PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2004;10(5):672-675
World Journal of Gastroenterology
 ISSN 1007-9327

Relationship of gastric *Helicobacter pylori* infection to Barrett's esophagus and gastro-esophageal reflux disease in Chinese

Jun Zhang, Xiao-Li Chen, Kang-Min Wang, Xiao-Dan Guo, Ai-Li Zuo, Jun Gong

Jun Zhang, Jun Gong, Ai-Li Zuo, Xiao-Dan Guo, Department of Gastroenterology, Second Hospital, Xi' an Jiaotong University, Xi' an 710004, Shaanxi Province, China
Xiao-Li Chen, Kang-Min Wang, Department of Pathology, Second Hospital of Xi' an Jiaotong University, Xi' an 710004, Shaanxi Province, China
Correspondence to: Dr. Jun Zhang, Department of Gastroenterology, Second Hospital, Xi' an Jiaotong University, Xi' an 710004, Shaanxi Province, China. jun3z@163.com
Telephone: +86-29-7678009
Received: 2003-09-06 **Accepted:** 2003-10-27

Abstract

AIM: To evaluate the relationship of *Helicobacter pylori* infection to reflux esophagitis (RE), Barrett's esophagus (BE) and gastric intestinal metaplasia (IM).

METHODS: RE, BE and gastric IM were determined by upper endoscopy. Patients were divided into 2 groups; those with squamocolumnar junction (SCJ) beyond gastroesophageal junction (GEJ) ⩾3 cm (group A), and those with SCJ beyond GEJ <3 cm (group B). Biopsy specimens were obtained endoscopically from just below the SCJ, gastric antrum along the greater and lesser curvature. Pathological changes and *H pylori* infection were determined by HE staining, Alcian blue staining and Giemsa staining.

RESULTS: The prevalence of *H pylori* infection was 46.93%. There was no difference in the prevalence between males and females. The prevalence of *H pylori* infection decreased stepwise significantly from RE grade I to III. There was no difference in the prevalence between the two groups, and between long-segment and short-segment BE. In distal stomach, prevalence of *H pylori* infection was significantly higher in patients with IM than those without IM.

CONCLUSION: There is a protective role of *H pylori* infection to GERD. There may be no relationship between *H pylori* infection of stomach and BE. *H pylori* infection is associated with the development of IM in the distal stomach.

Zhang J, Chen XL, Wang KM, Guo XD, Zuo AL, Gong J. Relationship of gastric *Helicobacter pylori* infection to Barrett's esophagus and gastro-esophageal reflux disease in Chinese. *World J Gastroenterol* 2004; 10(5): 672-675
http://www.wjgnet.com/1007-9327/10/672.asp

INTRODUCTION

The incidence of adenocarcinoma in the esophagus and gastroesophageal junction (GEJ) is increasing, whereas the incidence of distal gastric cancer is falling for the two decades in North America, Europe, Japan and China. In China, the incidence of adenocarcinoma at the GEJ is increasing even more significantly[1-3].

The adenocarcinomas at the esophagus and GEJ differ from those in the stomach[4]. They share epidemiological characteristics with each other, and often originate from segments of Barrett' s esophagus (BE). It has therefore been proposed that both of them can be called "esophagocardia adenocarcinoma"[5]. BE is a well-defined premalignant condition for esophageal adenocarcinoma and most of adenocarcinomas at GEJ[6,7]. Neoplastic progression of BE has been shown to involve multiple steps with intestinal metaplasia and dysplasia serving as histopathologic markers[5]. It is considered that the absence of specialized intestinal metaplasia in many patients with adenocarcinoma at the GEJ may be due to the complete replacement of the metaplastic epithelium by the tumor, and in these tumors, IM usually is confined to ultrashort segments that may easily be overgrown by the tumor[8].

