



**QUEEN'S
UNIVERSITY
BELFAST**

Malignancy and mortality in a population-based cohort of patients with coeliac disease or 'gluten sensitivity'

Anderson, LA., McMillan, SA., Watson, RGP., Monaghan, P., Gavin, AT., Fox, C., & Murray, LJ. (2007). Malignancy and mortality in a population-based cohort of patients with coeliac disease or 'gluten sensitivity'. *World journal of gastroenterology : WJG*, 13(1), 146-151. <https://doi.org/10.3748/wjg.v13.i1.146>

Published in:

World journal of gastroenterology : WJG

Document Version:

Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:

[Link to publication record in Queen's University Belfast Research Portal](#)

Publisher rights

© 2007 The WJG Press. All rights reserved.

Articles published by this open-access journal are distributed under the terms of the Creative Commons Attribution-Noncommercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Open Access

This research has been made openly available by Queen's academics and its Open Research team. We would love to hear how access to this research benefits you. – Share your feedback with us: <http://go.qub.ac.uk/oa-feedback>

CLINICAL RESEARCH

Malignancy and mortality in a population-based cohort of patients with coeliac disease or 'gluten sensitivity'

LA Anderson, SA McMillan, RGP Watson, P Monaghan, AT Gavin, C Fox, LJ Murray

LA Anderson, P Monaghan, LJ Murray, Queen's University Belfast, Centre for Clinical and Population Sciences, Belfast, United Kingdom

SA McMillan, Royal Group of Hospitals, Regional Immunology Service, Belfast, United Kingdom

RGP Watson, Royal Group of Hospitals, Institute of Clinical Science, Belfast, United Kingdom.

AT Gavin, C Fox, Queen's University Belfast, Northern Ireland Cancer Registry, Belfast, United Kingdom

Supported by the Research and Development Office, Northern Ireland who funded Dr. Anderson to undertake the research through the Ireland-Northern Ireland-National Cancer Institute Cancer Consortium Cancer Prevention Fellowship Programme. The Northern Ireland Cancer Registry is funded by the Department of Health, Social Services & Public Safety Northern Ireland

Correspondence to: Dr. Lesley A Anderson, Centre for Clinical and Population Sciences, Mulhouse Building, Grosvenor Road, Belfast, BT12 6BJ, United Kingdom, l.anderson@qub.ac.uk

Telephone: +44-28-90632602 Fax: +44-28-90231907

Received: 2006-09-09 Accepted: 2006-10-23

ity, mortality from malignant neoplasms, non-Hodgkin's lymphoma and digestive system disorders were significantly higher in gluten sensitive patients compared to the Northern Ireland population.

CONCLUSION: Patients with coeliac disease or gluten sensitivity had higher mortality rates than the Northern Ireland population. This association persists more than one year after diagnosis in patients testing positive for anti-gliadin antibodies. Breast cancer is significantly reduced in the cohort of patients with gluten sensitivity.

© 2007 The WJG Press. All rights reserved.

Key words: Coeliac disease; Cancer; Mortality; Gluten sensitivity

Anderson LA, McMillan SA, Watson RGP, Monaghan P, Gavin AT, Fox C, Murray LJ. Malignancy and mortality in a population-based cohort of patients with coeliac disease or 'gluten sensitivity'. *World J Gastroenterol* 2007; 13(1): 146-151

<http://www.wjgnet.com/1007-9327/13/146.asp>

Abstract

AIM: To determine the risk of malignancy and mortality in patients with a positive endomysial or anti-gliadin antibody test in Northern Ireland.

METHODS: A population-based retrospective cohort study design was used. Laboratory test results used in the diagnosis of coeliac disease were obtained from the Regional Immunology Laboratory, cancer statistics from the Northern Ireland Cancer Registry and mortality statistics from the General Registrar Office, Northern Ireland. Age standardized incidence ratios of malignant neoplasms and standardized mortality ratios of all-cause and cause-specific mortality were calculated.

