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Risk of Thyroid Cancer in a Nationwide Cohort of Patients with Biopsy-Verified Celiac Disease

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Background: In earlier studies based on selected populations, the relative risk for thyroid cancer in celiac disease has varied between 0.6 and 22.5. We aimed to test this relationship in a population-based setting.
Methods: We collected small intestinal biopsy report data performed in 1969–2008 from all 28 Swedish pathology departments. 29,074 individuals with celiac disease (villous atrophy; Marsh histopathology stage III) were matched for sex, age, calendar year, and county to 144,440 reference individuals from the Swedish general population. Through Cox regression, we then estimated hazard ratios (HRs) and confidence intervals (CIs) for any thyroid cancer and papillary thyroid cancer (defined according to relevant pathology codes in the Swedish Cancer Register) in patients with celiac disease.
Results: During follow-up, any thyroid cancer developed in seven patients with celiac disease (expected = 12) and papillary thyroid cancer developed in five patients (expected = 7). Celiac disease was not associated with an increased risk of any thyroid cancer (HR 0.6 [CI 0.3–1.3]) or of papillary thyroid cancer (HR 0.7 [CI 0.3–1.8]). All cases of thyroid cancer in celiac disease occurred in female patients. Risk estimates were similar before and after the year 2000 and independent of age at celiac diagnosis ($\leq$24 years vs. $\geq$25 years).
Conclusions: We conclude that, in the Swedish population, there is no increased risk of thyroid cancer in patients with celiac disease. This differs from what has been reported in smaller studies in Italy and the United States.

Introduction

Celiac disease (CD) is a lifelong immune-mediated disorder that is triggered by gluten exposure in genetically sensitive individuals (1). Gluten is present in wheat, rye, and barley. CD has been linked to a number of complications such as osteoporosis (2), adverse pregnancy outcome (3), and hematologic disease (4). Recently, we along with others have shown that individuals with CD are at increased risk of certain cancers (5–7), especially lymphoproliferative malignancies (8).

Thyroid cancer (TC) is often diagnosed after detection of a nodule or mass in the neck and ultrasound-guided biopsy, or on a histopathologic examination after partial thyroidectomy. More advanced TC may present with pain and voice involvement. The most common subtype of TC is papillary TC (PTC). Many reports have linked CD and thyroid disease (including autoimmune thyroiditis) (9–17), but few studies have been conducted on CD and the risk of future TC (18–21). We have identified three studies reporting relative risks of TC in CD, but numbers were small and the relative risks varied between 0.6 and 22.5 (19–21), and a fourth study that did not calculate relative risk estimates (18).

Considering this uncertainty, we decided to carry out a population-based study examining the risk of TC in a nationwide cohort of Swedish patients with biopsy-verified CD. Based on the findings of the two most recent papers where study participants were adults (and therefore at greater risk of developing TC) (20,21), we hypothesized that biopsy-verified CD would be positively associated with TC.

Methods

We linked data on CD from biopsy reports (22) obtained from Sweden's 28 pathology departments to data on TC in the Swedish Cancer Register (23). Linkages were made possible through the personal identity number (24) assigned to all Swedish residents.

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Collection of biopsy data

Data from duodenal and jejunal biopsy reports with villous atrophy (VA; Marsh stage 3, signifying CD) (22) were collected from Swedish pathology departments ($n = 28$) in 2006 through 2008. The small intestinal biopsies had been carried out between 1969 and 2008 (Table 1). Validation of VA has since shown a positive predictive value of 95% for CD (22). Although we did not require a positive CD serology for the CD diagnosis, earlier medical records reviews have shown that 88% of individuals with VA and available CD serology data were serologically positive at the time of biopsy (22). Each individual undergoing biopsy was matched with up to five reference individuals through the Total Population Register (matching criteria were age, sex, county, and calendar year).

In this study, we used the same CD cohort ($n = 29,096$) and matched reference individuals ($n = 144,522$) as in our previous study investigating mortality in CD (25). We then excluded individuals with a diagnosis of TC before CD diagnosis and study entry (22 individuals with CD and 82 controls), as well as an additional 40 controls whose index individual with CD had been excluded (all analyses were performed stratum-wise).

Outcome

Our main outcome was a diagnosis of any TC (international classification of disease, ICD7 code = 194 in the Swedish Cancer Register). In our definition of any TC, we excluded cases of medullary TC (pathology code "186") because medullary TC is a genetic TC variant and therefore highly unlikely to be associated with CD.

