Published in final edited form as:
Front Biosci. ; 14: 1490–1504.

Helicobacter Pylori associated global gastric cancer burden

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1. Abstract

Helicobacter pylori infection is ubiquitous, infecting close to one-half of the world's population, but its prevalence is declining in developed countries. Chronic *H. pylori* infection is etiologically linked to gastric adenocarcinoma, especially non-cardia type (63% of all stomach cancer or ~5.5% of the global cancer burden: ~25% of cancers associated with infectious etiology), and to gastric mucosal associated lymphoid tissue (MALT) lymphoma, which accounts for up to 8% of all non-Hodgkin lymphoma. Epidemiological, clinical, and animal studies have established a central role for *H. pylori* in gastric carcinogenesis and provided insights into the mechanisms and biologic relationships between bacterial infection, host genetics, nutrition, and environmental factors. These discoveries invite strategies to prevent infection to be the logical primary goals in a multi-pronged effort to curtail suffering and death from *H. pylori* infection-associated cancers.

Keywords

Gastric Cancer; African Enigma; Parasites; Prevention; Review

2. Introduction

Gastric cancer is the third most common cancer among males and fifth most common among females (1). In 2002, 930,000 cases were recorded accounting for 10% of all new cancers that year, and 700,000 deaths were recorded, making it the second most common cause of cancer death, after lung cancer (2). The incidence of gastric cancer is declining in developed countries (3), but the global burden is rising and is projected to top 1.1 million cases per year in 2010, mostly due to cases occurring in developing countries. The 5-year survival for late stage gastric cancer is low even in developed countries (20% in Japan), while aggressive screening programs, as has been done in Japan, improved 5-year survival of early stage cancers (~70%) (4).

Gastric cancer incidence shows considerable variation by geography, though a male preponderance is reported in much of the world (Figure 1). Age standardized incidence is highest in countries in Eastern Asia (including Japan), Eastern Europe (including former Soviet republics), and in some countries in central South America (overall age standardized rates 20-35/100,000). The incidence is low in North America, Western Europe (<5), sub-Saharan Africa (5-10) and in Southern Asia (<10). This geographic variation in incidence points to differential distribution of etiological factors, although biases in access to diagnosis and disease registries may also contribute.

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The isolation of *Helicobacter pylori* (*H. pylori*) in 1982 (5, 6) and subsequent association with gastric cancer have provided us with a unique model with which to understand infection-associated cancer (7). *H. pylori* was classified as a human carcinogenic agent in 1994 by the International Agency for Research on Cancer, based on careful evaluation of epidemiological and animal studies (8). Current statistics suggest that *H. pylori* is responsible for 74% of non-cardia gastric in the developed and 78% in less developed countries. These proportions translate to 592,000 cases of stomach cancers (63%, also referred to as the attributable fraction, i.e., that is the total number of incident cases that can theoretically be attributed to the infection) worldwide or 5.5% of the global cancer burden (9). These figures underscore the public health importance of *H. pylori* infection as well as the potential to translate our understanding of the disease pathogenesis into novel prevention strategies (10).

Here, we review the epidemiology of *H. pylori* infection and two associated malignancies, namely gastric adenocarcinoma and gastric mucosal associated lymphoid tissue (MALT) lymphoma, their pathogenesis, geographic variation in disease, and opportunities for primary, secondary and tertiary prevention.

3. Epidemiology of Helicobacter Pylori Infection

H. pylori is a Gram-negative, spiral shaped, micro-aerophilic bacillus, now known to infect chronically more than half of the world's population (11). It was isolated in 1982 from the gastric mucosal tissue in patients with acute gastritis by Barry Marshall and Robin Warren. These investigators hypothesized that the bacterial agent may cause acute gastritis and, possibly, gastric and duodenal ulcer disease, and gastric cancer (5). Despite initial resistance to the hypothesis, subsequent evidence prompted the International Agency for Research on Cancer to declare *H. pylori* a Class 1 carcinogen for humans in 1994 (11), and a Nobel Prize in Medicine to be awarded to Marshall and Warren for their discovery in 2005 (12).

Although *H. pylori* is ubiquitous worldwide (13), there is substantial variation in age at infection, peak prevalence, rate of sero-reversion and re-infection, and gastric associated consequences by region (14). Infection is generally acquired early in childhood through oral-fecal contact, infection rates peak at 80-100% during adolescence, and may persist throughout life, particularly in less developed countries (15-18). By contrast, in developed countries infection is acquired later in childhood or adolescence, is cleared in about 10% of cases, and peaks at 50-70% during young adulthood, although peak prevalence is declining (19, 20). Risk factors for infection include lower socioeconomic status and having family members who are infected (16, 21). The adult prevalence was estimated to be 62% in China (22), 62% in Central America, 82% in Eastern Europe, 71% in Japan, 60-70% in Jamaica (23), and, in the U.S, it is 53% in non-Hispanic blacks and 62% in Mexican Americans, but 26% among non-Hispanic whites (24).

In addition to socioeconomic factors, accumulating evidence suggests that host genetics may influence the acquisition and persistence of infection. In a study of 199 Jamaican children aged <2 years, Tseng *et al.*, (25) reported that *H. pylori* seropositivity in children was positively associated with maternal *H. pylori* seropositivity (odds ratio (OR) 7.98, 95% confidence interval (CI) 1.05-60.6) and inversely associated with carriage of a T allele at position 889 of the pro-inflammatory interleukin 1 (*IL1A*) cytokine gene. The risk for *H. pylori* further decreased 43% with each additional T allele for individuals homozygous for the T allele at *IL1A*-889 (95% CI 0.33-0.99, $p_{trend} = 0.05$). Other investigators have replicated these associations with polymorphisms in other cytokine genes, including *IL-1B* (26). In a study of 663 individuals undergoing routine health check-up in China, Liou *et al.*, (27) reported that possession of a C→T polymorphisms in the *IL-1B* cytokine gene at

position 511 was associated with increased risk for *H. pylori* positivity in analyses after controlling for age (OR 1.56, 95% CI 1.06-2.30).

