Cancer Risk in 47,241 Individuals With Celiac Disease: A Nationwide Cohort Study

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BACKGROUND & AIMS: **Celiac disease (CD) is associated with increased mortality, in part due to cancer. Most studies investigating this cancer risk involved patients diagnosed before widespread increases in CD diagnosis rates and access to gluten-free food. We performed a population-based study of the risk of cancer in CD.**

METHODS: **We identified all patients in Sweden with CD as defined as duodenal/jejunal villus atrophy, using the Epidemiology Strengthened by histoPathology Reports in Sweden cohort. Each patient was matched to ≤5 controls by age, sex, and county. We used stratified Cox proportional hazards model, following patients from diagnosis until first cancer, or by December 31, 2016.**

RESULTS: **Among 47,241 patients with CD, 30,080 (64%) were diagnosed since 2000. After a median follow-up of 11.5 years, the incidence of cancer was 6.5 and 5.7 per 1000 person-years in CD patients and controls, respectively. The overall risk of cancer was increased (hazard ratio [HR], 1.11; 95% confidence interval [CI], 1.07–1.15), but it was only significantly elevated in the first year after CD diagnosis (HR, 2.47; 95% CI, 2.22–2.74) and not subsequently (HR, 1.01; 95% CI, 0.97–1.05), although the risks of hematologic, lymphoproliferative, hepatobiliary, and pancreatic cancers persisted. The overall risk was highest in those diagnosed with CD after age 60 years (HR, 1.22; 95% CI, 1.16–1.29) and was not increased in those diagnosed before age 40. The cancer risk was similar among those diagnosed with CD before or after the year 2000.**

CONCLUSIONS: **There is an increased risk of cancer in CD even in recent years, but this risk increase is confined to those diagnosed with CD after age 40 and is primarily present within the first year of diagnosis.**

Keywords: Celiac Disease; Cancer; Epidemiology.

Patients with celiac disease (CD) are at increased risk of death,[1] and a recent analysis of cause-specific mortality in Sweden by our group found that death due to cancer is increased in those with CD (hazard ratio [HR], 1.29; 95% confidence interval [CI], 1.22–1.36),[2] but others have found mortality from cancers not to be increased.[3,4] Multiple prior studies have found that CD is associated with a risk of various malignancies,[5] particularly lymphomas,[6,7] small intestinal adenocarcinoma,[8] and other gastrointestinal malignancies.[9–12] However, these studies were mainly based on data from patients diagnosed in the 20th century before widespread serologic testing for CD, possibly representing a more severe disease phenotype. It is unknown whether a diagnosis of CD still carries an increased risk of cancer and whether that risk persists in the long-term.

Abbreviations used in this paper: **CD, celiac disease; CI, confidence interval; HR, hazard ratio; OR, odds ratio; VA, villus atrophy.**

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Methods

Study Design

Through the personal identity number[13] we linked data on CD to validated Swedish health registers to calculate absolute and relative risks of cancer, compared with reference individuals from the general population. During 2015–2017, we obtained gastrointestinal histologic report data on 2.1 million Swedish individuals biopsied in 1965–2016. Data were retrieved from Sweden's 28 pathology departments and part of the Epidemiology Strengthened by histoPathology Reports in Sweden cohort.[14]

Exposure: Biopsy-Verified Celiac Disease

Our exposure was CD and was defined as having relevant Systematized Nomenclature of Medicine (SnoMed) codes corresponding to villus atrophy (VA) (Supplementary Table 1) in the small intestine (other than the ileum) through December 31, 2016. Biopsy-reported VA has previously been validated with a positive predictive value of 95% for a clinical CD diagnosis.[15]

Controls

The government agency Statistics Sweden then matched each CD patient with up to 5 controls without CD from the Swedish general population.[16] Matching factors were age, sex, calendar year, and county.

In the main analysis, we excluded CD patients and controls with a record of cancer preceding the date of CD diagnosis (defined as the time of the first small intestinal biopsy showing VA) or the corresponding date for controls (Figure 1).

What You Need to Know

Background

Prior studies have linked celiac disease to risk of cancer but were largely done in the 20th century before widespread serologic testing and broad access to gluten-free food.

Findings

This cohort study of 47,241 individuals with celiac disease diagnosed through small intestinal biopsy found a 1.11-fold increased risk of cancer, where most of the excess risk was due to gastrointestinal and hematologic/lymphoproliferative cancer. The cancer incidence in celiac disease vs reference individuals from the general population was 6.5 and 5.7 per 1000 person-years, respectively. The risk increase for cancer overall was only seen in the first year after celiac disease diagnosis, but persistent increases beyond 1 year were seen in hematologic, hepatobiliary, and pancreatic cancers.

Implications for patient care

The excess risk of cancer in celiac disease is present, but it is small, primarily restricted to the first year after celiac disease diagnosis, and limited to certain gastrointestinal and hematologic cancers.

Outcomes

Our primary outcome was any solid organ or hematologic cancer recorded in the Swedish Cancer Register.[17] Our secondary outcomes consisted of solid organ cancers as a group, hematologic cancers as a group, and specifically gastrointestinal cancer, lung cancer, and breast cancer (Supplementary Table 2 lists

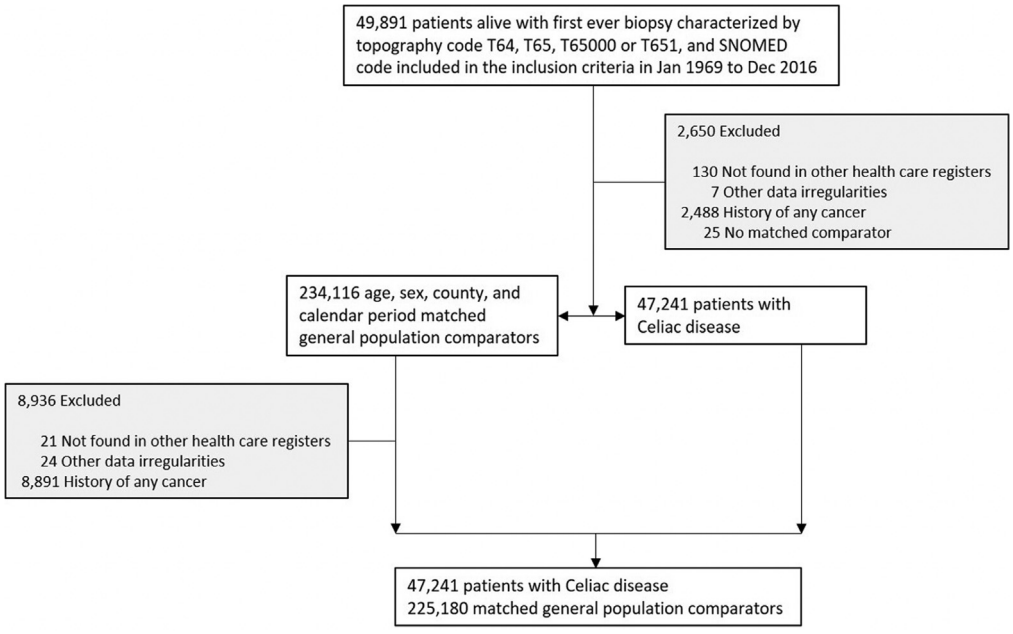

Figure 1. Identification of patients with celiac disease and matched controls.

relevant International Classification of Disease codes for each cancer).

Statistics

Using conditional Cox regression, we estimated HRs for incident diagnosis of cancer with associated 95% CIs. At a 0.05 significance level we had 80% power to detect a HR of 1.06 for incident cancer. The main analyses were conditioned on matching factors (age, sex, county, and calendar year), with multivariable analyses conditioned on the matching factors but also adjusted for the possible confounding effect from education level (derived from the longitudinal integrated database for health insurance and labor market studies),[18] country of birth (Nordic vs not Nordic),[18] and common immune-mediated diseases associated with CD and derived from the National Patient Register[19] Supplementary Table 3). We included immune-mediated diseases as separate time-dependent variables, meaning individuals were defined as having these immune-mediated diseases from the time of their diagnosis throughout follow-up. Education was categorized into compulsory school (0–9 years), upper secondary (10–12 years), and college or university (≥13 years). For study participants diagnosed <18 years of age, we instead retrieved data on the 2 parents' highest attained education. Missing data on education (<5%) and country of birth (<1%) were replaced by using a missing indicator category.

We tested the proportional hazards assumption by including an interaction term of CD and follow-up (survival) time in the model. The proportional hazards assumption was violated for overall follow-up and the first year of follow-up; beyond the first year, the proportional hazard assumption was valid. For this reason, we present an overall HR, follow-up time-specific HRs, and HRs in which follow-up time commences 1 year after CD diagnosis.

Follow-up began with the first biopsy with VA (or corresponding date in matched controls) and ended with first cancer, death, emigration, or December 31, 2016.

In subsequent stratified analyses, we examined HRs and incidence rates for any cancer according to follow-up time, age at diagnosis, sex, country of birth, education, and calendar period. To examine whether the cancer risk had changed over the calendar period, we carried out an additional analysis where we limited the follow-up of study participants to the first 5 years of follow-up.

Cancer Before Celiac Disease Diagnosis (Case-Control Study)

Through conditional logistic regression we estimated odds ratios for any cancer before CD diagnosis compared with matched general populations controls, using the same matching parameters as the primary analysis.

