), rheumatoid arthritis (HR=1.76 [1.07 – 2.90]), and total of 8 autoimmune diseases (HR=1.97 [1.60 – 2.42]) compared with control group without autoimmune diseases. When autoimmune diseases were divided into three types, thyroid-specific autoimmune diseases (HR=2.37 [1.85 – 3.03]) showed the strongest and significant association with thyroid cancer, followed by local autoimmune diseases (HR=1.83 [1.41 – 2.38]), and systemic autoimmune diseases (HR=1.77 [1.14 – 2.74]).

Conclusions: Specific autoimmune diseases – especially for thyroid specific autoimmune disease, vitiligo, inflammatory bowel disease and rheumatoid arthritis – were associated with increased risk for thyroid cancer.

Key words: Autoimmune diseases, Hashimoto's thyroiditis, Graves' disease, Inflammatory bowel disease, Vitiligo, Thyroid cancer

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INTRODUCTION

Autoimmune disease is a condition arising from abnormal immune response to own tissues of body due to dysregulation of immune system. Accumulating evidence has indicated that chronic inflammation is closely associated with autoimmune diseases including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and type 1 diabetes mellitus (type1 DM) [1-3]. The causative relationship between chronic inflammation and cancer has been well delineated since 1863 [4]. Thus, chronic inflammation subsequent to autoimmune disease arouses the interest on the association between autoimmune disease and cancer.

Thyroid cancer is the most common malignancy of endocrine system, presenting a gradual increase in incidence rate from high-income countries to some middle-income countries [5]. In particular, Korea is of the highest incidence rate of thyroid cancer (45 per 100,000) in world [5]. Thyroid gland is predisposed to autoimmune diseases such as Graves' disease and Hashimoto thyroiditis, affecting 2-5 % of population [6-8]. Meta-analyses and observational studies have shown that the risk of thyroid cancer increased in patients with several autoimmune diseases such as type1 DM [9], rheumatoid arthritis [10], Hashimoto thyroiditis [11], SLE [12,13], Sjogren's disease [14], IBD [15], and vitiligo [16]. Therefore, it seems plausible that the presence of autoimmune disease has a potential effect on the development of thyroid cancer.

However, epidemiological evidence is still controversial for the effect of autoimmune disease on the risk of thyroid cancer. In a recent cohort study of 478,753 participants from UK Biobank, despite significant association between immune-mediated diseases and increased risk of organ-specific cancer, autoimmune disease was not associated with the risk of thyroid cancer [17]. Additionally, there is ongoing debate whether the presence of autoimmune disease per se increases the risk of thyroid cancer [18].

To identify the effect of autoimmune diseases on the risk of thyroid cancer, we comprehensively investigated the association between thyroid cancer and 8 autoimmune diseases. Therefore, using large-scale cohort database representing entire Korean population and over 40,000 autoimmune disease patients, we matched general population

to patients with autoimmune diseases to examine the risk of thyroid cancer in patients with 8 autoimmune diseases compared with those without 8 autoimmune diseases.

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METHODS

Study population

A nationwide retrospective matched cohort study was constructed using the National Health Insurance Service- National Sample Cohort (NHIS-NSC) database. All Korean citizens are obligated to join the National Health Insurance, and if a Korean receives a prescription or treatment covered by medical insurance, all medical records will be recorded in the National Health Insurance database. The National Health Insurance Service-National Sample Cohort (NHIS-NSC) database includes information about health insurance qualifications, history of hospital visit, diagnosis, treatment, and health check-up examination results. from 2002 to 2019 (for 18 years) for 1 million people, which were collected via stratified random sampling based on sex, age, income level, and area [19,20].

The NHIS-NSC database was provided data without personal identification to researchers who want to conduct medical research through a remote access system. The cause of death data from Statistics Korea are also linked to the NHIS-NSC database. The last follow-up date was December 31, 2019. This study was reviewed and approved by Institute review board of Kyung Hee University (IRB number: KHSIRB-22-168).

Classification and definition of autoimmune disease

We could not cover all types of autoimmune diseases in this study, because there are too many different types of autoimmune diseases. Therefore, we selected 8 autoimmune diseases, which were reported to be closely associated with thyroid cancer or thyroid disease through a review of the previous studies [9-16]. In addition, it has been reported that these eight autoimmune diseases share genetic loci with similar functions as well as epidemiological relevance [21].

Thereafter, autoimmune diseases are classified into thyroid-specific autoimmune disease (Hashimoto's thyroiditis, Graves' disease), local autoimmune disease (type 1 DM,

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Sjogren's disease, inflammatory bowel disease (IBD), vitiligo), systemic autoimmune disease (SLE, rheumatoid arthritis) according to the anatomical location and distance.

Autoimmune diseases were defined using the main diagnosis code (ICD-10 code) among patients without cancer in the NHIS-NSC database (Supplementary table 1). Especially, type 1 DM was defined as those who had been diagnosed with the main diagnosis (ICD-10 code: E10) more than twice, and rheumatoid arthritis was defined as patients who had been diagnosed with ICD-10 code "M05" and prescribed DMARDs for more than 30 days.

Definition for thyroid cancer

Among patients without previous thyroid cancer history, patients newly diagnosed with the ICD-10 code "C73" as main diagnosis code were defined as thyroid cancer patients. The main diagnosis for cancer in the NHIS-NSC database showed relatively good accuracy when compared with the patients confirmed as cancer in the cancer registration database [22].

