Increasing Incidence of Enteropathy-Associated T-Cell Lymphoma in the United States, 1973-2008

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BACKGROUND: Enteropathy-associated T-cell lymphoma (EATL) is a rare lymphoma subtype that is strongly associated with celiac disease (CD), an autoimmune disease triggered by the ingestion of gluten. Because CD rates are increasing in the United States, the authors sought to determine whether the incidence rates of EATL also are increasing. METHODS: The authors identified patients with primary, pathologically confirmed lymphoma in the Surveillance, Epidemiology, and End Results database registries from 1973 to 2008. To ensure capture of all cases of EATL, the following lymphoma subtypes, limited to the small bowel, were included: non-Hodgkin lymphoma not otherwise specified (NOS) T-cell, peripheral T-cell lymphoma NOS, and enteropathy type T-cell lymphoma, and their age-adjusted and sex-adjusted incidence rates were calculated over time. Survival was estimated using Kaplan-Meier curves. RESULTS: In total, the authors identified 161 small bowel lymphomas that were diagnosed between 1973 and 2008. The overall age-adjusted and sex-adjusted annual incidence for all bowel lymphomas was 0.016 per 100,000 population, which increased over the study period from 0.006 to 0.024 per 100,000 population. These tumors were most common in men (age-adjusted incidence rate, 0.021 per 100,000) with the highest incidence rate in Hispanics (age-adjusted incidence rate, 0.033 per 100,000). The median overall survival was 7 months. There was no difference in survival by race/ethnicity (P = .09) or sex (P = .06). CONCLUSIONS: The current results indicated a significant increase in the incidence of EATL in the United States, which may reflect the increasing seroprevalence of CD and better recognition of rare types of T-cell lymphomas. The incidence may continue to rise given the large ratio of undiagnosed-to-diagnosed individuals with CD in the United States. Cancer 2012;118:3786-92. © 2011 American Cancer Society.

KEYWORDS: enteropathy-associated T-cell lymphoma, celiac disease, T-cell lymphoma, incidence, survival.

INTRODUCTION

Celiac disease (CD) is an autoimmune disease that affects genetically susceptible individuals and is triggered by the ingestion of gluten.¹ On the basis of seroprevalence studies, the incidence of celiac disease has increased markedly in the United States over the last 50 years.^{2,3} In addition, the rate of diagnosis has risen²⁻⁵ in part because of the availability of serologic tests and increased physician and patient awareness. Parallel to this is the increasing prevalence of CD in the United States,^{6,7} indicating that detection bias cannot fully explain the rise in cases. However, the vast majority of individuals with celiac disease remain undiagnosed.

CD is associated with a modest increased risk of mortality.^{8,9} Despite an increase in diagnosis and improvement in care, the mortality excess has remained unchanged over the last few decades. This excess is explained primarily by an increase in malignancy,^{8,10} notably lymphomas, especially those occurring in the small bowel.

Enteropathy-associated T-cell lymphoma (EATL) is a rare lymphoma subtype that is strongly associated with CD and carries a poor prognosis.^{11,12} The term "enteropathy-associated T-cell lymphomas" was introduced first by O'Farrelly et al in 1986,¹³ but it was only in 1991 when the World Health Organization International Classification Project updated the terminology to "enteropathy type intestinal T-cell lymphoma" that EATL formally became a recognized subtype.¹⁴

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Currently, 2 groups of EATL are recognized: type I, which refers to a large cell lymphoma believed to be associated exclusively with CD,¹² and EATL type II, the rarer form, which consists of small to medium-sized cells and presents often with obstruction or perforation of the small bowel. The latter type has no known association with CD.¹⁴ Despite the longstanding recognition of these entities, there has been a paucity of studies investigating the epidemiology of EATL in patients with CD.