Sensitivity Analyses

Discordant siblings as comparators. To minimize the influence of genetic and environmental factors shared within families, we performed a sibling comparison. We identified those CD patients in the main analysis with at least 1 full sibling recorded in the Swedish Total Population Register.[16] Siblings had to be alive and without a history of cancer at the time of the index case's CD diagnosis to be included in this subanalysis. We compared the risk of cancer among CD patients with their non-CD siblings, using calendar time as the scale, and conditioned on the family unit.

Era of non-biopsy diagnosis. In 2012, the European Society for Pediatric Gastroenterology Hepatology and Nutrition issued guidelines allowing children to be diagnosed without the use of small intestinal biopsy, if stipulated clinical and laboratory conditions were fulfilled.[20] To determine to what extent these new guidelines impact cancer risk estimates, we repeated the main analysis, comparing children (<18 years) diagnosed 2010–2011 with children diagnosed 2012–2014. In this analysis, we censored at 3 years of follow-up so that the relative importance of the first year of follow-up would be equal when the HR was estimated.

Exclusion criteria based on cancer history. Because cancer is a heterogeneous group of diseases, we repeated the analysis of the risk of specific cancers, now excluding individuals on the basis of their history of each specific cancer (and not any cancer). We also repeated the analysis, now not excluding any patient, regardless of their cancer history; in that analysis, the outcome was the first new cancer that developed after the start of follow-up.

Mucosal Healing and Cancer

A subset of patients with CD had a follow-up biopsy (ie, control biopsy) to document mucosal healing within 0.5–5 years after CD diagnosis. These individuals were divided according to the control biopsy appearance (persistent VA [Marsh 3] vs mucosal healing [Marsh 0–2]). We examined mucosal healing on follow-up biopsy and risk of any cancer as well as for specific cancers. We adjusted for matching factors as well as for the duration of CD diagnosis at the time of control biopsy, education, country of birth, and the above-mentioned immune-mediated diseases associated with CD.

Ethics

This study was approved by the Stockholm Ethics Review Board on August 27, 2014.

Results

Among 49,891 patients with CD, 2650 (5.3%) were excluded because of lack of data in other health care registers, data irregularities, lack of controls, or a history of any cancer at the start of follow-up (Figure 1). The remaining 47,241 patients with CD were matched to 225,180 controls. Some 64% of patients with CD had been diagnosed since January 1, 2000.

Characteristics of patients with CD and matched controls are shown in Table 1. At the start of follow-up, the mean age was 30.6 years for CD patients and 29.2 years for controls. In both groups, 62% were female. The median follow-up time was 11.3 years in CD patients and 11.5 years in controls. Type 1 diabetes, autoimmune thyroid disease, rheumatoid arthritis, and inflammatory bowel disease were more common in patients with CD than in controls (Table 1).

When examining any cancer as an outcome during follow-up, this outcome occurred in 8.2% of CD patients and 7.3% of controls (Table 2). The overall incidence of cancer was 6.5 and 5.7 per 1000 person-years in CD patients and controls, respectively (Figure 2) and corresponds to an absolute difference of 0.8 cancer cases per 1000 person-years or 1 extra case of cancer in 125 CD patients followed for 10 years. Hence, the cancer risk was increased in CD patients (HR, 1.11; 95% CI, 1.07–1.15).

The association between CD and cancer was restricted to the first year after CD diagnosis (HR, 2.47; 95% CI, 2.22–2.74). When starting follow-up 1 year after CD diagnosis, the association between CD and any cancer approximated 1 (HR, 1.01; 95% CI, 0.97–1.05). The association between CD and cancer was greater for men (HR, 1.22; 95% CI, 1.15–1.29) than for women (HR, 1.05; 95% CI, 1.00–1.10, P for interaction $<.001$). This sex difference was only partially attenuated when recalculating the risk for women, now excluding breast cancer as an outcome: HR, 1.10; 95% CI, 1.04–1.16. The cancer risk was increased among those diagnosed with CD at age $\geq$60 years (1.22; 95% CI, 1.16–1.29) or between 40 and 59 years (HR, 1.07; 95% CI, 1.01–1.14) but not for those diagnosed at a younger age. When starting follow-up at 1 year after diagnosis, these age differences were no longer present, and no age category was associated with an overall risk of cancer (Table 2). Restricting the follow-up to the first 5 years of diagnosis, the association between CD and cancer was similar among those diagnosed with CD after 2000 compared with earlier eras (Table 2).

When examining cancer subtypes (Table 3), the strongest association between CD and cancer was for hematologic cancers (HR, 1.90; 95% CI, 1.70–2.13), lymphoproliferative cancers (HR, 2.20; 95% CI, 1.94–2.49), and gastrointestinal cancers (HR, 1.34; 95% CI, 1.24–1.45). When examining gastrointestinal cancer subtypes, elevated risks were found for hepatobiliary cancer (HR, 1.80; 95% CI, 1.44–2.25) and pancreatic cancer (HR, 2.30; 95% CI, 1.87–2.82) but not for gastric cancer (HR, 1.21; 95% CI, 0.91–1.61) or colorectal cancer (HR, 1.06; 95% CI, 0.96–1.18). Patients with CD had a

Table 1. Baseline Characteristics of Study Cohort

Characteristic	Celiac disease (n = 47,241)	Matched comparators (n = 225,180)
Female, n (%)	29,381 (62.2)	139,332 (61.9)
Male, n (%)	17,860 (37.8)	85,848 (38.1)
Age (*y*)		
Mean (SD)	30.6 (24.6)	29.2 (24.0)
Median (IQR)	26.0 (7.7–50.9)	23.8 (7.1–48.6)
Range, minimum-maximum	0.0–95.4	0.0–95.1
Categories, n *(%)*		
<18 y	19,578 (41.4)	97,726 (43.4)
18 to <40 y	10,640 (22.5)	51,865 (23.0)
40 to <60 y	9276 (19.6)	43,121 (19.1)
≥60 y	7747 (16.4)	32,468 (14.4)
Country of birth, n (%)		
Nordic country	45.272 (95.8)	206,415 (91.7)
Other	1967 (4.2)	18,754 (8.3)
Missing	2 (0.0)	11 (0.0)
Level of education, n (%)		
≤9 y	7811 (16.5)	37,283 (16.6)
10–12 y	10,959 (23.2)	50,993 (22.6)
>12 y	7478 (15.8)	32,746 (14.5)
Missing	20,993 (44.4)	104,158 (46.3)
Level of education using highest level of education in parents when missing, n (%)		
≤9 y	8969 (19.0)	43,988 (19.5)
10–12 y	19,162 (40.6)	91,601 (40.7)
>12 y	17,216 (36.4)	80,432 (35.7)
Missing	1894 (4.0)	9159 (4.1)
Start year of follow-up		
1969–1989	4181 (8.9%)	20,278 (9.0)
1990–1999	12,980 (27.5)	62,070 (27.6)
2000–2009	18,860 (39.9)	89,493 (39.7)
2010–2016	11,220 (23.8)	53,339 (23.7)
Disease history ever before start of follow-up, n (%)		
Type 1 diabetes	1545 (3.3)	626 (0.3)
Autoimmune thyroid disease	999 (2.1)	1397 (0.6)
Rheumatoid arthritis	375 (0.8)	841 (0.4)
Inflammatory bowel disease	1274 (2.7)	312 (0.1)
Follow-up, *y*		
Mean (SD)	12.6 (8.3)	12.7 (8.3)
Median (IQR)	11.3 (5.8–18.3)	11.5 (5.9–18.6)
Range, minimum-maximum	0.0–47.5	0.0–47.5
Death during follow-up, n (%)	3523 (7.5)	13,999 (6.2)

IQR, interquartile range; SD, standard deviation.

Table 2. Risks and Hazard Ratios for Any Cancer Overall and by Subgroups in Patients With Celiac Disease and Matched General Population Comparators

