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ORIGINAL ARTICLE

Helicobacter pylori (*HP*) infection alone, but not *HP*-induced atrophic gastritis, increases the risk of gastric lymphoma: a case-control study in Japan

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Abstract

Infection with *Helicobacter pylori* (*H. pylori*) is associated with an increased risk of gastric malignant lymphoma. The chronic inflammation of gastric mucosa by *H. pylori* infection induces lymphomagenesis. Although this chronic mucosal inflammation also results in atrophic gastritis, evidence supporting the possible significance of atrophic gastritis in gastric lymphomagenesis is scarce. Here, to evaluate the association between gastric mucosal atrophy and the risk of gastric lymphoma, we conducted a matched case-control study at Aichi Cancer Center focusing on the attribution of *H. pylori* infection status and pepsinogen (PG) serum levels. In total, 86 patients with gastric lymphoma (including 49 cases of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) and 24 cases of diffuse large B cell lymphoma (DLBCL)) and 1720 non-cancer controls were included. Odds ratios (ORs) and 95% confidence intervals (CIs) were assessed by conditional logistic regression analysis with adjustment for potential confounders. Results failed to show a statistically significant association between atrophic gastritis and the risk of gastric lymphoma. The adjusted ORs of positive atrophic gastritis relative to negative for overall gastric lymphoma, MALT lymphoma, DLBCL, and other lymphomas were 0.77 (95% CI 0.45–1.33), 0.65 (0.30–1.39), 1.03 (0.38–2.79), and 0.84 (0.22–3.29), respectively. In contrast, a positive association between overall gastric lymphoma and *H. pylori* infection was observed (OR = 2.14, 95% CI 1.30–3.54). A consistent association was observed for MALT lymphoma, DLBCL, and other lymphomas with ORs of 1.96 (1.00–3.86), 1.92 (0.74–4.95), and 5.80 (1.12–30.12), respectively. These findings suggest that *H. pylori* infection triggers gastric lymphoma but that epithelial changes due to atrophic gastritis do not inherently affect the development of gastric lymphoma.

Keywords *Helicobacter pylori* · Gastric lymphoma · MALT lymphoma · Atrophic gastritis · Case-control study

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Introduction

Gastric malignant lymphoma accounts for 5–10% of all malignancies occurring in the stomach [1, 2]. The majority of primary gastric lymphomas are extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) and diffuse large B cell lymphoma (DLBCL). In some cases of DLBCL, components of MALT lymphoma are found in the same tissues. Peripheral T cell lymphoma, follicular lymphoma, and mantle cell lymphoma also occur in the stomach, but these types are rare [3].

More than 90% of gastric MALT lymphomas are associated with *H. pylori* and develop as a result of the chronic inflammation caused by *H. pylori* infection [4]. Previous studies, including ours, showed that *H. pylori* infection is associated with an increased risk of gastric malignant lymphoma

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[5–7]. In addition, our previous study showed that *H. pylori* infection was associated not only with MALT lymphoma but also with DLBCL [6].

Persistent infection with *H. pylori* causes prolonged chronic inflammation of the gastric mucosa, resulting in atrophic gastritis [8, 9]. With regard to gastric cancer, the risk of developing this cancer increases with the progression of atrophic gastritis [9, 10]. Pepsinogen (PG) can be used to serologically evaluate gastric mucosal atrophy. PG I and II are precursors of pepsin, a digestive enzyme produced in the mucosa of the stomach. When the gastric mucosa is atrophied due to *H. pylori* infection, PG I level and the PGI/II ratio decrease. Reflecting the increase in gastric cancer risk with the progression of gastric mucosal atrophy, the measurement of serum levels of PG in conjunction with *H. pylori* IgG testing has been found to be useful in gastric cancer screening [11–16]. In stark contrast, however, evidence for the association between gastric mucosal atrophy and gastric lymphoma, and between serum pepsinogen level and gastric lymphoma, is scarce.

Here, we evaluated the association of gastric mucosal atrophy with the risk of gastric lymphoma in a case-control study, with a focus on the attribution of *H. pylori* infection status and PG serum level.

