Helicobacter pylori and Malignant Lymphoma in Spain

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Abstract

***Helicobacter pylori* has been associated with gastric adenocarcinoma and gastric lymphoma. We report on the systematic evaluation of serologic detection of *H. pylori* in a lymphoma case-control study. Methods: Cases (*N* = 536) were consecutive patients newly diagnosed with a lymphoid malignancy between 1998 and 2002 in four centers in Spain. Lymphomas were diagnosed and classified using the WHO Classification. Controls (*N* = 603) were hospitalized patients frequency-matched to the cases by 5-year age group, sex, and study center. Severe immunocompromised patients were excluded as controls. Patients underwent a personal interview and blood sampling. *H. pylori* infection was evaluated by the presence of IgG antibodies using the Premier enzyme immunoassay kit (Meridian Diagnostics Inc., Cincinnati, OH). Logistic regression analysis was used to estimate the odds ratios and 95% confidence intervals (OR, 95% CI) for lymphoma categories. Results: Anti-*H. pylori* antibodies were detected in 68.5% of the cases and 71.3% of the controls (*P* = 0.29) *H. pylori* was associated with a 3-fold excess risk of splenic marginal B-cell lymphoma (OR = 3.97, 95% CI = 0.92-17.16). *H. pylori* was not associated with an overall increased risk of extranodal lymphomas (OR = 0.73, 95% CI = 0.44-1.22) but when specific sites were explored, the four mucosa-associated lymphoid tissue and the six diffuse large B-cell lymphomas primary localized in the stomach were all *H. pylori* seropositive. Conclusion: Persistent infection with *H. pylori* may be implicated in the development of lymphomas of the gastric mucosa and of the spleen. These results could have clinical implications in the management of splenic marginal zone lymphomas.** (Cancer Epidemiol Biomarkers Prev 2004;13(6):944–8)

Helicobacter pylori is a worldwide common bacterium that infects human gastric mucosa, and generally persists for life in the infected tissue unless adequately treated (1). Chronic infection with *H. pylori* has been associated with the development of peptic ulcer disease, gastric adenocarcinoma, and extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT; ref. 2). *H. pylori* is present in 80% to 90% of patients with gastric MALT lymphomas (2, 3) but successful eradication of *H. pylori* leads to temporal regression in about 75% of affected subjects if diagnosed at early stages of tumor development (1, 4). Diffuse large B-cell lymphomas (DLBCL) localized in the stomach generally show a weaker association with *H. pylori* although tumor remission has been observed after bacterial eradication (5). Apart from the gastric mucosa, *H. pylori* has been detected in ectopic or metaplastic gastric mucosa of the duodenum, ileum, colon, and sporadically in other non-gastrointestinal sites (6-8). *H. pylori* has been associated to a 2-fold increased risk of pancreatic cancer in two case-control studies (9, 10). In an experimental research, *H. pylori* infection has been associated with a worse clinical outcome after acute pancreatitis in infected rats (11). These observations suggest that *H. pylori* may participate in the development of diseases involving organs outside the gastrointestinal tract.

Chronic infection with *H. pylori* results in a strong local and systemic humoral and cellular response that may produce direct cell damage and induce clonal expansion of B cells (4, 12, 13). Advanced stages of gastric MALT commonly harbor abnormal immunoglobulin gene rearrangements t(11;18)(q21;q21), t(1;14)(p22;q32), and trisomy 3 (3). It has been proposed that some of these chromosomal anomalies are indicative of different etiopathogenic pathways. Low-grade gastric MALT lymphomas are characterized by a low frequency of t(11;18)(q21;q21) and good response to *H. pylori* eradication, whereas DLBCL or high-grade MALT lymphomas are more likely to have a wide range of chromosomal aberrations and are more resistant to eradication of *H. pylori* (14).

The objective of the current study was to estimate the association of lymphoma with serologic detection of *H. pylori* in a case-control study.

Methods

The study subjects were recruited at four centers in Spain (Barcelona, Tortosa, Reus, and Madrid) served by

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Note: This case-control study was undertaken within the framework of the EPILYMPH international study.

