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Relationship of Helicobacter pylori to gastric carcinogenesis

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The epidemiological evidence linking Helicobacter pylori infection to gastric carcinogenesis is reviewed. Only large geographical population studies have revealed a positive correlation between H. pylori infection and the incidence or mortality of gastric cancer. In case-control studies, the correlation varied in high-risk and low-risk countries, depending on the prevalence of H. pylori antibodies in the control group. In high-risk countries for gastric cancer, gastric atrophy is common in both the patient and control groups, and intestinal metaplasia is associated with a decrease of serum H. pylori antibody positivity. Both of these factors may be related to the negative correlation between gastric cancer and H. pylori infection.

In cohort studies, a significant positive correlation has been revealed between H. pylori infection and the risk of gastric cancer. Direct evidence on the progression of gastric atrophy in H. pylori-infected animal models and indirect evidence in clinical studies has been accumulated. H. pylori infection may be linked to gastric carcinogenesis via atrophy and intestinal metaplasia of the gastric mucosa, which accelerates cell proliferation and the exposure of epithelial cells to endogenous and exogenous mutagens. In addition, the secretion of ascorbic acid (anti-oxidant) into gastric juice is decreased.

As the WHO/IARC recently defined H. pylori as a group 1 carcinogen for gastric cancer based on these epidemiological studies, patients with H. pylori infection must be considered a high risk group for this cancer.


Key words: Helicobacter pylori, gastric cancer, cohort study, gastric atrophy

Gastric cancer is a common disease worldwide. In Japan, the incidence of gastric cancer per 100,000 has gradually decreased from approximately 78.8 for males and 46.3 for females in 1980\(^1\).

Nevertheless, approximately 60,000 patients died of gastric adenocarcinoma in 1994. In other parts of the world, such as China, other Asian countries, Western South America and Central America, the mortality rate from this cancer is higher than 30 per 100,000 among males. In the United States, the mortality rate per 100,000 was approximately 6 in 1985, and has remained stable over the past several years. These different rates are suggested to be associated with variations in dietary and environmental factors.

Current evidence obtained by cancer research suggests that carcinogenesis results from accumulated aberrations of genes linked to cell growth, growth factors, growth factor receptors, and intracellular signal transduction\(^2\)–\(^4\).

Long-term accumulation of genetic events is required for a multi-step process of carcinogenesis that includes initiation, promotion, and progression. A representative example is the development of colonic cancer, as proposed by the Vogelstein model\(^5\).

In the case of gastric cancer, chronic atrophic gastritis with intestinal metaplasia is thought to be a precancerous lesion on the basis of histological and epidemiological evidence\(^5\)–\(^6\). Although this concept has not been fully accepted in Japan, it is agreed that chronic atrophic gastritis and intestinal metaplasia are closely related to gastric cancer. The causes of gastric atrophy have not been fully elucidated, but both environmental factors and age-dependent genetic factors have been suggested as candidates.

The concept of human gastritis has been changed rapidly, since Helicobacter pylori (H. Pylori) was discovered in the human stomach by Warren & Marshall in 1983\(^7\(0,484),(1000,998). In 1994, WHO/IARC reported that H. Pylori is a Group 1 (definite) carcinogen for gastric cancer (Table 1)\(^8\). This report was mainly based on three cohort studies (nested case-control studies), that are described later.

Table 1 Carcinogenicity (WHO/IARC)

<table>
<thead>
<tr>
<th>Group</th>
<th>Carcinogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Definite carcinogen</td>
</tr>
<tr>
<td>2A</td>
<td>Probable carcinogen</td>
</tr>
<tr>
<td>2B</td>
<td>Possible carcinogen</td>
</tr>
<tr>
<td>3</td>
<td>Uncertain</td>
</tr>
<tr>
<td>4</td>
<td>Not a carcinogen</td>
</tr>
</tbody>
</table>

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In this review, the association between the development of gastric cancer and H. Pylori infection is discussed in detail.

### Geographical studies

A geographical study in 46 rural counties of the People's Republic of China revealed a weak but significant correlation between the prevalence of H. Pylori antibodies and the gastric cancer mortality rate\(^9\). This significant positive correlation remained even after adjusting for dietary factors known to be associated with an increasing gastric cancer risk. In 1992, a sex-specific correlation and multivariate regression analysis\(^10\) showed a significant positive correlation with the consumption of salted vegetables and eggs, the prevalence of H. Pylori antibodies, and the plasma albumin level, as well as a significant negative correlation with the intake of green vegetables and the plasma levels of selenium and \(\beta\) -carotene.

