The Clinical Evidence Linking *Helicobacter pylori* to Gastric Cancer

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**SUMMARY**

The vast majority of gastric cancer worldwide is attributable to *Helicobacter pylori*, a chronic and persistent infection that is usually acquired in childhood. In some regions of the world with especially high gastric cancer prevalence, intervention programs have been established to eradicate *H. pylori* with the expectation that this will significantly decrease mortality from this disease. This review focuses on the link between *H. pylori* and gastric cancer established from clinical studies, and discusses the consequences of novel insights into cancer biology, the gastrointestinal microbiome, and on individual and population-based gastric cancer prevention strategies that this work has stimulated.

Gastric cancer has long been recognized to be accompanied and preceded by chronic gastritis, lasting decades. Arguably, the most important development in our understanding of gastric cancer pathogenesis over the past 50 years has been the realization that, for most cases of gastric cancer, *Helicobacter pylori* is the cause of the underlying gastritis. Gastritis can promote gastric carcinogenesis, typically via the Correa cascade of atrophic gastritis, intestinal metaplasia, and dysplasia. Nested case-control studies have shown that *H. pylori* infection increases the risk of gastric cancer significantly, both of the intestinal and diffuse subtypes, and that *H. pylori* is responsible for approximately 90% of the world’s burden of noncardia gastric cancer. Based largely on randomized studies in high gastric cancer prevalence regions in East Asia, it appears that primary and tertiary intervention to eradicate *H. pylori* can halve the risk of gastric cancer. Some public health authorities now are starting screening and treatment programs to reduce the burden of gastric cancer in these high-risk areas. However, there is currently much less enthusiasm for initiating similar attempts in the United States. This is partially because gastric cancer is a relatively less frequent cause of cancer in the United States, and in addition there are concerns about theoretical downsides of *H. pylori* eradication, principally because of the consistent inverse relationship noted between *H. pylori* and esophageal adenocarcinoma. Nevertheless, establishing a link between chronic *H. pylori* infection and gastric cancer has led to novel insights into cancer biology, the gastrointestinal microbiome, and on individual and population-based gastric cancer prevention strategies.

**Keywords:** *Helicobacter pylori*; Gastric Cancer; Epidemiology; Cancer Prevention.

It is now appreciated that infection with *Helicobacter pylori* is the most important risk factor for the development of noncardia gastric cancer, responsible for almost 90% of such cases worldwide and approximately 5% of the total burden from all cancers globally.

It is remarkable that the critical contribution of *H. pylori* to gastric carcinogenesis was almost unknown when the Funderburg family started funding gastric cancer research in 1992. As the first recipient of the award to investigate *H. pylori* (my project, funded in 2002, was entitled “Regulation of Gastric Epithelial p27kip1 by *H. pylori*”), this review focuses on the clinicopathologic and epidemiologic data that have emerged over the past 30 years establishing *H. pylori* as the most important etiologic agent in gastric adenocarcinoma, and discusses the implications of this association for gastric cancer prevention.

**The Inflammatory Origins of Gastric Cancer**

Our understanding of *H. pylori*-induced inflammation leading to cancer is built on the work of 3 pioneering pathologists (Figure 1). Rudolf Virchow, a 19th century Prussian physician-scientist, is widely regarded as the father of modern pathology. Among his many contributions to outlining the scientific basis of disease was the idea, based on many of his own observations, that cancer arose from initially normal cells in response to chronic irritation, or inflammation.

Numerous examples of inflammation-induced cancers are now appreciated, including many of the common gastrointestinal tract and hepatobiliary malignancies, such as acid reflux–induced esophageal adenocarcinoma, inflammatory bowel disease–associated colon cancer, and hepatocellular neoplasms associated with chronic viral hepatitis.