Selection of the study participants

The index dates were defined as the first date of health examination between 2009 and 2010 year. The total number of source populations in 2009-2010 year was 495,060 individuals. Of those, 354,155 people who participated in the health examination in 2009-2010 year and had complete data for major covariates. In addition, 2,856 patients were excluded because of known prevalence thyroid cancer before the index date, leaving 351,299 to develop the matched cohort. The propensity score matching was used to match 1:1 (AID vs. control group) using age, sex, smoking, alcohol intake, fasting blood glucose, frequency of physical activity, body mass index (BMI), and income level based on the nearest neighbor matching algorithm, a maximum caliper distance was set to 0.1. Finally, 16,328 people with 8 autoimmune diseases and 16,328 control group without 8 autoimmune diseases were selected as final study population, respectively (Figure 1).

Follow-up of study participants

Study participants were followed from the index date (dates of health examination between 2009 and 2010 year) to December 31th, 2019 year. People who withdrew from the study or died from any causes during the follow-up period or those who observed

without any event until December 31, 2019 were considered as censoring cases. Person-year was calculated as the sum of the follow-up year from the index date to the occurrence of new thyroid cancer or censoring of the study.

Other covariates for thyroid cancer

Information on smoking status, alcohol intake and physical activity was obtained through questionnaires. Smoking status was classified into current smokers, former smokers, and never-smokers. Alcohol consumption was defined as those who drank alcohol 3 or more times a week.

The physical activity was classified into 0 days, 1-4 days, and 5 days or more per week using the number of days of moderate exercise of 30 minutes or more. BMI was calculated as weight (kg) divided by the square of height (meters). Fasting blood glucose level(mg/dL) was collected after 8 hours of fasting. Income level was divided into quintile groups and Medicaid based on insurance premiums.

Statistical analysis

The baseline characteristics of study participants were presented as number (percentage) for categorical variables and mean (standard deviation) for continuous variables. Incidence rates and 95% confidence intervals (CIs) for each group of 8 autoimmune diseases were calculated as new thyroid cases divided by total person-years. The plots of cumulative incidence rate were illustrated to compare the difference in the incidence rates of thyroid cancer between each group of 8 autoimmune diseases and the control group without autoimmune disease, and the differences between them was tested by the log-rank test. After adjusting for age, sex, BMI, fasting blood glucose level, smoking status, alcohol intake, physical activity and income level, the Cox proportional hazards models were used to calculate adjusted hazard ratios (HRs) and 95% CIs for the risk of thyroid cancer (adjusted HR [95% CI]) in relation to each of 8 autoimmune diseases and total of 8 autoimmune diseases, compared with control group. It was checked whether the log-log survival function was parallel and satisfied the proportional hazard assumption, and if it was visually parallel, it was considered not to violate the proportional hazard assumption.

The significance level was set to 0.05. All statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA) and R software (version 4.0.0, Vienna, Austria).

RESULTS

Baseline characteristics of study participants

Table 1 shows baseline clinical and demographic characteristics of patients with 8 autoimmune diseases compared with control group without autoimmune diseases. The overall proportions of total autoimmune diseases were higher in females (60.2%) than males (39.8%), but the proportion of males were higher than females in patients with type 1 DM and IBD. The propensity score matched cohort showed no significant difference in age, BMI, fasting glucose, smoking status, alcohol intake, physical activity, and income levels between patients with 8 autoimmune diseases and control group. Regarding the incidence of thyroid cancer, each group of individual autoimmune disease and group with total of autoimmune diseases had the higher incidence of thyroid cancer than control group, except for type 1 DM.

When comparing the prevalence of comorbidities between the autoimmune disease group and the control group, the autoimmune disease group showed higher prevalence of gastric cancer, colorectal cancer, and liver cancer than control group, except for lung cancer. The prevalence of acute myocardial infarction, stroke, and hypertension. were higher in the autoimmune disease group than control group (Supplementary table 2).

Incidence rates of thyroid cancer by specific types of autoimmune diseases

Crude incidences of thyroid cancer according to types of autoimmune diseases are presented in Table 2. In all of study participants, each group of individual autoimmune disease except for type1 DM had the higher incidence for thyroid cancer, compared with control group. Although the incidence rates of thyroid cancer were higher in females compared with those of males, the incidence rates of thyroid cancer were higher in both males and females with thyroid specific autoimmune diseases – Hashimoto's thyroiditis and Graves' disease - compared with control group. In addition, point estimates of crude

incidence rates were higher in patients with inflammatory bowel disease, SLE and vitiligo of females.

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Hazard ratios for risk of thyroid cancer by specific types of autoimmune diseases

Table 3 presents adjusted HRs and 95% CIs for the incident thyroid cancer of each types of autoimmune disease, total of autoimmune diseases, and control group. For all of study participants, the risk of thyroid cancer was significantly higher among patients with Hashimoto's thyroiditis (HR=2.10 [1.57 – 2.81]), Graves' disease (HR=2.67 [1.97 – 3.62]), IBD (HR=2.06 [1.50 – 2.83]), vitiligo (HR=1.71 [1.13 – 2.59]), RA (HR=1.76 [1.07 – 2.90]) and total of 8 autoimmune diseases (HR=1.97 [1.60 – 2.42]) compared with control group. In males, Graves' disease (HR=4.22 [1.95 – 9.13]), IBD (HR=2.58 [1.35 – 4.93]), and total of 8 autoimmune diseases (HR=1.97 [1.61 – 2.43]) were significantly associated with increased risk of thyroid cancer, compared with control group. In females, the HRs for thyroid cancer were higher in patients with Hashimoto's thyroiditis (HR=2.06 [1.52 – 2.80]), Graves' disease (HR=2.46 [1.77 – 3.43]), IBD (HR=1.92 [1.32 – 2.78]), vitiligo (HR=1.69 [1.07 – 2.66]), and total of 8 autoimmune diseases (HR=1.97 [1.61 – 2.43]) than control group. Although the point estimate of adjusted HRs for thyroid cancer among patients with Sjogren's disease, type 1 DM, and SLE were higher than 1, it was not statistically significant. This was partially because Sjogren's disease, SLE are rare diseases and have low statistical power (Figure 2).

