


ORIGINAL ARTICLE

Nodular gastritis in association with gastric cancer development before and after *Helicobacter pylori* eradication

Izumi Nishikawa,*  Jun Kato,[†] Satoshi Terasoma,* Hiroyoshi Matsutani,* Hidehiko Tamaki,* Tetsuya Tamaki,* Fumiaki Kuwashima,* Hiroya Nakata,[‡] Tatsuji Tomeki,* Hideyuki Matsunaka,* Yumiko Ibata,* Yasunobu Yamashita,[†] Takao Maekita,[†] Katsuhiko Higashi* and Masao Ichinose[†]

*First Department of Internal Medicine, Hidaka General Hospital, [†]Second Department of Internal Medicine, Wakayama Medical University and [‡]Nakata Medical Clinic, Wakayama, Japan

Key words

eradication, gastric cancer, gastritis, *Helicobacter pylori*.

Accepted for publication 23 February 2018.

Correspondence

Izumi Nishikawa, First Department of Internal Medicine, Hidaka General Hospital, 116-2 Sono, Gobo City, Wakayama 644-0002, Japan.

Email: hidaka-naishiky@hidakagh.gobo.wakayama.jp

Declaration of conflict of interest: None.

Financial support: No funding or financial support was received.

Abstract

Background and Aim: Nodular gastritis is caused by *Helicobacter pylori* infection and is associated with the development of diffuse-type gastric cancer. This study examined the clinical characteristics of patients with nodular gastritis, including cancer incidence before and after *H. pylori* eradication.

Methods: This was a retrospective study of patients who underwent upper endoscopy and were positive for *H. pylori* infection. We examined the clinical findings and follow-up data after *H. pylori* eradication in patients with and without nodular gastritis.

Results: Of the 674 patients with *H. pylori* infections, nodular gastritis was observed in 114 (17%). It was more prevalent in women (69%) and young adults. Among patients with nodular gastritis, six (5%) had gastric cancer, all of which were of the diffuse type. Among the 19 (4%) patients with gastric cancer and no nodular gastritis, 16 had intestinal-type cancer. White spot aggregates in the corpus, a specific finding in patients with nodular gastritis, were more frequently observed in patients with gastric cancer than in those without (83% vs 26%, $P = 0.0025$). Of 82 patients with nodular gastritis who had *H. pylori* eradicated successfully, none developed gastric cancer over a 3-year follow-up period, while 7 (3%) of 220 patients without nodular gastritis developed gastric cancer after *H. pylori* eradication.

Conclusions: In patients with nodular gastritis, white spot aggregates in the corpus may indicate a higher risk of developing diffuse-type gastric cancer. Nodular gastritis may be an indication for eradication therapy to reduce the risk of cancer development after *H. pylori* eradication.

Introduction

Eastham *et al.* initially reported nodular gastritis (NG) in 1988. Endoscopic features of NG, highlighted by indigo-carmin dye spraying, show antral nodularity. Histological examination of antral nodularity showed infiltration of inflammatory cells, with large and superficially located lymphoid follicles.^{1–8}

NG is considered a specific, but insensitive, endoscopic marker for gastric *Helicobacter pylori* (*H. pylori*) infection, which mostly occurs in children.¹ Recent studies have shown that NG also manifests in adults, particularly in women and young adults, and is strongly associated with *H. pylori* infection.^{2–4,9}

Observational studies of Japanese adults with NG have suggested an association with gastric cancer, particularly diffuse-type gastric cancer.^{3,5,10,11} However, the biological and epidemiological associations between NG and cancer development are largely unknown. Few reports exist on the differences in clinical

course and cancer development between patients with *H. pylori* infections with and without NG.

In this study, we examined the clinical characteristics of patients with *H. pylori* infections, including endoscopic findings, cancer development, and follow-up data after *H. pylori* eradication, particularly focusing on the presence or absence of NG.

Methods

Patients. We completed a retrospective chart review of patients who underwent esophagogastroduodenoscopy (EGD) at Hidaka General Hospital between January 2006 and December 2014, focusing on differences between patients with and without NG. All patients lived in the Wakayama prefecture, in the southwestern part of Japan, where gastric cancer is prevalent. Eligible criteria were age 20 years or older and suffering from a *H. pylori* infection at the time of EGD. *H. pylori* status was not uniformly

