Helicobacter Pylori and Gastric Cancer: An Update in the Literature

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Of the chronic bacterial infections that affect humans, *Helicobacter pylori* (*H. pylori*) infection is one of the most common. It inhabits the stomachs of half of the adult human population. In Puerto Rico, a US territory, it has an overall prevalence of 33%, similar to the prevalence reported in the population of the US as a whole. *Helicobacter pylori* infection is responsible for mucosal inflammation that may lead to chronic gastritis, most peptic ulcers, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma. The International Agency for Research on Cancer identified *H. pylori* as a definite carcinogen in 1994, the only bacterium to be given such a classification. Its oncogenic effect has been postulated to be caused by different mechanisms, including bacterial characteristics and host factors. Epidemiologic studies have shown that gastric cancer risk differs among regions. One of the top 10 causes of cancer death in Puerto Rico is gastric cancer. Although the eradication of *H. pylori* has well-known benefits, there are some concerns when considering mass screening and treatment of infected patients. These include the fact that such eradication could provoke an increase in antibiotic resistance rates, the disturbance of the gut microbiota, an increase in body weight, and the aggravation of existing gastroesophageal reflux symptoms. Gastric cancer is a major health concern, and we should understand the role of *H. pylori* eradication in its prevention. This article is geared to summarize current knowledge and controversies.

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In 1982, Drs. Barry Marshall and Robin Warren discovered *Helicobacter pylori* (*H. pylori*) and described for the first time it's association to gastritis and peptic ulcer disease. Since then, much has been learned about both the bacterium and its pathophysiology (1). In 2005, both investigators were awarded the Nobel Prize in Physiology because of their contribution to the discovery of this previously disregarded microorganism. Nowadays, *H. pylori infection*, which is not only common but also chronic, continue affecting humans around the world. It has been estimated to be present in the stomachs of half of the adult human population and is typically acquired during childhood (2). The most commonly recognized route of transmission is oral–oral, which is associated with a high occurrence within the same household. Fecal–oral transmission is also a well-documented route. This latter is associated with poor sanitary conditions and contaminated water and may be the reason for higher infection rates in undeveloped countries (2).

In 1994, the National Institutes of Health recognized *H. pylori* as the responsible for most duodenal and gastric ulcers. At that time, eradication treatment with antibiotics became the recommended regimen (3). In the same year, the International Agency for Research on Cancer declared *H. pylori* to be a human carcinogen and strongly associated with the development of gastric adenocarcinoma (4). It has also been linked to an increased risk of gastric mucosa-associated lymphoid tissue (MALT) lymphoma and to a decreased risk of developing esophageal adenocarcinoma (EAC). Since then, diagnosing and eradicating *H. pylori* has been encouraged (3,4).

Although the incidence of gastric cancer (GC) is declining, possibly because of the decrease in *H. pylori* prevalence, there are still questions regarding how eradication therapy reduces the risk of developing these cancers, especially in asymptomatic individuals in whom *H. pylori* is found incidentally.

The primary aim of this article is to provide a review of the current knowledge (local and global) about this important and most common human pathogen and its role in the development of GC. Our intent is to summarize the current literature, discuss what has been reported, and unveil gaps in the existing knowledge.

Helicobacter pylori infection

Helicobacter pylori is a gram-negative type of bacteria with characteristics that allow it to colonize the human stomach (Figure 1). *Helicobacter pylori* uses various mechanisms to survive the harsh gastric acid conditions in that environment and attaches to the mucosa, causing persistent colonization of the human gastric epithelium. Before it's attachment, the bacteria, aided by flagella, must first traverse the thick mucus layer (4). In addition to their kinetic capabilities, the bacteria act upon multiple chemotactic stimuli, possess adhesion molecules, and produce several enzymes (such as ureases and hydrogenases) that facilitate the colonization and creation of an appropriate microenvironment that allows their survival and perpetuation in a harsh and highly acidic gastric environment. Certain *H. pylori* species produce particular virulence factors associated with a high risk of developing GC.

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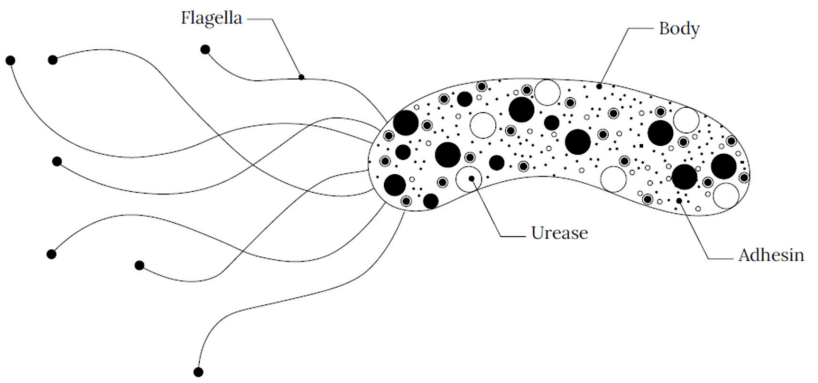
Figure 1. Diagrammatic Representation of Helicobacter pylori, a Gram-Negative, Microaerophilic Flagellated Bacteria



Furthermore, *H. pylori* colonization results in the development of a host inflammatory and immune response that influences mucosal changes. Moreover, in some individuals, the infection becomes chronic and leads to gastric inflammation, that can eventually lead to the destruction of normal gastric glands and their replacement by intestinal-type epithelium resulting in the atrophy of gastric mucosa (5).

Initial *H. pylori* infection is associated with an increase in gastric acid production due to an elevation in gastrin secretion and a reduction in somatostatin release. The acute infection is antral-predominant and may result in duodenal ulcers in some patients. As the infection progresses and becomes chronic, inflammatory changes ensue, causing the gradual loss of parietal cells and, consequently, hypochloridria. This inflammatory process results in gastric mucosal atrophy and intestinal metaplasia. These changes in the stomach milieu cause the migration of the bacteria to the body of the stomach, making important the appropriate tissue sampling of both, the antrum and body, to ascertain the presence of the bacteria. Patients having antral-predominant *H. pylori* infection tend to have duodenal ulcers, while those with body predominance are at a high risk of gastric ulcers and cancer.

