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

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Abstract

**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. Some 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) 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 7 patients with celiac disease (expected=12) and papillary thyroid cancer developed in 5 patients (expected=7). Celiac disease was not associated with an increased risk of any thyroid cancer (HR, 0.6; 95% CI, 0.3-1.3) or of papillary thyroid cancer (HR, 0.7; 95% CI, 0.3-1.8). All cases of thyroid cancer in celiac disease occurred in female patients. Risk estimates were similar before and after year 2000 and independent of age at celiac diagnosis (≤24 vs. ≥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 from smaller studies in Italy and the US.

**Keywords:** autoimmunity; cancer; celiac; inflammation; malignancy; thyroid
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 and 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.
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 5 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 stratumwise).

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) then excluding individuals with any of the following “SnoMed10” (Systematized Nomenclature of
pathology codes (83303-follicular, 82900-Hürthle cell oxyphilic, 82903- Hürthle cell oncocytic, 80313-giant cell, 80203-nondifferentiated (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 pre-defined 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 non-significant association between self-reported diabetes and TC (27), and CD has been linked to 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 co-variates may potentially influence health care consumption and the chance of having TC diagnosed.

We used SPSS 18.0 to perform all analyses. HRs with 95% 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.

**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 7 cases of TC vs. an expected 12. All 7 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 (95% 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 (95%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; 95%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 and onwards: HR=1.1)(Table 3; p for interaction between CD and calendar period=0.823). Risk estimates were similar in CD patients diagnosed before or after age 25 years (Table 3, p for interaction between CD and age at celiac diagnosis=0.691).

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) vs. 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) vs. 14/393,935 PYAR (3.6/100,000 PYAR).

**CD and PTC**

The HR for PTC was 0.7 (95%CI=0.3-1.8), based on 5 cases vs. 7 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; 95%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 95%CI did not rule out a substantially increased risk of TC (Askling et al. found 1 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 95%CI that included 1; 95%CI=0.93-5.55). Meanwhile, in a clinical cohort of 606 patients with CD we found 3 cases of PTC (21), compared with US national surveillance data that corresponded to a relative risk of 22.52 (95%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, other diseases 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 body mass index in CD patients and controls may therefore have contributed to the non-significantly 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 both to 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 dataset from the Swedish Cancer Register where TC cases were obtained for this study. In that dataset 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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JAM: The National Institutes of Health – DK071003 and DK057892.

Conflicts of interest/Disclosure statement:

JAM: Grant support: Alba Therapeutics (>50,000); Advisory board: Alvine Pharmaceuticals, Inc. (<$10,000), Nexpep (<$10,000), Consultant (none above 10,000 USD): Ironwood, Inc., Flamentera, Actogenix, Ferring Research Institute inc., Bayer Healthcare Pharmaceuticals, Vysera Biomedical, 2G Pharma, Inc, ImmunosanT, Inc and Shire US Inc.

PHG: Advisory board: Alvine Pharmaceuticals, Inc. (<$10,000), Nexpep (<$10,000),
(The other authors have no conflicts of interest to declare).

REFERENCES


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
## Table 1 Characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Matched reference individuals</th>
<th>Celiac disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>144,400</td>
<td>29,074</td>
</tr>
<tr>
<td>Age at study entry, years (median, range)</td>
<td>30, 0-95</td>
<td>30, 0-95</td>
</tr>
<tr>
<td>Attained age, years (median, range)</td>
<td>42; 1-107</td>
<td>42, 1-100</td>
</tr>
<tr>
<td>Age 0-19 (%)</td>
<td>58,852 (40.8)</td>
<td>11,802 (40.6)</td>
</tr>
<tr>
<td>Age 20-39 (%)</td>
<td>26,375 (18.3)</td>
<td>5,310 (18.3)</td>
</tr>
<tr>
<td>Age 40-59 (%)</td>
<td>32,206 (22.3)</td>
<td>6,470 (22.3)</td>
</tr>
<tr>
<td>Age ≥60 (%)</td>
<td>26,967 (18.7)</td>
<td>5,492 (18.9)</td>
</tr>
<tr>
<td>Follow-up†, years (median, range)</td>
<td>10, 0-40</td>
<td>10, 0-40</td>
</tr>
<tr>
<td>Females (%)</td>
<td>89,454 (61.9)</td>
<td>17,989 (61.9)</td>
</tr>
<tr>
<td>Males (%)</td>
<td>54,946 (38.1)</td>
<td>11,085 (38.1)</td>
</tr>
</tbody>
</table>