Risk of thyroid cancer for thyroid-specific, local and systemic autoimmune diseases

When autoimmune diseases were classified into thyroid-specific, local, and systemic autoimmune diseases, the crude incidence rate of thyroid cancer was highest in patients with thyroid specific autoimmune disease, followed by systemic autoimmune disease and local autoimmune disease (Supplementary table 3). The Kaplan-Meier curve also showed that the risks of thyroid cancer in patients with thyroid-specific, local, and systemic autoimmune diseases were higher than the control group (Supplementary figure 1-3). However, after adjusting for all covariates, thyroid-specific autoimmune diseases had the strongest and significant association with risk of thyroid cancer (HR=2.37 [1.85 – 3.03]),

followed by local autoimmune disease (HR=1.83 [1.41 – 2.38]), systemic autoimmune disease (HR=1.77 [1.14 – 2.74]), compared with control group (Table 4).

DISCUSSION

This large cohort study showed that thyroid-specific, local autoimmune diseases (vitiligo and IBD), and rheumatoid arthritis were associated with increased risk of thyroid cancer. Especially, among many autoimmune diseases, the Hashimoto's thyroiditis and Graves' diseases which were limited to the thyroid tissue had the strong and significant association with thyroid cancer. In addition, each of 7 autoimmune diseases (except for type1 DM) had the higher age-adjusted incidence rate of thyroid cancer than control group. Total patients of 8 autoimmune diseases also showed the increased incidence rate and higher risk for thyroid cancer, compared with control group. These results are line with previous showing thyroid- specific autoimmune disease is associated with the increased risk of thyroid cancer.

It is presumed that immune responses in autoimmune diseases are involved in carcinogenesis. Autoimmune disease is characterized by pro-inflammatory low regulatory T cells [23], which is frequently observed in the initiation of cancer [3]. Thus, we hypothesized that the presence of specific autoimmune diseases may have a carcinogenic effect on the development of thyroid cancer. To verify this hypothesis, we analyzed the risk of thyroid cancer in relation to each of 8 autoimmune disease including Hashimoto's thyroiditis, Graves' disease, IBD, type1 DM, Sjogren's disease, vitiligo, SLE, and rheumatoid arthritis, and total of 8 autoimmune diseases, compared with control group.

Hashimoto's thyroiditis is an autoimmune thyroid disease in which the immune system attacks the thyroid gland, leading to inflammation. Hashimoto's thyroiditis refers to chronic lymphocytic thyroiditis characterized by immune cells infiltration of the thyroid gland as a result of failure in immune tolerance [3,8,11]. Several meta-analysis studies showed that Hashimoto's thyroiditis was significantly associated with the increased risk for thyroid cancer [24-27]. Mechanisms linking Hashimoto's thyroiditis to thyroid cancer may include inflammatory reaction causing DNA damage through formation of reactive oxygen species, and elevated levels of TSH stimulating follicular epithelial proliferation [11,28,29]. A review

paper also reported that the serum TSH level, even within normal range was associated with higher risk of thyroid cancer and more advanced stage of thyroid cancer [30]. A recent Mendelian randomization study also reported that elevated TSH level has causal role in thyroid cancer [31]. Pani et al. reported that inflammation and proliferation play an important role in autoimmune thyroiditis and thyroid cancer, and that these pathological changes are regulated by various components of the immune system [32]. Graves' disease is also another type of autoimmune thyroid disease, occupying most common cause of hyperthyroidism [7,8]. Graves' disease seemed to be associated with larger, multifocal, and more aggressive thyroid cancer than single hot nodules or multinodular toxic goiter. A nationwide representative cohort study in Taiwan also showed that patients with Graves' disease had almost 10 times increased risk of thyroid carcinoma than those without Graves' disease [33]. However, Rotondi et al. reported that there was no significant association between chronic autoimmune thyroiditis and thyroid cancer, when 510 patients with chronic autoimmune thyroiditis were observed for 10 years [34].

The association between IBD and thyroid cancer is still controversial [35,36]. In a study for Finnish patients with ulcerative colitis and Crohn's disease, patients with ulcerative colitis showed an increased standardized incidence ratio (SIR) for thyroid cancer compared to those expected in general population [35]. However, a study for 2,621 Chinese patients with IBD failed to show the significant association between IBD and the risk of thyroid cancer [36]. Our result supports the hypothesis that IBD increases the risk of thyroid cancer. A recent large case-control study and meta-analysis also showed that IBD and ulcerative colitis was associated with elevated risk of thyroid cancer, similar with our findings [15].