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three pathology laboratories. Cases were consecutive patients newly diagnosed with a lymphoid malignancy between May 1998 and February 2002. The diagnosis of lymphoma was done locally by histology and supplemented by immunohistochemistry tests and flow cytometry. Cases were categorized according to the WHO Classification for Neoplastic Diseases of the Lymphoid Tissues (3). Subjects with a diagnosis of uncertain malignant potential, such as post-transplant lymphoproliferative disorder or monoclonal gammapathies of undetermined significance, were excluded. Synchronically with case detection, controls were hospitalized patients frequency-matched to the cases by age (±5 years), sex, and study center. Patients with severe immunosuppression and systemic infections as leading cause of hospitalization at the time of interview were excluded. Interviews were conducted to collect data on demographic, medical and family history, and environmental exposures. Cases and controls provided a blood sample. Informed consent was obtained from all subjects before enrollment, and the Institutional Review Boards of the participating centers approved the study.

Of 700 eligible cases, 536 (76.6%) were included in the seroepidemiologic study. Reasons for exclusion were refusal to participate (n = 28), death before the interview (n = 25), and absence of a blood sample (n = 106) or an interview (n = 5). Of 655 eligible controls, 603 (92.1%) were included in the study. Reasons for exclusion were refusal to participate (n = 23) and absence of a blood sample (n = 29).

No differences were observed between included and non-included subjects in terms of gender (53.3% versus 56.4% for males, P = 0.39) and number of school years (average years = 9 versus 10, P = 0.1). Non-included subjects were slightly older than included subjects (average age = 62 versus 59, P = 0.01).

A centralized pathology review was organized as part of the international Epilymph study which included a board of seven pathologists, not involved in the original diagnosis. As part of the preestablished protocol, a random sample of 20% of the lymphomas within each histologic category and within participating centers was reviewed. In addition, all cases with a diagnosis of not-otherwise–specified (NOS) lymphoma were reviewed. In the few cases for which there was a change from the original diagnosis, the panel review was used for the current analysis. Relevant to the analyses presented was the exclusion of two subjects with a primary diagnosis of a marginal zone B-cell lymphoma (MZL) and one patient with a splenic MZL that were reclassified as probably a reactive lymphoproliferative disorder by the panel review.

Site of lymphoma was categorized as nodal or extranodal according to the site of involvement at first diagnosis. Extranodal sites included affected organs other than lymph nodes, bone marrow, spleen, and Waldeyer's ring.

The distribution of the medical conditions of the controls was: 14.7% surgical procedures, 14% ocular diseases, 15.6% diseases of the circulatory system, 12% injury and poisoning, 9.1% diseases of the respiratory system, 8.9% diseases of the urogenital system, 8.2% diseases of the gastrointestinal system, 4.1% diseases of the gynecologic system, 3.3% infections, 2.6% skin disorders, 2.4% diseases of the liver, 1.9% behavioral problems, 1.4% diseases of the endocrin system, 0.2% diseases of the hematologic system, and 1.6% diseases of the cerebral system.

***H. pylori* Serology.** From each study subject, 200 μl of serum sample were stored in a central repository at −80°C until shipment to the Aberdeen laboratory. The laboratory was blinded to the case-control status of the subjects. All samples were tested in duplicate using the Meridian Diagnostics Premier *H. pylori* enzyme immunoassay kit as per manufacturer's specifications (Meridian Diagnostics Inc., Cincinnati, OH; supplied in the UK by Launch Diagnostics Ltd., Longfield, Kent). This commercial kit is used for *in vitro* qualitative and quantitative detection of IgG antibodies against *H. pylori* and its use has been validated for plasma and serum. The results were read spectrophotometrically using an enzyme immunoassay plate reader by absorbance of 450 nm absorbance.

The sensitivity and specificity of this test is 98.9% and 95.5%, respectively. The kit has been extensively used in the Aberdeen laboratory (EEO) for routine clinical diagnosis as well as for research purposes. The validation of this kit was done using subjects in whom *H. pylori* status was defined by urea breath test, rapid slide urease test, and stained tissue sections, yielding a sensitivity of 96.3% and specificity of 94.6% for all samples regardless of age. The optimal cut off point for the assay was 18 IU/mL. Although the manufacturers do not require testing samples in duplicate, we performed duplicate analyses on all samples in this study. The concordance was found to be 100% for samples tested within the same kit and also within the same batch of kits. Samples retested at different time intervals also gave 100% concordance.