Gastro-esophageal reflux disease (GERD) can give rise to BE, and reflux symptoms are important indicators that a patient is at risk of having Barrett' s metaplasia. Recently, interest has focused on the relationship between *H pylori* infection and GERD as well as BE, but controversial findings have been obtained Several retrospective studies have examined the association of Barrett' s adenocarcinoma with gastric *H pylori* infection, yielding discordant results. It has been known that the prevalence of *H pylori* infection in China is high. It is necessary to clarify whether *H pylori* infection is the causally associated with BE or whether it has a protective effect on BE. In addition, further investigations are also required to clarify the relationship between *H pylori* infection and GERD. Therefore, the aim of this prospective study was to evaluate the relationship between gastric *H pylori* infection and reflux esophagitis (RE), BE, and gastric IM in China.

MATERIALS AND METHODS

Patients

Consecutive patients undergoing esophagogastroendoscopy at Second Hospital, Xi' an Jiaotong University, Xi' an, China from August 1, 2000 to the end of August 1, 2001 were included in the study. Exclusion criteria included previous gastric or esophagus resection, contraindication to performing biopsies, prior history of *H pylori* eradication therapy, and/or use of bismuth-containing compounds or antibiotics within the previous 4 weeks.The study was approved by the Ethics Committee of the hospital, and informed consents were obtained from all patients before entry.

Endoscopy and biopsy

Endoscopy was performed in a standardized manner by experienced endoscopists. The appearance of the squamoucolumnar junction (SCJ) was carefully studied in the prograde view after insufflation of air and after retroversion in the stomach. According to the length from the GEJ to SCJ, patients were divided into two groups; those with velvety red gastric-like mucosa lining the distal esophagus for 3 cm or over (group A) and those with velvety red gastric-like mucosa lining the distal esophagus for less than 3 cm (group B). Endoscopic esophagitis was graded as I, mucosal erythema; II, non-circumferential mucosal breaks or erosions; III,

circumferential erosion or ulcer.

Four-quadrant biopsies were taken from the area immediately distal to the SCJ. Additional targeted biopsies were also taken from erosions, nodules or ulcers. For assessment of *H pylori* status biopsies were taken from antral greater curvature (two), and lesser curvature (two).

Biopsy specimens were fixed in 40 g/L buffered formaldehyde, embedded in paraffin, serially sectioned, and then stained with hematoxylin and eosin. BE was defined as the presence of distended, barrel-shaped goblet cells, indicative of intestinal metaplasia[6,31,32], which was further confirmed by staining with Alcian blue pH 2.5.

In addition, BE was divided into long-segment Barrett' s esophagus (LSBE, the segments of IM more than or equal to 3 cm in length) and short-segment Barrett' s esophagus (SSBE, the segment of IM less than 3 cm in length).

The presence of gastric *H pylori* infection was defined when one or more of Giemsa-stained gastric biopsy specimens demonstrated typical *H pylori*-like organisms.

The gastric IM was defined by the presence of barrel-shaped goblet cells.

Statistical analysis

Statistical analyses were performed using the χ^2 test.

RESULTS

Altogether, 391 patients were recruited. Of these patients, 253 had esophageal disorders; 103 with RE (39 grade I, 35 grade II and 29 grade III), 120 with BE (26 LSBE and 94 SSBE), 12 with dysplasia (seven low–grade and five high-grade), 17 with adenocarcinoma at the GEJ and one with adenocarcinoma at lower esophagus (Table 1). Males were more likely to have esophageal disorders than females. The average age ranged from 52.41 to 62.64 years old, with and increased progressively from RE→BE→LGD→HGD→adenocarcinoma.

Table 1 Clinic features of study population

	No.	Mean age (yr)	Male: Female
No. Of patients	391	52.41	211:180
RE I	39	52.12	26:13
II	35	53.67	26:9
III	29	55.56	24:5
BE SSBE	94	54.71	62:32
LSBE	26	58.66	20:6
Low-grade dysplasia	7	59.57	5:2
High-grade dysplasia	5	62.00	3:2
Adenocarcinoma at GEJ	17	62.64	14:3

Status of *H pylori* infection was available for 375 patients. The prevalence *of H pylori* infection was 46.93% (176/375). There was no significant difference in the prevalence between males and females (males, 48.71% and females, 45.00%) (P>0.05) (Table 2). The prevalence of *H pylori* infection in Group A was 41.84% (41/98), which was slightly lower than that 48.73% (135/277) in group B (P>0.05), The prevalence of *H pylori* infection decreased stepwise significantly from RE Grade I (51.72%), grade II (28.57%) to grade III (20.68%) (P<0.05) (Table 2).