Materials and methods

Study subjects

All subjects of the present study were enrolled in HERPACC-II (between January 2001 and November 2005) and HERPACC-III (between November 2005 and March 2013). Details of HERPACC have been described elsewhere [6, 17, 18]. In brief, HERPACC-II and HERPACC-III were conducted as self-administered questionnaire surveys among all first-visit outpatients, including both cancer and non-cancer patients, at Aichi Cancer Center Hospital (ACCH), Nagoya, Japan. The questionnaire included such items as height, weight, sleeping habits, exercise habits, drinking and smoking habits, dietary habits, medical history, reproductive history, family history (parents and brothers), and others. After participants responded to the questionnaire, the research nurse confirmed the content of responses. In addition, all participants were asked to provide a 7-mL blood sample. In HERPACC-II, 96.7% of 29,538 participants completed the questionnaire, of whom 50.7% provided a blood sample [18]. In HERPACC-III, 66.4% of 28,337 participants completed the questionnaire, of whom 62% provided a blood sample. The data were loaded into the HERPACC system of the ACCH and linked with the hospital-based cancer registry system to update the data on cancer incidence. Our previous research confirmed the consistency of the lifestyle of participants of HERPACC with that of ordinary citizens randomly selected from the area of Nagoya City, Aichi Prefecture {unpublished data: H. Ito, K. Matsuo, M. Inoue, K. Hirose, K. Tajima}. Accordingly, we used first-visit patients without cancer as a control for epidemiological studies. Informed consent was obtained from all individual participants included in the study, and the study was approved by the Ethics Committee of the Aichi Cancer Center.

Cases and controls

A total of 201 patients were histologically diagnosed with gastric lymphoma between January 2001 and March 2013 at ACCH by SN. The lymphoma subtypes were reclassified based on the WHO classification of 2008 by pathologists (NI, SK, and SN). We excluded 115 patients with a prior history of cancer or who declined blood sampling and eventually registered 86 patients with gastric lymphoma as cases (49 cases in HERPACC-II and 37 cases in HERPACC-III). Control subjects who were matched for sex and age at their first visit (± 2 years) were independently selected from among non-cancer outpatients included in the respective HERPACC-II and HERPACC-III datasets, with an overall case-control ratio set at 1:20, to maximize statistical power.

Assessment of exposure data

Of the items included in the HERPACC questionnaire, we obtained information about height and weight and smoking and drinking status as potential confounders based on the results of previous studies [19, 20]. Based on the reported height and weight, body mass index (BMI) was calculated as weight in kilograms divided by the height in meters squared and classified into the four categories of < 20.0, ≥ 20.0–< 22.5, ≥ 22.5–< 25.0, or ≥ 25.0. Smoking status was classified into four groups according to pack-years, defined as the product of the number of packs consumed per day and the number of years of smoking, namely as low (pack-years < 5), low-moderate ($5 \leq$ pack-years < 20), high-moderate ($20 \leq$ pack-years < 40), and heavy ($40 \leq$ pack-years). Non-smokers were classified as "low." Drinking status was classified into the four groups of non-drinker, and moderate, high-moderate, and heavy drinker, with those who seldom or never drank defined as non-drinkers. Moderate drinking was defined as consumption on 4 days or fewer per week. High-moderate drinking was defined as consumption of less than 46 g of ethanol on 5 or more days per week, and heavy drinking as consumption of more than 46 g ethanol on 5 or more days per week.

Evaluation of *H. pylori* infection and atrophic gastritis

The serum samples of the participants were immediately stored at − 20 °C until analysis. Serum IgG levels for *H. pylori* were measured using a commercially available direct enzyme-

linked immunosorbent assay (ELISA) kit (E Plate "Eiken" *H. pylori* Antibody, Eiken Chemical Co., Tokyo, Japan) in accordance with the manufacturer's instructions, with seropositive defined as an anti-*H. pylori* IgG antibody level greater than 10 U/mL in serum.

