

REVIEW

## *H pylori* and gastric cancer: Shifting the global burden

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### Abstract

Infection with *H pylori* leads to a persistent chronic inflammation of the gastric mucosa, thereby increasing the risk of distal gastric adenocarcinoma. Numerous studies have determined a clear correlation between *H pylori* infection and the risk of gastric cancer; however, general eradication is not recommended as cancer prophylaxis and time points for treatment remain controversial in different areas of the world. Prevalence rates in Western countries are decreasing, especially in younger people (< 10%); and a decline in distal gastric adenocarcinoma has been observed. Risk groups in Western countries still show considerably higher risk of developing cancer, especially in patients infected with *cagA*<sup>+</sup> strains and in persons harboring genetic polymorphism of the *IL-1B* promoter (-511T/T) and the corresponding *IL-1* receptor antagonist (*IL-1RN*\*2). Thus, general eradication of all infected persons in Western countries not recommended and is limited to risk groups in order to achieve a risk reduction. In contrast, infection rates and cancer prevalence are still high in East Asian countries. A prevention strategy to treat infected persons may avoid the development of gastric cancer to a large extent and with enormous clinical importance. However, studies in China and Japan indicate that prevention of gastric cancer is effective only in those patients that do not display severe histological changes such as atrophy and intestinal metaplasia. Thus, prophylactic strategies to prevent gastric cancer in high risk populations such as China should therefore especially aim at individuals now at younger age when the histological alterations caused by the bacterial infection was still reversible. In countries with a low prevalence of gastric cancer, risk groups carrying *cagA*<sup>+</sup> strains and *IL-1* genetic polymorphisms should be identified and treated.

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### INTRODUCTION

Since the discovery of *H pylori* in 1983, intensive research has led to the conclusion that infection with this bacterium is the major cause for the development of distal gastric cancer. Infection with the bacterium leads to a chronic inflammation of the gastric epithelium, associated with multifocal gastric atrophy, dysplasia, and malignant transformation in some of the infected patients<sup>[1-6]</sup>. Controversy remains why only a minority of infected patients develops distal adenocarcinoma, and how geographic differences between Western and Asian countries may contribute to these differences. *H pylori* infection rates average at about 30% in Western populations; in this part of the world, approximately 0.1%-1% of the patients with *H pylori* induced gastritis will develop distal gastric cancer<sup>[7,8]</sup>. Infection rates in Asian countries are higher and range at 60%-88%; distal gastric adenocarcinoma is even more frequent in these countries. Overall, gastric cancer was responsible for almost 650 000 deaths worldwide in the year 2000<sup>[9]</sup>. Death from gastric cancer is second only to lung cancer in men and thus contributes to approximately 10% of all cancer deaths annually (see: www.who.org). Since the diagnosis of early gastric cancer is difficult and in most cases diagnosis is made at a more progressed stage, treatment becomes cost-intensive. Therefore, there is a considerable interest to understand the underlining mechanisms and to find strategies to eradicate *H pylori* infection which could prevent gastric carcinogenesis. Such statistical calculations have already been anticipated 10 years ago in high risk populations of Japanese immigrants in Hawaii; currently, however, no guidelines exist when and whom to treat<sup>[10,11]</sup>.

### EPIDEMIOLOGICAL FEATURES IN EAST AND WEST

#### *H pylori* infection and gastric cancer in Western countries

In Germany in the year 2000, 21 000 patients suffered from gastric cancer with an equal distribution among males and females<sup>[12]</sup>. In the US (<http://seer.cancer.gov>),

a similar occurrence has been reported with more than 45000 deaths per year. In countries such as the USA or Germany, the prevalence of *H pylori* is decreasing, so that meanwhile less than 10% of the children are infected with this bacterium, underlining that a prophylactic eradication or vaccination in childhood is of little interest in these countries<sup>[8,13-15]</sup>. Nevertheless, infection rates are high in elderly populations above the age of 50, and this group is particularly suffering from gastric cancer. A reduction of cancer risk may be achieved when patients are cured from the infection. It may thus be important to identify those patients who are at increased risk.