RESULTS: A total of 13 338 people had an endomysial antibody and/or an anti-gliadin antibody test in Northern Ireland between 1993 and 1996. There were 490 patients who tested positive for endomysial antibodies and they were assumed to have coeliac disease. There were 1133 patients who tested positive for anti-gliadin antibodies and they were defined as gluten sensitive. Malignant neoplasms were not significantly associated with coeliac disease; however, all-cause mortality was significantly increased following diagnosis. The standardized incidence and mortality ratios for non-Hodgkin's lymphoma were increased in coeliac disease patients but did not reach statistical significance. Lung and breast cancer incidence were significantly lower and all-cause mortal-

INTRODUCTION

Coeliac disease (CD) is an autoimmune disorder characterised by inflammation and villous atrophy of the small intestine, resulting in the malabsorption of vitamins and nutrients. It is caused by an immune response to wheat gluten (gliadin). Ireland is thought to have one of the highest incidences of CD in the world with a prevalence in Northern Ireland of at least 1 person per 122 in the population^[1]. Diagnosis is normally confirmed by duodenal biopsy; however, highly sensitive and specific blood tests for CD are available including the transglutaminase antibody test (93% sensitive, > 99% specific) and the endomysial antibody (EMA) test (93% sensitive, > 98% specific)^[2]. Another test the anti-gliadin antibody (AGA) test is not as sensitive or specific for CD. It is a measure of the immune response to gliadin and may detect people with gluten sensitivity who don't have clinically detectable CD. Patients testing positive for CD are advised to adhere to a strict gluten free diet for life^[3,4] to avoid symptoms such as diarrhoea, anaemia and weight loss associated with this condition.

In addition to the significant morbidity that can be associated with this condition, CD is thought to be associated with an increased risk of malignancy and mortality. A recent European multi-centre study reported more than

a three-fold increased risk of non-Hodgkin's Lymphoma (NHL) in patients with clinically diagnosed CD^[5]. Other studies have also reported an increased incidence and/or mortality of NHL in patients with CD^[4,6-12]. Estimates of the standardised incidence ratio range from 3.3^[5] to 18.0^[10], although Card *et al* suggest that the risk of NHL is at the lower end of these estimates^[7].

CD has been associated with an increased risk of other cancers including cancers of the gastrointestinal tract^[7,9,11], in particular cancers of the small intestine^[7,9-11]. However, West *et al* in a recent study including 4732 people with CD found that most cancers, except NHL, were reported within one year of diagnosis of CD^[8].

Studies have also reported that CD may be associated with reduced risks of some cancers including breast cancer^[8,11,13] although the reason for this association remains unknown. West *et al*^[8] reported that lung cancer was less common in patients with CD with one possible explanation of the proposed protective effect of cigarette smoking^[14].

Overall, mortality was higher in patients with CD compared to the population^[8,10,15]. Metzger *et al* reported a standardised mortality ratio (SMR) of all-cause mortality of 2.53 (95% CI 1.50-4.25) with an increased mortality from malignant neoplasms^[15]. West *et al*^[8] observed that the association between all-cause mortality and CD remained significant more than one year after diagnosis.

The aim of this study was to identify the incidence of malignancy and mortality in patients with CD (positive EMA test) or patients with gluten sensitivity (positive AGA test) in a retrospective cohort study in Northern Ireland.

MATERIALS AND METHODS

Exposure measurement

A serological dataset of all patients investigated for suspected coeliac disease tested for IgA EMA and/or IgA AGA between 1993 and 1996 was obtained from the Regional Immunology Laboratory, Royal Group of Hospitals, Belfast. If patients had EMA/AGA tests on more than one occasion their date of inclusion in the study was the date of the first positive EMA or AGA result. Duplicates were removed and records with no date of birth excluded. Cases were defined as patients with 'coeliac disease' (positive EMA result) or 'patients with an intolerance to gliadin in the diet' (positive AGA, result more than 100×10^3 EU/L). No information was available on the EMA test results for 4585 patients who had an AGA test. These patients were excluded from the AGA positive, EMA negative analysis.

