Risk of Non-Hodgkin Lymphoma in Celiac Disease

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Context  Celiac disease is one of the most common lifelong disorders. Non-Hodgkin lymphoma is a possible complication of celiac disease and may lead to a large portion of lymphoma cases.

Objective  To quantify the risk for developing non-Hodgkin lymphoma of any primary site associated with celiac disease.

Design and Setting  Multicenter, case-control study conducted between January 1996 and December 1999 throughout Italy.

Patients  Cases were older than 20 years (median, 57; range, 20-92 years) with non-Hodgkin lymphoma of any primary site and histological type and were recruited at the time of the diagnosis. Controls were healthy adults (2739 men and 2981 women) from the general population.

Main Outcome Measure  Positive test result for class A serum antiendomysial antibody.

Results  Celiac disease was diagnosed in 6 (0.92%) of 653 patients with lymphoma. Of the 6 cases, 3 were of B-cell and 3 were of T-cell origin. Four of 6 cases had lymphoma primarily located in the gut. In the control group, 24 (0.42%) had celiac disease. The odds ratio (adjusted for age and sex) for non-Hodgkin lymphoma of any primary site associated with celiac disease was 3.1 (95% confidence interval [CI], 1.3-7.6), 16.9 (95% CI, 7.4-38.7) for gut lymphoma, and 19.2 (95% CI, 7.9-46.6) for T-cell lymphoma, respectively. The risk for non-Hodgkin lymphoma for the overall population, which was adjusted for age and sex, was 0.63% (95% CI, −0.12% to 1.37%).

Conclusion  Celiac disease is associated with an increased risk for non-Hodgkin lymphoma, especially of T-cell type and primarily localized in the gut. However, the association does not represent a great enough risk to justify early mass screening for celiac disease.

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See also Patient Page.
both new cases and mortality, with an incidence of 17.1 person-years per 100,000 among men and 11.5 among women. Patients with NHL of any primary site and histological type, at the first time of diagnosis, who had not yet started chemotherapy, were included in this study. The control group was obtained by merging the results of 2 population studies that have been separately described elsewhere. All these untreated persons are potentially exposed to the risk for long-term sequelae. This has led to renewed interest in the NHL connection because CD could be responsible for a large portion of the NHL burden. In the United States, NHL is the sixth most common cancer, in terms of both new cases and mortality, with an incidence of 17.1 person-years per 100,000 among men and 11.5 among women.

To accurately estimate the CD-associated risk for NHL, we conducted this multicenter, case-control study to compare the prevalence of CD in patients with newly diagnosed NHL and in population controls, using the class A serum antiendomysial antibody (EMA) as the screening test. The aims were to evaluate whether CD is a risk factor for developing NHL and to quantify the odds ratio (OR); measure the impact of CD in causing NHL in the general population by quantifying the population attributable risk (AR); and investigate the histopathological and clinical spectrum of CD-associated NHL.

**METHODS**

The study was carried out between January 1996 and December 1999. Cases were patients who were at least 20 years old with NHL of any primary site and histological type, at the first time of diagnosis, who had not yet started chemotherapy and/or radiotherapy. Patients with acquired immunodeficiency syndrome were excluded from the study. Cases were recruited on a consecutive basis (all eligible patients seen consecutively by each center were asked to enter this study). The control group was obtained by merging the results of 2 population studies that have been separately described elsewhere. All these untreated persons are potentially exposed to the risk for long-term sequelae. This has led to renewed interest in the NHL connection because CD could be responsible for a large portion of the NHL burden. In the United States, NHL is the sixth most common cancer, in terms of both new cases and mortality, with an incidence of 17.1 person-years per 100,000 among men and 11.5 among women.

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ity among both sex and age strata. The risk for NHL attributable to CD was quantified by the Mantel-Haenszel estimator of OR and the proportion of exposed cases. Asymptotic variance of AR and the corresponding 95% CI were computed according to Greenland. For all hypotheses tested, 2-tailed P values less than .05 were considered significant.

RESULTS

A total of 1390 NHL cases were contacted and 653 were included in this study (inclusion rate, 47%). Reasons for exclusion were lack of consent (25%), missing serological data (18%), and failing inclusion criteria (10%). A check performed at the end of the study showed that none of the participating departments of pathology saw any other cases of EATL during the recruitment period (apart from those included in this series).

The study group included 374 white men (57%) and 279 white women (43%) with a median age of 57 years (range, 20-92 years). According to the clinical staging, 364 (52%) of these were nodal, 275 (42%) extranodal, and 14 (2%) undefined. Based on the Working Formulation classification, the malignancy grading was low in 164 cases (25%), intermediate in 118 (18%), high in 338 (52%), and undefined in 33 (5%). Immunohistochemical analysis showed that none of the participating departments of pathology saw any other cases of EATL during the recruitment period (apart from those included in this series).

