Helicobacter pylori infection and Gastric Cancer

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Abstract

According to several prospective controlled epidemiologic studies, the positive rate of H. pylori antibody was shown to be higher in the patients with gastric cancer than in the control group. Retrospective studies on the association between gastric cancer and H. pylori have been conducted in a large number of subjects and the results can be classified broadly into two categories, i.e., findings affirming an association and others denying it. Research concerning the association between gastric cancer and H. pylori has achieved great progress over time, leading to the recognition of this relationship by the WHO. One of the greatest concerns is to ascertain whether the final outcome of H. pylori-induced gastritis may lead to gastric cancer. The onset of gastric cancer can be explained as being caused not only by H. pylori infection, but also by a combination of various factors such as food and the environment. However, the possibility that the occurrence of gastric cancer, like the recurrence of peptic ulcer, can be prevented by eradication of H. pylori has also been suggested. Further progress in clinical research is needed to resolve this issue. (Internal Medicine 41: 1-6, 2002)

Key words: atrophic gastritis, intestinal metaplasia

Introduction

It has been reported that superficial gastritis progresses to atrophic gastritis after 10 years or more, that atrophy extends from the pyloric glands to the fundic glands of the gastric body over time, and that intestinal metaplasia appears after another ten years or so (1-3). In view of the close association between H. pylori infection and histological gastritis, it is quite conceivable that infection with this organism may be related to the cause of atrophic gastritis and intestinal metaplasia.

Progression of Persistent H. pylori Infection to Atrophic Gastritis and Intestinal Metaplasia

A prospective study reported by Kuipers et al showed that H. pylori infection participates in the progression of superficial gastritis to atrophic gastritis and intestinal metaplasia (4). They observed two groups of subjects (49 patients who were negative for H. pylori and 58 patients who were positive) and determined the incidence of atrophic gastritis and intestinal metaplasia over 10-13 years. Such abnormalities were noted in 2 patients (4%) from the H. pylori-negative group versus 16 patients (28%) from the H. pylori-positive group. This finding indicates that H. pylori infection is involved in the progression of atrophic gastritis and intestinal metaplasia. Similar results were reported by Sakaki (5). In contrast, Niemela et al (6) conducted a 10-year follow-up study and reported that persistent infection with H. pylori was confirmed in 87% of the patients with gastritis, although there was no progression of atrophy. When patients with gastric ulcer were compared instead of patients with gastritis, however, an increased severity of gastritis at the pyloric antrum and an increased incidence of intestinal metaplasia were noted in the H. pylori-positive patients (7). This finding may suggest that the H. pylori strain causing gastric ulcer is likely to also cause gastric mucosal atrophy and intestinal metaplasia.

Asymptomatic individuals or gastritis patients were randomly selected in 21 centers in various areas in Japan, and endoscopic biopsy was performed. A total of 2,786 individuals who underwent endoscopic examinations were enrolled. H. pylori status was determined by a validated ELISA for anti-H. pylori IgG. Atrophic gastritis and intestinal metaplasia were diagnosed by histology following the Sydney system. The prevalence of atrophic gastritis in the population studies increased with age (e.g. from 9.4% in those <20 to >70% in those age 60 or older), it was strongly associated with H. pylori infection. The overall prevalence of atrophic gastritis among those with H. pylori infection was 82.9% (1,272/1,534) compared to 9.8% (90/921) of those without (OR=44.8; 95% CI=34.7–57.8). The pattern with intestinal metaplasia was similar increasing from 2.5% in those <20 to >45% in those 60 or older and being found predominantly among those with H. pylori infection (i.e., 43.1% (542/1,258) in H. pylori positive persons vs. 6.2% (51/
Another factor determining the severity of gastric mucosal atrophy in the Japanese population, which has been thought of as a manifestation of aging phenomenon, is strongly influenced by infection with *H. pylori*. If no infection occurs, progression of gastric mucosal atrophy in Japanese individuals may be as gradual as in Europeans or Americans.

An experimental model of persistent *H. pylori* infection has been difficult to develop, except in humans. In recent years, however, such models have been successfully created in monkeys (9), miniature pigs (10), mice (11, 12), Mongolian gerbils (13), and other animals. The finding that *H. pylori* infection is closely related to the onset of gastric mucosal lesions has been obtained, as in the case of humans (14). Fujioka et al infected Japanese monkeys with *H. pylori* and then followed the animals for a prolonged period, detecting the occurrence of gastric mucosal atrophy (15). Hirayama et al reported the appearance of intestinal metaplasia in Mongolian gerbils at 6 months after infection with *H. pylori* (13). It has become evident from these results that persistent *H. pylori* infection can cause atrophy and intestinal metaplasia, even in animals.

