

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 only the risk for 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 first year 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 in people with coeliac disease reported a twofold increase in risk of mortality and greatly increased risks of lymphoproliferative malignancies. These studies were mostly small or not population based, and the findings probably do not reflect risks today. Recent data from Sweden showed more modest increases in risks, but still found an excess risk of certain malignancies and death.^{1 2} Two studies showed a decrease in the risk of breast cancer in people with coeliac disease, the reasons for which were not clear.^{2 3} We carried out a large population based cohort study

in people with coeliac disease to provide robust estimates of the current absolute and relative risks of malignancy and mortality.

Methods

The UK general practice research database was established in 1987. It contains computerised medical records of more than 8 million patients. The data from contributing practices are audited regularly and must be at least 95% complete to be considered up to standard.

Our study population has been described in detail elsewhere.⁴ Between June 1987 and April 2002 we extracted the records of all people with a recorded diagnosis of coeliac disease. We selected five controls matched by age, sex, and general practice. Controls were alive and contributing data on the date of the first prospective 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. We assigned controls a "pseudodiagnosis" date identical to their matched case. We defined incident people 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 in the general practice research database. All others with coeliac disease were defined as prevalent.

Outcomes and potential confounders

Outcomes identified were the date of first occurrence of any malignancy or of a specific malignancy subgroup and date of death. We identified all malignancies by using the relevant codes in the general practice research database mapped to codes from the international classification of diseases. Follow up in our study began at the date of the first prospectively recorded code for coeliac disease or prescription for a



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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

We calculated the crude incidence of cancer and mortality for both the coeliac and the control cohorts. We used Cox regression modelling to estimate the hazard ratio, comparing outcomes in the coeliac cohort with those in the control cohort. For each model we checked the proportional hazards assumption 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. We fitted multiplicative interaction terms to assess possible interactions between coeliac disease status and age or sex.

To assess ascertainment bias—that is, whether any increase in cancer risk might have resulted from extra investigations performed after a diagnosis of coeliac disease or cancer—we examined the hazard ratios for each outcome within the first year after diagnosis and subsequently. To assess for possible misclassification of coeliac disease status, we restricted our analyses to only those patients 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 age at entry to follow up. 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 \leq 18.5) in the coeliac disease cohort (4.2% *v* 1.2%; see [bmj.com](#)).

Malignancy

Of the 4732 people with coeliac disease, 134 (2.8%) had at least one malignancy. We found around a 30% increase in the risk of any malignancy among people with coeliac disease (table). 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 and lymphoproliferative disease and decreases in the risk of breast cancer and lung cancer in the coeliac cohort compared with the control cohort. When we restricted our analyses to the first year after diagnosis, most of the hazard ratios were increased (see table). After excluding events within the first year 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 (see table). 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) than 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.

When we stratified our analyses by prevalent or incident status, having excluded events in the first 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 restricted our

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

Condition and cohort	No of participants*	Overall		First year of follow up after diagnosis			Follow up beyond year after diagnosis		
		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.

analyses to only those people 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).

Discussion

People with coeliac disease have a modestly increased risk of malignancy and mortality compared with the general population. The increase in risk was most apparent in the year after diagnosis. The decreased risks thereafter suggest that much of the excess risk may have been due to ascertainment. Although people with coeliac disease had an increased risk of gastrointestinal cancer and lymphoma, they had around one third the risk of breast or lung cancer.

A potential weakness of studies using routinely collected data is the validity of diagnoses; that for coeliac disease has not been specifically validated in the general practice research database. However when we restricted our analyses to people with coeliac disease with at least one prescription for a gluten-free product, there were no substantial changes in the effect estimates.

As people with coeliac disease are likely to attend their general practitioners more frequently than the general population, differences in ascertainment of some malignancies such as breast or prostate cancer are possible. In addition, when people are being investigated for coeliac disease or cancer, the likelihood of a second condition being detected will be increased. For example, the excess risk of gastrointestinal malignancy may be partly attributable to the detailed investigation of gastrointestinal symptoms, particularly at presentation. We were able to assess the effect of confounding by smoking and obesity but found no evidence of confounding despite incomplete data and the likely heterogeneous nature of people with missing data.

The risks of malignancy and mortality in our study are lower than in the recent Swedish study.^{1 2} The higher risks in that study probably reflect more severe disease at presentation and a period effect, as all their patients had been admitted to hospital at least once and follow up ended at least six years earlier than our study.

A decreased risk of breast cancer among women with coeliac disease was also found in two earlier studies, but was dismissed as possible chance observations.^{2 3} It seems unlikely that differences in socioeconomic status are the explanation as breast cancer is more common in the higher socioeconomic groups, and there is no evidence that people diagnosed as having coeliac disease are of lower socioeconomic status.⁵ The reduction in risk of lung cancer we found is in keeping with recent studies, which showed that people with coeliac disease report smoking less, even before diagnosis.^{6 7} Although the reduced risk is still apparent after adjusting for smoking status, our data on smoking habits were incomplete so residual confounding remains a possibility.

Most of the increases in the relative and absolute risk of malignancy and mortality in people with coeliac

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 and lung cancer is about a third that of the general population

disease occur in the year after diagnosis. Although people with coeliac disease are at increased risks of some malignancies such as certain gastrointestinal cancers and lymphomas there are reductions in the risk of other malignancies such as lung and breast cancer. The findings for breast cancer are of particular interest because it suggests a potentially fruitful area for research.

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