Vitiligo was significantly associated with the increased risk of thyroid cancer in only females. There have been studies indicating the significant association of type1 DM and vitiligo with thyroid cancer. A meta-analysis for 15 observation studies showed that type1 DM was associated with an increased risk of thyroid cancer [9]. In a nationwide population-based Korean study, patients with vitiligo were at increased risk of thyroid cancer, compared with the controls [16]. There was rare study on the relationship between rheumatoid arthritis and thyroid cancer. A review paper reported that rheumatoid arthritis and autoimmune thyroid disease have affected each other disease in a bidirectional

manner.[37] A recent Korean study has reported that standardized incidence ratio of thyroid cancer was 1.75 (95% CI=1.02-2.68) among women with rheumatoid arthritis.[10]

Some limitations should be considered in the present study. First, there is a possibility for the overestimation and detection bias in the incidence of thyroid cancer, especially for patients with thyroid autoimmune diseases. Major explanation for this phenomenon is high accessibility to screening exams using thyroid ultrasonography for thyroid cancer in Korea [38]. Patients with thyroid autoimmune diseases may have the more chance for screening for thyroid, which can be potential bias leading high detection rate of thyroid cancer. Second, we could not evaluate the stage and pathological specific thyroid cancer risk and diagnostic method for thyroid cancer, because stage, pathological information and diagnostic method on thyroid cancer was not available in the NHIS-NSC database. Third, we applied an operational definition for autoimmune diseases using ICD-10 codes and drug prescriptions, but misclassification bias for autoimmune diseases may occur. Our database is a secondary data source and is not collected for research purposes. However, we referred carefully to the published literature to reduce the misclassification bias, and applied different operational definition for each autoimmune disease. Fourth, there may be low statistical power especially for male autoimmune diseases and rare autoimmune diseases such as SLE and Sjogren's disease. This small number of thyroid cancer cases among subgroups may have lowered the statistical power, masking a significant association.

In conclusion, the risk of thyroid cancer was significantly increased in patients with Hashimoto's thyroiditis, Graves' disease, IBD, vitiligo, rheumatoid arthritis. These results suggest that specific autoimmune diseases potentiate the development of thyroid cancer. Further large-scale autoimmune disease-specific study may be needed to clarify the association between local and systemic autoimmune diseases and thyroid cancer.

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Authors' Contribution statement:

Chang-Mo Oh made substantial contributions to the conception of the work, acquisition and interpretation of the data, and data analysis. Sung Keun Park and Jae-Hong Ryoo wrote the manuscript and contributed to the study design and interpretation of data. Min-Ho Kim conducted data analysis and illustrated the figures. Min-Ho Kim, Ju Young Jung, Yuh-Seog Jung, Kyoung-Nam Kim, Soonsu Shin made substantial contributions to the acquisition of the data and critical revision of the study protocol and manuscript. All authors were involved in reviewing, editing and final approval of the manuscript. Chang-Mo Oh is responsible for the overall content.

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The authors have no conflicts of interest to disclose.

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Table 1. Baseline characteristics of the study participants

	Autoimmune diseases (AD)								All of AD	Control group	*p*-value
	Thyroid-specific AD		Local AD				Systemic AD				
	Hashimoto's thyroiditis	Graves' disease	IBD	Sjogren's syndrome	T1DM	Vitiligo	RA	SLE*			
Number	2,825	2,232	3,565	1,424	3,630	1,875	1,103	327	16,328	16,328	
Person-year (total)	9.65 ± 1.50	9.55 ± 1.69	9.55 ± 1.75	9.58 ± 1.65	9.04 ± 2.30	9.60 ± 1.63	9.28 ± 2.00	9.56 ± 1.52	9.45 ± 1.84	9.54 ± 1.78	
Continuous variables											
Age (years)	57.24 ± 7.66	57.60± 8.13	60.21 ± 9.30	60.73 ± 9.39	64.13 ± 9.01	60.24 ± 8.74	60.75 ± 8.19	57.70 ± 8.37	60.25 ± 9.02	60.20 ± 9.62	0.59
BMI (kg/m^2)	23.66 ± 2.83	23.83 ± 2.88	23.83 ± 2.83	23.81 ± 3.16	24.36 ± 3.26	23.83 ± 2.80	23.00 ± 2.89	23.35 ± 3.30	23.87 ± 2.99	23.87 ± 2.98	0.98
Fasting glucose (mg/dL)	96.87 ± 18.84	99.18 ± 23.27	99.88 ± 23.02	99.38 ± 24.00	140.87 ± 57.10	99.08 ± 20.69	94.67 ± 22.81	94.87±19.08	107.64 ± 37.25	107.28 ± 38.09	0.39
Categorical variables											
Sex											0.24
Male	457 (16.2)	678 (30.4)	1,923 (53.9)	496 (34.8)	2,002 (55.1)	815 (43.5)	271 (24.6)	67 (20.5)	6,558 (40.2)	6,453 (39.5)	
Female	2,368 (83.8)	1,554 (69.6)	1,642 (46.1)	928 (65.2)	1,628 (44.9)	1,060 (56.5)	832 (75.4)	260 (79.5)	9,770 (59.8)	9,875 (60.5)	
Smoking status											0.51
Never smoker	2,505 (88.7)	1,716 (76.9)	2,429 (68.1)	1,124 (78.9)	2,404 (66.2)	1,397 (74.5)	900 (81.6)	280 (85.6)	12,203 (74.8)	12,293 (75.3)	
Past smoker	190 (6.7)	304 (13.6)	666 (18.7)	180 (12.6)	656 (18.1)	281 (15.0)	110 (10.0)	29 (8.9)	2,355 (14.4)	2,309 (14.1)	
Current smoker	130 (4.6)	212 (9.5)	470 (13.2)	120 (8.4)	570 (15.7)	197 (10.5)	93 (8.4)	18 (5.5)	1,770 (10.8)	1,726 (10.6)	
Alcohol intake											0.60
Yes	2,274 (80.50)	1,665 (74.60)	2,302 (64.57)	1,057 (74.23)	2,561 (70.55)	1,293 (68.96)	905 (82.05)	271 (82.87)	11,796 (72.24)	11,839 (72.51)	
No	551 (19.50)	567 (25.40)	1,263 (35.43)	367 (25.77)	1,069 (29.45)	582 (31.04)	198 (17.95)	56 (17.13)	4,532 (27.76)	4,489 (27.49)	
Physical activity											0.81
None	1,304 (46.16)	1,085 (48.61)	1,760 (49.37)	745 (52.32)	2,014 (55.48)	889 (47.41)	657 (59.56)	170 (51.99)	8,276 (50.69)	8,334 (51.04)	