In 2 European studies in which large cohorts of patients with non-Hodgkin lymphoma (NHL) were screened serologically for CD and compared with controls, CD was associated with an overall increased risk for developing NHL with a standardized incidence ratio (SIR) of 2.2 (95% confidence interval [CI], 1.2-3.6)¹⁵ and 3.1 (95% CI, 1.3-7.6).¹⁶ The SIR for small bowel lymphoma was 16.9 (95% CI, 7.4-38.7), and it was 19.2 (95% CI, 7.9-46.6) for T-cell lymphoma.¹⁷ The odds of developing EATL were 28 times greater (95% CI, 6-144 times greater) in the CD group.¹⁶

In a nationwide study in the Netherlands, the crude incidence of EATL was 0.1 per 100,000 with a predominance among men.¹⁸ In contrast, the epidemiology of EATL in the United States is unknown. The risk of EATL may be increased in individuals with undiagnosed CD,^{15,19} and the diagnosis rates of CD in the United States remain low compared with the rates in European nations.⁴

The objective of the current study was to evaluate and describe trends in the incidence and survival of EATL in the United States. We hypothesized that this incidence is increasing, because of the increased prevalence of CD and the large proportion of patients with undiagnosed CD.

MATERIALS AND METHODS

Description of Surveillance, Epidemiology, and End Results Data

In the United States, the Surveillance, Epidemiology, and End Results (SEER) database is the National Cancer Institute-supported national cancer surveillance program that collects cancer statistics from 17 geographic areas representing approximately 26% of the US population.²⁰ The program collects demographic data, clinical information at diagnosis, first course of treatment, and active followup for vital status. These data are updated yearly and are publicly available for use in incidence and survival studies. For the current study, we used these data for the analysis of patients who were diagnosed between 1973 and 2008.

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Study Population/Case Selection

Our analysis was limited to patients with primary, pathologically confirmed lymphoma. EATL did not have a specific or discrete International Classification of Diseases code until 1991, because it had been described previously as "intestinal lymphoma" or "malignant histiocytosis of the intestine. "Therefore, to ensure capture of all cases of EATL, a subtype of T-cell lymphoma, we included the following lymphoma subtypes, limited to the small intestine: NHL not otherwise specified (NOS) T-cell, peripheral T-cell lymphoma NOS, and enteropathy type T-cell lymphoma. We reasoned that primary T-cell lymphomas of the small bowel in the western world, and specifically in the United States, are less likely to be associated with other etiologies. Because the SEER 9 registries, SEER 13 registries, and SEER 17 registries are linked to different population data sets, we computed the age-adjusted incidence by combining the time periods 1973 to 1991 for SEER 9, 1992 to 1999 for SEER 13, and 2000 to 2008 for SEER 17.

Variables

The variables of interest for the current study included age at diagnosis, sex, race, and ethnicity. Age at diagnosis was divided into 6 groups: ages 0 to 9 years, ages 10 to 19 years, ages 20 to 29 years, ages 30 to 39 years, ages 40 to 49 years, ages 50 to 59 years, ages 60 to 69 years, ages 70 to 79 years, and aged \geq 80 years. The age-adjusted (2000 US Standard Population) incidence rates were calculated per 100,000 person-years overall and by sex, race, and age category.

Observed survival rates (5-year) and survival case listing files for small bowel lymphomas were obtained by using the SEER*Stat software²⁰; only actively followed patients of known age were selected. Poisson regression was used to calculate the statistical difference in incidence between the different groups. The observed survival rate was obtained by using the Kaplan-Meier method. Survival curves were generated using the SAS statistical software package (version 9.2; SAS Institute Inc., Cary, NC). Overall survival from the date of diagnosis to the date of death in months was calculated along with survival stratified by sex, race, and age groups. Between-group comparisons were performed using the log-rank test.

RESULTS

Overall Incidence of Enteropathy-Associated T-Cell Lymphoma

There were 161 pathologically confirmed lymphomas of the small intestine diagnosed between 1973 and 2008.