Group	N (column %)		N events (row %)		Incidence rate (95% CI) per 1000 person-years		HR[a] (95% CI)	HR, starting 1 year later[b]	HR[c] (95% CI)
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators			
Overall	47,241 (100%)	225,180 (100%)	3887 (8.2%)	16,438 (7.3%)	6.5 (6.3–6.7)	5.7 (5.6–5.8)	1.11 (1.07–1.15)	1.01 (0.97–1.05)	1.08 (1.04–1.12)
Follow-up (*y*)									
0 to <1	47,241 (100%)	225,180 (100%)	571 (1.2%)	1043 (0.5%)	12.3 (11.3–13.3)	4.7 (4.4–5.0)	2.47 (2.22–2.74)	NA	1.37 2.13–2.64)
1 to <5	45,516 (96.3%)	218,699 (97.1%)	893 (2.0%)	3860 (1.8%)	5.4 (5.0–5.7)	4.8 (4.7–5.0)	1.05 (0.98–1.13)	NA	1.03 (0.95–1.11)
5 to <10	37,244 (78.8%)	178,702 (79.4%)	863 (2.3%)	4039 (2.3%)	5.4 (5.1–5.8)	5.3 (5.1–5.5)	0.99 (0.92–1.07)	NA	0.96 (0.89–1.04)
≥10	26,462 (56.0%)	127,295 (56.5%)	1560 (5.9%)	7496 (5.9%)	7.0 (6.6–7.3)	6.9 (6.7–7.0)	1.00 (0.95–1.06)	NA	0.97 (0.91–1.03)
≥1	45,516 (96.3%)	218,699 (97.1%)	3316 (7.3%)	15,395 (7.0%)	6.0 (5.8–6.3)	5.8 (5.7–5.9)	1.01 (0.97–1.05)	NA	0.98 (0.94–1.02)
Sex									
Female	29,381 (62.2%)	139,332 (61.9%)	2191 (7.5%)	9584 (6.9%)	5.9 (5.6–6.1)	5.4 (5.3–5.5)	1.05 (1.00–1.10)	0.97 (0.92–1.02)	1.03 (0.98–1.08)
Male	17,860 (37.8%)	85,848 (38.1%)	1696 (9.5%)	6854 (8.0%)	7.7 (7.3–8.0)	6.3 (6.1–6.4)	1.22 (1.15–1.29)	1.08 (1.02–1.15)	1.17 (1.10–1.24)
Age (*y*)									
<18	19,578 (41.4%)	97,726 (43.4%)	238 (1.2%)	1163 (1.2%)	0.8 (0.7–1.0)	0.8 (0.8–0.9)	1.00 (0.87–1.15)	0.99 (0.86–1.14)	1.00 (0.86–1.15)
18 to <40	10,640 (22.5%)	51,865 (23.0%)	524 (4.9%)	2473 (4.8%)	4.1 (3.8–4.5)	4.0 (3.9–4.2)	1.00 (0.91–1.10)	0.99 (0.90–1.10)	0.94 (0.85–1.04)
40 to <60	9276 (19.6%)	43,121 (19.1%)	1401 (15.1%)	6311 (14.6%)	11.6 (10.9–12.2)	11.0 (10.7–11.2)	1.07 (1.01–1.14)	1.01 (0.94–1.07)	1.05 (0.98–1.11)
≥60	7747 (16.4%)	32,468 (14.4%)	1724 (22.3%)	6491 (20.0%)	26.8 (25.5–28.0)	22.2 (21.7–22.7)	1.22 (1.16–1.29)	1.03 (0.96–1.10)	1.19 (1.13–1.27)
Year									
1969–1989	4181 (8.9%)	20,278 (9.0%)	653 (15.6%)	3001 (14.8%)	6.2 (5.7–6.7)	5.8 (5.6–6.0)	1.06 (0.97–1.16)	1.00 (0.91–1.10)	1.03 (0.94–1.13)
1990–1999	12,980 (27.5%)	62,070 (27.6%)	1524 (11.7%)	6732 (10.8%)	6.3 (6.0–6.6)	5.8 (5.6–5.9)	1.09 (1.03–1.16)	1.02 (0.96–1.08)	1.06 (1.00–1.13)
2000–2009	18,860 (39.9%)	89,493 (39.7%)	1377 (7.3%)	5668 (6.3%)	6.7 (6.3–7.0)	5.8 (5.6–5.9)	1.10 (1.03–1.17)	0.99 (0.93–1.06)	1.07 (1.00–1.14)
2010–2016	11,220 (23.8%)	53,339 (23.7%)	333 (3.0%)	1037 (1.9%)	7.7 (6.9–8.6)	5.0 (4.7–5.3)	1.44 (1.27–1.64)	1.14 (0.97–1.33)	1.40 (1.23–1.59)
Year – first 5 years of follow-up									
1969–1989	4181 (8.9%)	20,278 (9.0%)	653 (15.6%)	3001 (14.8%)	6.2 (5.7–6.7)	5.8 (5.6–6.0)	1.06 (0.97–1.16)	1.00 (0.91–1.10)	1.03 (0.94–1.13)
1990–1999	12,980 (27.5%)	62,070 (27.6%)	394 (3.0%)	1358 (2.2%)	6.3 (5.7–7.0)	4.5 (4.3–4.8)	1.37 (1.22–1.54)	1.02 (0.88–1.17)	1.33 (1.19–1.50)
2000–2009	18,860 (39.9%)	89,493 (39.7%)	630 (3.3%)	2226 (2.5%)	6.9 (6.4–7.5)	5.2 (4.9–5.4)	1.26 (1.15–1.38)	1.00 (0.90–1.12)	1.24 (1.13–1.36)
2010–2011	3929 (8.3%)	18,770 (8.3%)	143 (3.6%)	425 (2.3%)	7.6 (6.3–8.8)	4.7 (4.2–5.1)	1.54 (1.27–1.87)	1.06 (0.83–1.35)	1.48 (1.21–1.81)
Country of birth									
Nordic	45,272 (95.8%)	206,415 (91.7%)	3756 (8.3%)	15,539 (7.5%)	6.5 (6.3–6.7)	5.8 (5.7–5.9)	1.10 (1.06–1.14)	1.00 (0.96–1.04)	1.08 (1.04–1.12)
Other	1967 (4.2%)	18,754 (8.3%)	131 (6.7%)	899 (4.8%)	7.1 (5.9–8.3)	5.1 (4.8–5.5)	1.88 (1.20–2.95)	1.65 (1.00–2.71)	1.64 (1.02–2.64)
Level of education (*y*)									
≤9	8969 (19.0%)	43,988 (19.5%)	1239 (13.8%)	5364 (12.2%)	11.5 (10.8–12.1)	10.0 (9.7–10.2)	1.13 (1.04–1.22)	1.00 (0.91–1.08)	1.12 (1.03–1.21)
10–12	19,162 (40.6%)	91,601 (40.7%)	1365 (7.1%)	5683 (6.2%)	5.4 (5.1–5.6)	4.7 (4.6–4.8)	1.11 (1.03–1.19)	1.02 (0.94–1.11)	1.08 (1.00–1.16)
>12	17,216 (36.4%)	80,432 (35.7%)	791 (4.6%)	3316 (4.1%)	3.9 (3.6–4.1)	3.4 (3.3–3.5)	0.97 (0.87–1.08)	0.95 (0.85–1.07)	0.94 (0.84–1.06)

CI, confidence interval; HR, hazard ratio; NA, not applicable (time stratum with follow-up time starting 1 year after diagnosis).

[a]Conditioned on matching set (age, sex, county, and calendar period).

[b]Conditioned on matching set (age, sex, county, and calendar period), starting follow-up 1 year after celiac disease diagnosis.

[c]Conditioned on matching set and further adjusted for education, Nordic country of birth, and the onset of medical comorbidities: type 1 diabetes, autoimmune thyroid disease, rheumatoid arthritis, and inflammatory bowel disease.

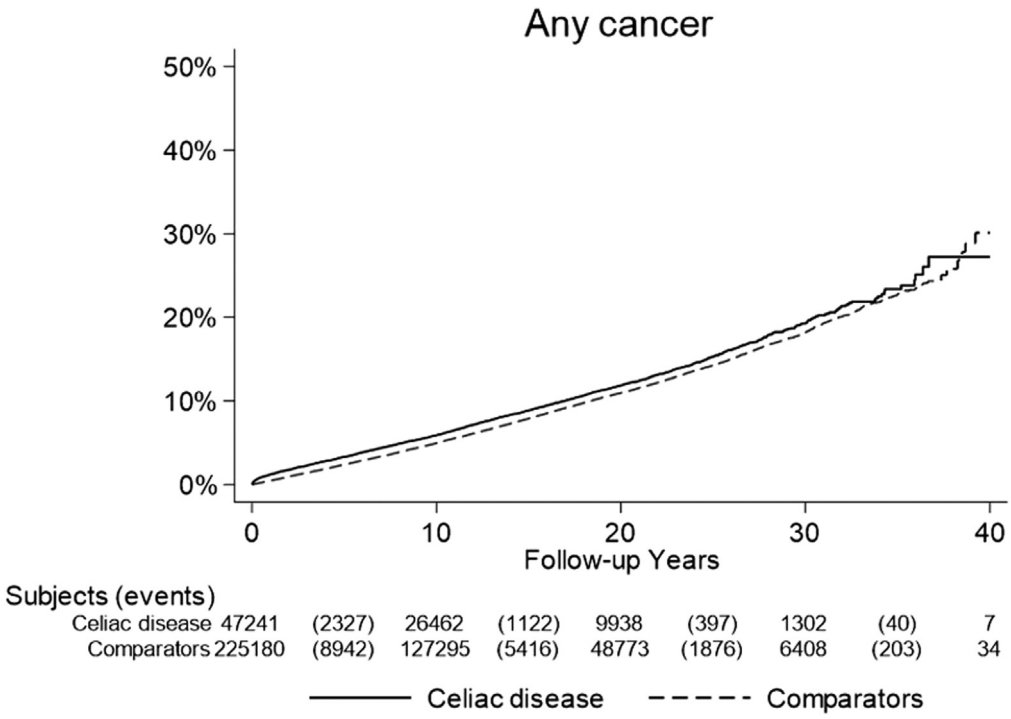

Figure 2. Risk of any cancer in patients with celiac disease and matched controls.

decreased risk of breast cancer (HR, 0.83; 95% CI, 0.74–0.92) and lung cancer (HR, 0.88; 95% CI, 0.75–1.03). Although there was no overall cancer risk when starting follow-up 1 year after CD diagnosis, there were significantly elevated risks in that time horizon for several cancer subtypes including hematologic cancers (HR, 1.52; 95% CI, 1.34–1.73) and lymphoproliferative cancers (HR, 1.75; 95% CI, 1.52–2.01). The increased risk of gastrointestinal cancers collectively was no longer significant beyond 1 year after CD diagnosis (HR, 1.05; 95% CI, 0.96–1.15) but persisted for hepatobiliary cancers (HR, 1.61; 95% CI, 1.26–2.05) and pancreatic cancer (HR, 1.66; 95% CI, 1.32–2.10).