Long-term *H. pylori* infection may be closely related to the development of gastric cancer, but it occurs in a minority of people with *H. pylori* infection and the majority remain asymptomatic throughout their lives (16-18). This phenomenon tends to be more notable in developing countries than in the developed countries. In developing countries, the rate of infection with *H. pylori* exceeds 80% from infancy, but the proportion of asymptomatic patients is overwhelmingly high (19-20) and the incidence of intestinal metaplasia or gastric cancer is low (21). One explanation for this phenomenon may be based on a difference in toxicity among *H. pylori* strains. Wyle and Chang suggested that infected with *H. pylori* consistently causes acute gastritis and non-atrophic chronic gastritis, but the subsequent course varies with the strain of *H. pylori*, e.g., some strains cause duodenal ulcer and others cause gastritis that proceeds to gastric cancer through gastric mucosal atrophy (22). Unfortunately, differences among *H. pylori* strains cannot be distinguished by the antibody assays currently used in epidemiologic studies, but methods for distinguishing differences in toxicity among strains may be developed in the future. Although differences in the severity of gastric mucosal damage among *H. pylori* strains should be an important factor, it still does not provide a complete explanation for individual differences of *H. pylori* infection-induced gastric mucosal injury. In fact, it has been found that the severity of infection varies with differences in host factors. Among the reports on host factors and the progression of atrophic gastritis, Beales et al have emphasized the role of HLA-DQ type (23).

Another factor determining the severity of gastric mucosal injury is the time of onset of *H. pylori* infection. When *H. pylori* infection occurs in neonates and infants, it leads to pangastritis that extends throughout the stomach, often because acid secretion is insufficient. In addition, when atrophy of the fundic glands is caused by persistent inflammation, the parietal cells are disturbed and this can lead to hypoacidity (24). Intestinal metaplasia occurs when atrophy progresses further. On the other hand, when *H. pylori* infection occurs after the neonatal period or infancy the development of parietal cells is already complete, so acid secretion is normal and it is difficult for the organism to survive in the fundic glands (25, 26). Therefore, *H. pylori* invades the pyloric antrum and causes antral gastritis. Accordingly, there is damage to the background mucosa in addition to normal acid secretion, conditions that suggest a high risk of duodenal ulcer or gastric ulcer. As described above, individual differences in gastric mucosal injury due to *H. pylori* infection are probably determined by differences between strains, variations in host immunity, situation of acid secretion and differences in the timing of infection (27).

**Long-term *H. pylori* Infection: from Gastritis to Gastric Cancer**

The association between *H. pylori* and gastric cancer has been explained by two possible mechanisms, with one being a carcinogenesis-promoting effect of *H. pylori* itself and the other being the creation of a carcinogenic substrate. That is, although *H. pylori* may have no carcinogenic effect itself, infection causes inflammation of the gastric mucosa that eventually leads to atrophy and intestinal metaplasia (2, 28). First of all, we need to determine whether *H. pylori* infection produces an unknown chemical initiator during the process of gastric carcinogenesis or directly acts as a promoter. Since *H. pylori* cannot reduce nitrates (29), it may not be a source for the direct production of nitroso compounds and no evidence has been presented to indicate that the concentration of N-nitroso compounds in gastric juice is increased in *H. pylori*-positive patients with chronic gastritis (30). Gastric mucosal infection with *H. pylori* is accompanied by infiltration of neutrophils and activated inflammatory cells are known to produce oxygen radicals (31-33). Davies et al reported an increase of oxygen radical production in both the duodenal and gastric pyloric mucosa after infection with *H. pylori* (34). Oxygen radicals are known as inducers and initiators because of the direct DNA damage they cause (35), but the relationship of these radicals with the onset of gastric cancer has not been sufficiently explored. Ammonia often increases in the gastric mucosa after infection with *H. pylori* (34). Ammonia acts as a promoter in a rat model of gastric cancer induced by MNNG (36). Ascorbic acid is known to react with nitroso compounds derived from nitrous acid, which produces nitric oxide, thereby inhibiting the formation of N-nitroso compounds (37). The gastric juice concentration of ascorbic acid is decreased in patients who are positive for *H. pylori*, and it has been demonstrated that *H. pylori* eradication brings about an increase in the secretion of ascorbic acid into gastric juice (38-40). As has been mentioned, many questions remain to be resolved about infection with *H. pylori*.
pylori. However, it has become evident that there are many mechanisms that cause a variety of chemical changes in both gastric juice and the gastric mucosa, providing an explanation for the association of H. pylori with the onset of gastric cancer (41).