Outcome measurement - incidence

Researchers within the Northern Ireland Cancer Registry (NICR)-LAA, LJM, CF; who are experienced in the procedures involved in linking datasets, used forename, surname, date of birth and when available hospital number or General Practitioner name to match patients in the serological database to patients within the NICR database. EMA and AGA positive patients were followed-up for between 7 and 11 years until the end of December 2003. Exact and "fuzzy" matching algorithms were used to link

patients in the two databases. "Fuzzy" matching used phonetic codes for the forename and surname to match similar sounding names which had different spellings (i.e. Smyth and Smith). If dates of birth were similar (i.e. 01/03/1975 and 03/01/1975) they were considered as potential matches. All "fuzzy" and potential matches were checked manually using all available information before being included in the study.

The main outcome measures were classified according to the International Classification of diseases (ICD) 9 before 2002 and ICD 10 thereafter: (1) Any malignant neoplasm (ICD 9: 140-208, 230-234; ICD 10: C00-C97); (2) NHL (ICD 9: 200, 202; ICD 10: C82-C85); (3) Gastrointestinal tract cancer (ICD 9: 150-154; ICD 10: C15-C21); (4) Small bowel cancer (ICD 9: 152; ICD 10: C17); (5) Lung cancer (ICD 9: 162-163; ICD 10: C34); (6) Breast cancer (ICD 9: 174-175; ICD 10: C50); (7) Prostate cancer (ICD 9: 185; ICD 10: C61); (8) Liver cancer (ICD 9: 155; ICD 10: C22).

Outcome measurement - mortality

The serological database was also linked by forename, surname and date of birth to death records held by the Registrar General's Office (GRO), Northern Ireland until the end of December 2003. These files contain cause-specific mortality data on all deaths occurring within Northern Ireland. Exact matching and "fuzzy" matching algorithms were used and potential matches were checked manually. Outcome measures included all-cause and cause-specific mortality. Ethical committee approval for this study was obtained from the Research Ethics Committee of the Queen's University Belfast to match the databases.

Statistical analysis

Total person-years of follow-up for the cohort of patients with a positive EMA test and for the cohort of patients with a positive AGA test were calculated by collating the person-years of follow-up for each patient from the date of entry into the cohort (1993 to 1996) until the date of death or 31st December 2003, whichever was earlier.

Indirect standardization was used to calculate standardised incidence ratios (SIRs) for all malignant neoplasms and for each cancer type (including NHL, gastrointestinal cancers, small bowel, breast, prostate, liver and lung cancer) for patients with a positive EMA test, for patients with a positive AGA test and for patients with a positive AGA test but a negative EMA test. The SIRs were calculated by taking the total number of observed cancers within the cohort of patients with a positive EMA or AGA test and dividing this by the expected number of cancers, calculated by applying age and sex-specific incidence rates within the Northern Ireland population to each cohort. CIs were estimated using the Poisson distribution. Standardised mortality ratios were calculated in a similar manner to the SIRs using all and cause-specific mortality figures obtained from the General Registrar Office, Northern Ireland.

RESULTS

Of the 13338 patients in Northern Ireland who under-

Table 1 Number of EMA and AGA positive and negative patients

AGA	+ve EMA	-ve EMA	Not recorded	Total
+ve	275	456	402	1133
-ve	215	7807	4183	12 205
Total	490	8263	4585	13 338

