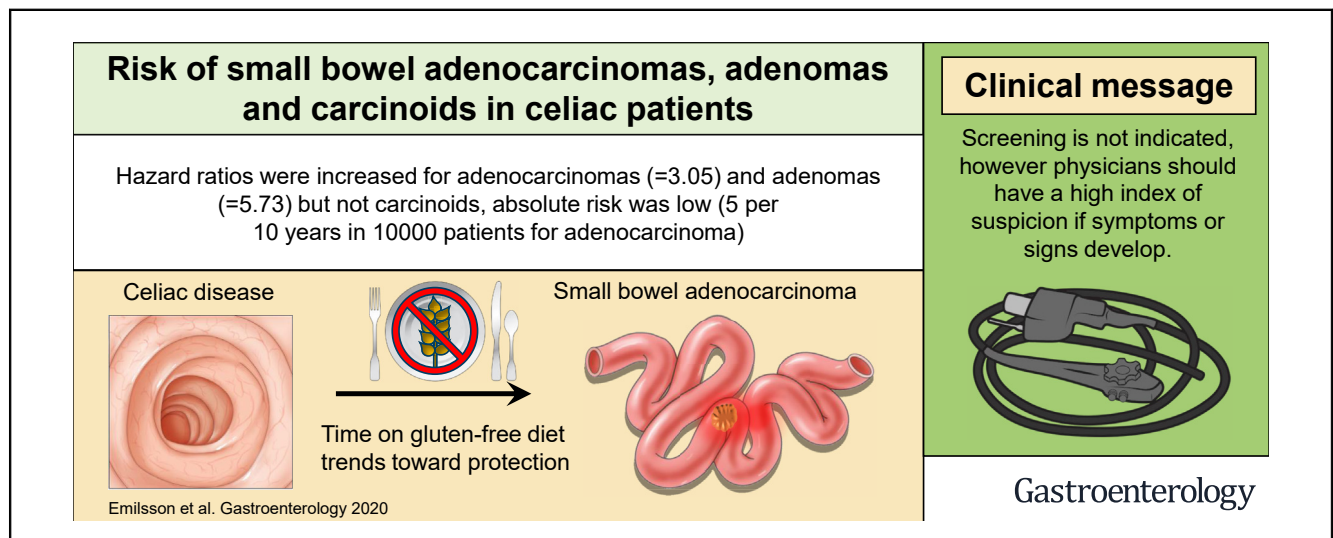# Risk of Small Bowel Adenocarcinoma, Adenomas, and Carcinoids in a Nationwide Cohort of Individuals With Celiac Disease

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Risk of small bowel adenocarcinomas, adenomas and carcinoids in celiac patients

Hazard ratios were increased for adenocarcinomas (=3.05) and adenomas (=5.73) but not carcinoids, absolute risk was low (5 per 10 years in 10000 patients for adenocarcinoma)

Clinical message

Screening is not indicated, however physicians should have a high index of suspicion if symptoms or signs develop.

Celiac disease

Small bowel adenocarcinoma

Time on gluten-free diet trends toward protection

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Gastroenterology

BACKGROUND & AIMS: The incidence of small bowel cancers is increasing. Associations have been made between celiac disease (CD) and small bowel cancers, but there have been no detailed studies of large cohorts. **METHODS:** Through the nationwide Epidemiology Strengthened by Histopathology Reports in Sweden cohort study, we retrieved data from Sweden's 28 pathology departments on all individuals who received a diagnosis of CD from 1965 through 2017. Individuals with CD, defined as duodenal or jejunal villous atrophy (stage 3 Marsh score), were matched with as many as 5 randomly selected reference individuals from the general population. We used stratified Cox regression to calculate hazard ratios (HRs) for small bowel adenocarcinoma, adenomas, and carcinoids. **RESULTS:** During a median follow-up of 11 years, we identified 48,119 individuals with CD (patients) and 239,249 reference individuals. Beginning at 1 year after a diagnosis of CD, 29 patients (0.06%) received a diagnosis of small bowel adenocarcinoma vs 45 reference individuals (0.02%), 7 patients received a diagnosis of carcinoids vs 31 reference individuals, and 48 patients received a diagnosis of adenomas vs 50 reference individuals. Corresponding HRs were small bowel adenocarcinoma 3.05 (95% confidence interval [CI], 1.86–4.99), carcinoids 0.59 (95% CI, 0.16–2.10), and adenomas 5.73 (95% CI, 3.70–8.88). HRs were independent of sex and age. Overall, there was 1 extra case of small bowel adenocarcinoma in every 2944 patients with CD followed for 10 years. There was an inverse association between mucosal healing risk of future small bowel adenocarcinoma (HR, 0.18; 95% CI, 0.02–1.61), although the HR failed to attain statistical significance. **CONCLUSIONS:** In an analysis of a nationwide pathology database in Sweden, we found the absolute risk of small bowel adenocarcinoma is low in individuals with CD. However, risks of small bowel adenocarcinoma and adenomas (but not carcinoids) are significantly increased in people with CD compared to people without this disease.

Primary small bowel cancer is a heterogeneous group of cancers including adenocarcinomas, carcinoids, lymphomas, sarcomas, and other cancers. Adenocarcinomas and carcinoids account for the majority of small bowel cancers and about 2%–3%[1,2] of all gastrointestinal cancers. They have been called "orphan" neoplasias,[2] as they have rarely been studied and there is a lack of evidence-based knowledge about risk factors and associated conditions.