The clinical features of the 6 NHL patients with associated CD. The possibility of associated CD was considered in another patient, a 48-year-old man with an anaplastic T-cell NHL of the tonsils. Two years before developing the NHL, he presented with signs of intestinal malabsorption at which time CD had been diagnosed. He also showed common variable hypogammaglobulinemia. This case was not included in the CD-affected group since it was not possible to ascertain whether the small intestinal damage was caused by the primary immunodeficiency or by true CD.

Table 3 shows the distribution of CD cases in the control group. The overall prevalence of CD in this population sample was 24 of 5720 (1 in 238, 0.42%).

The CD-associated ORs and ARs of NHL are shown in Table 4. Significant association between CD and NHL of any primary site was observed in both the overall and the male sample with significant differences in OR between sexes. Stronger associations were found between CD and either primary gastrointestinal or T-cell type NHL. The ARs were lower than 1% for overall NHL. Attributable risk values higher than 1% were observed for both primary gut and T-cell NHL without reaching statistical significance.

COMMENT

The strength of association between a suspected risk factor and the event, in this study CD and NHL, respectively, can be assessed by a case-control study, provided that both cases and controls are representative of the target population. Because the 47% recruitment rate in this study was low, selection bias cannot be excluded. Exclusion was more commonly related to logistics (eg, missing serological data or chemo-
therapy having just started) than to personal or disease-related factors. Lack of selection is suggested by the distribution of histological types and primary sites of the 653 NHL cases that were investigated for CD. From study inception, we excluded patients who were already receiving chemotherapy because this treatment could affect the immunological response and reliability of the serological screening tests (antiendomysial antibody). For the same reason, we did not test patients who escaped the initial recruitment. The proportion of T-cell lymphomas in this study was 8%, well within the range (6%-12%) expected from previous European33 and North American studies.34,35 Likewise, the percentage of primary gastrointestinal NHLs (15%) overlapped with the 12% to 16% prevalence reported in previous European, population-based studies.10,36 As far as the control group is concerned, we believe that the prevalence of CD in this healthy adult population sample (1:13,324) is substantially with previous data from European33 and North American studies.34,35

Although EMA-negative CD patients have occasionally been described,41 this has never been reported in association with NHL, a disease that is characterized, at least at the onset, by a preserved serological response against self-antigens.42 Serum EMA disappear after starting treatment with a GFD, usually after 3 to 6 months. Not surprisingly, 3 of the 6 patients with associated CD who were on a GFD when the diagnosis of NHL was made had negative EMA test results.

Although the proportion of T-cell type and intestinal NHL was greater than expected among the 6 patients with associated CD, a typical EATL was diagnosed in only 1 of the 6 cases, confirming that the spectrum of CD-associated NHL is not restricted to this specific form of intestinal T-cell lymphoma. This finding agrees with previous studies, 2 of which discussed pa-
patients with dermatitis herpetiformis (DH), a disorder that is currently regarded as a form of the gluten-sensitive enteropathy (“skin CD”). In a retrospective study on 109 patients with DH, Leonard et al13 found 3 cases of NHL, 1 of which was malignant histiocytosis of the intestine, which we interpreted as being EATL. The site of the other 2 cases was not reported by Leonard et al. A series of 976 Swedish patients with DH who were followed up for a mean period of 8.9 years had 13 NHL cases. Most of these tumors were of the B-cell phenotype and were found outside the gastrointestinal tract.8 In a Dutch study of 14 patients with CD-associated T-cell NHL, a significant number had non-EATL tumors, 4 having extranodal extraintestinal disease and 2 having nodal intestinal lymphoma.7 Given the high prevalence of CD in the general population, the association with non-EATL NHL may be due to chance. However, the involvement of the small intestine in NHL can occasionally be missed if it is not specifically looked for by performing a gastro-duodenoscopy and/or a small bowel x-ray examination9; then again, it may become evident later in the course of the disease.44

The diagnosis of CD preceded the NHL onset in most cases (4 out of 6), which somewhat limited the usefulness of the CD serological screening at the NHL onset. The finding that NHL manifestations appear shortly after a period of transitory response to the GFD (2 cases in this study) had previously been reported.4 As Marsh45 theorized, it is probable that the onset of malignancy is the factor which precipitates the shift from a silent to a clinically manifest form of CD, with the latter diagnosed first and the NHL soon afterwards. This eventually leads to a detection bias that could be responsible for the overestimation of the CD-associated lymphoma risk in previous studies (see below).

This study confirmed that the risk for NHL of any primary site is significantly greater in patients with CD than in the unaffected population. Since the estimate of the OR was based on a small number of CD cases, this result must be interpreted with caution. It is however interesting to note that the 3.1-fold increase in NHL risk was notably lower than most previously available estimates. In 1983 Leonard et al13 reported an RR of 100 for lymphoma in patients with DH. In a series of 210 patients with CD from Derby, England, followed up for at least 13 years, Holmes et al10 observed a highly significant excess of NHL of any primary site, with an RR of 42.7 (95% CI, 19.6-81.4). In a large series of patients with DH (n=976) followed up for a mean period of 8.9 years, Sigurgeirsson et al8 found an RR of 5.4 (95% CI, 2.2-11.1) for developing NHL. Although the diverse genetic and environmental backgrounds undoubtedly account for part of the wide variation in these results, there are other conflicting factors that have tended to produce misleading findings:

1. Due to the above mentioned detection bias, even cases of CD that have long been clinically silent or latent44 may be found in association with EATL. Conversely, uncomplicated CD cases often remain undiagnosed and then do not contribute (with a dilution effect) to the calculation of the lymphoma risk. In other words, previous studies counted CD-associated lymphomas from both the visible and the submerged part of the celiac iceberg, but these studies compared this figure only with the small number of clinically diagnosed cases (the tip of the celiac iceberg), therefore overestimating the magnitude of the cancer risk.