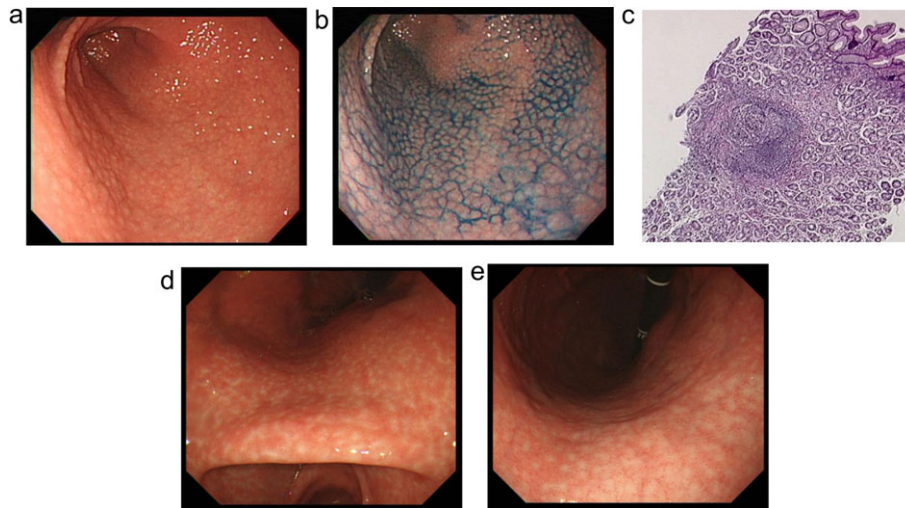


Figure 1 Endoscopic appearance and pathological features of nodular gastritis. (a) and (b) are typical endoscopic images of nodular gastritis (NG). (a) An unusual miliary pattern resembling “gooseflesh” in the antrum. (b) Antral nodularity is highlighted with chromoendoscopy using indigo-carmin dye spraying. (c) A pathological finding of biopsy specimens from NG. Pathological findings from biopsy specimens are characterized by superficially located prominent lymphoid follicles with a germinal center (hematoxylin and eosin staining). (d) and (e) White spot aggregates in gastric corpus (corpus white spots: CWS) in a patient with NG.

examined for patients with EGD. However, patients suspected of *H. pylori* infection due to specific EGD findings, including peptic ulcer, atrophic gastritis, intestinal metaplasia, gastric cancer, and NG, were examined. Patients who requested *H. pylori* examinations were examined regardless of EGD findings.

Exclusion criteria were history of stomach surgery; history of *H. pylori* eradication therapy; and medications with potential gastrointestinal effects, including proton pump inhibitors, H₂ receptor antagonists, corticosteroids, and nonsteroidal anti-inflammatory drugs. The study design was approved by the ethics committee of Hidaka General Hospital and was reviewed annually.

Evaluation of EGD. EGD was performed by endoscopists with at least 7 years' experience of upper endoscopy, using a videoscope (GIF-H260, Q260, XQ260, or XP260N; Olympus, Tokyo, Japan). Both transnasal and transoral approaches were allowed. Chromoendoscopy with 0.2% indigo carmine was applied if needed. The endoscopic definition of NG is a form of antral gastritis characterized by an unusual miliary pattern resembling so-called “gooseflesh” (Fig. 1a,b). If NG was not definite on endoscopic appearance alone, we obtained biopsy specimens to confirm the presence of superficially located and prominent lymphoid follicles (Fig. 1c). As some patients with NG show white spot aggregates in the corpus (corpus white spots: CWS) (Fig. 1d,e), the presence or absence of this was also noted.

In addition to the diagnosis of the presence or absence of NG, we noted clinically relevant findings, including gastric cancer, peptic ulcers, gastric erosions, hyperplastic polyps, gastric submucosal tumors, gastroesophageal reflux disease, and atrophic gastritis. The severity of atrophy was classified as closed or open type according to the Kimura–Takemoto endoscopic classification system for chronic gastritis.^{12,13} Closed-type atrophy

indicates that the leading edge of the atrophic border, starting from the greater curvature of the antrum, lies in the lesser curvature. Open-type atrophy indicates that the leading edge of the atrophic border is invisible on the lesser curvature, and the atrophic area is widespread on endoscopy, with the border extended toward the greater curvature. Gastric cancer was histopathologically assessed based on biopsy or resected specimens and classified as intestinal or diffuse type, according to the classification described by Laurén.¹⁴ Furthermore, gastric cancer was morphologically categorized as either superficial or advanced type based on the Japanese classification of gastric carcinoma: third English edition.¹⁵

All endoscopic reports and digitally stored images were reevaluated by two endoscopy specialists to confirm the presence or absence of NG and CWS.