Celiac disease is an immune-mediated disease induced by gluten ingestion and has been suggested as one of few predisposing factors for small bowel cancers. This has triggered a number of transcriptomic studies in individuals with both conditions.[3] A meta-analysis of gastrointestinal malignancy in individuals with celiac disease (CD) reported 75 cases of small bowel adenocarcinoma in 79,991 individuals with CD from 8 previous studies (Table 1), corresponding to a pooled odds ratio of 14.4 with heterogeneity >90% for the included studies.[4] The heterogeneity is partly due to mixing of incidence and morbidity ratios, the latter also including prevalent cancers in the risk estimates. The reported relative risks were also much higher in the peridiagnostic period,[5] when there is an imminent risk of detection bias, and symptoms from the small intestinal cancer can trigger diagnostic work for CD (a form of reverse causation). Earlier studies also had other limitations. First, they have rarely distinguished between different types of small bowel cancers. Second, most of the studies were performed before the introduction of modern diagnostic techniques, such as video capsules and double-balloon enteroscopy, which might have limited small bowel cancer detection in the general population. Third, outcomes data have been based on International Classification of Diseases (ICD) codes rather than histopathologic examination. Fourth, population-based studies in CD, other than a small study of 381 individuals,[6] have not reported the risk of small bowel adenomas. Small bowel adenocarcinomas are thought to develop through the adenoma–carcinoma sequence.[7]

In this study, we examined the risk for future small bowel adenocarcinomas, adenomas, and carcinoids in a contemporary nationwide cohort of more than 48,000 individuals with CD.

Methods

Study Population

Individual-level data from Swedish national registries were linked through the unique personal identity number assigned to all Swedish residents.[8] Participants with CD were identified from the Epidemiology Strengthened by Histopathology Reports in Sweden (ESPRESSO) study, which included gastrointestinal biopsies from all 28 pathology departments in Sweden between 1965 and 2017.[9] The data collection took place in 2015–2017. In ESPRESSO, histopathologic findings were defined by codes of topography and morphology (Systematized Nomenclature of Medicine [SnoMed] coding system). Celiac disease was defined as having a biopsy report with villous atrophy (March III) in the ESPRESSO study (relevant SnoMed codes are found in the Supplementary Table 1). An earlier validation found that 95% of individuals in Sweden with villous atrophy have CD.[10] In individuals for whom data on CD serology could be accessed, 88% had an elevated value in close temporal proximity to the celiac diagnosis (85% had positive anti-transglutaminase IgA), consistent with data from other clinical cohorts.[11]

Outcome Measures: Small Bowel Adenocarcinomas, Adenomas, and Carcinoids

Our outcome measure was defined as small bowel adenocarcinomas, adenomas, and carcinoids registered with relevant SnoMed codes (see Supplementary Table 1) in local pathology departments extracted for the ESPRESSO study.[9] Specifically for adenocarcinoma, we also defined an ICD-10 entry of "C17– malignant neoplasm of small intestine" in the national patient registry as individuals having the outcome adenocarcinoma (in total 6 patients added to the 72 identified from the pathology reports). Compared with diagnoses of small bowel adenocarcinoma registered in the Swedish Cancer registry (defined by ICD-7 152.X combined with morphology codes to identify adenocarcinomas [SnoMed "81403" or PAD = "096"]), only 39 of our 78 cases were also identified in the cancer registry. The cancer registry contained 8 entries of small bowel cancer that

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WHAT YOU NEED TO KNOW
BACKGROUND AND CONTEXT
Associations have been made between celiac disease and small bowel cancers, but there have been no detailed studies of large cohorts.
NEW FINDINGS
An analysis of a nationwide pathology database in Sweden found the absolute risk of small bowel adenocarcinoma to be low in individuals with celiac disease. However, risks of small bowel adenocarcinoma and adenomas (but not carcinoids) are significantly increased compared to people without celiac disease.
LIMITATIONS
This was a retrospective study from 1 country. Prospective studies and studies of other populations are needed. Studies are also needed to determine how celiac disease might contribute to development of intestinal neoplasias.
IMPACT
Patients with celiac disease have an increased risk for small bowel adenocarcinoma and adenomas.

Table 1. Previous Publications Reporting on Small Bowel Cancer in Individuals With Celiac Disease

First author, year	Study design	Country	Age, y	Individuals with CD, n	Small bowel cancer, n	Comparison	Reported HR (95% CI)
Ilus, 2014[19]	Retrospective	Finland	>15	32,439	27	6 expected from SIR	4.29 (2.83–6.24)
Caio, 2019[25]	Retrospective	Italy	18–80	770	5	NR	NR
Grainge, 2012[20]	Retrospective	UK	26.3 at diagnosis	435	1	0.09 (expected from SIR)	11.1 (0.28–61.6)
Elfstrom, 2012[5]	Prospective	Sweden	All ages	28,882	15	Matched reference individuals—first year excluded	
Anderson, 2007[21]	Retrospective	UK	All ages	490 (EMA+)	1	0.04 (expected from SIR)	23.33 (0.00–69.07)
Silano, 2007[22]	Prospective	Italy	36.2 at diagnosis	1968	5	0.19 (expected from standardized morbidity ratio—cancers preceded celiac diagnosis)	25 (8.5–51.4)
Card, 2004[30]	Prospective	UK	All ages	865	1	NR (case was in peridiagnostic period)	NR
Green, 2003[23]	Prospective	USA	52 at follow-up	381	3	0.1 (expected from standardized morbidity ratio—cancers preceded celiac diagnosis)	34 (24–42)
Askling, 2002[24]	Retrospective (inpatient diagnosed)	Sweden	All ages	11,019	8	SIR	10 (4.4–20)

EMA, endomysial antibody; NR, not reported; SIR, standardized incidence ratio.

were not found in the pathology reports or the patient registry, these were not included as cases because they were judged likely to have been erroneous entries because they were never communicated through clinicians or pathologists. Lymphomas were not included in this study.