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1-4 days/wk	1,164 (41.20)	3879 (39.38)	1,360 (38.15)	520 (36.52)	1,082 (29.81)	730 (38.93)	333 (30.19)	111 (33.94)	5,947 (36.42)	5,903 (36.15)	
≥5 days/wk	357 (12.64)	268 (12.01)	445 (12.48)	159 (11.17)	534 (14.71)	256 (13.65)	113 (10.24)	46 (14.07)	2,105 (12.89)	2,091 (12.81)	
Obesity											0.34
No	2,004 (70.94)	1,520 (68.10)	2,465 (69.14)	975 (68.47)	2,213 (60.96)	1,289 (68.75)	861 (78.06)	233 (71.25)	11,086 (67.90)	11,006 (67.41)	
Yes	821 (29.06)	712 (31.90)	1,100 (30.86)	449 (31.53)	1,417 (39.04)	586 (31.25)	242 (21.94)	94 (28.75)	5,242 (32.10)	5,322 (32.59)	
Income level											
Medicaid	5 (0.18)	1 (0.04)	3 (0.08)	7 (0.49)	14 (0.39)	5 (0.27)	2 (0.18)	2 (0.61)	35 (0.21)	36 (0.22)	0.16
1st quintile	389 (13.77)	282 (12.63)	460 (12.90)	214 (15.03)	549 (15.12)	220 (11.73)	181 (16.41)	53 (16.21)	2,249 (13.77)	2,328 (14.26)	
2nd quintile	357 (12.64)	279 (12.50)	433 (12.15)	193 (13.55)	506 (13.94)	195 (10.40)	140 (12.69)	38 (11.62)	2,071 (12.68)	2,184 (13.38)	
3rd quintile	395 (13.98)	346 (15.50)	595 (16.69)	222 (15.59)	585 (16.12)	265 (14.13)	185 (16.77)	44 (13.46)	2,537 (15.54)	2,562 (15.69)	
4th quintile	562 (19.89)	453 (20.30)	767 (21.51)	280 (19.66)	779 (21.46)	386 (20.59)	235 (21.31)	64 (19.57)	3,396 (20.80)	3,256 (19.94)	
5th quintile	1,117 (39.54)	871 (39.02)	1,307 (36.66)	508 (35.67)	1,197 (32.98)	804 (42.88)	360 (32.64)	126 (38.53)	6,040 (36.99)	5,962 (36.51)	
Incident thyroid cancer	72 (2.55)	61 (2.73)	54 (1.51)	19 (1.33)	23 (0.63)	27 (1.44)	18 (1.63)	6 (1.83)	268 (1.64)	138 (0.85)	<0.001

Footnote: AD= autoimmune disease, IBD= inflammatory bowel disease, T1DM= type 1 diabetes mellitus, RA= rheumatoid arthritis, SLE=systemic lupus erythematosus.

Students' t-test was used to examine the difference between patients with autoimmune diseases and control group and chi-square test was used to examine the difference between patients with autoimmune diseases and control group.

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Table 2. Incidence rates for thyroid cancer according to autoimmune diseases

Category of autoimmune diseases	Incidence cases (n)	Person-years	Crude incidence rates per 100,000 person-years
Total			
Control group	138	155,688	88.64 (73.85 – 103.43)
Hashimoto's thyroiditis	72	27,257	264.15 (203.14 – 325.17)
Graves' disease	61	21,319	286.12 (214.32 – 325.17)
IBD	54	34,050	158.59 (116.29 – 200.89)
Sjogren's disease	19	13,647	139.23 (76.63 – 201.83)
Type 1 DM	23	32,803	70.12 (41.46 – 98.77)
Vitiligo	27	17,996	150.03 (93.44 – 206.62)
RA	18	10,240	175.78 (94.57 – 256.98)
SLE	6	3,127	191.88 (38.35 – 345.42)
Total 8 autoimmune diseases	268	154,307	173.68 (152.89 – 194.47)

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Male			
Control group	21	60,685	34.61 (19.81 – 49.41)
Hashimoto's thyroiditis	4	4,395	91.02 (1.82 – 180.22)
Graves' disease	10	6,431	155.49 (59.12 – 251.86)
IBD	17	18,377	92.51 (48.53 – 136.48)
Sjogren's disease	3	4,710	63.70 (0 – 135.77)
Type 1 DM	9	17,769	50.65 (17.56 – 83.74)
Vitiligo	5	7,771	64.34 (7.95 – 120.74)
RA	2	2,375	84.21 (0 – 200.92)
SLE	1	642	155.87 (0 – 461.37)
Total 8 autoimmune diseases	50	61,068	81.88 (59.18 – 104.57)