4. Pathogenesis of *H. Pylori* Infection

H. pylori colonizes the mucus layer of the gastric epithelium, where it has evolved mechanisms to survive in the acidic environment (28). These mechanisms include production of a urease enzyme to metabolize gastric urea to form ammonium and carbon-dioxide thereby maintaining a periplasmic PH range of 6 to 8 (29). The bacteria also expresses a urea transport protein (UreI), which reduces the rate of urea entry into cytoplasm (30). Spontaneous loss of infection is thought to be rare without treatment (31), ensuring infection persists in gastric mucosa for decades in most populations.

Chronic bacterial infection elicits an inflammatory response, which is responsible for eroding the gastric mucosa, which may lead to ulceration and, in a smaller proportion of subjects, progression to gastric cancer (28). This inflammatory response is modulated by co-factors, including bacterial and host genes, and environmental factors, which interact to determine the specific outcome of *H. pylori* infection (32, 33). The extent, duration, and consequences of *H. pylori* infection in an individual are also influenced by their innate acid secretory capacity. Individuals with high acid output are at risk of developing antral-predominant gastritis, which is associated with increased risk of duodenal ulcer disease, but lower risk for gastric cancer (duodenal phenotype) (34). In contrast, low acid secretory capacity (genetic or pharmacologic) is associated with widespread and persistent colonization of the gastric mucosa. Individuals with low acid output (hypochlorhydria) are at risk of an infection spectrum spanning from asymptomatic mild pan-gastritis to corpus-predominant gastritis, which is associated with gastric atrophy and increased risk of gastric cancer (gastric cancer phenotype) (35). Colonization of the corpus mucosa elicits a severe local inflammatory response characterized by secretion of IL-1β and tumor necrosis factor (TNF)-α inflammatory cytokines (36), which inhibit gastric acid secretion, and lead to disruption of the structure and function of gastric mucosa, atrophy, metaplasia, and development of genetic errors in the cells, which sets the stage for progression to cancer.

5. *H. Pylori* and Gastric Cancer: a Brief Review of the Evidence

The association is stronger between *H. pylori* and gastric cancer involving the distal stomach or non-cardia, than that involving the proximal stomach or cardia (34). Histologically, gastric cancer is classified as intestinal or diffuse type (37), with distinct clinical and epidemiological features. Intestinal gastric cancer type is composed of tumors cells that form functional glands resembling intestinal mucosa; conversely, diffuse gastric cancer type is composed of non-functional tumor cells lacking cohesion. Non-cardia gastric cancer is most commonly of the intestinal type and develops through sequential steps of gastric atrophy, intestinal metaplasia, to gastric cancer. By contrast, cancer of the cardia is usually of the diffuse type, and its development does not follow the accepted sequential steps outlined above for non-cardia gastric cancer. Diffuse type cancer shows a greater propensity to spread and, therefore, has poorer prognosis (38).

Epidemiological studies linking *H. pylori* infection with gastric cancer include a plethora of case-control (39) and prospective cohort studies (40), whose evidence is now available as pooled estimates from meta-analyses (41). While case-control studies provided valuable initial evidence of association, their results generally under-estimated the association because they measured *H. pylori* infection after the onset of gastric cancer, which is typically associated with loss of *H. pylori* infection following gastric atrophy and intestinal metaplasia (42). In a review of 6 meta-analyses, including five that evaluated the association between *H. pylori* seropositivity and one that evaluated the association with cagA

seropositivity with gastric cancer, Eslick *at al.*, (41) reported a pooled estimate of the relative risk (RR) ranging from 1.92-2.56, and CI ranging from 1.32-3.55 from five mata-analyses looking at studies based on *H. pylori* seropositivity. Despite some differences in the number, type, and design of the included studies, the strength of association from each of the meta-analyses were consistent in size and precision, supporting the validity of the pooled estimate and conclusions regarding the association. However, the meta-analyses suggested heterogeneity in the association by anatomical site and, in some cases, by histological type. For example, the meta-analysis by Huang *et al.*, (39) included 14 case-control studies and 5 cohort studies totaling 2491 patients and 3959 controls, the pooled OR for the association of *H. pylori* seropositivity with gastric cancer was 1.92 (95% CI 1.32-2.78), but it was 3.08 (95% CI 1.78-5.31) for non-cardia and 1.23 (0.56-2.71) for cardia gastric cancer. The association was similar by histological type (OR 2.49, 95% CI 1.41-4.43 for intestinal and OR 2.58, 95% CI 1.47-4.53 for diffuse type). In the Helicobacter and Cancer Collaborative Group meta-analysis looking at 12 nested case-control studies (1228 cases and 3406 controls), similar results were reported (43). The pooled OR for gastric cancer was 2.36 (95% CI 1.98-2.81) in individuals with pre-cancer *H. pylori* infection (43) and the association was 2.97 (95% CI 2.34-3.77) for non-cardia, but it was 0.99 (95% CI 0.72-1.35) for cardia gastric cancer. The association of *H. pylori* with gastric cancer was stronger when antibodies were detected in serum collected 10 or more years before the cancer was diagnosed (RR 5.9, 95% CI 3.4-10.3), supporting the conclusion that gastric cancer is preceded by prolonged chronic *H. pylori* infection. Echoing results obtained by Huang *at al*, similar associations were reported between *H. pylori* infection with intestinal and diffuse non-cardia gastric cancer (OR 4.45, 95% CI 2.74-7.24 and OR 3.39, 95% CI 1.70-6.76, respectively) (43). In a case-cohort analysis of 600 gastric cardia, 363 non-cardia and 1050 healthy subjects randomly sampled from a cohort study in Linxian Province in China, Kamangar *et al.*, (44) also observed a significantly elevated risk for non-cardia (RR 1.60, 95% CI 1.15-2.21), and a significant association with cardia gastric cancer (RR 1.64, 95% CI 1.26-2.14) in individuals exposed to *H. pylori*. The strength of association increased with length of time from serum collection to cancer diagnosis. In another cohort study of 1246 *H. pylori* infected and 280 *H. pylori* negative individuals evaluated by endoscopy and biopsy at baseline and a follow-up endoscopy done 1 to 3 years after baseline then followed for a median of 7.8 years, Uemura and colleagues (45) reported gastric cancer in 36 (2.9%) of the infected individuals as compared to none in the uninfected group (45). The risk was highest in individuals who had corpus predominant gastritis, severe gastric atrophy, and intestinal metaplasia at baseline among infected individuals.

