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REVIEW

Helicobacter pylori associated chronic gastritis, clinical syndromes, precancerous lesions, and pathogenesis of gastric cancer development

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Abstract

Helicobacter pylori (*H. pylori*) infection is well known to be associated with the development of precancerous lesions such as chronic atrophic gastritis (AG), or gastric intestinal metaplasia (GIM), and cancer. Various molecular alterations are identified not only in gastric cancer (GC) but also in precancerous lesions. *H. pylori* treatment seems to improve AG and GIM, but still remains controversial. In contrast, many studies, including meta-analysis, show that *H. pylori* eradication reduces GC. Molecular markers detected by genetic and epigenetic alterations related to carcinogenesis reverse following *H. pylori* eradication. This indicates that these changes may be an important factor in the identification of high risk patients for cancer development. Patients who underwent endoscopic treatment of GC are at high risk for development of metachronous GC. A randomized controlled trial from Japan concluded that prophylactic eradication of *H. pylori* after endoscopic resection should be used to prevent the development of metachronous GC, but recent retrospective studies did not show the tendency. Patients with precancerous lesions (molecular alterations) that do not reverse after *H. pylori* treatment, represent the "point of no return" and may be at high risk for the development of GC. Therefore, earlier *H. pylori* eradication should be considered for preventing GC development prior to the appearance of precancerous lesions.

Key words: *Helicobacter pylori*; Gastric atrophy; Intestinal metaplasia; Gastric cancer; Eradication; Prevention; Molecular alteration

Core tip: This review provides a current understanding on *Helicobacter pylori*, pathogenesis of chronic gastritis, gastric intestinal metaplasia, gastric carcinoma, and prevention strategy.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is the most common chronic infection worldwide, with a prevalence of approximately 50%; however, the majority of the infected individuals are asymptomatic[1]. The country-to-country variance in prevalence ranges from as low as 30% in the United States to as high as 90% in developing countries such as Iran[2,3]. This large reservoir of asymptomatic carriers renders *H. pylori* a difficult infection to eradicate. Many factors determine a country's infection rate, with socio-economic status and living conditions in early childhood as the principle determinants. Another important factor is mode of transmission, with horizontal transmission amongst the general population as the predominant mode in developing countries verses transmission *via* family members in industrialized countries[4,5]. The person-to-person transmission of this infection is thought to occur *via* multiple routes: fecal-oral[6], oral-oral[7] as well as environmental transmission through a contaminated water supply[8]. There is evidence of earlier infection in developing nations compared to industrialized nations[9]. There are also reports of a higher prevalence of *H. pylori* in industrialized Asian countries compared to their western counterparts. For example the prevalence of *H. pylori* was noted to be 39% in Japan and 60% in South Korea[2], which are both industrialized, affluent countries with safe water supplies. One hypothesis is the potential increase in oral-oral transmission[7] of this infection due to the "family-style" sharing of meals and plates *etc.* typical in Asian countries.

Here we review *H. pylori* infection, diagnosis, and clinical syndromes with a primary focus on its effect on precancerous lesions, *i.e.*, chronic atrophic gastritis (AG) and gastric intestinal metaplasia (GIM), development of gastric cancer (GC) and discuss early diagnosis, efficient preventive strategies for GC based on the clinical literature, through original contributions, systematic reviews, and meta-analyses.

BACTERIOLOGY

H. pylori is a Gram-negative microaerophilic spiral-shaped bacterium with a flagella that enables it to colonize the human gastrointestinal tract. It has evolved various mechanisms to promote its survival in the stomach's acidic environment and increase its ability to cause infection. One such adaptation is urease, an enzyme that hydrolyzes urea and releases ammonia, which in turn neutralizes gastric acid, allowing *H. pylori* to survive and colonize the gastric mucosa[10]. The other main feature of *H. pylori* is its ability to adhere to the gastric epithelium, which is achieved through receptor-mediated adhesion[11] *via* an array of outer membrane proteins. These proteins include adherence lipoprotein A and B (AlpA/B), blood group antigen binding adhesion (BabA), outer inflammatory protein A (OipA) and sialic acid binding adhesion (SabA). Although many other proteins in this class may play a role in cell adhesion and infection, the aforementioned are the major players. Additionally, cellular damage is achieved predominantly through the effects of two genes: vacuolating cytotoxin A (*VacA*) and cytotoxin associated gene A (*CagA*) which mechanism of action and interaction will be discussed in depth later in this article. Even though *H. pylori* is considered a non-invasive bacterium, there is some data supports its ability for intracellular invasion through mechanisms not yet fully understood[12]. *H. pylori* is a truly heterogeneous bacterium, expressing a wide array of multiple clinically important virulence factors that also seem to have a geographic influence.

