MINI-REVIEW

Helicobacter Pylori and Gastric Cancer

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Abstract

***Helicobacter pylori* has been the subject of intense investigation since its culture from a gastric biopsy in 1982. From the beginning, this gram-negative bacterium has provoked the interest of bacteriologists, gastroenterologists, infectious disease specialists, cancer biologists, epidemiologists, pathologists, and pharmaceutical scientists. Pathologists were among the first groups of scientists to reevaluate their data in the context of the newly discovered bacterial etiological agent. Chronic inflammation elicited by the bacterium provided the missing link in the progression to gastric carcinoma; accordingly, *H. pylori* was named as a class 1 carcinogen by the World Health Organization. Two key papers published in 1991 in the Journal of the National Cancer Institute reported a positive association between gastric cancer and *H. pylori* infection. This fact provided a strong rationale to treat all who tested positive for *H. pylori*. Antibiotic regimens have been largely successful, but some agents such as metronidazole and clarithromycin have been rendered ineffective in several countries and geographical areas of the United States by the emergence of strains resistant to these compounds. Although there was some skepticism initially, within few years numerous research groups verified the association of *H.pylori* with gastric carcinoma. Host related factors for the development of disease can indicate genetic susceptibility (or resistance) or acquired influences, which may stimulate defenses of the host against environmental carcinogens like *H.pylori*. The present article is a mini-review of the history and epidemiology of the bacterium and its suggested association with the development and progression of gastric cancer.**

Key Words: Helicobacter pylori - epidemiology - factors - gastric cancer

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Helicobacter pylori (*H.pylori*) is a gram negative microaerophillic bacterium that inhabits various areas of stomach and duodenum. Normally the acidic environment of stomach prevents the survival of viruses, bacteria and other micro-organisms. However *H. pylori* have evolved to be uniquely suited to thrive in the harsh stomach environment. The *H. pylori* bacterium secretes urease, a special enzyme that converts urea to ammonia. Ammonia reduces the acidity of stomach, making it more hospitable home for *H.pylori* (Liddell et al., 1966; Stark et al., 1999; Olson and Maier, 2002; Yamaoka, 2008).

The ability to survive in the stomach provides *H.pylori* with a useful hiding place. White blood cells that would normally recognize and attack invading bacteria are unable to cross the blood vessels into the stomach lining. Instead the infective white blood cells continue to respond to the site of infection where they die and release nutrients that feed *H.pylori*. *H pylori* has co-existed with humans for thousands of years, however because the scientist believed the stomach was a sterile organ the bacterium was not discovered until 1980 (Marshall, 1983).

Interest in understanding the role of bacteria in stomach diseases was started in the 1970s with the visualization of bacteria in the stomach of gastric ulcer patients. The bacterium had been observed in 1979 by Australian pathologist Berry Marshal, who did further research on it with Australian physician, J Robin Warren, beginning in 1981. But, Marshal frustrated with lack of good animal model of infection, infected him with curved bacteria. He became ill, developed inflammation of stomach, and was able to culture the bacteria from his own ulcers. First successful culture of H. pylori in 1982 occurred almost by accident, there by they proved the bacterium to be the cause of stomach ulcers. They published the results of self-induced infection in 1985 (Marshall Barry, 1983). For their discovery of H.pylori and its role in gastric ulcer formation Marshal and Warren were awarded the 2005 Nobel Prize in medicine.

Although there was some skepticism initially, within few years numerous research groups verified the association of H.pylori with gastric carcinoma. Recently, H. pylori has been classified as a human carcinogen by the International Agency for Research on Cancer (International Agency for Research on Cancer (IARC)

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Working Group). Two key papers published in 1991 in the Journal of the National Cancer Institute reported a positive association between gastric cancer and *H. pylori* infection. They contributed substantially to the recognition of *H. pylori* as a human carcinogen. Parsonnet and coworkers (1991) reported on the prevalence of *H. pylori* infection in gastrectomy specimens from gastric cancer patients. The prevalence of infection was statistically significantly higher in specimens from patients with the intestinal type (89.2%) than in specimens from patients with the diffuse type (31.8%) gastric cancer. These results demonstrate a direct association between *H. pylori* infection and the intestinal type of gastric carcinoma. Talley and coworkers used stored serum samples of patients with histologically diagnosed gastric adenocarcinoma and tested for H. pylori antibodies. They found a significantly elevated infection rate for non-cardia cancer (odds ratio (OR)=2.67, 95% confidence interval (CI)=1.01 to 7.06) than for cancer-free controls (Talley et al., 1991).