### **Gastric cancer in Japan and East Asia**

Gastric cancer is the second highest cause of cancer-related deaths in Japan, and the death rate due to gastric adenocarcinoma has actually marginally increased to approximately 50000 deaths per year in this country<sup>[13,14,16]</sup>. In China, a similar prevalence of gastric cancer has been reported. *H pylori* infection rates in these countries are high and range from 60% in the younger population (10-40 years old) to 80%-90% in elderly patients above the age of 50. In Japan, mortality from distal gastric adenocarcinoma is among the highest scores of the world and could be attributed to the very high rates of *H pylori* infection in this country and the fact that the most common strain of *H pylori* found in Japan is extremely virulent. A prophylactic eradication in people at younger age could save millions of lives as well as enormous costs resulting from ulcer disease, gastrointestinal bleeding and gastric cancer treatment. Therefore, a successful eradication of this pathogen is of crucial socio-economical importance especially in countries such as Japan or China, particularly especially in persons who are at age < 50 years.

### **The "Asian paradox"**

Although there is a considerable high rate of *H pylori* infection in Asian countries such as China, Japan, Thailand and Indonesia, there is a remarkable difference regarding the outcome of gastric cancer within these countries. This observation has also been termed as the "Asian paradox": Although there is a high infection rate in Thailand and Indonesia, there is only little risk of developing gastric cancer in these countries<sup>[14,17]</sup>. As discussed below, bacterial virulence factors as well as the individual host immune response may be different among those countries and account for the differential development of the infection outcome. Questions remain whether to treat all infected patients, subgroups of patients, or wait until serious histological alterations have occurred in the various countries mentioned above. The outcome of infection, however, is difficult to predict. Recent studies have elucidated some of the mechanisms of chronic inflammation and thus enable a more precise prediction of the clinical course of infection in different countries.

### **Impact of strain types on development of distal gastric adenocarcinoma**

In recent studies, a new analytical investigation to overcome a potential underestimation of the association of *H pylori* with gastric cancer was performed in a

Western population. Applying various more stringent exclusion criteria to minimize a potential bias from this source increased the odds ratio (95% confidence interval) of non-cardia gastric cancer from 3.7 to 18.3 for any *H pylori* infection, and from 5.7 to 28.4 for *cagA*<sup>+</sup> *H pylori* infections in Germany<sup>[18-20]</sup>. A similar approach has been performed in a study from Sweden, and the results were remarkably consistent with the German study. The observations made in these studies are further supported by a recent cohort study from Japan, in which 36 out of 1246 *H pylori* infected subjects, but none of 280 uninfected subjects developed gastric cancer during a mean follow-up of 7.8 years<sup>[21]</sup>. These very stringent epidemiological studies strongly support that the *H pylori* gastric cancer association may have been strongly underestimated the risks in previous studies, and consequently, underline that infection especially with certain *cagA*<sup>+</sup> *H pylori* can be considered as a true carcinogenic factor. Determination of *cagA* status may thus help the physician to identify people who are at increased risk for gastric cancer. Meanwhile, tests have become available as a serological test and a specific antibody staining for histological specimens<sup>[16]</sup>.

## **IMPORTANCE OF BACTERIAL STRAIN TYPES: MOLECULAR AND IMMUNOLOGICAL MECHANISMS**

Bacterial virulence factors, especially genetic diversity in the *cagA* region, have been claimed to account for this diverging development. The *H pylori* *cag* pathogenicity island (*cagPAI*) is a 35 to 40 kb genetic element that encodes a type IV secretion system. One of the key factors of this system is the CagA protein; *cagA*<sup>+</sup> strains inject the CagA protein directly into host cells where it undergoes tyrosine phosphorylation by a host-cell kinase, and the phosphoprotein alters the physiology of the affected cells. Huang *et al* conducted a meta-analysis of the relationship between CagA seropositivity and gastric cancer<sup>[22]</sup>. Based on 7 studies with 1707 gastric cancer patients and 2124 matched controls the analysis showed that infection with *cagA*<sup>+</sup> *H pylori* strains increases the risk for gastric cancer 2.87 fold over the risk associated with *H pylori* infection alone.

Hatatekayama *et al* recently reported that CagA proteins isolated in East Asia, where gastric cancer is prevalent, have a distinct sequence at the phosphorylation site compared with CagA proteins from Western *H pylori* strains<sup>[23-25]</sup>. This CagA diversity may be one important variable in determining the biological activity of CagA and the clinical outcome of infection. Translocated CagA forms a physical complex with the SRC homology 2 domain (SH2)-containing tyrosine phosphatase (SHP-2) in a phosphorylation-dependent manner, and stimulates phosphatase activity. SHP-2 is known to play an important inductive role in mitogenic signal transduction. Deregulation of SHP-2 by CagA may induce abnormal proliferation of gastric epithelial cells. In addition, the CagA protein is polymorphic. Thus, CagA proteins isolated in northern parts of East Asia, where gastric cancer is prevalent, have a distinct sequence at the phosphorylation site and thus contribute to the differential outcome.

