Helicobacter pylori associated with a high prevalence of duodenal ulcer disease and a low prevalence of gastric cancer in a developing nation

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Abstract

This study examines the relationship between *Helicobacter pylori* infection and peptic ulcer disease and gastric cancer – in particular, the presence or absence of bacteria, the grading of gastritis, and the degree of inflammation in the antral and oxyntic mucosae. The grading of gastritis and the detection of *H pylori* were determined by histology using the Sydney system. Of the 1006 patients examined, 34.5% had duodenal ulcer disease, 3.5% gastric ulcer disease, and 2% with coexistent ulceration. Most patients (50.2%) were classified as having non-ulcer dyspepsia. Altogether 2.4% of patients had gastric cancer and two further patients had carcinoma in the gastric stump. Of the ulcer disease patients, 87.2% had histological evidence of *H pylori* infection. After patients who had taken antibiotics or bismuth compounds in the preceding four weeks were excluded, 98.9% of the duodenal ulcer disease, 100% of the gastric ulcer disease, and 100% of the coexistent ulcer disease patients had evidence of *H pylori* infection. In patients with gastric cancer who had not taken antimicrobial agents in the four weeks before endoscopy, 83.3% had evidence of *H pylori* infection. Thus, there was a high rate of duodenal ulcer disease and a low rate of gastric ulcer disease in southern China, an area of low gastric cancer mortality. There was a specific topographical relationship between *H pylori*, the histological response, and gastroduodenal disease. Our data suggest that the status of a nation as either 'developed' or 'developing' can not be used to predict the upper gastrointestinal disease profile of its population.

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Keywords: *Helicobacter pylori*, peptic ulcer disease, gastric cancer.

In recent years we have investigated the relationship between *Helicobacter pylori* infection and upper gastrointestinal disease in the People's Republic of China. In previous reports we have reviewed the relationship between *H pylori* and gastritis, examined the epidemiology of infection, and briefly addressed the relationship between infection and peptic ulcer diseases.¹⁻³ Although there is good current evidence supporting the role of

H pylori in duodenal ulcer disease,⁴⁻⁹ the relationship between *H pylori* infection and gastric ulcer disease has remained relatively neglected.¹⁰⁻¹³

Following a recent study of ours, we found that in southern China *H pylori* associated gastritis looked similar to that reported in other studies where both the antral and oxyntic mucosae had been investigated.³ In this study, however, we noted that in relation to upper gastrointestinal disease, there was a need to examine further the specific topographical relationship between *H pylori* and its associated histological response. This study aimed to extend our knowledge of the relationship between *H pylori* infection, peptic ulcer disease, and gastric cancer within a southern Chinese population. In this investigation we have focused on peptic ulcer disease and gastric cancer in relation to the presence or absence of bacteria, the grading of gastritis, and factors such as the degree of inflammation in the antral and oxyntic mucosae.

Methods

PATIENTS

This study examined 1006 consecutive patients who presented for endoscopic examination at the Affiliated First Hospital, Sun Yat-Sen University of Medical Science, Guangzhou, Peoples Republic of China. All patients were from the local population and were referred to the hospital for the investigation of upper gastrointestinal symptoms of unknown aetiology. The patients were not referred from other endoscopy clinics or selected because of the severity of symptoms. Patients consisted of both outpatients and inpatients from all social strata. Because of the medical system in this region of China, the outpatient population would represent a group similar to that investigated by a private outpatient practice in many parts of the developed world. Follow up patients were excluded from the study. Each patient was asked about their antibiotic intake over the previous four weeks. Informed consent was obtained from each patient. The project conforms to the declaration of Helsinki and was approved by the Director of the Guangzhou Health Bureau on advice from the Scientific Affairs Committee.

ENDOSCOPIC EXAMINATION

Patients were examined using an Olympus

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Q20 endoscope and the presence of lesions in the gastroduodenal mucosa was noted. Differentiation was made between erosions and true ulcers in the classification of disease. The criteria for inclusion in the ulcer group were a circumscribed break in the mucosa with apparent depth and covered by an exudate as well as those patients with healing ulcers or ulcer scarring. Ulcers located in the stomach or duodenum were classified as gastric and duodenal ulcers respectively. Where ulcers occurred in both the stomach and the duodenum simultaneously, these were classified as coexistent ulcers. Where an ulcer occurred coexistent with gastric malignancy, the patient was classified as being in the gastric cancer group.