Helicobacter Pylori as a risk factor for gastric cancer

Gastric cancers are among the most deadly and common malignant neoplasms. It is the fifth most common type of cancer and the third leading cause of cancer-related morbidity, globally (5). Most cases occur spontaneously, affecting patients older than 50 years old, although some cases arise before the age of 45; these last are usually associated with genetic factors (5). The risk factors for developing GC include, interactions between the environment and host genetics, diet, and, very importantly, *H. pylori* infection.

Multiple epidemiological studies have shown that *H. pylori* remains the strongest risk factor for and is a key player in the development of gastric inflammation (5–10). In 1994, the World Health Organization categorized *Helicobacter pylori* as a class I carcinogen (3). Although rates of infection vary significantly across the world, there is variance in the correlation between areas with high infection rates and those with a high prevalence of GC (6, 7). This variance could be explained by different elements, including the patient's age at infection, the type of *H. pylori* strain found, the genetic profile of the host, and environmental factors (6–9). Regardless of the variance, there is unequivocal evidence of the role of *H. pylori* eradication in GC prevention (11).

Although most individuals with *H. pylori* infection are asymptomatic, long term infection leads to inflammation of the gastric mucosa. Approximately 10% of infected individuals develop peptic ulcers, 1% to 3%, GC, and fewer than 1%, MALT lymphomas (9). It has been estimated that nearly 80% of all stomach cancer cases can be attributed to *H. pylori* infection (12, 13).

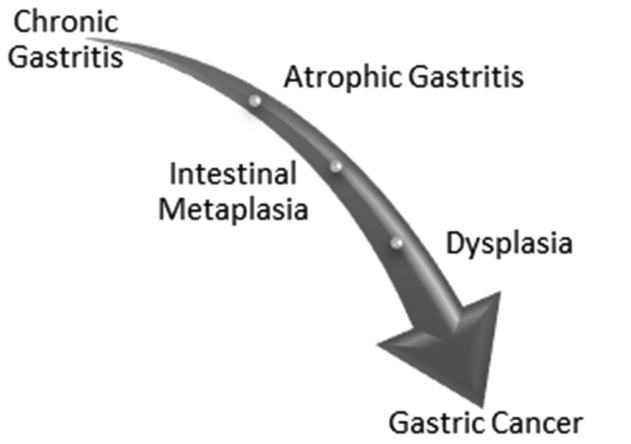
Helicobacter pylori carcinogenesis

The oncogenic effect of *H. pylori* has been suggested to occur through different mechanisms in which chronic infection may eventually lead to GC. The 2 main mechanisms in which infection may eventually result in intestinal type GC include a direct epigenetic effect on gastric epithelial cells and an indirect inflammatory process affecting the gastric mucosa (14). During the prolonged time of colonization, a combination of environmental and host factors will determine an individual's chances of developing GC (14).

Helicobacter pylori causes a long-lasting inflammatory response that increases cell turnover, which, over decades, may result in transcriptional errors. *Helicobacter pylori* initially causes antral gastritis, but with persistent infection, hypochlorhydria develops, allowing the bacteria to migrate proximally. This process leads to pangastritis and an increased risk of GC. Dr. Pelayo Correa was one of the first (1992) to describe this step-by-step progression of the inflammatory response (14). With his model, he hypothesized that *H. pylori* infection progressed from chronic active gastritis to atrophic gastritis, and intestinal metaplasia, eventually leading to dysplasia and adenocarcinoma (Figure 2) (14). Correa posited that persistent inflammation of the gastric corpus results in atrophic gastritis, which leads to a rise in pH and to hypochlorhydria. The alkaline environment in turn helps perpetuate *H. pylori* colonization and proliferation. In contrast, antral-predominant infection leads to hyperchlorhydria, resulting in a higher than normal risk for duodenal ulcer disease and a lower than normal risk for developing GC.

Helicobacter pylori can also have direct effects on the gastric mucosa through the action of various virulence factors, of which the cytotoxin-associated gene A (CagA) and the vacuolating cytotoxin A (VacA) are among the most researched, with both being closely associated with gastric epithelial cell pathogenicity. (15). Although GC can occur in infected patients without these virulence factors, these strains have been associated with a higher degree of inflammation and precancerous lesions. Other virulence factors that facilitate the initial colonization and delivery of virulence factors to host epithelial cells include adhesins and outer membrane proteins such as BabA (blood group antigen–

Figure 2. Progression of Inflammatory Processes and Histopathologic Stages, as Described by Pelayo Correa



binding adhesin), DupA (duodenal ulcer-promoting gene), FlaA (flagellin A), SabA (sialic acid–binding adhesin), and OipA (outer inflammatory protein A) (16).

Host polymorphisms can also influence the propensity toward GC development, which is explained by the fact that some individuals colonized with disease-associated strains remain asymptomatic. Host responses, such as a reduction in acid secretion and prolonged inflammation, influence the progression to *H. pylori*–induced carcinogenesis. Stimulating cytokine production molecules, such as interleukin 1β and tumor necrosis factor α, have been found to be increased within *H. pylori*–colonized gastric mucosa. Polymorphisms that increase these molecules' expression have been associated with an increased risk of GC (16, 17).

Environmental and dietary factors, such as cigarette smoking and high salt intake, are known to increase the risk of *H. pylori*–associated carcinogenesis. Thus, *H. pylori* infection appears to invoke a myriad of mechanisms to induce GC; however, many events in this tumorigenic process have yet to be clarified and investigated (16, 17).

Helicobacter pylori and gastric cancer epidemiology

As previously mentioned, epidemiological studies suggest that 74.7% to 89% of all GCs are associated with *H. pylori* infection (17). The infection increases the risk of GC by 5.9x after 10 years of being so infected. Its eradication may reduce the risk of cancer; however, the extent of risk reduction depends on the duration of the infection. Certain genetic alterations may occur with aging and/or chronic inflammation. At advanced stages of inflammation, GC may develop, even if *H. pylori* is eradicated (18).

