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.

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

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**Abbreviations:**
CD, celiac disease; CI, confidence interval; ESPRESSO, Epidemiology Strengthened by histoPathology Reports in Sweden; GI, gastrointestinal; HR, hazard ration; OR, odds ratio; SnoMed, Systematized Nomenclature of Medicine.
Abstract

**Background & Aims:** The incidence of small bowel cancers is increasing. Associations have been made between celiac disease and small bowel cancers, but there have been no detailed studies of large cohorts.

**Methods:** Through the nationwide ESPRESSO cohort study, we retrieved data from Sweden’s 28 pathology departments on all individuals who received a diagnosis of celiac disease diagnosed from 1965 through 2017. Individuals with celiac disease, 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 celiac disease (patients) and 239,249 reference individuals. Beginning at 1 year after a diagnosis of celiac disease, 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% 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 celiac disease 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 celiac disease. However, risks of small bowel adenocarcinoma and adenomas (but not carcinoids) are significantly increased in people with celiac disease compared to people without this disease.

KEY WORDS: intestine, neoplasm, etiology, gluten
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 (GI) cancers. They have been named “orphan” neoplasias\(^2\) as they have rarely been studied and there is a lack of evidence-based knowledge of 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 reported 75 cases of small bowel adenocarcinoma in 79,991 individuals with celiac disease from 8 previous studies (Table 1), corresponding to a pooled odds ratio (OR) 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\(^5\), where there is an imminent risk of detection bias, and symptoms from the small intestinal cancer may trigger diagnostic work for celiac disease (a form of reverse causation). Earlier studies also suffer from 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 may have limited small bowel cancer detection in the general population. Third, outcome data have been based on ICD-
codes rather than histopathological examination. Fourth, population-based studies in celiac
disease, other than a small study of 381 individuals have not reported the risk of small bowel
adenomas. Small bowel adenocarcinomas are thought to develop through the adenoma
carcinoma sequence.  

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

Study population

Individual-level data from Swedish national registries were linked through the unique personal identity number assigned to all Swedish residents. Participants with celiac disease were identified from the ESPRESSO study (Epidemiology Strengthened by histoPathology Reports in Sweden) that included gastrointestinal (GI) biopsies from all 28 pathology departments in Sweden between 1965 and 2017. 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 Appendix). An earlier validation found that 95% of individuals in Sweden with VA have celiac disease. In individuals where data on celiac disease 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.

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 Appendix) in local pathology departments extracted for the ESPRESSO study. 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 to diagnoses of small bowel adenocarcinoma registered in the Swedish Cancer registry (defined by International Classification of Diseases (ICD), ICD-7 152.X combined with morphology codes to identify adenocarcinomas (SnoMed “81403” or PAD= “096”)), only 39 out of our 78 cases were also identified in the cancer registry. On the other hand, the cancer registry contained 8 entries of small bowel cancer that were neither found in pathology reports or the Patient registry, these were not included as cases as they were judged likely to have been erroneous entries as they were never communicated through clinicians or pathologists. Lymphomas were not included in this study.

**Reference individuals**

For each individual with celiac disease, the government agency Statistics Sweden randomly identified up to 5 reference individuals from the Swedish Total Population Register\(^\text{12}\) matched for age, sex, county and calendar year of the date of celiac diagnosis. Reference individuals were free of celiac disease at matching date, and if diagnosed with celiac disease 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 celiac disease 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 celiac disease 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 (Dec 31, 2017), whichever occurred first. For analyses comparing individuals with celiac disease 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.  

Statistics

We calculated hazard ratios (HRs) using stratified Cox regression. In the stratified regression, each case is only compared to his/her matched reference individuals and a pooled summary HR is calculated from all strata. We further adjusted for categorical educational attainment (≤9, 10-12, ≥13, missing) 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 and were adjusted for age-group, sex and inclusion year. To avoid impact from comorbid diseases we further ran a sensitivity analysis excluding all individuals ever diagnosed with any of the following diagnoses (identified through the Swedish Patient registry): IgA deficiency, lymphoma, Crohns disease, familial adenomatous polyposis or Lynch syndrome (relevant ICD codes are found in the appendix). In another analysis we examined the outcome of individuals with data on follow-up biopsy, i.e. having a second biopsy performed between 6 and 60 months after the initial diagnosis date. In this analysis we calculated the risk of
small bowel cancer in individuals with celiac disease 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\textsuperscript{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 1,000 person-years of follow-up. For small bowel adenocarcinoma we also calculated a conditional logistics regression for the risk of future celiac disease 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 9.4.