5.1. *H. Pylori* virulence factors in gastric carcinogenesis

The risk of gastric cancer is associated with the strain of infecting *H. pylori* (46). *H. pylori* strains possessing the *cytotoxin associated gene* A (*cagA*, a marker for a pathogenicity island) are associated with a higher risk for gastric cancer (47). In a meta-analysis of 16 studies including 2284 cases and 2770 controls, the pooled estimate for the association of *H. pylori* seropositivity with gastric cancer was 2.28 (95% CI 1.71-3.05). However, the pooled estimate rose to 2.87 (95% CI 1.95-4.22) when cagA seropositivity was compared to disease-free controls (48). In subgroup analysis, cagA seropositivity was associated with all gastric cancer (1.64, 95% CI 1.21-2.24) and with non-cardia gastric cancer (2.01, 95% CI 1.21-3.32). Plummer and colleagues (46), in their study of 2145 participants in a chemoprevention trial in Táchira State, Venezuela, observed a strong association between cagA-positive *H. pylori* infection, measured in gastric biopsy specimens using polymerase chain reaction for *cag*A, with severity of gastric precancerous lesions (46). In addition, other *H. pylori* virulence factors, including: *vac*A, *ice*A, *bab*A, *oip*A, *sab*A, have been variously associated with gastric cancer (33).

5.2. Evidence from studies in animal models

Study of animal models has provided crucial insights to our understanding of the relationship between *H. pylori* and gastric cancer (49). Infection of the Mongolian gerbil or mouse models with *H. pylori* or *H. felis*, the closest relative to *H. pylori*, triggers development of gastric adenocarcinoma (50-53). These studies informed our understanding of the host inflammatory response to chronic *H. pylori* infection and how this may translate late the gastric cancer cascade (53), and provided some penetrating insights relevant to understanding the human disease.

First, animal models have shown us that gastric tumors can only develop following *H. pylori*-infection-associated inflammation, suggesting that *H. pylori* infection *per se*, may, in some instances, be sufficient to induce carcinogenesis. Second, a study of a *Helicobacter*-infected mouse model recently suggested the possibility that gastric cancer may arise from circulating bone marrow-derived, rather than gastric mucosa resident, stem cells (52). Finally, animal studies have focused attention on the potential for prevention of gastric carcinoma in human populations. In animal studies, eradication of *Helicobacter* infection leads to regression of inflammation, restoration of parietal cell mass, and re-establishment of normal architecture (54).

While these models inform human studies, the differences in biology between the gastric adenocarcinomas that erupt in animals and those in humans should be considered. For example, tumors in animal models are non-invasive and non-metastatic in nature. Second, there have been differences in the results obtained from animal models in different laboratories, which are reminiscent of geographic variation observed in human populations. Possibly these differences may arise from differences in environmental factors in the laboratory or differences in the *H. felis* strains used in different laboratories, which would echo the human experience.

5.3. Pathogenesis of *H. Pylori*-induced gastric cancer

Two mechanisms have been proposed to explain how *H. pylori* infection may induce gastric cancer. *H. pylori* may cause gastric cancer through direct action of its genes, which, when expressed, alter gastric mucosal physiology and induce abnormalities that result in cancer. Indirectly *H. pylori* induces an inflammatory response that creates a milieu that alters gastric mucosal physiology to cause cancer (34). It is likely a combination of both mechanisms.

H. pylori has been sub-divided into type 1 strains, which posses *cag-PAI* genes located on a 40 kb chromosomal DNA stretch containing approximately 31 genes, and type 2 strains, which lack these genes. Strains possessing c*ag*A deliver CagA protein, the 120-130 kDa protein product of *cag*A gene, into gastric epithelial cells by the bacterial type IV secretion system, where it deregulates the SHP2 oncoprotein and changes the cellular physiology of gastric mucosa (55). In epidemiological studies, the CagA seropositivity correlates with higher gastric cancer rates (56) and individuals infected with *cagA*-possessing *H. pylori* have an elevated risk for gastric cancer than those infected with *cagA* negative *H. pylori* (47). Studies of basic cell physiology show that *Cag-PAI* is intimately involved in cell surface remodeling, pedestal formation, activation of transcription factor AP-1 and expression of proto-oncogenes *c-fos* and *c-jun* by activation of the ERK/MAP kinase cascade (57). These molecular interactions alter gastric mucosa cellular biology, disrupt cellular signaling, differentiation, motility, and expression of growth receptors, leading to evasion of apoptosis, sustained angiogenesis, cell dissociation and tissue invasion, all hallmarks of malignant change. Polymorphisms in two other *H. pylori* genes: v*ac*A, which encodes for vacuolating cytotoxin vacA that induces vacuole formation in epithelial cells, and *bab*A, which encodes an outer membrane protein, BabA, that binds fucosylated Lewis B

blood group antigen on gastric cells, are associated with elevated risk for gastric cancer (58), providing further support for a direct role of *H. pylori* oncogenes in gastric carcinogenesis.