Does *Helicobacter pylori* eradication truly reduce the risk of gastric cancer?

Upon discovering that *H. pylori* has a role not only in the development of chronic gastritis but also in the progression first to atrophic gastritis and then to intestinal metaplasia, researchers eventually came to realize that the bacterium is a key factor in the advancement of most types of GC. (14, 19). For many years, investigators around the world have evaluated the effect of *H. pylori* eradication on both the risk of GC and the progression of gastric precancerous lesions (20–24). Initial investigations conducted after the discovery of *H. pylori's* role provided only weak evidence to support a link between *H. pylori* and GC or precancerous gastric lesions.More substantial evidence associating *H. pylori* and GC came from 3 large case-control studies from cohorts of British men, men and women from California, and Japanese Americans men living in Hawaii. In these studies, serum from cancer-free subjects had been banked, and the cohorts were followed for approximately a decade. In each cohort, evidence of prior *H. pylori* infection was found to be significantly more common in individuals who later developed GC than it was in those who did not (24–26). The subjects infected with *H. pylori* were 3 to 6 times more likely to develop GC compared with those who were not so infected. The results from these studies led the International Agency for Research on Cancer to determine that *H. pylori* was a class I human carcinogen, even though at that time there was no supporting evidence from either animal models or bench research. A systematic review and meta-analysis conducted by the Helicobacter and Cancer Collaboration Group in 2001 identified 12 nested prospective case-control studies and concluded that *H. pylori* was associated with an almost 3-fold increase in the development of non-cardia GC (27, 19).

Despite all the promising data, prospective interventional studies were needed before healthcare providers could seriously consider a possible screening policy (in particular, one that could be used in high-risk populations) that could theoretically lead to a reduction in GC. However, recruiting patients into the control arms of these prospective randomized studies became ethically challenging after the implementation of the Declaration of Helsinki (1994), and a properly powered study of many subjects has so far not been completed (28, 29).

In 2009, Fuccio et al. published their systematic review of the existing randomized control trials (RTCs) that assessed the effect of *H. pylori* eradication compared with placebo on the risk of developing GC. The review revealed that eradication decreased relative risk to a significantly greater degree than did placebos (30). However, the study included duplicated data from the same trial at different study points. The beneficial effect was no longer statistically significant when the data were adjusted. Nevertheless, 2 recent meta-analyses conducted by Ford et al. and Lee et al., respectively, were conclusive, indicating that *H. pylori* eradication decreases the risk of GC development by approximately 40% in asymptomatic individuals and by 54% in GC patients by preventing the occurrence of a second GC after the successful endoscopic resection of an early GC (19, 20).

In the meta-analysis conducted by Ford et al., which combined 6 RTCs, it was suggested that evaluating for and eradicating *H. pylori* infection in asymptomatic infected Asian individuals reduced the subsequent incidence of GC by 34% (19, 21). Although this finding adds to the evidence that the eradication of *H. pylori* has the potential to prevent GC, it did not show any impact on all-cause mortality and provides only limited, moderate-quality evidence since the results cannot be extrapolated to those parts of the world in which the incidence rates of GC are lower.

Effect of *Helicobacter pylori* eradication on gastric cancer in relation to baseline risk

The benefit of *H. pylori* eradication in terms of its preventing GC varies in relation to the baseline risks, which are different across regions and populations. Lee et al. (2016) evaluated 14 studies of primary prevention and 10 studies of tertiary prevention; combined, the studies included more than 48,000 individuals, who were followed for more than 340,000 person-years (20). Lee and team evaluated the benefit of *H. pylori* eradication in populations with different risk levels and clinical scenarios. Not surprisingly, the magnitude of the protective effect of *H. pylori* eradication was most obvious in subjects with higher baseline GC risks. However, the risk reduction was almost universal. Most of these studies were done in Asia and in the parts of the world where GC is the most common; thus, it is still unclear whether unselective *H. pylori* eradication will affect GC in terms of baseline risk. It also remains unclear whether interactions between host genetic and bacterial virulence factors, which can vary among populations, could harbor different levels of GC risk (20, 31). It is important to better understand the overall benefit to be expected after the eradication of *H. pylori* in populations with different levels of GC risk prior to implementing mass eradication strategies. Nevertheless, it may be reasonable to suppose that high-risk populations migrating to low-risk countries might benefit from *H. pylori* eradication, as well.

Effect of *Helicobacter pylori* eradication on gastric cancer in relation to baseline histology

It is not clear how protective *H. pylori* eradication is once atrophic gastritis and/or intestinal metaplasia develops. Some studies have reported that these precursor lesions improve after eradication, but other studies have found that the procedure does not lead to any significant change. It is very difficult to ascertain the effect since there are multiple variables that have to be considered.

Some studies that have examined the effect of *H. pylori* eradication on GC risk per baseline histology have stratified individuals (who have undergone the process of eradication) into 2 groups: subjects with chronic non-atrophic gastritis or atrophic gastritis, and subjects with intestinal metaplasia or dysplasia. In 2004, Wong et al. conducted an RCT in asymptomatic infected individuals in a high-risk region of China and found that the incidences of GC were similar for those receiving eradication treatment and those receiving a placebo (18). They also found that eradication in *H. pylori* carriers without premalignant gastric lesions significantly decreased the development of GC but did not do so in those with atrophic gastritis.

A meta-analysis performed by Rokkas et al. in 2017 also supported the belief that *H. pylori* is a substantial risk factor for the development of GC and that eradication is associated with a decrease in GC incidence. The analysis also suggested that eradication represents an appropriate preventive strategy in a specific subset of subjects but not in individuals who already developed advanced pre-neoplastic lesions (32). Similarly, other studies (33–35) have also suggested that eradicating *H. pylori* might not reduce the risk of GC in those with premalignant lesions. However, these studies had limited sample sizes in the subgroups of advanced premalignant lesions and therefore might have had inadequate statistical powers.