2. On the other hand, published series often included large proportions of treated CD patients who have been found to be at a lower risk for complications, especially if they were treated with GFD for more than 5 years.9 It is therefore not surprising that, occasionally, no increase in the lymphoma risk is reported, this finding being attributed to the strict adherence to the GFD.47

In our study, the CD-associated population AR of NHL was not significantly higher than 0. From the public health perspective, this finding suggests that the early diagnosis of all CD cases (eg, through serological mass screening) cannot be expected to reduce significantly the impact of NHL on the general population. Similarly, this study does not support the routine serological CD testing of all patients with NHL at the onset, because of both the rarity and the natural history of this association (CD being frequently diagnosed first). Rather, we suggest that CD should be actively searched for in at-risk NHL patients, such as those with a T-cell type lymphoma and/or a gut primary localization. In a series of 119 patients with primary small bowel NHL, at least 13 (10.9%) were associated with

### Table 4. The Celiac Disease–Associated Risks of Non-Hodgkin Lymphoma (NHL)*

<table>
<thead>
<tr>
<th>Adjusted Variables</th>
<th>Odds Ratio (95% CI)</th>
<th>Attributable Risk, % (95% CI)</th>
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<tbody>
<tr>
<td>NHL (overall)</td>
<td></td>
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<tr>
<td>Age and sex</td>
<td>3.1 (1.3 to 7.6)†</td>
<td>0.63 (–0.12 to 1.37)</td>
</tr>
<tr>
<td>Age in men</td>
<td>3.5 (1.0 to 12.3)†</td>
<td>0.57 (–0.34 to 1.49)</td>
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<tr>
<td>Age in women</td>
<td>2.8 (0.8 to 9.8)</td>
<td>0.70 (–0.53 to 1.93)</td>
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<tr>
<td>Primary gut NHL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>16.9 (7.4 to 38.7)†</td>
<td>3.84 (–0.08 to 7.77)</td>
</tr>
<tr>
<td>Age in men</td>
<td>13.7 (4.1 to 45.8)†</td>
<td>2.81 (–1.33 to 6.95)</td>
</tr>
<tr>
<td>Age in women</td>
<td>22.1 (7.2 to 68.0)†</td>
<td>5.97 (–2.44 to 14.38)</td>
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<tr>
<td>T-cell NHL</td>
<td></td>
<td></td>
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<tr>
<td>Age and sex</td>
<td>19.2 (7.9 to 46.6)†</td>
<td>5.17 (–0.85 to 11.19)</td>
</tr>
<tr>
<td>Age in men</td>
<td>11.6 (2.1 to 62.7)†</td>
<td>2.28 (–2.56 to 7.13)</td>
</tr>
<tr>
<td>Age in women</td>
<td>28.4 (10.4 to 77.7)†</td>
<td>12.9 (–4.42 to 30.2)</td>
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</tbody>
</table>

*CI indicates confidence interval.
†P<.05.
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CD.11Treatment with a GFD may ameliorate the prognosis of these cases, eg, by improving the nutritional status and the absorption of drugs given orally.

In conclusion, our study confirms that CD is associated with a significantly increased risk for NHL, especially of the T-cell type and primarily localized in the gut. The CD-lymphoma association seems, however, to be much less common than previously thought, thereby placing CD in the range of being a moderate risk factor (RR, 2–4) for NHL of any primary site.

Author Contributions: Study concept and design: Catassi, Fabiani, Corrao, Barbato, De Renzo, Carella, Gabrielli, Leoni, Carroccio, Baldassarre, Bertolani, Caramaschi, Sozzi, Guarino, Volta, Corazza. Acquisition of data: Catassi, Fabiani, Barbato, De Renzo, Carella, Gabrielli, Leoni, Carroccio, Baldassarre, Bertolani, Caramaschi, Sozzi, Guarino, Volta, Corazza. Critical revision of the manuscript for important intellectual content: Catassi, Fabiani. Statistical expertise: Corrao. Obtained funding: Catassi, Fabiani, Barbato, De Renzo, Carella, Gabrielli, Leoni, Carroccio, Baldassarre, Bertolani, Caramaschi, Sozzi, Guarino, Volta, Corazza. Study supervision: Fabiani.

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REFERENCES


When he [Darwin] said of species what Galileo had said of the earth, *e pur se muove*, he emancipated once for all, genetic and experimental ideas as an organon of asking questions and looking for explanations.
—John Dewey (1859-1952)