Cancer in first-degree relatives of people with celiac disease

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Abstract

Background: Celiac disease (CD) has been linked to cancer, especially lymphoproliferative malignancy (LPM). Earlier research has shown that first-degree relatives (FDRs) to individuals with CD are at increased risk of autoimmunity including CD, but data on their risk of cancer are scarce and contradictory. We aimed to assess whether Swedish FDRs to individuals with CD are at increased risk of cancer.

Methods: Individuals with CD (identified through biopsy reports equal to Marsh grade III) were matched on sex, age, county, and calendar year with up to 5 control individuals. All FDRs (father, mother, sibling, offspring) of CD individuals ("celiac FDRs": n = 109,391) and controls (n = 548,465) were identified through Swedish healthcare registries. Through Cox regression, we calculated hazard ratios (HRs) for cancer incidence (all cancer, breast cancer, gastrointestinal cancer, and LPM).

Results: During follow-up, celiac FDRs experienced 10,750 unique cancers as opposed to 54,686 in-control FDRs. Celiac FDRs were at a slightly lower risk of any cancer (HR 0.97, 95% confidence interval [CI] 0.95–0.99), partially due to the lower risk of breast cancer (HR 0.92, 95% CI 0.87–0.98). The relative risks of LPM (HR 0.99, 95% CI 0.91–1.08) and gastrointestinal cancer (HR 0.98, 95% CI 0.93–1.03) were both close to 1. As opposed to earlier research, we found no excess risk of LPM in siblings to individuals with CD (HR 0.98, 95% CI 0.81–1.19).

Conclusion: Celiac FDRs are not at increased risk of cancer, including LPM, arguing that shared genetics is unlikely to explain previous reports of an excess risk of LPM in patients with CD.

Abbreviations: CD = celiac disease, CI = confidence interval, FDR = first-degree relative, HR = hazard ratio, LPM = lymphoproliferative malignancy.

Keywords: cancer, celiac, risk factors, shared genetics

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1. Introduction

Celiac disease (CD) is a chronic gastrointestinal disease with systemic manifestations.[1] It is triggered by gluten exposure in genetically sensitive individuals who subsequently develop small intestinal inflammation.[2] The disease occurs in just under 1% of the US population,[3] but with substantial intercountry variation.[4] Common symptoms include growth failure, diarrhea, and other gastrointestinal complaints in children, whereas osteoporosis, depression, fatigue, and iron deficiency are also seen in adult patients. Of note, a proportion of both adult and pediatric patients are asymptomatic despite active CD.[1]

Whereas autoimmunity may be the most common comorbidity in CD,[5,6] patients are often worried by cancer, and cancer may be responsible for more than 30% of overall deaths in CD.[7] The cancer risk is especially increased for lymphoproliferative malignancy (LPM)[8] and gastrointestinal cancer,[9] whereas breast cancer seems to be inversely related to CD[10] (potentially through a lower average body mass index[11] in individuals with CD[12]).

First-degree relatives (FDRs) of individuals with CD are themselves at increased risk of developing CD.[13,14] Whereas most FDRs to individuals with CD are negative for CD on screening, earlier data suggest that FDRs may still be at increased risk of the comorbidities seen in CD, especially when genetic susceptibility is thought to be important. We have previously shown that FDRs to individuals with CD carry an increased risk of autoimmunity (+28%),[15] and a minimally increased risk of overall mortality (+2%)[16] and cardiovascular disease (+5%).[17]
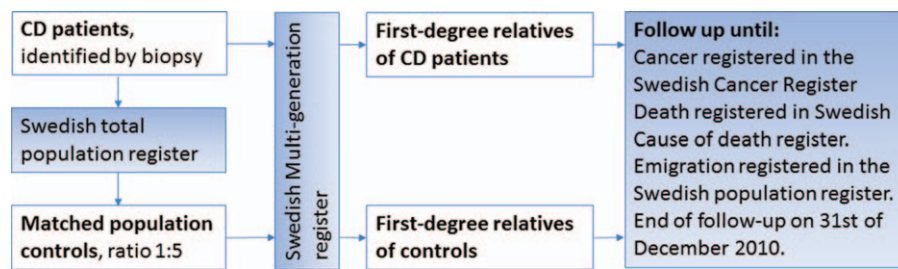
Figure 1. Linkage of registries. CD = celiac disease.