All these data suggest that there might be a point along the Correa pathway where eradication has no protective effect and molecular changes are irreversible and progressive. It could also potentially mean that *H. pylori* screening and eradication would be more effective if applied before the fourth decade of life, which is when the risk of cancer increases. Nevertheless, these results must be interpreted carefully in European and North American countries since most of the pertinent studies have been conducted in East Asia.

The results of other RCTs exploring *H. pylori* eradication argued against the existence of a "point of no return." Li et al. (2014) found that treatment significantly reduced overall GC incidence in those with baseline intestinal metaplasia or dysplasia and in those aged 55 years old or older (36). The investigators, arguing against the existence of such a point of no return, concluded that eradication could benefit older adults and those with an advanced baseline histopathology. Lee et al. (2016) also found that eradication was associated with a reduction of GC risk, even in high-risk individuals, thus supporting the notion that it could also be advantageous in patients with atrophic gastritis and/or intestinal metaplasia (20). Additionally, they found a 54% reduction in the risk of metachronous cancers in patients who had had eradication of *H. pylori* after the endoscopic resection of early GC (20). These findings suggest that *H. pylori* screening and eradication could be a worthwhile method of preventing GC and could be implemented in high-risk populations and/or regions (20). The question remains whether preventive methods should also be implemented in low-incidence populations.

Another randomized trial, this one from Korea, investigated the long-term effects of *H. pylori* eradication treatment in the prevention of metachronous GC (MGC) (37). The team found that eradication may reduce risk after a curative endoscopic resection. However, the limitations of the study included relatively small sample sizes, the use of the progression of precancerous lesions as the primary outcome, and a lack of data from non-East Asian populations (37, 38).

Other research groups, these in Japan, have reported quite the opposite. Their studies showed that the incidence of MGC increased after 4 to 5 years of successful *H. pylori* eradication (39). In Korea, however, a prospective trial performed by Choi et al. (2014) also failed to show that the eradication of *H. pylori* after the endoscopic resection of GC could lower the incidence of MGC (40).

Potential harms of eradication therapy

Although the eradication of *H. pylori* has well-accepted and unequivocal benefits and indications, there are some concerns about indiscriminate testing and treatment. The most common concerns have to do with increases in antibiotic resistance rates, the alteration of the gut microbiome, weight gain/obesity, and the aggravation of gastroesophageal reflux (38). The emergence of antibiotic resistance was observed and demonstrated by Jakobson et al. His study showed increased clarithromycin resistance in several other bacterial species, such as *Enterococcus*, *Bacteroides*, and *Staphylococcus*, immediately after triple therapy (38). There are studies evaluating the effects of the eradication of *H. pylori* on the gut microbiota. In general, it has been

demonstrated that the diversity of the gut microbiota is altered immediately after eradication therapy (38).

The selection of the appropriate antibiotic regimen for *H. pylori* treatment is a current challenge for clinicians since resistant strains have begun to emerge. The previously recommended antibiotic regimens are not as effective as they were in the past; for this reason, antibiotic usage history and selection are of cardinal importance to improve treatment response and to avoid antibiotic resistance and other potential complications (41).

Should screening and eradication programs be adopted worldwide?

Gastric cancer is a major health concern worldwide, and as previously discussed, *H. pylori* plays a major role in its development. Depending on ethnicity, gender, and geographical region, the risk and incidence of GC vary greatly (42). According to studies in countries with a high incidence of GC, *H. pylori* eradication programs have been proposed as a primary preventive strategy to reduce GC incidence (31). Mass screening and eradication strategies are already in place in high-risk regions (30). For example, in 2004, Taiwan implemented a mass screening and eradication strategy in a high-risk population of the Matsu Islands. This strategy resulted in a rapid decline in the incidence of GC and in the risk of peptic ulcer disease in this population (42). Nevertheless, these results must be interpreted with caution since they come from areas of high GC risk; more studies in North American countries and other parts of the world are needed to better define the role of *H. pylori* eradication in the primary prevention of GC (31).

Helicobacter pylori in Puerto Rico

There are several publications addressing *H. pylori* in Puerto Rico (PR). Toro et al. published the results of their initial study back in 1990 (43); in this study, a hundred consecutive patients scheduled for upper endoscopic procedures were enrolled. *Helicobacter pylori*, previously referred to as "campylobacter-like" organisms, were identified in 84% of the antral biopsies of the patients with antral gastritis. The intent of this initial study was to determine the prevalence of this infection in patients with active gastritis.

A subsequent population-based study published in 2018 and conducted by Gonzalez et al. reported an overall *H. pylori* prevalence of 33% in Hispanics living in PR (45). This cross-sectional study used an existing population-based biorepository of 528 frozen serum samples of non-institutionalized individuals ranging in age from 21 through 64 years and who lived in PR from 2005 through 2008. In this secondary analysis, the serum samples were tested for *H. pylori* immunoglobulin G antibodies. In this study, it was found that seroprevalence increased with age (≥40 years), in those having fewer than 12 years of education, and in those living in areas of low population density. The prevalence estimate found in this study was similar to those estimates reported in the general population of the US and lower than the reported prevalences for other Hispanic populations in the US, such as Mexican Americans and other Latin Americans (44).