Reference Individuals

For each individual with CD, the government agency Statistics Sweden randomly identified up to 5 reference individuals from the Swedish Total Population Register[12] matched for age, sex, county, and calendar year of the date of celiac diagnosis. Reference individuals were free of CD at matching date and, if diagnosed with CD, their follow-up was censored at the date of celiac diagnosis.

Follow-Up

Follow-up started 1 year (365 days) after celiac diagnosis and on the corresponding date in matched reference individuals to avoid including patients with CD who were detected in the process of a clinical workup due to symptoms from the small bowel cancer. The inclusion of such cases will bias the risk estimates (in a sensitivity analysis, these cases were, however, included to give a full picture of the association between CD and small bowel cancer).

Follow-up ended at date of death, emigration, outcome (small bowel adenocarcinoma, adenoma, or carcinoid in separate analyses), or on administrative end of follow-up

(December 31, 2017), whichever occurred first. For analyses comparing individuals with CD with mucosal healing to those with persistent villous atrophy, date of follow-up began at date of follow-up biopsy (6–60 months after first diagnosis), as reported in our previous publication.[13]

Statistics

We calculated hazard ratios (HRs) using stratified Cox regression. In the stratified regression, each case is only compared with its matched reference individuals and a pooled summary HR is calculated from all strata. We further adjusted for categorical educational attainment (≤9, 10–12, ≥13 years, missing)[14] in all analyses and provided results stratified to baseline subgroup characteristics (age, sex, educational attainment, year of inclusion, and country of birth). We also present HRs according to follow-up (0–1, 1–5, 5–10, 10–15, 15–20, and >20 years) and with outcome of small bowel adenocarcinoma stratified by location in the small bowel (duodenum vs jejunum or ileum). In a sensitivity analysis, we also started time of follow-up at date of celiac diagnosis. We further analyzed overall survival from adenocarcinoma comparing celiac patients and reference individuals; in this analysis, follow-up started at adenocarcinoma date and ended at death, emigration, or administrative end of follow-up, which were adjusted for age group, sex, and inclusion year. To avoid impact from comorbid diseases we also ran a sensitivity analysis excluding all individuals ever diagnosed with any of the following

Table 2. Baseline Characteristics of Study Cohort Adenocarcinoma

Characteristic	CD (n = 48,119)	Matched comparators (n = 239,249)
Women, n (%)	30,166 (62.7)	149,786 (62.6)
Men, n (%)	17,953 (37.3)	89,463 (37.4)
Age, y		
Mean (SD)	31.6 (24.9)	31.6 (25.0)
Median (IQR)	27.7 (8.1–52.6)	27.7 (8.1–52.6)
Range	0.0–95.4	0.0–95.8
Age, n (%)		
<20 y	20,353 (42.3)	101,245 (42.3)
20 to <40 y	9536 (19.8)	47,167 (19.7)
40 to <60 y	9672 (20.1)	48,148 (20.1)
60 to 80 y	7603 (15.8)	37,936 (15.9)
80 y	955 (2.0)	4753 (2.0)
Country of birth, n (%)		
Nordic country	46,174 (96.0)	220,112 (92.0)
Other	1944 (4.0)	19,128 (8.0)
Missing	1 (0.0)	9 (0.0)
Highest education attained, n (%)		
≤9 y	9397 (19.5)	48,854 (20.4)
10 to 12 y	18,070 (37.6)	89,173 (37.3)
>12 y	14,502 (30.1)	69,138 (28.9)
Missing	6150 (12.8)	32,084 (13.4)
Start year of follow-up		
1965 to 1989	4255 (8.8)	21,396 (8.9)
1990 to 1999	13,291 (27.6)	66,455 (27.8)
2000 to 2009	19,601 (40.7)	96,967 (40.5%)
2010 to 2017	10,972 (22.8%)	54,431 (22.8%)
Follow-up, y		
Mean (SD)	12.2 (8.1)	12.2 (8.1)
Median (IQR)	11.0 (5.5–17.9)	11.0 (5.5–18.0)
Range	0.0–46.5	0.0–46.5
Comorbidities (ever during follow-up), n (%)		
IgA deficiency	41 (0.1)	24 (0.01)
Crohn's disease	1512 (3.1)	946 (0.4)
Lynch syndrome	341 (0.7)	1171 (0.5)
Familiar adenomatous polyposis	68 (0.1)	120 (0.1)
Lymphoma	594 (1.2)	1369 (0.5)

IQR, interquartile range.

(identified through the Swedish Patient registry): IgA deficiency, lymphoma, Crohn's disease, familial adenomatous polyposis, or Lynch syndrome (relevant ICD codes are found in Supplementary Table 2). In another analysis, we examined the outcomes of individuals with data on follow-up biopsy, that is, having a second biopsy performed between 6 and 60 months after the initial diagnosis date.[15] In this analysis, we calculated the risk of small bowel cancer in individuals with CD with persistent villous atrophy (Marsh III remained at follow-up biopsy) vs mucosal healing (Marsh 0–II at follow-up biopsy).