When we examined the risk of a patient diagnosed with CD to have previously developed cancer (Table 4, Supplementary Figure 1), we found the OR for any previous cancer was 1.18 (95% CI, 1.12–1.24) in individuals diagnosed with CD compared with matched general population controls. There were significantly increased ORs for a history of solid cancers (OR, 1.13; 95% CI, 1.08–1.19), its subset of gastrointestinal cancers (OR, 5.24; 95% CI, 4.51–6.08), and hematologic cancers (HR, 2.11; 95% CI, 1.80–2.49). There was a reduced risk of lung cancer (HR, 0.81; 95% CI, 0.54–1.22) and breast cancer (OR, 0.88; 95% CI, 0.78–1.00) before CD diagnosis.

Sensitivity Analyses

We identified 30,998 patients with CD who had at least 1 sibling without CD (Supplementary Figure 2, Supplementary Tables 4, 5, and 6). When comparing these patients with their siblings (n = 52,546) and adjusting for age, we found an increased risk of cancer among those with CD (HR, 1.20; 95% CI, 1.12–1.28). Similar to the main analysis, this association was diminished beyond 1 year after diagnosis (HR, 1.08; 95% CI, 1.01–1.16). The sibling analysis of specific cancer types yielded mostly similar results as in our main analysis.

When examining pediatric patients diagnosed in 2010–2011 (before guidelines offering a non-biopsy approach to CD diagnosis) and those diagnosed in 2012–2013 (subsequent to non-biopsy guidelines), the risk of cancer in CD was increased in both eras (Supplementary Table 7).

When we repeated the analysis of cancer-specific subtypes, now excluding individuals on the basis of a history of each specific cancer (and not cancer as a whole), the risk was increased among CD patients for solid cancer (HR 1.05), hematologic cancer (HR 1.86), and gastrointestinal cancer (HR 1.37) and was decreased for lung cancer (HR 0.86) and breast cancer (HR 0.80; Supplementary Table 8). The results were similar when performing the analysis including individuals with any history of cancer (Supplementary Table 9).

Mucosal Healing

There were 9010 individuals with CD who underwent a follow-up biopsy after 0.5–5 years (Supplementary Table 10). After adjusting for age, sex, calendar year, duration of CD diagnosis at the time of follow-up biopsy, educational attainment, country of birth, and specific immune-mediated diseases, there was not an association between persistent VA and any cancer overall (HR, 1.01; 95% CI, 0.87–1.18) or within patient subgroups defined

Table 3. Risks and Hazard Ratios for Cancer Types in Patients With Celiac Disease and Matched General Population Comparators (N Celiac Disease/N Comparators = 47,241/225,180)

Group	N events (%)		Time at risk (*y*)		Incidence rate (95% CI) per 1000 person-years				
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	HR[a] (95% CI)	HR, starting 1 y later[b]	HR [c] (95% CI)
Any cancer	3887 (8.2)	16,438 (7.3)	594,858	2,870,069	6.5 (6.3–6.7)	5.7 (5.6–5.8)	1.11 (1.07–1.15)	1.01 (0.97–1.05)	1.08 (1.04–1.12)
Solid cancer	3495 (7.4)	15,514 (6.9)	596,393	2,874,724	5.9 (5.7–6.1)	5.4 (5.3–5.5)	1.05 (1.01–1.09)	0.97 (0.93–1.01)	1.07 (1.03–1.12)
Hematologic cancer	445 (0.9)	1150 (0.5)	613,160	2,952,932	0.7 (0.7–0.8)	0.4 (0.4–0.4)	1.90 (1.70–2.13)	1.52 (1.34–1.73)	1.92 (1.71–2.16)
Lymphoproliferative cancer	392 (0.8)	877 (0.4)	613,384	2,953,942	0.6 (0.6–0.7)	0.3 (0.3–0.3)	2.20 (1.94–2.49)	1.75 (1.52–2.01)	2.19 (1.93–2.50)
Gastrointestinal cancer	857 (1.8)	2989 (1.3)	611,725	2,947,348	1.4 (1.3–1.5)	1.0 (1.0–1.1)	1.34 (1.24–1.45)	1.05 (0.96–1.15)	1.32 (1.22–1.43)
Gastric	65 (0.1)	259 (0.1)	614,643	2,957,628	0.1 (0.1–0.1)	0.1 (0.1–0.1)	1.21 (0.91–1.61)	0.94 (0.68–1.29)	1.20 (0.89–1.61)
Colorectal	448 (0.9)	1972 (0.9)	612,479	2,948,829	0.7 (0.7–0.8)	0.7 (0.6–0.7)	1.06 (0.96–1.18)	0.85 (0.76–0.96)	1.08 (0.96–1.20)
Hepatobiliary (liver/gallbladder)	115 (0.2)	297 (0.1)	614,716	2,957,831	0.2 (0.2–0.2)	0.1 (0.1–0.1)	1.80 (1.44–2.25)	1.61 (1.26–2.05)	1.45 (1.13–1.86)
Pancreatic	152 (0.3)	302 (0.1)	614,734	2,957,969	0.2 (0.2–0.3)	0.1 (0.1–0.1)	2.30 (1.87–2.82)	1.66 (1.32–2.10)	2.29 (1.84–2.84)
Lung cancer	196 (0.4)	1029 (0.5)	614,495	2,956,551	0.3 (0.3–0.4)	0.3 (0.3–0.4)	0.88 (0.75–1.03)	0.84 (0.71–0.99)	0.92 (0.78–1.08)
Breast cancer (women)	383 (1.3)	2093 (1.5)	383,218	1,819,396	1.0 (0.9–1.1)	1.2 (1.1–1.2)	0.83 (0.74–0.92)	0.81 (0.72–0.90)	0.87 (0.77–0.97)

CI, confidence interval; HR, hazard ratio.

[a]Conditioned on matching set (age, sex, county, and calendar period).

[b]Conditioned on matching set (age, sex, county, and calendar period), starting follow-up 1 year after celiac disease diagnosis.

[c]Conditioned on matching set and further adjusted for education, Nordic country of birth, and time-dependent medical comorbidities (type 1 diabetes, autoimmune thyroid disease, rheumatoid arthritis, and inflammatory bowel disease).

Table 4. Risk of Cancer in Patients With Celiac Disease and Matched General Population Comparators Before Start of Follow-Up (N Celiac Disease/N Comparators = 49,744/246,009)

Group	N events (%)		Odds ratio[a] (95% CI)	Odds ratio[b](95% CI)
	Celiac disease	Comparators		
Any cancer	2488 (5.0)	10,377 (4.2)	1.18 (1.12–1.24)	1.10 (1.04–1.15)
Solid cancer	2305 (4.6)	9965 (4.1)	1.13 (1.08–1.19)	1.07 (1.01–1.12)
Hematologic cancer	212 (0.4)	484 (0.2)	2.11 (1.80–2.49)	1.73 (1.43–2.09)
Gastrointestinal cancer	383 (0.8)	347 (0.1)	5.24 (4.51–6.08)	3.87 (3.27–4.59)
Lung cancer	27 (0.1)	155 (0.1)	0.81 (0.54–1.22)	0.61 (0.34–1.08)
Breast cancer (women)	308 (1.0)	1679 (1.1)	0.88 (0.78–1.00)	0.90 (0.79–1.03)

CI, confidence interval.
[a]Conditioned on matching set (age, sex, county, and calendar period).
[b]Conditioned on matching set (age, sex, county, and calendar period), excluding cancers in the year preceding celiac disease diagnosis.

by these covariates (Supplementary Table 11). Persistent VA was associated with an increased risk of hematologic cancers (HR, 1.79; 95% CI, 1.09–2.93) and lymphoproliferative cancers (HR, 1.87; 95% CI, 1.11–3.16) but a lower risk of breast cancer (HR, 0.56; 95% CI, 0.35–0.92; Supplementary Table 12).

Discussion

This nationwide study of more than 47,000 individuals in Sweden with CD found a small excess risk of any cancer. This excess risk remained in the sensitivity analysis using siblings as controls, which reduces intrafamilial confounding. The increased overall cancer risk was only seen in the first year of follow-up, but the risk of malignancy subtypes including hematologic and lymphoproliferative cancers, as well as hepatobiliary and pancreatic cancer, persisted in the long-term. The cancer risk was similar among those diagnosed with CD before or after the year 2000.

Our finding that the increased risk of cancer was restricted to the first year of diagnosis is consistent with prior studies of morbidity and mortality in CD.[2,9,21] This excess risk, followed by a decline to no risk, may be due in part to the gluten-free diet's salubrious effect, which occurs within weeks for clinical symptoms and months to years for histologic improvement. Still, it may alternatively be due to the increased surveillance and medical investigation among CD patients. Moreover, symptoms of cancer (eg, weight loss) may lead to a broad diagnostic workup that reveals CD. Although the risk of cancer overall was no longer significantly elevated beyond 1 year after CD diagnosis, a long-term risk was still observed in certain cancer subtypes.

The sex-stratified analysis revealed that the cancer risk in CD was elevated in men but not women, only partly related to the reduced breast cancer risk found in this cohort. This sex discrepancy was still present when excluding breast cancer from the outcome. This discrepancy may be related to underlying sex-specific differences in cancer risk,[22] indications for CD testing, and the course of CD.