Evaluation and eradication of *H. pylori*. We examined *H. pylori* infection status using serum-specific IgG *H. pylori* antibodies with an enzyme immunoassay kit (SRL, Tokyo, Japan), the ¹³C-urea breath test, and/or a rapid urease test (CLO test; Serim Research Corp., Elkhart, Indiana, USA). When one or more tests were positive, the patient was determined to be positive for *H. pylori* infection.

We recommended eradication therapy for patients with *H. pylori* infection, including NG, but the decision to receive treatment was up to each patient. Those who opted for treatment received one week of triple therapy with clarithromycin 200 mg, amoxicillin 750 mg, and a proton pump inhibitor (lansoprazole 30 mg, omeprazole 20 mg, or rabeprazole 10 mg) twice daily as the first-line regimen. We confirmed the results of the eradication therapy through the ¹³C-urea breath test 6–8 weeks after the regimen was completed. If the first eradication was unsuccessful, the patient underwent second-line eradication. This consisted of

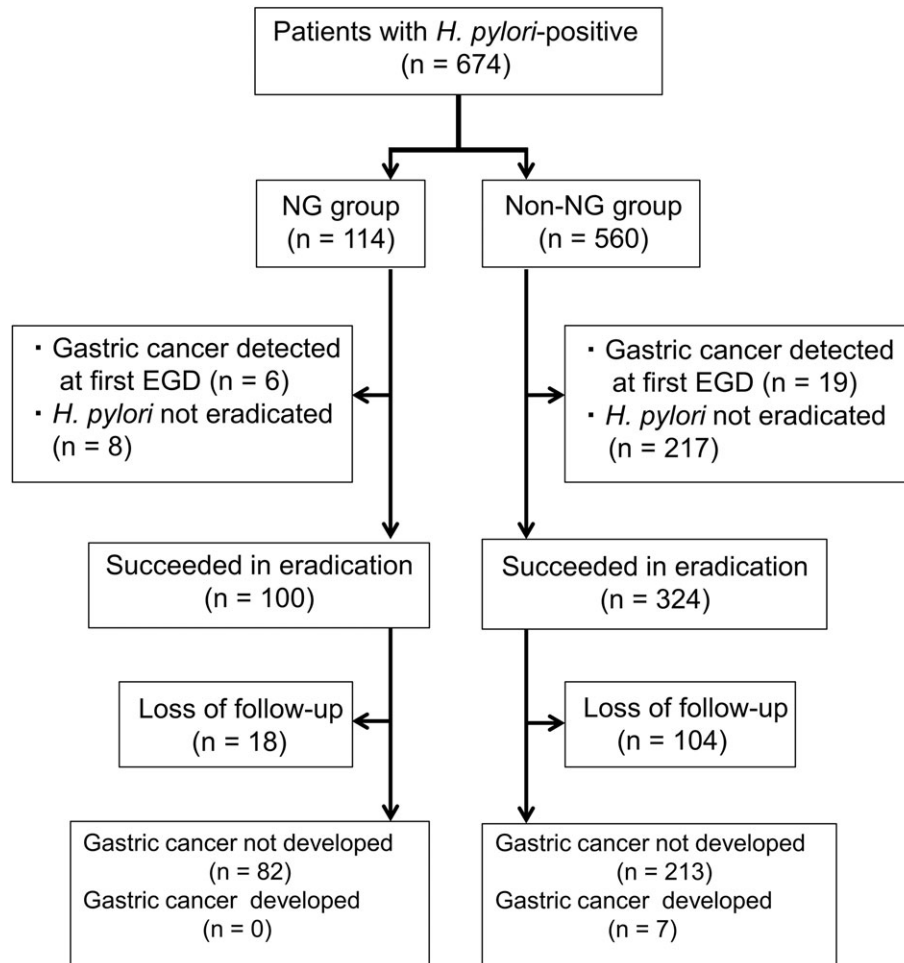


Figure 2 A schematic follow-up of study subjects. EGD, esophagogastroduodenoscopy; *H. pylori*, *Helicobacter pylori*; NG, nodular gastritis.

metronidazole (500 mg/day) instead of clarithromycin. Patients who failed second-line eradication therapy did not receive any further eradication regimens.

Follow-up of patients. Patients who had successful eradication therapy were followed up with EGD every 12 months. We calculated the observation period for each patient from the time of successful eradication to the time of diagnosis of gastric cancer or to the time of last surveillance.

Statistical analysis. Continuous variables were expressed as median (range), while categorical variables were presented as absolute values and percentages. We analyzed differences between continuous variables using the Mann–Whitney *U*-test, and the differences between categorical variables were analyzed using the chi-square test or Fisher's exact test. A *P* value <0.05 was considered statistically significant. Statistical analyses were performed with JMP 13 software (SAS Institute, Cary, NC, USA).

