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REVIEW

Causal role of *Helicobacter pylori* infection in gastric cancer: An Asian enigma

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Abstract

Helicobacter pylori (H pylori) has been etiologically linked to gastric cancer. *H pylori* infection is more frequent in less developed Asian countries like India, Bangladesh, Pakistan, and Thailand and is acquired at early age than in more developed Asian countries like Japan and China. Frequency of gastric cancer, however, is very low in India, Bangladesh, Pakistan and Thailand compared to that in Japan and China. Similar enigma has been reported from Africa as compared to the West. Seroprevalence of *H pylori* infection in adult populations of India, Bangladesh, Pakistan and Thailand varies from 55% to 92%. In contrast, seroprevalence of *H pylori* in Chinese and Japanese adults is 44% and 55%, respectively. Annual incidence rate of gastric cancer in India, Bangladesh, and Thailand is 10.6, 1.3, 7.1 per 100 000 populations, respectively; in contrast, that in China and Japan is 32-59 and 80-115 per 100 000 populations, respectively. Several studies from India failed to show higher frequency of *H pylori* infection in patients with gastric cancer than controls. Available evidences did not support difference in *H pylori* strains as an explanation for this enigma. Despite established etiological role of *H pylori*, situation is somewhat enigmatic in Asian countries because in countries with higher frequency of infection, there is lower rate of gastric cancer. Host's genetic make-up and dietary and environmental factors might explain this enigma. Studies are urgently needed to solve this issue.

Key words: Stomach cancer; *Helicobacter pylori;* Tropical countries; Carcinogenesis; Infectious diseases

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INTRODUCTION

Helicobacter pylori (*H pylori*) is a major cause of gastroduodenal diseases like peptic ulcer and an important risk factor for gastric carcinoma (GC) and primary gastric lymphoma (PGL). Evidences supporting the etiological role of *H pylori* in GC and PGL include higher frequency of isolation of *H pylori* in patients with GC and PGL[1,2], regression or lower rate of occurrence or recurrence of the tumor in patients in whom the infection is eradicated[3-6], occasional reports of recurrence following re-infection[7,8] and development of tumor in patients[5,9] or animals[10,11] infected with the organism. Several meta-analyses also revealed a strong relationship between *H pylori* and GC and PGL[12,13]. Though the evidences available in literature support causal relationship between *H pylori* and GC and PGL, some interesting observations from the Asian countries make such causal relationship somewhat enigmatic[14-15]. Similar enigmatic situation has also been reported from Africa[16]. Here we have reviewed the available evidences on this issue and attempted to explain possible reasons for such an enigma.

FREQUENCY OF *H PYLORI* INFECTION IN DIFFERENT ASIAN COUNTRIES

Figure 1 shows seroprevalence of *H pylori* infection in different Asian countries[4,15,17-29]. Frequency of *H pylori* infection differs markedly in different countries. In the developing countries like India, Bangladesh, Pakistan and Thailand, infection with *H pylori* is more frequent among general population and is acquired at an early age. There are several studies from India that showed that *H pylori* is acquired by most people in early childhood[30]. Gill *et al*[31] from India showed that the prevalence of IgG and IgA antibodies to *H pylori* was 22%, 56% and 87% in 0-4, 5-9 and 10-19 years age groups, respectively. In contrast, in more industrialized and developed regions of Asia like Japan, China and Singapore, frequency of *H pylori* infection has been reported to be somewhat lower[14]. The prevalence of *H pylori* in the United States has decreased to approximately 10% in the white middle and upper class population of 50 years of age or younger[32]. As *H pylori* is transmitted by feco-oral route, overcrowding, poor sanitation, lower socioeconomic status and poor water

