H. pylori and Gastric Cancer: The Asian Enigma

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ABSTRACT
The actual distribution of Helicobacter pylori infection and its related diseases in various Asian countries is controversial. Only limited information is available regarding this issue. We discuss the etiological role of H. pylori in gastric cancer through the Asian experience. Seroprevalence of H. pylori infection in asymptomatic subjects and the annual incidence rate of gastric cancer per 100,000 in various Asian countries are summarized from literature reviews and World Health Organization statistics, respectively. There is a large intercountry variation in incidence of gastric cancer and H. pylori seroprevalence among Asian countries. There is a strong link between H. pylori infection and gastric cancer in many countries, such as Japan. By contrast, the prevalence of H. pylori infection is high in some countries, including India and Bangladesh, but low gastric cancer rates have been reported. These disparate observations represent the Asian enigma. Factors that may influence the etiology of gastric cancer include the genetic diversity of the infecting H. pylori strains and differences in the host genetic background in various ethnic groups, including gastric acid secretion and genetic polymorphisms in proinflammatory cytokines. These factors, in addition to environmental factors, such as personal hygiene and dietary habits, reflect the multifactorial etiology of gastric cancer. (Am J Gastroenterol 2002;97:1106–1112. © 2002 by Am. Coll. of Gastroenterology)

INTRODUCTION
Accumulated evidence has shown that Helicobacter pylori is one of the most important pathogens for a wide spectrum of gastroduodenal diseases, including acute and chronic active gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, and gastric malignancy. However, the prevalence of H. pylori–related diseases differs in various geographic regions and patient populations. A report summarizing epidemiological studies in Africa, the African enigma (1), suggests that H. pylori infection does not always directly correlate with the risk for GI disease, such as peptic ulceration and gastric cancer.

Epidemiological studies indicate that Asian countries have a high prevalence of H. pylori infection, with a correspondingly high incidence of severe gastroduodenal diseases, especially gastric neoplasia. There have been some controversy about the actual H. pylori distribution and disease composition in various Asian countries, with only limited information available regarding this issue. In this discussion we summarize the epidemiological data on the prevalence of H. pylori infection and gastric cancer from several Asian countries and discuss the etiological role of H. pylori in gastric cancer through the Asian experience.

SEROPEPREVALENCE OF H. PYLORI INFECTION IN ASIAN COUNTRIES
The seroprevalence of H. pylori infection in asymptomatic subjects in various Asian countries is depicted in Table 1 (2–18), which contains those reports that we considered reliable and reflect the H. pylori infection in each country, even if multiple reports were available. The seroprevalence of H. pylori is considered in the setting of the age of the study population. The seroprevalence of H. pylori infection appears to gradually increase with age in developed countries (19, 20) with low child infection rates, which is likely due to a cohort phenomenon. In the developing Asian countries India and Bangladesh, a large part of the population is exposed to H. pylori at an early age (21, 22). By contrast, the seroprevalence in the younger generations in developed Asian countries, such as Korea and Japan, is significantly lower than that of the older population (10). One potential limitation in comparing many of these studies is that seroprevalence was based on imported (foreign) serological kits, which may not be fully accurate for Asian populations. The diagnosis of H. pylori infection using serological kits from Western countries is known to be insufficient in Asian countries because the performance of imported kits has been reported to be relatively low in many Asian countries (23, 24). In addition, a recent report suggests a low detection rate for previous exposure to H. pylori infection using the conventional IgG ELISA method (25). Table 1 shows that H. pylori infection is high in Asian countries.