Results

Clinical characteristics of patients. Between January 2006 and December 2014, 674 patients underwent EGD with positive results for *H. pylori* infection. Of these, 114 exhibited NG, while the remaining 560 did not. Study flow is depicted in Figure 2, and clinical profiles of subjects within the two groups are shown in Table 1. Patients with NG were significantly younger than those without (48.5 [23–78] years vs 63.0 [23–94] years, *P* < 0.0001). In addition, more female patients had NG (69% vs 41%, *P* < 0.0001) than male patients. Age distributions of patients with and without NG, according to gender, are shown in Figure 3. Few patients with NG were male and older than 40 years. We did not observe this tendency with female patients. The majority of patients with *H. pylori* infections, with and without NG, showed atrophic gastritis. The degree of atrophic grade in NG subjects was significantly milder than those subjects without NG (*P* < 0.0001).

Gastric cancer in patients with NG. Of those with NG, six patients (5%) had gastric cancer (Table 2). Of these, five were females, and all cancers were diffuse-type adenocarcinoma

Table 1 Characteristics of study subjects and endoscopic findings

	<i>Helicobacter pylori</i> -positive		<i>P</i> -value
	Non-NG subjects	NG subjects	
Subjects			
Cases (<i>n</i>)	560	114	—
Median age (range) (year)	63 (23–94)	48.5 (23–78)	<0.0001
Gender (%)			
Male	329 (59)	35 (31)	—
Female	231 (41)	79 (69)	<0.0001
Purpose of EGD (%)			
Epigastric pain	171 (31)	57 (50)	0.0001
Cancer screening	241 (43)	31 (27)	0.0017
Nausea	54 (10)	14 (12)	0.39
Anemia	46 (8)	1 (1)	0.0051
Others	48 (8)	11 (10)	0.71
Endoscopic main findings (%)			
Gastric cancer	19 (4)	6 (5)	0.34
Intestinal-type	16 (3)	0 (0)	—
Diffuse-type	3 (1)	6 (5)	0.0002
Peptic ulcer	220 (39)	27 (24)	0.0016
Gastric ulcer	147 (26)	19 (17)	0.030
Duodenal ulcer	73 (13)	8 (7)	0.072
Gastric erosion	28 (5)	4 (3)	0.49
Hyperplastic polyps	19 (3)	0 (0)	0.046
Gastric submucosal tumor	3 (1)	2 (2)	0.17
Gastroesophageal reflux disease	18 (3)	0 (0)	0.052
Atrophic gastritis	253 (45)	75 (66)	0.001
Atrophic grade			
Nonatrophic	6 (1)	11 (10)	—
Closed-type	174 (31)	70 (61)	<0.0001
Open-type	380 (68)	33 (29)	—

Atrophic grade: according to Kimura–Takemoto classification.

EGD, esophagogastroduodenoscopy; NG, nodular gastritis.

localized to the corpus. A total of 19 (4%) patients without NG had gastric cancer; 12 were male, 10 had the cancer located in the antrum, and 16 had intestinal gastric cancer. Cancer involving NG developed more frequently in females and was more likely to be diffuse-type gastric cancer ($P = 0.0002$).

In patients with NG, we compared those who had gastric cancer with those who did not (Table 3). CWS was more frequently observed in patients with gastric cancer than in those without (83% vs 26%, $P = 0.0025$), suggesting that this finding is associated with cancer development from NG. No significant differences were observed in other endoscopic findings, including atrophic grade, peptic ulcer, and hyperplastic polyp, between patients with NG who had and did not have gastric cancer.

Treatment of *H. pylori* infection and follow-up.

Patients with and without NG post-*H. pylori* eradication were followed up after initial EGD (Fig. 2). Of 108 patients with NG who did not have gastric cancer, 100 underwent successful eradication of *H. pylori*. However, of the 541 patients without NG who did not have gastric cancer, 324 underwent successful eradication of *H. pylori*. Analysis of demographic factors, including age, gender, comorbidities, and atrophic grade, in patients

receiving the follow-up (82 with NG and 220 without NG) was performed, and the results were not so different from those for the whole cohort (Table S1, Supporting information).