Others have reported an excess risk of certain cancers in FDRs to individuals with CD, more specifically Gao et al[18] reported a 2-fold increased risk of LPM in siblings to CD patients. However, the study by Gao et al[18] defined CD as having an inpatient diagnosis of CD, and this may have resulted in the identification of patients with a more severe CD than the average patient, and also families more prone to develop comorbidity than most celiac families. In addition, none of the earlier studies has explored the overall risk of cancer, or nonhematological cancer. Hence the risk of cancer in celiac FDRs is still largely unknown and could possibly be of any direction since the genetic contra exposure contribution of the increased risks of some cancers, and also decreased risk of breast cancer, has not been established.

The objective of this study was to examine the overall risk of cancer, and also LPM, gastrointestinal cancer, and breast cancer in 109,000 FDRs to individuals with CD (hereby called "celiac FDRs") compared with 548,000 control FDRs.

2. Methods

2.1. Defining celiac cases and reference individuals (controls)

Data on CD were collected through computerized duodenal/jejunal biopsies performed between 1969 and 2008 from all Swedish pathology departments. Villous atrophy equal to histopathology stage Marsh III[19] were considered as CD with date of first pathological biopsy as the date of diagnosis. In total, we identified 29,096 celiac individuals. During the study period, small intestinal biopsy was clinical routine in Sweden,[20] and more than 95% of individuals with Marsh III changes have CD in a Swedish setting.[20] All celiac individuals were matched with up to 5 nonceliac controls by the government agency *Statistics Sweden* using the Swedish Total Population Register.[21] In total, 144,522 controls matched for sex, county, age, and calendar year of birth were identified (Fig. 1). Patients with CD and their matched controls have been described in detail earlier.[7]

2.2. FDRs

Through the Swedish Multigeneration Register,[22] we obtained data on celiac FDRs (mother, father, sibling, and offspring) and control FDRs (Fig. 1). A number of celiac FDRs, and also control FDRs, had a diagnosis of CD themselves (Table 1). Each FDR was only counted once in the overall analysis (irrespective of type of relation), and we chose to use the first entry as a FDR (at first corresponding celiac or controls study entry date) as the one to keep to maximize time of follow-up. However, since FDRs could be both father and brother of different individuals, they could be

counted as both in the family member-specific analyses (exact numbers available in Table 1).

2.3. Follow-up time

Lifetime was modeled from birth until diagnosis of cancer, death, first emigration or the December 31, 2010, whichever occurred first. Alternatively, time since study entry of the index individual with CD (and corresponding matching date in controls) was modeled with similar end date as in the lifetime analysis. The reason for modeling time since diagnosis was that it is only at that time-point a person could know if he or she is a celiac FDR.

2.4. Exposure

Being a celiac FDR was defined as the exposure, whereas control FDRs served as the reference.

2.5. Outcome measure

We used the cancer registry to ascertain any incident cancer diagnoses.[23] We also performed separate analyses according to some different types of cancer incidence (defined according to relevant International of Classification [ICD] codes) categorized into breast cancer, gastrointestinal cancer, or LPM.

2.6. Statistical analyses

We used Cox regression to estimate hazard ratios (HRs) adjusted for sex and age group (not in matching strata since matching was primarily performed for cases and controls, not their FDRs). In our main analysis, we examined the future risk of any cancer in celiac FDRs (all relatives combined). Analyses stratified by relative (mother, father, sibling—brother, sister—and offspring—son, daughter) were also performed. We also analyzed the risk of any cancer when adjusting for CD diagnosis in the FDRs themselves. Proportional hazard assumptions were checked using log minus log curves. In a post-hoc analysis, we set study entry to age 40 to assess risks in older FDRs possibly exposed to undiagnosed CD for decades.

Statistical significance was defined as 95% confidence intervals (CIs) for risk estimates not including 1.0. We used SAS version 9.4 for all analyses.

2.7. Ethics

This study was approved by the Ethics Review Board in Stockholm, Sweden, that deemed that no informed consent was needed since this is a registry-based study with de-identifiable data.

Table 1

Characteristics of celiac and control first-degree relatives (FDRs).

