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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THE ASSOCIATION BETWEEN CELIAC disease (CD) and lymphoma has long been established. In 1937, Fairly and Mackie[1] reported the association of malignant lymphoma of the small intestine with steatorrhea. In 1962, Gough et al[2] described 5 cases of small intestinal lymphoma in patients with long-standing CD. A series of celiac-associated lymphomas have since been reported.[3-5] The most frequent malignancy associated with CD is a high-grade, T-cell non-Hodgkin lymphoma (NHL) of the upper small intestine, currently defined as *enteropathy-associated T-cell lymphoma* (EATL), that peaks in the sixth or seventh decade of life.[6] Also CD may be associated with other

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NHL types of both the B- and T-cell type in either the gut or other primary sites.[7-8] Holmes et al provided evidence that dietary compliance to a gluten-free diet (GFD) reduces the risk of lymphoma and other malignancies in CD.[9]

Although it is widely accepted that EATL is a possible complication of CD, this is a rare malignancy accounting for less than 0.5% of new NHL cases.[10-11] From the public health perspective, the overall NHL risk associated with CD is more important, but this is far from clear.[12] Available studies indicate a strongly increased relative risk (RR), in the range of 40 through 100,[9,13] emphasizing the high prevalence of this cancer's association in adults with CD. Such a "pessimistic" view is apparently confirmed by mortality analysis in CD patients showing (1) a 31- to 69-fold increased risk for dying from lymphoma,[14,15] (2) an 18% prevalence of lymphoma as cause of death.[16] It has recently become clear that CD is one of the most common lifelong disorders both in Europe and the United States, affecting around 1 in 200 persons in the general population. Most cases currently remain undiagnosed due to lack of symptoms or atypical complaints (5 to 10 for each patient clinically diagnosed with CD).[17,18] All these untreated persons are potentially exposed to the risk for long-term sequelae.[19,20] 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,[21] with an incidence of 17.1 person-years per 100 000 among men and 11.5 among women.[22]

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.[23,24] The overall control sample included 5720 adults who participated in 2 mass CD screening projects performed in small towns with low immigration; thus, 99% of the population is homogeneous (3483 in Campogalliano in Northern and 2237 in San Marino in Central Italy).

After obtaining informed consent, we first asked each participant for detailed clinical information that focused on NHL characteristics (cases only) and asked them whether they had ever had a previous diagnosis of and had received treatment for CD. The type of NHL was recorded according to the Revised European-American Lymphoma (REAL)[25] and the Working Formulation[26] classifications. We then measured serum levels of IgA class EMA and total IgA. Measurement of IgG– and IgA–antigliadin antibodies (AGA) was performed in patients with NHL and associated CD. The small intestinal biopsy was offered to 2 participants having either positive EMA results or a deficiency in IgA serum levels (before starting chemotherapy). The study protocol was approved by the ethical committee of the University of Ancona.

In each participating center, the EMA determination was performed on serum samples diluted 1:5 by indirect immunofluorescence, using either monkey esophagus or human umbilical cord as the antigenic substrate, as previously described.[27] The quality control on EMA determination was performed prior to the study and then yearly (5 EMA-positive and 5 EMA-negative sera sent by the coordinating center to each participating center) showed full, intercenter, consistent EMA readings. Every EMA-positive sera from all NHL cases were checked by the coordinating center. The AGA levels were measured by an enzyme-linked immunosorbent assay, using a commercially available kit (Alfagliatest, Eurospital, Trieste, Italy).

In participants who tested positive for EMA, a minimum of 4 biopsy specimens were taken by endoscopy from different levels of the descending duodenum.

According to current criteria,[28] patients with NHL were diagnosed as having CD if they had a positive EMA test result that was associated with a typical celiac enteropathy at the small bowel biopsy (partial or subtotal villous atrophy with an increase in the intraepithelial lymphocyte count) or had a clinical history of treated CD as documented by the previous findings of subtotal or partial villous atrophy at the small intestinal biopsy and clinical and/or histological improvement after treatment with a GFD. All slides of the intestinal biopsies were re-evaluated by the coordinating center that finally assigned the patient to either the CD group or the CD-unaffected group.

Preliminary calculations showed that with a sample size of at least 640 NHL cases, a study power of 0.92 was reached, given (1) the fixed number of controls (n=5720), (2) an estimated prevalence of CD in the general population of 1 in 300 subjects, (3) an expected OR of 5, and (4) a .05 2-sided type I error.

The risk for NHL associated with CD was estimated after adjustment for sex and age and expressed as the Mantel-Haenszel estimator of the OR and the corresponding 95% confidence interval (CI).[29] Differences in ORs were evaluated by testing their heterogene-

ity among both sex and age strata.[30] The risk for NHL attributable to CD was quantified by the Mantel-Haenszel estimator of OR and the proportion of exposed cases.[29] Asymptotic variance of AR and the corresponding 95% CI were computed according to Greenland.[31] 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 (56%) 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 543 (83%) of these NHL specimens were of B-cell origin, 55 (8%) of T-cell origin, 3 (1%) of null type, and 52 (8%) undefined. Overall there were 98 (15%) primary gut NHLs. These were localized in the mouth (2), stomach (64), intestine nonspecified (6), small intestine (10), duodenum (2), jejunum (2), ileum (5), colon (6), and rectum (1). TABLE 1 shows the NHL distribution according to the REAL classification. No case of serum IgA deficiency was found in this NHL series.