The prevalence of IM in group A (LSBE) (26.53%) was slightly lower than that in group B (SSBE) (33.94%) (P>0.05). In groups A and B the prevalence of *H pylori* infection (46.15% and 51.06%, respectively) in patients with IM was slightly higher than that (40.27% and 47.54%, respectively) in those without IM (both P>0.05) (Table 3). The prevalence of *H pylori* infection of LSBE (46.15%) is slightly lower than that of SSBE (51.06%) (P>0.05). However, in the distal stomach, the prevalence of *H pylori* infection in patients with IM (56.29%) was significantly higher than that in those without IM (37.89%) (P<0.05) (Table 3).

Table 2 Comparisons of *H pylori* status among patients with sex, length of SCJ, grade of RE

	No.	Hp^+ (%)	Hp^- (%)	P
No. Of patients	375	176 (46.93)	199 (53.06)	
Male: Female	195:180	95: 81	100:99	0.534
Group A	98	41 (41.84)	57 (58.16)	0.239
Group B	277	135 (48.73)	142 (51.26)	
RE I	29	15 (51.72)	14 (48.28)	0.032
II	35	10 (28.57)	25 (41.43)	
III	29	6 (20.68)	23 (79.31)	

Table 3 Comparisons of *H pylori* status between patients with IM in LSBE, SSBE and distal stomach

IM	Group A		Group B		Distal stomach	
	+ (%)	– (%)	+ (%)	– (%)	+ (%)	– (%)
HP+	12 (46.15)	29 (40.27)	48 (51.06)	87 (47.54)	76 (56.29)	97 (37.89)
HP-	14 (53.84)	43 (59.72)	46 (48.93)	96 (52.45)	59 (43.70)	159 (62.11)
Total	26	72	94	183	135	256

Comparision of *H pylori* status between LSBE (IM+ in group A) and SSBE (IM+ in group B), P=0.658, (χ^2=0.196); Comparision of *H pylori* status between IM "+" and IM "–" in group A, P=0.603, (χ^2=0.271); Comparision of *H pylori* status between IM "+" and IM "–" in group B, P=0.579, (χ^2=0.308); Comparision of *H pylori* status between IM "+" and IM"–" in distal stomach, P=0.000, (χ^2=12.14).

DISCUSSION

Since the isolation of *H pylori* from gastric mucosa by Warren and Marshall in 1983, there has been renewed interest in a possible bacterial cause of upper gastrointestinal diseases[9]. *H pylori* is now widely accepted as a major cause of antral gastritis and peptic ulcer disease[10,11]. Epidemiological evidence for an association with gastric carcinoma has also been reported[12,13]. In addition, gastric mucosa-associated lymphoid tissue (MALT) lymphoma has been linked to *H pylori* infection[14,15]. The relationship of *H pylori* to GERD and BE is less clear. Some groups have reported a lower prevalence of *H pylori* infection in individuals with GERD, and have postulated that infection may reduce the risk of reflux esophagitis[16-18]. However, other epidemiological studies have found little or no association between *H pylori* infection and GERD[19-21]. With regard to Barrett' s esophagus the majority of studies have found no association with *H pylori* infection[22,23]. However, there is also evidence to the contrary[18]. Our prospective study tried to evaluate the relation between gastric *H pylori* infection and RE, BE, and gastric IM in Chinese.

