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Clinical Research Article

Risk of Thyroid Cancer in People With Type 1 Diabetes by Autoimmune Thyroid Diseases and Tumor Histology

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Abstract

Context: Thyroid cancer is the most common endocrine cancer, but little is known about it in type 1 diabetes (T1D) and its potential association with autoimmune diseases.

Objective: This study aims to assess the risk of thyroid cancer in adults with long-term T1D compared to individuals without diabetes and the proposed association of thyroid autoimmune diseases with thyroid cancer.

Methods: The study included 4758 individuals with T1D participating in the Finnish Diabetic Nephropathy Study and 12 710 controls. Thyroid cancers were obtained from the Finnish Care Registers for Health Care.

Results: 27 (0.57%) individuals with T1D had thyroid cancer compared to 27 (0.21%) in the controls (standardized incidence ratio 2.43; 95% confidence interval 1.59-3.56). The absolute increase in incidence was modest, with a 0.36%-unit rise. This translates to 17 additional cases among 4710 individuals with T1D. Cancer type was papillary in 81.5% of individuals with T1D and 88.9% of the controls; the rest were follicular. In T1D the distribution of hypothyreosis was similar between those with (n = 5, 18.5%) and without (18.1%) cancer, but hyperthyreosis was diagnosed more often with thyroid cancer (n = 3, 11.1%) than without (2.3%, $P = .003$). None of the thyroid cancers were invasive or had metastatic characteristics.

Conclusion: Although there is an excess risk of thyroid cancer, it is only marginally increased (0.36%-unit) in individuals with T1D compared to control individuals and was not associated with increased morbidity or mortality. An overdiagnosis effect due to regular health care contacts is the most likely explanation for the higher risk.

Key Words: type 1 diabetes, thyroid cancer, autoimmune thyroid disease

Thyroid cancer, the most common endocrine cancer, shows increasing incidence worldwide [1]. An overdiagnosis effect due to increased access to ultrasound detection might account for this epidemiological pattern [2]. As overdiagnosis has led to a public health problem of global relevance, it is essential to assess whether there is a subgroup of people with a true excess risk of thyroid cancer.

The only clearly established risk factor for thyroid cancer is exposure to ionizing radiation, especially during childhood [3]. Other proposed factors are exposure to endocrine-disrupting chemicals, medical radiation, heavy metals during volcano activity, increased iodine intake, and genetic predisposition. Thyroid dysfunction may be involved in carcinogenesis as thyroid hormones and TSH can directly enhance tumor proliferation and angiogenesis through their cell surface receptors, and they may also affect gene expression regulation [4]. Thyroiditis has been suggested to be a precancerous condition [5]. The association between hypothyreosis and papillary thyroid cancer was first described by Dailey and colleagues in 1955 [6]. Since then, autoimmune thyroid diseases have been repeatedly reported to coexist with thyroid cancer [7-10].

Diabetes has been linked to thyroid cancer through long-term exposure to insulin, hypertriglyceridemia, hyperglycemia, insulin resistance, obesity, and vitamin D deficiency [3, 9, 11-13], mostly in studies in type 2 diabetes, but findings in type 1 diabetes (T1D) have been inconsistent [14-16].

Assuming a relationship between thyroid autoimmunity and cancer, it would most likely occur in individuals with T1D who have a high prevalence of thyroid autoimmune diseases [17]. Until now, only case reports have been available of this population [18, 19]. In this study, we evaluated the possible excess risk of thyroid cancer and the role of autoimmune thyroid diseases on the risk in adults with long-term T1D and control individuals.

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Materials and Methods

Study Design and Participants

As the goal was to evaluate the coexistence of autoimmune thyroid diseases and thyroid cancer, the same population as in our previous study on autoimmune diseases was utilized [17]. A total of 4758 individuals with T1D were included from the Finnish Diabetic Nephropathy Study (FinnDiane) cohort, an ongoing, nationwide, multicenter study initiated to identify genetic and environmental risk factors for complications of diabetes. A detailed description of the recruitment protocol has previously been presented [17]. Briefly, adult individuals (≥18 years old) with T1D across Finland were asked to participate. T1D was defined as age at onset of diabetes less than 40 years and initiation of insulin treatment within 1 year of the diagnosis. The study protocol followed the principles of the Declaration of Helsinki as revised in 2000 and was approved by the Ethical Committee of Helsinki and Uusimaa Hospital District. Written informed consent was obtained from each participant. For each FinnDiane participant, up to 3 control individuals matched for sex, age, and place of residence in the year of the diagnosis of diabetes of the FinnDiane participant were selected from the Population Register Center. A total of 1357 individuals from the control group had diabetes and were excluded from the analyses. After exclusion of people with diabetes, there were 12 710 control individuals left.