The seroprevalence of H. pylori infection in Western countries has been reported to be much lower than in Asia. However, there is considerable variability in the H. pylori seroprevalence distribution among Asian countries. Table 1 shows that H. pylori seroprevalence in developing countries, such as Bangladesh, India, and Thailand, is especially high. In the more industrialized countries, such as Singapore, H. pylori seroprevalence is low. These findings correlate with
However, the incidence rate of gastric cancer per 100,000 in various Asian countries is summarized in Table 2 (27). It should be noted that these kinds of statistics sometimes may not be completely accurate because of often poor diagnostic techniques, different reporting systems, and limited access to medical care, especially in the poorer, developing countries. As shown in Table 2, the incidence of gastric cancer is very high in the northern parts of the Asian region (27). Indeed, it is remarkably high in both Japan and Korea. The annual incidence of gastric cancer in Miyagi, Japan is very high (male, 82.7/100,000; female, 32.8/100,000), more than 10–20 times and 100 times higher than those in Thailand and India, respectively. By contrast, the incidence of gastric cancer is comparatively low in the southern and southeastern Asian countries such as India, Philippines, or Thailand. Interestingly, as described above, the seroprevalence in these countries with high *H. pylori* infection rates in the population over 40 yr of age (10).

**INCIDENCE OF GASTRIC CANCER IN ASIAN COUNTRIES**

Gastric cancer has declined over the last several decades in Western and developed countries relative to Asian countries, so its current incidence is relatively low. The annual incidence rate of gastric cancer per 100,000 in various Asian countries is summarized in Table 2 (27). It should be noted that these kinds of statistics sometimes may not be completely accurate because of often poor diagnostic techniques, different reporting systems, and limited access to medical care, especially in the poorer, developing countries. However, the figures in this table are from World Health Organization (WHO) statistics, with well-organized and standardized data collection by cancer registries, so these data will be the most accurate reflection of trends in gastric cancer incidence in these Asian countries. As shown in Table 2, the incidence of gastric cancer is very high in the northern parts of the Asian region (27). Indeed, it is remarkably high in both Japan and Korea. The annual incidence of gastric cancer in Miyagi, Japan is very high (male, 82.7/100,000; female, 32.8/100,000), more than 10–20 times and 100 times higher than those in Thailand and India, respectively. By contrast, the incidence of gastric cancer is comparatively low in the southern and southeastern Asian countries such as India, Philippines, or Thailand. Interestingly, as described above, the *H. pylori* seroprevalence in these countries has been relatively high. *H. pylori* infection is strongly associated with gastric cancer risk, but this large intercountry variation of gastric cancer incidence and *H. pylori* seroprevalence among Asian countries suggests that *H. pylori* infection is not the only factor related to gastric cancer risk (28, 29). Forman (30) has previously shown a 6-fold variation in the association between gastric cancer risk and *H. pylori* infection in different patient populations based on a worldwide survey.

**GENETIC DIVERSITY OF *H. PYLORI* STRAINS IN ASIA AND GASTRIC CANCER**

The genetic diversity of *H. pylori* strains has been reported to be associated with pathogenicity of gastroduodenal dis-
orders. It is postulated that bacterial cytotoxins might account for disease-specific pathogenicity in developed and Western countries. Among various H. pylori-derived cytotoxic proteins, cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) are recognized as important virulent factors for mucosal damage of gastric epithelial cells (31, 32). The cagA gene is a marker gene for the cag pathogenicity island; it is believed to evoke an increased inflammatory response through epithelial cell release of interleukin 8, a chemokine for polymorphonuclear cells, leading to active inflammation (33). The presence of this gene has been strongly linked to gastric mucosal cell damage (34). Recent studies show that the CagA protein is inserted into host epithelial cells at the site of H. pylori attachment to the epithelial surface (35, 36). The CagA protein then undergoes tyrosine phosphorylation in addition to cytoskeletal reorganization in the host cell. These steps may be involved in downstream events leading to H. pylori-associated apoptosis and cellular proliferation. Multiple studies have shown that CagA-positive strains are associated with increased levels of gastric inflammation (37). An international survey identified a strong association between CagA status and pepsinogen levels that are markers of gastric atrophy (38).