**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\textsuperscript{18}. 
We identified 48,119 individuals with celiac disease and 239,249 reference individuals still at risk one year after the celiac disease 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 more than 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 the Appendix).

Small bowel adenocarcinomas

In total, 29 individuals with celiac disease (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 one extra case of small bowel adenocarcinoma for every 2,944 individuals with celiac disease 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 ten years of follow-up, but did not differ by sex, age groups or calendar-year at celiac diagnosis. In the most recently diagnosed individuals (celiac diagnosis in 2010-2017) the HR was 2.63 (0.36-19.07). The risk of small bowel cancer was slightly higher in individuals with celiac disease with lower educational attainment (HR=5.11) although confidence intervals were wide and interaction terms were not significant (Table 3). In total, 18 individuals with celiac disease and 31 reference individuals were diagnosed with a duodenal adenocarcinoma, corresponding to an HR of 2.69 (1.46-4.96).
another 13 vs 18 had a registered location in either jejunum or ileum (HR=3.92; 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 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 HR=3.18 (95%CI=1.92-5.27).

In a conditional logistics regression model, the odds ratio (OR) 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 celiac disease 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 celiac disease were at a 5.73-fold increased risk of small bowel adenoma (95%CI=3.70-8.88). Interestingly 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 than 15 years of follow-up (Table 4). The risk of carcinoids was not increased as it was only observed in 3 individuals with celiac disease 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 celiac disease. Small bowel adenocarcinoma was seen in only 1/6,745 (0.01%) individuals with mucosal healing vs. in 5/2,787 (0.18%) individuals 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 (0.09%) individuals with celiac disease were diagnosed with later small bowel adenocarcinoma compared to 45 (0.02%) reference individuals (HR=5.28; 95%CI=3.37-8.27). The median time between celiac disease 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 1-5 years and 18 cases >5 years after celiac diagnosis). Including the first year after celiac diagnosis, there was one extra case of small bowel adenocarcinoma for every 1,346 individuals with celiac disease 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 age at adenocarcinoma 72 years, SD 10 years) and 41 reference individuals (median age at adenocarcinoma 70 years, SD 10 years) that survived their adenocarcinoma diagnosis date was better in celiac patients HR=0.56 (95%CI=0.34-0.94).

Including the first year of follow-up, there were 7 carcinoids (0.01%) in individuals with celiac disease 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 to previous literature

In this study we found an increased risk of adenocarcinomas in individuals with celiac disease compared to age and sex-matched reference individuals. The HRs were lower than reported by most previous studies\textsuperscript{19-24} and similarly the absolute risk (0.06\%) was 10 times lower than in another recent publication\textsuperscript{25} suggesting that 0.65\% (5 out of 770) celiac individuals develop small bowel adenocarcinoma. Compared to lymphomas (table 2) small bowel adenocarcinomas was approximately 10-times less common in celiac disease patients. In an earlier validation of 1,534 reports (identified by free text histopathological examination showing signs of other comorbidity) in 29,148 of the celiac disease patients included in the cohort, only 3 showed signs of refractory celiac disease (this equals 0.01\% of the total cohort). We are only aware of one previous study of small bowel adenomas reporting 3 cases in individuals with celiac disease (0.78\%) compared to 381 cases in other patients having performed an upper endoscopy and a corresponding HR of 2.39 (95\% CI 0.67-8.48)\textsuperscript{6}. Our study showed 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 having performed upper endoscopy). Indeed 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 OR of 4.14 for future celiac disease in individuals diagnosed with small bowel adenocarcinoma. Even though there is an increased risk of small bowel adenocarcinomas in individuals with celiac disease compared to matched reference individuals, the low absolute risk implies no need to screen individuals diagnosed with celiac disease 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 celiac disease\textsuperscript{26}. No prior study has examined whether mucosal healing alters the risk of small bowel adenocarcinoma. Our study showed a strong but non-significant protective effect indicating that even our study including more than 8000 patients with celiac disease 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 celiac disease and small bowel adenocarcinoma. During the entire follow-up of the ESPRESSO study 3,885 individuals were ever diagnosed with small bowel adenocarcinoma, hence celiac disease was diagnosed in 1.3\% of Swedish patients with small bowel adenocarcinoma. This study further showed that celiac disease status was associated with better small bowel adenocarcinoma survival, which is in line with previous publications\textsuperscript{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 histopathological examination and fourth we also report estimates for small bowel adenomas. Further the diagnosis of celiac disease has been validated and suggested to be correct in 95\% of the cases\textsuperscript{10}. Despite the high validity, it is still possible that some of the individuals diagnosed with celiac disease and small bowel adenocarcinomas were indeed misclassified, however we believe this had very limited impact on our results. Another strength of our study is that we also investigated neuroendocrine tumors, carcinoids, and found no association. This suggests lead time and detection bias to be limited also for adenocarcinoma, as these biases would affect both adenocarcinoma and carcinoid estimates equally. Further 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 that a pathological review could not be performed. Indeed, the ESPRESSO histopathology cohort identified more cases than the national cancer registry or the patient registry. On the other hand, 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. Previous work\textsuperscript{28} suggests a 10%-missingness in the cancer registry for digestive tract cancers compared to the patient registry, in our data we have a 50% missing compared to local pathology reports. Underreporting in the Swedish cancer registry to similar extent (44%) has been suggested for several other cancers such as pancreatic and biliary\textsuperscript{29}. We believe that using the cancer registry for small bowel adenocarcinoma may therefore not be as adequate in terms of sensitivity, and therefore believe that our study using histopathologic definitions confers more complete and correct data than in earlier reports\textsuperscript{5}.