The definition of mucosal healing was not validated but has been used in several previous publications.[15–17] Follow-up biopsy analyses were not performed with internal stratification but were instead adjusted for age, sex, time between biopsies, and educational attainment. Incidences of small bowel adenocarcinoma were calculated as the number of events per 1000 person-years of follow-up. For small bowel adenocarcinoma, we also calculated a conditional logistics regression for the risk of future CD diagnosis in individuals diagnosed with previous small bowel adenocarcinoma. The proportional hazards assumption was verified to hold by creating interaction terms with log(time).

All analyses were performed using SAS software, version 9.4 (IBM Corp, Armonk, NY).

Ethics

The current study was approved by the Stockholm Ethics Review Board (2014/1287-31/4) on August 27, 2014. The ethics review board did not require informed consent as it is a strictly register-based study.[18]

Results

We identified 48,119 individuals with CD and 239,249 reference individuals still at risk 1 year after the CD diagnosis date and corresponding date in reference individuals (Table 2). Individuals were followed for a median of 11 years. The majority of patients were women and >40% were children (Table 2). We performed similar but separate analyses for outcomes of adenomas and carcinoids of the small bowel (the number and characteristics of study participants in these analyses were very similar to those of the adenocarcinoma cohort, exact numbers can be found in Supplementary Table 3).

Small Bowel Adenocarcinomas

In total, 29 individuals with CD (0.06%) and 45 reference individuals (0.02%) developed small bowel adenocarcinoma (HR, 3.05; 95% CI, 1.86–4.99). In absolute numbers, this risk increase corresponds to 1 extra case of small bowel adenocarcinoma for every 2944 individuals with CD followed for 10 years. The excess risk can also be expressed as 3.4 extra adenocarcinoma cases (4.9 vs expected 1.5) per 10,000 celiac patients followed for 10 years. The HR was highest during the first 10 years of follow-up, but did not differ by sex, age groups, or calendar year at celiac diagnosis. In the individuals diagnosed most recently (celiac diagnosis in 2010–2017), the HR was 2.63 (95% CI, 0.36–19.07). The risk of small bowel cancer was slightly higher in individuals with CD with lower educational attainment (HR, 5.11), although CIs were wide and interaction terms were not significant (Table 3). In total, 18 individuals with CD and 31 reference individuals were diagnosed with a duodenal adenocarcinoma, corresponding to an HR of 2.69 (95% CI, 1.46–4.96) another 13 vs 18 had a registered location in either jejunum or ileum (HR, 3.92; 95% CI, 1.80–8.56) (2 vs 3 had multiple locations and were counted in both subgroup analyses). A sensitivity analysis excluding all individuals ever diagnosed with IgA deficiency, lymphoma, Crohn's

Table 3. Risk of Small Bowel Adenocarcinoma Overall and by Subgroups in Patients With Celiac Disease and Matched General Population Comparators

Group	n (%)		No. of events (%)		Incidence rate (95% CI) per 1000 PY		HR[a] (95% CI)
	CD	Comparators	CD	Comparators	CD	Comparators	
Overall	48,119 (100.0)	239,249 (100.0)	29 (0.1)	45 (0.0)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	3.05 (1.86–4.99)
Follow-up							
0 to <1 y	48,119 (100.0)	239,249 (100.0)	5 (0.0)	5 (0.0)	0.1 (0.0–0.2)	0.0 (0.0–0.0)	2.86 (0.73–11.15)
1 to <5 y	46,219 (96.1)	229,602 (96.0)	8 (0.0)	12 (0.0)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	4.98 (1.61–15.40)
5 to <10 y	37,248 (77.4)	184,768 (77.2)	7 (0.0)	7 (0.0)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	4.65 (1.39–15.56)
10 to <15 y	26,073 (54.2)	129,738 (54.2)	3 (0.0)	11 (0.0)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	1.01 (0.26–3.93)
15 to <20 y	16,248 (33.8)	81,326 (34.0)	2 (0.0)	5 (0.0)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	1.30 (0.23–7.42)
≥20 y	9520 (19.8)	47,664 (19.9)	4 (0.0)	5 (0.0)	0.1 (0.0–0.2)	0.0 (0.0–0.0)	2.31 (0.47–11.30)
Sex							
Women	30,166 (62.7)	149,786 (62.6)	15 (0.0)	23 (0.0)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	3.11 (1.55–6.21)
Men	17,953 (37.3)	89,463 (37.4)	14 (0.1)	22 (0.0)	0.1 (0.0–0.1)	0.0 (0.0–0.0)	3.15 (1.53–6.50)
Age at CD diagnosis or study entry							
<20 y	20,353 (42.3)	101,245 (42.3)	2 (0.0)	4 (0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	3.69 (0.53–25.77)
20 to <40 y	9536 (19.8)	47,167 (19.7)	(0.0)	2 (0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	NA
40 to <60 y	9672 (20.1)	48,148 (20.1)	10 (0.1)	20 (0.0)	0.1 (0.0–0.1)	0.0 (0.0–0.0)	2.50 (1.13–5.54)
60 to <80 y	7603 (15.8)	37,936 (15.9)	15 (0.2)	19 (0.1)	0.2 (0.1–0.3)	0.1 (0.0–0.1)	3.45 (1.69–7.08)
≥80 y	955 (2.0)	4753 (2.0)	2 (0.2)	(0.0)	0.4 (0.0–1.0)	0.0 (0.0–0.0)	NA
Year							
1965 to 1989	4255 (8.8)	21,396 (8.9)	6 (0.1)	10 (0.0)	0.1 (0.0–0.1)	0.0 (0.0–0.0)	3.13 (0.96–10.22)
1990 to 1999	13,291 (27.6)	66,455 (27.8)	10 (0.1)	20 (0.0)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	2.31 (1.02–5.22)
2000 to 2009	19,601 (40.7)	96,967 (40.5)	11 (0.1)	12 (0.0)	0.1 (0.0–0.1)	0.0 (0.0–0.0)	4.34 (1.79–10.51)
2010 to 2017	10,972 (22.8)	54,431 (22.8)	2 (0.0)	3 (0.0)	0.1 (0.0–0.1)	0.0 (0.0–0.0)	2.63 (0.36–19.07)
Year, first 5 y of follow-up							
1965 to 1989	4255 (8.8)	21,396 (8.9)	1 (0.0)	1 (0.0)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	3.87 (0.24–63.34)
1990 to 1999	13,291 (27.6)	66,455 (27.8)	6 (0.0)	4 (0.0)	0.1 (0.0–0.2)	0.0 (0.0–0.0)	2.408E16 (0.00–0.00)
2000 to 2009	19,601 (40.7)	96,967 (40.5)	4 (0.0)	9 (0.0)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	2.31 (0.65–8.24)
2010 to 2017	4083 (8.5)	20,318 (8.5)	1 (0.0)	1 (0.0)	0.1 (0.0–0.2)	0.0 (0.0–0.0)	2.45 (0.15–39.72)
Country of birth							
Nordic	46,174 (96.0)	220,112 (92.0)	28 (0.1)	43 (0.0)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	2.83 (1.71–4.70)
Other	1944 (4.0)	19,128 (8.0)	1 (0.1)	2 (0.0)	0.1 (0.0–0.2)	0.0 (0.0–0.0)	NA
Highest education attained							
≤9 y	7037 (14.6)	34,949 (14.6)	6 (0.1)	8 (0.0)	0.1 (0.0–0.1)	0.0 (0.0–0.0)	5.11 (0.96–27.14)
10 to 12 y	14,041 (29.2)	68,365 (28.6)	2 (0.0)	8 (0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.60 (0.06–5.95)
>12 y	11,991 (24.9)	57,464 (24.0)	1 (0.0)	1 (0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.73 (0.10–30.76)
Education missing	15,050 (31.3)	78,471 (32.8)	20 (0.1)	28 (0.0)	0.1 (0.1–0.2)	0.0 (0.0–0.0)	3.31 (1.69–6.49)