H pylori infection can be diagnosed by a variety of noninvasive or invasive tests. Histological examination with special staining of gastric biopsy specimens is accepted as the gold standard for *H pylori* diagnosis[24,25]. Gastric antrum is the most common place for *H pylori* colonization[26,27]. Modified Giemsa staining, which has been shown to have a high specificity and sensitivity[25,28], was used to detect *H pylori* status in this study.

In early studies, BE was defined as the presence of specialized IM in a columnar-lined mucosa encompassing more than 3 cm proximal to GEJ or a LSBE[29]. Any columnar-lined mucosa less than 3 cm above the GEJ was thought to be a

normal variant. However studies over the past years have indicated that there is a spectrum of involvement that includes the distal 3 cm of esophagus or a SSBE[30,31]. What is important is the presence of IM relating to adenocarcinoma. It has been shown that a patient with LSBE has a higher risk to develop dysplasia or cancer[32]. It also has been shown that the development of LSBE is more closely related to gastresophageal reflux[33]. Therefore, in our study, patients were divided into two groups; those with a velvety red gastric-like mucosa lining the distal esophagus for 3 cm or over and those with a velvety red gastric-like mucosa lining the distal esophagus for less than 3 cm. Because esophageal hiatal hernia is often complicated by GERD and BE, many researchers think that to define an esophageal hiatal hernia, the presence of a velvety red gastric-like mucosa lining the distal esophagus for 2 cm should be considered as normal. In our study, therefore, we referred to this definition; the length from the GEJ to SCJ for esophageal hiatal hernia reduced 2 cm[34,35].

Altogether, 391 patients were evaluated over the course of the study (Table 1), The presence of IM was confirmed in 26 cases of the 98 patients suspected of having LSBE, and in 94 cases of the 277 patients suspected of having SSBE. Seven BE cases with dysplasia, 103 RE and 17 adenocarcinoma at GEJ were diagnosed. The average age of patients increased gradually with the sequence of RE, BE, LGD, HGD and adenocarcinoma at GEJ from 52.41 to 62.64 years old. Males were more likely to have the diseases. Cameron *et al* reported that the age after 40 had a high incidence of BE, and development of adenocarcinoma from BE required about 20 years[36].

Of the entire study population, 375 subjects received histological examination for *H pylori* infection, with a prevalence of *H pylori* infection of 46.93%. There was no significant difference between males and females. These results are similar to the report by Hui *et al* about *H pylori* infection in the same area of China[37].

The first change in BE, is the replacement of the normal stratified epithelium with metaplastic columnar epithelium in the distal esophagus, making the SCJ rising upward above the GEJ. It is accepted that BE is an acquired condition, and is related to gastro-esophageal reflux. An excellent overview and hypothesis detailing the role of *H pylori* infection in the pathogenesis of duodenal ulcer, gastric cancer, and GERD has been given by Graham and Yamaoka[38,39]. *H pylori* infection has been shown to decrease acid secretion in patients with body-predominant *H pylori* colonization[40]. With less acid production, the offensive potency of the refluxate may be reduced. An additional mechanism could be neutralization of acid by ammonia produced by *H pylori*, with subsequence reduction in intragastric acid load and in the reflux of acid into the esophagus, as proposed by Bercik *et al*[41]. Ammonia may also promote protective adaptation of the esophageal mucosa[42]. So, if *H pylori* infection can decrease the offensive potency of the refluxate, we could infer indirectly whether *H pylori* infection has the protective effect in GERD and BE by comparing the RE grade and the prevalence of *H pylori* infection in different length from the GEJ to the SCJ (*i.e.* between group A and group B). In our study there was no significant difference in the prevalence of *H pylori* infection between group A (41.84%) and group B 48.73%. Furthermore, the prevalence of *H pylori* infection decreased stepwise significantly from RE Grade I (51.72%), grade II (28.57%) to grade III (20.68%) (P=0.032). These findings suggest that there is no relationship between gastric *H pylori* infection and GERD, although gastric *H pylori* infection had an apparent protective effect against the progression of GERD.