Table 1. Incidence and Survival of Enteropathy-Associated T-Cell Lymphoma in Adults in theSurveillance, Epidemiology, and End Results Registries, 1973 to 2008

Variable of Interest	No. of Cases (%)	Incidence Rate per 100,000 PY	Р
Overall	161	0.016	.001
Age at diagnosis, y			<.001
20-29	6 (4)	0.003	
30-39	13 (8.2)	0.006	
40-49	20 (12.3)	0.010	
50-59	25 (16.4)	0.017	
60-69	40 (25.3)	0.039	
70-79	32 (17.8)	0.046	
≥80	25 (15.1)	0.063	
Sex			
Men	100 (62)	0.021	.003
Women	61 (38)	0.012	
Race			.004
White	111 (69)	0.015	
Black	14 (9)	0.017	
Hispanic	15 (9)	0.033	
Other	21 (13)	0.011	

Abbreviations: PY, person years.



Figure 1. The overall age-adjusted incidence of small bowel lymphoma increased significantly over time between 1973 and 2008. EATL indicates enteropathy-associated T-cell lymphoma; PY, person years.

Table 1 lists the demographics and basic characteristics of the patients with EATL. The overall age-adjusted annual incidence for all small bowel lymphomas was 0.016 per 100,000 population. These tumors had a higher incidence in men (age-adjusted incidence rate, 0.021 per 100,000) and Hispanics (age-adjusted incidence rate, 0.033 per 100,000), although 69% of the population of patients with EATL were white.



Figure 2. The overall age-adjusted incidence of small bowel lymphoma increased significantly with increasing age. EATL indicates enteropathy-associated T-cell lymphoma; PY, person years.

Incidence Patterns Over Time and Age

The overall age-adjusted incidence of small bowel lymphoma had a statistically significant increase over time between 1973 and 2008 (P < .001), from 0.006 per 100,000 to 0.024 per 100,000, respectively (Fig. 1), as well as with increasing age (P < .0001) (Fig. 2).



Figure 3. (a) The overall survival of patients with enteropathy-associated T-cell lymphoma (EATL) is illustrated. (b,c) The survival of patients with EATL is stratified according to (b) sex and (c) race. The x-axis in each graph represents survival in months, and the y-axis represents the survival probability. The *P* value in each graph was calculated using the log-rank test and comparing differences between groups.

For both men and women, the incidence increased significantly with age, but men had a higher incidence than women at all time points. Overall, the incidence was statistically significantly higher in men (P = .003) (Fig. 2), and 58% of all patients with EATL patients in the group aged >50 years. The incidence of EATL among women peaked in the group ages 70 to 79 years and then declined in the older age groups; whereas, in men, it did not peak until age \geq 80 years.

Overall Survival

The median overall survival was 7 months (Fig. 3a). Survival was not significantly different between the sexes (P = .062) (Fig. 3b) or between race/ethnicity groups (P = .093) (Fig. 3c). There was a statistically significant difference in survival for patients who were diagnosed in their 40s and 60s compared with patients who were diagnosed in their 80s (P = .004) and P = .0003, respectively).

This increasing incidence of EATL was compared with the overall incidence of T-cell lymphoma over the same period (data not shown). There was no significant increase in T-cell lymphoma (P = .1) compared with the increase in EATL incidence (P = .001) from 1973 to 2008.

DISCUSSION

Our results indicate a significant increase in the incidence of EATL over time in the United States based on cases in the SEER database. There were more men than women with EATL. Although the overall incidence was 0.016 per 100,000, in the population aged >60 years, the incidence was 0.05 per 100,000, and the highest incidence was in individuals aged \geq 80 years (0.06 per 100,000). These findings are consistent with other studies demonstrating the increasing incidence of EATL in the elderly.^{18,21,22}

The reasons for the lower incidence of EATL in the United States than in Europe are unclear. This may reflect differences in the pattern or rate of detection of CD in the US population. The only other population study that we identified is the Netherlands-based Nationwide Network and Registry of Histopathology and Cytopathology (PALGA) study, which estimated the incidence of EATL in Europe at 0.1 per 100,000 population with an increasing incidence noted with age and with men affected more commonly than women.¹⁸ This may be caused in part by different rates of CD and, hence, EATL in the US population.