Atrophy of the gastric mucosa was evaluated by the measurement of serum PG using a chemiluminescence enzyme immunoassay. Gastric mucosa was defined as normal when serum PG I level ≥ 70 ng/mL and PG I/II ratio [serum PG I (ng/mL)/serum PG II (ng/mL)] > 3.0 [13, 14, 21]. All other cases were defined as atrophic gastritis. And, we defined the level of atrophic gastritis into three categories; (1+): PG I ≤ 70 ng/mL and PG I/II ratio ≤ 3.0; (2+): PG I ≤ 50 ng/mL and PG I/II ratio ≤ 3.0; (3+): PG I ≤ 30 ng/mL and PG I/II ratio ≤ 2.0.

Statistical analysis

The effect of *H. pylori* infection status and atrophic gastritis for the risk of gastric lymphoma was assessed in terms of the odds ratios (ORs) and 95% confidence interval (CIs) calculated with uni- and multivariable conditional logistic regression models. In multivariable model, all ORs and 95% CIs were adjusted for atrophic gastritis status (positive or negative), smoking status, drinking status, and BMI. P-heterogeneity was evaluated by Cochran's *Q* test to assess heterogeneity by meta-analysis of three subgroups (MALT, DLBCL, and other).

Statistical analyses were carried out using Stata version 14 (StataCorp LP, College Station, TX), and *p* values < 0.05 were considered statistically significant.

Results

Eighty-six gastric lymphoma cases and 1720 controls were used for analysis. Table 1 shows the distribution of cases and controls by background characteristics. Age and sex were well balanced between cases and controls, as were smoking status, drinking status, and BMI. Regarding histological subtype, 49 cases (57%) were MALT lymphoma, 24 (28%) were DLBCL, 3 (3%) were mantle lymphoma, 3 (3%) were follicular lymphomas, and 7 (8%) were other types of lymphoma. Four of the DLBCLs contained components of MALT lymphoma. This distribution of subtypes is consistent with previous reports in Japan [22–24]. Details of histological subtype are presented in Supplementary Table 1.

Table 2 shows the association between *H. pylori* infection and the risk of gastric lymphoma. We observed a positive association between overall gastric lymphoma and *H. pylori* infection (adjusted OR = 2.14 (95% CI 1.30–3.54)). Consistent associations were observed for MALT lymphoma, DLBCL, and other lymphomas (gastric lymphoma without MALT lymphoma and DLBCL), with ORs of 1.96 (95% CI 1.00–3.86), 1.92 (95% CI 0.74–4.95), and 5.80 (95% CI 1.12–30.12), respectively. We observed no difference in histology with respect to *H. pylori* infection, but the association with DLBCL appears less remarkable. Supplemental Table 2 shows the association between atrophic gastritis defined by pepsinogen and the risk of overall malignant lymphoma. We observed no significant

Table 1 Background characteristics of gastric lymphoma cases and controls

	Cases	Controls
Total	86	1720
Sex		
Male	56	1120
Female	30	600
Age (years)		
23–39	7	138
40–59	34	687
60–79	45	895
Smoking status[*1]		
Low	42	837
Low-moderate	15	206
High-moderate	8	314
Heavy	21	340
Unknown	0	23
Drinking status[*2]		
Non-drinker	34	622
Moderate	20	514
High-moderate	24	339
Heavy	8	235
Unknown	0	10
BMI (kg/m^2)		
< 20	11	292
≥ 20–< 22.5	22	502
≥ 22.5–< 25	31	549
≥ 25	21	361
Unknown	1	16
Histology		
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	49	
Diffuse large B cell lymphoma	20	
Diffuse large B cell lymphoma with MALT component	4	
Follicular lymphoma	3	
Mantle cell lymphoma	3	
Other types of lymphoma	7	

[*1] Low smoking was defined as 0 ≤ pack-years < 5; low-moderate smoking as 5 ≤ pack-years < 20; high-moderate smoking as 20 ≤ pack-years < 40; and heavy smoking as 40 ≤ pack-years