Barrett' s metaplasia is precancerous lesion of esophageal adenocarcinoma and most of adenocarcinoma at the GEJ. Progression from metaplasia, LGD, HGD to invasive cancer occurs in a stepwise process. It is unquestionably BE, especially LSBE, is linked with gastresophageal reflux. Our study shows that *H pylori* infection has the protective effect in GERD. But how about BE? The present study demonstrated that there was no significant difference in IM prevalence between group A and group B. Marian *et al* reported that the prevalence of LSBE was higher than that of SSBE and the prevalence of IM is directly proportional to the length of column-lined esophagus[33]. This finding, which is different from ours, may explain the reason why the incidence of esophageal adenocarcinoma is on the increase in North America and Europe. However, in our study, the prevalence of SSBE was higher than that of LSBE, which may explain the reason why the incidence of adenocarcinoma at the GEJ is more common than that at the esophagus in China. There was no significant difference in the prevalence of *H pylori* infection between patients with and without IM in both group A and group B. Similarly, there was no significant difference in the prevalence of *H pylori* infection between LSBE and SSBE. However, in distal stomach, the prevalence of *H pylori* infection in patients with IM (56.29%) is much higher than that in those without IM (37.89%) (P<0.001), which is in agreement with previous observations[22,23,43]. It is suggested that *H pylori* infection is associated with IM in the distal stomach, but may have no protective effect in BE. The distal gastric IM is thought to be less dangerous to progress to gastric carcinoma, and thus it is not suggested to supervise routinely the patients with distal gastric IM[44]. However, patients with BE has an overrated risk, about 30 to 125 times to progress to adenocarcinoma than patients without BE[45, 46].

In conclusion, *H pylori* infection may have a protective role in GERD. There is no relationship between gastric *H pylori* infection and BE. *H pylori* infection is associated with IM in the distal stomach.

REFERENCES

1 **Devesa SS**, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998; **83**: 2049-2053

2 **Blot WJ**, Devesa SS, Kneller RW, Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991; **265**: 1287-1289

3 **Zhou Q**, Wang LD. Biological characteristics of cardiac cancer. *Huaren Xiaohua Zazhi* 1998; **6**: 636-637

4 **Ruol A**, Parenti A, Zaninotto G, Merigliano S, Costantini M, Cagol M, Alfieri R, Bonavina L, Peracchia A, Ancona E. Intestinal metaplasia is the probable common precursor of adenocarcinoma in barrett esophagus and adenocarcinoma of the gastric cardia. *Cancer* 2000; **88**: 2520-2528

5 **Rabinovitch PS**, Reid BJ, Haggitt RC, Norwood TH, Rubin CE. Progression to cancer in Barrett's esophagus is associated with genomic instability. *Lab Invest* 1989; **60**: 65-71

6 **Weston AP**, Krmpotich PT, Cherian R, Dixon A, Topalovski M. Prospective evaluation of intestinal metaplasia and dysplasia within the cardia of patients with Barrett's esophagus. *Dig Dis Sci* 1997; **42**: 597-602

7 **Cameron AJ**, Lomboy CT, Pera M, Carpenter HA. Adenocarcinoma of the esophagogastric junction and Barrett's esophagus. *Gastroenterology* 1995; **109**: 1541-1546

8 **Clark GW**, Smyrk TC, Burdiles P, Hoeft SF, Peters JH, Kiyabu M, Hinder RA, Bremner CG, DeMeester TR. Is Barrett's metaplasia the source of adenocarcinomas of the cardia? *Arch Surg* 1994; **129**: 609-614

9 **Warren JR**, Marshall BJ. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983; **1**: 1273-1275

10 **Marshall BJ**, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; **16**: 1311-1315

