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Primary care

Malignancy and mortality in people with coeliac disease: population based cohort study

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Abstract

Objective To quantify the risks of malignancy and mortality in people with coeliac disease compared with the general population.
Design Population based cohort study.
Setting General practice research database.
Participants 4732 people with coeliac disease and 23 620 matched controls.
Main outcome measures Hazard ratios for malignancy and mortality.
Results Of the 4732 people with coeliac disease, 134 (2.8%) had at least one malignancy and 237 (5.0%) died. The overall hazard ratios were: for any malignancy 1.29 (95% confidence interval 1.06 to 1.55), for mortality 1.31 (1.13 to 1.51), for gastrointestinal cancer 1.85 (1.22 to 2.81), for breast cancer 0.35 (0.17 to 0.72), for lung cancer 0.34 (0.13 to 0.95), and for lymphoproliferative disease 4.80 (2.71 to 8.50). The increased risk was primarily in the first year after diagnosis, with the risk for only lymphoproliferative disease remaining significantly raised thereafter. After excluding events in the year after diagnosis, the hazard ratio for malignancy was 1.10 (0.87 to 1.39) and for mortality was 1.17 (0.98 to 1.38), giving absolute excess rates of 6 and 17 per 10 000 person years, respectively.
Conclusions People with coeliac disease have modest increases in overall risks of malignancy and mortality. Most of this excess risk occurs in the year of follow up after diagnosis. People with coeliac disease also have a noticeably reduced risk of breast cancer. The mechanism of this merits further attention as it may provide insights into the cause of this common malignancy.

Introduction

Early studies reported a twofold increase in risk of mortality and greatly increased risks of lymphoproliferative malignancies in people with coeliac disease.[1–6] These studies were mostly small or not population based, and the findings probably do not reflect risks today.[1–6] Data from Sweden's hospital inpatient register showed more modest increases in the risks in people with coeliac disease, but still found an excess risk of certain malignancies and death.[7 8] In contrast, two studies showed a decrease in the risk of breast cancer in people with coeliac disease, the reasons for which are not clear.[4 8] We carried out a large population based cohort study in people with coeliac disease to provide robust estimates of the absolute and relative risks of malignancy and mortality.

Methods

The UK general practice research database was established in 1987 and is the largest longitudinal database in primary care. It contains the medical records of more than 8 million patients. When people are seen in primary care in the United Kingdom, information on important medical diagnoses, hospital letters, discharge summaries, and prescriptions are entered onto a desktop computer. The data from practices entering information into the general practice research database are audited regularly, and at least 95% of data on morbidity and prescribing must be included for the practice to be contributing data that are considered up to standard.[9]

Study population

Our study population has been described in detail elsewhere.[10] In brief, between June 1987 and April 2002 we extracted the records of all people within the general practice research database with a recorded diagnosis of coeliac disease. We selected five controls matched to each person with coeliac disease by age, sex, and general practice. Controls were alive and contributing data on the date of the first prospective, up to standard, record of coeliac disease or prescription for a gluten-free product for people with coeliac disease. We excluded controls who had any record of a gluten-free prescription or a non-specific reference to coeliac disease, such as gluten-free diet or gluten sensitivity.

Each person with coeliac disease was assigned a date of diagnosis, defined as the first date of recognised coeliac disease. Since general practitioners enter some data for important historical events retrospectively, in some cases this date preceded the start of their up to standard record. We assigned controls a "pseudo-diagnosis" date identical to their matched case. We defined incident people with coeliac disease as those whose date of diagnosis for coeliac disease or first prescription for a gluten-free product occurred at least one year after the start of their record on the general practice research database. All other people with coeliac disease were defined as prevalent.

Outcomes and potential confounders

Outcomes included the date of first occurrence of any malignancy or of a specific malignancy subgroup and date of death during up to standard data. We defined all malignancies by using the relevant codes in the general practice research database mapped to codes 140-208 and 230-234 from the international classification of diseases, ninth revision. The subgroups we chose were gastrointestinal cancers (codes 150-154), lung cancer (162-163), breast cancer (174-175), prostate cancer (185), and lymphoproliferative disease (200-202). Follow up in our study began at the date of the first prospectively recorded code

for coeliac disease or prescription for a gluten-free product, and we used the matched case's relevant date for controls.