In separate analyses, we also examined the risk of PTC, defined as: (a) ICD7 = 194, minus pathology code "186" (medullary); (b) restricting pathology codes to "096"; and (c) excluding individuals with any of the following: "SnoMed10" (Systematized Nomenclature of Medicine) pathology codes (83303—follicular, 82900—Hürthle cell oxyphilic, 82903—Hürthle cell oncocytic, 80313—giant cell, 80203—non-differentiated (anaplastic), 80703—squamous epithelium, 83503—sclerosing "Graham," 80413—small cell, and 80123—large cell).

Statistics

Hazard ratios (HRs) for TC were estimated through internally stratified Cox regression. In internally stratified Cox regression, each index individual with CD was compared only with his or her reference individuals within the same stratum. A summary risk estimate was then calculated on the basis of all stratum-specific results. In this way, we eliminated the influence of sex, age, calendar year, and county. The proportional hazards assumption was tested through plotting log minus log curves (available upon request). Expected numbers of TC cases were calculated as the observed number of cases divided by the HR. Hence, the expected number was based on age- and sex-matched data from our general population control cohort, rather than from national trend data.

Follow-up began on the date of the first biopsy with VA and the corresponding date in matched reference individuals. Follow-up ended with TC diagnosis, death, emigration, or on December 31, 2009, whichever occurred first.

In predefined subanalyses, we calculated the HR for TC according to follow-up, age, and calendar year at CD diagnosis. We had initially intended to estimate HRs for both male and female patients with CD, but because of the lack of TC cases in male patients, we calculated only the risk of TC in female patients. Incidence rates as the number of first recorded TC events divided by person years at risk (PYAR) are given in Tables 2 and 3.

Although type 1 diabetes mellitus has not been linked to the risk of TC (26), we chose to adjust for "any diabetes" because a recent paper found a nonsignificant association between self-reported diabetes and TC (27), and CD has been linked to

Table 1. Characteristics of Study Participants

	Matched reference individuals	*Celiac disease*
Total (*n*)	144,400	29,074
Age at study entry, years [median (range)]	30 (0–95)	30 (0–95)
Attained age, years [median (range)]	42 (1–107)	42 (1–100)
Age 0–19 [*n* (%)]	58,852 (40.8)	11,802 (40.6)
Age 20–39 [*n* (%)]	26,375 (18.3)	5310 (18.3)
Age 40–59 [*n* (%)]	32,206 (22.3)	6470 (22.3)
Age ≥60 [*n* (%)]	26,967 (18.7)	5492 (18.9)
Entry year [median (range)]	1998 (1969–2008)	1998 (1969–2008)
Follow-up,[a] years [median (range)]	10 (0–40)	10 (0–40)
Females [*n* (%)]	89,454 (61.9)	17,989 (61.9)
Males [*n* (%)]	54,946 (38.1)	11,085 (38.1)
Calendar year of biopsy and study entry		
1969–1989 [*n* (%)]	20,369 (14.1)	4103 (14.1)
1990–1999 [*n* (%)]	59,809 (41.4)	12,048 (41.4)
2000–2008 [*n* (%)]	64,222 (44.5)	12,923 (44.4)
Country of birth		
Nordic[b] [*n* (%)]	136,163 (94.3)	28,117 (96.7)
Any diabetes [*n* (%)]	6658 (4.6)	2173 (7.5)

[a]Follow-up time until diagnosis of thyroid cancer, death from other cause, emigration, or December 31, 2009. In reference individuals, follow-up can end through small intestinal biopsy.
[b]Sweden, Denmark, Finland, Norway, and Iceland.

Table 2. Hazard Ratios and Corresponding Confidence Intervals for Any Thyroid Cancer and Papillary Thyroid Cancer in Patients with Celiac Disease Diagnosed in Sweden in 1969–2008

Follow-up	Observed events	Expected events	HR [CI]	Absolute risk/ 100,000 PYAR
Thyroid cancer				
All	7	12	0.6 [0.3–1.3]	2.1
<5 years	2	4	0.6 [0.1–2.4]	1.5
5+ years	5	8	0.6 [0.2–1.6]	2.6
Papillary thyroid cancer				
All	5	7	0.7 [0.3–1.8]	1.5
<5 years	1	2	0.5 [0.07–3.9]	0.7
5+ years	4	5	0.8 [0.3–2.2]	2.1

Reference is general population comparator cohort. Estimates from the Cox proportional hazards model internally stratified for age, sex, county, and calendar period.

HR, hazard ratio; CI, confidence interval; PYAR, person years at risk.

type 1 diabetes mellitus (28). We also adjusted for hyperparathyroidism because this disorder has been linked to CD (29), and individuals with hyperparathyroidism may be at increased risk of discovery of TC on neck examination.