Timeframe	Lifetime, n		From index individuals celiac diagnosis, n	
	Celiac FDRs	Control FDR	Celiac FDRs	Control FDR
Number, total	109,391	548,465	96,132	482,881
Relation*				
Father	21,973	110,028	15,971	81,405
Mother	22,391	112,779	17,060	87,126
Sibling	35,665	172,491	32,365	160,256
Offspring	33,607	164,397	30,736	154,094
Age group (birth date)				
1939	20,332	99,171	10,646	52,896
1940–1963	36,276	187,030	33,614	52,896
1964–1986	31,430	155,481	30,611	150,978
1987–2010	21,353	106,783	21,261	106,244
Calendar year study entry†				
1989			13,227	68,032
1990–1999			39,051	199,380
2000–2010			43,854	215,469
Own celiac disease in the relative				
Father	342	151	314	130
Mother	632	315	581	286
Sibling	1773	600	1746	579
Offspring	1120	534	1110	523
Sex				
Female	54,369	271,319	47,841	238,393
Male	55,022	277,146	48,291	244,488
Events (any cancer)				
Father	3409	16,746	1193	6119
Mother	3976	20,877	1333	7120
Sibling	2269	10,979	1249	5892
Offspring	1313	6838	752	3952
Total unique events	10,750	54,686	4419	22,752
Follow-up time, y				
Median	46	46	11	11
Range	0–115	0–115	0–41.6	0–41.6
Person-years of follow-up (1000 y)	5000	24,980	1182	5983

* The sum is greater than the total number since you can be both mother and sibling etc.
† Calendar year of index individual's celiac diagnosis not relevant when counting lifetime.

3. Results

3.1. Background data

In total, we obtained data on 109,391 celiac FDRs and 548,465 control FDRs. The median time of follow-up in the lifetime perspective was 41.5 years. In total, we had data on almost 30 million person-years of follow-up (Table 1). Own CD diagnosis in the FDRs was more often seen in the celiac FDRs (3.13%) than in the control FDRs (0.27%). Apart from that, the FDR groups were similar with regards to age, sex, and time of follow-up (Table 1).

3.2. Different types of cancer

The risk of any cancer was minimally decreased in celiac FDRs (HR 0.97, 95% CI 0.95–0.99) (corresponding survival plot available in Fig. 2). Adding own CD in the FDR as a covariate did not influence our risk estimates (data not shown). The decreased risk of any cancer was seen mainly due to a decreased risk of breast cancer (HR 0.92, 95% CI 0.87–0.98), whereas there were no differences in risk of gastrointestinal cancer or LPM (Table 2). In a sensitivity analysis excluding all individuals experiencing breast cancer, the risk of any other cancer was nonsignificant (HR 0.98, 95% CI 0.96–1.00, $P=0.08$). When limiting follow-up of

the FDRs from lifetime to time since date of biopsy of the index individual (and corresponding date of study entry in the controls), HRs remained close to 1 (Table 2); however, more than half of the lifetime events were excluded (Table 1).

3.3. Different categories of FDRs

We also analyzed the outcome according to different types of relation to the index individuals. In general, we found no differences compared with the average risk of cancer in all FDRs except for any cancer being significantly less common in mothers and siblings (the latter due to a decrease among sisters), but not in the other FDRs, and that the risk of breast cancer was significantly reduced (overall and specifically in mothers; Table 2). LPM was also significantly less common in children and particularly so in sons to individuals with CD when restricting follow-up to time since CD diagnosis (and corresponding in controls) (Table 2). The observed number of LPM was 14 and 128 in sons of celiac and control FDRs; this correspond to an absolute risk of 6.4 and 11.8 cases per 100.000 years of follow-up. Corresponding absolute risks for daughters were 6.2 and 8.0 cases per 100,000 years of follow-up. The mean age at the end of follow-up was around 34 years in the cohort of offspring. In a post-hoc analysis, we analyzed the risk of any cancer in all
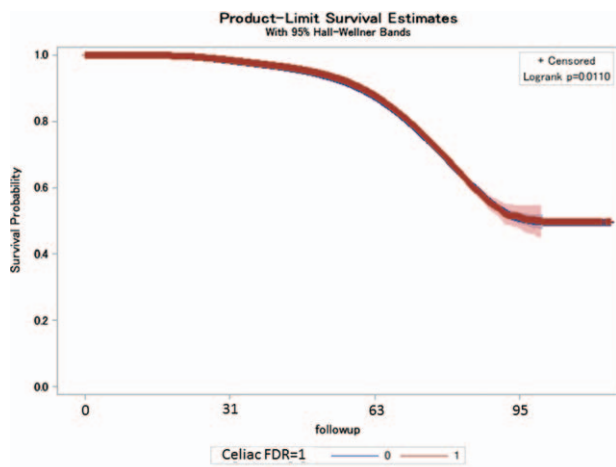
Figure 2. Lifetime cancer-free survival in celiac FDRs compared with control FDRs. FDR = first-degree relative.