In 1994, the International Agency for Research on Cancer (IARC), a subordinate organization of the WHO, identified H. pylori as a “definite carcinogen” (indicating that H. pylori is definitely related to carcinogenesis) (42). In the WHO carcinogen classification, substances are classified into four groups that range from Group 1 (definite carcinogen) to Group 4 (non-carcinogen). Like tobacco smoking and hepatitis B virus, H. pylori was classified as Group 1, i.e., a certain relationship to carcinogenesis. Generally, experimental data tend to be required in addition to epidemiologic data when a substance is identified as a Group 1 carcinogen. In the case of H. pylori, however, the classification was assigned on the basis of epidemiologic data alone. Epidemiologic investigations on the association between H. pylori and cancer date from 1991 when results of studies conducted on a vast number of subjects were successively published (43–45). These reports showed that the H. pylori antibody-positive rate was higher in patients with gastric cancer than in the controls. Since these were prospective studies, the findings were very persuasive and had a strong impact on subsequent investigations. In 1993, a comparison of H. pylori antibody-positive rates between young and old patients in various countries, who were matched for the incidence and mortality rate of gastric cancer, was reported. The countries in which asymptomatic patients showed a high H. pylori antibody-positive rate also had high morbidity rates for gastric cancer (46). On the other hand, Rudi et al made a comparison of the H. pylori antibody-positive rate in 111 patients with gastric cancer and 111 patients with large bowel cancer who were matched with respect to age and sex (47). They reported that the positive rate was 58.6% in the gastric cancer patients and 50.5% in the bowel cancer group, with no significant difference between them. As has been mentioned, investigators are divided as to whether or not the H. pylori antibody-positive rate is higher in patients with gastric cancer than in controls. To clarify this point, we collected serum samples from 213 cancer patients in different districts of Japan (Sapporo, Niigata, Tokyo, and Osaka) and determined the H. pylori antibody titer in these serum samples as well as in samples from an identical number of healthy persons (collected mainly at multiphasic health screening centers) who matched the patients with respect to age and sex. The H. pylori antibody-positive rate was much higher in the gastric cancer patients (88.2%) than in the controls (74.6%). When the odds ratio was calculated, the highest value (4.9) was obtained in patients with early gastric cancer and patients with advanced cancer showed an odds ratio of 1.9. These values did not differ significantly from that of the control group. When the H. pylori antibody titer and the tumor histology were compared with respect to the odds ratio, only the odds ratio (4.0) for intestinal type of early gastric cancer was higher than that for the serum H. pylori antibody titer in patients without cancer. These findings strongly suggest that infection with H. pylori mainly causes intestinal type of early gastric cancer via the sequence of acute gastritis, atrophic gastritis, and intestinal metaplasia (48). Since the extent of intestinal metaplasia increases before early gastric cancer progresses to the advanced stage, it seems likely that H. pylori almost completely disappears from the stomach as a result and the antibody titer declines. Accordingly, the different finding, regarding the association between positivity for H. pylori antibodies and gastric cancer is considered to be due to the study population containing a variable percentage of patients with advanced cancer.

In developing countries and Japan, the H. pylori antibody-positive rate of the asymptomatic controls exceeds 70% (24, 25, 49). Consequently, it has been suggested that one reason why there is no significant difference of the H. pylori antibody-positive rate between gastric cancer patients and controls is the excessively high positive rate in the controls (50). Kikuchi et al investigated younger patients with gastric cancer (51). Patients aged 34 years on average were compared with age- and sex-matched controls. The odds ratio was an extremely high value of 13.3. This result showed the potent association between H. pylori infection and gastric cancer in young patients who predominantly have the diffuse type of gastric cancer.