The vacA gene is also associated with host pathogenicity, although this genotype does not closely correlate with its host phenotype presentation. Signal and midgene region sequences of this gene are associated with in vitro cytotoxicity but also mucosal damage in vivo (39). Specifically, bacterial strains with the vacA gene of signal sequence type s1 and midgene region sequence m1 are probably more virulent, and are frequently detected in patients with peptic ulcers (40) or gastric cancer (41). Interestingly, most H. pylori clinical isolates in Japan have been reported to possess both cagA and vacA genes with vacA genotype s1/m1, which have been associated with more severe disease presentation (42–44). Similar to Japan, most clinical H. pylori strains in Korean patients are cagA and vacA positive with vacA genotype s1/m1 (45). However, only limited data are available on genotypes of H. pylori isolates in countries such as Thailand and India, where the prevalence of H. pylori is high and that of gastric cancer is low. A report from India suggested that the majority of their isolates are of type s1 signal sequence and m1 middle region, although about 35% were of the m2 subtype (46). In Taiwan, vacA s1a/m2 strains are significantly more frequent than s1a/m1 strains (47, 48). Another report described another specific s1 genotype, subtype s1c, in clinical isolates from Asian countries, with approximately 80% of the bacterial strains in Asia having this subtype (49). These differences in vacA genotype might result in the lower gastric cancer risk despite the high seroprevalence of H. pylori infection in some countries or vice versa. A recent seroepidemiological study from Bangladesh showed that anti-VacA antibody was detected in about 85% of infected children (50). This suggests a high prevalence of virulent strains in this country (50) and that the VacA protein is highly expressed irrespective of the variances in s1 genotype.

Many studies support the strong association of H. pylori genetic factors and certain bacterial genotypes with gastric cancer risk (38, 41, 51). However, a recent report described variable H. pylori cytotoxin profiles from two different areas.
in Japan: Fukui, where the prevalence of gastric cancer is high, and Okinawa, where its prevalence is low (52). This report supports a potential role of *H. pylori* strain genotype diversity in the various presentations of gastric disease in different regions and populations. Further molecular epidemiological studies in Asian countries are needed to clarify this issue.

**ACID SECRETION, GENETIC POLYMORPHISMS, AND GASTRIC CANCER**

Thus, the basis for the lower incidence of gastric cancer in Thailand and India despite a high seroprevalence of *H. pylori* infection cannot fully depend on strain genetic diversity, as most patients are infected by more virulent strains than appear in Western countries. Other factors that may enhance gastric cancer risk are ethnicity and environmental factors. It is recognized that there are many minor racial differences in various Asian districts. What is interesting is that acid secretion and gastric atrophy may be altered according to ethnic background. Gastric acid secretion in Japanese is much lower than that in Western populations (53). Acid secretion in the Japanese population has been reported to be gradually increasing during the last 2 decades, but it is still lower than in Western populations. Although several factors, such as a lower *H. pylori* infection rate or improved nutrition, may partially account for this phenomenon, host genetic differences probably also have an important role. The level of acid secretion may be a determinant of gastric mucosal atrophy that an individual develops in response to chronic *H. pylori* infection and susceptibility to initial bacterial infection. Specifically, gastric atrophy more readily occurs in subjects with lower acid secretion than in those with high acid secretion (54). The observation by Kuipers et al. (55) that suppression of gastric acid by proton pump inhibitors in subjects with reflux esophagitis is associated with increased severity of gastritis caused by *H. pylori* supports this hypothesis. *H. pylori*-infected subjects with decreased or lower acid secretion would be more likely to have increased atrophy than those with unaffected or increased acid secretion. Therefore, atrophic gastritis is more commonly observed in the Japanese population, where acid secretion is lower than in Western populations.

Gastric ulcers are associated with gastric atrophy and lower gastric acid secretion and are commonly seen in the Japanese population, whereas duodenal ulcers are associated with higher acid secretion and are commonly observed in Western populations. Indeed, patients with gastric ulcers are more likely to develop gastric cancer than those with duodenal ulcers (56). These observations, in conjunction with the widely accepted observation that atrophic gastritis is closely related to gastric cancer risk (57), suggest that the various gastric cancer risks in different countries or races may be due to altered gastric acid secretory function related to different ethnic backgrounds. In contrast, acid secretion in normal Thai subjects, where the prevalence of gastric cancer is low, has been reported to be similar to that of the Japanese (58). However, the exact ratio of patients whose acid secretory function is significantly impaired remains to be investigated.