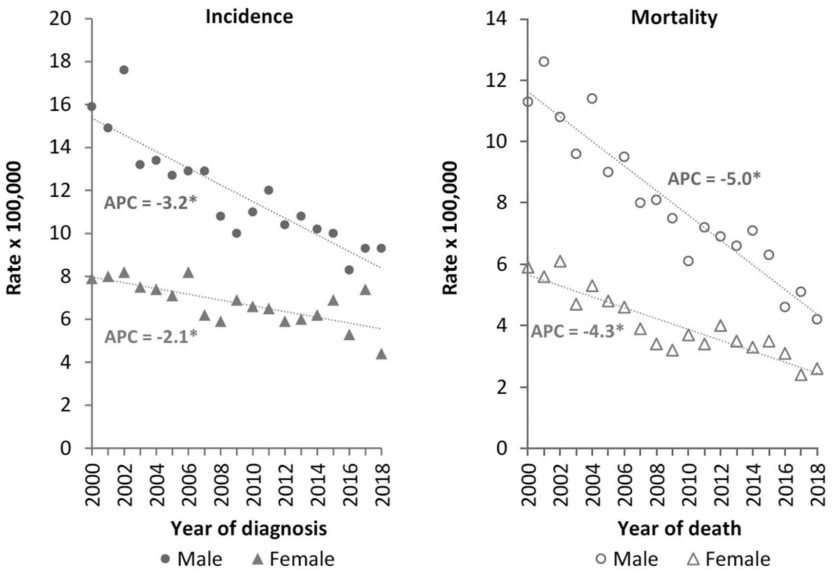
A recent abstract published by De León et al. (2018) established that *H. pylori* prevalence has markedly decreased in PR during the last 20 years (46). In their study, De León and his team evaluated antral biopsies for the presence of *H. pylori* in consecutive patients undergoing upper endoscopy. They compared their results with those of previous studies conducted at the same hospital in 1998 and 2011, respectively. Again, in this study, the prevalence of *H. pylori* infection increased with age. Compared with previous years, the prevalence had decreased over time. In their abstract, they reported a prevalence of 38.2% in 1998, 31.5% in 2011, and 16% in 2017, which is consistent with the worldwide tendency. This study may have underestimated the prevalence of *H. pylori* since only antral biopsies were taken and examined for the presence of *H. pylori* infection. Current recommendations are to take biopsies from the antrum and body. This strategy increases histology sensitivity that occurs because of the known proximal migration of the organisms in patients using proton-pump inhibitors. In addition, there was no reference to withholding medications, such as proton-pump inhibitors, or to the prior use of antibiotics, which could have impacted their study results.

We would expect that the prevalence of GC would show a decreasing trend similar to the trends observed for *H. pylori* infection. In an abstract published in 2017, Cruz-Correa et al. described epidemiological trends among Hispanics living in PR (47). The data were obtained from the PR Central Cancer Registry (PRCCR) and included all the gastric cancers occurring during 2 study periods: from 1998 through 2002 and from 2003 through 2007. The investigators reported a mild reduction in the age-adjusted incidence of GC, falling from 10.0 per 100,000 population during the 1998-2002 period to 8.4 per 100,000 for the 2003-2007 period. Interestingly, the investigators evaluated incidence rates based on geographical distribution and demonstrated that there was a higher GC incidence in the mountainous regions of PR. Moreover, they reported an improvement in the overall 5-year relative survival rate for those regions, which rose from 22.1% to 28.2%, although the overall survival rate is still appalling.

In the most recent PRCCR publication, which covers the period from 2014 to 2018, GC represented 2.3% of all cancer cases in men and 2.0% in women. It also represented 3.8% of all cancer deaths in men and 3.4% in women (44). The report shows a decline in the incidence of and mortality from GC in both women and men over the years (Figure 3a and 3b). This report also demonstrates the persistence of the previously noted higher incidence in the mountainous regions (Figure 4). Compared to that reported by Cruz-Correa et al., the 2014-2018 overall 5-year survival rate, 31.71%, remains dismal.

As *H. pylori* is the major cause of GC, the proper evaluation of patients at risk is the most effective tool we have at hand to reduce GC incidence and associated mortality. The identification of gastric intestinal metaplasia is critical since is considered the precursor of this malignancy. There are a few studies in PR addressing gastric metaplasia in the island population. Cruz-Cruz et al. did a large cross-sectional study evaluating histological slides of gastric biopsies at a single pathology laboratory, from which all the study specimens came and which is a referral center for 50% of the private-practice gastroenterologists in PR. Of a total of 43,993 endoscopic biopsies, 6,806 were from patients with a diagnosis of gastric intestinal metaplasia, and all of these were included in the study. Data points such as patient age,

Figure 3a and 3b. Age-adjusted (2000 US Standard Population) Incidence and Mortality Rates of Gastric Cancer by Sex (Puerto Rico Cancer Registry Annual Report, 2014-2018)



gender, city of residence, date of biopsy/ies, the presence of *H. pylori* (when such was the case), and histological changes were recorded. Analyses were done for the years of 2012, 2013, and 2014. The overall prevalence of gastric intestinal metaplasia in this study was 10.7%, which is higher than that reported in the US (4.8%). Also, a higher prevalence was found in females than in males. During the course of the study it also became evident that most biopsies are not being done following the updated Sydney protocol (biopsy mapping protocol), which protocol results in the proper characterization of the type and extent of gastric intestinal metaplasia (49). This protocol recommends having separate biopsies obtained from the lesser and greater curvatures of the antrum and body, with an additional biopsy taken from the incisura, for a total of 5 biopsies (Figure 5). Additionally, targeted biopsies should also be obtained from mucosal lesions (either flat or elevated). The OLGA (operative link on gastritis assessment) staging system uses the results of these 5 biopsies to characterize the risk of evolution to cancer. Adherence to this protocol has been demonstrated to increase the yield of diagnosis of *H. pylori* and intestinal metaplasia, therefore facilitating the identification of patients at risk (49).

Recently published guidelines consider the best practice to be testing, treating accordingly, and confirming eradication in any patient with atrophic gastritis and gastric intestinal metaplasia, for which appropriate biopsy sampling is needed (49).

Current guidelines on testing—when to test and why

The American College of Gastroenterology has established a series of indications (influenced by current knowledge in the field) pointing to the need to test for *H. pylori* (50). The guidelines are intended for the populations of the US and other North American countries with GC prevalences similar to that of PR (Table 1).

Testing is currently recommended in patients with peptic ulcer disease (active or past), in patients with uninvestigated dyspepsia who are 60 years old or younger, in those who are on or will be starting on long-term non-steroidal anti-inflammatory drugs, in those with a diagnosis of MALT lymphoma, and in those with endoscopically resected early GC.

Testing is also indicated in conditions not usually suspected to be associated with *H. pylori* infection, such as idiopathic thrombocytopenic purpura (in adults) and unexplained iron deficiency anemia.