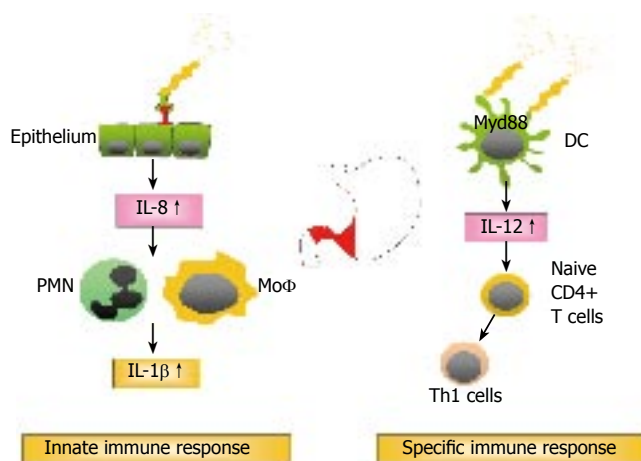


Figure 1 *H pylori*: Immune response and suppression.

### Importance of bacterial adherence factors

*cagA*<sup>+</sup> *H pylori* strains also are more likely to express the *babA* product, which mediates adherence to Lewis<sup>b</sup> antigens on gastric epithelial cells<sup>[26]</sup>. European studies have determined that bacteria expressing the adherence factor BabA are detected more frequently in patients with gastric cancer or severe histological changes in the mucosa. Comparing several independent studies in different countries, the relative risk for the development of distal gastric adenocarcinoma was increased up to 20-fold. These results support the hypothesis, that the risk of developing severe gastric pathologies is dramatically increased once the correct determination of the *cagA* status is performed<sup>[27-31]</sup>.

### Current model for the initiation of heightened gastric inflammation

A new concept has now emerged why *cagA*<sup>+</sup>/*babA*<sup>+</sup> *H pylori* strains induce higher levels of the proinflammatory cytokines IL-1β and IL-8. Adherence of *H pylori* to epithelial cells *via* BabA favors a more tight adhesion to the epithelial cell and thus promotes bacterial colonisation. Injection of CagA into epithelial cells is associated with IL-8 secretion, which in turn, acts as a local chemoattractant for polymorphic mononuclear cells (PMN)<sup>[29]</sup>. These PMNs are considered to be of critical importance for the breakdown of the local epithelial barrier and may lead to a further infiltration of the bacteria into the submucosa. Thus, several studies outline the view that bacterial virulence and adherence factors contribute to the development of severe diseases in the stomach. Infection with certain *H pylori* strain types is therefore more dangerous than smoking a pack of cigarettes per day, leading to a 21-fold increased relative risk for the development of lung cancer.

### Figure 1: Events during the initial infection process with *H pylori*

Infection with so called type 1 strains harboring *cagA/vacAs1* and *babA* is associated with a dramatically increased risk to develop distal gastric adenocarcinoma. Infection with specific strain types thus is the major determinant of the further sequence of events.

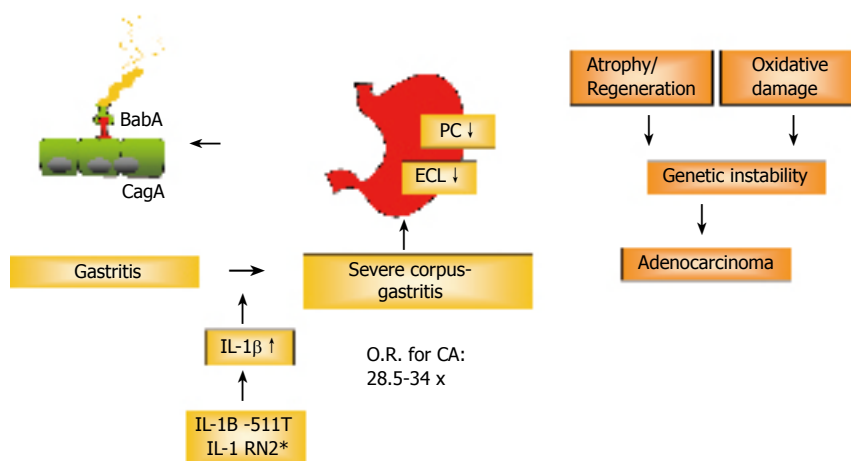
## IMPORTANCE OF HOST GENETICS FOR THE *H PYLORI* INDUCED INFLAMMATION AND CANCER DEVELOPMENT