relatives using age 40 years as the study entry (since risk of cancer due to undetected CD would take decades to occur). This did not influence our risk estimate (HR 0.99, 95% CI 0.96–1.01).

4. Discussion

4.1. Main findings

This study found a minimally decreased risk of cancer among celiac FDRs (−3%), partially due to the lower risk of breast cancer. The HR of LPM and gastrointestinal cancer was close to 1, with the HR for LPM in siblings being 0.98.

4.2. Comparison with other studies

In 2009, Gao et al[18] reported a 2.03-fold increased risk of non-Hodgkin lymphoma (NHL) in siblings to CD patients, although of note, other FDRs were at no increased risk or potentially even at a *lower* risk of NHL (mothers: odds ratio [OR] 0.67, fathers 0.92, and offspring 0.94). Whereas NHL is not the only cancer in LPM, it is the dominant cancer form, expected to account for 72,580 of 81,080 (90%) new cases of lymphomas in the US 2016.[24] The Swedish incidence of NHL is 25.9 in men and 19.4

in women per 100,000 person-years compared with 2.2 and 1.9 for Hodgkin lymphomas,[25] and had there been an excess risk, we would have noted it. Instead, we found very similar HRs in all FDRs (except for sons) consistently around 1 (which is biologically plausible). We believe the lower risk in sons is most likely due to multiple testing as absolute numbers are very small.

In contrast, Landgren et al detected no increased risk of Hodgkin lymphoma[26] or chronic lymphocytic leukemia[27] in celiac FDRs. However, all the above studies defined CD as having an inpatient diagnosis of CD, and this may have resulted in the identification of patients with a more severe CD than the average patient, and also families more prone to develop comorbidity than most celiac families.

Many relatives to individuals with CD eat a gluten-free or gluten-reduced diet, and we cannot exclude that this has influenced our findings. Both direct[28] and indirect evidence (assuming that mucosal healing in patients with initial villous atrophy is linked to dietary adherence[29]) suggests that a gluten-free diet (GFD) protects against LPM, and this may have driven the HRs towards 1. In our study, the overall risk was 0.99, strongly suggesting a neutral risk of LPM in celiac FDRs.

4.3. Strengths and limitations

This is the largest study so far on cancer risk in celiac FDRs. The great power allowed us to calculate narrow CIs and rule out larger excess risks for cancer. For instance, the upper 95%CI for LPM in FDRs was 1.08, ruling out a more than 8% increased relative risk of a condition that is still rare in absolute terms. We were also able to demonstrate a slightly lower risk of overall cancer in celiac FDRs, although this finding should not be over interpreted as it is of little importance to single individuals. More importantly, our study strongly suggests that shared genetics is unlikely to explain the excess risks of LPM in patients with CD, as we found no excess risk for this cancer among FDRs. This conclusion is further strengthened by a recent study from the InterLymph consortium.[30] In a pooled analysis of more than 8000 NHL cases from 14 centers, InterLymph researchers investigated shared genetics in NHL and in a number of autoimmune disease, including CD. They found no association between CD and either rs10484561, rs2647012, and rs6457327 (all linked to HLA I/II), and which had otherwise been identified as important susceptibility loci in NHL.[30]

We identified CD through biopsy registry data from all Swedish pathology departments. While adult guidelines from

Table 2

Risk of cancer within different groups of FDRs.