Ascertainment of Thyroid Cancer and Thyroid Autoimmunity

Thyroid cancers were identified by linking the data with the Finnish nationwide health registries, the Finnish Care Register for Health Care including specialized outpatient care (data available since 1970). and the Causes of Death Register using the International Classificiation of Diseases codes 193 (version 8/9) and C73 (version 10) until the end of 2015. The types of cancers and the presence of metastases as well as their treatment and recovery were assessed by reviewing the medical records (no detailed data available on 3 individuals). Thyroid autoimmune diseases were identified by linking the data with the Finnish nationwide health registries, the Finnish Care Register for Health Care, the Finnish National Drug Reimbursement Register, and the Drug Prescription Register [17].

Statistical Analysis

The baseline characteristics are presented as mean (±SD) for normally distributed values, otherwise they are presented as median (interquartile range). Categorical variables are reported as percentages. Differences between groups were analyzed by ANOVA for normally distributed continuous variables; otherwise they were analyzed by the Mann–Whitney U test. Differences between the categorical variables were analyzed using the χ^2 test and Fisher's exact test (when the sample size was small).

In order to study possible excess thyroid cancer morbidity in individuals with T1D, the data were compared with control individuals without diabetes. Standardized incidence ratios (SIRs) were calculated as ratios of observed and expected numbers. The expected numbers were derived by multiplying the number of person-years at risk by sex-, 1-year age-specific, and 1-year period-specific morbidity rates observed in the control population. The follow-up started from the diagnosis date of diabetes and ended at the diagnosis date of thyroid cancer, death, or the end of the year 2015. Follow-up of survival after the diagnosis of thyroid cancer was done until the end of 2020.

The statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

There were 27 (0.57%) thyroid cancer diagnoses in participants with T1D, compared to 27 (0.21%) in the control individuals, giving rise to a SIR of 2.43 (95% confidence interval 1.59–3.56). The SIR was 3.88 (1.97–6.92) in men, while it was 1.92 (1.09–3.14) in women. Female preponderance for thyroid cancers was seen in the controls with a women-to-men relative risk of 3.07 (1.30–7.26), while men and women had equal risk in T1D (relative risk 1.61; 95% confidence interval 0.75–3.45). Six individuals with T1D and thyroid cancer had also undergone kidney transplantation, 3 of which took place before the diagnosis of thyroid cancer, which might have affected the cancer risk. However, after excluding these cases, the risk was still increased, SIR = 2.13 (1.35–3.2).

The median age at the end of the follow-up in 2015 or death was 51.4 (interquartile range 42.6–60.1) years. The median age at diagnosis of thyroid cancer was 38.2 years (33.1–46.6) in individuals with T1D and 42.8 years (29.4–49.9) in the controls ($P = 0.83$). In those with T1D and autoimmune hyperthyreosis or hypothyreosis, the median age at diagnosis of thyroid cancer was 38.2 years (32.4–44.9) and 33.1 years (30.9–35.3), respectively. Eight individuals with thyroid cancer died before the end of 2020, but thyroid cancer was not their cause of death.

The distribution of different types of thyroid cancers was similar in those with T1D and the controls: 22 papillary cancers in T1D and 24 in the controls, while 4 were follicular in those with T1D and 3 in the controls. Cancer was found in both thyroid lobes in 6 individuals with T1D and in 2 control subjects. Table 1 shows the size, invasive characteristics, presence of metastases, and recorded treatment of the thyroid cancers.

In individuals with T1D, the cancer was most often an incidental finding during a control visit for diabetes, or it was detected coincidently with hyperparathyreosis (n = 5), autoimmune thyroid disease (n = 2), sarcoidosis (n = 1), or enlarged lymphoid nodules (n = 2). Most of the control subjects had contacted a physician after first detecting a nodule themselves (Table 1), or it was found by the physician during a general health care check-up or incidentally while diagnosing autoimmune thyroid disease (n = 1), goiter (n = 1), or a salivary gland tumor (n = 1).

Table 2 shows the baseline clinical variables of the FinnDiane participants according to thyroid cancer. The proportion of hyperthyreosis was higher in the individuals with thyroid cancer while that of autoimmune hypothyreosis was similar in those with and without thyroid cancer. In the controls, only 1 had concomitant thyroid cancer and autoimmune thyroid disease.

