Causal role of Helicobacter pylori infection in gastric cancer

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Abstract
Gastric cancer is the second most frequent cancer in the world, accounting for a large proportion of all cancer cases in Asia, Latin America, and some countries in Europe. Helicobacter pylori (H. pylori) is regarded as playing a specific role in the development of atrophic gastritis, which represents the most recognized pathway in multistep intestinal-type gastric carcinogenesis. Recent studies suggest that a combination of host genetic factors, bacterial virulence factors, and environmental and lifestyle factors determine the severity of gastric damage and the eventual clinical outcome of H. pylori infection. The seminal discovery of H. pylori as the leading cause of gastric cancer should lead to effective eradication strategies. Prevention of gastric cancer requires better screening strategies to identify candidates for eradication.

INTRODUCTION
Helicobacter pylori (H. pylori) is a Gram-negative, microaerophilic bacterium which expresses an abundant amount of urease. Infection with this bacterium is a worldwide phenomenon. Prevalence increases with age, but differs quite dramatically among populations. In the USA, prevalence is less than 20% at 20 years old and approximately 50% at 50 years. In Japan, it is less than 20% under 20 years, increasing to a plateau of 70-80% at 40 years, while in Korea, it is 50% at 5 years and 90% at 20 years.

The epidemiological data suggest that H. pylori gastritis is associated with gastric carcinogenesis. H. pylori colonizes the gastric mucosa and elicits both inflammatory and immune lifelong responses, including the release of various bacterial and host-dependent cytotoxic substances. Pathological and clinical studies have convincingly proved the etiological role of H. pylori in the development of chronic gastritis and peptic ulcer. Moreover, H. pylori infection has been recognized as a risk factor for both the diffuse and intestinal types of gastric cancer, and the bacterium itself is classified as a class I carcinogen by the World Health Organization and International Agency for Research on Cancer Consensus Group.

H. pylori strains carrying the cytotoxin-associated gene A (cagA) gene are strongly associated with an increased risk of gastric adenocarcinoma. Recent studies suggest that the severity of gastric damage and eventual clinical outcome of H. pylori infection are determined by a combination of host genetic and bacterial virulence factors. H. pylori infection has been recognized as a risk factor for both the diffuse and intestinal types of gastric cancer. The grade of gastric atrophy (and therefore gastric cancer risk) is higher in patients with East Asian cagA-positive strains than in those with cagA-negative or Western cagA-positive strains. Of interest is that atrophy grade varies even among patients with East Asian cagA-positive strains, and that most H. pylori-infected subjects in fact develop no significant disease, remaining asymptomatic throughout their lives. The reasons for this are not explained by bacterial virulence factors alone; rather, genetic factors of the host should also be considered to play a role in H. pylori-induced outcomes.

Here, we discuss recent developments in gene-environment interaction and the importance of H. pylori eradication in the prevention of gastric cancer.

Association between H. pylori and gastric cancer
H. pylori has been associated with the location of gastric cancers, specifically those of the body and antrum. No association is seen with the location of cardiac tumors. H. pylori gastritis is characterized by severe, acute and chronic inflammation which would last for decades if not treated. Such persistent inflammation likely has serious biological implications. For example, activated neutrophils generate reactive oxygen and nitrogen species, which are mutagenic and carcinogenic. Atrophic
Recent studies have suggested that patients infected with \textit{cagA}-positive strains of \textit{H. pylori} are at a significantly higher risk for gastric cancer than those carrying \textit{cagA}-negative strains\cite{35,36}. \textit{CagA} protein, encoded by the \textit{cagA} gene, is one of the most studied virulence factors of \textit{H. pylori} and is a highly immunogenic protein. The \textit{cagA} gene is one of several genes of a pathogenicity island (PAI) called the \textit{cag} PAI. The \textit{cag} PAI contains 31 genes, 6 of which are thought to be encoded by a putative type IV secretion system. Although \textit{H. pylori} \textit{cagA}-positive isolates from the USA and Japan induce similar IL-8 and apoptosis levels\cite{37}, the grade of gastric atrophy (and gastric cancer risk) is higher in patients with the East Asian \textit{cagA}-positive strains than in those with \textit{cagA}-negative or Western \textit{cagA}-positive strains\cite{38}. In Asian populations, however, almost all infected subjects harbor \textit{cagA}-positive strains, raising legitimate questions about the relevance of this virulence factor as a risk determinant in such populations.