DIAGNOSIS

The American College of Gastroenterology guideline in 2007 recommended testing for *H. pylori* only with the intention to treat a positive test result[13]. Absolute indications for testing and treatment include patients with active peptic ulcer disease, confirmed history of peptic ulcer but not previously treated, gastric mucosa-associated lymphoid tissue (MALT), and early GC. Relative indications include testing in patients with unexplained dyspepsia without alarming features. In the United States, a majority of these patients may have symptoms of gastroesophageal reflux disease (GERD) rather than *H. pylori* infection. Also testing for *H. pylori* prior to initiating non-steroidal anti-inflammatory drug treatment is usually not recommended in areas with low prevalence of *H. pylori*. Rarely unexplained iron deficiency anemia[14] or immune thrombocytopenic purpura can be reversed with *H. pylori* treatment, again the incidence of these finding would be low in the United States[15,16]. For asymptomatic patients, if they have a first degree relative with GC or are of high risk populations (Asians, Eastern Europeans, or Meso-american descent), are considered as higher risk populations for the development of GC[17].

Diagnostic testing for *H. pylori* can be divided into endoscopic and nonendoscopic techniques. The techniques could be direct (culture, histology, or detection of bacterial antigen in the biopsy tissue or stool) or indirect (using urease breath test, or an antibody response as a marker of disease). Serologic test for antibody indicates exposure to bacteria but does not help to assess active infection. The choice of a suitable test depends upon a variety of issues such as cost, accessibility, clinical situation, any family history of GC, and pretest probability of infection which is affected by population prevalence of infection. Also factors include the use of proton pump inhibitors, antibiotics or bismuth-containing compounds that may influence the accuracy of some test results.

CLINICAL SYNDROMES

Although the majority of *H. pylori* infections are thought to be asymptomatic, their clinical manifestations can be confounded by other disease processes such as functional dyspepsia and GERD. However a certain population of individuals infected with *H. pylori* can develop pathological findings of non-malignant and malignant diseases.

FUNCTIONAL DYSPEPSIA/GERD

The relationship between *H. pylori* and a host of other gastrointestinal diseases is currently under investigation. Functional dyspepsia is a common ailment which occurs in 10%-30% of the population each year with no clear understanding of the pathophysiology of this disorder[18]. The underlying cause of functional dyspepsia is likely multi-factorial and the role of *H. pylori* is unclear. However, a large meta-analysis which examined 14 randomized controlled trials demonstrated that treating *H. pylori* improved dyspeptic symptoms up to 1 year later with an OR of 1.38; 95%CI: 1.18-1.62[19]. Due to these studies that evidenced improvement in dyspeptic symptoms with *H. pylori* eradication, many guidelines now recommend treating patients who test positive for the bacterium and suffer from functional dyspepsia[20].

GERD is an extremely common disease and its relationship with *H. pylori* is somewhat controversial. Several studies demonstrated an increase in GERD symptoms and esophagitis even after successful eradication of *H. pylori*[21]. However, upon further review, this relationship did not hold true in a meta-analysis comparing 10 trials and showed that reflux symptoms were similar in the *H. pylori*-treated groups and the controls. Although, improvement of reflux symptoms post treatment is also reported[22]. It is evident that *H. pylori* may be involved in more disease processes than previously thought, however before any definitive relationship can be established, more research is needed for clarification.

GASTRITIS

Gastritis is defined by inflammation of the stomach lining associated with mucosal injury. The duration of mucosal inflammation can be used to separate this condition from acute gastritis and chronic active gastritis. *H. pylori* is the most common infectious etiology associated with gastritis.

The majority of patients infected with *H. pylori* develop acute gastritis which may spontaneously resolve. The ability of *H. pylori* to cause acute gastritis is best demonstrated from studies where healthy volunteers have been intentionally infected with the organism. This acute infection is associated with the development of hypochlorhydria and neutrophilic infiltration on gastric biopsy[23-25].

After an acute *H. pylori* infection, the majority of acute gastritis evolves into chronic active gastritis that is histologically characterized by mononuclear cells, predominantly lymphocytes, plasma cells and macrophages. Lymphoid follicles with germinal centers are frequently seen and are characteristic of an *H. pylori* infection[26-28]. Three types of chronic gastritis are recognized: pangastritis, antrum predominant, and corpus predominant. Diffuse antral gastritis with normal or increased acid secretion. This is associated with little or no gastric atrophy and duodenal ulcers (DUs). Persistent inflammation results in the development of gastric atrophy with hypochlorhydria, or achlorhydria[29,30]. These changes facilitate the proximal migration of the bacteria, leading to corpus or multifocal gastritis, which tends to progress through intestinal metaplasia, then to intestinal type GC.