According to the clinical guidelines and regardless of the reason or reasons for testing, all patients who test positive for active *H. pylori* infection should be treated. Nevertheless, neither indiscriminate nor universal testing is recommended on the basis of both an extensive review of the literature and current knowledge.

In summary

Despite the global decline in *H. pylori* prevalence, this infection is still an important public health concern. In PR, although the prevalence has declined, a third of the population may be infected, especially those who are older and living in rural areas.

Figure 4. Age-adjusted Incidence Rates (2000 PR Standard Population) of Gastric Cancer by Municipality (Puerto Rico Cancer Registry Annual Report, 2014-2018)

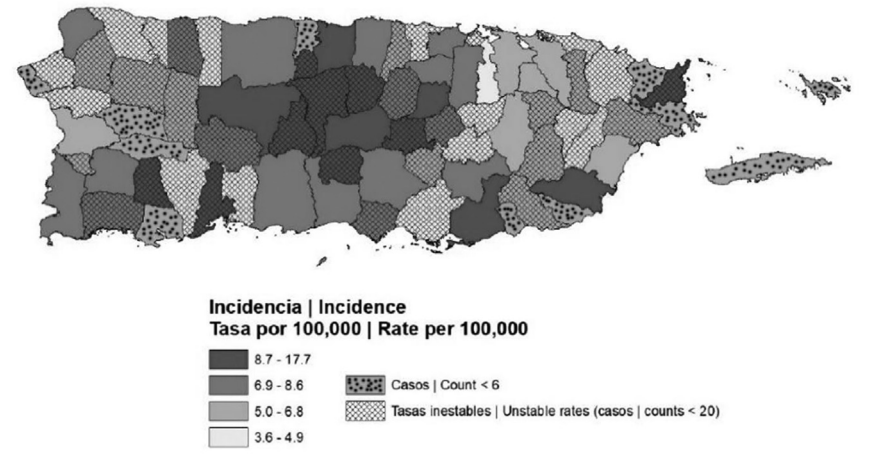
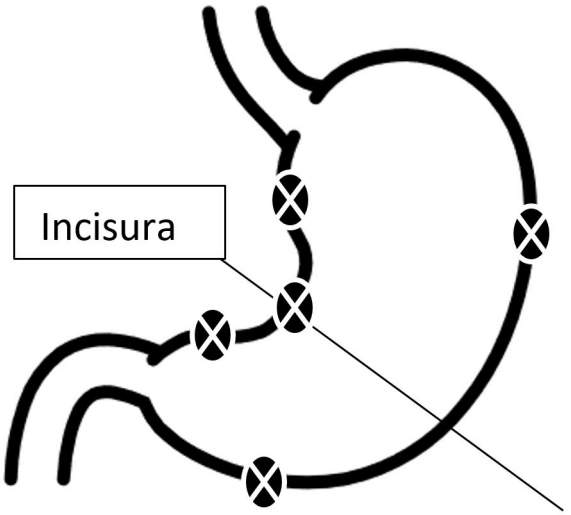


Figure 5. Diagnosing Gastric Intestinal Metaplasia: Gastric Biopsy Mapping Protocol



The enforcement of the current guidelines on indications for testing is needed since universal screening is currently not recommended. All the patients diagnosed with *H. pylori* infection should be offered eradication treatment, and the efficacy of treatment should be confirmed to assure that a cure has been effected. Initial treatment alternatives are now less effective, resulting in frequent treatment failures. The eradication of *H. pylori* remains the most effective tool physicians have in the fight to reduce GC incidence. Furthermore, identifying patients at risk of GC is a shared responsibility among physicians. Adequate history taking, testing appropriately, performing high-quality endoscopies, adhering to sampling protocols to identify gastric intestinal metaplasia extension, and reporting histological findings in accordance with the established staging protocol are all key elements. Gastric cancer is among the most common causes of cancer mortality, worldwide, and the prevention and screening of those at risk are the most valuable tools available.

Table 1. ACG Guideline Indications for *H. pylori* Testing

Should be tested
Active PUD
History of PUD
Low-grade MALT lymphoma
History of endoscopic resection of early gastric cancer
Under 60 years of age with uninvestigated dyspepsia without alarm features
Initiating chronic treatment with NSAID
Unexplained iron deficiency anemia
Adult with ITP
Consider testing
Long-term, low-dose aspirin

Abbreviations: ACG, American College of Gastroenterology; GERD, gastroesophageal reflux disease; ITP, idiopathic thrombocytopenic purpura; MALT, mucosa-associated lymphoid tissue; NSAID, non-steroidal anti-inflammatory drugs; PUD, peptic ulcer disease

Resumen

Helicobacter pylori (*H. pylori*) es una de las infecciones bacterianas más comunes que afectan al hombre; infectando el estómago de aproximadamente el 50% de la población mundial. En Puerto Rico, la prevalencia es de aproximadamente 33%, similar a la de Estados Unidos. La infección crónica por *H. pylori* es la causa principal de inflamación gástrica, la gastritis crónica y la metaplasia intestinal. Es la causante de la mayoría de las ulceras pépticas y los cánceres de estómago; y del linfoma de tejido linfoide asociado a la mucosa. En el 1994, la Agencia Internacional de Investigación en Cáncer la clasificó como un carcinógeno, siendo la única bacteria así catalogada. Se ha postulado que su efecto oncogénico se debe tanto a las características de la bacteria como a factores asociados a la respuesta del huésped. Varios estudios epidemiológicos reflejan que el riego de cáncer gástrico varía a través del mundo. En Puerto Rico, es una de las primeras 10 causas de cáncer. Aunque la erradicación tiene beneficios probados, existen varias preocupaciones sobre la identificación en masa y la erradicación indiscriminada. Estas incluyen: la resistencia a los antibióticos; cambios en la microbiota intestinal; aumento de peso; y el empeoramiento de los síntomas de reflujo gastroesofágico. El cáncer gástrico es un problema de salud pública serio por lo que es importante que todos entendamos el rol de la erradicación de *H. pylori* en la prevención de esta terrible enfermedad. Este articulo busca repasar el conocimiento actual y aquellas preguntas que aun restan por contestar.