Patients with CD whose symptoms and villous atrophy do not respond to a gluten-free diet are said to have refractory CD (RCD). There are 2 main groups of RCD: type I and II.²³ A study by Roshan et al demonstrated that the rates of RCD, both type I and type II, are lower in the



Figure 4. The age-adjusted and sex-adjusted incidence rates of enteropathy-associated T-cell lymphoma (EATL) and celiac disease are illustrated from 1950 to 2008. Data on the celiac rate were adapted from the report by Rubio-Tapia et al regarding seroprevalance.⁷ The EATL rate is indicated based on our study using the Surveillance, Epidemiology, and End Results registry. The y-axis represents the EATL rate using a log scale of 100,000 person-years (PY), and the x-axis represents the decade of diagnosis.

US population (<2% of all CD patients) compared with the European population.²³⁻²⁵ Those authors also demonstrated that the incidence of RCD II, which is considered a precursor to or a more indolent variant of EATL, was proportionally lower in the US population (17%) compared with the European population (range, 28%-75%),²⁵ which may explain why the rate of EATL also is lower in the United States.

These differences also may be caused in part by the different genetic backgrounds of the US population compared with the more homogenous European genetic pool. It has been reported that RCD II correlates with human leukemic antigen-DQ2 (HLA-DQ2) homozygosity, and it is noteworthy that the HLA-DQ8 allele was more common in patients who were diagnosed with CD at a US center compared with a European center.^{26,27} It is also possible that other modifier genes and environmental factors also are different. The amount or type of gluten consumed before diagnosis also may contribute to the discrepancy.

There is no established, standard, first-line treatment for patients with EATL. They usually are treated with anthracycline-containing chemotherapy, preceded at times by resection of the tumor or surgical debulking, followed by stem cell transplantation.²⁸ A more promising treatment has been an induction regimen with ifosfamide, etoposide, and epirubicin alternating with intermediate-dose methotrexate and followed by autologous stem cell transplantation.²⁹ Relapse occurs in approximately 80% of the patients who respond to initial therapy.²¹ Despite these therapies, the outcome of patients with EATL remains very poor, with a 5-year mortality rate of 80% to 92% from either progressive disease or complications of therapy.^{19,28} The poor overall survival in our analysis was similar to that reported in a recent study by the International Peripheral T-Cell lymphoma Project, which demonstrated a median overall survival of only 10 months.²²

This increasing incidence of EATL is in stark contrast to the relatively stable overall incidence of T-cell lymphomas in general. We postulate several reasons for this. In the last 5 years, with the advent of immunophenotyping using flow cytometry, there has been an increase in the more accurate diagnosis of intestinal lymphoma as EATL, and this may have led to and/or may account in part for the increasing incidence in diagnosing this entity. However, these techniques also enable the more precise diagnosis and lineage assignment of other rare, non-CDassociated types of intestinal T-cell lymphoma. In an attempt to account for these potential confounders, we compared the rate of EATL with the overall rate of intestinal lymphoma in the United States, thus helping us control for new techniques; however, despite this attempt, there was an actual increase in cases diagnosed as EATL (data not shown). This increase likely reflects in part the better detection of EATL because of early symptomatology, but it also mat be attributed to the rise in CD incidence that has been demonstrated in several studies and, hence, the greater number of patients developing EATL as a complication of longstanding, undiagnosed CD.^{6,7}