We found that the risk of cancer in CD varied by cancer subtype, and that it was increased in gastrointestinal malignancies but decreased in breast and lung cancer. The decreased risk of lung cancer may be attributed to lower smoking rates observed in individuals with CD,[23] whereas the decreased risk of breast cancer may also be due to lower body mass index in patients with CD.[24] Breast cancer incidence is also reduced in women with anorexia nervosa,[25] another disorder characterized by low weight. Within the category of gastrointestinal malignancies, risk varied as well, with significantly elevated risks of hepatobiliary and pancreatic cancer but not gastric or colorectal cancer. A prior analysis of this cohort found that the risk of small intestinal adenocarcinoma persists for up to 10 years in CD.[8] The incidences of cancer types vary widely by secular trends, the age and geographical region of the study population, as does the ascertainment of CD, which all may explain why increased cancer (or cancer-related mortality) risk as a whole has been identified in some[2,26] but not all[1,3] studies examining this association.

Patients with persistent VA were at increased risk for lymphoproliferative cancers. This is compatible with a prior estimate using a subset in this cohort from an earlier calendar period.[27] Although the mechanism by which persistent VA (apart from the rare refractory CD[28]) confers this risk is unknown, this study suggests that this risk is confined to lymphoproliferative cancer and does not apply to other cancers. Our finding of a substantially reduced risk of breast cancer (HR 0.56) among those with persistent VA warrants further study.

Strengths and Limitations

We used histopathology data from Sweden's all 28 pathology departments to identify individuals with VA, which

was equaled to CD. An earlier validation study has shown that 95% of Swedish patients with VA have CD,[15] and a high positive predictive value has also been confirmed in individuals undergoing small intestinal biopsy with VA in the last decade.[29] Serology was not incorporated into this analysis; serology has become increasingly important in CD diagnostics, and in 2012 the pediatric gastrointestinal organization European Society for Pediatric Gastroenterology, Hepatology, and Nutrition allowed for the nonbiopsy diagnosis of CD.[20] We examined the importance of that diagnostic change and found that the risk of cancer remained increased after this change.

Nevertheless, we acknowledge the lack of data on symptoms, and we cannot rule out that some individuals diagnosed with CD having lymphoma or gastrointestinal cancer actually underwent CD investigation because of symptoms from the cancers, thereby artificially inflating risk estimates. The large number of participants and the median follow-up period of more than a decade allowed us to calculate both incidence rates and HRs in important subgroups of patients. Of particular interest is the higher risk of cancer compared with controls in patients diagnosed with CD at age $\geq$60 years, a population with the most pronounced rise in CD incidence in recent years[30,31] and with a higher risk of developing severe outcomes related to refractory CD.[32] Ours is an observational study, and we cannot prove causality. It is beyond the scope of this study to explore mechanisms behind an association between CD and cancer, particularly hematologic and gastrointestinal cancer. The calculation of cancer hazard in this study may be affected by competing risks, because there is an increased mortality risk in people with CD[2]; this may have diminished our cancer risk estimates. Because of the relatively homogenous ethnic population of Sweden, the generalizability of these findings to other settings is uncertain.

Conclusions

This Swedish nationwide study found a persistent small excess risk of cancer in CD. This risk increase was mostly limited to the first year of follow-up and those diagnosed after age 40; long-term risk was only seen for hematologic and certain gastrointestinal malignancies.

Supplementary Material

Note: To access the supplementary material accompanying this article, please click here.

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Conflicts of interest
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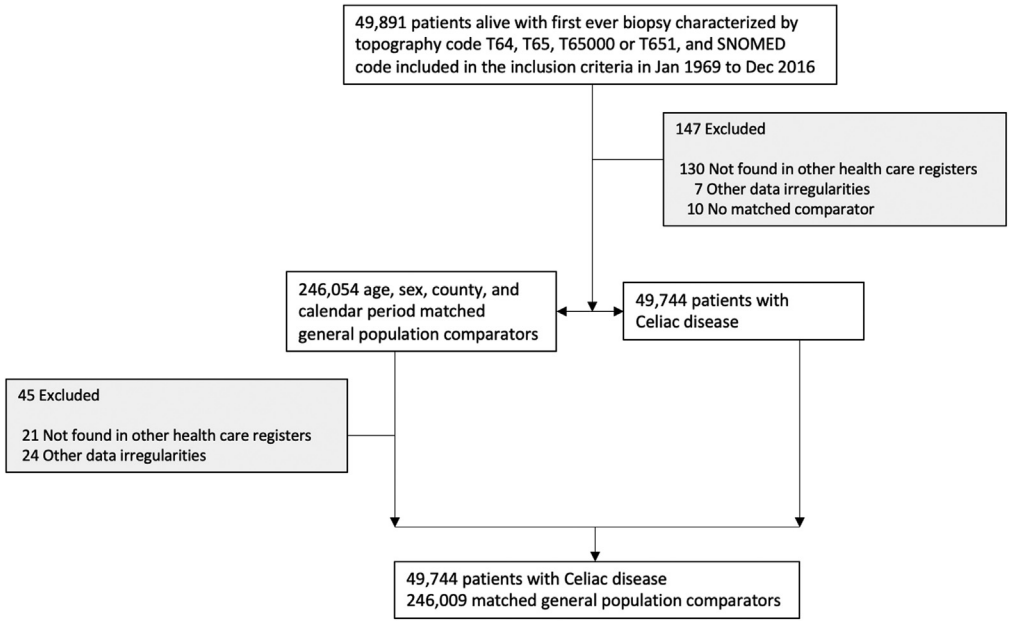
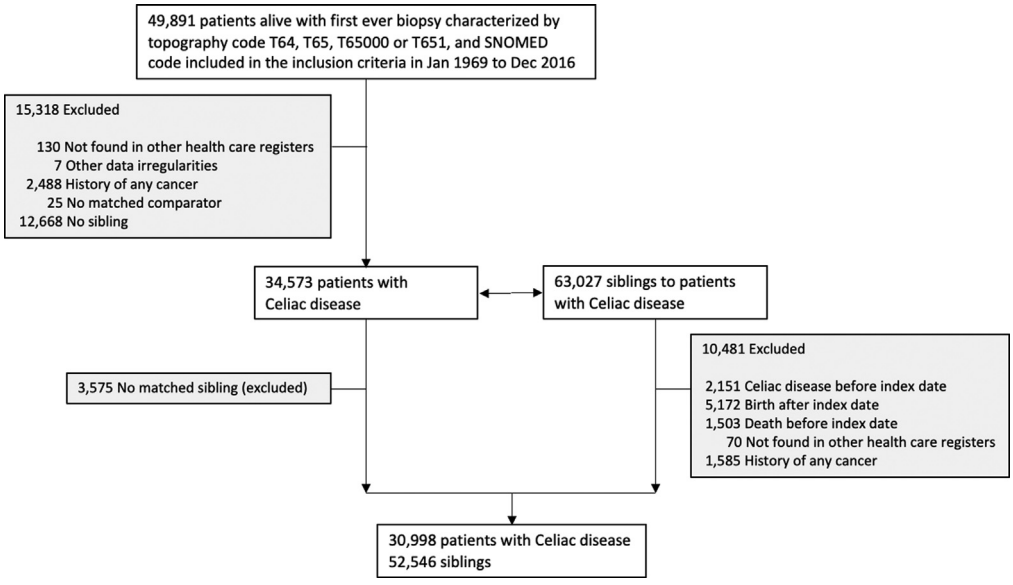


Supplementary Figure 1. Identification of patients with celiac disease and matched controls, identifying cancers before diagnosis of celiac disease.



Supplementary Figure 2. Identification of patients with celiac disease and their siblings without celiac disease.

Supplementary Table 1. Definitions of Celiac Disease and Normal Mucosa Using SNOMED Codes

Disease/condition	Topographic code	SNOMED codes
Celiac disease	All T64, only T65, T65000, and T651	D6218, D62180, D62188, D6218X, D6218Y; M58, M5800, M58000, M58001, M58005, M58006, M58007
Normal mucosa	Same as for celiac disease	M00100, M00110

SNOMED, Systemized Nomenclature of Medicine.

Supplementary Table 2. ICD Codes Used for Cancer Outcomes

Cancer outcome	ICD-7 codes
Any cancer	140–208
Solid cancer	140–199
Hematologic cancer	200–208
Lymphoproliferative cancer	200–204
Gastrointestinal cancer	150–159
Gastric	151
Colorectal	153–154
Hepatobiliary (liver/gallbladder)	155–156
Pancreatic	157
Lung cancer	162
Breast cancer (women)	170

NOTE. In the Cancer Register, all ICD-8, -9, and -10 codes are back-translated to ICD-7.
ICD, International Classification of Diseases.