These results suggested that H. Pylori infection might be a determinant of the geographical variations in gastric cancer risk that was independent of diet, because the prevalence of H. Pylori antibodies ranged from 27% to 96% in the counties for which data were available\(^10\).

On the other hand, a positive correlation with H. Pylori was not found in two other geographical studies. The prevalence of H. Pylori antibodies did not show a significant correlation with the cumulative mortality rate due to gastric cancer in 5 areas of Japan where the incidence of gastric cancer varied over 2.5-fold\(^11\), nor in the rate of children with gastric cancer from 2 areas in Costa Rica which also showed 2.5-fold difference in the incidence of this cancer\(^12\). However, these studies were based on only 2-5 sites and thus seem to be of limited value. As the variation in the incidence of gastric cancer is very large between countries, a large population is needed for accurate comparisons to be made.

Recently, the EUROGASTRO Study Group\(^13\) assessed 17 populations from 11 European countries, the USA, and Japan, and conducted that the prevalence of H. Pylori positivity was significantly related to both the cumulative incidence and mortality rates for gastric cancer. \((r=2.68 \ (P=0.001) \text{ and } r=1.79 \ (P=0.002), \text{ respectively})\). This study indicated that a 6-fold increase in the risk of gastric cancer for a population with a 100% prevalence of H. Pylori infection when compared with an uninfected population.

### Case-control studies

In several case-control studies, the prevalence of H. Pylori antibodies in patients with gastric cancer has been compared with the prevalence in a control group (Table 2). A significant association with H. Pylori was reported in the USA\(^14\), Finland\(^15\), and Sweden\(^16\), with the odds ratio ranging from 2.2 to 2.7. However, the case-control studies performed in high-risk countries for gastric cancer produced conflicting results. In Portugal\(^17\), the prevalence of H. Pylori antibodies was not significantly different between patients with gastric cancer and controls (70.0% vs 81.0%; odds ratio=0.6). Oppositely, the prevalence of H. Pylori infection was lower in patients with gastric cancer. In Japan, Asaka et al.\(^18\) compared the prevalence of H. Pylori IgG antibodies in 213 patients with gastric cancer and 213 asymptomatic controls matched for age and sex (recruited at a health screening center). Overall, gastric cancer patients showed a significantly higher positivity rate for H. Pylori antibodies than the controls (88.2% vs 81.0%; odds ratio=0.6). Oppositely, the prevalence of H. Pylori infection was lower in patients with gastric cancer. In Japan, Asaka et al.\(^18\) compared the prevalence of H. Pylori IgG antibodies in 213 patients with gastric cancer and 213 asymptomatic controls matched for age and sex (recruited at a health screening center). Overall, gastric cancer patients showed a significantly higher positivity rate for H. Pylori antibodies than the controls (88.2% vs 74.6%). However, this was especially true for early gastric cancer (93.0%) , while the increase of H. Pylori in advanced gastric cancer was not significant (84.7%). These observations were hard to understand if it is assumed that advanced gastric cancer develops by progression from early cancer.

Fukuda et al.\(^19\) also studies the prevalence of H. Pylori antibodies in 282 patients and 767 age- and sex- matched controls from the same hospital. The overall odds ratio was 1.04, and this was not statistically significant. In addition,
deeply invasive and large tumors showed a negative correlation with H. Pylori infection when compared to small intramucosal tumors.

These results suggested that some unknown factors may have decreased the prevalence of H. Pylori antibodies during the progression of gastric cancer. H. Pylori finds it difficult to colonize site of intestinal metaplasia in the stomach, probably due to the loss of receptors on the metaplastic cells and/or the active production of specific secretory IgA for H. Pylori by metaplastic mucosa. The extent of intestinal metaplasia is closely related to the grade of gastric atrophy. Accordingly, they performed conditional logistic regression analysis to adjust for the negative effect of advanced intestinal metaplasia by using the pepsinogen I/II ratio. After adjustment for the grade of gastric atrophy, patients with gastric cancer showed a significantly higher odds ratio of 1.69 (95% confidence interval (CI); 1.01–2.81) (Table 2). In particular, the intestinal type of gastric cancer showed a strong association with H. Pylori infection when compared to the diffuse type (odds ratio: 3.76 vs 1.14).

### Cohort (nested case-control) studies

Three cohort (nested case-control) studies have shown consistent results (Table 3). In these studies, H. Pylori antibodies were measured in serum collected several years prior to the diagnosis of gastric cancer. In an UK study, the prevalence of H. Pylori antibodies in 29 men with a subsequent diagnosis of gastric cancer (the interval between sampling and diagnosis was less than 5 years in 11 subjects and 5-14 years in 18) was compared with that in 116 controls matched for the date of birth and date of blood sampling from over 22,000 middle-aged men. The odds ratio for gastric cancer in the individuals with preceding H. Pylori infection was 2.77 (95% CI: 1.04–7.97), although the study size was limited.