Of 653 patients with NHL, 6 (0.92%) of them had an associated diagnosis of CD, 3 were of B-cell and 3 of T-cell origin. Four out of 6 cases had lymphoma primarily located in the gut. TABLE 2 shows 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 without 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.[32] 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-

Table 1. The Non-Hodgkin Disease Lymphoma Distribution According to the Revised European-American Lymphoma (REAL) Classification*

REAL Classification	No. (%)
B-cell neoplasms	
Precursor B-call neoplasm: precursor B-lymphoblastic leukemia or lymphoma	3 (0.4)
Peripheral B-cell neoplasms	
B-cell chronic lymphocytic leukemia or prolymphocytic leukemia or small lymphocytic lymphoma	21 (3)
Lymphoplasmacytoid lymphoma or immunocytoma	27 (4)
Mantle cell lymphoma	27 (4)
Follicle center lymphoma, follicular	68 (10)
Provisional subtype: diffuse, predominantly small cell type	26 (4)
Marginal zone B-cell lymphoma	53 (8)
Extranodal (MALT-type +/– monocytoid B cells)	48 (7)
Nodal (+/– monocytoid B-cells)	5 (1)
Provisional entity: splenic marginal zone lymphoma (+/– villous lymphocytes)	4 (1)
Hairy cell leukemia	1 (0.1)
Diffuse large B-cell lymphoma	289 (44)
Subtype: Primary mediastinal (thimic) B-cell lymphoma	39 (6)
Provisional entity: High-grade B-cell lymphoma, Burkitt-like	16 (2)
T-cell and putative natural killer cell neoplasms	
Precursor T-cell neoplasm: precursor T-lymphoblastic lymphoma leukemia	8 (1)
Peripheral T-cell and natural killer cell neoplasms	
T-cell chronic lymphocytic leukemia or prolymphocytic leukemia	1 (0.1)
Mycosis fungoides or Sezary syndrome	5 (1)
Peripheral T-cell lymphomas, unspecified	17 (3)
Angioimmunoblastic T-cell lymphoma	5 (1)
Angiocentric lymphoma	1 (0.1)
Intestinal T-cell lymphoma (+/– enteropathy associated)	2 (0.3)
Anaplastic large cell lymphoma, CD 30+ cell count, T- and null-cell types	13 (2)
Undefined	66 (10)

*MALT indicates mucosa-associated lymphoid tissue.

Table 2. Clinical Findings in the 6 Patients With Non-Hodgkin Lymphoma (NHL) and Associated Celiac Disease (CD)*

Sex	Age, y	NHL Primary Site	NHL Classification	CD Histology	Serological CD Markers: At CD Diagnosis IgA-EMA	At CD Diagnosis IgA-AGA	At CD Diagnosis IgG-AGA	At NHL Diagnosis IgA-EMA	At NHL Diagnosis IgA-AGA	At NHL Diagnosis IgG-AGA	Interval Between CD and NHL Diagnosis, y	CD: Presenting Symptoms and Family History	CD: Clinical Course	Follow-up From NHL Diagnosis to June 2000
CD Diagnosis Before NHL Diagnosis														
Man	49	Neck lymph nodes	Diffuse large B cell	SVA	Unknown			–	–	–	8.0	Dermatitis herpetiformis	Good adherence to GFD and histological improvement after 6 mo	Alive after 1 year
Woman	34	Stomach	B Cell (REAL undefined)	PVA	ND	+	+	–	+	+	0.75	Chronic diarrhea	Clinical and histological improvement 9 mo after starting GFD	Unknown
Woman	67	Small intestine	Anaplastic large T cell	SVA	ND	+	+	+	–	–	17	Anemia	Poor adherence to GFD, improved small intestinal histology 3 years after diagnosis	Dead after 1 month (1996)
Woman	40	Mediastinum	Anaplastic T cell	SVA	+	+	+	–	ND	ND	1	Family history of lymphoma (mother), anemia during adolescence, protracted diarrhea after first pregnancy	Good adherence to GFD, clinical and histological improvement 1 year after starting GFD	Dead after 2 years (1999)
Diagnosed at the Same Time as NHL (Following Serological Screening)														
Man	30	Ileum	Diffuse large B cell	SVA	. . .	. . .	. . .	+	+	+	0	A sister affected with CD		Dead after 3 years (1999)
Man	56	Small intestine	EATL	PVA	. . .	. . .	. . .	+	–	–	0	Family history of intestinal lymphoma (Father and 2 paternal uncles		Dead after 2 years

*EMA indicates antiendomysial antibody; AGA, antigliadin antibodies; SVA, subtotal villous atrophy; GFD, gluten-free diet; PVA, partial villous atrophy; ND, not done; EATL, enteropathy-associated T-cell lymphoma, and ellipses, not applicable.

Table 3. Distribution of Celiac Disease in the Control Group

Age Range, y	No. (No. With Celiac Disease) Men	Women	Overall
20-39	918 (6)	1201 (10)	**2119 (16)**
40-59	1071 (2)	1102 (3)	**2173 (5)**
≥60	750 (1)	678 (2)	**1428 (3)**
Total	**2739 (9)**	**2981 (15)**	**5720 (24)**

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 European[33] 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 (1:238) reflects the frequency of the disease in the general Italian population because of the large size of the sample and the homogeneous genetic background. This prevalence result agrees substantially with previous data from both Italy[37] and other Western countries.[18,38] The IgA class serum EMA test, used for the celiac screening in this study, is a powerful diagnostic tool with a reported sensitivity of 70% to 100%.[39] It has recently been shown that tissue transglutaminase is the autoantigen responsible for serum EMA positivity.[40] 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-

tients 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 al[13] 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[7] 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 gastroduodenoscopy and/or a small bowel x-ray examination[43]; 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 Marsh[45] 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 al[13] 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 al[9] 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 al[8] 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 latent[46] 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)*

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

*CI indicates confidence interval.
†$P<.05$.

CD.[11] Treatment 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.

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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)