Alternatively, *H. pylori* may act indirectly by inducing severe pro-inflammatory response in the gastric mucosal following colonization (47). This pro-inflammatory response (gastritis), if severe, will destroy the parietal (acid producing) cells leading to hypoacidity in the stomach and bacterial overgrowth, worsening of bacterial infection and inflammation leading to gastric atrophy (59). Gastric atrophy is a pre-malignant lesion characterized by low acid output (hypochlorhydria), bacterial overgrowth, and infiltration of the gastric mucosa with T lymphocytes (secreting pro-inflammatory cytokines), reactive oxygen species and up-regulation of Cox-2, which jointly or separately disrupt gastric mucosal cellular growth (60). Chronic colonization establishes sustained insult to the gastric mucosa, and hyper-proliferation of gastric epithelium in response to injury. This in turn increases the risk of DNA damage (mutations), epigenetic and morphological changes (intestinal metaplasia, dysplasia), loss of responsiveness to apoptotic signals and, presumably, emergence of a clone of malignant cells that develop into gastric cancer (59).

5.4. Host genetics in *H. Pylori*-induced gastric cancer

Gastric cancer risk is also modulated by polymorphisms in host genes (36, 61). Polymorphisms in cytokine genes such as in the interleukin-1 (*IL-1*) gene cluster, which modulate inflammatory response to *H. pylori* infection, modify gastric cancer risk (62). El-Omar *et al.*, (62) were the first to show that polymorphisms in the pro-inflammatory *IL-1* gene (*IL-1B* encoding IL-1β and *IL-IRN* encoding its naturally occurring receptor antagonist) were associated with elevated risk for hypochlorhydria and gastric cancer in the persons with *H. pylori* infection (62). Possession of *IL-1B*-31C or 511T and *IL-IRN**2/*2 polymorphisms was associated with a 2-3-fold increase in risk for both intestinal and diffuse non-cardia gastric cancer among *H. pylori*-infected persons (63). The association was not observed with cancer of the gastric cardia, esophageal adenocarcinoma or esophageal squamous cell carcinoma, suggesting specificity of effect for non-cardia gastric cancer. Biologically, the genetic polymorphisms are thought to modulate risk by increasing expression of pro-inflammatory cytokine IL-1β, which is a potent inhibitor of gastric acid secretion. This phenotype would allow *H. pylori* to spread forming a pan-gastritis, atrophy, and ultimately gastric cancer.

These pioneering studies have now been replicated, strengthening the evidence associating the *IL-1B* gene polymorphisms with gastric cancer (64, 65). Importantly, polymorphisms in host genes appear to interact synergistically with bacterial virulence factors (*cag*A positive, *vac*A *s*I and *vac*A *m*I) (66-68). For each combination of host/bacterial virulence factor, gastric cancer risk is highest among those with both host and bacterial high-risk genotypes (69). Further evidence comes from animal models (70). Transgenic mice models over expressing IL-1β in the stomach produce lower amounts of gastric acid and develop severe gastritis, atrophy, intestinal metaplasia, dysplasia and adenocarcinoma, thereby recapitulating the gastric cancer cascade observed in humans (36).

Polymorphisms in other cytokine genes have also been implicated. For example, polymorphisms in *TNF-A*, coding for a powerful pro-inflammatory cytokine (TNF-α), produced in gastric mucosa in response to *H. pylori* infection and is thought to act through a similar mechanism as IL-1β, is associated with heightened risk for non-cardia gastric cancer (63, 71). Possession of the high producing A allele of *TNF-A* at position 308 (G→A) was associated with increased risk for non-cardia gastric cancer (OR 2.2, 95% CI 1.4-3.7) (64). Polymorphisms in *IL-10* gene, which codes for an anti-inflammatory cytokine (IL-10) that down-regulate gene expression or protein production of pro-inflammatory cytokine genes including *IL-1B*, *TNF-A*, and interferon-γ, is associated with non-cardia gastric cancer (63).

Thus, relative reduction in *IL-10* expression allows pro-inflammatory Th-1 driven responses to dominate the immune response to *H. pylori* infection. Individuals carrying the *IL-10* ATA haplotype associated with low IL-10 production (-592, -819, -1082) have an increased risk for non-cardia gastric cancer (OR 2.5, 95% CI 1.1-5.7) compared to those with the high IL-10 haplotype (63).

Possession of multiple high-risk host polymorphisms is associated with dose-dependent increase in risk for gastric cancer. Possession of 3-4 of the polymorphisms (*IL-B1-511*T, IL-IRN*2/*2, *TNF-A308*A and *IL-10* ATA/ATA) confers a 27-fold increase in risk of non-cardia gastric cancer (63). Investigators continue to search for other polymorphisms that may influence gastric cancer risk. A polymorphisms in *IL-8* (-251 T→A) is associated with increased production of IL-8 in *H. pylori* infected gastric mucosa and with precancerous gastric abnormalities in Caucasians and gastric cancer in Asian populations (72). IL-8 is a CXC family cytokine that is a potent chemoattractant for neutrophils and lymphocytes affecting proliferation, migration, and tumor angiogenesis. However, not all studies have replicated the positive associations between pro-inflammatory cytokines polymorphisms and gastric cancer risk (73). Studies conducted in Asian populations in China (74) and Korea (75) have failed to replicate observations made in Caucasian populations, though interpretation of many of the Asian studies is made difficult by the fact that they have been small, or sometimes used inappropriate controls.