Supplementary Table 3. Definitions of Baseline Comorbidities Ever Before Start of Follow-up

Comorbidity	ICD-7 (1964–1968)	ICD-8 (1969–1986)	ICD-9 (1987–1996)	ICD-10 (1997–)
Type 1 diabetes[a]	260	250	250	E10
Autoimmune thyroid disease	252.00; 252.01; 252.02; 253.10; 253.19; 253.20; 253.29; 254.00	242.00; 242.09; 244; 245.03	242A, 242X, 244X, 245C, 245W	E035, E039, E050, E055, E059, E063, E065
Rheumatoid arthritis		712.3; 714.93	714	M05, M06, M08, M123
Inflammatory bowel disease	572.09; 572.20; 572.21	572.00; 572.09; 563.00; 572.20; 572.21; 563.10	555, 556	K50, K51, K523

ICD, International Classification of Diseases.
[a]Age <31 years at date of diagnosis

Supplementary Table 4. Baseline Characteristics of Study Cohort: Celiac Disease Patients and Siblings

Characteristic	Celiac disease (n = 30,998)	Siblings (n = 52,546)
Female, n (%)	19,543 (63.0)	25,230 (48.0)
Male, n (%)	11,455 (37.0)	27,316 (52.0)
Age, *y*		
Mean (SD)	25.8 (20.4)	29.0 (20.2)
Median (IQR)	20.9 (7.7–42.1)	26.0 (10.6–45.8)
Range, minimum-maximum	0.0–84.1	0.0–83.5
Categories, n (%)		
<18 y	14,182 (45.8)	20,153 (38.4)
18 to <40 y	8333 (26.9)	15,245 (29.0)
40 to <60 y	6261 (20.2)	12,951 (24.6)
≥60 y	2222 (7.2)	4197 (8.0)
Country of birth, n (%)		
Nordic country	30,514 (98.4)	51,177 (97.4)
Other	483 (1.6)	1363 (2.6)
Missing	1 (0.0)	6 (0.0)
Level of education, n (%)		
≤9 y	4157 (13.4)	8336 (15.9)
10–12 y	7369 (23.8)	14,411 (27.4)
>12 y	5372 (17.3)	8478 (16.1)
Missing	14,100 (45.5)	21,321 (40.6)
Level of education using highest level of education in parents when missing, n (%)		
≤9 y	5025 (16.2)	10,288 (19.6)
10–12 y	12,978 (41.9)	22,707 (43.2)
>12 y	12,662 (40.8)	18,649 (35.5)
Missing	333 (1.1)	902 (1.7)
Start year of follow-up		
1969–1989	2223 (7.2)	4029 (7.7)
1990–1999	7600 (24.5)	13,420 (25.5)
2000–2009	12,951 (41.8)	21,935 (41.7)
2010–2016	8224 (26.5)	13,162 (25.0)
Disease history ever before start of follow-up, n (%)		
Type 1 diabetes	1246 (4.0)	404 (0.8)
Autoimmune thyroid disease	570 (1.8)	426 (0.8)
Rheumatoid arthritis	194 (0.6)	234 (0.4)
Inflammatory bowel disease	878 (2.8)	362 (0.7)
Follow-up, *y*		
Mean (SD)	12.6 (8.1)	12.6 (8.2)
Median (IQR)	11.4 (6.0–18.2)	11.5 (5.8–18.2)
Range, minimum-maximum	0.0–40.3	0.0–44.0

IQR, interquartile range; SD, standard deviation.

Supplementary Table 5. Risks and Hazard Ratios for Cancer Overall and by Subgroups in Patients With Celiac Disease and Siblings

Group	N (%)		N events (%)		Incidence rate (95% CI) per 1000 person-years			
	Celiac disease	Siblings	Celiac disease	Siblings	Celiac disease	Siblings	HR[a] (95% CI)	HR[b] (95% CI)
Overall	30,998 (100)	52,546 (100)	1815 (5.9)	2970 (5.7)	4.6 (4.4–4.8)	4.5 (4.3–4.6)	1.24 (1.17–1.33)	1.20 (1.12–1.28)
Follow–up								
0 to <1 y	30,998 (100)	52,546 (100)	210 (0.7)	130 (0.2)	6.9 (5.9–7.8)	2.5 (2.1–2.9)	3.39 (2.70–4.27)	1.52 2.75–4.49)
1 to <5 y	30,167 (97.3)	50,917 (96.9)	383 (1.3)	621 (1.2)	3.5 (3.1–3.8)	3.4 (3.1–3.6)	1.22 (1.06–1.39)	1.18 (1.02–1.35)
5 to <10 y	24,723 (79.8)	41,511 (79.0)	411 (1.7)	706 (1.7)	3.9 (3.5–4.3)	4.0 (3.7–4.3)	1.12 (0.98–1.28)	1.05 (0.91–1.20)
≥10y	17,484 (56.4)	29,701 (56.5)	811 (4.6)	1513 (5.1)	5.6 (5.2–6.0)	6.1 (5.8–6.4)	1.11 (1.01–1.22)	1.06 (0.96–1.17)
≥1y	30,167 (97.3)	50,917 (96.9)	1605 (5.3)	2840 (5.6)	4.4 (4.2–4.7)	4.6 (4.5–4.8)	1.14 (1.06–1.22)	1.08 (1.01–1.16)
Sex								
Female	19,543 (63.0)	25,230 (48.0)	1110 (5.7)	1546 (6.1)	4.5 (4.2–4.8)	4.8 (4.6–5.1)	1.13 (1.02–1.25)	1.12 (1.01–1.25)
Male	11,455 (37.0)	27,316 (52.0)	705 (6.2,)	1424 (5.2)	4.9 (4.5–5.2)	4.1 (3.9–4.3)	1.42 (1.24–1.62)	1.37 (1.19–1.58)
Age (*y*)								
<18	14,182 (45.8)	20,153 (38.4)	158 (1.1)	211 (1.0)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	1.01 (0.80–1.27)	0.93 (0.69–1.26)
18 to <40	8333 (26.9)	15,245 (29.0)	403 (4.8)	556 (3.6)	4.0 (3.6–4.4)	2.9 (2.7–3.2)	1.47 (1.26–1.72)	1.15 (0.97–1.36)
40 to <60	6261 (20.2)	12,951 (24.6)	858 (13.7)	1627 (12.6)	10.7 (10.0–11.4)	9.4 (9.0–9.9)	1.16 (1.05–1.28)	1.12 (1.01–1.24)
≥60	2222 (7.2)	4197 (8.0)	396 (17.8)	576 (13.7)	24.1 (21.7–26.5)	17.3 (15.9–18.7)	1.51 (1.27–1.79)	1.59 (1.33–1.90)
Year								
1969–1989	2223 (7.2)	4029 (7.7)	264 (11.9)	466 (11.6)	4.2 (3.7–4.7)	4.2 (3.8–4.6)	1.17 (0.99–1.39)	1.10 (0.91–1.32)
1990–1999	7600 (24.5)	13,420 (25.5)	646 (8.5)	1196 (8.9)	4.3 (3.9–4.6)	4.6 (4.3–4.8)	1.13 (1.01–1.25)	1.07 (0.96–1.20)
2000–2009	12,951 (41.8)	21,935 (41.7)	705 (5.4)	1123 (5.1)	4.8 (4.5–5.2)	4.6 (4.4–4.9)	1.24 (1.12–1.37)	1.20 (1.08–1.33)
2010–2016	8224 (26.5)	13,162 (25.0)	200 (2.4)	185 (1.4)	6.3 (5.4–7.2)	3.7 (3.2–4.2)	2.12 (1.70–2.63)	2.12 (1.69–2.66)
Year – first 5 years of follow–up								
1969–1989	2223 (7.2)	4029 (7.7)	264 (11.9)	466 (11.6)	4.2 (3.7–4.7)	4.2 (3.8–4.6)	1.17 (0.99–1.39)	1.10 (0.91–1.32)
1990–1999	7600 (24.5)	13,420 (25.5)	106 (1.4)	171 (1.3)	2.8 (2.3–3.4)	2.6 (2.2–3.0)	1.35 (1.05–1.74)	1.26 (0.96–1.65)
2000–2009	12,951 (41.8)	21,935 (41.7)	278 (2.1)	386 (1.8)	4.4 (3.9–4.9)	3.6 (3.3–4.0)	1.43 (1.22–1.69)	1.42 (1.20–1.68)
2010–2011	2850 (9.2)	4494 (8.6)	79 (2.8)	77 (1.7)	5.7 (4.4–6.9)	3.5 (2.8–4.3)	2.05 (1.46–2.90)	2.18 (1.51–3.15)
Country of birth								
Nordic	30,514 (98.4)	51,177 (97.4)	1802 (5.9)	2946 (5.8)	4.7 (4.4–4.9)	4.5 (4.4–4.7)	1.24 (1.16–1.32)	1.19 (1.11–1.27)
Other	483 (1.6)	1363 (2.6)	13 (2.7)	24 (1.8)	3.1 (1.4–4.8)	1.9 (1.1–2.7)	1.61 (0.69–3.73)	1.49 (0.53–4.20)
Level of education								
≤9 y	5025 (16.2)	10,288 (19.6)	519 (10.3)	951 (9.2)	7.8 (7.2–8.5)	6.8 (6.3–7.2)	1.42 (1.22–1.65)	1.40 (1.19–1.64)
10–12 y	12,978 (41.9)	22,707 (43.2)	750 (5.8)	1152 (5.1)	4.4 (4.1–4.7)	4.0 (3.8–4.2)	1.42 (1.25–1.61)	1.36 (1.19–1.55)
>12 y	12,662 (40.8)	18,649 (35.5)	460 (3.6)	654 (3.5)	3.1 (2.9–3.4)	3.1 (2.8–3.3)	1.18 (1.00–1.40)	1.14 (0.96–1.36)

CI, confidence interval; HR, hazard ratio.

[a]Conditioned on family.

[b]Conditioned on family and further adjusted for age (as linear and quadratic term), sex, education, Nordic country of birth, and time-dependent medical comorbidities (type 1 diabetes, autoimmune thyroid disease, rheumatoid arthritis, and inflammatory bowel disease).