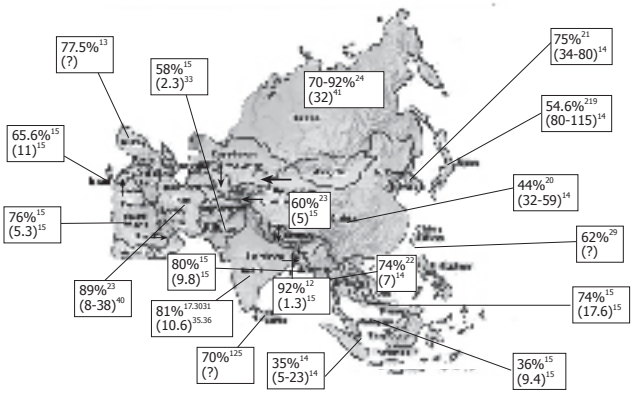

Figure 1 Map of Asia showing frequency of *Helicobacter pylori* infection in each country, crude annual incidence of gastric cancer per 100 000 populations (shown within parenthesis, where data are available). The reference from where data are obtained is shown in superscript. **A:** frequency in the year 1984; **B:** lower annual incidence of gastric cancer for Indians and higher values for Chinese living in Singapore; **C:** studies using PCR among patients with dyspepsia; #: annual-age standardized incidence rates; $: annual age-standardized death certification rate estimated from the graph that appeared in the report (year 1998-99).

supply are some of the major factors that result in higher frequency and lower age of acquisition of *H pylori* in less developed Asian countries[30,33] . Though frequency of *H pylori* as shown in the Figure 1 is not age-standardized, all these data are in adults. As *H pylori* is acquired in early childhood in most developing countries and later in life in most developed countries and as average life expectancy is higher in developed countries as compared to developing countries, age standardization of frequency of infection is unlikely to alter our conclusions.

FREQUENCY OF GASTRIC CANCER IN DIFFERENT ASIAN COUNTRIES

Gastric cancer is the world's second commonest malignancy, having been overtaken only by lung cancer in 1980's[34]. There is a marked international variation in gastric cancer incidence with highest rates reported from Japan. Figure 1 shows annual incidence of gastric cancer per 100 000 populations from Asian countries[14,15,35-41]. It is interesting to note that despite Japan being a developed country with a lower frequency of *H pylori* infection, it has highest frequency of gastric cancer. Similarly, frequency of gastric cancer is quite high in China despite a lower frequency of *H pylori* infection. In contrast, people living in less developed countries of Asia with high frequency of *H pylori* infection[17,18,22,30,31,42-44] that is acquired at an earlier age have the lowest risk of developing gastric cancer[14]. It has also been observed that frequency of gastric cancer differs in different parts within many countries; for example, in Japan[45], variation in gastric cancer risk has been well-documented in different regions and has been presumed to be related to variation in nutrient consumption. In China[46], gastric cancer mortality in Changle county is about 10-fold higher than that in Hong Kong and has been attributed to variation in frequency of *H pylori* infection in the two regions. In India, southern[35] and eastern parts (personal observation) of the country experience somewhat higher frequency of gastric cancer than the northern parts of the country. Interestingly, similar epidemiological observations were made long ago in India in respect of another *H pylori*-related gastroduodenal ailment, i.e., peptic ulcer disease[47].

STUDIES ON ASSOCIATION BETWEEN *H PYLORI* INFECTION AND GASTRIC CANCER IN ASIA

Studies from India failed to show an association between *H pylori* infection and gastric cancer[48-51]. In a study on 50 patients with gastric cancer and 50 controls with non-ulcer dyspepsia, *H pylori* infection was detected less frequently in gastric cancer (38%, 19/50) than those with non-ulcer dyspepsia (68%, 34/50)[48]. An another study demonstrated that 64.7% (33/51) patients with gastric carcinoma and 74.4% (32/43) with non-ulcer dyspepsia had infection with *H pylori* [49]. These studies can be criticized due to small sample size with a consequent type II statistical error. Also, in most of these studies, endoscopy-based tests were used to diagnose *H pylori* infection. Endoscopy-based tests can be false negative in patients with gastric cancer due to gastric atrophy and intestinal metaplasia[52]. However, a recently completed large study from our center in which 279 patients with gastric neoplasms (263 gastric cancer and 16 primary gastric lymphoma) failed to show a higher frequency of *H pylori* infection in patients with gastric neoplasms as compared with the controls (101 non-ulcer dyspepsia and 355 healthy subjects)[53]. In contrast, studies from China and Japan showed association between *H pylori* infection and gastric cancer[54,55].