All 3 individuals with T1D with thyroid cancer and autoimmune hyperthyreosis were female. Of those with hypothyreosis, 2 were female and 3 were men. In individuals with T1D and autoimmune thyroid disease, the cancer type was papillary in all but 1 case, who had follicular cancer type and

Table 1. Distribution of selected characteristics of thyroid cancer in type 1 diabetes and control individuals in the Finnish Diabetic Nephropathy Study cohort

	Type 1 diabetes, n = 27	Controls, n = 27
Number of cancer focuses	1.3 (1–4)	1.3 (1–4)
Largest size of the cancer nodule(s) (mm)	13.3 (3.6–40)	23.0 (5–80)
Invasion to vessel (yes/number of reported)	1/12	3/15
Invasion to capsules (yes/number of reported)	2/13	9/18
Metastases of lymphoid nodules (yes/number of reported)	3/19	9/23
Radioiodine treatment after surgery (yes/number of reported)	13/22	23/25
Age at diagnosis of thyroid cancer (years)	39.6 (20-72)	40.4 (13-70)
First detection of pathologic nodule		
Palpated self	6	17
Palpated by physician	10	4
Incidental radiological or surgery finding	8	3
Not reported	3	3

Data are expressed as median (range).

Table 2. Baseline characteristics of adults with type 1 diabetes from the Finnish Diabetic Nephropathy Study cohort according to thyroid cancer

	No thyroid cancer, n = 4731	Thyroid cancer, n = 27
Sex (female %)	47.5	57.1
Age (years)	37.8 (28.9–47.3)	47.3 (43.4–50.6)*
Autoimmune hyperthyreosis, n (%)	109 (2.3)	3 (11.1)†
Autoimmune hypothyreosis, n (%)	854 (18.1)	5 (18.5)
Age at diabetes diagnosis (years)	14.2 (9.2–22.7)	19.1 (9.2–31.1)
Duration of diabetes	21.5 (12.2–31.2)	21.8 (14.6–32.9)
Hemoglobin A1c (%)	8.3 (7.4–9.2)	8.8 (8.2–9.5)
Hemoglobin A1c (mmol/mol)	67.2 (57.4–77.0)	72.7 (6.1–80.3)
Smoking history (%)	47.1	46.9
Body mass index (kg/m^2)	25.1 ± 3.7	25.1 ± 4.5
Waist-to-hip ratio	0.88 ± 0.09	0.85 ± 0.08
Waist-to-height ratio	0.43 ± 0.07	0.43 ± 0.08
Systolic blood pressure (mmHg)	135 ± 19	139 ± 23
Diastolic blood pressure (mmHg)	79 ± 10	82 ± 11
Total cholesterol (mmol/L)	4.92 ± 0.99	4.86 ± 0.88
LDL cholesterol (mmol/L)	3.05 ± 0.86	3.01 ± 0.80
HDL cholesterol (mmol/L)	1.34 ± 0.40	1.33 ± 0.33
Triglycerides (mmol/L)	1.04 (0.78–1.48)	1.24 (0.81–1.84)

Data are expressed as mean (SD), median (interquartile range), or percentages. *P*-value refers to ANOVA, Mann–Whitney U test, χ^2-test, or Fisher's exact test. Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein. *$P < .05$, †$P < .01$ comparison.

hypothyreosis. The tumor sizes ranged from 4 to 12 mm in those with hyperthyreosis and was 15 mm in all individuals with hypothyreosis. None of these cancers were invasive or had metastatic characteristics. No one with T1D and autoimmune hypertyreosis received radioiodine treatment after surgery, whereas all but 1 with hypothyreosis received such treatment.

Age at onset, duration of diabetes, as well as other metabolic confounders did not differ between those with or without thyroid cancer, although hemoglobin A1c tended to be higher in individuals with thyroid cancer (Table 2).

Conclusions

Our study showed that the incidence of thyroid cancer is increased 2.4-fold in individuals with T1D compared to the control population. However, it is crucial to note that thyroid cancer is very rare also in individuals with T1D. Additionally, the absolute increase in incidence was modest, with a 0.36%-unit rise. This translates to 17 additional cases among 4710 individuals with T1D.

In this Finnish cohort of adult T1D, with a mean follow-up of 35.3 years, the risk of thyroid cancer appeared to be higher compared to previous studies, especially in men. In a large Swedish population-based T1D cohort, the risk of thyroid cancer was not increased compared to the background population [14]. The modest number of observed cancers may be explained by the young age of the cohort. In an Australian study of individuals with T1D, an excess risk was seen only in women. While the excess risk in men was of similar magnitude, it did not reach statistical significance [15]. Likewise, higher risk only in women was seen in a large 5-country combined T1D register with data from Australia, Denmark, Finland, Scotland, and Sweden [16]. All these countries are among the very high Human Development Index countries in which thyroid cancer incidence rates have been found to be 5 times higher than in the low or medium Human Development Index countries, suggesting an effect of overdiagnosis [2].