H. pylori attaches to gastric epithelium via receptors. Thus, polymorphisms in the innate immune response genes, which interact with these receptors, could influence outcome of infection and potentially the risk of gastric cancer (76). A polymorphism in the Toll-like receptor 4 gene (*TLR4* +896 A→G), which codes for a lipopolysaccharide (LPS) receptor molecule involved in innate immune recognition of microbe pathogen-associated molecular patterns, has been associated with hypochlorhydria among Caucasians with upper gastrointestinal cancer and *H. pylori* infection (OR 11, 95% CI 2.5-48) (77). Furthermore, possession of 1 or 2 *TLR4* variant alleles, versus none, was associated with an increased risk of gastric cancer (OR 2.3, 95% CI 1.6-3.4) (77). Biologically, the *TLR4* 896 polymorphisms results in the replacement of a conserved aspartic acid residue with glycine (Asp299Gly), which causes a change in the conformation of the extra cellular domain of the TLR4 receptor and rendering carriers hypo-responsive to LPS challenge. These changes blunt the response by IL-10-secreting type 1 regulatory cells and associated anti-inflammatory response to *H. pylori* infection (78).

Other studies have attempted to unravel the relationship between human leukocyte antigen (HLA) class I and II alleles and gastric cancer (79), but the results are variable. In a small study of 50 patients with gastric adenocarcinoma, 80 patients with colonic adenocarcinoma, and 179 healthy subjects with comparable *H. pylori* infection prevalence (range 72-77%), no differences were observed in the frequency of *HLA-DQA1* or *-DQB1* across patient groups, prompting the authors to conclude that *HLA-DQA1* or *-DQB1* alleles may not be important in gastric carcinogenesis (80). Lee *et al.*, (79) in their study of 52 gastric cancer cases and 260 non-cancer controls, found HLA class II allele *DQB1*0301* was more frequent in Caucasian patients with gastric adenocarcinoma than non-cancer controls (54% vs. 27%, p=0.003). In a case-control study involving 52 gastric cancer patients and 139 non-cancer controls conducted in Linqu County, China, an area with a high incidence of gastric cancer, two alleles, *Cw*03* and *DRB1*01*, (of 48 class I and 19 class II HLA alleles evaluated) were associated with gastric cancer (OR 1.95, 95% CI 1.13-3.35 and OR 4.39, 95% CI 1.39-13.84, respectively) (81), providing limited evidence for a role of host HLA genotypes in gastric cancer. Azuma *et al.*, (82) studied 82 cancer cases and 167 controls and observed decreased *DQA1*0102* allele frequency in *H. pylori*-infected patients with intestinal type gastric adenocarcinoma patients compared with all controls (infected and uninfected).

However, Magnusson *et al.*, (83) did not find a protective effect on risk of gastric cancer in a study of 130 cancer cases and 263 population controls, but instead reported carriage of the *DRB1**1601 allele to be associated with increased gastric cancer (OR 8.7, 95% CI 2.7-28.0). This effect was stronger from those with the diffuse, rather than with the intestinal cancer, and, somewhat surprisingly, in those who were *H. pylori* negative. *DQB1**0301 was not associated with gastric cancer in this study. Based on this limited review, HLA seems to exert a null or variable role in gastric cancer etiology. The variability, in this and other studies, may be artifactual due, in part, to the small size of the studies, multiple comparisons made, increasing the risk for false-positive results, or variation related to population evolution. Future studies should carefully consider ethnicity in design or analysis because local disease associations in certain ethnic groups influence HLA variation.

Gastric cancer has, nonetheless, proved an invaluable model for understanding the interplay of bacterial, host, and environmental characteristics and how they impinge disease pathogenesis and phenotypic expression. We now know that higher risk for gastric cancer might be modulated by possession of an overall pro-inflammatory host genetic makeup in the adaptive and innate immune systems genes (e.g. *IL-1B, TNF-A, IL-10, IL-8, and TLR4*) (36). This pro-inflammatory profile might skew the immune response to *H. pylori* infection to a more severe chronic inflammatory phenotype, reduced gastric acid secretion, bacterial over growth, and oxidative/genotoxic stress to the gastric mucosa leading to gastric precursors. A pro-inflammatory genotype provides unique opportunities to individualized prevention therapy, while the exaggerated response to *H. pylori* provides unique opportunities for secondary prevention.

6. *H. Pylori* Prevalence and Risk for Gastric Cancer: “the African Enigma”

International variation in gastric cancer incidence argues for the contribution of geographically varying co-factors be they genetic or environmental. Following the discovery of *H. pylori*, it was quickly established that infection is universal, is usually acquired early in life and persists through adult life. However, investigators have noted an apparent discordance between the age-standardized incidence of gastric cancer (Figure) and prevalence of *H. pylori* infection. This paradox is variably referred to in the literature as the “African” or “Asian” enigma, i.e., the paradoxical deficit of gastric cancer in the context of high *H. pylori* prevalence (84-87).