PEPTIC ULCER DISEASE

There is a clear association between *H. pylori* infection and the development of peptic ulcer disease. The prevalence rate of peptic ulcer disease caused by *H. pylori* remains high in Asia at about 93%[31]. In the United States and in Western Europe the prevalence rate of peptic ulcer disease have been lowered in the range of 40%-75% due to a declining occurrence of *H. pylori* infection[32-34].

Certain *H. pylori* genes and virulent factors have been suggested for the development of peptic ulcer disease. Virulent factor such as *VacA* m1 is possibly associated with an increased risk of peptic ulcer disease[35]. In China, the prevalence of dupA gene was highest in DU and inversely related to gastric ulcer and GC[36,37].

H. pylori eradication has been shown to be a cost effective approach to reduce peptic ulcer disease recurrence and increase DU healing rate[38-41]. According to a recent prospective, long-term study that 1000 patients were followed up for at least 12 mo to assess ulcer rebleeding rate after *H. pylori* eradication, the cumulative incidence of rebleeding was 0.5% (95%CI: 0.16%-1.16%), and the incidence rate of rebleeding was 0.15% (95%CI: 0.05%-0.36%) per patient-year of follow up. The authors concluded that peptic ulcer rebleeding virtually does not occur in patients with complicated ulcers after *H. pylori* eradication. Maintenance antisecretory therapy is not necessary if eradication is achieved[42]. Similarly, a recent systematic review and meta-analysis of five randomized controlled trials with 401 patients were performed to evaluate the effects of *H. pylori* eradication on prevention of ulcer recurrence after simple closure of perforated peptic ulcers. A high prevalence of *H. pylori* infection was found in patients with perforated peptic ulcers. Eradication of *H. pylori* has significantly reduced the incidence of ulcer recurrence at 8 wk (RR = 2.97; 95%CI: 1.06-8.29) and 1 year (RR = 1.49; 95%CI: 1.10-2.03) post-operation[43].

H. PYLORI AND GC

It has been postulated that *H. pylori* infection causes chronic gastritis, AG, usually with GIM and dysplasia, and GC, especially intestinal-type[44-46]. The stepwise course of this infection, which usually continues over decades, has been defined as a sequence of histological events that confer an increasing risk of malignant transformation, as described in Correa's hypothesis[44]. A meta-analysis showed that *H. pylori* eradication seems to reduce GC[47]. However, a recent study from Japan showed that there is a risk of developing GC of both the intestinal (0.17% per year) and diffuse (0.13% per year) types even after the cure of *H. pylori* infection and extinction of gastric inflammation[48]. It has been also reported from Japan that *H. pylori* treatment reduces the risk of developing new GC in patients who have a history of GC and are thus at high risk for this development[49]. However, recent retrospective studies show that *H. pylori* eradication does not reduce the incidence of metachronous GC[50,51]. These results indicate that the establishment of predictable markers for the development of GC from patients cured of *H. pylori* infection is needed.

Up to now, a number of genetic and epigenetic alterations of tumor suppressor and tumor related genes involve the development or progression of precancerous lesions as well as GC have been reported.

GC is the second-leading cause of cancer death both worldwide and in Japan. GC is histologically divided into two types, intestinal and diffuse types[52]. One of the main risk factors for the development of both type of GC is considered to be *H. pylori* infection[53-57]. Therefore, in uninfected persons GC does not develop[58] besides cardia/junctional GC[59].

GEOGRAPHICAL ENIGMA

Observations of geographical differences in the prevalence of *H. pylori* and its related diseases, especially in Asia, have been intriguing. Although there is a strong link between *H. pylori* infection and GC in East Asia including Japan, the prevalence of *H. pylori* infection is high in some countries such as India and Bangladesh with low GC rates. There are several possible factors that affect this enigma[60-62]. First, the presence of virulent factors in the infecting *H. pylori* strain is a known determinant factor of the outcome of the infection. The *CagA* and *VacA* of *H. pylori*, have been associated to phenotypic characteristics of virulence. It has long been noted that patients infected with strains with an intact *cag* pathogenicity island have a more intense inflammatory response and this was also associated with an increased chance of developing GC or peptic ulcer disease[63]. Infection with *Cag*-positive *VacA* s1/m1 strains is associated with precancerous lesions and the development of GC, while persistent non-atrophic gastritis associated to *Cag* negative *Vac*A s2/m2 does not increase the risk of cancer[64]. Most *H. pylori* clinical isolates in Japan and South Korea have been reported to possess both *Cag*A and *Vac*A genes with *Vac*A genotype s1/m1, and this genotype is associated with progression of gastric preneoplastic lesions and cancer risk[65-68]. In contrast, *Vac*A genotype in India and Taiwan, where the prevalence of *H. pylori* is high and that of GC is low, is different[69,70]. Taken together, previous reports show a potential role of *H. pylori* strain genotype diversity in various presentation of gastric disease in different regions and populations.