WHAT IS ASIAN ENIGMA?

Oxford dictionary describes the term "enigma" as a mysterious or puzzling thing. What is puzzling about gastric cancer and *H pylori* infection in Asia? The countries with highest frequency of *H pylori* infection have the lowest risk of gastric cancer in contrast to the countries like Japan and China where gastric cancer risk is highest in the world despite a lower occurrence of *H pylori* infection. This casts major objection to some of the simplified model of gastric carcinogenesis resulting from *H pylori* infection that stated that if the infection is acquired at an early age particularly in presence of malnutrition, it may reduce gastric acid secretion, pangastritis and gastric cancer may be the likely outcome. In contrast, infection acquired later in life and in person with good nutritional status and normal gastric acid secretion would result in hyperchlorhydria and duodenal ulcer disease[56]. It is well documented in the literature that patients with duodenal ulcer infrequently or never develop gastric cancer[5,57]. If this simplified model of gastric carcinogenesis would have been true, India, Bangladesh, Pakistan would have higher frequency of gastric cancer than Japan and China.

WHAT ARE THE POSSIBLE EXPLANATIONS FOR THE ASIAN ENIGMA?

Agent factors

All strains of *H pylori* are not pathogenic. Is it possible

that people living in countries with lower frequency of gastric cancer are infected with non-pathogenic strains of *H pylori* than people living in China or Japan? However, available evidences do not support this hypothesis. Peptic ulcer disease, which is associated with infection by pathogenic strains of *H pylori,* has been reported a common problem in India and Bangladesh[47]. Genotypic analysis of *H pylori* strains from India showed pathogenic strains to be present in more than 80% of adults and children with gastroduodenal diseases as well as in control population[58-59]. Studies that used CagA antibody in patients with non-ulcer dyspepsia have shown that CagA antibody is detected in sera of most patients[60]. From our center, a recently completed large study on 279 patients with gastric neoplasms (263 gastric cancer and 16 primary gastric lymphoma) and controls (101 non-ulcer dyspepsia and 355 healthy subjects) showed that frequency of CagA IgG antibody was similar among the patients with gastric carcinoma and the controls, suggesting that difference in virulence factor of *H pylori*, at least CagA, is unlikely to explain the variation in outcome of *H pylori* infection[53]. In a study from US, Korea and Colombia[61] in which the first-degree relatives of patients with gastric cancer were evaluated to know whether similar strains of *H pylori* or similar environmental factors are responsible for pattern of gastritis. However, this study failed to show any relationship between specific virulence factors or *H pylori* strains and specific histologic pattern or outcome even among those sharing the same environment in childhood[61]. However, several studies from Japan and China[62,63] showed that virulence factors of *H pylori* are strongly associated with gastric carcinoma. Based on the available evidences, one can not conclude that in Asian countries, despite high frequency of *H pylori* infection, low frequency of gastric cancer is related to infection with non-pathogenic strains. Though a study from Africa showed that virulence-associated genes of *H pylori* may partially explain the African enigma[64], the same corollary may not hold well to explain the Asian enigma.

Host's genetic factors

Host's genetic make-up determines in a major way response to any infection, including that to *H pylori*. This is evidenced by the fact that relatives of patients with gastric cancer infected with *H pylori* developed precancerous abnormalities like gastric atrophy and hypochlorhydria more often than those with non-ulcer dyspepsia[65]. Patients with duodenal ulcer, which is also caused by *H pylori,* do not develop gastric cancer in contrast to other conditions associated with *H pylori* infection, such as gastric ulcer, non-ulcer dyspepsia and hyperplastic gastric polyp[5]. These also depict variations in host's response despite infection with the same organism. Japanese immigrants to the United States have higher gastric cancer risk than native-born Americans, though lesser than Japanese living in Japan[66]; this suggests importance of the genetic factors with additive effects of environmental factors.