El-Omar et al. (59) recently reported that certain gene cluster polymorphisms of interleukin 1, a proinflammatory cytokine with a potent acid inhibitory effect, are closely related to gastric cancer risk. Patients with gastric cancer are likely to have certain DNA mutations in several points in 5′ and 3′ flanking regions and interleukin 1RN, which enhances the expression of this cytokine; gastric acid secretion is suppressed and associated with gastric atrophy in the setting of *H. pylori* infection with increased gastric cancer risk. The proportion of subjects with this polymorphism may vary depending on ethnic background. There are many examples for altered genetic polymorphisms related to different ethnic backgrounds in Asia, such as mitochondrial DNA nine–base pair deletion and Lewis (FUT3) genotypes (60, 61). A recent report from Japan described a negative impact of the polymorphism of this gene on differences in gastric cancer risk in different patient populations (62). The study presented no significant differences in the frequency of the genetic polymorphisms between Japanese and Thai subjects. However, the entire cluster of these genetic polymorphisms has not been fully investigated and compared. There are several other candidate cytokine genes, such as tumor necrosis factor α and interleukin 10, that possess genetic polymorphisms and may enhance or suppress inflammation of the GI mucosa (63, 64). Genetic involvement in gastric cancer development may not be as significant as other still undefined factors because familial gastric cancers are relatively rare (65, 66). Nevertheless, the above findings suggest that polymorphisms in specific genes or combinations of genes may account, in part, for alterations in acid secretory rates and gastric cancer risks in Asian countries.

**ENVIRONMENTAL FACTORS AND GASTRIC CANCER**

Environmental factors also may be important factors for increased cancer risk. High prevalence and mortality due to gastric cancer in the Japanese population are well recognized, but there are geographic differences for gastric cancer risk even in the Japanese population. Northern districts such as the Akita prefecture have reported a higher prevalence of gastric cancer than the southern Okinawa prefecture district. Because the Japanese have a relatively homogenous genetic background, one of the reasons for the variable cancer risks in Japan may be differences in salt and nutrient consumption among different districts. Consumption of salt and certain nutrients, such as β-carotene, have been reported to differ among regions where prevalence of gastric cancer is variable (67). Salt consumption in Akita is reported to be double that in Okinawa (68). Similar observations have been reported in India; the rate of gastric cancer was 3–6 times higher in the Indian province of Kashmir than in other
Indian districts such as Bangalore, Madras, and Bombay (69). Indians have special personal and dietary habits that may result in increased and variable exposure to dietary amines and nitrates (70). As discussed above, many epidemiological studies have shown that salted, smoked, pickled, and preserved foods are strongly associated with gastric cancer risk (71), and the enhancing effect of salt consumption on gastric cancer risk has been experimentally demonstrated in a rat animal model (72). High consumption of fresh fruits and raw vegetables has been associated with a reduced risk of gastric cancer (71). Generally, consumption of preserved foods is greater in the northern districts than in the southern districts. These findings, in conjunction with the observations that Japanese immigrants to the United States have significantly less gastric cancer than Japanese residents, though its ratio is still higher than that of native-born Americans, suggest the importance of personal and dietary habits (73).

**FUTURE APPROACH TO THE ASIAN ENIGMA**

Each of the factors discussed above is likely to play a role in the variable prevalence of gastric cancer in Asian countries, which has been previously proposed. To investigate the Asian enigma and determine how these factors might be involved in the occurrence and development of gastric cancers, further detailed investigations and international comparative studies of each risk factor need to be performed. The recent consensus that the risk of gastric cancer increases only 2-to 4-fold in *H. pylori*-infected subjects suggests that not only *H. pylori* infection but also host genetic and/or environmental cofactors are important, as previously suggested by Forman (74). *H. pylori* is a significant and certainly initiating factor in chronic gastritis and later development of gastric cancer (30, 75). Our summary and analysis of Asian studies and those of other populations indicate that gastric neoplasms have a multifactorial etiology. Lessons from epidemiological studies in Kashmir and of Japanese immigrants would support this concept. Host genetic analyses of cytokine polymorphisms affecting mucosal inflammation and gastric acid secretion would provide additional information to identify predictive markers for an individual’s risk for gastric atrophy and malignancy. In the future, an individual gastric cancer risk may be predicted by the quantitative estimation of additive or synergistic effects of these bacterial, genetic, and environmental risk factors.

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