**Conclusion**

This study found an increased HR of small bowel adenomas and adenocarcinomas in patients with diagnosed celiac disease, 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 even though the association failed to reach statistical significance.
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Figure 1. Histogram of time between diagnoses in 23 patients with small bowel adenocarcinoma diagnosed before start of follow-up (defined as one year after celiac diagnosis) in total 6 were diagnosed before celiac disease, 7 same day and 10 during the first year after diagnosis.
| Author/Publication Year | Design     | Country | Age       | No. of individuals with celiac disease | No. of small bowel cancer | Comparison                      | Reported HR          |
|-------------------------|------------|---------|-----------|---------------------------------------|---------------------------|---------------------------------|----------------------|
| Ilus/2014               | Retrospective | Finland | >15       | 32439                                 | 27                        | 6 expected from SIR             | 4.29 (2.83 – 6.24)   |
| Caio/2019               | Retrospective | Italy   | 18-80     | 770                                   | 5                         | NR                              | NR                   |
| Grainge/2012            | Retrospective | UK      | 26.3 at diagnosis | 435                                    | 1                         | 0.09 (expected from SIR)        | 11.1 (0.28–61.6)     |
| Elfstrom/2012           | Prospective | Sweden  | All age   | 28882                                 | 15                        | Matched reference individuals – first year excluded |                      |
| Anderson/2007           | Retrospective | UK      | All age   | 490                                   | 1                         | 0.04 (expected from SIR)        | 23.33 (0.00-69.07)   |
| Study          | Type         | Country | Age | Follow-up | SIR | CI          | Mean (CI)   |
|---------------|--------------|---------|-----|-----------|-----|-------------|-------------|
| Silano/2007\textsuperscript{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\textsuperscript{30}   | Prospective  | UK      | All age | 865 | 1 | NR (case was in peridiagnostic period) | NR |
| Green/2003\textsuperscript{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\textsuperscript{24} | Retrospective | Sweden  | All age | 11019 | 8 | SIR | 10 (4.4–20) |

NR-Not reported.
Table 2 Baseline characteristics of study cohort adenocarcinoma

| Characteristic       | Celiac disease (n=48,119) | Matched comparators (n=239,249) |
|----------------------|---------------------------|---------------------------------|
| Women, no. (%)       | 30 166 (62.7%)            | 149 786 (62.6%)                 |
| Men, no (%)          | 17 953 (37.3%)            | 89 463 (37.4%)                  |
| Age                  |                           |                                 |
| 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, min-max       | 0.0-95.4                  | 0.0-95.8                        |
| Age (years), no. (%) |                           |                                 |
| <20                  | 20 353 (42.3%)            | 101 245 (42.3%)                 |
| 20 - <40             | 9 536 (19.8%)             | 47 167 (19.7%)                  |
| 40 - <60             | 9 672 (20.1%)             | 48 148 (20.1%)                  |
| 60 - 80              | 7 603 (15.8%)             | 37 936 (15.9%)                  |
| 80 -                 | 955 (2.0%)                | 4 753 (2.0%)                    |
| Country of birth, no (%) |                       |                                 |
|                                      | Nordic country | Other | Missing |
|--------------------------------------|----------------|-------|---------|
|                                      | 46 174 (96.0%) | 220 112 (92.0%) | 1 (0.0%) |
|                                      | 1 944 (4.0%) | 19 128 (8.0%) | 9 (0.0%) |