We extracted information on height, weight, and smoking status from the whole of each person's data period. Body mass index (weight (kg)/(height (m)^2)) was calculated for people over 15 years of age.

Statistical analysis

Initially we calculated the crude incidence of cancer and mortality for both the coeliac and the control cohorts. We used Cox regression modelling (release 7.0; Stata Statistical Software) to estimate the hazard ratio, comparing outcomes in the coeliac cohort with those in the control cohort. We checked the proportional hazards assumption of each model using log-log plots. The possible confounding effects of age, sex, body mass index, and smoking status were assessed by using a series of multivariable models. Missing data for confounders were fitted as a separate category to ensure that nested models contained the same number of people. We fitted multiplicative interaction terms to assess possible interactions between coeliac disease status and age or sex.

To assess ascertainment bias (whether the increased risk of cancer was related to increased investigation as a result of having a diagnosis of coeliac disease or cancer) we examined the hazard ratios for each outcome within the year after diagnosis and during follow up. To assess the validity of our findings for possible misclassification of coeliac disease status, we restricted our analyses to only those people with coeliac disease who had had at least one prescription for a gluten-free product. To assess the possibility of survival bias we stratified our censored analysis by prevalent or incident status.

Results

Our cohorts included 4732 people with coeliac disease and 23 620 matched controls, contributing 18 923 and 94 323 person years at risk, respectively. Of the people with coeliac disease, 3143 (66.4%) were prevalent cases. The cohorts were closely matched for sex and on age at entry to follow up (table 1). More current smokers were present in the control cohort (15.4% *v* 13.0%) than coeliac disease cohort and more people were underweight (body mass index ≤18.5) in the coeliac disease cohort (4.2% *v* 1.2%).

Malignancy

Of the 4732 people with coeliac disease, 134 (2.8%) had at least one malignancy. The overall rate of any malignancy for the coeliac cohort was 72.0 per 10 000 person years compared with 55.9 per 10 000 person years for the control cohort, giving around a 30% increase in the risk of any malignancy among people with coeliac disease (hazard ratio 1.29, 95% confidence interval 1.06 to 1.55; table 2). The absolute excess rate of any malignancy was 16 per 10 000 person years. For malignancy subgroups we found an increase in the risk of gastrointestinal cancer (hazard ratio 1.85) and lymphoproliferative disease (4.80) and decreases in the risk of breast cancer (0.35) and lung cancer (0.34) in the coeliac cohort compared with the control cohort. When we restricted our analyses to the year after diagnosis, most of the hazard ratios were increased (see table 2). After excluding events within the year of follow up after diagnosis the risks were generally decreased. The absolute excess rate of any malignancy in this period was 6 per 10 000 person years.

Mortality

Overall, there were 237 deaths among people in the coeliac cohort and 902 in the control cohort, giving overall crude mortalities of 125.3 and 95.7 per 10 000 person years, respectively. These rates corresponded to a hazard ratio of 1.31 (95% confidence interval, 1.13 to 1.51). The absolute excess rate was 30 per 10 000 person years. The risk in the year after diagnosis was considerably higher (hazard ratio 1.97, 1.50 to 2.59) compared with that later (1.17, 0.98 to 1.38). The absolute excess rate when deaths were excluded within the year of follow up after diagnosis was 17 per 10 000 person years (see table 2).

Table 1 Details on observation time and personal characteristics of coeliac disease cohort and control cohort. Values are numbers (percentages) unless stated otherwise