Statistical Analyses. Comparison between categorical variables and *H. pylori* infection was done with a χ^2 test. P values were considered statistically significant at the 0.05 level by two-sided tests. Unconditional logistic regression was used to estimate the odds ratios and 95% confidence intervals (OR, 95% CI) to measure association between specific variables and the risk of lymphoma. Variables associated with *H. pylori* or with case-control status at $P < 0.10$ in univariate analysis were considered for inclusion in the regression model. The contribution to the models by other potential confounding variables was tested with the likelihood ratio test. The logistic regression analysis for lymphoma subgroups was done comparing each lymphoma subgroup to all controls. All models were adjusted for age, sex, and study center.

Results

Table 1 shows the distribution of the study subjects by age in quintiles, sex, study center, and ever school attendance. Overall, no statistical differences were observed in the distribution of these characteristics between cases and controls. The average age was 59.9 years for cases and 58.0 years for controls (P value = 0.14).

Anti-*H. pylori* antibodies were detected in 367 lymphoma cases (68.5%) and in 430 (71.3%) control subjects. Table 2 presents different characteristics that were statistically related to the prevalence of *H. pylori* among

Table 1. Characteristics of the included subjects

	Controls number (%)	All lymphoid neoplasms number (%)	*P* value
Age			
<42	130 (21.6)	95 (17.7)	
43-56	123 (20.4)	107 (20.0)	
57-67	126 (20.9)	106 (19.8)	
68-73	99 (16.4)	108 (20.1)	
>73	125 (20.7)	120 (22.4)	0.30
Gender			
Males	314 (52.1)	294 (54.9)	
Females	289 (47.9)	242 (45.1)	0.35
Study center			
Barcelona	504 (83.6)	423 (78.9)	
Madrid	55 (9.1)	68 (12.7)	
Tarragona (Reus and Tortosa)	44 (7.3)	45 (8.4)	0.10
Ever school attendance			
Never	63 (10.4)	70 (13.1)	
Ever	540 (89.6)	466 (86.9)	0.17
Total	603 (100)	536 (100)	

control subjects. *H. pylori* prevalence differed by age, with subjects younger than 43 having lower prevalence of antibodies as compared with all other age categories. *H. pylori* prevalence also increased with number of residencies during lifetime, for those sharing the bed with a sibling during childhood and taking fewer drugs or fewer antibiotics than siblings during childhood. No association with *H. pylori* prevalence was observed for smoking habit, regular alcohol drinking, history of intravenous drug use, or visiting Africa, Asia, or Latin America. Regular use of drugs for medical conditions, such as high blood pressure, diabetes, inflammation, stomach problems, depressive symptoms, or pain, was not associated to *H. pylori* prevalence (data not presented).

Table 2. *H. pylori* prevalence by different characteristics among control subjects

	H. pylori +/total (% positive)
Age (years in quintiles)	
<43	72/130 (55.4)
43-56	90/123 (73.2)
57-67	98/126 (77.8)
68-73	76/99 (76.8)
>73	94/125 (75.2)
P value trend	0.001
Number of residencies during lifetime	
1	15/29 (51.7)
2	37/66 (56.1)
3-5	171/243 (70.4)
>5	207/265 (78.1)
P value trend	<0.001
Sharing bed with siblings during childhood	
Yes	186/246 (75.6)
No	244/357 (68.3)
P value	0.053
Taking more medicines than siblings during childhood	
Yes	31/54 (57.4)
No	394/543 (72.6)
P value	0.019
Taking more antibiotics than siblings during childhood	
Yes	25/45 (55.6)
No	400/552 (72.5)
P value	0.016
Total	430/603 (71.3)