Table 2 Standardised incidence ratio (SIR) of malignancies

	EMA +ve			AGA +ve			AGA +ve, EMA -ve		
	<i>n</i>	Expected <i>n</i>	SIR (95% CI)	<i>n</i>	Expected <i>n</i>	SIR (95% CI)	<i>n</i>	Expected <i>n</i>	SIR (95% CI)
All malignancies	24	25.41	0.94 (0.57-1.32)	96	86.13	1.11 (0.89-1.34)	68	37.28	1.82 (1.39-2.26)
All malignancies (> 6 mo after diagnosis)	20	24.26	0.82 (0.46-1.19)	75	86.05	0.87 (0.67-1.07)	52	39.84	1.31 (0.95-1.66)
All malignancies (> 12 mo after diagnosis)	18	24.24	0.74 (0.40-1.09)	67	85.94	0.78 (0.59-0.97)	44	37.15	1.18 (0.83-1.53)
Non-Hodgkin's lymphoma	2	0.27	7.47 (0.00-17.83)	6	2.59	2.32 (0.46-4.17)	3	0.52	5.76 (0.00-12.28)
Gastrointestinal cancer	4	2.97	1.35 (0.03-2.67)	14	11.70	1.20 (0.57-1.82)	9	5.24	1.72 (0.60-2.84)
Small intestine	1	0.04	23.33 (0.00-69.07)	1	0.14	7.28 (0.00-21.54)	1	0.06	15.51 (0.00-45.90)
Lung cancer	1	2.60	0.39 (0-1.14)	5	9.98	0.50 (0.06-0.94)	4	4.51	0.89 (0.02-1.76)
Breast cancer	4	3.92	1.02 (0.02-2.02)	5	10.53	0.47 (0.06-0.89)	1	4.09	0.24 (0.00-0.72)
Prostate cancer	2	1.12	1.78 (0.00-4.24)	8	6.30	1.27 (0.39-2.15)	3	3.13	0.96 (0.00-2.04)
Liver cancer	2	0.06	31.62 (0.00-75.45)	3	0.60	5.01 (0.00-10.69)	2	0.27	7.48 (0.00-17.86)

went EMA and/or AGA tests between 1993 and 1996 490 were EMA positive (5.6% of EMA tests), 1,133 AGA positive (8.5% of all AGA tests) and 456 patients were AGA positive and EMA negative (5.2% of those tested for both EMA and AGA) (Table 1).

The average age (age range) of patients with a positive EMA or AGA test were 45 (0-88) years and 50 (0-91) years respectively. Included in the database were 46 children (< 18 years) with a positive EMA test (9.2% of cohort) and 71 children with a positive AGA test (6.3% of cohort). In total 68.2% of EMA positives and 63.2% of AGA positives were male. The average AGA score in those testing positive was 215.4×10^3 EU/L (range 100-1163 $\times 10^3$ EU/L).

Standardised incidence ratios-EMA

In total 24 (4.90%) of the EMA positive patients developed a malignant neoplasm during the follow-up period, 6 of which were diagnosed within 12 mo of the test. There were no significant associations between a positive EMA test and developing a malignant neoplasm (Table 2). Due to the small number of EMA positive patients developing malignancy the confidence intervals for the site specific cancers are large resulting in no significant associations despite a raised SIR being found for NHL [SIR 7.47 (95% CI 0.00-17.83)], small bowel cancer [SIR 23.33 (95% CI 0.00-69.07)] and primary liver cancer [SIR 31.62 (95% CI 0.00-75.45)]. Lung cancer appeared to be less common in EMA positive patients than in the Northern Ireland population [SIR 0.39 (95% CI 0-1.14)].

Standardised incidence ratios - AGA

In total 96 (8.47%) of the AGA positive population de-

veloped a malignant neoplasm. There were no significant associations between a positive AGA result and the development of malignant neoplasms (Table 2). However, malignancy was significantly raised in the AGA positive, EMA negative group [SIR 1.82 (95% CI 1.39-2.26)] (Table 2). This association was confined to males, SIR 2.90 (95% CI 2.11-3.69), and remained significant 6 and 12 mo after the AGA test, SIR 2.16 (95% CI 1.48-2.84) and SIR 1.91 (95% CI 1.27-2.55), respectively. Overall incidence of malignant neoplasms occurring 6 and 12 mo after the AGA test were significantly reduced in females SIR 0.60 (95% CI 0.27-0.92) and SIR 0.51 (95% CI 0.19-0.83) respectively. There was a significant inverse relationship between lung and breast cancer and a positive AGA result; however, only breast cancer was significantly reduced in the AGA positive EMA negative group. The SIR was raised for both small bowel and liver cancer but the results were not statistically significant.