| Highest attained level of education, n (%) |                                      |       |
|-------------------------------------------|--------------------------------------|-------|
| ≤9 years                                   | 9 397 (19.5%)                        | 48 854 (20.4%) |
| 10-12 years                                | 18 070 (37.6%)                       | 89 173 (37.3%) |
| >12 years                                  | 14 502 (30.1%)                       | 69 138 (28.9%) |
| Missing                                    | 6 150 (12.8%)                        | 32 084 (13.4%) |

| Start year of follow-up                   |                                      |       |
|-------------------------------------------|--------------------------------------|-------|
| 1965-1989                                  | 4 255 (8.8%)                         | 21 396 (8.9%) |
| 1990-1999                                  | 13 291 (27.6%)                       | 66 455 (27.8%) |
| 2000-2009                                  | 19 601 (40.7%)                       | 96 967 (40.5%) |
| 2010-2017                                  | 10 972 (22.8%)                       | 54 431 (22.8%) |

| Follow-up, years                          |                                      |       |
|-------------------------------------------|--------------------------------------|-------|
| 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, min-max                             | 0.0-46.5                              | 0.0-46.5 |
| Comorbidities (ever during follow-up)            | Group A | Group B |
|------------------------------------------------|---------|---------|
| IgA deficiency                                  | 41 (0.1%) | 24 (0.01%) |
| Crohn’s disease                                 | 1,512 (3.1%) | 946 (0.4%) |
| Lynch Syndrome                                  | 341 (0.7%) | 1,171 (0.5%) |
| Familiar adenomatous polyposis                  | 68 (0.1%) | 120 (0.1%) |
| Lymphoma                                        | 594 (1.2%) | 1,369 (0.5%) |
Table 3 Risk of small bowel adenocarcinoma overall and by subgroups in patients with Celiac disease and matched general population comparators

| Group                  | N (%)     | N events (%) | Incidence rate (95% CI) per 1000 PY | HR* (95% CI) |
|------------------------|-----------|--------------|--------------------------------------|--------------|
|                        | Celiac disease | Comparators | Celiac disease | Comparators | Celiac disease | 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-<1y                  | 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-<5y                  | 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-<10y                 | 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-<15y                | 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-<20y                | 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) |
| ≥20y                   | 9 520 (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 celiac diagnosis / study entry
| Year – First 5 years of follow-up | Year | Country of birth | Nordic | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 |
|---------------------------------|------|-----------------|--------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| 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                           | 1 944 (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 |

| Year | Nordic | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 |
|------|--------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| 1965-1989 | 4 255 (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) |
| 1990-1999 | 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) |
| 2000-2009 | 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) |
| 2010-2017 | 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 | Country of birth | Nordic | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 | 1965-1989 | 1990-1999 | 2000-2009 | 2010-2017 |
|------|-----------------|--------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| 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 | 1 944 (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 |
| Level of education | | | | | | |
|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                   | 7 037 (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) |
| ≤9 years          | 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)  |
| 10-12 years       | 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) |
| >12 years         | 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)  |
| Education missing |                  |                  |                 |                 |                 |                 |                  |

*Conditioned on matching set (age, sex, county, and calendar period) and further adjusted for highest attained education