Besides genetic diversity of the infecting *H. pylori* strains, other factors that may influence the etiology of GC include differences in the host genetic background in various ethnic groups, *i.e.*, gastric acid secretion and genetic polymorphisms in pro-inflammatory cytokines. These factors, in addition to environmental factors, such as personal hygiene and dietary habits, reflect the multifactorial etiology of GC[61].

PRECANCEROUS LESIONS

Atrophic gastritis

AG is characterized by chronic inflammatory processes of gastric mucosa that leads to the loss of appropriate glands[71] and a reduction of gastric secretory function. The extensive spread AG, which is associated with the state of achlorhydria or hypochlorhydria, is known to be a significant risk of GC[72,73]. The relation between *H. pylori* and GC depends on the factors that determine the severity and rate of progression of AG. Several studies show, furthermore, that precancerous conditions including AG and GIM are indicators of an increased risk for GC as compared with chronic gastritis in the absence of these lesions[73-75]. A prospective study by Uemura *et al*[58] also has showed that RR for GC was 1.7 (95%CI: 0.8-3.7) in moderate AG and 4.9 (95%CI: 2.8-19.2) in severe AG compared to none or mild AG (control).

It is generally considered that AG has a relatively high prevalence rate in countries with a higher prevalence of *H. pylori* infection and GC[74]. However, despite a high rate of *H. pylori* infection, there are some regions with a low prevalence of precancerous lesions and GC. This phenomenon is reported as the geographical enigmas (African, Asian, Indian and Costa Rican enigmas)[60-62]. Moreover, GC and DU occupy opposite ends of the spectrum of *H. pylori*-related disease. Most DU are categorized as antral-predominant gastritis[58] or nonatrophic gastritis[76], which have a low risk for GC and different from gastric and gastro-duodenal ulcers in pathophysiology[58,77].

Up to now, Miki *et al*[78] have reported that progression of AG correlates strongly with stepwise reductions in serum pepsinogen (PG) Ⅰ levels and the PG Ⅰ/Ⅱ ratio. In other words, measuring serum PG Ⅰ and the PG Ⅰ/Ⅱ ratio offers the opportunity to evaluate the progression of AG, a precursor of GC[79]. As criteria for the serum PG test used for GC screening, the combination of PG Ⅰ $\leqslant$ 70 ng/mL and PG Ⅰ/Ⅱ $\leqslant$ 3.0 is widely accepted as a reference value[79,80]. According to a recent meta-analysis of PG test, pooled sensitivity and specificity for GC detection were 77.3% (95%CI: 69.8-83.8) and 73.2% (95%CI: 72.8-73.6), respectively[81]. Thereafter, a combination of the serum PG test and *H. pylori* infection diagnosis was conducted to overcome the low sensitivity for GC detection[82,83]. The stage of *H. pylori*-related chronic gastritis was classified into 4 stages based on the combination of both test results: Group A [*H. pylori* (-), PG (-)]; Group B [*H. pylori* (+), PG (-)]; Group C [*H. pylori* (+), PG (+)]; and Group D [*H. pylori* (-), PG (+)].

Table 1 Operative link for gastritis assessment staging system

Atrophy score		Corpus			
		No atrophy (score 0)	Mild atrophy (score 1)	Moderate atrophy (score 2)	Severe atrophy (score 3)
Antrum	No atrophy (score 0) (including incisura angularis)	Stage 0	Stage Ⅰ	Stage Ⅱ	Stage Ⅱ
	Mild atrophy (score 1) (including incisura angularis)	Stage Ⅰ	Stage Ⅰ	Stage Ⅱ	Stage Ⅲ
	Moderate atrophy (score 2) (including incisura angularis)	Stage Ⅱ	Stage Ⅱ	Stage Ⅲ	Stage Ⅳ
	Severe atrophy (score 3) (including incisura angularis)	Stage Ⅲ	Stage Ⅲ	Stage Ⅳ	Stage Ⅳ

The stage of gastritis results by combining the atrophy score values as obtained in antral and corpus biopsy samples[84,85].

As a result, annual incidences of GC development were: Group A, 0%; Group B, 0.11%; Group C, 0.24%; and Group D, 1.31%. Thus, with *H. pylori* infection and AG progression, the rate increased in a stepwise and significant manner.