Female			
Control group	117	95,004	123.15 (100.84 – 145.47)
Hashimoto's thyroiditis	68	22,863	297.43 (226.74 – 368.12)
Graves' disease	51	14,888	342.56 (248.54 – 436.57)
IBD	37	15,673	236.07 (160.01 – 312.14)
Sjogren's disease	16	8,937	179.04 (91.31 – 266.76)
Type 1 DM	14	15,034	93.12 (44.34 – 141.90)
Vitiligo	22	10,225	215.15 (125.25 – 305.06)
RA	16	7,865	203.43 (103.75 – 303.10)
SLE	5	2,485	201.18 (24.84 – 377.52)
Total 8 autoimmune diseases	218	93,239	233.81 (202.77 – 264.84)

Footnote: IBD= inflammatory bowel disease, T1DM= type 1 diabetes mellitus, RA= rheumatoid arthritis, SLE=systemic lupus erythematosus.

The crude incidence rates are presented as number of thyroid cases per 100,000 person-years and Poisson method was used to estimate 95% confidence intervals.

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Table 3. Hazard ratios (HRs) and 95% confidence intervals (CI) for thyroid cancer according to autoimmune diseases

Categories	Unadjusted model	Age adjusted model	Multivariable model1	Multivariable model2
Total				
Control group	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Hashimoto's thyroiditis	2.99 (2.25 – 3.97)	2.77 (2.08 – 3.69)	2.16 (1.62 – 2.89)	2.10 (1.57 – 2.81)
Graves' disease	3.23 (2.39 – 4.37)	3.01 (2.22 – 4.07)	2.70 (1.99 – 3.66)	2.67 (1.97 – 3.62)
IBD	1.79 (1.31 – 2.45)	1.80 (1.32 – 2.47)	2.05 (1.49 – 2.82)	2.06 (1.50 – 2.83)
Sjogren's disease	1.57 (0.97 – 2.54)	1.62 (1.01 – 2.61)	1.48 (0.91 – 2.39)	1.48 (0.91 – 2.40)
Type 1 DM	0.78 (0.50 – 1.22)	0.93 (0.60 – 1.46)	1.36 (0.84 – 2.19)	1.38 (0.86 – 2.23)
Vitiligo	1.70 (1.12 – 2.56)	1.74 (1.15 – 2.62)	1.76 (1.16 – 2.66)	1.71 (1.13 – 2.59)
RA	1.97 (1.21 – 3.23)	2.05 (1.25 – 3.35)	1.74 (1.06 – 2.86)	1.76 (1.07 – 2.90)
SLE	2.17 (0.96 – 4.90)	2.01 (0.89 – 4.54)	1.63 (0.72 – 3.70)	1.60 (0.70 – 3.62)
Total 8 autoimmune diseases	1.96 (1.59 – 2.40)	1.98 (1.62 – 2.44)	1.98 (1.61 – 2.43)	1.97 (1.60 – 2.42)

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Male				
Control group	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Hashimoto's thyroiditis	2.63 (0.90 – 7.66)	2.62 (0.90 – 7.65)	2.47 (0.84 – 7.22)	2.40 (0.82 – 7.04)
Graves' disease	4.50 (2.12 – 9.54)	4.46 (2.09 – 9.50)	4.21 (1.96 – 9.05)	4.22 (1.95 – 9.13)
IBD	2.68 (1.41 – 5.08)	2.71 (1.43 – 5.13)	2.54 (1.33 – 4.85)	2.58 (1.35 – 4.93)
Sjogren's disease	1.83 (0.55 – 6.14)	1.86 (0.55 – 6.22)	1.77 (0.53 – 5.95)	1.88 (0.56 – 6.34)
Type 1 DM	1.44 (0.66 – 3.15)	1.62 (0.73 – 3.57)	1.93 (0.84 – 4.44)	2.05 (0.88 – 4.75)
Vitiligo	1.86 (0.70 – 4.94)	1.88 (0.71 – 4.99)	1.78 (0.67 – 4.74)	1.80 (0.67 – 4.81)
RA	2.42 (0.57 – 10.30)	2.51 (0.58 – 10.74)	2.72 (0.63 – 11.83)	2.94 (0.67 – 12.88)
SLE	4.48 (0.60 – 33.33)	4.42 (0.60 – 32.89)	4.78 (0.65 – 35.83)	5.07 (0.67 – 38.49)
Total 8 autoimmune diseases	1.96 (1.59 – 2.40)	1.98 (1.62 – 2.44)	1.98 (1.61 – 2.43)	1.97 (1.61 – 2.43)