In sub-Saharan Africa, *H. pylori* infection peaks (>80%) early in childhood and persists throughout life, yet, the age-standardized gastric cancer incidence rates for both males and females are relatively low at 2–21 per 100,000 person-years (2). By comparison, prevalence of infection increases more gradually with age in Japan to reach between 40% and 70% among adults (88, 89), yet, the age-standardized gastric cancer incidence rates are substantially higher, ranging from 65–92 and 24–39 per 100,000 person-years among males and females, respectively (2). The average age at infection is later in the U.S. where infection in adults peaks between 10 to 20% (89). With the age-standardized gastric cancer incidence rates among white US males and females are 6.6 and 2.6 per 100,000 person-years, respectively (2). The apparent lack of correlation between age of infection, peak prevalence, and incidence of gastric cancer in some parts of the world has led to many explanations and hypotheses (90). Agha and Graham recently dismissed the enigma, arguing that it is artifactual, due to reasons such as incomplete case ascertainment and competing mortality (91). While pertinent, those reasons do not fully explain the low rates of gastric cancer in countries such as South Africa, where life expectancy among blacks prior to the AIDS epidemic was reasonably high (63 years) and access to medical services substantially better (85). Moreover, gastric cancer rates have remained low (<5%) since the end of apartheid, when, we presume, access to care has improved. Furthermore, within Africa, and

indeed some countries in Asia (86), gastric cancer rates show substantial variation even across populations with comparable access to medical care (90). For example, in Tanzania, gastric cancer is distinctly rare in populations residing on the lake shores of Lake Victoria (92), but substantially more common for those residing on the mountainous slopes of Mt. Kilimanjaro (93). Gastric cancer was observed in only 4.3% of all cancer cases diagnosed at Shirati Hospital in a population residing in the Lake shore North Mara District in Tanzania (92). However, the relative frequency was 15% in those residing on the slopes of Mt. Kilimanjaro (93). This relative variation in the frequency of gastric cancer describes a pattern of low gastric cancer frequency in lowland regions and higher relative frequency in highland areas, a pattern observed repeatedly in different countries throughout Africa, including Kenya (94), Uganda (95), and Rwanda (96). These differences in the relative incidence of gastric cancer are notable because *H. pylori* seroprevalence is comparable, as are mortality, and access to medical care (97).

Outside Africa, a similar pattern has been reported in Colombia (98). The incidence of gastric cancer and precancerous lesions associated with *H. pylori* infection is higher among persons residing high in the Andes region of Pasto and Tuquerres, but lower among persons residing on the Pacific Coast at sea level (99), despite similar prevalence and age of acquisition of *H. pylori* (26). Similar differences have been observed in Japan where gastric cancer mortality varies along a north-south axis, closely mirroring the high vs. low altitude patterns observed in Africa (100). This pattern likely indicates influence of environmental factors that modify the risk of progression to cancer among *H. pylori*-infected individuals (32). In fact, the relative lack of gastric cancer mortality in southern Japan as compared to northern Japan despite similarly high *H. pylori* seroprevalence has been attributed, in part, to a higher prevalence of *cagA* positive *H. pylori* infection in the latter as compared to the former (100).

6.1. Hypotheses to explain the african enigma

In addition to the bacterial and genetic factors, several hypotheses have been proposed to explain the apparent paradox. Diet, specifically a Western type diet, including processed foods, is associated with increased risk of gastric cancer, whereas a diet high in fruits and vegetables is associated with decreased cancer risk (101, 102). Greater consumption of fresh fruit and vegetables is associated with lower risk for gastric cancer, in part, because dietary Vitamin C in fruits reduces the formation of N-nitroso compounds and scavenges reactive oxygen species involved in gastric mucosal inflammation (103). However, dietary factors are unlikely to explain the enigma in Africa or the differing rates in Columbia because dietary habits are generally similar in those populations.

A novel hypothesis posits that modulation of the inflammatory immune response to *H. pylori* infection by concurrent infection with parasites, which are climate dependent, may reduce the risk of gastric cancer (32). Briefly, parasites and, to a lesser extent, other bacterial infections elicit an anti-inflammatory host response, T helper (Th) 2-dominant cytokines, such as IL-4, IL-10, and transforming growth factor (TGF)-β to thwart their elimination. These self-preservation responses induced by the parasite could, coincidentally, help to systemically lessen the severity of gastric-mucosa-damaging inflammation, thereby lowering risk of gastric cancer carcinogenesis (104). Ecologic studies have provided preliminary support for this parasite hypothesis. A study comparing Th1/Th2 immune responses in symptomatic, but gastric cancer free, black patients from Soweto, South Africa, where gastric cancer incidence is low, with symptomatic but gastric cancer free, patients from Austria and Germany, where gastric cancer incidence is high, found Th2-dominant *H. pylori*-specific responses in the Sowetans and Th1-dominant responses in the Europeans (105). A study in Colombia found Th2-dominant immune responses and a higher prevalence of helminthic parasites in persons from low and mountainous regions of Tumaco, where

gastric cancer incidence is low (99). Conversely, the group reported Th1-dominant immune responses and a lower prevalence of helminthic parasites in persons from a high altitude area of Pasto, where gastric cancer incidence is high (99). A study from our group of a population residing in the low-lying, low-gastric incidence area of Shirati, northern Tanzania, observed Th2-dominant responses among the population (97), prompting our speculation that concurrent infection with parasites may explain the Th2-dominant responses and, in part, the low risk for gastric cancer in that population (92). The relatively low incidence of gastric cancer in Okinawa, southern Japan, coincides with a documented high endemicity of tropical parasitic infections such as *Strongyloides* specific in that part of the country (9, 106). We concede, however, that these studies are limited by their ecologic design, and we highlight the need for additional research using analytic studies to test the hypothesis.