Variable	Coeliac disease cohort (n=4732)	Control cohort (n=23 620)
Median observed time (years)	3.4	3.5
Total observed time (years)	18 923	94 323
Female	3095 (65.4)	18545 (65.4)
Age groups at entry to follow up (years):		
0-3	196 (4.1)	985 (4.2)
>3-15	385 (8.1)	1915 (8.1)
>15-25	455 (9.6)	2270 (9.6)
>25-35	676 (14.3)	3375 (14.3)
>35-45	812 (17.2)	4045 (17.1)
>45-55	858 (18.1)	4285 (18.1)
>55-65	610 (12.9)	3050 (12.9)
>65-75	469 (9.9)	2342 (9.9)
>75	271 (5.7)	1353 (5.7)
Smoking status:		
Non-smoker	2082 (44.0)	8623 (36.5)
Former smoker	221 (4.7)	1265 (5.4)
Current smoker	613 (13.0)	3630 (15.4)
Unknown	1816 (38.4)	10 102 (42.8)
Body mass index*:		
≤18.5	197 (4.2)	273 (1.2)
>18.5 to 25.0	2010 (42.5)	6949 (29.4)
>25.0 to 30.0	653 (13.8)	4319 (18.3)
>30.0	148 (3.1)	1920 (8.1)
Unknown	1724 (36.4)	10 159 (43.0)

*Weight (kg)/(height (m)^2).

The adjusted estimates for all analyses were similar to the crude analyses (see table 2). When we stratified our analyses by prevalent or incident status, having excluded events in the year after diagnosis, the hazard ratios for overall malignancy were 1.11 (0.86 to 1.44) and 1.03 (0.59 to 1.79), respectively. For mortality, the hazard ratio for the prevalent group was 1.09 (0.90 to 1.33) and for the incident group was 1.46 (1.04 to 2.07). When we repeated our analyses restricted to only those people with coeliac disease who had had at least one gluten-free prescription, we found no important differences in the risk estimates (overall malignancy hazard ratio 1.20, 0.97 to 1.45; mortality 1.20, 1.07 to 1.45). No clear evidence was found against the proportional hazards assumption in any of the presented models.

Discussion

People with coeliac disease are at a modestly increased risk of malignancy and mortality than the general population. The risks were most apparent in the year after diagnosis, and the decreased risks thereafter suggest that some of the overall excess risk was likely to be due to ascertainment. Although people with coeliac disease had an increased risk of gastrointestinal and lymphoproliferative malignancy compared with the general population they had around one third the risk of breast or lung cancer.

A potential weakness of epidemiological studies using routinely collected data such as that in the general practice

Table 2 Overall number of events, rates per 10 000 person years, crude and adjusted hazard ratios for coeliac cohort compared with control cohort (reference group)

	Overall			First year of follow up after diagnosis			Follow up beyond year after diagnosis		
Condition and cohort	No of participants*	Hazard ratio (95% CI)	Adjusted hazard ratio† (95% CI)	No of events	Rate/10 000 years	Adjusted hazard ratio† (95% CI)	No of events	Rate/10 000 years	Adjusted hazard ratio† (95% CI)
Any malignancy:							*		
Control	23 433	1	1	111	52.7	1	395	56.5	1
Coeliac disease	4695	1.29 (1.06 to 1.55)	1.31 (1.08 to 1.59)	44	104.2	2.07 (1.45 to 2.96)	87	62.2	1.10 (0.87 to 1.39)
Gastrointestinal cancer:									
Control	23 605	1	1	14	6.6	1	64	9.0	1.00
Coeliac disease	4724	1.85 (1.22 to 2.81)	1.95 (1.27 to 3.00)	9	21.1	3.31 (1.40 to 7.83)	20	14.1	1.65 (0.99 to 2.76)
Breast cancer:									
Control	23 562	1	1	24	11.3	1	87	12.3	1
Coeliac disease	4725	0.35 (0.17 to 0.72)	0.31 (0.15 to 0.63)	3	7.0	0.60 (0.18 to 2.04)	5	3.5	0.24 (0.10 to 0.60)
Lung cancer:									
Control	23 616	1	1	14	6.6	1	43	6.0	1
Coeliac disease	4728	0.34 (0.13 to 0.95)	0.37 (0.13 to 1.02)	1	2.3	0.40 (0.05 to 3.09)	3	2.1	0.37 (0.11 to 1.20)
Lymphoproliferative disease:									
Control	23 612	1	1	6	2.8	1	17	2.4	1
Coeliac disease	4724	4.80 (2.71 to 8.50)	4.27 (2.36 to 7.74)	11	25.8	7.32 (2.65 to 20.24)	12	8.4	3.40 (1.58 to 7.34)
Prostate cancer:									
Control	23 614	1	1	4	1.9	1	25	3.5	1
Coeliac disease	4730	0.99 (0.41 to 2.38)	1.05 (0.42 to 2.57)	1	2.3	1.30 (0.14 to 12.19)	5	3.5	1.03 (0.38 to 2.76)
Mortality:									
Control	23 609	1	1	184	86.7	1	697	98.0	1
Coeliac disease	4728	1.31 (1.13 to 1.51)	1.39 (1.20 to 1.61)	73	171.0	2.09 (1.59 to 2.76)	163	114.6	1.23 (1.04 to 1.47)