Of the 82 subjects with NG who were seen for follow-up, none developed gastric cancer (mean observation period, 42.6 ± 28.3 months). In contrast, of 220 subjects without NG who were seen during follow-up (mean observation period, 35.1 ± 28.5 months), 7 (3%) developed gastric cancer (male = 5, female = 2; five subjects had intestinal-type cancers, and two had diffuse-type cancer). Among the 32 patients with gastric cancer at initial EGD or throughout the follow-up, 6 developed from NG and 26 from non-NG. Cancer from NG was more likely to be observed in younger subjects ($P = 0.0037$), in females ($P = 0.030$), and in patients with a lower atrophic grade ($P = 0.0089$), dominantly presenting diffuse-type pathology ($P = 0.0002$). Meanwhile, in comparing 7 patients who developed gastric cancer during the follow-up period with 295 patients who did not, the former was significantly older than the latter ($P = 0.003$) (Table S2). These results suggest that patients with NG have a lower risk of developing gastric cancer after *H. pylori* eradication.

Discussion

This study confirmed the results of previous reports regarding NG, including prevalence in females and young adults and susceptibility to diffuse-type gastric cancer. In addition, we report

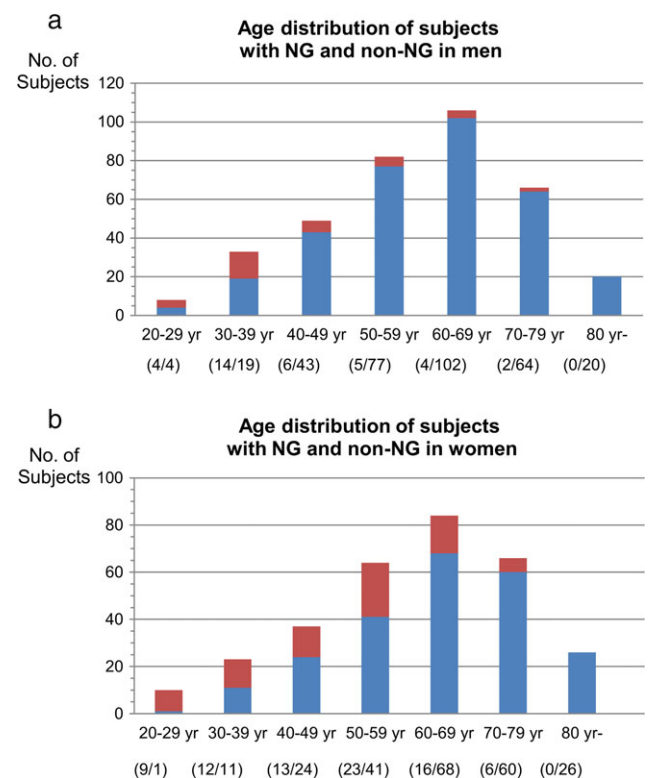


Figure 3 Age distribution of subjects with nodular gastritis (NG) and non-NG in men (a) and in women (b). HP, *Helicobacter pylori*. (■) HP(-); (■) HP(+)/NG(+).

Table 2 Gastric cancer in patients with NG

	Age (year)	Gender	Location	Size (mm)	Morphological type	Histopathological type	Atrophic grade	CWS
Case 1	35	Female	Corpus	>50	Type 4	Diffuse-type	Open	+
Case 2	50	Female	Corpus	4	0-IIc	Diffuse-type	Closed	+
Case 3	51	Female	Corpus	15	0-IIc	Diffuse-type	Closed	+
Case 4	55	Female	Antrum	20	0-IIc	Diffuse-type	Open	+
Case 5	61	Female	Corpus	30	0-IIc	Diffuse-type	Closed	+
Case 6	61	Male	Corpus	8	0-IIc	Diffuse-type	Closed	–

Atrophic grade: according to Kimura–Takemoto classification.

CWS, corpus white spots; NG, nodular gastritis.

that new insights regarding NG-related cancer development can be obtained with meticulous endoscopic observations and follow-up of patients after *H. pylori* eradication. The presence of CWS was found to be a risk factor for cancer development, and *H. pylori* eradication was highly effective for the risk reduction of cancer development. Use of *H. pylori*-positive and NG-negative control subjects and collection of follow-up data after *H. pylori* eradication were the strengths of this investigation.

NG was previously considered to be a specific finding in children with *H. pylori* infections.^{6,7,16} However, recent reports indicated that NG is occasionally observed in adults with *H. pylori* infections,^{3,4,8} particularly in women and young adults. More recently, NG was observed in elderly subjects. Niknam *et al.* reported 258 adult cases of patients with NG, including 35 (14%) who were 60 years or older.¹⁷ Nakamura *et al.* reported on 58 patients with NG who were at least 20 years old and found that 17 (29%) were 60 years or older.⁸ The percentage of older patients in our cohort (25%) was consistent with previous reports. Our data indicated that a relatively high percentage of *H. pylori*-infected patients exhibited NG, particularly young women. Examination for NG in older patients may alter the clinical course, in association with cancer development after *H. pylori* eradication, in those patients.