Standardised mortality ratios - EMA

Overall mortality was significantly higher in the EMA positive population compared to the Northern Ireland population (Table 3). However, the statistically significant association did not remain when deaths within 6 mo or 1 year of the EMA test were excluded from the analysis. Although there were no other statistically significant associations mortality from NHL, endocrine deaths and urinary deaths appeared increased.

Standardised mortality ratios - AGA

Overall, mortality was higher in the AGA positive and in the AGA positive/EMA negative populations than in the Northern Ireland population (Table 3). This association

Table 3 Standardised mortality ratios (SMR) of all cause and cause-specific mortality

	EMA +ve			AGA +ve			AGA +ve, EMA -ve		
	<i>n</i>	Expected <i>n</i>	SMR (95% CI)	<i>n</i>	Expected <i>n</i>	SMR (95% CI)	<i>n</i>	Expected <i>n</i>	SMR (95% CI)
All cause mortality	46	26.01	1.77 (1.26-2.28)	234	101.25	2.31 (2.01-2.61)	114	47.25	2.41 (1.97-2.86)
All cause mortality (> 6 mo after diagnosis)	35	25.9	1.35 (0.90-1.80)	184	100.79	1.83 (1.56-2.09)	85	46.91	1.81 (1.43-2.20)
All cause mortality (> 12 mo after diagnosis)	32	25.91	1.24 (0.81-1.66)	165	100.09	1.65 (1.40-1.90)	75	46.59	1.61 (1.25-1.97)
Malignant neoplasms	9	7.05	1.28 (0.44-2.11)	52	32.28	1.61 (1.17-2.05)	27	14.55	1.86 (1.16-2.56)
NHL deaths	2	0.29	6.89 (0.00-16.44)	8	1.12	7.12 (2.18-12.05)	3	0.51	5.88 (0.00-12.53)
Endocrine deaths	1	0.16	6.10 (0.00-18.07)	2	0.24	8.19 (0.00-19.53)	1	0.58	1.73 (0.00-5.14)
Nervous system	1	0.25	3.96 (0.00-11.72)	2	2.92	0.69 (0.00-1.63)	1	2.92	0.34 (0.00-1.01)
Circulatory system	9	12.11	0.74 (0.26-1.23)	42	59.95	0.70 (0.49-0.91)	22	28.65	0.77 (0.45-1.09)
Respiratory system	3	2.67	1.12 (0.00-2.40)	35	25.18	1.39 (0.93-1.85)	2	1.45	1.38 (0.00-3.29)
Digestive system disorders	2	0.58	3.42 (0.00-8.17)	19	4.12	4.61 (2.54-6.68)	10	1.90	5.26 (2.00-8.52)

remained significant even when deaths occurring within 6 mo and one year of the test were excluded. Mortality caused by malignant neoplasms was also significantly raised in both groups as was mortality from digestive system disorders. Mortality from NHL was significantly higher and mortality from circulatory system disease was significantly lower in the AGA positive group but not in the AGA positive/EMA negative group.

DISCUSSION

In this retrospective cohort study the incidence of malignant neoplasms in patients with CD (positive EMA test) was similar to that of the Northern Ireland population. However, patients with gluten sensitivity (positive AGA test) had an increased incidence of malignant neoplasms within six months of diagnosis. In keeping with the findings of other studies all cause mortality was significantly raised in patients with CD; however, this was limited to the six month period following diagnosis. Patients with gluten sensitivity had a significantly raised SMR; this association remained significant more than 12 mo after diagnosis. Compared to the general population breast and lung cancer incidence were significantly lower in patients with gluten sensitivity. Mortality from malignant neoplasms, NHL and digestive system disorders was significantly increased.