NA, not possible to calculate; PY, person-years.
[a]Conditioned on matching set (age, sex, county, and calendar period) and further adjusted for highest education attained.

disease, familiar adenomatous polyposis, or Lynch syndromes (including 28 cases of adenocarcinomas in 45,692 celiac patients and 42 cases of adenocarcinoma in 235,698 reference individuals) gave an HR of 3.18 (95% CI, 1.92–5.27).

In a conditional logistics regression model, the odds ratio for future or same date celiac diagnosis given a previous/simultaneously diagnosed small bowel adenocarcinoma was 4.14 (95% CI, 2.10–6.17). This analysis was based on 17 individuals with CD and 1 reference individual with earlier small bowel adenocarcinoma (Figure 1 depicts a histogram with time between diagnoses also including those diagnosed within first year after celiac diagnosis).

Small Bowel Adenomas and Carcinoids

Individuals with CD were at a 5.73-fold increased risk of small bowel adenoma (95% CI, 3.70–8.88). The HRs differed to a large extent between different subgroups (even though none of the interaction terms were statically significant) and the risk was highest during the first year of follow-up (actually year 1–2 after celiac diagnosis) and after more

CLINICAL AT

Distribution of follow-up
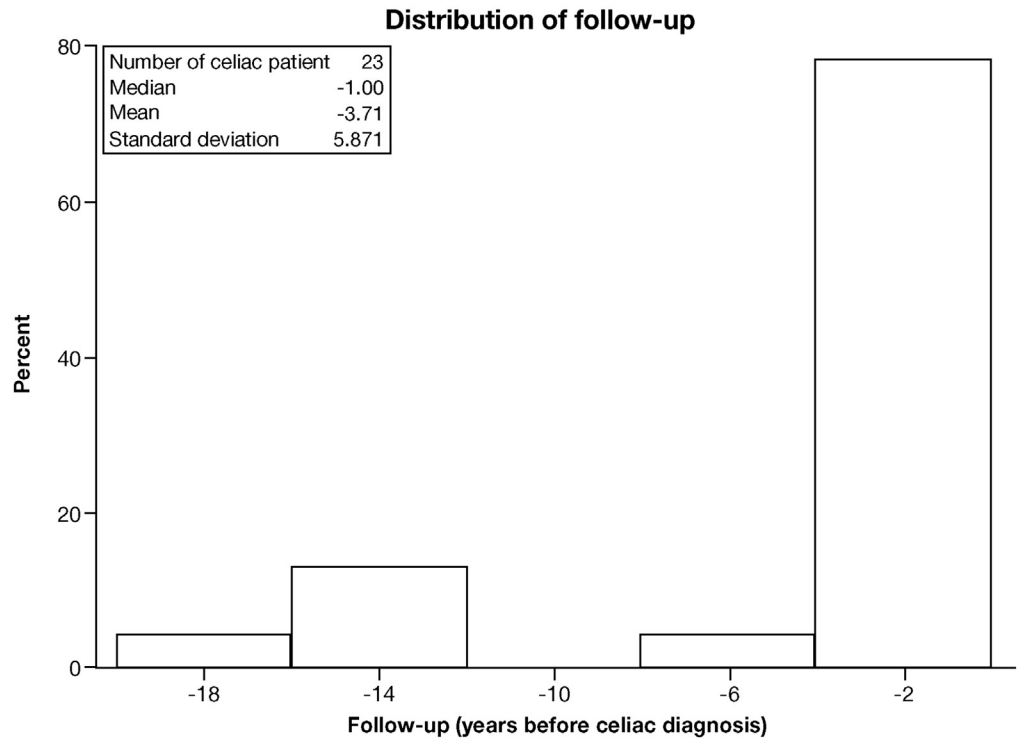
Figure 1. *Histogram of time between diagnoses in 23 patients with small bowel adenocarcinoma diagnosed before start of follow-up (defined as 1 year after celiac diagnosis) in total 6 were diagnosed before CD, 7 same day, and 10 during the first year after diagnosis.*