In histological diagnosis of AG, the Sydney System and its Houston updated version provide a uniform nomenclature for gastritis, as well as visual analogue scales[71] The system, however, lacks the element of prognosis and the same pathologists who use it in their research activities found it too cumbersome for routine diagnostic activities[84]. In 2005, Operative Link for Gastritis Assessment (OLGA) staging system was proposed by an international group of gastroenterologists and pathologists (Table 1)[84,85]. As the risk of GC directly relates to the extent of AG, an atrophy based staging system will provide implications for the prognosis and, possibly, the management of patients. This OLGA staging system may offer clinicians an immediate overall perception of the extent of gastric disease and also provides information regarding cancer risk, especially intestinal-type. In this system, stages Ⅲ and Ⅳ are significantly associated with GC development[86-88], thus being consistent with the biological assumption that the extent and location of atrophy correlate with the risk of cancer[58,89,90]. It has been reported, furthermore, that a significant association emerged between mean PG Ⅰ/Ⅱ values and OLGA stage (the lower the ratio, the higher the stage; by ordinal logistic regression: OR = 0.82; 95%CI: 0.72-0.94; $P < 0.006$), and the mean PG Ⅰ/Ⅱ ratio declined significantly as the OLGA stage increased (test for trend; $P < 0.001$)[88].

Gastric intestinal metaplasia

GIM is defined as the replacement of the gastric epithelium by two types of intestinal-type epithelium, which can be seen by Haematoxylin-eosin staining: (1) absorptive enterocytes with brush border along with goblet cells; and (2) columnar cells with foamy cytoplasm but lacking brush border[91]. Furthermore, it is divided into three phenotypes by alcian blue and high-iron diamine (AB/HID) staining as described by Filipe and Jass[92], namely type Ⅰ (complete or small intestinal type) and types Ⅱ and Ⅲ (incomplete or colonic type). When more than one type of GIM coexisted in a given sample, the case was classified according to the dominant type present in the section[92]. GIM is generally considered to be a condition that predisposes to malignancy, and also the presence of incomplete-type GIM (type Ⅲ) and a higher proportion of this type indicate a higher cancer risk, especially intestinal-type GC[91-94]. Shiotani *et al*[95] reported that incomplete GIM in the corpus lesser curve (OR = 6.4; 95%CI: 2.0-21, $P = 0.002$) is associated with an increased risk factor for GC. In contrast, there are opposite studies that detection of incomplete-type GIM (type Ⅲ) as detected by AB/HID staining is of limited value as an indicator of risk of GC, and AB/HID subtyping does not provide useful information to the clinician[96-98]. Therefore, the pattern, extent, and severity of atrophy with/without GIM may be the most important predictor of increased cancer risk than GIM subtype.

Some investigators consider incomplete-type GIM to be a mild form of dysplasia[99]. However, there are some other reports which intestinal-type GC does not necessarily arise from GIM, thus it remains controversial whether GIM is actually a precancerous lesion or not[100-102]. Indeed, previous studies have showed that GIM was not always noted in the surrounding mucosa of minute intestinal-type GC[102], indicating that GIM may be a paracancerous lesion, but not a precancerous lesion.

Detection of molecular alterations in precancerous lesion

GC develops through the accumulation of genetic and epigenetic alterations, but the mechanisms of induction have remained unknown. Similarly, molecular alterations are identified even in precancerous lesions including AG and GIM[103]. Preferential expression of COX-2 in colonic-phenotype (type Ⅲ) intestinal metaplasia associated with *H. pylori* and GC has been reported by Sun *et al*[104]. This has been further confirmed by using a colon epithelial specific antibody Das-1 as described below[105].

We have developed a novel monoclonal antibody (mAb), Das-1 (formerly known as 7E12H12, IgM isotype), which specifically reacts with the colonic epithelium[105], and have reported that GIM of a colonic phenotype, detected by mAb Das-1, is strongly associated with GC (Figure 1)[106,107]. Non-cancerous samples from 93% of patients having GIM as well as GC were found to react with mAb Das-1, whereas GIM samples from patients without GC reacted less frequently (35%) with the mAb ($P < 0.0001$)[106]. Subsequently, in a prospective study using a large cohort of patients infected with *H. pylori* and