The main strength of this study is its population-based design. All patients within Northern Ireland with clinical symptoms suspicious of CD and who also had a positive EMA and/or AGA test during the study period (1993 to 1996) were included. Since a wide spectrum of patients were included in the study the results should be more generalisable to patients with gluten sensitivity than the results of studies where CD was diagnosed in hospital or at referral centres^[9-11,16,17]. It is likely that cases diagnosed as hospital in-patients or at referral centres have more severe disease and therefore cancer incidence and mortality may be higher in this group of patients than in all CD patients. CD may go undetected in the population and without screening it is difficult to generalise any of the results to all patients with CD within the population.

Population-based registers of cancer incidence and cause-specific mortality facilitated the matching process. Incomplete matching of patients on the serological database to the NICR and/or GRO database may result in an underestimation of the risk of malignancy and/or mortality compared to the general population. To minimize the possibility of observer bias the staff was blinded to the positive/negative result status of the patients during the matching process. Cancer incidence and mortality in EMA positive, AGA positive and AGA positive/EMA negative patients were compared to the rates in the Northern Ireland population. Other studies have used population-based controls^[8] or population rates for comparison^[7,10-12]; however, the study by Collin *et al* used hospital outpatients undergoing upper gastrointestinal endoscopy as controls^[17]. These patients are likely to have been under investigation because of upper gastrointestinal symptoms and are unlikely to be representative of the general population. One of the proposed explanations for previous reports of increased gastrointestinal cancer incidence in CD patients^[7-9,11] is that CD was diagnosed coincidentally when the patients were under investigation for tumour related symptoms. Several studies have reported cancer incidence and/or mortality rates with lag periods of between 1 and 5 years^[7,10-12,16] after diagnosis of CD. We, therefore, included SIRs and SMRs excluding patients with an event in the 6-or 12-mo period post diagnosis.

There were 3908 person years of follow-up for malignancy and 3718 person years of follow-up for mortality in the cohort of patients with CD. Bias may have been introduced by loss to follow-up although emigration rates are low in Northern Ireland; data from the GRO (Northern Ireland) estimates that less than 0.1% of the population migrated from the province per year during the 1990s^[18]. One of the potential weaknesses of this study was the lack of histological confirmation of CD. Although it is likely that jejunal biopsies were taken from patients with a positive EMA test gaining access to these records without patient consent would have required further ethical considerations. However, the sensitivity and specificity of the EMA test are high^[2] and it is, therefore, likely to give a relatively accurate measure of the incidence of CD in the

cohort. The EMA test detects antibodies to an antigen (tissue transglutaminase) present in the endomysial lining of smooth muscle cells. The AGA test measures antibodies to gliadin which do not remain in patients who adhere to a strict gluten free diet. The assay will become negative if the patient is compliant with a gluten free diet. Therefore some patients with CD may not be detected within the cohort. The study by Logan *et al* showed that cancer incidence was decreased in those who were diagnosed early and placed on a gluten-free diet^[13]. If this is the case then the incidence of malignancy in CD patients may be lower than reported. However, we had no way to determine whether or not the patients included in the study adhered to a strict gluten-free diet.

Another issue is that multiple comparisons may inflate the possibility of a Type 1 error occurring (i.e. the apparent association resulting by chance). However, only malignant neoplasms/causes of mortality where there had been a previous association or where there was an a priori hypothesis were investigated.