	HR (95% CI)							
	Lifetime risk (from birth of the relative) adjusted for sex (when not naturally stratified by type of FDR) and age group of the relative				Risk from FDR celiac diagnosis date adjusted for sex, age group of the relative, and calendar year of celiac diagnosis			
	Any cancer	Breast cancer	Gastrointestinal cancer	Lymphoproliferative cancer	Any cancer	Breast cancer	Gastrointestinal cancer	Lymphoproliferative cancer
Fathers	1.02 (0.98–1.06)	0.95 (0.42–2.13)	1.02 (0.95–1.09)	0.99 (0.86–1.14)	1.02 (0.96–1.09)	1.04 (0.23–4.76)	1.08 (0.95–1.23)	0.84 (0.65–1.09)
Mothers	0.95 (0.92–0.98)	0.90 (0.84–0.97)	0.95 (0.87–1.03)	1.04 (0.89–1.22)	0.96 (0.91–1.02)	0.90 (0.80–1.01)	0.91 (0.78–1.05)	0.97 (0.73–1.28)
Siblings	0.96 (0.91–1.00)	0.94 (0.83–1.06)	0.93 (0.82–1.05)	0.98 (0.81–1.19)	0.99 (0.93–1.05)	1.01 (0.86–1.18)	0.96 (0.83–1.12)	0.99 (0.76–1.28)
Brothers	1.00 (0.93–1.08)	0.93 (0.11–7.90)	0.92 (0.74–1.09)	1.05 (0.82–1.34)	1.01 (0.92–1.10)	1.56 (0.16–15.14)	0.99 (0.81–1.20)	1.21 (0.88–1.66)
Sisters	0.93 (0.88–0.99)	0.94 (0.83–1.06)	0.94 (0.79–1.13)	0.88 (0.65–1.20)	0.98 (0.90–1.06)	1.00 (0.85–1.18)	0.93 (0.74–1.18)	0.70 (0.44–1.10)
Offspring	0.97 (0.92–1.03)	0.98 (0.83–1.16)	1.05 (0.87–1.28)	0.86 (0.66–1.12)	0.96 (0.89–1.04)	1.07 (0.89–1.30)	1.07 (0.85–1.33)	0.66 (0.44–0.98)
Sons	1.08 (0.97–1.20)	1.08 (0.13–9.25)	1.11 (0.86–1.44)	0.76 (0.53–1.08)	1.03 (0.90–1.18)	0.32 (0.15–11.81)	1.13 (0.84–1.52)	0.56 (0.32–0.97)
Daughters	0.93 (0.87–1.00)	0.98 (0.83–1.16)	0.99 (0.74–1.32)	1.01 (0.68–1.50)	0.92 (0.84–1.02)	1.07 (0.88–1.30)	0.98 (0.70–1.39)	0.80 (0.45–1.45)
All FDRs	0.97 (0.95–0.99)	0.92 (0.87–0.98)	0.98 (0.93–1.03)	0.99 (0.91–1.08)	0.99 (0.96–1.02)	0.96 (0.88–1.05)	1.00 (0.92–1.08)	0.89 (0.78–1.03)

CI = confidence interval, FDR = first-degree relative, HR = hazard ratio.

Europe[31] and the USA[32] recommend biopsy before celiac diagnosis, European Society for Paediatric Gastroenterology Hepatology and Nutrition allows for a nonbiopsy diagnosis in selected children with suspected CD and symptoms, but this option was only made available in Sweden after the data collection for this study had ended, and has never been available to adults. Earlier validation data suggest that, during the study period in Sweden, more than 95% of individuals with suspected CD underwent biopsy[7]; in fact, this is higher than the positive predictive value for a physician-assigned celiac diagnosis in the Swedish Patient Registry.[33] Data on LPM were obtained through linkage with the Swedish Cancer Registry. The cancer registry started in 1958 and has a completeness of >96%.[23] During follow-up, celiac FDRs developed more than 10,000 cancers, as compared with more than 54,000 cancers in control FDRs. Considering our matching of 1:5, this well illustrates that celiac FDRs were at no increased risk of cancer.

Among the weaknesses, the large number of comparisons increases the risk of multiple-chance findings and we cannot rule out that some of the statistically significant findings were due to type 1 errors. Furthermore, we lacked data on gluten-free diet in celiac FDRs (and in control FDRs as the GFD is becoming increasingly popular in the general population as well), and it is beyond the scope of this study to evaluate the effect of GFD on cancer risk in individuals without CD. Arguing against a major role for GFD is the fact that relative risks for cancer, including that for LPM, were similar, independent of the start of follow-up in FDRs (at birth or at the date of the celiac diagnosis in the index individual).

5. Conclusions

Celiac FDRs are at no increased risk of cancer, including LPM, arguing that shared genetics is unlikely to explain the excess risk of LPM in patients with CD.

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