It is evident from various findings reported to date that acute inflammatory cell infiltration into the gastric mucosa is caused by infection with any H. pylori strain that survives in the mucosa (52). The course of this process is considered to vary with the H. pylori strain or the immune response, thereby leading to a difference in the severity of gastric mucosal inflammation. Chronic inflammation due to the long-term persistence of H. pylori infection is considered to lead to gastric mucosal atrophy, though it may vary considerably in severity in Japan (53, 54). The occurrence of intestinal metaplasia, for which a relationship to gastric cancer, has been strongly suggested, is demonstrated in approximately 60% of persons with H. pylori infection (8, 55). This suggests that there is unlikely to be major differences among strains or in relation to the host immune response. Since the serum antibody titer is considered to reflect both of these factors, it may be said that a high antibody titer indicates severe gastric mucosal inflammation and that its long-term persistence is likely to cause metaplasia of the gastric mucosa (56, 57). Environmental factors (e.g., diet) and genetic factors may also participate in this progression to intestinal metaplasia (58). Metaplasia may then progress to gastric cancer, especially to tumors that are intestinal (52). Recently, Shimizu et al conducted a carcinogenesis experiment by infecting Mongolian gerbils with H. pylori and reported that progression to gastric cancer was chiefly seen in animals that showed a high H. pylori antibody titer (59).

To consider the association between H. pylori infection and the onset of diffuse type of gastric cancer, the process from infection with H. pylori through gastric mucosal atrophy, intestinal metaplasia, and development of cancer must be excluded, unlike the situation for intestinal type of gastric cancer (60, 61). Direct evidence must therefore be found to indicate the progression from infection with H. pylori through persis-
tent inflammatory cell infiltration resulting in DNA damage by oxygen radicals, point mutations of genes, and finally carcinogenesis.

As has been discussed, there is little doubt that persistent infection with H. pylori is closely related to the development of gastric cancer. However, if we assume that the number of Japanese infected with H. pylori is around 60,000,000, gastric cancer arises in only 0.4% of them because the number of patients with gastric cancer was 235,000 in 1993 (62). This finding suggests that factors other than H. pylori are involved in the onset of gastric cancer. A conventional approach that only looks at the H. pylori strain and host factors will not suffice. It might be reasonable to consider that gastric cancer is caused by a combination of the effects of various factors in addition to H. pylori (Table 1). However, when the incidence of gastric cancer is assessed epidemiologically, the lifetime morbidity is not expressed by a single rate, but by the cumulative rate. According to the 1997 report of the IARC, the probability of suffering from gastric cancer between the ages of 0 and 74 in Japan is estimated to be 6.5% on average (63). When the odds ratio of 4.9 that we found for H. pylori infection in patients with early gastric cancer (8, 52) is applied to this estimate, the lifetime morbidity from gastric cancer is estimated to be 1.8% for persons not infected with H. pylori and 11.2% for infected persons, being far higher in the infected group.

Uemura et al tried to confirm the relationship between H. pylori infection and gastric cancer. The study performed by them was one of the first long-term and prospective studies of infected and uninfected patients with various gastric diseases who underwent endoscopy and in whom the development of gastric cancer was the endpoint. They have just reported in the New England Journal of Medicine (64) that gastric cancer development of research in this field.

Table 1. Factors Contributing to Gastric Carcinogenesis in Addition to H. pylori Infection

- Environmental factors
- Duration of H. pylori infection
- Situation of acid secretion
- The virulence of the H. pylori strains
- Host genetics
- H. pylori antibody titers
- Vitamin C levels in gastric juice

These results suggest the possibility that the histologic type of gastric carcinoma is determined by the order of infection with H. pylori and exposure to environmental carcinogens. Therefore, it was reported that gastric cancer could occur even after infection with H. pylori alone. In other words, H. pylori was found to have a direct carcinogenic effect (66, 67). It is of great interest that the type of gastric cancer was well-differentiated in both cases.

As described above, an association between H. pylori infection and gastric cancer has not only been shown by epidemiologic investigation, but also by animal experiments. Eradication of H. pylori can prevent peptic ulcers from recurring, so eradication also seems likely to prevent gastric cancer from occurring. Uemura et al studied two groups of patients who underwent endoscopic mucosal resection (EMR) for early gastric cancer (68). Of these two groups, one underwent eradication of H. pylori and the other did not. After a 5-year follow-up period, no second cancer occurred in the H. pylori eradication group, whereas 9% of patients in the non-eradication group had a second cancer. However, there have been no other papers reporting that H. pylori eradication prevents gastric cancer.

Since a large percentage of the population is infected with H. pylori throughout the world, its eradication from all infected persons is not practical. Important data (whether gastric mucosal atrophy and intestinal metaplasia are reversible or not, and whether or not reversibility is influenced by age, sex, or severity) needed to determine the indications for H. pylori eradication are still insufficient. However, there seems to be little doubt that the future incidence of gastric cancer is very likely to depend on how the indications for H. pylori eradication are established. Therefore, much is expected with regard to the progress of research in this field.

References

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