We used relevant ICD codes to identify individuals with any diabetes and hyperparathyroidism in the Swedish Patient Register. In separate analyses, we also adjusted for education and country of birth (Nordic country vs. non-Nordic country). These covariates may potentially influence healthcare consumption and the chance of having TC diagnosed.

We used SPSS v18.0 to perform all analyses. HRs with confidence intervals (CIs) that did not include a value of 1 were regarded as statistically significant.

Ethics

The study was approved by the Research Ethics Committee of Karolinska Institutet. Since none of the participants was contacted and individual information was anonymized prior to the analyses, informed consent was not required by the Research Ethics Committee.

Table 3. Hazard Ratios and Corresponding Confidence Intervals for Any Thyroid Cancer in Subgroups of Patients with Celiac Disease Diagnosed in Sweden in 1969–2008

Subgroup	Observed events	Expected events	HR [CI]	Absolute risk/ 100,000 PYAR
Sex				
Males	0	2	n.e.	—
Females	7	10	0.7 [0.3–1.5]	3.4
Age (years)				
<24	2	3	0.8 [0.2–2.3]	1.2
>25	5	9	0.6 [0.2–1.4]	3.0
Calendar period				
Pre 1999	5	8	0.6 [0.2–1.5]	2.0
2000 onward	2	2	1.1 [0.2–4.8]	2.5

Reference is general population comparator cohort. Estimates from the Cox proportional hazards model internally stratified for age, sex, county, and calendar period.

n.e., not estimated.

Results

The study sample consisted of 29,074 individuals with CD and 144,400 reference individuals matched for sex, age, calendar year, and county. Some 62% of study participants were female (Table 1). The median age at CD diagnosis was 30 years.

CD and any TC

During follow-up, there were seven cases of TC versus an expected 12. All seven cases of TC in CD occurred in women. The incidence of any TC in this population was 2.1/100,000 PYAR compared with 3.5/100,000 PYAR in reference individuals. The HR for any TC in CD was 0.6 [CI 0.3–1.3] and did not vary more than marginally with follow-up after diagnosis (Table 2). Adjusting risk estimates for any diabetes, country of birth or education did not affect risk estimates (data not shown), nor was the risk estimate affected by the presence of hyperparathyroidism (data not shown). Excluding the first year of follow-up, the HR remained 0.6 [CI 0.2–1.3], and we found similar risk estimates within the first five years after celiac diagnosis and thereafter (Table 2). When the analysis was restricted to females, the association between CD and TC remained null (HR 0.7 [CI 0.3–1.5]). Because of the lack of TC in male patients with CD, we could not estimate any HR in this group. Risk estimates were similar for each calendar period (until 1999: HR = 0.6; and 2000 onwards: HR = 1.1; Table 3; $p = 0.823$ for interaction between CD and calendar period). Risk estimates were similar in CD patients diagnosed before or after age 25 years (Table 3; $p = 0.691$ for interaction between CD and age at celiac diagnosis).

In a *post hoc* analysis, we examined TC incidence according to calendar year of celiac diagnosis. The incidence rate of TC in individuals diagnosed with CD until 1999 was 5/247,651 PYAR (2.0/100,000 PYAR) versus 43/1,247,493 PYAR (3.5/100,000 PYAR). The TC incidence rate in individuals diagnosed with CD from year 2000 or later was 2/78,654 PYAR (2.5/100,000 PYAR) versus 14/393,935 PYAR (3.6/100,000 PYAR).

CD and PTC

The HR for PTC was 0.7 [CI 0.3–1.8], based on five cases versus seven expected (Table 2). The incidence of PTC in this population was 1.5/100,000 PYAR compared with 2.2/100,000 PYAR in reference individuals. The HRs for PTC were similar in the first five years after celiac diagnosis and thereafter (Table 2).

As was the case with TC overall, HRs did not change with adjustment for any diabetes, country of birth, or education (data not shown). Risk estimates for PTC were almost identical to those for any TC with regards to female patients with CD), and according to age at CD diagnosis as well as calendar period (data not shown).

Discussion

This study found no increased risk of any TC or of PTC in patients with CD. We linked nationwide data on biopsy-verified CD from more than 29,000 patients with CD to the Swedish Cancer Register. The Cancer Register was established in 1958 and has a virtually 100% coverage.