The second study was conducted in a cohort of Japanese American men living in Hawaii. The 109 patients with gastric cancer in this cohort were enrolled, while control subjects matched for age and the date of serum collection were selected from among approximately 6,000 men. The average time from serum collection to diagnosis of gastric cancer was 13±5 years and the odds ratio for gastric cancer was 6.0 (95% CI: 2.1–17.3). An association with H. Pylori infection was found for both intestinal and diffuse types of cancer, and was stronger when the diagnosis was made 10 or more years after serum collection (odds ratio: 10.5).

The third study was performed in California, employing the largest cohort (128,992 persons); 186 patients with gastric cancer were matched according to age, sex, and race with 186 controls. The average time between serum collection and the diagnosis of gastric cancer was 14.2 years. Of the 109 patients with histologically confirmed gastric adenocarcinoma, 84.4% had prior H. Pylori infection, while 60.6% of the controls were infected. The odds ratio was 3.6 (95% CI: 1.8–7.3). The risk of gastric cancer was higher in women (odds ratio: 18.0) and blacks (odds ratio: 9.0) with H. Pylori infection. The etiologic fraction calculations done in this study suggested that H. Pylori infection was involved in 60% of gastric adenocarcinoma in the United States.

Although these cohort studies strongly suggested a close relationship between H. Pylori infection and gastric cancer, they did not provide direct evidence. A causative relationship can be only shown by randomized intervention trials, which demonstrate that long-term eradication of H. Pylori by antibiotic therapy leads to the regression of gastric atrophy and intestinal metaplasia or a reduction in the risk of gastric cancer. Pilot trials of this kind are currently in progress under the auspices of the Japanese Ministry of Health and Welfare.

### H. Pylori infection and gastric carcinogenesis

Numerous independent studies have shown that chronic gastritis, especially atrophic gastritis, is a precancerous condition. It has been shown that the spread of mucosal atrophy is accelerated by H. Pylori infection in clinical and animal studies. The current hypothesis is that chronic inflammation due to H. Pylori infection accelerates the proliferation of gastric epithelial cells and potentiates the risk of DNA damage by endogenous mutagens generated by infiltrating inflammatory cells (e.g., superoxide and hydroxyl radicals) and by exogenous mutagens ingested in foods. As atrophy involves the fundic glands, acid secretion decreases and commensal bacteria can colonize the stomach more easily.
These bacteria may reduce nitrate to nitrite, leading to the production of carcinogenic nitrosamines, and may promote the generation of nitric oxide by inflammatory cells. Additionally, H. Pylori infection affects the intragastric secretion of ascorbic acid, which is an anti-oxidants and prevents the formation of nitrosamines (Fig. 2).

However, the high prevalence of H. Pylori infection in developing countries (Fig. 3) with a low incidence of gastric cancer indicates that only a small population of infected patients will develop cancer, even if gastric atrophy progresses with aging. Therefore, other risk factors also appear to be involved in the development of gastric cancer. This possibility is supported by the African enigma: 70–80% of the inhabitants of Africa have H. Pylori infection at an early age (55% under age 10 in the Ivory Coast and 50% under age 5 in Nigeria and Gambia), but gastric cancer is uncommon. Although accurate population statistics are not available, gastric cancer appears to account for less than 2% of all malignant tumors in Nigeria and for only 2–3% of malignancies in Uganda and Zimbabwe.

Another missing link is the association between the type of intestinal metaplasia and the prevalence of H. Pylori infection in Yemeni and British patients. Although Yemeni patients had a significantly higher prevalence of H. Pylori infection than British patients (92% vs 46%), Yemeni patients show a significantly lower prevalence of all types of intestinal metaplasia (19% vs 34%). This is particularly true for type III intestinal metaplasia (3% vs 22%), which is a major risk factor for a gastric cancer.

These findings suggest that genetic or the environmental factors may be involved in the development of gastric cancer or in the progression of the dysplasia-carcinoma sequence. An alternative explanation could be the presence of different strains of H. Pylori with a varying oncogenic potential. Recently, Blaser et al. reported that infection with a cagA-positive H. Pylori strain increased the risk of developing gastric cancer when compared with a cagA-negative strain (odds ratio: 1.9).

At present, the H. Pylori strains with a strong carcinogenic potential have not been identified, but such research may allow screening for a high-risk group of infected individuals and contribute to the prevention of gastric cancer.

References