Held \textit{et al} reported that although patients with antibodies to \textit{CagA} at greatest risk of gastric cancer, risk is still significantly higher in those with \textit{cagA}-negative \textit{H. pylori} infections than in uninfected persons\cite{39}. Anti-\textit{CagA} responses correlate with neutrophil infiltration, a low anti- \textit{H. pylori} IgG titer or combined with \textit{H. pylori} seronegativity was closely associated with non-cardia gastric cancer, independently of ethnicity\cite{40}. A meta-analysis of the relationship between \textit{CagA} seropositivity and gastric cancer showed that infection with \textit{cagA}-positive \textit{H. pylori} increased the risk for gastric cancer over that with \textit{H. pylori} infection alone\cite{41}. Because antibodies to \textit{CagA} remain positive for longer than IgG antibodies to \textit{H. pylori}\cite{42,43}, the risk for gastric cancer based on \textit{H. pylori} IgG antibody might be underestimated\cite{38,44}.

\textit{CagA} is delivered into epithelial cells by the \textit{cag} type IV secretion system, then phosphorylated on tyrosine residues and wired to the eukaryotic signal transduction pathway, which plays a major role in \textit{H. pylori} -host cell interactions and pathogenesis (Figure 1)\cite{45-48}. In the injected gastric epithelial cell, \textit{CagA} induces cellular spreading and elongation, termed the hummingbird phenotype, and this is thought to play a crucial role in the pathogenesis of \textit{cagA}-positive \textit{H. pylori} infection. This \textit{CagA}-dependent morphological transformation of gastric epithelial cells requires src homology 2 domain-containing protein tyrosine phosphatase-2 (SHP-2)\cite{49}. SHP-2 plays a key role in the intracellular signaling elicited by a number of growth factors, hormones and cytokines\cite{50-53}. East Asian-type \textit{CagA} exhibits stronger SHP-2-binding activity than Western-type \textit{CagA}\cite{49,54}. \textit{CagA}-SHP-2 signaling may induce apoptosis and elevate the epithelial cell turnover associated with \textit{cagA}-positive \textit{H. pylori} infection\cite{55-58}. Extra cycles of DNA replication would increase the chance of genetic mutation leading to abnormal proliferation.

We have reported the association of a frequent single nucleotide polymorphism (SNP, JST057927, G-to-A) in the \textit{PTPN11} gene that encodes SHP-2 with gastric atrophy and gastric cancer\cite{59}. We found that this polymorphism increased the risk of gastric atrophy and gastric cancer among \textit{H. pylori} -seropositive Japanese subjects. Carriage of the G allele of \textit{PTPN11} increased the risk of atrophy.

\textbf{Role of \textit{cagA}-positive \textit{H. pylori} in the pathogenesis of gastric cancer}

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whereas the A/A genotype was protective against it. The SHP-2-binding activity of CagA influences the virulence in the induction of gastric atrophy, the precursor lesion of gastric cancer. PTPN11 G/A polymorphism may constitute a genetic trait of the host predisposing to atrophy among those infected (Figure 2). CagA-SHP-2 complex formation may induce abnormal proliferation and movement of gastric epithelial cells, cellular changes that may eventually lead to gastric atrophy and gastric carcinoma. Against this, however, several groups have reported that SHP-2 is not involved in CagA action\(^\text{[33,34]}\). The resolution of this controversy is awaited.