BIOPSIES

Jumbo biopsy forceps (FB-25K) were used to collect biopsy specimens from both the oxyntic and antral gastric mucosae. In the antrum, two specimens, one each from the anterior and posterior wall 2 cm from the pylorus, were taken for histology. Similarly in the body, two biopsy specimens, one each from the anterior and posterior wall, midway between the antral-body junction and cardia, were collected for histology. Specimens were not taken from patients in whom there was a risk of complications such as gastric bleeding.

HISTOLOGY

Biopsy specimens for histological examination were fixed in 10% buffered formalin and processed routinely. Paraffin sections (5 µm) were cut and stained by haematoxylin and eosin, and for the presence of *H pylori* by modified Giemsa stain. Sections were graded for bacteria, inflammation (chronicity), polymorphonuclear leukocytes (activity), atrophy, and intestinal metaplasia in accordance with the recommendations of the working party that developed the Sydney system for the histological grading of gastritis.¹⁴

STATISTICS

χ² analysis with Yates's correction were performed using the SPSS program (SPSS Inc, IL, USA). Where multiple comparisons were performed, the Bonferroni inequality was taken into account to adjust the p values.

Results

Examination of the 1006 patients by gastro-duodenoscopy showed that 403 (40%), aged from 16 to 70 years, had an endoscopic finding of peptic ulcer disease (348 duodenal ulcer, 35 gastric ulcer, and 20 with coexistent ulceration) (Table I). Most patients, 505 (50.2%) aged 17 to 65 years, had no significant endoscopically definable findings and were classified as having non-ulcer dyspepsia (Table I). Twenty four (2.4%) of the patients were diagnosed as having gastric cancer and were in the age range of 32 to 72 years, with two

TABLE I Diagnosis of disease in the patient population

Disease	No (%)	Sex ratio (male:female)	Mean age (y)
Duodenal ulcer	348 (34.5)	2.05:1	42.7
Gastric ulcer	35 (3.5)	2.89:1	51.0
Coexistent ulcer	20 (2.0)	5.67:1	50.5
Gastric cancer	24 (2.4)	2.0:1	53.8
Non-ulcer dyspepsia	505 (50.2)	0.94:1	38.4
Peristomal gastritis	28 (2.78)	3.65:1	55.7
Stomal ulcer	2 (0.2)	—	42.5
Gastric stump carcinoma	2 (0.2)	—	52.5
Oesophageal carcinoma	8 (0.8)	1:1	61.3
Other	34 (3.4)	—	—

additional patients aged 50 and 55 years having carcinoma in the gastric stump. The remaining patients aged 39 to 80 years had other disease manifestations, including stomal ulceration, peristomal gastritis, and oesophageal carcinoma (Table I). Except for the non-ulcer dyspepsia group and the oesophageal cancer patients (where men and women were in almost equal proportions) men predominated in the disease groups (Table I).

Of the 937 patients from whom biopsy material was available, 885 were classified as having either ulcer disease, gastric cancer, or non-ulcer dyspepsia (Table II). Three hundred and twenty eight of 376 patients with ulcer disease (87.2%) had histological evidence of *H pylori* infection (87.2% in duodenal ulcer disease, 90% in gastric ulcer disease, and 83.3% in coexistent ulcer disease – gastric plus duodenal ulceration) (Table II). Of the 22 gastric cancer patients from whom biopsy specimens were collected, 16 (72.7%) had histological evidence of *H pylori* infection (Table II).

When patients who had taken antibiotics or bismuth compounds in the four weeks before endoscopy were excluded from the above groups, 308 of 311 (99%) of the ulcer disease patients had evidence of *H pylori* infection (98.9% in duodenal ulcer disease, 100% in gastric ulcer disease, and 100% in coexistent ulcer disease) (Table II). *H pylori* infection was evident in 15 of 18 (83.3%) of the gastric cancer group (Table II). There was a significant association between the presence of *H pylori* and peptic ulcer disease compared with those patients diagnosed as having non-ulcer dyspepsia (χ²=157.35, DF=1, p<0.001).

