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REVIEW

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. *(Cell Mol Gastroenterol Hepatol 2017;3:183–191; http://dx.doi.org/10.1016/j.jcmgh.2016.12.001)*

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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.[1]

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 $p27^{kip1}$ 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.[2] 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.[2]

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

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Figure 1. Three pathologists who shaped our understanding of *H pylori*–induced gastric carcinogenesis. *Left to right*: Rudolf Virchow, Pelayo Correa, and Robin Warren. Reproduced with permission from: https://commons.wikimedia.org/wiki/File:Rudolf_Virchow_NLM3.jpg; and http://news.vicc.org/2013/06/correa-honored-for-gastroenterological-research/.

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.[3] 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,[4] 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.[5] A more detailed model, published in 1988,[6] 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.[7,8] 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.[9] 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 recognized 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.[10] 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.[11–14] 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[15] 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

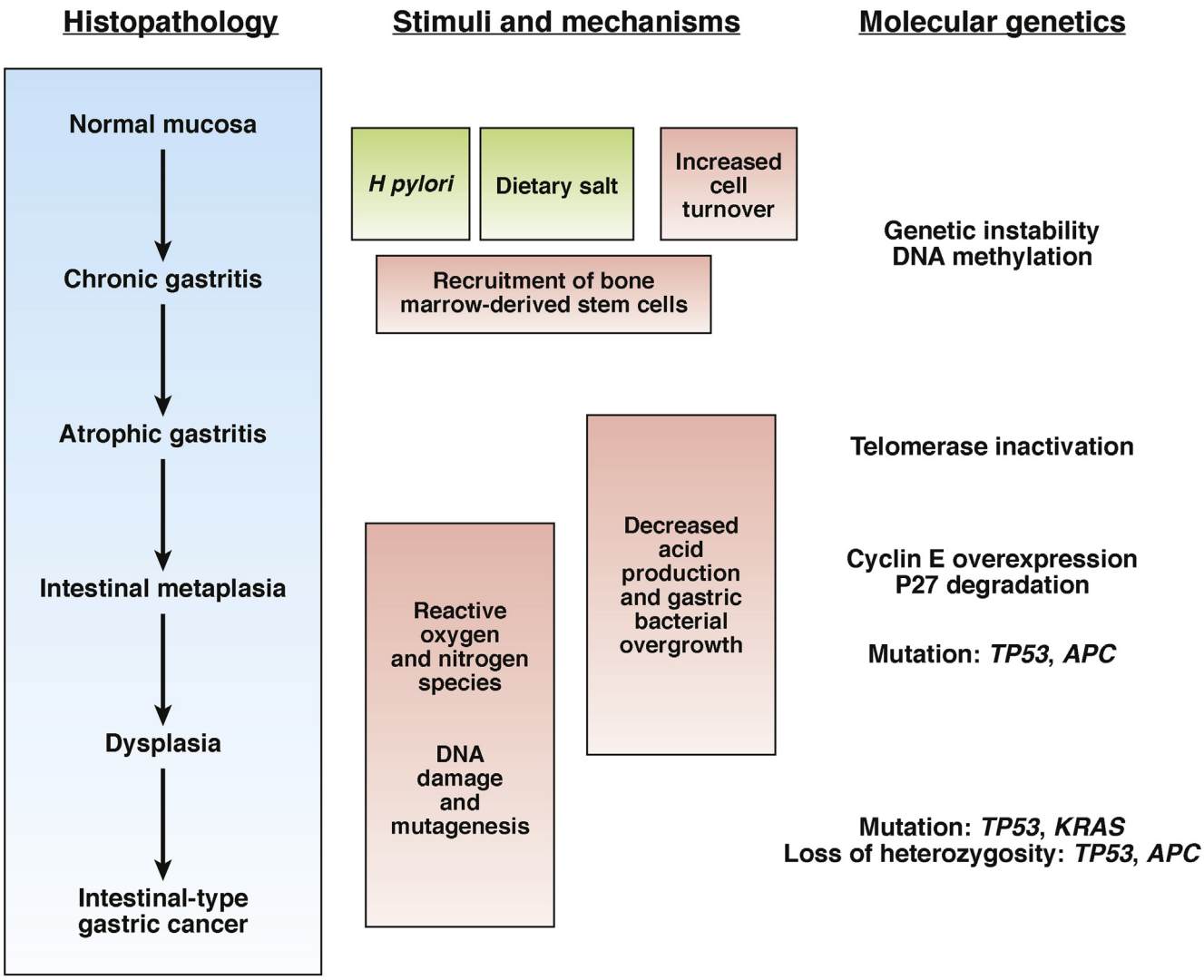

Figure 2. Current model of the decades-long sequence of intestinal-type gastric carcinogenesis, based on the classical histopathologic Correa cascade in *grey box* (*left*), with (*center*) postulated stimuli (*green boxes*) and mechanisms (*red boxes*), and some of the key accompanying molecular genetic events (*right*).