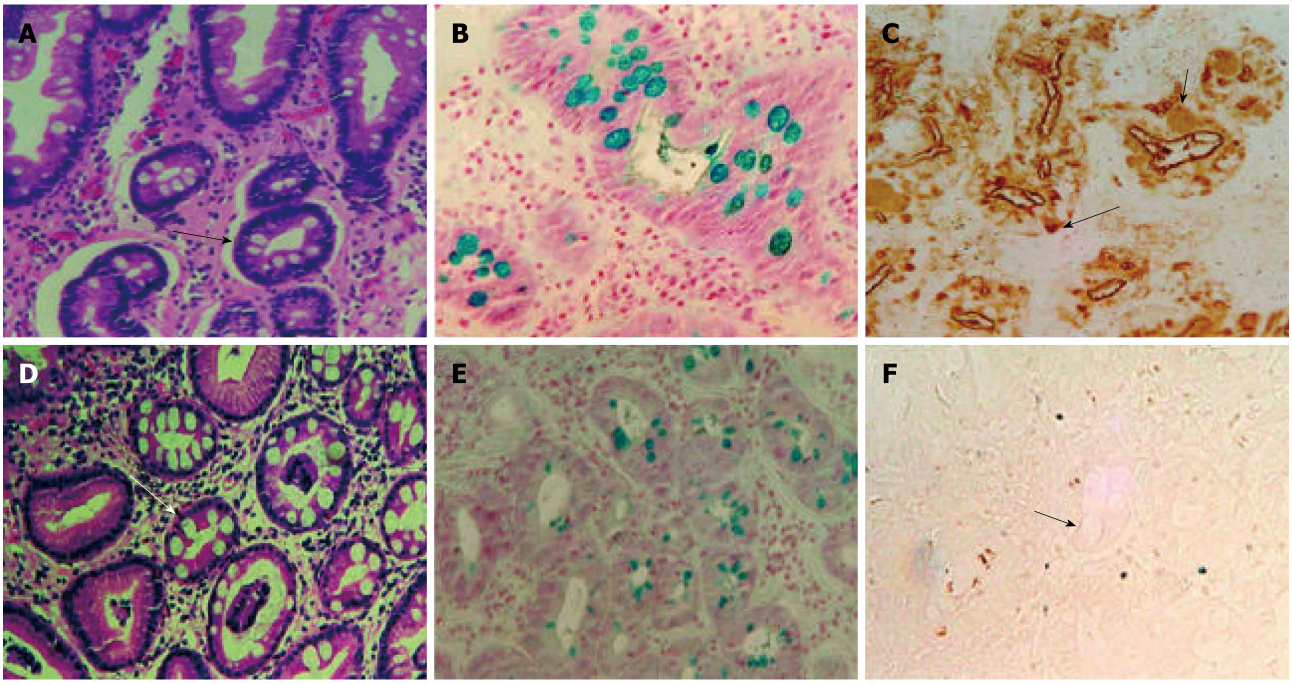

Figure 1 Serial sections of formalin fixed paraffin embedded biopsy tissue from two patients with gastric intestinal metaplasia without carcinoma. Haematoxylin-eosin staining (A, D), alcian blue/high iron diamine staining (B, E), and immunoperoxidase assay with the monoclonal antibody mAb Das-1 (C, F); (A-C) is from the same patient and (D-F) from the second patient. mAb Das-1 stained both goblet cells (shorter arrow) and metaplastic non-goblet cells (longer arrow) in the glands (C), suggesting colonic phenotype (incomplete type); While GIM is clearly evident with the presence of goblet cells (D, E) in the second patient, but mAb Das-1 did not stain the glands including goblet cells (F). The arrow shows the unstained goblet cells suggesting complete phenotype or small intestinal phenotype (original magnification × 160 for each part)[106].

with and without chronic gastritis who were followed up to 4 years showed a change in the phenotype of metaplasia which may be an important factor in the induction of GC. These results suggested that mAb Das-1 positivity in GIM could be a risk marker related to gastric carcinogenesis[106,107]. It has been reported that microsatellite instability (MSI) are frequently detected in GIM[108,109] and chronic gastritis mucosa[110], but there is little evidence of mismatch repair defects in these tissues[111]. We have also found that genomic instability, including MSI and loss of heterozygosity (LOH) in GIM may be associated with gastric carcinogenesis[57,58,112], and MSI or mAb Das-1 reactivity in GIM. This strongly predicts that the development of metachronous GC after endoscopic treatment to early stage GC is irrespective of the eradication of *H. pylori*[113].

Intestine-specific homeobox genes, caudal-type homeobox (*Cdx1*) and *Cdx2*, are transcription factors that regulate both proliferation and differentiation in intestinal epithelial cells[114,115]. CDX2 expression in the gastric mucosa is found in patients with chronic gastritis and is closely associated with GIM[116]. As to the important role of *Cdx2* in transdifferentiation of the gastric epithelial cells into GIM, Mutoh *et al*[117] reported that *Cdx2*-expressing transgenic mice induced GIM with an increase of epithelial cell proliferation. Also, they showed that invasive GC developed from GIM in Cdx2-transgenic mice[118], thus suggesting GIM itself may play a significant role in the genesis and progression of GC.