The difference in incidence according to sex is striking. Women are more likely to be diagnosed with CD,³ but men more often have unrecognized CD compared with women.³⁰ Men also appear to have evidence of more severe CD than women at diagnosis.³¹ A possible explanation may be that more men remain undiagnosed, with a greater duration of gluten exposure, and, thus, are more likely to present with EATL; and CD is only diagnosed after the lymphoma has developed. The risk of EATL appears to be increased in individuals who have undiagnosed CD.^{15,19} It is noteworthy that the seroprevalence of CD is equal across sexes despite the higher diagnosis rate among women.³² Women who are diagnosed and treated would be on a gluten-free diet and, thus, would have less inflammation, which, in turn, also may decrease the rate of lymphoma genesis. The diagnosis of CD is important, because adherence to a

gluten-free diet may prevent or reduce the risk of developing lymphoma in patients with this disease.³³

There has been a demonstrable rise in the incidence of CD over the last 40 years.^{6,7} These studies have demonstrated a 4-fold rise in the prevalence of CD in the United States. Figure 4 illustrates the rise in the seroprevalence of CD depicted from the study by Rubio-Tapia et al⁷ in parallel to the rise in EATL described in our current report. This further supports the theory of an increasing incidence of undiagnosed CD in the general population, leading to an increased duration of intestinal inflammation and, thus, malignancy.

The main limitations of this study are the underreporting and estimation of the incidence, the misclassification of other rare lymphomas that may have been included in this analysis (such as rare T-cell and natural killer [NK]-cell lymphoma subtypes), and the inability to differentiate between the 2 types of currently recognized EATL. It is important to note, however, that, in the SEER registry, there is a separate entity for nasal type and T/NK-cell lymphoma.

Although the highest incidence of EATL was in the Hispanic population, it was most common in whites. There have been several studies from South and Central America (Brazil, Argentina, Chile, and Mexico) indicating that CD is quite common among individuals from those regions (range, 1%-8%).³⁴⁻³⁷ A possible explanation may be that more Hispanics remain undiagnosed and, thus, are more likely to present with EATL. However, it is also important to note that recent publications have described and better characterized intestinal T-cell lymphomas, including those occurring in the Asian and Hispanic populations.³⁸⁻⁴⁰ Those studies have indicated that EATL II may be frequent in these populations.³⁸⁻⁴¹ Moreover, it has been demonstrated that several cases with histopathologic presentation similar to that of the EATL type II were derived from gamma-delta T-cells, again arguing an etiology distinct from CD associated with the pathogenesis of such lymphomas.^{18,41} Because histopathology and phenotype data are not available from the SEER database, and patients with EATL type II could not be distinguished from patients with EATL type I in our study, we acknowledge that some of the increase in incidence of intestinal lymphomas observed, especially that in the Hispanic population, may reflect the inadvertent classification of the aforementioned non-CDassociated intestinal T-cell lymphomas as EATL.

We also do not have data regarding the incidence of CD in the SEER population. However, the increased incidence of EATL persisted in our study despite excluding the Hispanic population from analysis, the majority of the patients captured in this study likely reflect EATL type I, and type II EATL and other types of intestinal lymphomas would make up not more than 10% to 20% of the total number of patients based on disease distribution in published case series.^{22,28,29} To minimize misclassification, we limited the current analysis only to patients with disease of the small intestine.

Although our method of obtaining patients was novel, it may have limited the detection of EATL diagnosed at sites other than the small intestine. An additional concern is that the rise in incidence of EATL observed in our study may represent an overall improvement in the detection of T-cell lymphoma. However, when comparing the incidence of T-cell lymphoma overall versus EATL in the same period, no significant increase in T-cell lymphomas was observed (P = .1), thus suggesting a true rise in EATL.

In conclusion, we note that the incidence of EATL in the United States is increasing in parallel to the increasing seroprevalence of CD. This incidence may continue to rise in the future given the large ratio of undiagnosed-to-diagnosed individuals with CD in the United States. Survival, however, remains dismal. In addition to further research on therapeutics for this disease, which carries a poor prognosis, efforts should be made to increase the recognition and treatment of CD among symptomatic individuals.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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