**Abbreviations used in this paper:** CI, confidence interval; ELISA, enzyme-linked immunosorbent assay.

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Throughout the 20th century, evidence accrued that gastric cancers tended to arise in stomachs already affected by chronic inflammation, especially atrophic gastritis with its accompanying hypochlorhydria, and that gastric cancer was a consequence and not a mere accompaniment of the gastritis. These ideas set the stage for Pelayo Correa, a pathologist from Colombia, a country with a particularly high gastric cancer prevalence. After training in pathology in Colombia and in the United States (Emory University), Correa devoted his professional career at home and subsequently in the United States (at the National Cancer Institute, Louisiana State University, and now Vanderbilt University) to understanding the etiology of gastric cancer. In 1975, Correa et al, from the National Cancer Institute, Massachusetts Institute of Technology, and from his home country, published a “Model for Gastric Cancer Development.” In this landmark report, it was hypothesized that the development of the more common intestinal subtype of gastric cancer resulted from a stepwise process, beginning with chronic atrophic gastritis and progressing to intestinal metaplasia and cancer over the next 30–50 years. The initial changes were postulated to occur in the first decade of life, which we now know to be when H pylori colonization occurs. A more detailed model, published in 1988, included what was known of the phenotypic markers accompanying these sequential changes. Correa initially thought that the agent(s) responsible for promoting this slow progression from gastritis to cancer were environmental, based on studies of migrants from high gastric cancer risk areas. For example, Japanese immigrants to Hawaii and European immigrants to the United States had been shown to have lower gastric cancer rates than their parents and grandparents, more similar to those of the native population where they settled. The prime environmental culprit originally was thought to be a diet high in salt and N-nitroso-compounds and low in micronutrients from fresh fruits and vegetables. It was postulated that this led to the promotion of gastric mutagenesis and, together with hypochlorhydria, bacterial overgrowth, thereby contributing to further nitrosamine formation. Interestingly, in his 1988 publication, Correa briefly discussed a possible role for Campylobacter pylori, a newly discovered gastric bacterium, in the initiation of the disease. Correa’s subsequent work has focused primarily on the role of H pylori in gastric cancer, and this model has stood the test of time (Figure 2). For his outstanding contributions to the field of gastric carcinogenesis, Correa received the American Gastroenterological Association’s Distinguished Achievement Award in 2013.

The third pathologist of note is Robin Warren from Australia who, together with Barry Marshall, was awarded the Nobel Prize in Physiology or Medicine in 2005 for the discovery of H pylori and its role in gastritis and peptic ulcer disease. In the 1970s, the widespread use of gastrointestinal endoscopy allowed pathologists the opportunity to view gastric tissue that had been removed during a biopsy and fixed rapidly, without the artifacts inherent to the ischemia and autolysis of surgical specimens. Warren observed that spiral gastric bacteria were common in fresh gastritis specimens. He then recruited Marshall, a medical resident looking for a research project, to correlate the pathologic findings with the endoscopic features. Together, they discovered that these bacteria (initially termed Campylobacter pyloridis, then C pylori, and, subsequently, H pylori) were very common in peptic ulcer patients. Eventually, they successfully cultured these formerly elusive bacteria and showed that they caused gastritis and ulcer disease.1-14 In retrospect, other investigators also had observed such bacteria over the preceding century, but their clinical significance had not been appreciated and they had even been proven to be a post mortem artifact before their rediscovery in Australia. Although Warren and Marshall did not investigate the role of H pylori in gastric cancer directly, they were aware of the relationship between gastritis and cancer. Indeed, Marshall speculated with amazing prescience in their very first publications (in unusual side-by-side, single-author letters in 1983) that “if these bacteria are truly associated with antral gastritis, as described by
Warren, they may have a part to play in other poorly understood, gastritis associated diseases (ie, peptic ulcer and gastric cancer)."12

Evidence of the H pylori–Cancer Connection

Initial investigations into a possible association of H pylori with gastric cancer that were conducted in the 1980s and early 1990s provided only weak evidence for a link between H pylori and gastric cancer. A positive correlation between H pylori seroprevalence and gastric cancer in cross-sectional sampling was reported in a study conducted among 13 European nations.16 However, although some other publications reported similar trends,17,18 several others did not find a positive correlation between the presence of H pylori antibodies and either gastric cancer or precancerous gastric lesions.19–22

Around this time, clinicopathologic studies performed to look for evidence of H pylori infection (by serum antibodies) or in gastric tissue directly in cases of gastric cancer also yielded inconsistent results. Some studies showed H pylori infection rates no higher than those observed in noncancer controls. This is most likely because by the time gastric cancer has developed, extensive intestinal metaplasia and hypochlorhydria had rendered the stomach less hospitable to persistent H pylori colonization,23 thus also explaining some of the negative findings in the cross-sectional studies discussed earlier.