One key element in the acceptance of *H. pylori* as a carcinogen was the evidence brought forth by three independent historical cohort studies. In Hawaii, California (Parsonnet et al., 1991) and the United Kingdom 11 cohorts had been assembled in the 1960s and followed up for decades. At the initiation of each study, blood serum was collected and frozen. During the follow-up period, a total of 247 subjects developed gastric cancer. When their sera were tested for the presence of antibodies against *H. pylori* and compared with the sera of cohort subjects who remained free of gastric cancer, a significantly increased risk of cancer was found in subjects who were infected decades before cancer developed. The risk increased as time intervals between documented infection and the diagnosis of cancer increased (Forman et al., 1994). This study design practically ruled out any recall bias.

Human infection with the bacterium is common; the Centers for Disease Control and Prevention estimatethat approximately two-thirds of the worlds population harbors the bacterium, with infection rates much higher in developing nations than in Europe and North America. A very small fraction of infected subjects develop gastric cancer. The infection prevalence is high in several high-cancer-risk populations, such as Japan and Colombia. But several large populations with high infection prevalence display a very low rate of gastric cancer. This so-called "African enigma"(Holcombe, 1992) remains unexplained, but it does point out a very important fact: not all *H. pylori* infected patients have increased risk of gastric cancer.

Studies on prevalence of *H. pylori* infection in gastric cancer from several countries have yielded widely varying results ranging from 19 to 80% (Correa and Ruiz, 1989; Loffeld et al., 1990; Parsonnet et al., 1991). Various epidemiological studies in India show a high rate of gastric cancer incidence in Southern India as compared with North India (Malhotra SL, 1967). The prevalence of *H. pylori* infection is high (49.9% to 83.3%) in India (Prasad et al., 1994; Alagnatham et al., 1999) but the incidence of gastric cancer is comparatively lower suggesting mixed results with association between H.pylori and gastric cancer. Quigley et al in their review quoted that human epidemiological studies have produced mixed results with association between *H. pylori* and gastric cancer in 50% patients, while the rest of patients showed negative relationship (Quigley and Eslick, 2006).

In North India the prevalence of *H. pylori* in patients with gastric carcinoma was assessed and correlated with gross appearance and histological type (Misra et al., 2007). The prevalence of *H. pylori* in controls was slightly higher than patients group (80% vs 78%). Prevalence of H. pylori was more in diffuse type of gastric cancer than intestinal type (86% vs 68%). A significant association between *H. pylori* and grades of gastritis was noted ($P<0.01$) in controls as well as in patient group but it failed to show a significant association with tumor grades, intestinal metaplasia, site of tumor and age of patient. It was inferred that prevalence of *H. pylori* infection is not directly associated with pathogenesis of gastric cancer but it may act as a co-carcinogen by damaging the mucosa and thereby making it more susceptible to effects of carcinogen.

This point to a major scientific challenge: what mechanisms lead to cancer in certain subjects and what mechanisms prevent the development of cancer in other chronically infected subjects. This conundrum leads us to the search for answers in the events that precede cancer development, namely the precancerous process.

The precancerous process had been the subject of inquiry much before the scientific world was aware of *H. pylori* as a human pathogen. The histopathology of the precancerous stages has long been recognized: chronic gastritis, gland loss (atrophy), intestinal metaplasia (complete and incomplete), and epithelial dysplasia (Correa, 1990). The steady progression of the process in high-risk populations has been documented (Correa, 1990). It has been shown that progression represents a steady state characterized by episodes of progression to more advanced stages as well as episodes of "regression" to less advanced stages. The risk factors associated with the development of precancerous lesions are very similar to those associated with gastric cancer. A number of factors increase the risk, most prominently irritants of the gastric mucosa, such as excessive dietary salt. Others ("protectors") decrease the risk, especially adequate intake of fruits and fresh vegetables.

Clinical and epidemiologic studies have shown that diseases associated with *H. pylori* differ drastically in terms of cancer risk. Gastric peptic ulcer is considered part of the precancerous complex known as multifocal atrophic gastritis (MAG)(Correa, 1995). A retrospective ("historical") cohort study of 57,936 patients with peptic ulcer diagnosed in Swedish hospitals decades earlier were linked to gastric cancer records at the National Cancer Registry (Hansson et al., 1996). Patients diagnosed with gastric ulcer not subjected to gastrectomy had an increased relative risk of gastric cancer in approximately two decades of follow-up (relative risk (RR)=1.8, 95% CI=1.1 to 2.8). Patients with a previous diagnosis of duodenal ulcer displayed a lower RR of gastric cancer (approximately 0.7). Because both locations of peptic ulcer are linked to *H. pylori* infection, it follows that the infection increases cancer risk in gastric ulcer but not

in duodenal ulcer patients. Ulcers of both locations are associated with chronic inflammatory changes linked to *H. pylori* infection. A comprehensive literature review of the natural history of duodenal ulcer before effective treatment of *H. pylori* infection was available registered the fact that clinical manifestations of the ulcer tend to persist for decades (Neil et al).