Earlier literature

While Schweizer *et al.* found more TC cases in children ($n = 3$) than expected (18), they were unable to calculate a relative risk of TC because of the lack of reference individuals. Askling *et al.* did not find any risk increase for TC in patients with CD (standardized incidence ratio = 0.6 [CI 0.0–3.3]) (19). But 73% of their study participants were also children, so potentially very few individuals with CD reached an age when TC is prevalent. In addition, their CI did not rule out a substantially increased risk of TC (Askling *et al.* found one case with TC vs. an expected 1.7 cases) (19). In contrast, two recent studies reported increased risks of TC (20,21). An Italian collaborative study of 1757 patients with CD found a 2.5-fold increased risk of PTC (20) (but with a CI that included 1; [CI 0.93–5.55]). Meanwhile, in a clinical cohort of 606 patients with CD, we found three cases of PTC (21), compared with US national surveillance data that corresponded to a relative risk of 22.52 [CI 14.90–34.04] (21).

The discrepancies between the results of the current study and that of Volta *et al.* (20) and Kent *et al.* (21) may be attributable to different study designs and how cases with CD were ascertained. In addition, both these studies were based on patients followed in specialist centers for their CD and thereby were more than likely being examined on a frequent basis. To avoid the risk of selection bias, we used biopsy registers to identify patients with CD in this study; patients identified in referral centers may have a more severe disease than the average patient, and this increase in disease severity can increase the estimate for complications. More than 96% of Swedish pediatricians and gastroenterologists will biopsy at least 90% of patients with CD (22). Although VA may be caused by other diseases than CD, in a Swedish setting, VA has a very high positive predictive value for CD, as demonstrated in a previous validation study (22). When two independent researchers evaluated more than 1500 biopsy reports, diseases other than CD were only rarely mentioned in the biopsy reports (0.3% of VA reports mentioned inflammatory bowel disease) (22).

From an international perspective, the incidence of TC in this study was low in both CD patients and controls. This is probably accounted for by the high number of children who participated in the study (lower absolute risk of TC), but may also be attributable to the low national rates for TC in Sweden (30).

Potential limitations

It is unlikely that the null association between CD and TC was attributable to low statistical power. Although the number of actual TC cases in our study was small, this was mostly because of the lack of positive association between CD and any TC. The expected number of cases with TC in our study was 12 [compared to 1.7 in Askling *et al.* (19); 0.13 in Kent *et al.* (21); and 2.4 in Volta *et al.* (20)]. The expected number of TC in adults was 10 during a follow-up of 179,065 PYAR. This corresponds to an incidence of 5.6/100,000 PYAR in adults, which is consistent with international estimates (31).

We did not have data on dietary adherence in patients with CD. This is a minor shortcoming, since we found no increased risk of TC in CD. In the Italian study by Volta *et al.*, dietary adherence did not protect against TC (20).

We also had no data on body mass index (BMI) or smoking. Obesity is positively associated with TC (32) but inversely related to CD (33). Different BMI in CD patients and controls may therefore have contributed to the nonsignificantly lower risk of TC seen in our cohort of CD patients. Although we lacked data on smoking, smoking is unlikely to explain the neutral relationship seen in this study, as most studies suggest that smoking is inversely related to both thyroid cancer (34) and CD (35).

We were unable to examine the relative risk of TC in male patients with CD. To explore the lack of cases, we went back to our original data set from the Swedish Cancer Register where TC cases were obtained for this study. In that data set, we found a female-to-male ratio of 3:1 in TC cases, consistent with earlier research (36). We therefore believe the lack of TC in male patients with CD was due to insufficient power in this subgroup analysis, especially given the female predominance of CD in this database. The lack of TC cases in male patients with CD is, however, consistent with the main finding of this study that Swedish patients with biopsy-verified CD were at no increased risk of TC.

In conclusion, this study found no association between CD and TC.

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(***Appendix follows →***)

Appendix

ICD coding for type 1 diabetes mellitus

Before 1997, the ICD coding for diabetes (ICD-7: 260, ICD-8: 250, ICD-9: 250) did not distinguish between type 1 and type 2 diabetes. We defined individuals with type 1 diabetes as those who were ≤30 years of age at their first hospitalization for diabetes (ICD-7–ICD-10).

ICD coding for primary hyperparathyroidism

ICD-7: 271.0 and ICD-8: 252.0 (hyperparathyroidism); ICD-9: 252A and ICD-10: E21.0 (primary hyperparathyroidism); Surgery codes: 0851, 0852, 0853, BBA30, BBA40 and BBA50 (Swedish surgical codes for removal of single or multiple parathyroid glands or subtotal parathyroidectomy). *Cancer Register*: ICD-7: 195.1