[*2] Moderate drinking was defined as consumption ≤ 4 days/week; high-moderate drinking as < 46 g ethanol and ≥ 5 days/week; and heavy drinking as ≥ 46 g ethanol and ≥ 5 days/week

Table 2 Association between *H. pylori* infection and gastric lymphoma

H. pylori status	Cases	Controls	OR1[*1]	95% CI	95% CI	*p* value	OR2[*2]	95% CI	95% CI	*p* value	p-heterogeneity[*3]
Overall											
Negative	32	906	1 (reference)				1 (reference)				0.467
Positive	54	814	1.97	1.24	3.13	0.004	2.14	1.30	3.54	0.003	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)											
Negative	20	527	1 (reference)				1 (reference)				–
Positive	29	453	1.77	0.96	3.27	0.066	1.96	1.00	3.86	0.051	
Diffuse large B cell lymphoma (including diffuse large B cell lymphoma with MALT component)											
Negative	9	248	1 (reference)				1 (reference)				–
Positive	15	232	1.79	0.76	4.20	0.18	1.92	0.74	4.95	0.178	
Other lymphomas											
Negative	3	131	1 (reference)				1 (reference)				–
Positive	10	129	3.90	0.98	15.48	0.053	5.80	1.12	30.12	0.037	

[*1] Univariable analysis in conditional logistic regression

[*2] Multivariable conditional logistic regression adjusted for atrophic gastritis status, smoking status, drinking status, and BMI

[*3] Evaluated by Cochran's Q test to assess heterogeneity by meta-analysis of three subgroups (MALT, DLBCL, and other)

association between the risks of malignant lymphoma across levels of atrophic gastritis (none; reference, (1+); OR = 1.24 (95% CI 0.55–2.81), (2+); OR = 0.71 (95% CI 0.30–1.68), (3+); OR = 1.63 (95% CI 0.80–3.29)).

Table 3 shows the adjusted ORs and 95% CIs for the association between atrophic gastritis and risk by lymphoma subtype. Compared with atrophic gastritis (−), the adjusted OR with atrophic gastritis (+) for overall, MALT lymphoma, DLBCL, and other lymphomas were 0.77 (95% CI 0.45–1.33), 0.65 (95% CI 0.30–1.39), 1.03 (95% CI 0.38–2.79), and 0.84 (95% CI 0.22–3.29), respectively, without statistical significance.

Table 3 Association between atrophic gastritis and gastric lymphoma

AG status	Cases	Controls	OR1[*1]	95% CI	95% CI	*p* value	OR2[*2]	95% CI	95% CI	*p* value	p-heterogeneity[*3]
Overall											
Negative	62	1263	1 (reference)				1 (reference)				0.395
Positive	23	453	1.04	0.62	1.73	0.886	0.77	0.45	1.33	0.347	
Unknown	1	4									
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)											
Negative	37	731	1 (reference)				1 (reference)				–
Positive	11	247	0.87	0.43	1.78	0.713	0.65	0.30	1.39	0.266	
Unknown	1	2									
Diffuse large B cell lymphoma (including diffuse large B cell lymphoma with MALT component)											
Negative	16	332	1 (reference)				1 (reference)				–
Positive	8	147	1.14	0.46	2.82	0.777	1.03	0.38	2.79	0.948	
Unknown	0	1									
Other lymphomas											
Negative	9	200	1 (reference)				1 (reference)				–
Positive	4	59	1.54	0.44	5.36	0.497	0.84	0.22	3.29	0.806	
Unknown	0	1									

[*1] Univariable analysis in conditional logistic regression

[*2] Multivariable conditional logistic regression adjusted for atrophic gastritis status, smoking status, drinking status, and BMI

[*3] Evaluated by Cochran's Q test to assess heterogeneity by meta-analysis of three subgroups (MALT, DLBCL, and other)

Discussion

In this study, we failed to observe an association between atrophic gastritis and the risk of gastric lymphoma. In contrast, as expected, *H. pylori* infection was associated with an increased risk of overall gastric lymphoma. Furthermore, this association with *H. pylori* infection was consistently observed with MALT lymphoma, DLBCL, and other lymphomas.