### Genetic polymorphisms contribute to severe gastric inflammation

In addition to bacterial factors, but less important in terms of relative risk increment, are host factors that seem to influence the inflammatory response and the development of a more severe pathology. *H pylori* induced inflammation is implicated in the development of mucosal damage and is characterised by strong granulocytic and lymphocytic infiltration. The T helper cell response towards *H pylori* is generally considered to be of the Th1 phenotype, leading to a cell mediated immune response<sup>[32-35]</sup> (Figure 1). There is increasing evidence that the *H pylori* induced Th1 response contributes to cancer development. Downregulation of the Th1 response in mice by concurrent enteric helminth infection or p53 mutation was shown to protect against the development of atrophy, intestinal metaplasia, and invasive gastric carcinoma<sup>[35-37]</sup>. Important cytokines characterising Th1 mediated immune responses are interferon-γ (IFN-γ), tumour necrosis factor-α (TNF-α), and interleukin-1β (IL-1β), all being upregulated during chronic *H pylori* infection<sup>[38-40]</sup>. IL-10, which is also highly expressed in the *H pylori* infected stomach, is one of the most important regulatory cytokines, inhibiting cell mediated immune responses<sup>[38,41,42]</sup>.

Genes encoding cytokines and related molecules harbour polymorphic regions, which are considered to alter gene transcription and thereby influence inflammatory processes in response to infectious diseases. Polymorphisms in the human *IL-10*, *IL-1B*, *TNF-α*, *IFN-γ*, and *IL-1* receptor antagonist (*IL-1RN*) genes have been reported to influence cytokine expression<sup>[43-47]</sup>. In the promoter region of the *IL-1B* gene, *IL-1B-511T*, which is in complete linkage disequilibrium with *IL-1B-31C*, was previously associated with slightly, but not significantly, increased IL-1β secretion from stimulated PBMC. The *IL-1RN* gene has a penta-allelic 86 bp variable number of tandem repeat region (VNTR) in intron 2, of which allele 2 (*IL-1RN\*2*) was previously associated with enhanced IL-1β secretion<sup>[46]</sup> and the development of gastric cancer<sup>[44]</sup>. Presence of certain genetic polymorphisms of the host, in contrast to the bacterial factors, increase the relative risk for distal gastric adenocarcinoma by 1.5-4 fold. In a German population<sup>[48]</sup>, the homozygous genotype *IL-1RN\*2/2* of the *IL-1RN* gene was strongly associated with early-stage gastric cancer ( $P < 0.0001$ ), whereas further associations with the *IL-1* gene cluster were not observed. A Korean group<sup>[49]</sup> determined that patients with intestinal-type gastric cancer showed a higher frequency of *IL-1B-31T* homozygotes [odds ratio (OR) = 2.2; 95% confidence interval (CI) = 1.1-4.3] compared with controls. Risk was also significantly increased in these patients for *IL-1B-31T* homozygotes compared with patients with diffuse-type gastric cancer (OR = 3.4; 95% CI = 1.5-7.7). In a Chinese study, it was reported that the relative risks associated with the *IL-1B* variant genotypes were 1.64





**Figure 2** *H. pylori*: Chronic inflammation and carcinogenesis.

(95% CI, 1.01-2.66) for -31TT and 1.52 (95% CI, 0.91-2.54) for -511CC, respectively, compared with their wild-type homozygotes<sup>[50]</sup>. The risks were significantly more evident in individuals with *H. pylori* infection (adjusted OR = 2.14; 95% CI, 1.13-4.06 for -31TT; adjusted OR = 2.00; 95% CI, 1.02-3.89 for -511CC), which was consistent with the biological effects of IL-1 $\beta$ .