References

1. Marshall B Helicobacter pylori: a Nobel pursuit? Can J Gastroenterol. 2008;22(11):895-896. doi:10.1155/2008/459810
2. Hooi JKY, Lai WY, Ng WK, et al. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. Gastroenterology. 2017;153(2):420-429. doi:10.1053/j.gastro.2017.04.022
3. NIH Consensus Conference. Helicobacter pylori in peptic ulcer disease. NIH Consensus Development Panel on Helicobacter pylori in Peptic Ulcer Disease. JAMA. 1994 Jul 6;272(1):65-9. PMID: 8007082.
4. Anonymous Live flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, Lyon, 7–14 June 1994. IARC Monogr. Eval. Carcinog. Risks Hum. 1994;61:1–241.
5. Khatoon J, Rai RP, Prasad KN. Role of Helicobacter pylori in gastric cancer: Updates. World J Gastrointest Oncol. 2016;8(2):147-158. doi:10.4251/wjgo.v8.i2.147
6. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Prz Gastroenterol. 2019;14(1):26-38. doi:10.5114/pg.2018.80001
7. Marghalani AM, Bin Salman TO, Faqeeh FJ, Asiri MK, Kabel AM. Gastric carcinoma: Insights into risk factors, methods of diagnosis, possible lines of management, and the role of primary care. J Family Med Prim Care. 2020;9(6):2659-2663. Published 2020 Jun 30. doi:10.4103/jfmpc.jfmpc_527_20
8. Li Z, Ying X, Shan F, Ji J. The association of garlic with Helicobacter pylori infection and gastric cancer risk: A systematic review and meta-analysis. Helicobacter. 2018;23(5):e12532. doi:10.1111/hel.12532

