Risk of Malignancy in Patients with Celiac Disease

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PURPOSE: Studies from Europe have demonstrated an increased risk of malignancy, especially non-Hodgkin's lymphoma, in patients with celiac disease. However, there are no data on the risk for similar patients in the United States. Our aim was to estimate the risk of malignancy in a cohort of patients with celiac disease compared with the general U.S. population and to determine if a gluten-free diet is protective.
METHODS: Patients with celiac disease seen between July 1981 and January 2000 at a referral center were included. Standardized morbidity ratios (SMRs) (ratio of observed to expected) and corresponding 95% confidence intervals (CI) were calculated, using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program.
RESULTS: Forty-three (11%) of 381 celiac disease patients had a diagnosis of cancer; 9 were after the diagnosis of celiac disease, 7 were simultaneous (during same month or admission), and 27 were before the diagnosis. The standardized morbidity ratio for

all cancers combined was 1.5 (95% CI: 0.3 to 7.5), with significantly increased values for small bowel cancer (SMR = 34; 95% CI: 24 to 42), esophageal cancer (SMR = 12; 95% CI: 6.5 to 21), non-Hodgkin's lymphoma (SMR = 9.1; 95% CI: 4.7 to 13), and melanoma (SMR = 5.0; 95% CI: 2.1 to 12). Following the diagnosis of celiac disease, patients were at increased risk of non-Hodgkin's lymphoma only (SMR = 6.2; 95% CI: 2.9 to 14), despite adherence to a gluten-free diet. The non-Hodgkin's lymphoma included both T-cell and B-cell types and occurred in both gastrointestinal (n = 5) and extraintestinal sites (n = 4).
CONCLUSION: In this cohort of patients with celiac disease, we observed increased risks of small intestinal adenocarcinoma, esophageal cancer, melanoma, and non-Hodgkin's lymphoma. The risk of non-Hodgkin's lymphoma persisted despite a gluten-free diet. **Am J Med. 2003;115:191–195.** ©2003 by Excerpta Medica Inc.

Celiac disease is a genetically determined condition in which persons with specific human leukocyte antigen types (DQ2 or DQ8) mount an immunologic reaction to an environmental factor, gluten (1), a general term for the storage proteins of wheat, barley, and rye. These proteins cause an inflammatory process, and villous atrophy in the small intestine; their withdrawal results in regression of these changes (2). The disease occurs worldwide and is one of the most common inherited disorders (3). Patients are treated with a lifelong gluten-free diet (3).

Population-based studies from Europe have demonstrated increased mortality in patients with celiac disease (4–7), mainly due to malignancy, with deaths occurring in the first few years after diagnosis (4,6). An increased rate of malignancy in patients with celiac disease has been confirmed in other studies (8–10), particularly for lymphoma, adenocarcinoma of the small intestine, and squamous cell carcinomas of the esophagus, mouth, and

pharynx. There is considerable evidence that a gluten-free diet is protective against the development of malignancy (4,6,8,11).

In the United States, in contrast with Europe, celiac disease is considered uncommon (12), although there is increasing evidence that this may be due to underdiagnosis (13,14). As a result, there are no reported studies on the risk of malignancy for patients with this disease in the United States. We therefore investigated the cancer risk in a large cohort of patients with celiac disease who were seen at our medical center.

METHODS

Patients were seen between July 1, 1981, and January 1, 2000, at New York–Presbyterian Hospital, which has a referral center for celiac disease. The patients were older than 18 years and had diagnoses established by accepted criteria (15,16). Information was obtained prospectively on age, sex, date of diagnosis of celiac disease, and duration of symptoms before diagnosis. Adherence to a gluten-free diet was recorded at initial contact and at subsequent visits following thorough questioning by an investigator (PHRG). Patients were asked how often they had knowingly ingested gluten in the prior month. A history of malignancy was obtained, including the date of diagnosis and type of malignancy (confirmed by review of pathology reports). After 1993, annual serologic assessment to determine adherence to the diet was performed with gliadin and endomysial antibody assays, performed by several commercial laboratories.