than 15 years of follow-up (Table 4). The risk of carcinoids was not increased, as it was only observed in 3 individuals with CD vs 28 reference individuals (HR, 0.59; 95% CI, 0.16–2.10; subgroup analyses were underpowered and therefore not performed (Table 4).

Follow-Up Biopsy: Role of Mucosal Healing

We examined the risk of small bowel adenocarcinoma according to follow-up biopsy in CD. Small bowel adenocarcinoma was seen in only 1 of 6745 individuals (0.01%) with mucosal healing vs in 5 of 2787 individuals (0.18%) with persistent villous atrophy, corresponding to an HR of 0.18 (95% CI, 0.02–1.61). Eight small bowel adenomas were seen in patients with mucosal healing vs 6 in those with persistent villous atrophy, corresponding to an HR of 0.79 (95% CI, 0.26–2.36).

Sensitivity Analyses Including the First Year After Celiac Diagnosis

During a median follow-up time of 12.5 years, 46 individuals (0.09%) with CD were diagnosed with later small bowel adenocarcinoma compared with 45 reference individuals (0.02%) (HR, 5.28; 95% CI, 3.37–8.27). The median time between CD and small bowel adenocarcinoma was 2.7 years (7 cases identified on the same date, an additional 10 cases during the first year, 19 between 1 and 5 years, and 18 cases more than 5 years after celiac diagnosis). Including the first year after celiac diagnosis, there was 1 extra case of small bowel adenocarcinoma for every 1346 individuals with CD followed for 10 years or equal to 7.5

extra cases (9.2 vs expected 1.7) per 10,000 patients followed for 10 years. The overall survival from small bowel carcinoma date in 44 celiac patients (median [SD] age at adenocarcinoma 72 [10] years) and 41 reference individuals (median [SD] age at adenocarcinoma 70 [10] years) that survived their adenocarcinoma diagnosis date was better in celiac patients (HR, 0.56; 96% CI, 0.34–0.94).

Including the first year of follow-up, there were 7 carcinoids (0.01%) in individuals with CD and 31 (0.01%) in reference individuals (HR, 1.36; 95% CI, 0.57–3.24). Corresponding numbers for adenomas were 83 (0.17%) and 53 (0.02%), respectively (HR, 9.58; 95% CI, 6.52–14.06).

Discussion

Comparison With Previous Literature

In this study, we found an increased risk of adenocarcinomas in individuals with CD compared with age- and sex-matched reference individuals. The HRs were lower than reported by most previous studies[19–24] and, similarly, the absolute risk (0.06%) was 10 times lower than in another recent publication[25] suggesting that 0.65% (5 of 770) of individuals with CD develop small bowel adenocarcinoma. Compared with lymphomas (Table 2), small bowel adenocarcinomas were approximately 10 times less common in patients with CD. In an earlier validation of 1534 reports (identified by free text histopathologic examination showing signs of other comorbidity) in 29,148 of the patients with CD included in the cohort, only 3 showed signs of refractory CD (this equals 0.01% of the total cohort). We are only aware of 1 previous study of small bowel adenomas

Table 4. Risk of Small Bowel Adenoma and Carcinoids Overall and by Subgroups in Patients With Celiac Disease and Matched General Population Comparators