11 **Rauws EA**, Langenberg W, Houthoff HJ, Zanen HC, Tytgat GN. Campylobacter pyloridis-associated chronic active antral gastritis. A prospective study of its prevalence and the effects of

antibacterial and antiulcer treatment. *Gastroenterology* 1988; **94**: 33-40
12 **Parsonnet J**, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, Sibley RK. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med* 1991; **325**: 1127-1131
13 **Nomura A**, Stemmermann GN, Chyou PH, Kato I, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. *N Engl J Med* 1991; **325**: 1132-1136
14 **Isaacson PG**. Gastrointestinal lymphoma. *Hum Pathol* 1994; **25**: 1020-1029
15 **Sigal SH**, Saul SH, Auerbach HE, Raffensperger E, Kant JA, Brooks JJ. Gastric small lymphocytic proliferation with immunoglobulin gene rearrangement in pseudolymphoma versus lymphoma. *Gastroenterology* 1989; **97**: 195-201
16 **Werdmuller BF**, Loffeld RJ. *Helicobacter pylori* infection has no role in the pathogenesis of reflux esophagitis. *Dig Dis Sci* 1997; **42**: 103-105
17 **Koike T**, Ohara S, Sekine H, Iijima K, Kato K, Toyota T, Shimosegawa T. Increased gastric acid secretion after *Helicobacter pylori* eradication may be a factor for developing reflux oesophagitis. *Aliment Pharmacol Ther* 2001; **15**: 813-820
18 **Weston AP**, Badr AS, Topalovski M, Cherian R, Dixon A, Hassanein RS. Prospective evaluation of the prevalence of gastric *Helicobacter pylori* infection in patients with GERD, Barrett's esophagus, Barrett's dysplasia, and Barrett's adenocarcinoma. *Am J Gastroenterol* 2000; **95**: 387-394
19 **Walker SJ**, Birch PJ, Stewart M, Stoddard CJ, Hart CA, Day DW. Patterns of colonisation of Campylobacter pylori in the oesophagus, stomach and duodenum. *Gut* 1989; **30**: 1334-1338
20 **Newton M**, Bryan R, Burnham WR, Kamm MA. Evaluation of *Helicobacter pylori* in reflux oesophagitis and Barrett's oesophagus. *Gut* 1997; **40**: 9-13
21 **Befrits R,** Granstrom M, Rylander M, Rubio C. *Helicobacter pylori* in 205 consecutive endoscopy patients. *Scand J Infect Dis* 1993; **25**: 189-191
22 **Talley NJ**, Cameron AJ, Shorter RG, Zinsmeister AR, Phillips SF. Campylobacter pylori and Barrett's esophagus. *Mayo Clin Proc* 1988; **63**: 1176-1180
23 **Abbas Z**, Hussainy AS, Ibrahim F, Jafri SM, Shaikh H, Khan AH. Barrett's esophagus and *H pylori*. *J Gastroenterol Hepatol* 1995; **10**: 331-333
24 **Genta RM**, Graham DY. Comparison of biopsy sites for the histopathologic diagnosis of *Helicobacter pylori*: a topographic study of *H pylori* density and distribution. *Gastrointest Endosc* 1994; **40**: 342-345
25 **EI-Zimaity HM**, al-Assi MT, Genta RM, Graham DY. Confirmation of successful therapy of *H pylori* infection: number and sites of biopsies or a rapid urease test. *Am J Gastroenterol* 1995; **90**:1962-1964
26 **Bayerdorffer E**, Lehn N, Hatz R, Mannes GA, Oertel H, Sauerbruch T, Stolte M. Difference in expression of *Helicobacter pylori* gastritis in antrum and body. *Gastroenterology* 1992; **102**: 1575-1582
27 **Bayerdorffer E**, Oertel H, Lehn N, Kasper G, Mannes GA, Sauerbruch T, Stolte M. Topographic association between active gastritis and Campylobacter pylori colonisation. *J Clin Pathol* 1989; **42**: 834-839
28 **Brown KE**, Peura DA. Diagnosis of *Helicobacter pylori* infection. *Gastroenterol Clin North Am* 1993; **22**: 105-115