**Effect of pro- and anti-inflammatory cytokine gene polymorphism on H pylori-induced gastric cancer**

High mucosal levels of cytokines in *H pylori*-infected patients have been reported, including IL-8, IL-6, IL-1B, TNF-A, MIP 1α and IL-2\(^\text{[15,62]}\). Host cytokine gene polymorphisms IL-1B, IL-1RN, TNF-A and IL-10 are suggested to be part of the genetic background predisposing patients to noncardia gastric cancer in response to *H pylori*\(^\text{[13,15,17,63]}\). IL-1B and TNF-A are functional polymorphisms that affect the production of IL-β and TNF-α, which inhibit gastric acid secretion\(^\text{[60,63]}\). The IL-1B gene encoding IL-1β is highly polymorphic, and several diallelic polymorphisms have been reported, two in the promoter region at positions -511 and -31, representing C-T and T-C transitions, respectively. Several studies have shown that these two polymorphisms are in near-total linkage disequilibrium\(^\text{[13,63]}\). They have been shown to significantly affect gastric mucosal IL-1β production in response to *H pylori* infection\(^\text{[62,64]}\), and it is this higher production of IL-1β which most likely mediates their effect on gastric acid secretion. Zambon *et al* have reported that among host genetic factors contributing to *H pylori* disease outcome, IFN-G AA favors the *H pylori* infection, TNF-A TT favors duodenal ulcer, while IL-10 TT favors intestinal metaplasia and noncardia gastric cancer\(^\text{[58,63]}\). In Japan and Korea, however, these associations appear less clear\(^\text{[58,70]}\).

**H pylori-induced gastric cancer and environmental and lifestyle factors**

A joint World Health Organization/Food and Agriculture Organization Expert Consultation concluded that salt and salt-preserved food probably increase the risk of gastric cancer\(^\text{[73]}\). Substantial evidence from ecological, case-control and cohort studies suggest that cancer risk may also increase with a high intake of some traditional salt-preserved foods and salt *per se*, and that this risk could be decreased with a high intake of fruits and vegetable\(^\text{[73,74]}\).

Other established non-dietary factors include cigarette smoking\(^\text{[73]}\). Tsugane *et al* have documented that the consumption of salted food (pickled vegetables and miso soup) appears to increase the risk of *H pylori* infection\(^\text{[75]}\). Salted food intake has been shown to act synergistically to promote the development of gastric cancer in Mongolian gerbils treated with N-methyl-N-nitrosourea (MNNU)\(^\text{[77]}\), and a synergistic enhancing effect between salted food intake and *H pylori* infection has also been reported in a case-control study in Korea\(^\text{[76]}\). Motani *et al*\(^\text{[79]}\) reported that smoking and a high intake of miso soup were associated with noncardia cancer regardless of *H pylori* infection, and also a strong association between cag-A-positive *H pylori* and noncardia cancer. Although *H pylori* infection is clearly an important risk factor for gastric cancer, smoking cessation and dietary modification may be practical strategies for the prevention of non-cardia gastric cancer among both *H pylori*-positive and -negative subjects.

Conclusive 'proof' for a preventive effect of *H pylori* eradication on gastric carcinogenesis will never be available, because doing so would require the inclusion of individuals in a placebo trial in which the end point is gastric cancer; for not only practical but also ethical and economic reasons, no such study will ever be performed. The alternative is randomized controlled studies that are designed to examine the regression of preneoplastic conditions, such as intestinal metaplasia and gastric atrophy, as surrogate end points of eradication treatment success. One such study is a prospective, randomized, placebo-controlled, population-based primary prevention study of 1630 healthy carriers of *H pylori* infection from Fujian Province, China, recruited in July 1994 and followed up until January 2002\(^\text{[80]}\). A total of 988 participants did not have precancerous lesions (gastric atrophy, intestinal metaplasia, or gastric dysplasia) on study entry. Patients were randomly assigned to receive *H pylori* eradication treatment by a 2-wk course of omeprazole 20 mg, a combination product of amoxicillin and clavulanate potassium, 750 mg, and metronidazole 400 mg, all twice daily (n = 817); or placebo (n = 813). Among the 18 new cases of gastric cancer that developed, no overall reduction was observed in participants who received *H pylori* eradication treatment (n = 7) compared with those who did not (n = 11). In a subgroup of patients with no precancerous lesions on entry, no patient developed gastric cancer during a follow-up of 7.5 years after *H pylori* eradication treatment compared with those who received placebo (0 vs 6; P = 0.02). Although the incidence of gastric cancer development at the population level was similar between participants receiving *H pylori* eradication treatment and those receiving placebo over 7.5 years in a high-risk region of China, eradication of *H pylori* significantly decreased the development of gastric cancer in the subgroup of *H pylori* carriers without precancerous lesions.