There have been only a few reports of this oncogene in *H. pylori*-associated chronic gastritis and GIM either with or without GC[119,120]. There is an interesting report that individuals with baseline K-*ras* mutations were more likely to progress from either atrophy to metaplasia or from complete-type GIM (type Ⅰ) to incomplete-type GIM (type Ⅲ); and those individuals with G→A transitions (Gly→Ser) were more likely to progress from atrophy to GIM than those individuals who lacked this mutation[119]. Similarly, mutations with AGT (Ser) were considered more likely to be advantageous in K-*ras* gene alterations and are important in gastric tumorigenesis in our study[121].

Epigenetic abnormalities are also important as cancer gene abnormalities in addition to gene structural abnormalities such as mutations and chromosomal deletions. In GC, inactivation of various genes because of methylation is more frequently observed compared to inactivation due to mutations or chromosomal deletions[122]. Even in noncancerous mucosa, aberrant methylation can be present. These findings suggest that aberrant methylation is deeply involved in gastric carcinogenesis, and aberrant methylation seems to be useful as a new target for diagnostics and prevention of GC[122]. Epigenetic methylation-associated inactivation of the *hMLH1* mismatch repair gene is a potent trigger of MSI, especially high-frequency MSI (MSI-H)[123]. DNA methylation of *hMLH1* promoter region CpG island is tightly associated with the loss of hMLH1 expression in GC exhibiting MSI[124]. In contrast, there are a few reported that mean methylation levels for

Table 2 Studies that examined histological improvements with a follow-up duration of more than 5 years after *Helicobacter pylori* eradication[129-134]

Ref.	Authors	Year	Country	Number of patients	Study design	Observation period (yr)	Gastric atrophy		Intestinal metaplasia	
							Antrum	Corpus	Antrum	Corpus
129	Forbes	1996	Australia	54	Prospective	7.1	No		No	
130	Ito	2002	Japan	22	Prospective	5.0	Yes	Yes	Yes	Yes
131	Zhou	2003	China	552	RCT	5.0	No	No	Yes	No
132	Leung	2003	Hong Kong	435	RCT	5.0	ND		Yes	
133	Vannella	2010	Italy	300	Observational	5.2	No	Yes	No	Yes
134	Kodama	2012	Japan	323	Prospective	10.0	Yes	Yes	No	Yes

RCT: Randomized control trial.

the tumor suppressor genes *CDKN2A* (*p16*) and *hMLH1* were very low, thus evaluating the correlation with GC risk was difficult[125,126]. Genes methylated by *H. pylori* infection show specificity. With *H. pylori* infection, resistant genes show no methylation at all while susceptible genes display a high frequency of methylation[127]. The hypermethylation of *E-cadherin* gene is accelerated by *H. pylori* infection[128].

CAN *H. PYLORI* TREATMENT REDUCE THE RISK OF GC?

Changes of preneoplastic lesions by H. pylori eradication

Some studies reported that the precancerous lesions including AG and GIM had improved after eradication, but other studies did not find any change[107]. Therefore, little consensus has been obtained as to the improvement of AG or GIM after eradication. Some of the reasons for these discrepancies may be ethnic variations, completeness of eradication, stage of the disease when treatment was initiated, and the short follow-up period (the follow-up period did not exceed 1 year). When evaluating the studies followed-up more than 5 years following *H. pylori* eradication, AG and GIM tended to improve histologically especially in the corpus (Table 2)[129-134].

Up to now, there are two meta-analyses regarding the long-term effects of *H. pylori* eradication on gastric histology[135,136]. According to a meta-analysis by Rokkas *et al*[135], for histological changes of AG, the pooled OR with 95%CI was 0.554 (0.372-0.825) ($P = 0.004$) in antrum and corpus 0.209 (0.081-0.538, $P < 0.001$) respectively. However, no histological improvement of GIM was seen; the pooled OR = 0.795, 95%CI: 0.587-1.078 ($P = 0.14$) in the antrum and the pooled OR = 0.891, 95%CI: 0.663-1.253 ($P = 0.506$) in the corpus. Their results showed significant improvement of AG, whereas improvement was not shown for GIM. In contrast, another meta-analysis by Wang *et al*[136] showed that comparing the histological alterations before and after *H. pylori* eradication, the pooled weighted mean difference (WMD) with 95%CI was 0.12 (0.00-0.23) ($P = 0.06$) for antral AG and 0.32 (0.09-0.54) ($P = 0.006$) for corpus AG; whereas the pooled WMD was 0.02 (-0.12-0.16) ($P = 0.76$) for antral GIM and -0.02 (-0.05-0.02) ($P = 0.42$) for corpus GIM, respectively. Their result has revealed that *H. pylori* eradication significantly improved AG in the corpus but not in the antrum; it also did not improve GIM[136]. As to difference of the results between these 2 meta-analysis, Wang *et al*[136] discussed that the study by Rokkas *et al*[135] used different selection criteria, extracted different data from each article, and did not include a recent trial with negative results.