29 **Skinner DB**, Walther BC, Riddell RH, Schmidt H, Iascone C, DeMeester TR. Barrett's esophagus. Comparison of benign and malignant cases. *Ann Surg* 1983; **198**: 554-565
30 **Spechler SJ**, Zeroogian JM, Antonioli DA, Wang HH, Goyal RK. Prevalence of metaplasia at the gastro-esophageal junction. *Lancet* 1994; **344**: 1533-1536
31 **Weston AP**, Krmpotich P, Makdisi WF, Cherian R, Dixon A, McGregor DH, Banerjee SK. Short segment Barrett's esophagus: clinical and histologic features associated endoscopic findings and association with gastric intestinal metaplasia. *Am J Gastroenterol* 1996; **91**: 981-986
32 **Menke-Pluymers MB**, Hop WC, Dees J, van Blankenstein M, Tilanus HW. Risk factors for the development of an adenocarcinoma in columnar-lined (Barrett) esophagus. The rotterdam esophageal tumor study group. *Cancer* 1993; **72**: 1155-1158
33 **Csendes A**, Maluenda F, Braghetto I, Csendes P, Henriquez A, Quesada MS. Location of the lower oesophageal sphincter and the spuamous columnar mucosal junction in 109 healthy controls and 778 patients with different degrees of endoscopic oesophagitis. *Gut* 1993; **34**: 21-27
34 **Tytgat GN**, Hameeteman W, Onstenk R, Schotborg R. The spectrum of columnar-lined esophagus–Barrett's esophagus. *Endoscopy* 1989; **21**: 177-185
35 **Voutilainen M**, Farkkila M, Mecklin JP, Juhola M, Sipponen P. Classical Barrett esophagus contrasted with Barrett-type epithelium at normal-appearing esophagogastric junction. Central finland endoscopy study group. *Scand J Gastroenterol* 2000; **35**: 2-9
36 **Cameron AJ**. Epidemiologic studies and the development of Barrett's esophagus. *Endoscopy* 1993; **25**: 635-636
37 **Hui YP**, Liu Y, Li YH, Ma FC, Wang YM. The relationship between *H pylori* and chronic gastritis. *J Fourth Mil Med Univ* 2001; **22**: 574-575
38 **Graham DY**. *Helicobacter pylori* infection in the pathogenesis of duodenal ulcer and gastric cancer: a model. *Gastroenterology* 1997; **113**: 1983-1991
39 **Graham DY**, Yamaoka Y. *H pylori* and cagA: relationships with gastric cancer, duodenal ulcer, and reflux esophagitis and its complications. *Heclicobacter* 1998; **3**: 145-151
40 **Stolte M**, Stadelmann O, Bethke B, Burkard G. Relationships between the degrees of *Helicobacter pylori* colonization and the degree and activity of gastritis, surface epithelial degeneration and mucus secretion. *Z Gastroenterol* 1995; **33**: 89-93
41 **Bercik P**, Verolu E, Armstrong D. Reflux esophagitis and *H pylori*. *Gastroenterology* 1997; **113**: 2020-2021
42 **Labenz J**, Malfertheiner P. *Helicobacter pylori* in gastrooesophageal reflux disease: causal agent, independent or protective factor? *Gut* 1997; **41**: 277-280
43 **Spechler SJ**. The role of gastric carditis in metaplasia and neoplasia at the gastroesophageal junction. *Gastroenterology* 1999; **117**: 218-228
44 **Provenzale D,** Kemp JA, Arora S, Wong JB. A guide for surveillance of patients with Barrett's esophagus. *Am J Gastroenterol* 1994; **89**: 670-680
45 **Spechler SJ**, Robbins AH, Rubins HB, Vincent ME, Heeren T, Doos WG, Colton T, Schimmel EM. Adenocarcinoma and Barrett's esophagus: an overrated risk? *Gastroenterology* 1984; **87**: 927-933
46 **Williamson WA**, Ellis FH Jr, Gibb SP, Shahian DM, Aretz HT, Heatley GJ, Watkins E Jr. Barrett's esophagus. Prevalence and incidence of adenocarcinoma. *Arch Intern Med* 1991; **151**: 2212-2216

Edited by Xia HHX **Proofread by** Xu FM