H. pylori infection was not associated with an overall increased risk of lymphoma (Table 3). Within all lymphoma categories, *H. pylori* was associated with an almost 4-fold increased risk of splenic MZL (OR = 3.97, 95% CI = 0.92-17.16, *P* value = 0.065). Of 26 patients with splenic MZL, 24 had detectable antibodies against *H. pylori*. Four cases were restricted to the spleen. All others had a positive bone marrow, in two cases there was additional liver involvement, and in one the central nervous system was also involved. All splenic MZL were Ann Arbor stage IV. *H. pylori* was not associated with non-splenic MZLs overall. However, all four MZLs of the stomach (stomach MALT) were positive for *H. pylori*. *H. pylori* was not associated with an overall increased risk of extranodal lymphomas (OR = 0.73, 95% CI = 0.44-1.22). However, when specific sites were explored, all 10 lymphomas localized primarily in the stomach were *H. pylori* seropositive. No other lymphoma category shown in Table 3 showed an association with *H. pylori*. The adjustment for the characteristics listed in Table 2 did not modify the estimates.

Table 4 describes the histology and clinical stage of the extranodal lymphomas involving the stomach. As with MZL of the stomach, all six DLBCL of the stomach were *H. pylori* positive.

Table 3. Risk of lymphoma associated to detection of antibodies to *H. pylori*

Diagnosis	*H. pylori* positive/ no. of subjects	(%)	OR* (95% CI)
Controls	430/603	71.3	Reference
By histology:			
All lymphomas	367/536	68.5	0.83 (0.64-1.08)
B-cell lymphoma	307/439	69.9	0.85 (0.65-1.12)
Chronic lymphocytic leukemia	82/117	70.1	0.71 (0.45-1.12)
Lymphoplasmocytic lymphoma	15/21	71.4	0.81 (0.30-2.19)
Diffuse large B cell	64/93	68.8	0.97 (0.59-1.59)
Plasma cell myeloma	51/74	68.9	0.78 (0.45-1.33)
Marginal zone B cell	17/27	63.0	0.71 (0.31-1.62)
Stomach MALT	4/4	100.0	∞
Splenic marginal zone lymphoma	24/26	92.3	3.97 (0.92-17.16)
Follicular lymphoma	28/38	73.7	1.13 (0.52-2.47)
Others B cell	26/43	60.5	0.62 (0.32-1.20)
Hodgkin lymphoma	34/58	58.6	0.82 (0.46-1.47)
T-cell lymphoma	26/39	66.7	0.72 (0.36-1.47)
Mycosis fungoides	13/17	76.5	1.04 (0.33-3.30)
By site:			
Nodal lymphomas	313/454	68.9	0.85 (0.65-1.12)
Extranodal lymphomas	54/82	65.9	0.73 (0.44-1.22)
Stomach	10/10	100	∞

*Adjusted for age, gender, and study center.

Table 4. Diagnosis, clinical stage, and *H. pylori* serostatus among extranodal lymphomas localized in the stomach

Diagnosis	Number	*H. pylori* serostatus	Ann Arbor (I-IV)
Stomach	10	All positive	
Marginal zone	4	All positive	3 I, II
Diffuse large B cell	6	All positive	3 I, III, 2 IV

Discussion

Our analysis confirms that *H. pylori* infection is associated with an increased risk of gastric lymphomas, both MALT and DLBCL, and of splenic MZL. No other histologies, nor other sites of lymphoma, were associated with *H. pylori* infection. In addition to corroborating established clinical and pathologic knowledge on gastric lymphoma (15), our data offer new insight into the potential implication of *H. pylori* infection in splenic MZL. Although our OR estimates were not statistically significant at the 0.05 level, the magnitude of the OR was considerable and close to a statistical significance particularly for the association between *H. pylori* and splenic MZL ($P = 0.065$).

We identified that 100% of the subjects with a gastric lymphoma categorized as MALT or as DLBCL histology had antibodies against *H. pylori* in agreement with previous data (6) but in disagreement with a study by Watanobe et al. (16) which failed to identify *H. pylori* in three of three patients with DLBCL.