A recent Japanese experience report by Uemura et al (2001) provides strong confirmation of the previous Swedish findings. A total of 1,246 patients with *H. pylori*infection were followed for approximately 7 years; 36 of them (2.9%) developed cancer. A total of 280 not infected patients and 253 cured of their infection did not develop any gastric cancer during the follow-up period. Infected patients with gastric ulcer (229) or gastric atrophy (208) had a statistically significantly increased risk of cancer. A total of 275 infected patients with duodenal ulcer, however, did not develop any gastric cancer in the follow-up period.

The classical epidemiologic approach to causality postulates that such outcomes depend on the interplay of three sets of factors: those associated with the agent, with the host, and with the environment. Recent scientific inquiries have focused on these premises.

Factors associated with the agent have been explored and have led to interesting and intriguing findings. Studies of virulence factors of the bacterium have concentrated on two genes: cagA and vacA. Polymorphisms of the vacA gene have shown a peculiar association with ethnicity and human migration (Van Doorn et al., 1999). The type vacA s_1a is strongly associated with populations of northern European origin. Type vacA s_1c is characteristic of Southeast Asia. Populations of Mediterranean origin have both s_1a and s_1b genotypes; the same combination is found in the United States. In Africa, type s_1b predominates. In Latin America, including aboriginal Indian tribes, type s1b is also predominant. In most populations with historically high gastric cancer risk (present or past) type s_1 (a or b) predominates. In low-risk populations the genotype distribution is not well documented. A number of preliminary reports indicate a relatively higher frequency of s_2 genotypes, which tend to be less pathogenic. One common problem in international comparisons is that many studies are based on patients with duodenal ulcer or other severe clinical manifestations that are known to be associated with more virulent (mostly s_1) bacterial genotypes. Selection bias, therefore, interferes with relevant findings, especially in low-cancer-risk populations. Relevant progress, therefore, has been made recently. In the near future it may be possible to classify H. pylori genotypes as "oncogenic" or "non-oncogenic".

Host related factors can indicate genetic susceptibility (or resistance) or acquired influences, which may stimulate defenses of the host against environmental carcinogens. Recent research has pointed to genetic trends associated with the expression of cytokines during the inflammatory process. El-Omar has reported that genetic polymorphisms of the interleukin 1 beta (IL-1β) determine outcomes of gastric inflammation toward oncogenic or non-oncogenic pathways (El-Omar et al., 2000). Certain (IL-1β) subtypes increase gastric cancer risk and are also associated with inhibition of acid secretion by the gastric mucosa. Similar effects are linked to the expression of tumor necrosis factor alpha (TNα) or 1L-10. Other genetic polymorphisms possibly associated with cancer risk have been reported for mucins (MUC-1) (Reis et al., 1999) and human lymphocyte antigens (HLA) (Magnusson et al., 1996). This type of research may lead to the identification of individuals within a community that may especially be at high risk.

Environmental factors linked to gastric cancer risk have been described by multiple epidemiologic studies. They are mostly associated with poverty and diet: excessive use of salt and deficient intake of fresh fruits and vegetables in the diet. Excessive salt may be an irritant to the gastric mucosa. Fresh fruits and vegetables have been linked to antioxidants such as ascorbic acid, beta-carotene, vitamin E, folates, and non-nutrients such as polyphenols (Buiatti et al., 1984; 1990; Fontham, 1994).

Taken together, factors associated with gastric cancer risk may be conceived as dominated by infection of the gastric mucosa with *H. pylori*. The infection results in chronic active inflammation that lasts for decades. The inflammatory process can be modulated by multiple forces. These may be genetic: inherited traits determining either susceptibility or resistance to carcinogenesis. Environmental factors playing a role in carcinogenesis may also act as enhancers or inhibitors of the inflammatory process. Enhancers may be gastric irritants, whereas inhibitors appear to act mostly as antioxidants, which points to the possible role of reactive oxygen species (ROS) as a common final pathway of carcinogenesis (Miller et al., 1998).

A good example of environmental factors as determinants of "oncogenic" outcomes of the infection has been provided by epidemiologic studies (Blaser et al., 1995). Early infection in Japanese–Hawaiian children is associated with elevated gastric cancer risk. Later infection increases the risk of duodenal ulcer, a non-oncogenic outcome.

