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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

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 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.[4] to avoid symptoms such as diarrhoea, anaemia and weight loss associated with this condition.

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 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 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.

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


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CD has been associated with an increased risk of other cancers including cancers of the gastrointestinal tract\(^{[5,6,11]}\), in particular cancers of the small intestine\(^{[5,6,11]}\). 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\(^{[5]}\).

Studies have also reported that CD may be associated with reduced risks of some cancers including breast cancer\(^{[8,10,12]}\), 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\(^{[10]}\).

Overall, mortality was higher in patients with CD compared to the population\(^{[8,10,12]}\). Metzger et al.\(^{[12]}\) 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\(^{[12]}\). 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 gluten in the diet' (positive AGA, result more than 100 \times 10^8 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 13,338 patients in Northern Ireland who under-
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 $215.4 \times 10^3$ 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 0.1-1.14)].

Standardised incidence ratios - AGA
In total 96 (8.47%) of the AGA positive population developed 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 association’s 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 1 Number of EMA and AGA positive and negative patients

<table>
<thead>
<tr>
<th>AGA</th>
<th>+ve EMA</th>
<th>-ve EMA</th>
<th>Not recorded</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ve</td>
<td>275</td>
<td>456</td>
<td>402</td>
<td>1133</td>
</tr>
<tr>
<td>-ve</td>
<td>215</td>
<td>7807</td>
<td>4183</td>
<td>12205</td>
</tr>
<tr>
<td>Total</td>
<td>490</td>
<td>8263</td>
<td>4585</td>
<td>13338</td>
</tr>
</tbody>
</table>

### Table 2 Standardised incidence ratio (SIR) of malignancies

<table>
<thead>
<tr>
<th>Malignancies</th>
<th>EMA +ve</th>
<th>AGA -ve</th>
<th>AGA +ve, EMA -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Expected</td>
<td>SIR (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>All malignancies</td>
<td>24</td>
<td>25.41</td>
<td>0.94 (0.57-1.32)</td>
</tr>
<tr>
<td>All malignancies (&gt; 6 mo after diagnosis)</td>
<td>20</td>
<td>24.26</td>
<td>0.82 (0.46-1.19)</td>
</tr>
<tr>
<td>All malignancies (&gt; 12 mo after diagnosis)</td>
<td>18</td>
<td>24.24</td>
<td>0.74 (0.40-1.09)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>2</td>
<td>0.27</td>
<td>7.47 (0.00-17.83)</td>
</tr>
<tr>
<td>Gastrointestinal cancer</td>
<td>4</td>
<td>2.97</td>
<td>1.35 (0.03-2.67)</td>
</tr>
<tr>
<td>Small intestine</td>
<td>1</td>
<td>0.04</td>
<td>23.33 (0.00-69.07)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1</td>
<td>2.60</td>
<td>0.39 (0.1-1.14)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>4</td>
<td>3.92</td>
<td>1.02 (0.02-2.02)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2</td>
<td>1.12</td>
<td>1.78 (0.00-4.24)</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>2</td>
<td>0.06</td>
<td>31.62 (0.00-75.45)</td>
</tr>
</tbody>
</table>
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.\(^{[11]}\) 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\(^{[7,10-12]}\) 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\(^{[9]}\) and it is, therefore, likely to give a relatively accurate measure of the incidence of CD in the

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

<table>
<thead>
<tr>
<th></th>
<th>EMA +ve</th>
<th>AGA +ve</th>
<th>AGA +ve, EMA -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td><strong>n</strong></td>
<td><strong>n</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td><strong>Expected</strong></td>
<td><strong>SMR</strong></td>
<td><strong>SMR</strong></td>
<td><strong>SMR</strong></td>
</tr>
<tr>
<td><strong>(95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo after diagnosis</td>
<td>234</td>
<td>101.25</td>
<td>2.31 (2.01-2.61)</td>
</tr>
<tr>
<td>&gt; 12 mo after diagnosis</td>
<td>184</td>
<td>100.79</td>
<td>1.83 (1.56-2.09)</td>
</tr>
<tr>
<td><strong>All cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| AGA positive/negative result status of the patients 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.\(^{[11]}\) 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\(^{[7,10-12]}\) 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\(^{[9]}\) and it is, therefore, likely to give a relatively accurate measure of the incidence of CD in the
potential confounding variables

...with CD have reported reduced risks of breast cancer in patients that breast cancer appears to be reduced. Other studies...

There was a significant reduced risk 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.

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