The grading of gastritis in 642 patients diagnosed as having either peptic ulcer disease or non-ulcer dyspepsia who had not taken antimicrobial agents in the preceding four weeks was determined. Of these patients, 498 of 642 (77.6%) had histological evidence of *H pylori* infection. All of these infected individuals had some degree of inflammation at one

TABLE II Incidence of Helicobacter pylori in principal disease groups*

Disease	No infected/total (%)	No infected/total (%) adjusted group†
Duodenal ulcer	286/328 (87.2)	271/274 (98.9)
Gastric ulcer	27/30 (90.0)	25/25 (100)
Coexistent ulcer	15/18 (83.3)	12/12 (100)
Gastric cancer	16/22 (72.7)	15/18 (83.3)
Non-ulcer dyspepsia	247/467 (52.9)	190/331 (57.4)

*Biopsy specimens contraindicated in 69 cases. †Adjusted to exclude patients who had a record of taking bismuth or antibiotics in the four weeks before endoscopy.

TABLE III Histological grading of gastritis in relation to *Helicobacter pylori* status in ulcer and non-ulcer dyspepsia patients who had not taken antimicrobial agents before endoscopy

<i>Helicobacter pylori</i>	Chronic gastritis		
	Mild	Moderate-severe	Total (%)
Positive	16	482	498 (84.7)
Negative*	82	8	90 (15.3)
Total (%)	98 (16.7)	490 (83.3)	588 (100)

*Fifty eight patients negative for *H. pylori* had no evidence of gastritis.

or more sites in the stomach. Pangastritis-antral predominant was the most common gastritis presentation in 365 (73.3%) of this group of *H. pylori* positive patients, followed by antral only gastritis (13.9%) and uniform pangastritis (11.2%). In the site where the gastritis was most predominant, 96.3% of this group of 498 patients had chronic gastritis graded as moderate to severe (Table III). Of the 144 of 642 (22.4%) patients in the *H. pylori* negative group, 90 had some degree of inflammation at one or more sites in the stomach. This gastritis was graded as mild in 82 of 90 (91.1%) cases (Table III) and was usually confined to the antrum (80%). There was a significant difference between the severity of gastritis in the *H. pylori* infected group compared with the uninfected group ($\chi^2=417.71$, $DF=1$, $p<0.001$).

Of the 328 duodenal ulcer disease patients from whom biopsy specimens had been taken, the topography of gastritis was pangastritis-antral dominant in 236 (71.9%), antral gastritis in 16.8%, and uniform pangastritis in 11.3% (Table IV). Of the 30 gastric ulcer disease patients, the topography of gastritis was pangastritis-antral dominant in 13 (43.3%), uniform pangastritis in 11 (36.7%), pangastritis-body dominant in four (13.3%), and

antral only gastritis in two cases (6.7%) (Table IV). Where there was coexistent ulceration (gastric plus duodenal), the topography of gastritis tended to be more antral than in gastric ulcer disease, whereas in gastric cancer the topography of gastritis was similar to that seen in gastric ulcer disease (Table IV). For the purposes of statistical analysis, the antral and antral predominant groups were combined, as were the body and body predominant groups, giving three broad groups (antral/antral predominant, pangastritis, and body/body predominant). Based on this classification, there was a significant difference between one or more of the disease states (duodenal ulcer, gastric ulcer, coexistent ulcer, and gastric cancer) in relation to the topography of gastritis ($\chi^2=62.44$, $DF=6$, $p<0.001$). There was, however, no significant difference seen between the topography of gastritis in the gastric ulcer, gastric cancer, and coexistent ulcer groups ($\chi^2=5.491$, $DF=4$, $p=0.482$ – adjusted for Bonferroni inequality). Thus, it may be concluded that there was a significant difference between the topography of gastritis in cases of duodenal ulcer disease compared with the three other disease groups.