This finding of an increased risk of overall gastric lymphoma in *H. pylori*–positive subjects (OR = 2.14) is consistent with the results of previous studies [6, 7, 21] and indicates that *H. pylori* infection plays an essential role in lymphomagenesis in the stomach. In addition, the consistent association with gastric MALT lymphoma and DLBCL (OR = 1.96 and 1.92, respectively) might indicate that the two histological subtypes share the same *H. pylori*–associated mechanism. The results of this study are consistent with the literature, suggesting that *H. pylori* is the causative factor of gastric MALT lymphoma and DLBCL [25].

H. pylori infection in the stomach causes chronic gastritis. Gastric mucosal atrophy and intestinal metaplasia occur as a consequence of long-lasting inflammation [5, 26]. Regarding gastric cancer, severe atrophic gastritis with intestinal metaplasia has been shown to confer a high risk of intestinal-type gastric cancer [5]. We observed the association between the risk of gastric lymphoma and *H. pylori* infection, while we did not observe any significantly association with atrophic gastritis even considering the levels of severity of atrophy in this study. Our results indicate that epithelial changes do not directly affect the development of lymphoma in contrast to gastric cancer. This might be simply explained by the fact that lymphoma arises after neoplastic change in lymphocytes. For example, gastric MALT lymphoma was shown to occur from MALT (mucosa-associated lymphoid tissue), which was acquired by *H. pylori* infection-induced chronic inflammation [2]. In gastric MALT lymphoma, complete remission is clinically obtained in 78% of cases by *H. pylori* eradication therapy [27]. There is a report that showed the efficacy of eradication therapy for *H. pylori*-positive DLBCL (with or without MALT component) in the gastric localized stage [28]; however, a confirmation in prospective clinical trials are needed.

Taken together, these findings indicate that chronic inflammation due to *H. pylori* infection is of sole importance in the development of MALT lymphoma and perhaps other types of lymphoma in the stomach. In other words, atrophic change in the gastric mucosa is of no biological significance in the process of lymphomagenesis.

In MALT lymphoma, a marked inverse association was observed for atrophic gastritis, albeit without statistical significance (adjusted OR = 0.65). One possible explanation for this inverse association is that severe atrophic gastritis with intestinal metaplasia leads to decreased formation of lymphoid follicles compared with usual gastric mucosa. It is known that the local immunity in the gastric intestinal metaplasia owes to secretory IgA rather than IgG from lymphoid follicles in gastric mucosa [29]. The risk of MALT lymphoma in severe atrophic gastritis with intestinal metaplasia is therefore presumed to decrease as a consequence of the alleviated inflammation and lack of formation of lymphoid follicles leading to MALT.

Our study has several methodological strengths. First, potential confounding by age, sex, smoking, and drinking was considered by matching in the study design and by multivariable analysis. Therefore, our findings for atrophic gastritis and *H. pylori* infection were independent of these factors. Secondly, we employed a high case-control ratio to increase statistical power as well as to avoid random error.

There are also several potential limitations of our study. First, we used a hospital-based case-control design, so there may have been some selection bias. However, the non-cancer controls of this study were selected from HERPACC-II and HERPACC-III studies, namely from the same population base as the cases. It is therefore reasonable to assume the internal validity of the study. Second, information on smoking and drinking status was collected by self-administered questionnaire, leaving the possibility of recall bias. However, the HERPACC test design requires the completion of the questionnaire before diagnosis, likely minimizing recall bias. Thirdly, we evaluated atrophic gastritis by pepsinogen levels, but there remains controversy of its usefulness in clinical setting. Therefore, this could be a limitation. However, taken the study design and size of population in mind, it is not feasible to evaluate atrophic gastritis histologically.

In conclusion, we confirmed that *H. pylori* infection triggers gastric lymphoma but that epithelial changes (atrophic gastritis) associated with chronic *H. pylori* infection do not inherently affect the development of gastric lymphoma.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval and consent to participate All procedures performed in this study involving human participants have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards of the institutional Ethics Committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

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