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Female

Control group	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Hashimoto's thyroiditis	2.42 (1.79 – 3.26)	2.17 (1.60 – 2.93)	2.12 (1.51 – 2.64)	2.06 (1.52 – 2.80)
Graves' disease	2.78 (2.00 – 3.87)	2.52 (1.81 – 3.51)	2.50 (1.42 – 2.20)	2.46 (1.77 – 3.43)
IBD	1.92 (1.32 – 2.77)	1.96 (1.35 – 2.83)	1.92 (1.28 – 2.61)	1.92 (1.32 – 2.78)
Sjogren's disease	1.46 (0.86 – 2.46)	1.50 (0.89 – 2.53)	1.45 (0.83 – 2.31)	1.48 (0.86 – 2.44)
Type 1 DM	0.75 (0.43 – 1.31)	0.99 (0.56 – 1.74)	1.13 (0.58 – 1.87)	1.14 (0.63 – 2.07)
Vitiligo	1.75 (1.11 – 2.76)	1.81 (1.15 – 2.86)	1.76 (1.08 – 2.63)	1.69 (1.07 – 2.66)
RA	1.65 (0.98 – 2.76)	1.67 (0.99 – 2.82)	1.65 (0.75 – 2.32)	1.66 (0.98 – 2.81)
SLE	1.63 (0.67 – 2.78)	1.46 (0.60 – 3.58)	1.42 (0.56 – 3.31)	1.66 (0.57 – 3.42)
Total autoimmune diseases	1.96 (1.59 – 2.40)	1.98 (1.62 – 2.44)	1.98 (1.61 – 2.43)	1.97 (1.61 – 2.43)

Footnote: IBD= inflammatory bowel disease, T1DM= type 1 diabetes mellitus, RA= rheumatoid arthritis, SLE=systemic lupus erythematosus.

The Cox-proportional hazard models were performed after adjusting for multiple covariates.

Multivariable model 1 was adjusted for age, sex, body mass index(BMI), fasting blood glucose.

Multivariable model 2 was adjusted for Multivariable model 1 and smoking status, alcohol intake, physical activity and income level.

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Table 4. Hazard ratios (HRs) and 95% confidence intervals (CI) for thyroid cancer in patients with thyroid-specific, local and systemic autoimmune diseases

	Unadjusted Model	Age adjusted Model	Multivariate 1	Multivariate 2
Total				
Thyroid-specific AD	3.08 (2.42 – 3.91)	2.88 (2.26 – 3.66)	2.41 (1.89 – 3.08)	2.37 (1.85 – 3.03)
Local AD	1.72 (1.33 – 2.23)	1.75 (1.35 – 2.26)	1.84 (1.42 – 2.39)	1.83 (1.41 – 2.38)
Systemic AD	2.06 (1.33 – 3.17)	2.08 (1.35 – 3.21)	1.76 (1.13 – 2.73)	1.77 (1.14 – 2.74)
Male				
Thyroid-specific AD	3.84 (1.95 – 7.54)	3.85 (1.95 – 7.59)	3.66 (1.85 – 7.27)	3.64 (1.83 – 7.26)
Local AD	2.36 (1.32 – 4.22)	2.40 (1.35 – 4.29)	2.23 (1.24 – 4.00)	2.25 (1.25 – 4.05)
Systemic AD	2.89 (0.86 – 9.69)	2.96 (0.88 – 9.94)	3.34 (0.98 – 11.42)	3.52 (1.03 – 12.08)
Female				
Thyroid-specific AD	2.54 (1.96 – 3.28)	2.30 (1.77 – 2.98)	2.26 (1.74 – 2.93)	2.22 (1.71 – 2.88)
Local AD	1.75 (1.31 – 2.34)	1.80 (1.34 – 2.41)	1.76 (1.31 – 2.36)	1.74 (1.30 – 2.32)
Systemic AD	1.68 (1.05 – 2.67)	1.66 (1.04 – 2.64)	1.62 (1.02 – 2.59)	1.62 (1.01 – 2.58)

Footnote: AD=autoimmune disease.

The Cox-proportional hazard models were performed after adjusting for multiple covariates.

Multivariable model 1 was adjusted for age, sex, body mass index(BMI), fasting blood glucose.

Multivariable model 2 was adjusted for Multivariable model 1 and smoking status, alcohol intake, physical activity and income level.

Autoimmune diseases were classified into three groups: Thyroid specific autoimmune diseases=Hashimoto's thyroiditis, Graves' disease; Local autoimmune disease= Type 1 diabetes mellitus, Sjogren's disease, inflammatory bowel disease, vitiligo; Systemic autoimmune disease =systemic lupus erythematosus, rheumatoid arthritis.