Group	No. of events adenoma (%)		Adenoma, HR[a] (95% CI)	No. of events carcinoid (%)		Carcinoid, HR[a] (95% CI)
	CD	Comparators		CD	Comparators	
Overall	48 (0.1)	50 (0.0)	5.73 (3.70–8.88)	3 (0.0)	28 (0.0)	0.59 (0.16–2.10)
Follow-up						
0 to <1 y	5 (0.0)	2 (0.0)	15.88 (1.77–142.58)	(0.0)	3 (0.0)	NA
1 to <5 y	10 (0.0)	11 (0.0)	5.10 (1.92–13.58)	1 (0.0)	7 (0.0)	0.46 (0.04–5.40)
5 to <10 y	11 (0.0)	15 (0.0)	3.68 (1.56–8.70)	1 (0.0)	6 (0.0)	1.33 (0.14–12.31)
10 to <15 y	11 (0.0)	13 (0.0)	6.90 (2.47–19.31)	1 (0.0)	5 (0.0)	1.40 (0.14–13.80)
15 to <20 y	5 (0.0)	7 (0.0)	7.22 (1.25–41.71)	(0.0)	3 (0.0)	NA
≥20 y	6 (0.1)	2 (0.0)	11.23 (2.19–57.55)	(0.0)	4 (0.0)	NA
Sex						
Women	25 (0.1)	30 (0.0)	4.66 (2.61–8.32)	1 (0.0)	16 (0.0)	NA
Men	23 (0.1)	20 (0.0)	8.83 (4.18–18.64)	2 (0.0)	12 (0.0)	1.19 (0.24–5.88)
Age at CD diagnosis or study entry						
<20 y	4 (0.0)	1 (0.0)	13.76 (1.48–127.79)	(0.0)	(0.0)	NA
20 to <40 y	13 (0.1)	6 (0.0)	22.02 (4.90–99.06)	(0.0)	2 (0.0)	NA
40 to <60 y	13 (0.1)	20 (0.0)	3.99 (1.84–8.65)	2 (0.0)	13 (0.0)	0.66 (0.11-3.93)
60 to <80 y	18 (0.2)	22 (0.1)	5.06 (2.48–10.35)	1 (0.0)	13 (0.0)	0.36 (0.04–2.94)
≥80 y	(0.0)	1 (0.0)	NA	(0.0)	(0.0)	NA
Year						
1965 to 1989	12 (0.3)	4 (0.0)	22.41 (4.91–102.33)	(0.0)	7 (0.0)	NA
1990 to 1999	15 (0.1)	21 (0.0)	5.49 (2.50–12.05)	1 (0.0)	10 (0.0)	0.47 (0.05–4.44)
2000 to 2009	18 (0.1)	22 (0.0)	4.13 (2.14–7.95)	2 (0.0)	10 (0.0)	0.91 (0.16–5.15)
2010 to 2017	3 (0.0)	3 (0.0)	11.87 (1.08–130.04)	(0.0)	1 (0.0)	NA
Country of birth						
Nordic	44 (0.1)	48 (0.0)	5.06 (3.21–7.97)	3 (0.0)	27 (0.0)	0.59 (0.16–2.12)
Other	4 (0.2)	2 (0.0)	2.1863E8 (0.00–.)	(0.0)	1 (0.0)	NA
Highest education attained						
≤9 y	10 (0.1)	10 (0.0)	2.02 (0.68–5.96)	1 (0.0)	7 (0.0)	0.55 (0.06–5.39)
10 to 12 y	7 (0.0)	9 (0.0)	8.92 (1.80–44.23)	1 (0.0)	5 (0.0)	NA
>12 y	5 (0.0)	4 (0.0)	6.09 (0.65–56.83)	(0.0)	2 (0.0)	NA
Education missing	26 (0.2)	27 (0.0)	4.92 (2.54–9.53)	1 (0.0)	14 (0.0)	0.28 (0.04-2.14)

NA, not possible to calculate.
[a]Conditioned on matching set (age, sex, county, and calendar period) and further adjusted for highest attained education.

reporting 3 cases in individuals with CD (0.78%) compared with 381 cases in other patients undergoing an upper endoscopy (corresponding HR, 2.39; 95% CI, 0.67–8.48).[6] Our study found a lower absolute risk (0.1%) but a higher HR (5.73), reflecting the nationwide design as well as the difference in reference group (general populations vs individuals undergoing upper endoscopy). Our data indicated slightly higher HR for adenoma than for adenocarcinoma. This supports an increased risk mediated by the adenoma–carcinoma sequence. We also performed a conditional logistic regression showing an odds ratio of 4.14 for future CD in individuals diagnosed with small bowel adenocarcinoma. Even though there is an increased risk of small bowel adenocarcinomas in individuals with CD compared with matched reference individuals, the low absolute risk implies no need to screen individuals diagnosed with CD for small bowel adenocarcinomas. For carcinoids, previous literature is scarce but similar to our results, an earlier study of small bowel neoplasia found no correlation with CD.[26] No prior study has examined whether mucosal healing alters the risk of small bowel adenocarcinoma. Our study showed a strong but nonsignificant protective effect, indicating that even our study including more than 8000 patients with CD and a second biopsy lacked statistical power to detect a difference. Nevertheless, we conclude that mucosal healing is probably associated with lower risk of future small bowel adenocarcinoma. In total, 52 patients were identified with both CD and small bowel adenocarcinoma. During the entire follow-up of the ESPRESSO study, 3885 individuals were ever diagnosed with small bowel adenocarcinoma; CD was diagnosed in 1.3% of Swedish patients with small bowel adenocarcinoma. This study also found that CD status was associated with better small bowel adenocarcinoma survival, which is in line with previous publications.[27]

Strengths and Limitations

The nationwide cohort design has several strengths. First, it distinguishes between different types of small bowel cancers and different locations within the small bowel. Second, a large proportion of the cohort was diagnosed in the most recent era after introduction of modern techniques, such as video capsule and double-balloon enteroscopy. Third, outcome data were based on histopathologic examination. Fourth, we also report estimates for small bowel adenomas. In addition, the diagnosis of CD has been validated and suggested to be correct in 95% of the cases.[10] Despite the high validity, it is still possible that some of the individuals diagnosed with CD and small bowel adenocarcinomas were misclassified; however, we believe that this had very limited impact on our results. Another strength of our study is that we also investigated neuroendocrine tumors and carcinoids and found no association. This suggests lead-time and detection bias to be limited for adenocarcinoma also, as these biases would affect both adenocarcinoma and carcinoid estimates equally. The result remained virtually unchanged even after excluding all individuals with comorbidities. A limitation of the study is that the diagnosis of small bowel cancer in Swedish pathology registers has not been validated and a pathologic review could not be performed. The ESPRESSO histopathology cohort identified more cases than the national cancer registry or the patient registry. However, only 8 of the 47 cases identified in the cancer registry were not found in either patient registry or in ESPRESSO and may result from unverified data in patients who were unaware of their small bowel cancer. A previous study[28] suggested a 10% missingness in the cancer registry for digestive tract cancers compared with the patient registry; in our data, we have a 50% missing rate compared with local pathology reports. Underreporting in the Swedish cancer registry to a similar extent (44%) has been suggested for several other cancers, such as pancreatic and biliary.[29] We believe that using the cancer registry for small bowel adenocarcinoma might not be as adequate in terms of sensitivity and, therefore, believe that our study using histopathologic definitions confers more complete and correct data than earlier reports.[5]