Chen *et al.*<sup>[51]</sup> identified that the carriage of IL-1RN\*2 polymorphism, male gender, old age and *H. pylori* infection independently increased the risk of gastric cancer, with odds ratios of 3.3 (95% CI, 1.4-7.7), 2.1 (95% CI, 1.2-3.8), 5.3 (95% CI, 3.1-9.0) and 2.2 (95% CI, 1.3-3.8), respectively. *H. pylori*-infected individuals who were carriers of IL-1RN\*2 showed increased risks for both intestinal and diffuse types of gastric cancer, with odds ratios of 11.0 and 8.7, respectively. Thus, IL-1RN\*2 was interpreted to be an independent factor governing the development of gastric cancer in Asian individuals.

In areas of high and low prevalence of gastric cancer in China<sup>[52]</sup>, the IL-1B -511T/T genotype frequency was significantly higher among patients with gastric cancer (25.0%) than control subjects (12.5%) in a region with low GC prevalence. While *H. pylori* infection alone had only a modest effect on the risk of gastric cancer development (OR = 5.0, 95% CI 1.5-16.3), combined with the IL-1B -511T/T genotype the risk was markedly elevated (OR = 17.1, 95% CI 3.8-76.4). The study underlines the synergy between *H. pylori* infection and the host immune response to induce gastric cancer.

A recent German study confirmed this synergistic effect also in regard to the induction of premalignant changes. In a large group of *H. pylori* infected patients<sup>[29]</sup>, carriers of the proinflammatory IL-1B -511T/-31C and IL-1RN\*2 alleles had an increased risk for the development of atrophic gastritis (AG), intestinal metaplasia (IM), and severe inflammation, ORs of 1.7 (95% CI, 0.8-3.4) to 4.4 (95% CI, 1.5-12.9). The highest prevalence of severe gastric abnormalities was found in patients with both host and bacterial high-risk genotypes (*cagA*<sup>+</sup>/*vacAs1*<sup>+</sup>/IL-1B -511T/IL-1RN\*2), with ORs of 24.8 (95% CI, 5.2-117.3) for severe lymphocytic infiltration, 9.5 (95% CI, 2.8-32.1) for severe granulocytic infiltration, 6.0 (95% CI, 2.4-15.5) for IM, and 2.4 (95% CI, 0.93-6.2) for AG. These dramatically elevated values underline the importance

of the infection for gastric cancer development. It may thus be concluded from the above studies, that combined bacterial/host genotyping thus may provide a clinical tool to identify patients at high risk of developing gastric cancer. This current concept of gastric carcinogenesis is illustrated in Figure 2.

### Figure 2: Concept of gastric carcinogenesis

There is overwhelming evidence that *H. pylori* infection, especially with *cagA*<sup>+</sup> strains, leads to a strong granulocytic and lymphocytic infiltration; a subgroup of infected patients will develop gastric cancer, especially in high-risk countries such as Japan, China and East-European countries. Reasons for this progression include genetic polymorphisms, e.g. IL-1B/IL-1RN polymorphisms associated with high levels of IL-1 $\beta$ . IL-1 $\beta$  is a strong antisecretory cytokine. These genetic polymorphisms lead to a heightened cytokine release, which in turn decreases acid secretion. Subsequently, the association of hypochlorhydric conditions with the persistent inflammation in the gastric corpus is considered to be a true risk factor (RR: 34.5-fold!) for the development of gastric cancer. Studies should therefore aim not only at preventing gastric cancer, but also at preventing the development of severe corpus gastritis, leading to potentially irreversible atrophy and hypochlorhydria.

## PROPHYLAXIS OF GASTRIC CANCER

### Prospective intervention studies

Data from a Chinese trial<sup>[53]</sup> investigating *H. pylori* eradication in gastric cancer showed that the incidence of gastric adenocarcinoma development was similar in patients undergoing eradication therapy compared with placebo over a 7.5-year period. Interestingly, in a subgroup of *H. pylori*-positive patients without atrophy, intestinal metaplasia or dysplasia (pre-cancerous lesions), eradication therapy significantly decreased the development of gastric adenocarcinoma to a frequency of zero. The data are in accordance with a recent study in Japan<sup>[4]</sup>: in this prospective study, no carcinomas were observed in the *H. pylori* negative group. This study supports the view that a prospective eradication study should be performed in young adults in which histological alterations have not

proceeded too far and may be reversible.