9. Ishaq S, Nunn L. Helicobacter pylori and gastric cancer: a state of the art review. Gastroenterol Hepatol Bed Bench. 2015;8(Suppl 1):S6-S14.
10. Fock KM. Review article: the epidemiology and prevention of gastric cancer. Aliment Pharmacol Ther. 2014;40(3):250-260. doi:10.1111/apt.12814
11. IARC Helicobacter pylori Working Group. Helicobacter pylori Eradication as a Strategy for Gastric Cancer Prevention. Lyon, France: International Agency for Research on Cancer (IARC Working Group Reports, No. 8). http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk8/index.php.
12. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31-49. doi: 10.1111/apm.1965.64.1.31
13. Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric Cancer: Epidemiology, Risk Factors, Classification, Genomic Characteristics and Treatment Strategies. Int J Mol Sci. 2020;21(11):4012. Published 2020 Jun 4. doi:10.3390/ijms21114012
14. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res. 1992;52(24):6735-6740.
15. Basso D, Zambon CF, Letley DP, et al. Clinical relevance of Helicobacter pylori cagA and vacA gene polymorphisms. Gastroenterology. 2008;135(1):91-99. doi:10.1053/j.gastro.2008.03.041
16. Wroblewski LE, Peek RM Jr, Wilson KT. Helicobacter pylori and gastric cancer: factors that modulate disease risk. Clin Microbiol Rev. 2010;23(4):713-739. doi:10.1128/CMR.00011-10
17. Plummer M, Franceschi S, Vignat J, Forman D, de Martel C. Global burden of gastric cancer attributable to Helicobacter pylori. Int J Cancer. 2015;136(2):487-490. doi:10.1002/ijc.28999
18. Wong BC, Lam SK, Wong WM, et al. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA. 2004;291(2):187-194. doi:10.1001/jama.291.2.187
19. Ford AC, Forman D, Hunt R, Yuan Y, Moayyedi P. Helicobacter pylori eradication for the prevention of gastric neoplasia. Cochrane Database Syst Rev. 2015;2015(7):CD005583. Published 2015 Jul 22. doi:10.1002/14651858.CD005583.pub2
20. Lee YC, Chiang TH, Chou CK, et al. Association Between Helicobacter pylori Eradication and Gastric Cancer Incidence: A Systematic Review and Meta-analysis. Gastroenterology. 2016;150(5):1113-1124.e5. doi:10.1053/j.gastro.2016.01.028
21. Ford AC, Forman D, Hunt RH, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. BMJ. 2014;348:g3174. Published 2014 May 20. doi:10.1136/bmj.g3174
22. Romero-Gallo J, Harris EJ, Krishna U, Washington MK, Perez-Perez GI, Peek RM Jr. Effect of Helicobacter pylori eradication on gastric carcinogenesis. Lab Invest. 2008;88(3):328-336. doi:10.1038/labinvest.3700719
23. Wong BC, Lam SK, Wong WM, et al. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA. 2004;291(2):187-194. doi:10.1001/jama.291.2.187
24. Forman D, Newell DG, Fullerton F, et al. Association between infection with Helicobacter pylori and risk of gastric cancer: evidence from a prospective investigation. BMJ. 1991;302(6788):1302-1305. doi:10.1136/bmj.302.6788.1302
25. Nomura A, Stemmermann GN, Chyou PH, Kato I, Perez-Perez GI, Blaser MJ. Helicobacter pylori infection and gastric carcinoma among Japanese Americans in Hawaii. N Engl J Med. 1991;325(16):1132-1136. doi:10.1056/NEJM199110173251604
26. Parsonnet J, Friedman GD, Vandersteen DP, et al. Helicobacter pylori infection and the risk of gastric carcinoma. N Engl J Med. 1991;325(16):1127-1131. doi:10.1056/NEJM199110173251603
27. Helicobacter and Cancer Collaborative Group. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. Gut. 2001;49(3):347-353. doi:10.1136/gut.49.3.347
28. Moss SF. The Clinical Evidence Linking Helicobacter pylori to Gastric Cancer. Cell Mol Gastroenterol Hepatol. 2016;3(2):183-191. Published 2016 Dec 27. doi:10.1016/j.jcmgh.2016.12.001
29. Schistosomes, liver flukes and Helicobacter pylori. IARC Monogr Eval Carcinog Risks Hum. 1994;61:1-241.
30. Fuccio L, Zagari RM, Eusebi LH, et al. Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? [published correction appears in Ann Intern Med. 2009 Oct 6;151(7):516]. Ann Intern Med. 2009;151(2):121-128. doi:10.7326/0003-4819-151-2-200907210-00009
31. Rokkas T, Rokka A, Portincasa P. A systematic review and meta-analysis of the role of Helicobacter pylori eradication in preventing gastric cancer. Ann Gastroenterol. 2017;30(4):414-423. doi:10.20524/aog.2017.0144
32. Kosunen TU, Pukkala E, Sarna S, et al. Gastric cancers in Finnish patients after cure of Helicobacter pylori infection: A cohort study. Int J Cancer. 2011;128(2):433-439. doi:10.1002/ijc.25337
33. Choi J, Kim SG, Yoon H, et al. Eradication of Helicobacter pylori after endoscopic resection of gastric tumors does not reduce incidence of metachronous gastric carcinoma. Clin Gastroenterol Hepatol. 2014;12(5):793-800.e1. doi:10.1016/j.cgh.2013.09.057
34. Lee YC, Chen TH, Chiu HM, Shun CT, Chiang H, Liu TY, Wu MS, Lin JT. The benefit of mass eradication of Helicobacter pylori infection: a community-based study of gastric cancer prevention. Gut. 2013 May;62(5):676-82. doi: 10.1136/gutjnl-2012-302240. Epub 2012 Jun 14. PMID: 22698649; PMCID: PMC3618687.
35. Kim N, Park YS, Cho SI, et al. Prevalence and risk factors of atrophic gastritis and intestinal metaplasia in a Korean population without significant gastroduodenal disease. Helicobacter. 2008;13(4):245-255. doi:10.1111/j.1523-5378.2008.00604.x
36. Li WQ, Ma JL, Zhang L, et al. Effects of Helicobacter pylori treatment on gastric cancer incidence and mortality in subgroups. J Natl Cancer Inst. 2014;106(7):dju116. Published 2014 Jun 12. doi:10.1093/jnci/dju116
37. Choi IJ, Kook MC, Kim YI, et al. Helicobacter pylori Therapy for the Prevention of Metachronous Gastric Cancer. N Engl J Med. 2018;378(12):1085-1095. doi:10.1056/NEJMoa1708423
38. Liou JM, Lee YC, El-Omar EM, Wu MS. Efficacy and Long-Term Safety of H. pylori Eradication for Gastric Cancer Prevention. Cancers (Basel). 2019;11(5):593. Published 2019 Apr 28. doi:10.3390/cancers11050593
39. Kato M, Nishida T, Yamamoto K, et al. Scheduled endoscopic surveillance controls secondary cancer after curative endoscopic resection for early gastric cancer: a multicentre retrospective cohort study by Osaka University ESD study group. Gut. 2013;62(10):1425-1432. doi:10.1136/gutjnl-2011-301647
40. Choi J, Kim SG, Yoon H, et al. Eradication of Helicobacter pylori after endoscopic resection of gastric tumors does not reduce incidence of metachronous gastric carcinoma. Clin Gastroenterol Hepatol. 2014;12(5):793-800.e1. doi:10.1016/j.cgh.2013.09.057
41. Suzuki S, Esaki M, Kusano C, Ikehara H, Gotoda T. Development of Helicobacter pylori treatment: How do we manage antimicrobial resistance? World J Gastroenterol. 2019;25(16):1907-1912. doi:10.3748/wjg.v25.i16.1907
42. Liou JM, Malfertheiner P, Lee YC, et al. Screening and eradication of Helicobacter pylori for gastric cancer prevention: the Taipei global consensus. Gut. 2020;69(12):2093-2112. doi:10.1136/gutjnl-2020-322368
43. Toro DH, Bravo-Fernández EF, Marcial MA, González C. Gastric campylobacter-like organisms and active antral gastritis in Puerto Rico. Bol Asoc Med P R. 1990;82(3):107-110.
44. Torres-Cintrón CR, Alvarado-Ortiz M, Roman-Ruiz Y, Zavala-Zegarra D, Tortolero-Luna G. Puerto Rico Central Cancer Registry; 2021. Cancer in Puerto Rico, 2014–2018. rcpr.org/Portals/0/20220425 informe 2014-2018 - Ingles_FINAL.PDF?ver=7pWVNlSgJWwb8E7wHdEUBg%3d%3d
45. González-Pons M, Soto-Salgado M, Sevilla J, et al. Seroprevalence of Helicobacter pylori in Hispanics living in Puerto Rico: A population-based study. Helicobacter. 2018;23(1):e12453. doi:10.1111/hel.12453

46. De León Morilla DM, Serallés J, Vázquez, W. 20 Years of H. pylori in Puerto Rico. Abstract. Am J Gastroenterol. 2018;113:S693. American College of Gastroenterology Annual Scientific Meeting and Postgraduate Course abstract P1714.
47. Cruz-Correa, M, Cora-Morges A, Gonzalez-Cordero A, et al, Gastric Cancer Epidemiological Trends among Hispanics: A 10-year Population-Based Analysis. Cancer Epidemiol Biomarkers Prev. 2017;26(2-Supplement):B55. Proceedings of the Ninth AACR Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved abstract B55.
48. Cruz-Cruz JJ, González-Pons M, Cora-Morges A, et al. Gastric Intestinal Metaplasia: Demographic and Epidemiological Characterization in Puerto Rican Hispanics (2012-2014). Gastroenterol Res Pract. 2021;2021:9806156. Published 2021 Feb 23. doi:10.1155/2021/9806156
49. Shah SC, Piazuelo MB, Kuipers EJ, Li D. AGA Clinical Practice Update on the Diagnosis and Management of Atrophic Gastritis: Expert Review. Gastroenterology. 2021;161(4):1325-1332.e7. doi:10.1053/j.gastro.2021.06.078
50. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection [published correction appears in Am J Gastroenterol. 2018 Jul;113(7):1102]. Am J Gastroenterol. 2017;112(2):212-239. doi:10.1038/ajg.2016.563