Much more convincing evidence for the role of H pylori in gastric cancer came from 3 large cohorts with nested case-controls, in which serum had been banked from cancer-free subjects and the cohort had been followed up for approximately a decade.24–26 In each cohort, evidence of prior H pylori infection (evaluated by enzyme-linked immunosorbent assay [ELISA] in the banked serum) was

Figure 2. Current model of the decades-long sequence of intestinal-type gastric carcinogenesis, based on the classical histopathologic Correa cascade in grey box (left), with (center) postulated stimuli (green boxes) and mechanisms (red boxes), and some of the key accompanying molecular genetic events (right).
found to be significantly more common in those subjects who subsequently developed gastric cancer compared with a sample of those who had not (Table 1). In a meta-analysis, these 3 studies provided an overall odds ratio for gastric cancer development in H pylori–infected vs -uninfected persons of 3.8 (95% confidence interval [CI], 2.3–6.2). Based on the compelling results of these cohort studies, the World Health Organization’s International Agency for Research on Cancer declared in 1994 that there was sufficient evidence to classify H pylori as a definite (group 1) carcinogen. This was despite the fact that at that time there was no significant supporting evidence from either animal models or mechanistic basic science research.

Subsequent research worldwide has confirmed and expanded upon the early epidemiologic studies, with the key additional clinical findings as follows:

1. Cardia cancers are not associated strongly with H pylori infection, supporting the idea that cardia cancers arise via alternative mechanisms, with risk factors more similar to cancers of the gastroesophageal junction and lower esophagus.

2. In pooled meta-analysis, the odds ratio for H pylori in gastric cancer was no different when considering intestinal vs diffuse histologic cancer subtypes. Thus, in addition to promoting the well-established Correa cascade of intestinal-type cancers, H pylori is just as great a risk factor for the much less well-defined pathway leading to diffuse-type gastric cancer.

3. Measuring H pylori exposure by ELISA underestimates prior exposure and, therefore, the attributable H pylori risk in noncardia cancer, because of false-negative results. For example, in a retrospective Swedish case-control study, measuring prior exposure through a Western blot against H pylori cytotoxin-associated gene A (CagA), rather than a conventional IgG ELISA, increased the odds ratio from 2.2 (95% CI, 1.4–3.6) to 21.0 (95% CI, 8.3–53.4).

4. In noncardia gastric cancers, CagA-positive H pylori strains (which are the more common strains worldwide) increase the risk of gastric cancer to a greater extent than do infections by the more rare CagA-negative strains. This is consistent with the oncogenic effects of the CagA protein that have been evaluated mainly in vitro.

5. H pylori eradication can reduce the risk of developing gastric cancer (see later).

### Conclusions From Gastric Cancer Prevention Studies

In a prolonged observational study following patients who had attended a Japanese endoscopy unit, Uemura et al showed that those who were H pylori–infected (and in whom the infection was not treated) had a much higher rate of progression to gastric cancer over the subsequent 12 years than the patients who had no initial evidence of H pylori. However, to prove conclusively that H pylori is responsible for the increased gastric cancer risk, prospective interventional studies were necessary.

Recruitment into such studies was hampered by the 1994 declaration of H pylori as a definite carcinogen, after which it became ethically problematic to enter patients into the control arms of eradication studies designed to determine the gastric cancer risk reduction. Consequently, an appropriately powered, definitive study of a large number of subjects followed up for many years to the end point of gastric cancer was never completed. Nevertheless, recent meta-analyses of the many underpowered studies that were conducted are conclusive, indicating that H pylori eradication decreases the risk of gastric cancer development by approximately 40% in studies of primary prevention (asymptomatic individuals), and by 54% as a tertiary prevention strategy (preventing the occurrence of a second gastric malignancy after endoscopic resection of an early gastric cancer). It is not known whether or not there is a point of no return along the Correa pathway, beyond which H pylori eradication will not prevent progression to gastric cancer. In the analysis by Lee et al, which included 24 publications of more than 48,000 individuals followed up for more than 340,000 person-years (14 studies of primary prevention, 10 studies of tertiary prevention), the benefit of H pylori eradication was, not surprisingly, most evident in subjects living in areas with the highest gastric cancer prevalence. However, the risk reduction was evident in almost every individual study evaluated. Because all investigations were conducted in parts of the world where gastric cancer is most prevalent (mostly in South-East Asia), it is uncertain if similar reductions can be extrapolated to regions where noncardia gastric cancer is less common, such as the United States. However, it may be reasonable to