Supplementary Table 6. Risks and Hazard Ratios for Cancer in Patients With Celiac Disease and Siblings (N Celiac Disease/N Comparators = 30,998/52,546)

Group	N events (%)		Time at risk (*y*)		Incidence rate (95% CI) per 1000 person-years		HR[a] (95% CI)	HR[b] (95% CI)
	Celiac disease	Siblings	Celiac disease	Siblings	Celiac disease	Siblings		
Any cancer	1815 (5.9)	2970 (5.7)	391,585	663,849	4.6 (4.4–4.8)	4.5 (4.3–4.6)	1.24 (1.17–1.33)	1.20 (1.12–1.28)
Solid cancer	1642 (5.3)	2777 (5.3)	392,364	664,844	4.2 (4.0–4.4)	4.2 (4.0–4.3)	1.20 (1.12–1.28)	1.18 (1.10–1.26)
Hematologic cancer	192 (0.6)	227 (0.4)	400,522	679,252	0.5 (0.4–0.5)	0.3 (0.3–0.4)	1.74 (1.42–2.14)	1.75 (1.41–2.18)
Gastrointestinal cancer	331 (1.1)	492 (0.9)	400,072	678,471	0.8 (0.7–0.9)	0.7 (0.7–0.8)	1.42 (1.22–1.65)	1.35 (1.15–1.59)
Gastric	30 (0.1)	27 (0.1)	401,227	680,317	0.1 (0.0–0.1)	0.0 (0.0–0.1)	2.36 (1.34–4.16)	3.77 (1.71–8.30)
Colorectal	174 (0.6)	308 (0.6)	400,425	678,869	0.4 (0.4–0.5)	0.5 (0.4–0.5)	1.16 (0.95–1.42)	1.13 (0.92–1.40)
Hepatobiliary (liver/gallbladder)	45 (0.1)	53 (0.1)	401,271	680,313	0.1 (0.1–0.1)	0.1 (0.1–0.1)	1.66 (1.09–2.51)	1.32 (0.79–2.20)
Pancreatic	54 (0.2)	58 (0.1)	401,289	680,363	0.1 (0.1–0.2)	0.1 (0.1–0.1)	2.29 (1.53–3.42)	1.98 (1.29–3.06)
Lung cancer	79 (0.3)	176 (0.3)	401,226	680,075	0.2 (0.2–0.2)	0.3 (0.2–0.3)	1.00 (0.75–1.33)	0.99 (0.73–1.36)
Breast cancer (women)	225 (1.2)	392 (1.6)	251,647	325,632	0.9 (0.8–1.0)	1.2 (1.1–1.3)	0.89 (0.72–1.10)	0.91 (0.73–1.14)

CI, confidence interval; HR, hazard ratio.
[a]Conditioned on family.
[b]Conditioned on family and further adjusted for age (as a linear and quadratic term), sex, education, Nordic country of birth, and time-dependent medical comorbidities (type 1 diabetes, autoimmune thyroid disease, rheumatoid arthritis, and inflammatory bowel disease).

Supplementary Table 7. Risks and Hazard Ratios for Cancer in Children (<18 Years) With Celiac Disease Diagnosed in 2010–2011 and 2012–2013 and Matched General Population Comparators, Restricted to 3 Years of Follow-up

Year of diagnosis/ index date	N (%)		N events (%)		Incidence rate (95% CI) per 1000 person-years		HR[a] (95% CI)	HR[b] (95% CI)
	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators		
Overall	7458 (100)	35,559 (100)	261 (3.5)	885 (2.5)	7.2 (6.3–8.0)	5.1 (4.7–5.4)	1.33 (1.16–1.54)	1.29 (1.12–1.50)
Year								
2010–2011	3929 (52.7)	18,770 (52.8)	101 (2.6)	253 (1.3)	8.8 (7.1–10.5)	4.6 (4.0–5.1)	1.84 (1.45–2.33)	1.78 (1.39–2.28)
2012–2013	3529 (47.3)	16,789 (47.2)	84 (2.4)	275 (1.6)	8.1 (6.4–9.8)	5.6 (4.9–6.2)	1.30 (1.01–1.66)	1.30 (1.01–1.67)

CI, confidence interval; HR, hazard ratio.
[a]Conditioned on matching set (age, sex, county, and calendar period).
[b]Conditioned on matching set and further adjusted for education, Nordic country of birth, and time-dependent medical comorbidities (type 1 diabetes, autoimmune thyroid disease, rheumatoid arthritis, and inflammatory bowel disease).

Supplementary Table 8. Risk and Hazard Ratios for Cancer in Patients With Celiac Disease and Matched General Population Comparators Excluding Individuals on Basis of Their Specific History of Cancer (and Not Any Cancer)

	N		N events (%)		Incidence rate (95% CI) per 1000 person-years			
Group	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	HR[a] (95% CI)	HR[b] (95% CI)
Any cancer	47,241	225,180	3887 (8.2)	16,438 (7.3)	6.5 (6.3–6.7)	5.7 (5.6–5.8)	1.11 (1.07–1.15)	1.08 (1.04–1.12)
Solid cancer	47,425	226,341	3522 (7.4)	15,697 (6.9)	5.9 (5.7–6.1)	5.4 (5.4–5.5)	1.05 (1.02–1.10)	1.08 (1.03–1.12)
Hematologic cancer	49,532	244,510	486 (1.0)	1361 (0.6)	0.8 (0.7–0.8)	0.4 (0.4–0.5)	1.86 (1.67–2.07)	1.88 (1.68–2.10)
Gastrointestinal cancer	49,358	243,926	953 (1.9)	3597 (1.5)	1.5 (1.4–1.6)	1.1 (1.1–1.2)	1.37 (1.27–1.47)	1.35 (1.25–1.46)
Lung cancer	49,716	245,723	225 (0.5)	1319 (0.5)	0.4 (0.3–0.4)	0.4 (0.4–0.4)	0.86 (0.74–0.99)	0.89 (0.77–1.03)
Breast cancer (women)	30,722	150,683	411 (1.3)	2517 (1.7)	1.0 (0.9–1.1)	1.3 (1.2–1.3)	0.80 (0.72–0.89)	0.84 (0.75–0.93)

CI, confidence interval; HR, hazard ratio.

[a]Conditioned on matching set (age, sex, county, and calendar period).

[b]Conditioned on matching set and further adjusted for education, Nordic country of birth, and time-dependent medical comorbidities (type 1 diabetes, autoimmune thyroid disease, rheumatoid arthritis, and inflammatory bowel disease).

Supplementary Table 9. Risks and Hazard Ratios for Cancer in Patients With Celiac Disease and Matched General Population Comparators Not Excluding Any Individual, Regardless of Their Cancer History (N Celiac Disease/N Comparators = 49,744/246,009)

	N events (%)		Time at risk (*y*)		Incidence rate (95% CI) per 1000 person-years			
Group	Celiac disease	Comparators	Celiac disease	Comparators	Celiac disease	Comparators	HR[a] (95% CI)	HR[b] (95% CI)
Any cancer	4344 (8.7)	19,896 (8.1)	614,713	3,064,974	7.1 (6.9–7.3)	6.5 (6.4–6.6)	1.12 (1.08–1.16)	1.09 (1.05–1.13)
Solid cancer	3911 (7.9)	18,803 (7.6)	616,390	3,070,381	6.3 (6.1–6.5)	6.1 (6.0–6.2)	1.06 (1.02–1.10)	1.08 (1.04–1.12)
Hematologic cancer	494 (1.0)	1385 (0.6)	634,952	3,163,029	0.8 (0.7–0.8)	0.4 (0.4–0.5)	1.87 (1.68–2.08)	1.89 (1.70–2.12)
Gastrointestinal cancer	980 (2.0)	3684 (1.5)	633,178	3,156,107	1.5 (1.5–1.6)	1.2 (1.1–1.2)	1.38 (1.28–1.48)	1.37 (1.27–1.47)
Lung cancer	225 (0.5)	1323 (0.5)	636,404	3,167150	0.4 (0.3–0.4)	0.4 (0.4–0.4)	0.86 (0.74–0.99)	0.89 (0.76–1.03)
Breast cancer (women)	424 (1.4)	2674 (1.7)	399,216	1,975,379	1.1 (1.0–1.2)	1.4 (1.3–1.4)	0.80 (0.72–0.89)	0.83 (0.75–0.92)

CI, confidence interval; HR, hazard ratio.

[a]Conditioned on matching set (age, sex, county, and calendar period).

[b]Conditioned on matching set and further adjusted for education, Nordic country of birth, and time-dependent medical comorbidities (type 1 diabetes, autoimmune thyroid disease, rheumatoid arthritis, and inflammatory bowel disease).