Atrophic changes were noted most commonly in cases of gastric cancer (Table V). Four of 22 gastric cancer patients (18.2%) had severe atrophy occurring either predominantly in the antrum or uniformly throughout the stomach. A further 18.2% of the gastric cancer patients had moderate atrophy ranging in distribution from the antrum to uniformly throughout the stomach. Moderate atrophy was noted in 6.1% of patients with duodenal ulcer disease, 26.7% of patients with gastric ulcer disease, and 18.75% of patients with coexistent ulceration. Atrophy was rare in cases of non-ulcer dyspepsia (Table V).

TABLE IV Topography of gastritis in relation to gastroduodenal disease

Site of gastritis	Disease state (no (%))			
	Duodenal ulcer (DU)	Gastric ulcer (GU)	Coexistent ulcer (GU plus DU)	Gastric cancer
Antral only	55 (16.8)	2 (6.7)	2 (11.1)	2 (9.1)
Pangastritis – antral predominant	236 (72.0)	13 (43.3)	12 (66.7)	13 (59.1)
Pangastritis	37 (11.3)	11 (36.7)	4 (22.2)	6 (27.3)
Pangastritis – body predominant	0 (0)	4 (13.3)	0 (0)	1 (4.5)
Body only	0 (0)	0 (0)	0 (0)	0 (0)
Normal	0 (0)	0 (0)	0 (0)	0 (0)
Total	328	30	18	22

TABLE V Topography of atrophy in relation to gastroduodenal disease

Distribution of atrophy	Severity of atrophy	Disease state (no (%))				NUD
		Duodenal ulcer	Gastric ulcer	Coexistent ulcer	Gastric cancer	
Antral only	Moderate	20 (6.1)	5 (16.7)	3 (18.75)	1 (4.5)	10 (2.1)
Body only	Severe	–	–	–	–	–
	Moderate	–	–	–	–	–
Antral predominant	Severe	–	–	–	–	–
	Moderate	–	3 (10)	–	1 (4.5)	2 (0.4)
Body predominant	Severe	–	–	–	2 (9.1)	–
	Moderate	–	–	–	1 (4.5)	–
Uniform	Severe	–	–	–	–	–
	Moderate	–	–	–	1 (4.5)	3 (0.6)
No atrophy	Severe	–	–	–	2 (9.1)	–
	Moderate	–	–	–	–	–
No atrophy		308 (93.9)	22 (73.3)	13 (81.25)	14 (63.6)	452 (96.8)
Total with atrophy		20/328 (6.1)	8/30 (26.7)	3/16 (18.75)	8/22 (36.4)	15/467 (3.2)

NUD=non-ulcer dyspepsia.

Discussion

Whereas there are numerous reports confirming the relationship between *H. pylori* infection and duodenal ulcer disease,⁴⁻⁹ data in relation to gastric ulcer disease is not as abundant. In addition, while the recent data on the association between *H. pylori* infection and gastric cancer is sufficiently strong for us to claim that a link exists between the two,¹⁵⁻²⁸ it should be noted that association is the weakest test of an hypothesis. Further confirmatory studies are required.

This study aimed to investigate the relationship between infection with the gastric bacterium *H. pylori* and significant gastroduodenal pathology in a patient population from southern China. In addition, a further examination of the relationship between infection, disease, and the presentation of gastritis was undertaken. Histology alone was used to assess the presence or absence of *H. pylori* as we have previously shown a high specificity and sensitivity using this approach.³

This study has confirmed the strong association between *H. pylori* infection and duodenal ulcer disease. Indeed, when we looked at the patient group in whom a recent history of

antimicrobial intake had been excluded, the association between infection and disease was almost absolute. Further, the prevalence of duodenal ulcer disease in this patient population was high (~35%) by world standards, consistent with previous comparisons between centres such as Hong Kong and Sydney, Australia.²⁹

In Guangdong province, 90% of the gastric ulcer patients had evidence of *H pylori* infection. When we again excluded those with a recent history of antimicrobial ingestion, the data showed that all gastric ulcer patients were infected. In contrast, in many studies in developed countries, *H pylori* has been associated with only about 70% of gastric ulcers.¹⁰⁻¹³ A high proportion of patients with gastric ulceration not associated with *H pylori* have, however, been found to be taking non-steroidal anti-inflammatory drugs (NSAIDs).³⁰⁻³³ In Guangdong province the ingestion of NSAIDs is not widespread: in many respects in relation to gastric ulcer disease, therefore, it is perhaps a 'cleaner' population. This may be a characteristic of this region of the world, as Indochinese migrants living in Australia tend to ingest less NSAIDs than Australian born inhabitants, yet have a high incidence of ulcer disease.³⁴ In conjunction with the recent treatment studies of Graham *et al*,¹³ the implication to be drawn from the southern China data is that in the absence of NSAID ingestion, *H pylori* should be considered the single most important contributor to the genesis of gastric ulceration.