NG relates to cancer susceptibility. In this study, six (5%) cases of gastric cancers, all of which were of the diffuse type, were observed in patients with NG. Previous reports indicate that NG is a risk factor for the development of diffuse-type gastric cancer in the gastric corpus,^{3,9–11,18,19} and our results were in line with those of previous reports. NG appears to increase the risk of developing diffuse-type cancer due to highly active gastric inflammation and lower levels of atrophy. Watanabe *et al.* indicated that mucosal inflammation relates to carcinogenesis for patients with *H. pylori*-infected nonatrophic stomach and that higher activity of mucosal inflammation is associated with a higher risk of cancer, particularly diffuse-type cancer with higher malignant potential.²⁰ In this context, Yoshida *et al.* reported that both a higher pepsinogen II level due to active gastric inflammation and the absence of extensive atrophy were risk factors for the development of diffuse-type gastric cancer.²¹ Moreover, Uemura *et al.* reported that many of the patients with diffuse-type gastric cancer had moderate atrophic changes and pangastritis.²²

According to our results, the grade of atrophy in subjects with NG was likely to be lower, regardless of age. In addition, previous studies reported that active inflammation was observed in the corpus mucosa of patients with NG.³ NG appears to be a

specific endoscopic finding, histologically reflective of highly active inflammation with mild atrophy, both of which are risk factors for developing diffuse-type cancer.

No cancer was observed in patients with NG who completed *H. pylori* eradication, while in the seven without NG (3%), cancer developed. The higher rate of gastric cancer development after eradication compared to those of the previous studies (1–2%)^{23,24} may be due to the older age of our patients (61.4 years; more than 10 years older than those of previous reports). Although *H. pylori* infection is related to both intestinal- and diffuse-type cancer,^{22,25} the effect of *H. pylori* eradication on preventing gastric cancer remains controversial. Moreover, the difference in the cancer-preventive effects of *H. pylori* eradication according to cancer histology has scarcely been reported. Takenaka *et al.* reported that patients, post-*H. pylori* eradication, had reduced incidence of gastric cancer, particularly intestinal type, compared to patients with persistent *H. pylori*.²⁶ Take *et al.* reported that diffuse-type cancer was observed only in patients post-*H. pylori* eradication but not in patients where *H. pylori* persisted.²⁷ However, these results may be biased. The cohorts of both Takenaka's and Take's studies consisted mostly of male subjects (two-thirds of Takenaka's population was composed of males, and Take's population had approximately 10 times more males than females). In contrast, two-thirds of our patients with NG (55/84) were female. Diffuse-type cancer is more prevalent in women than in men,^{28,29} and therefore, the gender bias is a critical consideration for outcomes analyses. Our findings clearly demonstrated that *H. pylori* eradication in patients with NG was effective at preventing diffuse-type cancer; however, longer follow-up studies are warranted.

Table 3 NG patients with and without gastric cancer

	NG with gastric cancer	NG without gastric cancer	<i>P</i> -value
Cases (<i>n</i>)	6	108	
Median age (range) (year)	53 (35–61)	45.5 (23–78)	0.51
Gender (%)			0.66
Male	1 (17)	34 (31)	
Female	5 (83)	74 (69)	
Atrophic grade (%)			0.075
Closed-type	4 (67)	77 (71)	
Open-type	2 (33)	31 (29)	
CWS (%)	5 (83)	28 (26)	0.0025

Atrophic grade: according to Kimura–Takemoto classification.

CWS, corpus white spots; NG, nodular gastritis.

Previous studies have shown that rugal hyperplastic gastritis (RHG) is also characterized by highly active inflammation in the corpus of the nonatrophic stomach. RHG increases the risk of diffuse-type gastric cancer, particularly of the gastric corpus.^{20,30,31} *H. pylori* eradication for the prevention of diffuse-type cancer in patients with RHG has also been suggested. NG and RHG share several features. Both are characterized by increased *H. pylori*-induced inflammatory cell infiltration in the gastric corpus.^{3,20} Second, both display less atrophic change, lower gastric acid secretion, and high concentrations of serum pepsinogen II and gastrin.^{3,20} Finally, eradicating *H. pylori* improves the nodularity and hypertrophy.^{3,32,33} Therefore, NG and RHG harbor common biological characteristics associated with gastric inflammation and gastric cancer development. Because RHG mostly affects men,^{34,35} RHG may, in effect, be a male version of NG.