One issue with using these datasets and using a retrospective cohort design is that potential confounding variables were not collected at the time the cohort was established and therefore these could not be adjusted for in the analyses. Potential confounding variables could include co-existing medical conditions, smoking, body mass index, diet, age, sex, *etc.* For example, diabetes is associated with CD and possibly with endocrine deaths which were non-significantly raised and smoking which is less common in patients with CD^[14] is associated with lung cancer incidence. There was a significantly reduced risk of lung cancer in patients with a positive AGA test and a non-significant reduced risk in patients with a positive EMA test. West *et al* was the only study to attempt to adjust for potential confounding variables^[8]. Adjusting for BMI and smoking did not dramatically alter the observed associations; however, the authors suggest that data on potential confounders may be incomplete as it was obtained from routinely collected information.

Although some AGA positive/EMA negative patients may have CD there were a larger number that were AGA positive than expected according to the sensitivity of the EMA test. Therefore, some of these patients may be gluten sensitive but as yet have no damage to the endomysial muscle. If this is the case then this is the first study to investigate the risk of malignancy and mortality in this group of patients, who were excluded from the recent large study by West *et al*^[8]. Mortality was significantly increased in this group of patients and remained elevated more than one year after the positive AGA test. Mortality from digestive system disorders was increased which was not surprising as a positive AGA test may be a marker for other gastrointestinal disorders. Interestingly, it is in this group of patients that breast cancer appears to be reduced. Other studies have reported reduced risks of breast cancer in patients with CD^[8,11,13] although there were no significant associations between breast cancer and a positive EMA test in this study. Although the reason(s) for this association remain unknown Askling *et al* suggest that the reduced risk of breast cancer may be a consequence of immune system dysfunction^[11].

The size of the current study is smaller than the more recently published studies e.g. the study by West *et al*^[8] who used the General Practice Research Database which had 4,732 CD patients. Malignancy was increased in patients in the first year after diagnosis but not beyond one year of follow-up. In the current study malignancy was not increased in patients with a positive EMA test but was in patients with a positive AGA test. Other studies have also reported no overall increased risk of malignancy in CD patients^[7,16]. The size of the current study meant that there was insufficient power to detect any associations between cancer type and CD. However, the risk of NHL appeared to be increased which is in keeping with the results of other studies^[3-5,7-12]. There was a significant increased risk of NHL deaths in patients with a positive AGA test. This group of patients is likely to include some patients with CD as there were a number of patients that had no EMA record in the database.

Malignancy and mortality were not significantly increased in patients with CD more than one year after diagnosis; however, overall mortality and mortality from malignant neoplasms were increased in patients who were gluten sensitive with a negative EMA test. If these patients do not have the histological characteristics of CD then it is important to determine the cause of the increased mortality. If this is limited to other digestive system disorders then patients with a negative EMA test but with symptoms should be further investigated for other digestive system disorders. Further investigations into this area are warranted to determine if it is gluten sensitivity that is associated with increased mortality and malignancy or to determine if it is just a marker for other gastrointestinal conditions.

In addition, it is important to determine the risk of malignancy and mortality in patients with a histological confirmation of CD. This study could be extended further by collecting pathology reports on all patients within the study and looking for evidence of villous atrophy. Information on confounding variables such as smoking status could also be collected. However, it is unlikely that patients could be approached because of data confidentiality issues. It is possible that cancer incidence and mortality change depending on the length of time since diagnosis. Therefore, an extension to this study would be to follow-up the patients for a longer period of time. The association with reduced breast cancer incidence is interesting and further studies to investigate this association may identify factors that are associated with reduced breast cancer incidence.