### Table 1. The Three Cohort Studies That Led to the Classification of H pylori as a Class 1 Carcinogen in 1994

| Study          | Cohort description     | Time from cohort inception to cancer, mean | Cases of H pylori seroprevalence, n (%) | Controls with H pylori seroprevalence, n (%) | Odds ratio (95% CI) |
|----------------|------------------------|------------------------------------------|----------------------------------------|--------------------------------------------|-------------------|
| Forman et al.  | British men            | 6 y                                      | 29 (69)                                | 116 (47)                                   | 2.8 (1.0–8.0)     |
| Parsonnet et al| Californian men and women | 14 y                                      | 109 (84)                                | 109 (61)                                   | 3.6 (1.8–7.3)     |
| Nomura et al.  | Japanese-American men in Hawaii | 13 y                                      | 109 (94)                                | 109 (76)                                   | 6.0 (2.1–17)      |
suppose that high-risk populations in low-risk countries, including immigrants from Central and South America and South-East Asia to the United States who remain *H pylori*–infected from childhood, should benefit greatly from *H pylori* eradication too.

### Should Widespread Screening and Eradication Programs Be Adopted to Prevent Gastric Cancer?

Gastric cancer is the third most common cause of cancer death worldwide. However, with the exception of endoscopic screening in South Korea, and radiologic and endoscopic programs in Japan, there had been little effort made previously to control this burden with public health programs. The results of the recent intervention studies reported earlier have now prompted renewed interest in screening for *H pylori* and eradicating the organism when found as a potentially cost-effective strategy, especially in parts of the world that have a high prevalence of *H pylori* and gastric cancer.

A pilot study of mass population screening and eradication started in the Matsu Islands of Taiwan in 2004, and the initial results are very promising. Gastric cancer incidence has decreased by approximately 25%, peptic ulcers by two thirds, and gastric atrophy by 77% compared with historical data. Several other population-based trials are underway, including one with almost 100,000 Chinese subjects from Linqu County, a region of high gastric cancer prevalence.

The eradication of *H pylori* from a community should help prevent much gastric cancer, as well as greatly diminish the morbidity of peptic ulcers too. It has been calculated that the number needed to treat to prevent a case of gastric cancer may be as low as 15 in Chinese men, to as high as 245 in women in the United States. Although there is a concern regarding the ecologic consequences of using multiple antibiotics in a large proportion of the population to prevent *H pylori*–related disease, the recent exciting results of vaccination against *H pylori* with an oral urease B construct suggest that a nonantibiotic strategy may be possible in the future, with potentially less impact on the general human microbiome. Further investigation of this vaccine should be a priority, particularly because promising preclinical models with a variety of vaccine candidates since the 1990s had never resulted previously in impressive results in clinical trials. If preventive or therapeutic vaccination emerges as a viable alternative for *H pylori* eradication, it will help avert widespread antibiotic administration and the consequent problems of microbiome perturbation and the generation of microbial antibiotic resistance among *H pylori* and other innocent bystander bacteria.

### Why the Hesitancy to Adopt Widespread *H pylori* Eradication in the United States?

In the midst of growing optimism for implementing *H pylori* eradication strategies in high gastric cancer risk regions, it is important to recognize that there is considerable hesitation to adopt similar approaches in the developed world, mainly out of concern for a beneficial effect of *H pylori* on esophageal diseases.

The results of multiple studies have indicated that *H pylori* is significantly less common in patients with esophageal adenocarcinoma than in matched controls, although *H pylori* infection has no association, positive or negative, with esophageal squamous cancer (Figure 3). This places *H pylori* in a unique position among the World Health Organization’s list of biological agents that cause cancer, in that its presence is associated positively with certain cancers (gastric noncardia adenocarcinoma, gastric marginal zone B-cell lymphoma) although related inversely to another cancer type (esophageal adenocarcinoma).

How *H pylori* infection might prevent esophageal cancer is not known. The absence of *H pylori* may promote more severe esophageal mucosal damage, Barrett’s metaplasia, and the consequent development of esophageal adenocarcinoma. A postulated mechanism is through a greater gastric acid secretory capacity from a pristine, uninfamed, parietal cell mass in the absence of *H pylori* gastritis, although there is little evidence that this actually leads to enhanced esophageal acid exposure. An inverse relationship between *H pylori* and esophageal adenocarcinoma does not necessarily imply that *H pylori* is protective any more than a positive association can be taken to be evidence of causation. *H pylori* has been an almost universal inhabitant of the human stomach from the dawn of mankind until the 1980s. Its recent disappearance from the 21st human microbiome, one of the “missing microbes” has been linked to extragastric immune dysregulation (for which there is good evidence from animal models) and a multitude of other contemporary maladies (eg, asthma, obesity, and inflammatory bowel disease), for which the evidence is questionable and the biological plausibility equally uncertain.