A striking result of this study was the link between CWS and risk of cancer development in patients with NG. The histological findings of CWS, examined via surgical specimens, included hyperplasia of lymphoid follicles with intense mucosal inflammation, similar to NG. Patients with NG and CWS have highly active inflammation of the corpus, which is implicated in the development of diffuse-type cancer. Consequently, the presence of CWS, observed during upper endoscopy for patients with NG, should be dutifully noted. Patients who display CWS should undergo urgent *H. pylori* eradication therapy.

This study had several limitations. First, the study was a retrospective analysis performed at a single center; our results should be validated in diverse settings for generalizability. In particular, no development of gastric cancer in patients with NG during the follow-up may be related to younger age or female dominance. The lack of the statuses of alcohol and smoking in our patients may also be a drawback. Second, the status of *H. pylori* infection was not consistently examined in patients undergoing EGD at our hospital, and therefore, an inclusion bias is possible. In addition, the diagnosis of *H. pylori* infection might not be very accurate in our study because positivity could be determined based on one test result. Third, NG was diagnosed based on endoscopic findings, without histopathological confirmation each time. In clinical practice, however, endoscopic findings are more relevant than histological findings due to the relative ease with which they are obtained. Last, the lower rate of gastric cancer development with NG may be related to younger age or female gender.

In conclusion, NG was relatively more frequently observed in older subjects with *H. pylori* infection, and CWS may indicate patients at a higher risk for diffuse-type gastric cancer development. The fact that no cancers developed in patients with NG after *H. pylori* eradication suggests that findings of NG on endoscopy are indications for eradication therapy. Prospective studies are required to verify the findings of this study.

References

- Eastham EJ, Elliott TSJ, Berkeley D, Jones DM. *Campylobacter pylori* infection in children. *J. Infect.* 1988; **16**: 77–9.
- Sbeih F, Abdullah A, Sullivan S, Merenkov Z. Antral nodularity, gastric lymphoid hyperplasia, and *Helicobacter pylori* in adults. *J. Clin. Gastroenterol.* 1996; **22**: 227–30.
- Miyamoto M, Haruma K, Yoshihara M *et al.* Nodular gastritis in adults is caused by *Helicobacter pylori* infection. *Dig. Dis. Sci.* 2003; **48**: 968–75.
- Shiotani A, Kamada T, Kumamoto M *et al.* Nodular gastritis in Japanese young adults.: endoscopic and histological observations. *J. Gastroenterol.* 2007; **42**: 610–15.
- Kamada T, Hata J, Tanaka A *et al.* Nodular gastritis and gastric cancer. *Dig. Endosc.* 2006; **18**: 79–83.
- Bujanover Y, Konikoff F, Baratz M. Nodular gastritis and *Helicobacter pylori*. *J. Pediatr. Gastroenterol. Nutr.* 1990; **11**: 41–4.
- Czinn SJ, Dahms BB, Jacobs GH, Kaplan B, Rothstein FC. *Campylobacter*-like organisms in association with symptomatic gastritis in children. *J. Pediatr.* 1986; **109**: 80–3.
- Nakamura S, Mitsunaga A, Imai R *et al.* Clinical evaluation of nodular gastritis in adults. *Dig. Endosc.* 2007; **19**: 74–9.
- Haruma K, Komoto K, Kamada T *et al.* *Helicobacter pylori* infection is a major risk factor for gastric carcinoma in young patients. *Scand. J. Gastroenterol.* 2000; **35**: 255–9.
- Kamada T, Haruma K, Sugi K *et al.* Case of early gastric cancer with nodular gastritis. *Dig. Endosc.* 2004; **16**: 39–43.
- Kitamura S, Yasuda M, Mugeruma N *et al.* Prevalence and characteristics of nodular gastritis in Japanese elderly. *J. Gastroenterol. Hepatol.* 2013; **28**: 1154–60.
- Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy.* 1969; **3**: 87–97.
- Kimura K. Chronological transition of the fundic-pyloric border determined by stepwise biopsy of the lesser and greater curvatures of the stomach. *Gastroenterology.* 1972; **63**: 584–92.
- Laurén P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma: an attempt at a histological classification. *Acta Pathol. Microbiol. Scand.* 1965; **64**: 31–49.
- Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer.* 2011; **14**: 101–12.
- Hassall E, Dimmick JE. Unique features of *Helicobacter pylori* disease in children. *Dig. Dis. Sci.* 1991; **36**: 417–23.
- Niknam R, Manafi A, Maghbool M, Kouhpayeh A, Mahmoudi L. Is endoscopic nodular gastritis associated with premalignant lesions? *Neth. J. Med.* 2015; **73**: 236–41.
- Miyamoto M, Haruma K, Yoshihara M *et al.* Five cases of nodular gastritis and gastric cancer: a possible association between nodular gastritis and gastric cancer. *Dig. Liver Dis.* 2003; **34**: 819–20.
- Kamada T, Tanaka A, Yamanaka Y *et al.* Nodular gastritis with *Helicobacter pylori* infection is strongly associated with diffuse-type gastric cancer in young patients. *Dig. Endosc.* 2007; **19**: 180–4.
- Watanabe M, Kato J, Inoue I *et al.* Development of gastric cancer in nonatrophic stomach with highly active inflammation identified by serum levels of pepsinogen and *Helicobacter pylori* antibody together with endoscopic rugal hyperplastic gastritis. *Int. J. Cancer.* 2012; **131**: 2632–42.
- Yoshida T, Kato J, Inoue I *et al.* Cancer development based on chronic active gastritis and resulting gastric atrophy as associated by serum levels of pepsinogen and *Helicobacter pylori* antibody titer. *Int. J. Cancer.* 2014; **134**: 1445–57.
- Uemura N, Okamoto S, Yamamoto S *et al.* *Helicobacter pylori* infection and the development of gastric cancer. *N. Engl. J. Med.* 2001; **345**: 784–9.
- Wong BC, Lam SK, Wong WM *et al.* *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA.* 2004; **291**: 187–94.
- Take S, Mizuno M, Ishiki K *et al.* The long-term risk of gastric cancer after the successful eradication of *Helicobacter pylori*. *J. Gastroenterol.* 2011; **46**: 318–24.