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Figure legends

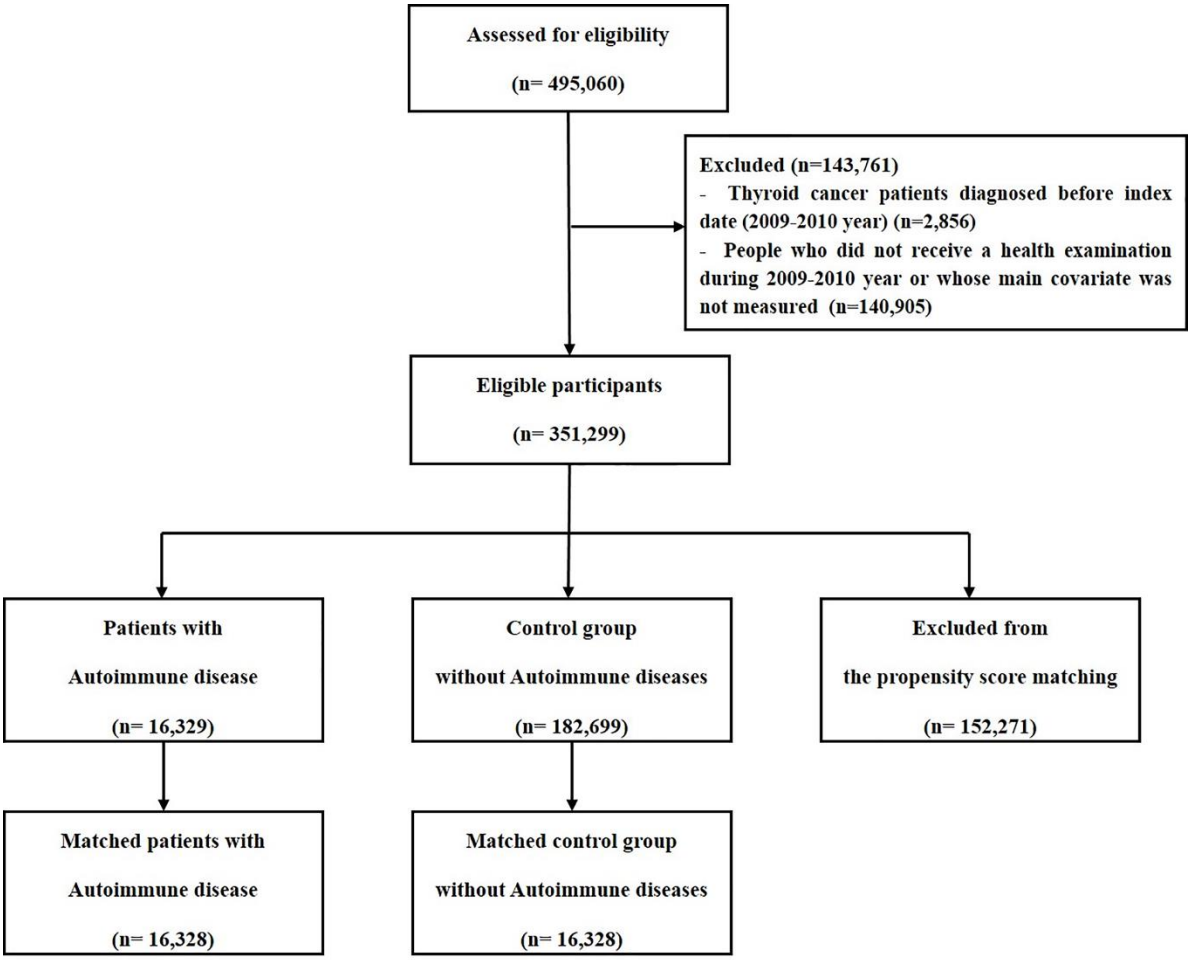

Figure 1. Flow chart for selection of study participants

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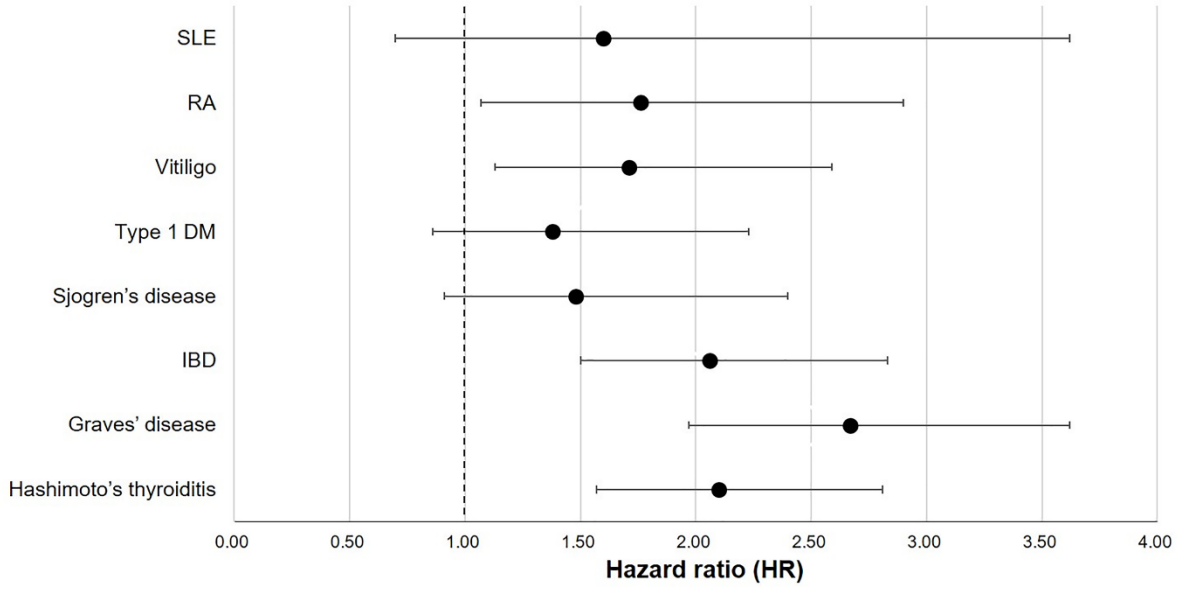

Figure 2. Hazard ratios and 95% confidence intervals for thyroid cancer according to types of autoimmune diseases

Footnotes: SLE=Systemic Lupus Erythematosus; RA=Rheumatoid Arthritis; Type1 DM=Type 1 Diabetes Mellitus; IBD=Inflammatory Bowel Disease

The hazard ratios were adjusted for age, sex, body mass index(BMI), fasting blood glucose, smoking status, alcohol intake, frequency of physical activity, income level. The dotted line represents that the hazard ratio is equal to 1.

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