The interactions among different etiologic factors have been illustrated recently in the Journal of the National Cancer Institute. Figueiredo et al (2002) examined the influence of more virulent ("oncogenic?") *H. pylori*genotypes on more susceptible hosts and suggested Cag A positive, Vac s1m1 bacterial genotypes infecting IL-1 B-511*T carriers have a much higher risk: (OR=87, CI=11-679) of producing cancer (Hansson et al., 1996).

The association of *H. pylori* infection and development of non cardia gastric cancer is published in a report in journal of National Cancer Institute (Nicholas et al., 1991). A significant association was found between *H. pylori* infection and non-cardia gastric cancer (odds ratio 2.67; 99% confidance interval 1.01-7.06).

In a lecture on human gastric carcinogenesis Palayo Correa (1992) has provided a human model of gastric carcinogenesis with following sequential stages: chronic gastritis atrophy intestinal metaplasia and dysplasia. The initial stages of gastritis and atrophy have been linked to excessive salt intake and *H. pylori* infection.

In order to understand diverse effects of infection with Helicobacter pylori on epithelial mucosal mass and

consequence clinical outcome, the relationship between *H. pylori* infection and gastric cellular turnover is investigated (Moss, 1998). The results indicate that the *H. pylori* increases epithelial cell proliferation and apoptosis in-vivo but that infection with bacteria of cagA genotype leads to relatively more proliferation than apoptosis. This review explores the cause of induction of apoptosis in gastric epithelial cells by *H. pylori* and the consequences of alterations in apoptosis to the maintenance of gastric mucosal homeostasis.

The molecular mechanism of *H. pylori* associated gastric carcinogenesis (Zhang and Farting, 1999) shows involvement of many molecules in H. pylori associated gastric carcinogenesis. Over many years, *H. pylori*infected mucosa may experience sequential exposure to "damage regeneration". Following the long standing repeated damage-regenerate cycle; gastric atrophy and intestinal metaplasia gradually develop which finally results in adenocarcinoma. *H. pylori* infection may cause disturbance of p53 function and subsequently this may not only lead to defects in the DNA damage-p53 mediated pathway but the mutated p53 protein may also provide a possible selective advantage for tumor cell proliferation by attenuating apoptosis (Ishida et al., 1997). Furthermore the *H. pylori* infection has been shown to induce reactivation of telomerase and to cause telomerase dysfunction, which may cooperate with p53 deficiency to accelerate carcinogenesis (Chin et al., 1999). In early stages of *H. pylori* infection CD95 and bax mediated apoptosis may play an important role in eliminating damaged DNA or gene mutated cells, thereby maintaining genetic stability. However, *H. pylori* infection induces CD95L expression, which may suppress host immune responses by causing immunocyte apoptosis. Therefore as shown in Figure 1 loss of p53 function, reactivation of telomerase activity, inhibition of host immune responses together with host genetic factors may play important role in the development of *H.pylori* associated carcinogenesis (Zhang and Farting, 1999).

A specific antibody pattern in sera from patients suffering from *H. pylori* related gastric adenocarcinoma (GAC) suggest the significance of Anti CagA antibodies (Moss, 1998). The serological response of patients suffering from GAC, patients with gastro duodenal ulcer and asymptomatic subjects were analyzed using immunoblotting performed with three *H. pylori* strains: strain ATCC 43579; strain B110, isolated from a patient with ulcers; and strain B225, isolated from a patient with GAC. In addition, the latex agglutination test Pyloriset Dry was used to analyze ambiguous sera. H. pylori seropositivity was 75% in the GAC group, 61.3% in the ulcer group, and 56.4% in the asymptomatic group. Anti-CagA antibodies were found more often in the GAC group (48.8%) and in the ulcer group (47.3%) than in the asymptomatic group (21.2%). These percentages depended on the strain used as an antigen: in the GAC group, the anti-CagA frequencies were 93.3, 40, and 13.3% with strains B225, B110, and ATCC 43579, respectively. This data suggest the existence of a CagA protein specifically expressed by *H. pylori* strains isolated from GAC patients.