**Calendar year of biopsy and study entry**

<table>
<thead>
<tr>
<th>Year</th>
<th>Matched reference</th>
<th>Celiac disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1969-1989</td>
<td>20,369 (14.1)</td>
<td>4,103 (14.1)</td>
</tr>
<tr>
<td>1990-99</td>
<td>59,809 (41.4)</td>
<td>12,048 (41.4)</td>
</tr>
<tr>
<td>2000-2008</td>
<td>64,222 (44.5)</td>
<td>12,923 (44.4)</td>
</tr>
</tbody>
</table>

**Country of birth**

<table>
<thead>
<tr>
<th>Country</th>
<th>Matched reference</th>
<th>Celiac disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nordic ‡</td>
<td>136,163 (94.3)</td>
<td>28,117 (96.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Any diabetes</th>
<th>Matched reference</th>
<th>Celiac disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6,658 (4.6)</td>
<td>2,173 (7.5)</td>
</tr>
</tbody>
</table>

†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.

‡ Sweden, Denmark, Finland, Norway and Iceland.
TABLE 2. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for any thyroid cancer and papillary thyroid cancer in patients with celiac disease diagnosed in Sweden in 1969-2008.

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Observed events</th>
<th>Expected events</th>
<th>HR (95% CI)</th>
<th>Absolute risk/100,000 PYAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thyroid</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>7</td>
<td>12</td>
<td>0.6 (0.3-1.3)</td>
<td>2.1</td>
</tr>
<tr>
<td>Year &lt;5</td>
<td>2</td>
<td>4</td>
<td>0.6 (0.1-2.4)</td>
<td>1.5</td>
</tr>
<tr>
<td>5+</td>
<td>5</td>
<td>8</td>
<td>0.6 (0.2-1.6)</td>
<td>2.6</td>
</tr>
<tr>
<td><strong>Papillary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thyroid</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>5</td>
<td>7</td>
<td>0.7 (0.3-1.8)</td>
<td>1.5</td>
</tr>
<tr>
<td>Year &lt;5</td>
<td>1</td>
<td>2</td>
<td>0.5 (0.07-3.9)</td>
<td>0.7</td>
</tr>
<tr>
<td>5+</td>
<td>4</td>
<td>5</td>
<td>0.8 (0.3-2.2)</td>
<td>2.1</td>
</tr>
</tbody>
</table>

PYAR, Person-years at risk.
Reference is general population comparator cohort.
Estimates from the Cox Proportional hazard model internally stratified for age, sex, county and calendar period.
**TABLE 3.** Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for any thyroid cancer in subgroups of patients with celiac disease diagnosed in Sweden in 1969-2008.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Observed events, No.</th>
<th>Expected events, No.</th>
<th>HR (95% CI)</th>
<th>Absolute risk/100,000 PYAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0</td>
<td>2</td>
<td>Not estimated</td>
<td>-</td>
</tr>
<tr>
<td>Females</td>
<td>7</td>
<td>10</td>
<td>0.7 (0.3-1.5)</td>
<td>3.4</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-24</td>
<td>2</td>
<td>3</td>
<td>0.8 (0.2-2.3)</td>
<td>1.2</td>
</tr>
<tr>
<td>25-</td>
<td>5</td>
<td>9</td>
<td>0.6 (0.2-1.4)</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Calendar period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1999</td>
<td>5</td>
<td>8</td>
<td>0.6 (0.2-1.5)</td>
<td>2.0</td>
</tr>
<tr>
<td>2000-</td>
<td>2</td>
<td>2</td>
<td>1.1 (0.2-4.8)</td>
<td>2.5</td>
</tr>
</tbody>
</table>

PYAR, Person-years at risk.
Reference is general population comparator cohort
Estimates from the Cox Proportional hazard model internally stratified for age, sex, county and calendar period.