Like the global records [1], there was a female preponderance in thyroid cancers in the controls in our study. However, in the people with T1D, the risk was equal between the sexes. Regular health care contacts for diabetes may explain this finding as it increases the possibility of having the thyroid inspected, regardless of sex. This is supported by the way thyroid cancer was primarily detected. In the individuals with T1D, 75% of the cancers were detected during a routine health check-up, compared to 29% in the control subjects. This does not, however, rule out the possibility of other diabetes-related, genetic or environmental reasons.

Except for the case reports [18, 19], our study is also the first that stratifies thyroid cancers by histological type in individuals with T1D. Papillary carcinoma comprised 85% of the cancers in T1D and 89% in the controls. The number of tumors, lymphoid nodule metastases, and age during diagnosis of thyroid cancer were similar between the groups, but larger tumor sizes and signs of invasion were more often seen in the controls.

Consequently, 92% of the controls, whereas only 59% of those with T1D, received radioiodine treatment after thyroid surgery. This difference can again be explained by an earlier diagnosis or overdiagnosis of thyroid cancer in those with T1D. Interestingly, the cancers in the individuals with T1D and autoimmune thyroid disease showed less invasive or metastatic character than the cancers in those with T1D

without autoimmune thyroid disease or in the controls. In previous studies in individuals with autoimmune hypothyreosis, tumors were smaller and showed less angioinvasion or lymph node metastases [10]. Whether that is true also for the individuals with T1D needs further investigation.

Until now, no comprehensive studies on the coexistence of autoimmune thyroid diseases and thyroid cancer in adults with long-term T1D compared to sex- and age-matched control individuals have been conducted. In our study, nearly 30% of individuals with T1D and thyroid cancer had a diagnosis of autoimmune thyroid disease. We did not find an association between hypothyreosis and thyroid cancer in our study, while the proportion of hyperthyreosis was higher in the T1D individuals with thyroid cancer. However, the 3 individuals with thyroid cancer and hyperthyreosis could also be a chance finding. In the general population, hyperthyroidism has been associated with up to a 4.5-fold higher risk and hypothyroidism with up to a 3.3-fold risk of thyroid cancer compared to euthyroidism [8, 9, 20-23]. The time frame for increased risk of thyroid cancer in hypothyreosis was observed during the first 10 years after the diagnosis, while in hyperthyreosis the risk remained elevated over time in a large meta-analysis [9].

Histological findings support an association between papillary thyroid carcinomas and autoimmune thyreoiditis [5]. Autoimmune hypothyreosis is a chronic lymphocytic inflammatory disease, in which high TSH concentrations can stimulate thyroid cell proliferation and inflammation can induce dysregulation of genes and biofunctions resulting in oncogenic transformation. These processes involve reactive oxygen species, oxidative stress, apoptosis, and DNA damage [5]. Similar rearrangements of the RET oncogene and cellular changes have been detected both in papillary thyroid cancer as well as in the thyroids of individuals affected by autoimmune hypothyreosis [24]. Autoimmune hyperthyreosis has also been shown to favor the tumorigenic process, as thyroid-stimulating antibodies may promote tumor growth by activating TSH receptors by altering host immune tolerance and enhancing tumor invasiveness by upregulating various growth factors [7]. Furthermore, some studies [25, 26], but not all [27], have identified a more aggressive course in those with autoimmune hyperthyreosis, with increased frequency of invasion and nodal metastasis.

The major limitation of this study is its retrospective nature. We had no data on the timing of the autoimmune disease, the thyroid hormone concentrations, or antibody titers that would have allowed assessment of the relationship between autoimmune diseases and thyroid cancer. On the other hand, this study's major strength is the large number of subjects followed up for a long period of time and their matched control subjects.

Our results show that although there is an excess risk of thyroid cancer, it is only marginally increased in individuals with T1D compared to control individuals and was not associated with increased morbidity or mortality. An overdiagnosis effect due to regular health care contact is the most likely explanation for the higher risk.

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Author Contributions

S.M. and V.H. were responsible for the study design. S.M. was responsible for reviewing the medical files and preparation of the first draft of the manuscript. V.H. acquired the data and performed the statistical analyses. All authors interpreted the data and critically reviewed the manuscript. P.-H.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the manuscript.

Disclosures

P.-H.G. reports receiving lecture honorariums from Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, Peer Voice, and Sanofi and being an advisory board member of AbbVie, Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Medscape, MSD, Novartis, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

Data Availability

Study data will not be available because the General Data Protection Regulation does not allow the distribution of individual-level data.

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