Changes of molecular alterations by H. pylori eradication

We previously reported that although *H. pylori* eradication does not reduce the histologic GIM score, but it changes the cellular phenotype of GIM, as identified by mAb Das-1 and TC22-4 which related to carcinogenesis of colon epithelium→colon cancer[137]; therefore this change of phenotype may be an important factor in the reduction of cancer incidence after eradication of *H. pylori*[107]. It has bee also reported that *H. pylori* eradication reduced MSI in GIM[57,113].

Chan *et al*[138] and Leung *et al*[139] showed that *H. pylori* eradication therapy could reverse methylation of *E-cadherin* gene in patients with chronic gastritis. In addition, decreased methylation levels of other genes after *H. pylori* eradication have been confirmed in specific genes[140]. Once methylation has occurred in a cell, it is difficult to conceive that demethylation would again occur in the same region. The decrease in methylation levels observed after *H. pylori* eradication is thus probably due to cell turnover (temporary methylation). Residual aberrant methylation even after eradication is thought to reflect methylation in gastric gland stem cells (permanent methylation)[141]. Therefore, individuals with residual methylation after *H. pylori* eradication have a risk of GC.

Does H. pylori eradication actually reduce the risk of GC incidence?

According to a systematic review in total of 15 papers by Ito *et al*[142], the *H. pylori* eradication statistically reduces the prevalence of clinical GC by approximately one-third. Interestingly, the studies from Japan support this conclusion; however, studies from other countries have reported conflicting results. GC that developed after eradication revealed a mainly intestinal-type histology and depressed-type appearance. They mentioned, furthermore, that the following are possible reasons for reduction of GC: (1) eradication therapy inhibits the new occurrence of GC; (2) eradication regresses or inhibits the growth of GC; and (3) eradication interferes with the discovery of GC[142]. A recent meta-analysis of randomized, controlled trials (*n* = 7), mostly in Asia (*n* = 6), also show that *H. pylori* treatment seems to reduce GC risk (RR = 0.65, 95%CI: 0.43-0.98)[47]. Wong *et al*[143] found that although no overall reduction was observed in participants who received *H. pylori* treatment compared with those who did not, in the subgroup of *H. pylori* carriers without precancerous lesions, *i.e.*, AG or GIM, eradication of *H. pylori* significantly decreased the development of GC. Thus, they emphasized the concept of "point of no return"[144], in which the benefit of *H. pylori* eradication diminish after GIM stage was reached (in which many molecular changes had been detected).

Effect of eradication of H. pylori on incidence of metachronous gastric carcinoma after endoscopic treatment of GC

In 1997, Uemura *et al*[145] reported that eradication of *H. pylori* after endoscopic resection of early GC reduced the development of metachronous GC by a non-randomised study. Thereafter, Japan Gast Study Group concluded by a multi-center, open-label, randomized controlled trial that prophylactic eradication of *H. pylori* after endoscopic resection of early GC should be used to prevent the development of metachronous GC[49]. However, two retrospective studies from Japan showed that *H. pylori* eradication does not reduce the incidence of metachronous GC[50,51]. As mentioned by these studies, it should be noted that follow-up time longer than 5 years might be determined to be one of the independent risk factors for metachronous GC.

Surveillance of AG/GIM and perspectives

Recent study by de Vries *et al*[146] showed the incidence of pre-malignant gastric lesions such as AG and GIM is declining and a further decrease of at least 24% in the incidence of GC in the coming decade may be anticipated in Western countries without specific intervention. The precancerous lesions with molecular alterations may represent the "point of no return" when the development of GC can no longer be prevented by *H. pylori* eradication. Thus, earlier eradication of *H. pylori* is considered to be more effective in preventing GC by inhibiting the progression of AG or GIM[147]. As current surveillance of patients with precancerous lesions is inconsistent with their cancer risk, development of guidelines may be indicated[148]. A recent systematic review also indicates that *H. pylori* serology or endoscopic population screening is cost-effective, while endoscopic surveillance of precancerous lesions presents conflicting results, therefore better implementation of published guidelines with the addition of molecular markers may provide more efficient and cost effective outcomes[149].

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