Although it is accepted that MALT lymphoma cells may disseminate into the splenic marginal zone through homing mechanisms (15, 17-19), to our knowledge, there has been no report of *H. pylori* playing a role in the development of lymphomas localized in the spleen with no evidence of gastric lymphoma. Search of similarities in the etiopathogenia of gastric MALT and splenic MZL has relied on the genetic evaluation of the tumor cells. The lack of t(11;18) but the presence of trisomy 3 or t(11;14) in splenic MZ lymphomas as compared with that observed in stomach MALT are some examples that indicate significant differences between the two histologies (20-23). The mechanism by which *H. pylori* is likely to induce proliferation of the gastric MALT lymphoma cells may be different from the one inducing splenic MZL. It could be speculated that a strong immune response against *H. pylori* involving an abnormal B-cell proliferation could lead to an increased chances for abnormal immunoglobulin gene rearrangements or to an uncontrolled cell survival (24). A similar mechanism has been proposed to explain the increased risk for B-cell lymphomas, and in particular splenic MZL in subjects chronically infected with hepatitis C virus (25, 26).

Previous epidemiologic studies systematically exploring a potential role of *H. pylori* in lymphomagenesis are scanty and have provided an overall estimate of no increased risk of lymphomas in the presence of *H. pylori* infection. Cuttner et al. (27) found that *H. pylori* seroprevalence was significantly higher for MALT lymphomas as compared with other lymphoma types, whereas Anttila et al. (28) did not identify an increase in the seroprevalence of IgG anti-*H. pylori* among patients with non-Hodgkin's lymphomas (OR = 0.8 95% CI = 0.4-1.9). No data were presented by lymphoma subtype.

The strong association between the prevalence of *H. pylori* among the control population and age that we have also observed could be partially explained by a cohort effect in which older people were more exposed to the infection due to poor water sanitation or infrequent use of antibiotics. In our population, it is suggested that people with lower socioeconomic status during childhood may have been more likely to have been exposed to *H. pylori* or may have had fewer chances to eradicate the infection. In the data presented, *H. pylori* prevalence was increased among people who reported a higher number of residencies during lifetime and among those sharing a bed with a sibling during childhood, both variables probably reflecting higher chances of contact with infected people. *H. pylori* prevalence was lower among people reporting more consumption of medicines or antibiotics during childhood as compared with their siblings. Although the biological significance of these associations is not fully understood, they indicate the relevance of the social environment as a determinant of *H. pylori* prevalence. As observed previously in other geographical settings, childhood social conditions may be an important determinant of *H. pylori* acquisition (29). Intake of antibiotics or medicines was taken into account in the analysis of lymphoma risk but no effect modification was observed (data not shown). As previously reported, *H. pylori* was not related to smoking or alcohol use (no data shown; refs. 30, 31).

Our data based on systematic inclusion of all lymphoid neoplasms showed that the proportion of B-cell lymphomas with an extranodal MALT histology was similar (5.6%) to the 7% to 8% reported in the WHO Classification. However, the proportion of splenic MZL (4.8%) within all B-cell lymphomas was much higher than the 1% estimated by WHO. This discrepancy is unlikely to be explained by differences in the *H. pylori* prevalence because our study population showed remarkable similarity with the prevalence observed in other European communities (31-33). Studies reporting on systematic inclusion of lymphoma cases using the WHO Classification in different geographical settings are referral series that do not clearly allow a reliable approximation of incidence rates (7, 34). Analysis of data from population-based cancer registries are needed to evaluate geographical differences of lymphoma subtypes.

Our study reflects a comparison between lymphoma cases and hospital controls. It could be argued that hospital controls may represent a biased population with higher prevalence of *H. pylori* than would be expected in the general population due to oversampling of patients with gastric or duodenal problems. However, the presence of patients selected from Gastroenterology departments was less than 5% of the overall population controls. Moreover, the prevalence estimate among controls is in concordance with other independent estimations in a close geographical area (35).

In conclusion, persistent infection with *H. pylori* may be implicated in the development of lymphomas of the

gastric mucosa and of the spleen. These results could have clinical implications in the management of splenic MZL lymphomas. Genetic characterization of these tumors in relation to *H. pylori* infection is warranted.

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