Difference in carcinogenic risk in people living in different geographical areas might be related to variation in genetic make-up among different races. Specific allelic variation of different genes (polymorphism) present in a proportion of general population may determine variation in carcinogenic potential in different populations in response to environmental carcinogenic exposure, including that to *H pylori* infection[67]. Genetic susceptibility of a person may be important in a number of carcinogenic processes that include: (1) mucosal protection against *H pylori* infection and injury by other carcinogens; (2) mucosal inflammatory response to infection with *H pylori*; (3) degree of apoptotic cell death[68]; (4) carcinogen activation and detoxification by various enzyme systems of the hosts; (5) variability in the repair of mutated DNA; and (6) ability of the cell to proliferate in a controlled manner to repair the damage.

Several studies have been carried out on single nucleotide polymorphism in relation to gastric carcinogenesis[67]. However, many of these studies did not take into account the role of *H pylori* infection and dietary factors in addition to the genetic factors. Therefore, there is need of more data on genetic polymorphism in relation to *H pylori* infection and dietary factors. In fact, genetic studies comparing Asian population with high gastric cancer risk like Japan and China and low cancer risk despite a very high prevalence of *H pylori* infection like India are needed to understand the explanation for the Asian enigma at a molecular level.

Dietary and environmental factors

Diet may play a major role in gastric carcinogenesis. In India, southern[35] and eastern parts (personal observation) of the country experience somewhat higher frequency of gastric cancer than the northern parts of the country. Rice is the staple cereal in eastern India. Non-vegetarian foods, particularly fish, are very common in eastern Indian diet, which is also spicy with more salts. Diet in southern India is somewhat similar to that in eastern India with rice, fish, excess spice and salt being commonly eaten. In contrast, northern Indian diet is mainly wheat-based and a greater proportion of people are vegetarian. Tobacco smoking, high-temperature food intake, spicy food and rice eating have been shown to be risk factors for gastric cancer in India[69,70]. In another study, consumption of dry fish has been shown to be a risk factor for gastric cancer in India[71]. Diet has been considered to be a major factor for increased frequency of gastric and esophageal cancer in Kashmir province of India[72]. Similar observations have also been made in several countries, including Japan where northern districts have reported a higher frequency of gastric cancer than southern district and this has been related to increased dietary intake of salts in northern districts[14]. Tobacco use and alcohol consumption are the other factors that may influence the international variation in frequency of gastric cancer[15]. Possible explanation of Asian enigma might be related, at least in part, to difference in diet between different countries.

CONCLUSIONS AND FUTURE DIRECTIONS

The available evidences clearly show that *H pylori* alone is not the only independent factor in gastric carcinogenesis. Host's genetic make-up and dietary factors play a major role in determining whether or not a person infected with *H pylori* will develop gastric atrophy, intestinal

metaplasia and gastric cancer. This has major importance in preventive strategies of gastric cancer. Despite *H pylori* being an important agent for causing gastric cancer, a recent randomized controlled trial from high risk region of gastric cancer in China failed to show benefit of eradicating *H pylori* in preventing gastric cancer[73]. This might be related to the fact that only 1-2% people infected with *H pylori* develop atrophic gastritis per year, which is a precancerous lesion[74]. Racial and genetic factors are also important as evidenced by difference in gastric cancer risk in different populations, and a recent study, though not from Asia, showed differences in IgG subclass responses between subjects from Gambia and United Kingdom[75]. Unless randomized controlled trials of eradication of *H pylori* among people who are not only infected with *H pylori* but also carry multiple genetic factors which increase their predisposition to developing gastric cancer are undertaken, it is difficult to obtain meaningful conclusions about how useful *H pylori* eradication would be to prevent gastric carcinoma. In fact, in foreseeable future, a day may come when an individual infected with *H pylori* may be able to know, using mathematical modeling and his genetic make-up, as to what would be his risk of developing gastric cancer, and based on that his physician may advise him whether he should undergo *H pylori* eradication treatment and/or modification of his diet to reduce risk of gastric cancer. Since gastric cancer is likely to be a multifactorial disease, which include genetic, dietary and environmental factors and not *H pylori* alone, all these factors need to be considered while constructing the model.

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