Zhou *et al*<sup>[54]</sup> investigated histopathological changes in *H pylori* eradicated subjects in China over a period of more than 5 years. The authors report in a group of 552 *H pylori*-positive subjects that, the severity and activity of inflammation in both the antrum and body were markedly reduced after *H pylori* eradication. Within the five years after eradication of *H pylori*, intestinal metaplasia in the antrum regressed or showed no progression, while the proportion of intestinal metaplasia in the *H pylori*-positive group increased significantly. After *H pylori* eradication, the atrophy in both the antrum and body had no significant regression. After eight years of observation, the authors report a significantly higher incidence of gastric cancer in the *H pylori* infected group (5/1530) than in the *H pylori*-negative (1/1230) group in the Yantai area of China, underlining the need for eradication in early stages.

### Serum pepsinogen levels as risk factors for developing gastric cancer

A recently published study<sup>[55]</sup> reports that subjects seropositive for either *H pylori* or CagA who had low pepsinogen (PG) I levels had the highest OR (9.21 95% CI 4.95-17.13) for noncardia cancer, compared with subjects with neither factor. The results suggest that individuals with both *H pylori* or CagA seropositivity and a low PG I level or low PG I / II ratio are highly susceptible to development of noncardia gastric cancer. Such tests can easily be performed in clinical routine. Watabe *et al*<sup>[56]</sup> have confirmed that *H pylori* infection and gastric atrophy are both risk factors for gastric cancer in a study group with a total of 9293 participants. The annual incidence of gastric cancer was 0.04%-0.60%. As expected, the highest relative risk for gastric cancer was found in *H pylori* infected subjects with gastric atrophy and high serum pepsinogen levels [OR = 8.2 (3.2-21.5)].

### *H pylori* eradication and the risk of esophageal cancer

Concerns exist whether eradication of *H pylori* might lead to the development of esophageal cancer. To clarify the role of *H pylori* infection in these tumors with divergent incidence trends, Chow *et al*<sup>[57]</sup> analyzed serum IgG antibodies to *H pylori* and to a recombinant fragment of CagA by antigen-specific ELISA among 129 patients newly diagnosed with esophageal/gastric cardia adenocarcinoma, 67 patients with noncardia gastric adenocarcinoma, and 224 population controls. Infection with *cagA*<sup>+</sup> strains was not significantly related to risk for noncardia gastric cancers (OR = 1.4; CI = 0.7-2.8) but was significantly associated with a reduced risk for esophageal/cardia cancers (OR = 0.4; CI = 0.2-0.8). The study thus contradicts previous reports and may be biased by the selection of patients in a rather small group. While Wu *et al*<sup>[58]</sup> found no significant association, Ye *et al*<sup>[59]</sup> determined the opposite: *H pylori* infection may protect from esophageal cancer (OR = 0.3). Thus, at this point, several works indicate that CagA has a protective effect on the development of esophageal cancer, however, no general conclusions can be made.

However, this association does not justify a general refusal of *H pylori* eradication because of two reasons. First, esophageal adenocarcinoma is far less common

than gastric cancer. Second, the risk of developing adenocarcinoma of the esophagus is lowered by a factor 2-2.5 in the presence of *cagA*-positive *H pylori* infection whereas the risk for distal gastric cancer associated with *cagA*-positive strains is much higher (5-28x).

## CONCLUSIONS

*H pylori* is a clear cut carcinogen. Infection with certain strain types in the presence of genetic polymorphisms leading to a heightened inflammatory response is associated with a dramatically increased relative risk to develop gastric cancer. Such developments can be foreseen by evaluating gastric biopsies, but also by determining serum pepsinogen levels as a marker of gastric atrophy. Endoscopy of the upper gastrointestinal tract (GI) should be performed before eradication to determine the status of gastric inflammation. Eradication of *H pylori* as prophylaxis of gastric adenocarcinoma is effective in early stages in which no severe histological changes have occurred. In countries with a high prevalence of infection and high cancer risks such as Japan or China, a general prophylactic eradication strategy seems to be beneficial especially in younger patients (< 50 years); nevertheless, the outcome of such long term prospective prophylactic studies needs to be evaluated. In Western countries with low prevalence rates and low cancer rates, a test-and-treat strategy is not cost-effective to prevent cancer; however, identification and treatment of risk groups seems rationale. Risk groups can be identified by evaluation of family history, presence of histological alterations in the gastric corpus, or by determining infection with *cagA*<sup>+</sup> strains as well as determining the status of genetic polymorphisms in the IL-1RN\*2 gene.

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