This study found an increased HR of small bowel adenomas and adenocarcinomas in patients with diagnosed CD, but only a very marginal increase in terms of absolute risk. Our results do not imply a need for surveillance but celiac individuals with signs or symptoms of malignancy should merit further investigation for small bowel adenocarcinoma. Mucosal healing was strongly associated with lower risk of small bowel adenocarcinoma, although the association failed to reach statistical significance.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.07.007

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Supplementary Table 1. Definition of Exposure and Outcomes From the ESPRESSO Study

Characteristics	SnoMed code	Topography
Celiac disease	D6218 (celiac diagnosis), M58, M5800, M58000, M58001, M58005, M58006, M58007	T64 and T65
Adenoma	M82632, M82112, M82611, M81400, M81400, M72040, M82612, M82630, M82100, M82102	T64 and T65
Adenocarcinoma	M81403	T64 and T65
Carcinoid	M82403, M82463, M82493	T64 and T65

Supplementary Table 2. Definition of Comorbidities From the Swedish National Patient Register

Characteristic	ICD-8	ICD-9	ICD-10
IgA deficiency	NA	279J	D80.2
Crohn's	563	555	K50
Lynch syndrome	NA	V16A	Z82, Z80
Lymphoma	200–202	200–202	C81–C88 + C91

NA, not available.

Supplementary Table 3. Baseline Characteristics of Study Cohort Carcinoids

Characteristic	CD (n = 48,125)	Matched comparators (n = 239,275)
Women, n (%)	30,167 (62.7)	149,795 (62.6)
Men, n (%)	17,958 (37.3)	89,480 (37.4)
Age, y		
Mean (SD)	31.6 (24.9)	31.6 (25.0)
Median (IQR)	27.8 (8.1–52.6)	27.7 (8.1–52.7)
Range	0.0–95.4	0.0–95.8
Age, n (%)		
<20 y	20,352 (42.3)	101,241 (42.3)
20 to <40 y	9536 (19.8)	47,168 (19.7)
40 to <60 y	9672 (20.1)	48,147 (20.1)
60 to 80 y	7611 (15.8)	37,974 (15.9)
80 y	954 (2.0)	4745 (2.0)
Country of birth, n (%)		
Nordic country	46,179 (96.0)	220,144 (92.0)
Other	1945 (4.0)	19,122 (8.0)
Missing	1 (0.0)	9 (0.0)
Highest education attained, n (%)		
≤9 y	9399 (19.5)	48,868 (20.4)
10 to 12 y	18,073 (37.6)	89,177 (37.3)
>12 y	14,502 (30.1)	69,145 (28.9)
Missing	6151 (12.8)	32,085 (13.4)
Start year of follow-up, n (%)		
1973 to 1989	4255 (8.8)	21,392 (8.9)
1990 to 1999	13,295 (27.6)	66,476 (27.8)
2000 to 2009	19,604 (40.7)	96,986 (40.5)
2010 to 2016	10,971 (22.8)	54,421 (22.7)
Follow-up, y		
Mean (SD)	12.2 (8.1)	12.2 (8.1)
Median (IQR)	11.0 (5.5–17.9)	11.0 (5.5–18.0)
Range	0.0-46.5	0.0-46.5

IQR, interquartile range.

Supplementary Table 4. Baseline Characteristics of Study Cohort Adenoma of the Small Bowel

Characteristic	CD (n = 48,091)	Matched comparators (n = 239,114)
Women, n (%)	30,156 (62.7)	149,739 (62.6)
Men, n (%)	17,935 (37.3)	89,375 (37.4)
Age, y		
Mean (SD)	31.6 (24.9)	31.6 (25.0)
Median (IQR)	27.7 (8.1–52.6)	27.7 (8.1–52.6)
Range	0.0–95.4	0.0–95.8
Age, n (%)		
<20 y	20,351 (42.3)	101,236 (42.3)
20 to <40 y	9535 (19.8)	47,162 (19.7)
40 to <60 y	9660 (20.1)	48,089 (20.1)
60 to 80 y	7592 (15.8)	37,881 (15.8)
80 y	953 (2.0)	4746 (2.0)
Country of birth, n (%)		
Nordic country	46,145 (96.0)	219,993 (92.0)
Other	1945 (4.0)	19,112 (8.0)
Missing	1 (0.0)	9 (0.0)
Highest education attained, n (%)		
≤9 y	9384 (19.5)	48,810 (20.4)
10 to 12 y	18,059 (37.6)	89,112 (37.3)
>12 y	14,498 (30.1)	69,115 (28.9)
Missing	6150 (12.8)	32,077 (13.4)
Start year of follow-up, n (%)		
1973 to 1989	4255 (8.8)	21,396 (8.9)
1990 to 1999	13,287 (27.6)	66,439 (27.8)
2000 to 2009	19,586 (40.7)	96,894 (40.5)
2010 to 2016	10,963 (22.8)	54,385 (22.7)
Follow-up, y		
Mean (SD)	12.2 (8.1)	12.2 (8.1)
Median (IQR)	11.0 (5.5–17.9)	11.0 (5.5–18.0)
Range	0.0–46.5	0.0–46.5

IQR, interquartile range.