Burnstein *et al*³⁵ stated that in developed countries infection with *H pylori* induces more peptic ulcer disease than gastric cancer, with the reverse being true in the developing world. Whereas this may be true in relation to the Peruvian population studied by Burnstein's group compared with Europeans, it cannot be accepted as a general principle. Even allowing for probable patient selection bias, there was a significantly higher prevalence of duodenal ulcer disease in our southern Chinese patient group (34.5%) than in either the Peruvian (5.2%) or the European country groups (11.6%) studied by Burnstein *et al* (χ^2 , $p < 0.001$), and a higher ratio of duodenal ulcer disease to gastric ulcer disease (China 10.2:1, Peru 1.2:1, Europe 2:1). The prevalence of gastric ulcer was similar, if not slightly lower, than that seen in both Peruvian patients and those from Europe. In our series, the prevalence of gastric cancer (2.4%) was intermediate to that seen in the Peruvian patients and those from Europe.³⁵ The finding of a lower rate of gastric cancer in our series compared with Peru is consistent with the knowledge that Guangdong province in southern China is an area of relatively low gastric cancer mortality by Chinese standards (8.3 deaths/100 000 (age standardised-world)).^{36 37} Our previous studies in southern China, however, have shown the overall prevalence of *H pylori* to be 44.2%, with infection rates of 23% in children under 5 years.² These rates are comparable with those reported by Klein *et al* in Peru.³⁸ Thus, based on such comparisons, we found no absolute correlation between the prevalence

of *H pylori* infection in a population and the profile of upper gastrointestinal disease.

The topography of gastritis and the development of atrophy, intestinal metaplasia, and dysplasia seem to be important factors associated with gastric cancer of Lauren's intestinal type.³⁹⁻⁴³ Sipponen has noted that gastritis of different topographic types is broadly associated with different gastrointestinal disease states, and that gastric and duodenal ulcers are extremely rare in patients in whom the gastritis accompanies severe atrophic changes in the corpus mucosa.⁴² In this study there was a lack of extensive atrophy in the patient population; including the gastric cancer patients, in whom only 36% had evidence of gastric atrophy. Distinct topographical patterns were noted for the gastritis in gastric cancer and gastric ulcer patients compared with duodenal ulcer patients. Pangastritis-antral predominant and antral only gastritis predominated in the duodenal ulcer patients; these forms occurring in almost 89% of patients. In the gastric ulcer patients, pangastritis of various forms was found in just over 93% of patients. A similar pattern to this was seen in the gastric cancer patients.

As we and others have asserted in the past, levels of gastric acidity may influence the distribution of *H pylori* or gastritis, or both, which in turn may influence the disease profile.^{3 42 44-47} Factors leading to gastric cancer may tend to change the pattern of colonisation of the bacterium and the topography of gastritis and thereby decrease the incidence of duodenal ulcer disease. Given that atrophic gastritis and gastric atrophy precede the development of a high proportion of gastric cancers, we suggest that in areas where there is a high prevalence of *H pylori* and a high incidence of duodenal ulcer disease, important co-factors required for the development of atrophy, intestinal metaplasia and gastric cancer may occur less commonly. Where such co-factors are present, decreased acid output associated with atrophic changes may lead to a significant decrease in the incidence of duodenal ulcer disease.

In conclusion, we have found a high rate of duodenal ulcer disease and a relatively low rate of gastric ulcer disease in an area of low gastric cancer mortality in southern China. We have also shown a topographical relationship between *H pylori*, the inflammatory response, and gastroduodenal disease. Our data indicate that a high prevalence of *H pylori* infection will lead to a high overall incidence of upper gastrointestinal disease, however, the form of such disease may be dictated by key environmental triggers.

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