Supplementary Table 10. Baseline Characteristics of Patients With Celiac Disease Who Had Follow-up Biopsy After Diagnosis

Characteristic	Persistent villus atrophy (n = 2573)	Mucosal healing (n = 6437)
Female, n (%)	1516 (58.9)	4157 (64.6)
Male, n (%)	1057 (41.1)	2280 (35.4)
Age (*y*)		
Mean (SD)	42.0 (23.9)	31.4 (22.0)
Median (IQR)	45.3 (21.9–61.9)	29.0 (11.3–48.5)
Range, minimum–maximum	1.1–90.9	1.0–91.3
Categories, n *(%)*		
<18 y	549 (21.3)	2108 (32.7)
18 to <40	530 (20.6)	2074 (32.2)
40 to <60	785 (30.5)	1424 (22.1)
≥60 y	709 (27.6)	831 (12.9)
Duration since diagnosis, *y*		
Mean (SD)	1.5 (0.9)	1.6 (1.0)
Median (IQR)	1.1 (0.9–1.7)	1.3 (1.0–1.9)
Range, minimum–maximum	0.5–5.0	0.5–5.0
Country of birth, n (%)		
Nordic country	2456 (95.5)	6139 (95.4)
Other	117 (4.5)	298 (4.6)
Level of education, n (%)		
≤9 y	542 (21.1)	855 (13.3)
10–12 y	818 (31.8)	1862 (28.9)
>12 y	591 (23.0)	1629 (25.3)
Missing	622 (24.2)	2 091 (32.5)
Level of education using highest level of education in parents when missing, n (%)		
≤9 y	590 (22.9)	953 (14.8)
10–12 y	1099 (42.7)	2767 (43.0)
>12 y	806 (31.3)	2636 (41.0)
Missing	78 (3.0)	81 (1.3)
Start year of follow-up (date of follow–up biopsy)		
1969–1989	169 (6.6)	230 (3.6)
1990–1999	778 (30.2)	1462 (22.7)
2000–2009	1009 (39.2)	2870 (44.6)
2010–2016	617 (24.0)	1875 (29.1)
Disease history ever before start of follow–up, n (%)		
Type 1 diabetes	44 (1.7)	149 (2.3)
Autoimmune thyroid disease	68 (2.6)	199 (3.1)
Rheumatoid arthritis	21 (0.8)	48 (0.7)
Inflammatory bowel disease	148 (5.8)	299 (4.6)
Follow–up, *y*		
Mean (SD)	12.3 (8.0)	11.3 (7.4)
Median (IQR)	11.3 (5.6–17.9)	10.4 (5.1–16.1)
Range, minimum–maximum	0.0–39.0	0.0–34.0

IQR, interquartile range; SD, standard deviation.

Supplementary Table 11. Risks and Hazard Ratios for Any Cancer Overall and by Subgroups in Patients With Celiac Disease and Persistent Villus Atrophy vs Mucosal Healing

Group	N (%)		N events (%)		Incidence rate (95% CI) per 1000 person-years		
	Persistent VA	Mucosal healing	Persistent VA	Mucosal healing	Persistent VA	Mucosal healing	HR[a] (95% CI)
Overall	2573 (100)	6437 (100)	289 (11.2)	404 (6.3)	9.2 (8.1–10.2)	5.6 (5.0–6.1)	1.01 (0.87–1.18)
Follow–up (*y*)							
0 to <1	2573 (100)	6437 (100)	30 (1.2)	45 (0.7)	11.9 (7.6–16.1)	7.1 (5.0–9.2)	1.00 (0.62–1.61)
1 to <5	2485 (96.6)	6220 (96.6)	79 (3.2)	106 (1.7)	8.9 (6.9–10.8)	4.8 (3.9–5.7)	1.05 (0.78–1.42)
5 to <10	1979 (76.9)	4840 (75.2)	69 (3.5)	112 (2.3)	8.1 (6.2–10.0)	5.5 (4.5–6.5)	0.86 (0.63–1.17)
≥10	1421 (55.2)	3350 (52.0)	111 (7.8)	141 (4.2)	9.5 (7.8–11.3)	6.0 (5.0–6.9)	1.12 (0.87–1.44)
≥1	2485 (96.6)	6220 (96.6)	259 (10.4)	359 (5.8)	8.9 (7.8–10.0)	5.4 (4.9–6.0)	1.02 (0.86–1.20)
Sex							
Female	1516 (58.9)	4157 (64.6)	147 (9.7)	247 (5.9)	7.7 (6.4–8.9)	5.3 (4.7–6.0)	0.94 (0.76–1.16)
Male	1057 (41.1)	2280 (35.4)	142 (13.4)	157 (6.9)	11.5 (9.6–13.4)	6.0 (5.1–6.9)	1.08 (0.86–1.36)
Age (*y*)							
<18	549 (21.3)	2108 (32.7)	10 (1.8)	23 (1.1)	1.0 (0.4–1.6)	0.7 (0.4–1.0)	0.94 (0.43–2.03)
18 to <40	530 (20.6)	2074 (32.2)	29 (5.5)	72 (3.5)	4.9 (3.1–6.6)	3.8 (2.9–4.7)	1.14 (0.73–1.77)
40 to <60	785 (30.5)	1424 (22.1)	104 (13.2)	156 (11.0)	10.6 (8.5–12.6)	10.4 (8.8–12.0)	0.95 (0.74–1.22)
≥60	709 (27.6)	831 (12.9)	146 (20.6)	153 (18.4)	25.6 (21.4–29.7)	23.5 (19.8–27.2)	1.00 (0.79–1.26)
Year							
1969–1989	169 (6.6)	230 (3.6)	37 (21.9)	33 (14.3)	9.2 (6.2–12.1)	5.7 (3.7–7.6)	1.24 (0.76–2.03)
1990–1999	778 (30.2)	1462 (22.7)	115 (14.8)	140 (9.6)	8.0 (6.5–9.4)	5.0 (4.2–5.8)	1.04 (0.81–1.34)
2000–2009	1009 (39.2)	2870 (44.6)	114 (11.3)	191 (6.7)	10.5 (8.6–12.4)	6.0 (5.1–6.8)	0.93 (0.73–1.18)
2010–2016	617 (24.0)	1875 (29.1)	23 (3.7)	40 (2.1)	10.4 (6.1–14.6)	6.0 (4.1–7.9)	1.08 (0.64–1.83)
Year – first 5 years of follow–up							
1969–1989	169 (6.6)	230 (3.6)	6 (3.6)	3 (1.3)	7.3 (1.5–13.2)	2.7 (0.0–5.7)	1.71 (0.42–6.97)
1990–1999	778 (30.2)	1462 (22.7)	29 (3.7)	27 (1.8)	7.8 (4.9–10.6)	3.8 (2.4–5.2)	1.30 (0.75–2.25)
2000–2009	1009 (39.2)	2870 (44.6)	53 (5.3)	83 (2.9)	11.0 (8.0–13.9)	5.9 (4.7–7.2)	0.92 (0.64–1.31)
2010–2011	188 (7.3)	534 (8.3)	6 (3.2)	20 (3.7)	6.6 (1.3–12.0)	7.7 (4.3–11.1)	0.56 (0.22–1.44)
Country of birth							
Nordic	2456 (95.5)	6139 (95.4)	280 (11.4)	388 (6.3)	9.1 (8.1–10.2)	5.5 (5.0–6.1)	1.01 (0.86–1.18)
Other	117 (4.5)	298 (4.6)	9 (7.7)	16 (5.4)	9.2 (3.2–15.2)	6.3 (3.2–9.4)	0.88 (0.37–2.08)
Level of education							
≤9 y	590 (22.9)	953 (14.8)	81 (13.7)	102 (10.7)	11.9 (9.3–14.5)	9.8 (7.9–11.7)	0.81 (0.60–1.09)
10–12 y	1099 (42.7)	2767 (43.0)	119 (10.8)	155 (5.6)	8.6 (7.1–10.2)	4.7 (4.0–5.4)	1.25 (0.98–1.59)
>12 y	806 (31.3)	2636 (41.0)	63 (7.8)	132 (5.0)	6.5 (4.9–8.1)	4.8 (3.9–5.6)	0.75 (0.55–1.02)

CI, confidence interval; HR, hazard ratio; VA, villus atrophy.

[a]Adjusted for age (as a linear and quadratic term), sex, start year of follow-up, duration since diagnosis (continuous), highest attained education in parents, and Nordic country of birth, and time-dependent medical comorbidities (type 1 diabetes, autoimmune thyroid disease, rheumatoid arthritis, and inflammatory bowel disease).

Supplementary Table 12. Risks and Hazard Ratios for Cancer in Patients With Celiac Disease and Persistent Villus Atrophy vs Mucosal Healing (N Persistent VA/N Mucosal Healing = 2573/6437)

	N events (%)		Time at risk (*y*)		Incidence rate (95% CI) per 1000 person-years		
Group	Persistent VA	Mucosal healing	Persistent VA	Mucosal healing	Persistent VA	Mucosal healing	HR[a] (95% CI)
Any cancer	289 (11.2)	404 (6.3)	31,584	72,545	9.2 (8.1–10.2)	5.6 (5.0–6.1)	1.01 (0.87–1.18)
Solid cancer	254 (9.9)	379 (5.9)	31,722	72,626	8.0 (7.0–9.0)	5.2 (4.7–5.7)	0.94 (0.80–1.10)
Hematologic cancer	39 (1.5)	29 (0.5)	32,747	74,495	1.2 (0.8–1.6)	0.4 (0.2–0.5)	1.79 (1.09–2.93)
Lymphoproliferative cancer	36 (1.4)	25 (0.4)	32,752	74,506	1.1 (0.7–1.5)	0.3 (0.2–0.5)	1.87 (1.11–3.16)
Gastrointestinal cancer	69 (2.7)	75 (1.2)	32,703	74,320	2.1 (1.6–2.6)	1.0 (0.8–1.2)	1.15 (0.82–1.61)
Lung cancer	11 (0.4)	25 (0.4)	32,881	74,553	0.3 (0.1–0.5)	0.3 (0.2–0.5)	0.54 (0.26–1.12)
Breast cancer (women)	23 (1.5)	61 (1.5)	19,775	47,280	1.2 (0.7–1.6)	1.3 (1.0–1.6)	0.56 (0.35–0.92)

CI, confidence interval; HR, hazard ratio; VA, villus atrophy.

[a]Adjusted for age (as a linear and quadratic term), sex, start year of follow-up, duration since diagnosis (continuous), highest attained education in parents, and Nordic country of birth, and time-dependent medical comorbidities (type 1 diabetes, autoimmune thyroid disease, rheumatoid arthritis, and inflammatory bowel disease).