- 25 Huang JQ, Sridhar S, Chen Y, Hunt RH. Meta-analysis of the relationship between *Helicobacter pylori* seropositivity and gastric cancer. *Gastroenterology*. 1998; **114**: 1169–79.
- 26 Takenaka R, Okada H, Kato J *et al.* *Helicobacter pylori* eradication reduced the incidence of gastric cancer, especially of the intestinal type. *Aliment. Pharmacol. Ther.* 2007; **25**: 805–12.
- 27 Take S, Mizuno M, Ishiki K *et al.* The effect of eradicating *Helicobacter pylori* on the development of gastric cancer in patients with peptic ulcer disease. *Am. J. Gastroenterol.* 2005; **100**: 1037–42.
- 28 Yoshimura T, Shimoyama T, Fukuda S, Tanaka M, Axon ATR, Munakata A. Most gastric cancer occurs on the distal side of the endoscopic atrophic border. *Scand. J. Gastroenterol.* 1999; **34**: 1077–81.
- 29 Eto K, Ohya S, Yamaguchi T *et al.* Familial clustering in subgroups of gastric cancer stratified by histology, age group and location. *Eur. J. Surg. Oncol.* 2006; **32**: 743–8.
- 30 Murayama Y, Miyagawa J, Shinomura Y *et al.* Morphological and functional restoration of parietal cells in *Helicobacter pylori* associated enlarged fold gastritis after eradication. *Gut*. 1999; **45**: 653–61.
- 31 Stolte M, Bätz CH, Bayerdörffer E, Eidt S. *Helicobacter pylori* eradication in the treatment and differential diagnosis of giant folds in the corpus and fundus of the stomach. *Z. Gastroenterol.* 1995; **33**: 198–201.
- 32 Yasunaga Y, Shinomura Y, Kanayama S *et al.* Increased production of interleukin 1 β and hepatocyte growth factor may contribute to foveolar hyperplasia in enlarged fold gastritis. *Gut*. 1996; **39**: 787–94.
- 33 Shimatani T, Inoue M, Iwamoto K *et al.* Gastric acidity in patients with follicular gastritis is significantly reduced, but can be normalized after eradication for *Helicobacter pylori*. *Helicobacter*. 2005; **10**: 256–65.
- 34 Miyazaki T, Murayama Y, Shinomura Y *et al.* *E-cadherin* gene promoter hypermethylation in *H. pylori*-induced enlarged fold gastritis. *Helicobacter*. 2007; **12**: 523–31.
- 35 Nishibayashi H, Kanayama S, Kiyohara T *et al.* *Helicobacter pylori*-induced enlarged-fold gastritis is associated with increased mutagenicity of gastric juice, increased oxidative DNA damage, and an increased risk of gastric carcinoma. *J. Gastroenterol. Hepatol.* 2003; **18**: 1384–91.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Baseline characteristics of patients who ended the follow-up.

Table S2. Baseline characteristics of patients who developed *versus* did not develop gastric cancer throughout the follow-up.