Table 1. Characteristics of 381 Patients with Celiac Disease

Characteristic	Number (%) or Mean ± SD
Female sex	245 (64)
Age at follow-up (years)	52 ± 18
Age at diagnosis of celiac disease (years)	44 ± 18
Duration of symptoms of celiac disease (years)	5 ± 8

We calculated the expected number of incident malignancies in each sex- and 5-year age-specific stratum by multiplying the number of patient-years in each stratum by site-specific incidence rates from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. Because the majority of the patients were of European extraction, we used the incidence rates for whites. Patient-years at risk were calculated from the date of diagnosis of celiac disease to either the date of the cancer diagnosis or the date of the most recent follow-up, whichever came first. For cancers occurring before the diagnosis of celiac disease, we estimated the person-years at risk as the duration of symptoms before diagnosis. We calculated standardized morbidity ratios (SMRs) (ratio of observed to expected); the corresponding 95% confidence intervals were calculated on the assumption that the observed number of cancers had a Poisson distribution. We stratified the standardized morbidity ratios by the timing of the diagnosis of the malignancy (before/simultaneous or after diagnosis of celiac disease), and the specific type of malignancy.

RESULTS

About two thirds of the patients were women (Table 1). Thirteen patients died during the study period, 8 due to cancer. Forty-three patients were diagnosed with a malignancy: 9 after the diagnosis of celiac disease, 7 within 1 month of the diagnosis, and 27 before the diagnosis. The mean (± SD) age at diagnosis of the cancer was 59 ± 10 years. The most common malignancy was non-Hodgkin's lymphoma (n = 9 patients), followed by melanoma (n = 5), breast cancer (n = 5), small bowel cancer (n = 3), colon cancer (n = 3), esophageal cancer (n = 3), lung cancer (n = 3), chronic lymphocytic leukemia (n = 2), ovarian cancer (n = 2), and cervical cancer (n = 2); there were single cases of liver cancer, prostate cancer, bladder cancer, thyroid cancer, endometrial cancer, and Hodgkin's disease.

There were 34 cancers diagnosed before or simultaneous with the diagnosis of celiac disease, versus 14 expected (SMR = 2.4; 95% CI: 0.7 to 8.5). The malignancies preceded the diagnosis of celiac disease by a mean of 10 ± 18 years, and the average age at diagnosis of malignancy was 58 ± 10 years. Compared with expected rates, the risks of small bowel adenocarcinoma, esophageal cancer, non-Hodgkin's lymphoma, and melanoma were increased significantly (Table 2). The age-adjusted incidence rates for these cancers, among the celiac disease group, were elevated: for non-Hodgkin's lymphoma, 135 per 100,000 person-years (normal, 14.8 per 100,000 person-years); small bowel cancer, 40 per 100,000 person-years (normal, 1.2 per 100,000 person-years); esophageal cancer, 50 per 100,000 person-years (normal, 3.9 per 100,000 person-years); and melanoma, 60 per 100,000 person-years (normal, 11.5 per 100,000 person-years).

Patients were followed for a mean of 6 ± 11 years following the diagnosis of the celiac disease, giving 1977 person-years at risk. We observed nine cancers, with 24 expected (SMR = 0.3; 95% CI: 0 to 10). The malignancies followed the diagnosis of celiac disease by a mean of 16 ± 17 years, occurring at an average age of 62 ± 8 years. The

Table 2. Standardized Morbidity Ratios for All Cancers and for Cancers Diagnosed before or Simultaneously with Celiac Disease