The decrease in noncardia gastric cancer in North America and Western Europe over the past 100 years that coincided with (or maybe even preceded) decreasing *H pylori* prevalence, was famously described as the “epidemiology of an unplanned triumph.” The rapid increase in esophageal adenocarcinoma in the same population more recently (such that it is now approaching the prevalence of noncardia gastric cancer) perhaps may be considered the unplanned downside of the disappearance of *H pylori* from Western stomachs. It is this unexpected accompaniment of *H pylori* eradication that largely has tempered enthusiasm for population-based *H pylori* eradication efforts in the developed world. Whether to pursue population-based *H pylori* screening and treatment strategies therefore will need to be individualized according to the current and projected future medical needs of each community, and these differ quite markedly around the globe.

### Conclusions

The declaration of *H pylori* as a definite gastric carcinogen in 1994 and the subsequent realization that the vast
majority of noncardia cancers are attributable to *H pylori* infection has led to a fundamental change in the way that we view gastric cancer pathogenesis in the Funderburg era. Considering gastric cancer as the consequence of an infection has led to enthusiasm for screening for and eradicating *H pylori* in areas of high gastric cancer prevalence, but the fact that gastric cancer remains a rare consequence of *H pylori* infection provides plenty of opportunity for investigating the co-factors that promote gastric neoplastic development after *H pylori* colonization.

Recent research in this field has focused on genetic susceptibility (such as polymorphisms in genes governing gastric inflammatory responses), *H pylori* heterogeneity, and on other environmental influences, such as dietary salt or the presence of non-*Helicobacter* species within the gastrointestinal microbiome that may explain why only a small proportion of individuals who are colonized by *H pylori* go on to develop gastric cancer. This knowledge ultimately may have clinical utility in stratifying individuals with *H pylori* infection into high vs low gastric cancer risk, and to the creation of personalized surveillance, chemoprevention, and dietary intervention programs focused on patients at highest risk. As an example, an early study reported enormous differences (up to 90-fold) in gastric cancer susceptibility in *H pylori*-infected cases from Portugal, when stratified by polymorphisms in interleukin 1β and the interleukin 1 receptor antagonist, together with *H pylori* Vacuolating cytotoxin A (VacA) and CagA typing.

Investigating the precise molecular and cellular mechanisms of gastric cancer development associated with *H pylori* infection is likely to provide additional insights into gastric cancer, as well as stimulate ideas about the pathogenesis of other cancers that are known to be associated with inflammation, although not necessarily with specific constituents of the microbiome. Since 1994, considerable progress has been made on dissecting the role of *H pylori* in the molecular pathogenesis of inflammation-associated gastric cancer (as outlined in the review by Crowe in this issue). The multiplicity of animal models to study *H pylori*-associated gastric carcinogenesis (reviewed...
in Tsukamoto et al.\textsuperscript{65} and Krueger et al.\textsuperscript{66} as well as by Wang in this issue) also has provided many important mechanistic insights that were not conceivable back in 1994, when rodent infection studies were in their infancy and the evidence for \textit{H pylori} as a carcinogen was based on a limited number of clinical studies.

Support from the Funderburg family has been instrumental in promoting new ideas about gastric cancer and its origins, as well as opening new therapeutic possibilities. The work that started in our laboratory in 2002 as a result of this funding has allowed us to investigate how \textit{H pylori} misregulates the expression of p27, a cyclin-dependent kinase inhibitor that is an important constitutive endogenous cell-cycle regulator.\textsuperscript{67,68} We also subsequently explored the p27-deficient mouse as a model with which to study the mechanisms of \textit{H pylori}-induced gastric carcinogenesis,\textsuperscript{69,70} and to examine its reversibility after \textit{H pylori} eradication.\textsuperscript{71}

Our understanding of gastric carcinogenesis continues to grow rapidly. For many years, pathologists were at the cutting edge of this knowledge, based on their meticulous observations of the unfortunate patients who died of this largely untreatable disease. The realization that a single bacterial species was the inciting cause of the majority of gastric cancers went against the prevailing clinical and scientific dogma. As a result of this initially uncomfortable discovery, gastric cancer, which was a disease that formerly was principally the focus of pathologists and surgeons, has become widely embraced by the scientific and clinical community as a model of bacterial carcinogenesis and a window to inflammation-associated cancers in general.

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The author discloses no conflicts.