Experimental studies in mouse models are shedding further light on the potential mechanism of parasite modulation (104). Mice co-infected with *H. felis* and *Heligmosomoides polygyrus*, a murine intestinal nematode, experience amelioration of their gastric atrophy, though mice without co-infection do not (32). The improvement observed in the co-infected mice is thought to coincide with a shift from Th1-biased response to a Th2-like phenotype of gastritis in response to *H. felis*, increased expression of anti-inflammatory IL-4, IL-10, and TGF-β cytokines in the gastric mucosa and reduced expression of pro-inflammatory IFN-γ, TNF-α IL1-β and other pro-inflammatory proteins (32).

Taken together, epidemiologic and animal studies support a role for helminthic parasites as biologically relevant environmental co-factors that could explain the paradoxical deficit of gastric cancer in some regions, commonly known as “African” or “Asian” enigma. Definitive conclusions must await results from large well-designed epidemiological studies.

7. *H. Pylori* and Gastric Malt Lymphoma

H. pylori is also causally linked to gastric mucosa associated lymphoid tissue (MALT) lymphoma, which comprise about 8% of non-Hodgkin lymphoma (107). Histologically, MALT lymphomas are diffuse large B cell lymphoma and low-grade lymphomas, classified as marginal zone lymphomas of the MALT-type under the REAL/WHO classification system. Anatomically, MALT lymphomas occur most frequently in the stomach, but they can also occur in other tissues including the salivary glands, conjunctiva, lung and thyroid (34). Cytogenetically, primary gastric MALT lymphomas typically display aberrations involving t (11;18) (q21;q21) in ~ 40% of cases (108), and t (1;14) (p22;q32) and t (1;2) (p22;p12) in a smaller percentage of cases. The role of *H. pylori* in MALT lymphoma was first suggested by Isaacson and Wright in 1983 (109), and subsequent studies demonstrated concurrent *H. pylori* infection in 92-98% of low grade MALT lymphoma (110). Chronic antigenic stimulation from *H. pylori* infection is associated with development of lymphoid follicles, the precursor lesion to MALT lymphoma (111). In a large cohort in the U.S., (112) pretumor serological evidence of *H. pylori* infection was associated with elevated risk for development of gastric non-Hodgkin lymphoma (OR 6.3, 95% CI 2.0-19.9), but not lymphomas at other sites. An etiological role for *H. pylori* in MALT lymphoma is supported by studies showing that eradication of *H. pylori* leads to clinical regression of gastric lymphoma (110). Wotherspoon *et al.*, (113) in 1993 were the first to report a study demonstrating regression of histologically confirmed low-grade MALT lymphoma in five of six patients who were treated with *H. pylori* eradication therapy. This finding has been confirmed in subsequent studies, with complete response observed in a variable percentage (~75%) of treated *H. pylori*-positive patients (114, 115). In long-term follow-up studies, patients achieve 90% five-year survival with complete or continuous complete histological remission (116). However, about 3% of patients in clinical remission may relapse,

necessitating alternative treatment and ~ 17% may show histological residual disease during follow-up, necessitating close follow-up (116).

Interestingly, clinical regression of gastric low-grade MALT lymphoma, lasting more than 12 months, has been observed in 6 patients treated with antibiotic therapy despite being *H. pylori*-negative (117). This observation raises the question whether early stage gastric MALT lymphoma negative for *H. pylori* might still benefit from antibiotic treatment as a sole or adjunct treatment. This may be dependent, in part, upon determining whether these results might be indicative of other causative bacterial infections, such as *H. heilmannii* (118, 119), or whether these reports result from false-negative tests of *H. pylori* status, perhaps because of low bacterial load in atrophic gastric mucosa (110). It is worth noting too that close to one-third of MALT lymphoma patients with demonstrable *H. pylori* infection do not respond to *H. pylori* eradication therapy. Non-response has been reported more frequently in tumors harboring cytogenetic aberrations, including the t (11;18) (q21;q21) translocation, which are associated with strong nuclear expression of BCL10, and could be considered as markers for poor tumor response.

8. Prevention of Cancer through *H. Pylori* Eradication

H. pylori is the single most important cause of infection-associated cancer globally, contributing 5.5% (~25% of all infection-associated cancers) of the global cancer burden (9). Intensive and extensive multi-disciplinary studies conducted over the past three decades have brought us to a cross-road where prevention is arguably within reach to curtail morbidity and mortality from *H. pylori*-associated gastric cancer (34). The proximal relationship between *H. pylori* infection and the gastric mucosa damaging inflammatory response indicate logical points for preventive approaches (120). Optimal approaches will have to be tailored to local communities, and should include strategies for primary prevention, to interrupt transmission; secondary prevention, to identify individuals with infection and treat with *H. pylori* eradication therapy; and tertiary prevention, to identify individuals with propensity for disease progression or with early disease for timely curative multimodality treatment (121, 122). The long-term decline in gastric cancer mortality in developed countries have resulted, in part, from interrupting *H. pylori* transmission through provision of improved basic sanitation, housing, socioeconomic status. Similar approaches should be encouraged in communities where infection is still highly prevalent. Secondary prevention may be attempted where simple diagnostic tests and treatment follow-up (urea breath test), and effective, short-term eradication treatment are available to mitigate individual risk (121). Tertiary prevention may be cost-effective in high incidence populations such as in some regions in China (123). Consensus guidelines for treatment have been developed and should guide such efforts (124). Clearly, the scale of the problem is substantial and will require integrated multi-disciplinary and multi-sectoral approaches (125), but the benefits should be, nonetheless, rewarding, and the impact could be seen very quickly.