REFERENCES

- 1 Johnston SD, Watson RG, McMillan SA, Sloan J, Love AH. Prevalence of coeliac disease in Northern Ireland. *Lancet* 1997; **350**: 1370
- 2 Lewis NR, Scott BB. Systematic review: the use of serology to exclude or diagnose coeliac disease (a comparison of the endomysial and tissue transglutaminase antibody tests). *Aliment Pharmacol Ther* 2006; **24**: 47-54
- 3 Holmes GK, Prior P, Lane MR, Pope D, Allan RN. Malignancy in coeliac disease--effect of a gluten free diet. *Gut* 1989; **30**: 333-338

- 4 **Loftus CG**, Loftus EV Jr. Cancer risk in celiac disease. *Gastroenterology* 2002; **123**: 1726-1729
- 5 **Mearin ML**, Catassi C, Brousse N, Brand R, Collin P, Fabiani E, Schweizer JJ, Abuzakouk M, Szajewska H, Hallert C, Farre Masip C, Holmes GK. European multi-centre study on coeliac disease and non-Hodgkin lymphoma. *Eur J Gastroenterol Hepatol* 2006; **18**: 187-194
- 6 **Smedby KE**, Akerman M, Hildebrand H, Glimelius B, Ekblom A, Askling J. Malignant lymphomas in coeliac disease: evidence of increased risks for lymphoma types other than enteropathy-type T cell lymphoma. *Gut* 2005; **54**: 54-59
- 7 **Card TR**, West J, Holmes GK. Risk of malignancy in diagnosed coeliac disease: a 24-year prospective, population-based, cohort study. *Aliment Pharmacol Ther* 2004; **20**: 769-775
- 8 **West J**, Logan RF, Smith CJ, Hubbard RB, Card TR. Malignancy and mortality in people with coeliac disease: population based cohort study. *BMJ* 2004; **329**: 716-719
- 9 **Green PH**, Fleischauer AT, Bhagat G, Goyal R, Jabri B, Neugut AI. Risk of malignancy in patients with celiac disease. *Am J Med* 2003; **115**: 191-195
- 10 **Peters U**, Askling J, Gridley G, Ekblom A, Linet M. Causes of death in patients with celiac disease in a population-based Swedish cohort. *Arch Intern Med* 2003; **163**: 1566-1572
- 11 **Askling J**, Linet M, Gridley G, Halstensen TS, Ekstrom K, Ekblom A. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. *Gastroenterology* 2002; **123**: 1428-1435
- 12 **Corrao G**, Corazza GR, Bagnardi V, Brusco G, Ciacci C, Cottone M, Sategna Guidetti C, Usai P, Cesari P, Pelli MA, Loperfido S, Volta U, Calabro A, Certo M. Mortality in patients with coeliac disease and their relatives: a cohort study. *Lancet* 2001; **358**: 356-361
- 13 **Logan RF**, Rifkind EA, Turner ID, Ferguson A. Mortality in celiac disease. *Gastroenterology* 1989; **97**: 265-271
- 14 **Suman S**, Williams EJ, Thomas PW, Surgenor SL, Snook JA. Is the risk of adult coeliac disease causally related to cigarette exposure? *Eur J Gastroenterol Hepatol* 2003; **15**: 995-1000
- 15 **Metzger MH**, Heier M, Maki M, Bravi E, Schneider A, Lowel H, Illig T, Schuppan D, Wichmann HE. Mortality excess in individuals with elevated IgA anti-transglutaminase antibodies: the KORA/MONICA Augsburg cohort study 1989-1998. *Eur J Epidemiol* 2006; **21**: 359-365
- 16 **Viljamaa M**, Kaukinen K, Pukkala E, Hervonen K, Reunala T, Collin P. Malignancies and mortality in patients with coeliac disease and dermatitis herpetiformis: 30-year population-based study. *Dig Liver Dis* 2006; **38**: 374-380
- 17 **Collin P**, Reunala T, Pukkala E, Laippala P, Keyrilainen O, Pasternack A. Coeliac disease--associated disorders and survival. *Gut* 1994; **35**: 1215-1218
- 18 **Northern Ireland Statistics and Research Agency**. Northern Ireland Migration Flows 1991-2005. Population statistics online, cited 2006-18-08. Available from: URL: http://www.nisra.gov.uk/archive/demography/population/net_migration_by_ageandsex05.xls

S- Editor Yang XX L- Editor Rippe RA E- Editor Liu WF