	All Cancers				Cancers Diagnosed before or Simultaneously			
Cancer	Observed	Expected	Standardized Morbidity Ratio (95% Confidence Interval)	*P* Value	Observed	Expected	Standardized Morbidity Ratio (95% Confidence Interval)	*P* Value
Non-Hodgkin's lymphoma	9	1.0	9.1 (4.7–13)	<0.001	4	0.7	5.3 (2.3–13)	<0.001
Small bowel	3	0.1	34 (24–42)	<0.001	3	0.1	45 (34–61)	<0.001
Colon	3	3.7	0.8 (0.1–7.2)	0.72	3	2.6	1.2 (0.2–7.2)	0.80
Esophageal	3	0.3	12 (6.5–21)	<0.001	3	0.2	16 (9.7–26)	<0.001
Melanoma	5	1.0	5.0 (2.1–12)	<0.001	4	0.8	5.0 (2.1–12)	<0.001
Breast	5	4.2	1.2 (0.2–7.2)	0.69	5	4.0	1.3 (0.2–7.2)	0.61
Lung	3	3.8	0.8 (0.1–7.2)	0.68	2	2.8	0.7 (0.1–7.2)	0.64
Total*	43	28	1.5 (0.3–7.5)	0.62	34	14	2.4 (0.7–8.5)	0.16

* The total cancers also include chronic lymphatic leukemia (n = 2 patients), ovarian cancer (n = 2), cervical cancer (n = 2), and liver, prostate, bladder, endometrial, and thyroid cancer, and Hodgkin's disease (n = 1 each).

Table 3. Characteristics of Non-Hodgkin's Lymphoma in Patients with Celiac Disease

Patient No.	Type and Location of Lymphoma	Immunohistochemical Profile	Time between Diagnosis of Lymphoma and Celiac Disease*
1	Peripheral T cell, small bowel, inguinal nodes	CD3$^+$, TIA-1$^+$, CD4$^{+/-}$, CD5$^{+/-}$, CD8$^-$, CD56$^-$	−1 week
2	Peripheral T cell, small and large bowel	CD3$^+$, CD4$^+$, TIA-1$^+$, CD8$^-$	4 years
3	Mycosis fungoides, skin (T cell)	CD4$^+$, CD3$^+$	3 years
4	Peripheral T cell, small bowel and intra-abdominal nodes	CD3$^+$, CD4$^+$, CD43$^+$, CD8$^-$, TIA-1$^-$	7 months
5	Diffuse large B cell, gastric	LCA$^+$, CD20$^+$	−5.3 years
6	Mantle cell, axillary nodes (B cell)	CD20$^+$, CD5$^+$, CYCLIN-D1$^+$	−3 months
7	Mantle cell, iliac nodes (B cell)	CD20$^+$, CD5$^+$, CYCLIN-D1$^+$	2.3 years
8	Diffuse large cell, jejunum†		−8.6 years
9	Diffuse large cell, mesenteric and mediastinal nodes†	LCA$^+$	12 years

* A minus sign indicates that the lymphoma was diagnosed before celiac disease.
† Insufficient material for further immunohistochemical classification.

cancers included non-Hodgkin's lymphoma (n = 5 patients), melanoma (n = 1), liver cancer (n = 1), chronic lymphatic leukemia (n = 1), and prostate cancer (n = 1). The only significantly increased risk was for non-Hodgkin's lymphoma (SMR = 6.2; 95% CI: 2.9 to 14). All but 1 (with liver cancer) of these 9 patients claimed to have adhered strictly to a gluten-free diet.

There were three B-cell lymphomas (which included two mantle cell lymphomas), four T-cell lymphomas, and two large cell lymphomas that were incompletely classified because of insufficient material for review (Table 3). Five lymphomas were primarily gastrointestinal in origin (stomach, small bowel, and colon); three involved primarily lymph nodes, and one involved the skin (mycosis fungoides). Two of the B-cell lymphomas were nodal (mantle cell) and one extranodal, a diffuse large B-cell lymphoma of the stomach (without evidence of *Helicobacter pylori* infection). The T-cell lymphomas included three intestinal peripheral T-cell lymphomas. One patient had the conventional enteropathy-associated T-cell lymphoma immunophenotype (Table 3; patient 1), and 2 patients had CD4$^+$ primary intestinal lymphomas, including 1 with a cytotoxic (TIA-1$^+$) phenotype. Two of the T-cell intestinal lymphomas had nodal involvement; one conventional enteropathy-associated T-cell lymphoma had mesenteric node involvement, whereas one CD4$^+$ T-cell lymphoma had involvement of inguinal lymph nodes. One of the unclassified lymphomas presented as an ulcerated jejunal mass, whereas the other involved mesenteric and mediastinal lymph nodes, as well as a lymphomatous pleural effusion.