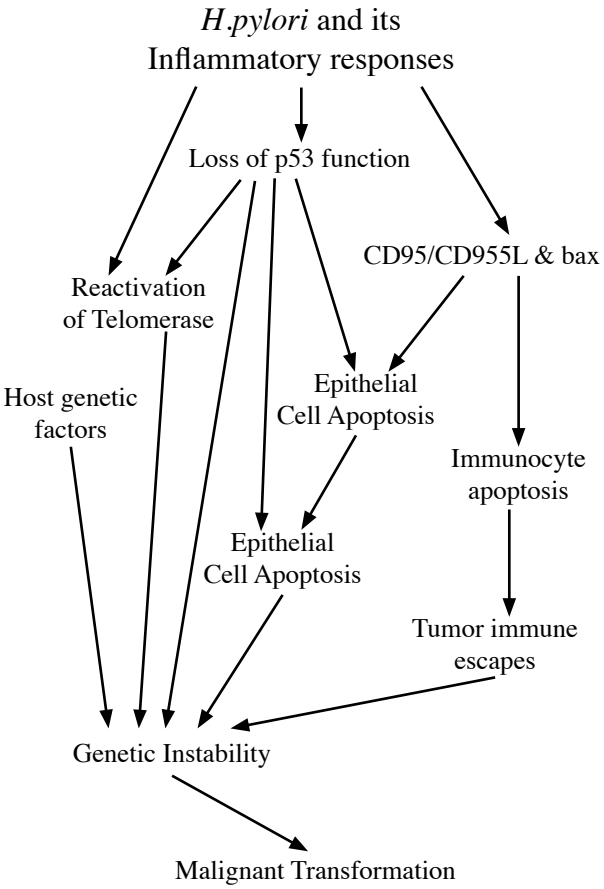

Figure 1. Possible Molecular Mechanisms of *H.pylori* -associated carcinogenesis

The ability of *H. pylori* to stimulate an oxidative burst in neutrophils and epithelial apoptosis was examined in biopsy specimens by TUNEL method. The oxidative burst in neutrophils was measured by flow cytometry. There was a significant positive correlation between number of epithelial apoptotic cells and fluorescence intensity. Increased neutrophil oxidative burst stimulated by *H. pylori* may play a role in enhanced gastric mucosal DNA damage and consequent atrophic gastritis (Mizuki., 2000).

A combined analysis of 12 case control studies (1,228 gastric cancer cases) nested with in prospective cohorts showed that the association with *H.pylori* was restricted to non-cardia cancers (Helicobacter pylori and cancer collaborative group, 2001) (odds ratio=3.0, 95%confidance interval 2.3-3.8) and was stronger when blood samples for *H.pylori* serology were collected 10+years before cancer diagnosis (5.9, 3.4-10.3) *H.pylori* infection was not associated with an altered overall risk of cardia cancer (1.0; 0.7-1.4). These results suggest 5.9 is the best estimate of the relative risk of non-cardia cancer associated with *H.pylori* infection and that *H.pylori* does not increase cardia cancer. They also support the idea that when *H.pylori* status is assessed close to cancer diagnosis, the magnitude of non cardia association may be underestimating.

A possible pathway leading from *H. pylori* gastritis to either gastric adenoma or gastric cancer was given by Menning et al., (2002). They suggested that gastric adenomas and gastric intestinal cancer arise by analogous mechanism. However, owing to severe atrophic gastritis

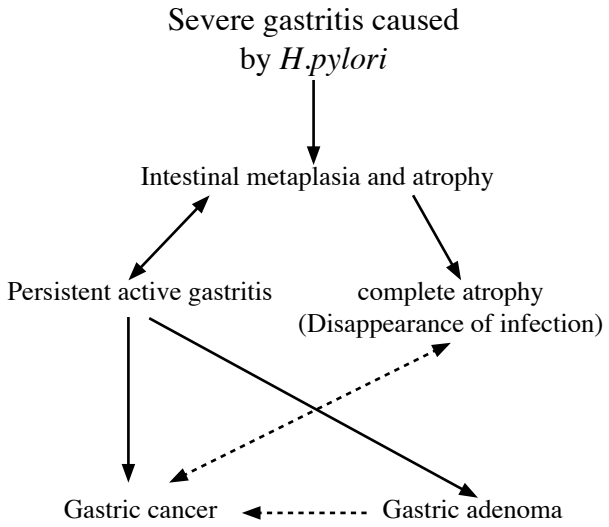

Figure 2. Possible Pathways Leading from Helicobacter Pylori Gastritis to Either Gastric Adenoma or Gastric Cancer

and a lower incidence of *H.pylori*, adenomas do not appear to be definite precursor for gastric cancer.

The molecular features of gastric cancer and premalignant stages are explored using DNA microarray based gene expression profiling in a total of 124 tumors and adjacent mucosa samples. Chronic gastritis exhibits a pronounced mitochondrial gene expression signature, which may be linked to *H. pylori* pathogenesis (Boussioutas et al., 2003).

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