NA – Not possible to calculate
Table 4. Risk of small bowel adenoma and carcinoids overall and by subgroups in patients with Celiac disease and matched general population comparators

| Group                  | Celiac disease | Comparators | HR* Adenoma (95%CI) | Celiac disease | Comparators | HR* Carcinoid (95%CI) |
|------------------------|----------------|-------------|---------------------|----------------|-------------|-----------------------|
|                        | N events adenoma (%) | N events adenoma (%) |                       | N events adenoma (%) | N events adenoma (%) |                       |
| 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-<1y                  | 5 (0.0%)   | 2 (0.0%)   | 15.88 (1.77-142.58) | (0.0%) | 3 (0.0%) | NA |
| 1-<5y                  | 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-<10y                 | 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-<15y                | 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-<20y                | 5 (0.0%)   | 7 (0.0%)   | 7.22 (1.25-41.71)  | (0.0%) | 3 (0.0%) | NA |
| ≥20y                   | 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 celiac diagnosis / study entry
|       | 0-19 years | 20-39 years | 40-59 years | 60-79 years | 80+ years | NA  |
|-------|------------|-------------|-------------|-------------|-----------|-----|
| <20   | 4 (0.1%)   | 1 (0.0%)    | 13.76 (1.48-127.79) | (0.0%)      | (0.0%)    | NA  |
| 20-<40| 13 (0.1%)  | 6 (0.0%)    | 22.02 (4.90-99.06)  | (0.0%)      | 2 (0.0%)  | NA  |
| 40-<60| 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-<80| 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+   | (0.0%)     | 1 (0.0%)    | NA            | (0.0%)   | (0.0%)    | NA  |

| Year                          | 0-19 years | 20-39 years | 40-59 years | 60-79 years | 80+ years | NA  |
|-------------------------------|------------|-------------|-------------|-------------|-----------|-----|
| 1965-1989                     | 12 (0.3%)  | 4 (0.0%)    | 22.41 (4.91-102.33) | (0.0%)      | 7 (0.0%)  | NA  |
| 1990-1999                     | 15 (0.1%)  | 21 (0.0%)   | 5.49 (2.50-12.05)  | 1 (0.0%)    | 10 (0.0%) | 0.47 (0.05-4.44) |
| 2000-2009                     | 18 (0.1%)  | 22 (0.0%)   | 4.13 (2.14-7.95)   | 2 (0.0%)    | 10 (0.0%) | 0.91 (0.16-5.15) |
| 2010-2017                     | 3 (0.0%)   | 3 (0.0%)    | 11.87 (1.08-130.04) | (0.0%)    | 1 (0.0%)  | NA  |

| Country of birth               | 0-19 years | 20-39 years | 40-59 years | 60-79 years | 80+ years | NA  |
|--------------------------------|------------|-------------|-------------|-------------|-----------|-----|
| 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  |

| Education                      | 0-19 years | 20-39 years | 40-59 years | 60-79 years | 80+ years | NA  |
|--------------------------------|------------|-------------|-------------|-------------|-----------|-----|
| ≤9 years                       | 10 (0.1%)  | 10 (0.0%)   | 2.02 (0.68-5.96) | 1 (0.0%)    | 7 (0.0%)  | 0.55 (0.06-5.39) |
| 10-12 years                    | 7 (0.0%)   | 9 (0.0%)    | 8.92 (1.80-44.23) | 1 (0.0%)    | 5 (0.0%)  | NA  |
| >12 years                      | 5 (0.0%)   | 4 (0.0%)    | 6.09 (0.65-56.83) | (0.0%)      | 2 (0.0%)  | NA  |
| Education                      | 26 (0.2%)  | 27 (0.0%)   | 4.92 (2.54-9.53)  | 1 (0.0%)    | 14 (0.0%) | 0.28 (0.04-2.14) |
missing

*Conditioned on matching set (age, sex, county, and calendar period) and further adjusted for highest attained education

NA – Not possible to calculate
### Definition of exposure and outcomes from ESPRESSO

| 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 |

### Definition of comorbidities from the Swedish national patient register

| Characteristics    | 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 |

### Baseline characteristics of study cohort carcinoids

| Characteristic   | Celiac disease (n= 48 125) | Matched comparators (n=239,275) |
|------------------|-----------------------------|---------------------------------|
| Women, no. (%)   | 30 167 (62.7%)              | 149 795 (62.6%)                 |
| Men, no (%)      | 17 958 (37.3%)              | 89 480 (37.4%)                  |

| Age              |                          |                                |
|------------------|--------------------------|--------------------------------|
| Mean (SD)        | 31.6 (24.9)              | 31.6 (25.0)                    |
| Median (IQR)     | 27.8 (8.1-52.6)          | 27.7 (8.1-52.7)                |
Baseline characteristics of study cohort adenoma of the small bowel