The four non-Hodgkin's lymphomas that were diagnosed before the diagnosis of celiac disease occurred a mean of 4 ± 4 years earlier; the 5 cases that were diagnosed after the diagnosis of celiac disease occurred a mean of 5 ± 4 years later. Each of these 5 patients claimed strict adherence to a gluten-free diet, as determined by thorough questioning, and had negative celiac serologies. Based on these 5 patients, the standardized morbidity ratio for non-Hodgkin's lymphoma for patients following a gluten-free diet was 6.2 (95% CI: 2.9 to 14).

DISCUSSION

Our study revealed an increased risk of malignancy in patients with celiac disease compared with the general U.S. population, confirming the European studies that have reported increased rates of small bowel cancer, esophageal carcinoma, and lymphoma (8,10). The majority of these cancers occurred before the diagnosis of celiac disease. We used the duration of symptoms before the diagnosis of celiac disease as an estimate of the period at risk of the development of malignancy. We consider this justifiable because there is usually a long duration of symptoms before the diagnosis of celiac disease in the United States (17), and patients with symptomatic disease are at greatest risk of malignancy (6). However, it is difficult to determine how long a patient has had celiac disease because it is frequently asymptomatic (18) and patients with celiac disease have an increased rate of associated conditions that are usually diagnosed before the celiac disease (19,20).

We confirmed an increased risk of non-Hodgkin's lymphoma in patients with celiac disease; this occurred despite following a gluten-free diet for a mean of about 5 years. Our patients had about a ninefold increased risk of non-Hodgkin's lymphoma. Previous studies have reported relative risks from about 3 to about 100 (8,11,21–23). Our results suggest that the risk of non-Hodgkin's lymphoma persists beyond the first few years after the diagnosis of celiac disease, despite a gluten-free diet, as has been observed in other studies (7,23).

The mechanism for the development of malignancies in patients with celiac disease is not known. However, increased intestinal permeability of environmental carcinogens, chronic inflammation, chronic antigenic stimulation, the release of proinflammatory cytokines, immune surveillance problems, and nutritional deficiencies due to the disease or the gluten-free diet have been suggested (24,25). A relation between celiac disease and the development of lymphoma is well-established (26–29). The predominant celiac-associated lymphoma is an enteropathy-associated T-cell phenotype that is typically poorly responsive to chemotherapy and rapidly fatal (28). In most cases, enteropathy-associated T-cell lymphomas display the phenotype $CD3^+CD4^-CD8^-$; less commonly, the malignant T cells are $CD3^+CD8^+CD56^+$ (30,31). Our series of celiac-associated lymphomas was somewhat atypical in that both B-cell and T-cell lymphomas, arising in intestinal and extraintestinal sites, were identified (11,22,23,32–35).

Our patients also had a significantly increased risk of melanoma. We cannot explain this finding, which should be interpreted in recognition of a persistent increase in the incidence of melanoma in the United States that has started to slow in recent years (36).

Our study has several potential limitations. Patients were seen at one medical center, and we only included patients in whom we had follow-up data. In addition, referral bias is likely because patients were assessed for their malignancy at a center with a clinical interest in celiac disease. The presence of a malignancy or its treatment may have resulted in symptoms that led to the diagnosis of celiac disease, or the development of the malignancy may have caused patients to seek medical care at our institution. There is also bias introduced by our method of obtaining the dietary history.

Our study confirms an increased risk of malignancy in celiac disease (37). Most of this risk occurs before the diagnosis of celiac disease and might be reduced by earlier diagnosis and strict adherence to a gluten-free diet (8,37). The risk of non-Hodgkin's lymphoma, however, appears to persist despite treatment with a gluten-free diet. If our results are confirmed in larger cohorts of patients, especially the elderly with celiac disease, there are important implications for screening for celiac disease in patients with certain types of cancer, and for the management of patients with celiac disease.

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