A second study was conducted in Hong Kong\(^\text{[81]}\).
The authors randomized 435 subjects into placebo and eradication groups, the latter of whom received a one-week course of anti-\textit{H pylori} therapy of OAC (omeprazole 20 mg, amoxicillin 1g, and clarithromycin 500 mg twice a day). Clearance of \textit{H pylori} infection at 5 years was confirmed by histology in 164 (74.5\%) who had received the eradication therapy versus only 20 (9.3\%) subjects in the placebo group. Ten subjects developed invasive gastric cancer during the 5-year follow-up period, four in the eradication and six in the placebo group. Overall progression of gastric intestinal metaplasia (IM), defined as a surrogate marker of cancer, was seen in 52.9\% of subjects. Eradication of \textit{H pylori} was significantly associated with a decrease in the risk of IM progression. Patients assigned to receive OAC had a significantly lower risk of progression compared with those who received placebo (OR for progression 0.63; 95\% CI, 0.43-0.93). When those in the OAC group with eradication were compared with those in the placebo group with persistent infection, the OR of histological progression was further reduced to 0.48 (95\% CI, 0.32-0.74). Although this intervention study failed to demonstrate an effect on gastric cancer risk, eradication of \textit{H pylori} was protective against the progression of a premalignant gastric lesion, namely IM.

Another study was reported from Mexico\textsuperscript{[83]}. A total of 316 \textit{Cag}-A-positive subjects were randomized into placebo (\(n=155\)) and eradication groups (\(n=161\)), who received 20 mg of omeprazole, 1 g of amoxicillin and 500 mg of clarithromycin, all twice a day for 1 week. Endoscopy was performed at baseline and at 6 weeks and 1 year, with seven biopsies from each endoscopy reviewed by two pathologists. Cure rates in the eradication group were 79.2\% and 75.7\% at 6 weeks and 1 year, respectively, compared with respective placebo rates of 2.9\% and 1.9\% (\(P<0.001\)). Outcome measures were both a consensus “worst biopsy” diagnosis and a weighted index score that incorporated the degree of severity of preneoplasia, with changes in these outcomes compared over time. No significant change in the worst biopsy diagnosis was observed between groups (improvement/worsening: placebo, 19.4\%/10.5\%; treatment, 22.5\%/8.3\%; \(P=0.74\)). The change in index score was favorably greater in the treatment than in the placebo subjects (intention-to-treat analysis, \(P=0.03\)). These studies of intermediate biomarkers provide circumstantial evidence that \textit{H pylori} eradication diminishes the risk of gastric cancer.

Following partial gastrectomy, the mucosa of the residual stomach usually undergoes severe changes, such as gastric atrophy, intestinal metaplasia and dysplasia\textsuperscript{[83-85]}. The 1996 Maastricht Consensus Report strongly recommended eradication in infected patients who had undergone gastrectomy for early gastric cancer\textsuperscript{[89]}. Definite proof of the merit of eradication awaits the completion of a large randomized trial using cancer as the outcome. Nevertheless, the evidence now available supports a conclusion for eradication.

Effective \textit{H pylori} eradication along with a natural decrease in infection due to improved living conditions have resulted in declining gastric cancer rates in Western countries, although this still remains a significant cause of morbidity and mortality in other parts of the world. While the genes in \textit{cag} PAI are the most strongly virulence-related among those reported to date, other genes have also been reported as candidates that determine outcome in \textit{H pylori}-infected persons\textsuperscript{[86,87]}. Studies that identify further bacterial as well as host genetic factors that place the patient at greatest risk of disease progression may enhance our approach to better screening strategies, and will improve the control of \textit{H pylori} infection in affected subjects.

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