A number of uncertainties should be addressed. For example, a large randomized, placebo-controlled, population-based primary prevention study of 1630 healthy carriers of *H pylori* infection (988 without gastric atrophy, intestinal metaplasia, or gastric dysplasia at baseline) in China given *H. pylori* eradication treatment (n = 817) or placebo (n = 813), found no difference in gastric cancer incidence in the treated vs. placebo group (126). None of the dysplasia free patients given *H. pylori* eradication treatment developed gastric cancer during a median follow-up of 7.5 years versus 6 in the placebo group (P =.02), suggesting that benefit may occur only if individuals have not progressed beyond some pathological threshold, or a theoretical “point of no return” in the gastric cancer cascade. Such a threshold

has not been defined, but any widespread *H. pylori* eradication-based strategies should give due consideration to this point (123).

The long-term effects of prevention programs are unknown, but could include negative effects, such as the development and spread of antibiotic resistance, which needs to be monitored carefully (127). Another theoretical negative by-product of widespread eradication of *H. pylori* is a potential increase in the prevalence of Barrett's esophagus and, consequently an increase in the incidence of esophageal adenocarcinoma. Fear of such serious consequences must be allayed by ongoing vigorous surveillance to confirm expected decreases in *H. pylori*-associated cancers and detect early signals of possible emergence of any adverse outcomes (128).

9. Future Directions

Gastric cancer is a model disease with which to study cancer etiology and pathogenesis. While future efforts should focus on prevention, some lingering questions should be addressed. For example, the male predominance of gastric cancer has not been fully explained. Biological reasons for this may be related to the intensity of colonization or the degree of inflammatory response in the gastric mucosa related to contraceptive use (129). Similar male preponderance has been reported with other malignancies caused by an infectious agent, including hepatitis virus associated hepatocellular carcinoma (130), and a retrovirus-associated adult-T-cell leukemia/lymphoma (131).

The quality of data from developing countries is low, complicating our ability to study and find epidemiologically and biologically plausible explanations for the wide geographic variation. Studies using sound approaches to investigate the role of parasites and mechanisms for immuno-modulation may suggest novel ways to ameliorate inflammatory consequences of *H. pylori* infection, especially as societies rapidly modernize. The role of *H. pylori* eradication treatment as the primary or additional approach to the treatment of primary low-grade gastric MALT lymphomas needs further clarification. Additional studies are needed to better characterize the long-term clinical outcomes of individuals with continuous histological remission, but with demonstrable lymphoma clones and the paradoxical sustained response to eradication therapy in MALT lymphoma observed in patients who are *H. pylori*-negative.

To summarize, the discovery of *H. pylori* and subsequence association with gastric cancer allowed unprecedented era of unraveling the infection and genetic basis of cancer. This work has brought us to a pivotal point where concerted efforts can deliver effective preventive strategies that eliminate death and suffering from one of the major cancers.

Acknowledgments

The authors wish to thank Dr. Gwen Murphy of Infections and Immunoepidemiology Branch for comments on the manuscript. S.M.M. is a tenure-track investigator in the Infections and Immunoepidemiology Branch, U.S. National Cancer Institute. This work was supported, in part, by the Intramural Research Program of the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services.

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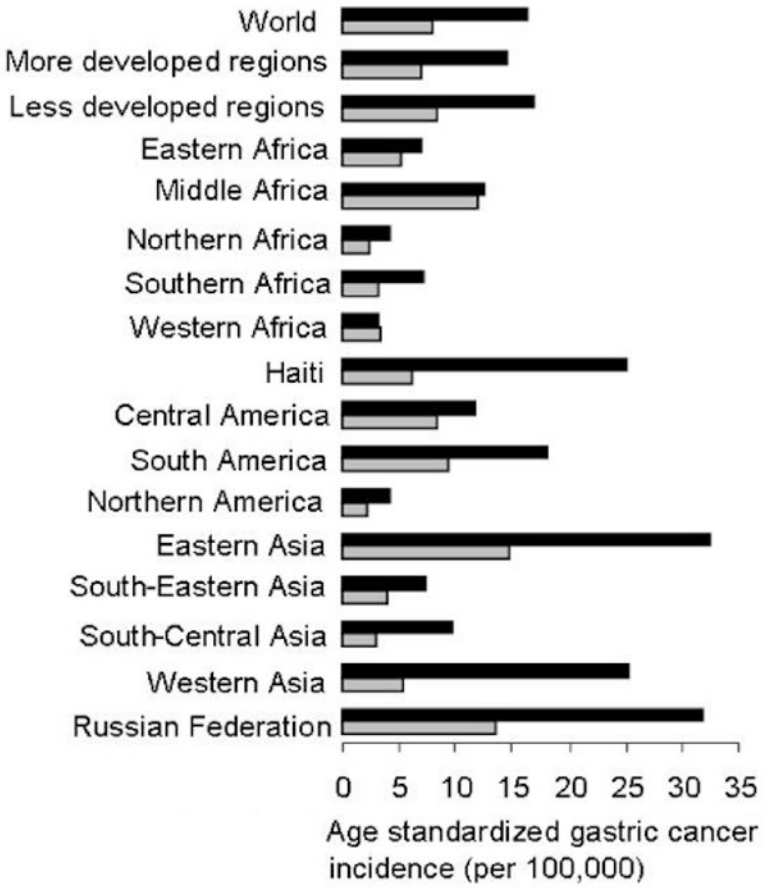

Figure 1.
International and gender-related variation in age-standardized gastric cancer incidence (adjusted to the world population) based on data from Cancer Incidence in Five Continents. Black bars represent rates for males; gray bars represent rates for females. Reproduced with permission from (2).