*Numbers vary as participants with event on same date or before start of follow up were excluded.
†Adjusted for age, sex, body mass index, and smoking status.

research database is the validity of diagnostic data for each person, particularly histological status; the diagnosis of coeliac disease has not been specifically validated in the database. One study looked in detail at the accuracy of the diagnosis of inflammatory bowel disease (92%) and one similarly evaluated cancer diagnoses (>90%).[11–14] Furthermore, to increase the specificity of the diagnosis, we restricted our analyses to people with coeliac disease who had at least one prescription for a gluten-free product. In these analyses there were no substantial changes in the effect estimates.

The likelihood of detecting an occult or overt malignancy may be increased during the investigation of coeliac disease and conversely coeliac disease is more likely to be detected during the investigation of cancer. The excess risk of gastrointestinal malignancy is therefore likely to be attributable to the more detailed investigation of gastrointestinal symptoms, particularly at presentation. We were able to assess the effect of potential confounders such as body mass index and smoking status on risk of malignancy and mortality. We found no evidence of confounding despite incomplete data and the likely heterogeneous nature of those people with missing data.

The risks of overall malignancy and mortality in people with coeliac disease suggest more modest increases than in other studies. The most recent study found slightly greater risks of malignancy (standardised incidence ratio 1.3) and mortality (standardised mortality ratio 2.0) compared with our study.[7 8] These greater risks may reflect more severe disease at presentation or a period effect, as all the patients had been admitted to hospital at least once and follow up ended at least six years earlier than in our study. People being diagnosed more recently seem to have less severe disease.[15–18] Most other studies have found increased risks of twofold or more for malignancy or mortality.[1 2 4 5]

Two previous studies have also suggested a decreased risk of breast cancer among women with coeliac disease, but it is not clear whether these were chance observations.[4 8] It seems unlikely that socioeconomic status is an important confounder in this relation as breast cancer has been consistently associated with higher socioeconomic groups, and there is no evidence that people with coeliac disease are of lower socioeconomic status.[19] The reduction in incidence of lung cancer found by us is in keeping with recent studies, which showed that people with coeliac disease report smoking less even before they were diagnosed as having the disease.[20 21] That the reduced incidence is still apparent after adjusting for smoking status is surprising, but our data on smoking were incomplete so residual confounding remains a possibility.

Most of the modest increases in the relative and absolute risk of malignancy and mortality in people with coeliac disease occurs in the year after diagnosis, and although there are noticeably increased risks of some malignancies such as gastrointestinal cancers and lymphoma there are substantial reductions in the risk of other, common, cancers such as those of the lung and breast. The findings for lung and breast cancer are of interest because of possible genetic, nutritional, or environmental factors that may protect people with coeliac disease against certain malignancies. By understanding the mechanism of protection in people with coeliac disease we may gain insight into the causes of breast cancer.

What is already known on this topic

People with coeliac disease may be at increased risk of gastrointestinal malignancy and lymphoma

These risks have not been quantified in contemporary, population based studies

What this study adds

People with coeliac disease have a modestly increased risk of malignancy and mortality

Most of the excess risk occurs in the year after diagnosis

The risk of breast cancer is about a third that of the general population

The risk of lung cancer is about a third that of the general population, probably because people with coeliac disease smoke less

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Contributors: JW designed the study and carried out most of the data management, analyses, interpretation, and writing of this study; he will act as guarantor for the paper. RFAL, CJS, RBH, and TRC contributed to the design, analyses, interpretation, and writing.

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