| Characteristic | Celiac disease (n= 48,091) | Matched comparators (n=239,114) |
|---------------|---------------------------|---------------------------------|
| Range, min-max | 0.0-95.4                  | 0.0-95.8                        |
| **Categories, no. (%)** |                          |                                 |
| <20           | 20 352 (42.3%)            | 101 241 (42.3%)                 |
| 20 - <40      | 9 536 (19.8%)             | 47 168 (19.7%)                  |
| 40 - <60      | 9 672 (20.1%)             | 48 147 (20.1%)                  |
| 60 - 80       | 7 611 (15.8%)             | 37 974 (15.9%)                  |
| 80 -          | 954 (2.0%)                | 4 745 (2.0%)                    |
| **Country of birth, no (%)** |                          |                                 |
| Nordic country| 46 179 (96.0%)            | 220 144 (92.0%)                 |
| Other         | 1 945 (4.0%)              | 19 122 (8.0%)                   |
| Missing       | 1 (0.0%)                  | 9 (0.0%)                        |
| **Highest attained level of education, n (%)** |                          |                                 |
| ≤9 years      | 9 399 (19.5%)             | 48 868 (20.4%)                  |
| 10-12 years   | 18 073 (37.6%)            | 89 177 (37.3%)                  |
| >12 years     | 14 502 (30.1%)            | 69 145 (28.9%)                  |
| Missing       | 6 151 (12.8%)             | 32 085 (13.4%)                  |
| **Start year of follow-up** |                          |                                 |
| 1973-1989     | 4 255 (8.8%)              | 21 392 (8.9%)                   |
| 1990-1999     | 13 295 (27.6%)            | 66 476 (27.8%)                  |
| 2000-2009     | 19 604 (40.7%)            | 96 986 (40.5%)                  |
| 2010-2016     | 10 971 (22.8%)            | 54 421 (22.7%)                  |
| **Follow-up, years** |                          |                                 |
| 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, min-max| 0.0-46.5                  | 0.0-46.5                        |
| Category                                      | Women, no. (%) | Men, no (%) |
|-----------------------------------------------|----------------|-------------|
| Women, no. (%)                               | 30 156 (62.7%) | 149 739 (62.6%) |
| Men, no (%)                                  | 17 935 (37.3%) | 89 375 (37.4%) |

| Age                                           |                |             |
| 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, min-max                                | 0.0-95.4       | 0.0-95.8    |

| Categories, no. (%)                          |                |             |
| <20                                          | 20 351 (42.3%) | 101 236 (42.3%) |
| 20 - <40                                     | 9 535 (19.8%)  | 47 162 (19.7%) |
| 40 - <60                                     | 9 660 (20.1%)  | 48 089 (20.1%) |
| 60 - 80                                      | 7 592 (15.8%)  | 37 881 (15.8%) |
| 80 -                                         | 953 (2.0%)     | 4 746 (2.0%) |

| Country of birth, no (%)                     |                |             |
| Nordic country                               | 46 145 (96.0%) | 219 993 (92.0%) |
| Other                                        | 1 945 (4.0%)   | 19 112 (8.0%) |
| Missing                                      | 1 (0.0%)       | 9 (0.0%)    |

| Highest attained level of education, n (%)   |                |             |
| ≤9 years                                     | 9 384 (19.5%)  | 48 810 (20.4%) |
| 10-12 years                                  | 18 059 (37.6%) | 89 112 (37.3%) |
| >12 years                                    | 14 498 (30.1%) | 69 115 (28.9%) |
| Missing                                      | 6 150 (12.8%)  | 32 077 (13.4%) |

| Start year of follow-up                     |                |             |
| 1973-1989                                    | 4 255 (8.8%)   | 21 396 (8.9%) |
| 1990-1999                                    | 13 287 (27.6%) | 66 439 (27.8%) |
| 2000-2009                                    | 19 586 (40.7%) | 96 894 (40.5%) |
| 2010-2016                                    | 10 963 (22.8%) | 54 385 (22.7%) |

| Follow-up, years                            |                |             |
| 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, min-max                               | 0.0-46.5       | 0.0-46.5    |
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Title: Risk of Small Bowel Adenocarcinoma, Adenomas, and Carcinoids in a Nationwide Cohort of Individuals With Celiac Disease

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.

Lay Summary: People with celiac disease have an increased risk for intestinal adenomas and cancer compared to people without celiac disease, but the absolute risk is low.