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

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).[27]

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.[28] 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,[29] supporting the idea that cardia cancers arise via alternative mechanisms, with risk factors more similar to cancers of the gastroesophageal junction and lower esophagus.[30]
2. In pooled meta-analysis,[31] 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[4] 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).[32]
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.[33] This is consistent with the oncogenic effects of the CagA protein that have been evaluated mainly in vitro.[34]
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[35] 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,[28] 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).[36,37] It is not known whether or not there is a point of no return along the Correa pathway,[4] beyond which *H pylori* eradication will not prevent progression to gastric cancer. In the analysis by Lee et al,[37] 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,[24] 1991	British men	6 y	29 (69)	116 (47)	2.8 (1.0–8.0)
Parsonnet et al,[25] 1991	Californian men and women	14 y	109 (84)	109 (61)	3.6 (1.8–7.3)
Nomura et al,[26] 1991	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.[38] 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.[39–41]

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.[42] 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.[43]

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.[44] 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[45] 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.[46] 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[47,48] (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).[49]

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,[50] and the consequent development of esophageal adenocarcinoma. A postulated mechanism is through a greater gastric acid secretory capacity from a pristine, uninflamed, parietal cell mass in the absence of *H pylori* gastritis,[51] 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.[52] Its recent disappearance from the 21st human microbiome, one of the "missing microbes,"[53] has been linked to extragastric immune dysregulation (for which there is good evidence from animal models)[54] 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.[55–57]

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."[58] The rapid increase in esophageal adenocarcinoma in the same population more recently (such that it is now approaching the prevalence of noncardia gastric cancer[59]) 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[28] and the subsequent realization that the vast

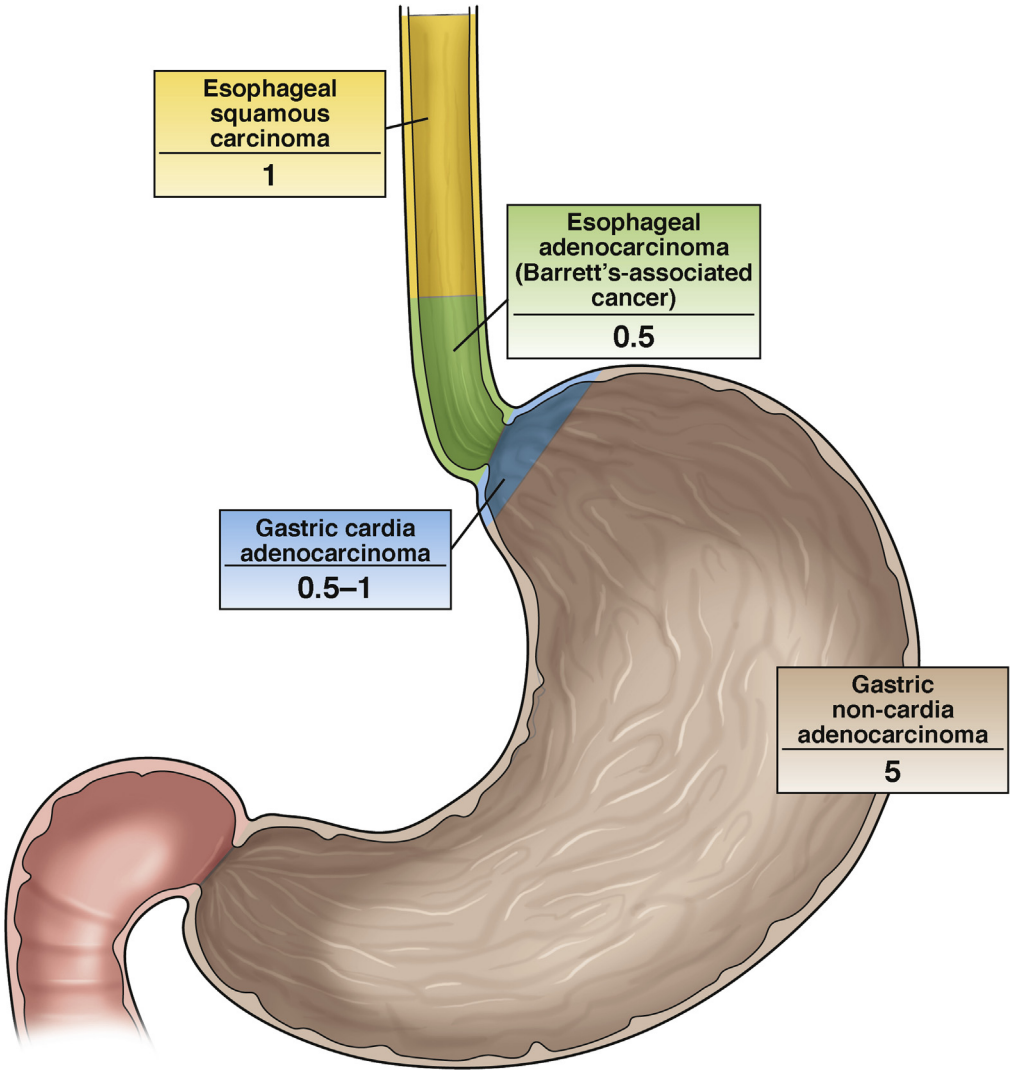

Figure 3. Complex relationship between *H pylori* and the common cancers of the esophagus and stomach. Data are shown as odds ratios for the development of cancer in *H pylori*–infected vs uninfected persons.

majority of noncardia cancers are attributable to *H pylori* infection[1] 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[60]), *H pylori* heterogeneity,[61] and on other environmental influences, such as dietary salt[62] 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.[63] 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.[64]

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* role 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[65] and Krueger et al,[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 *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 *H pylori* misregulates the expression of p27, a cyclin-dependent kinase inhibitor that is an important constitutive endogenous cell-cycle regulator.[67,68] We also subsequently explored the p27-deficient mouse as a model with which to study the mechanisms of *H pylori*–induced gastric carcinogenesis,[69,70] and to examine its reversibility after *H pylori* eradication.[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.

References

1. Plummer M, Franceschi S, Vignat J, et al. Global burden of gastric cancer attributable to *Helicobacter pylori*. Int J Cancer 2015;136:487–490.
2. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539–545.
3. Hurst AF. Schorstein lecture: on the precursors of carcinoma of the stomach. Lancet 1929;214:1023–1028.
4. Correa P, Haenszel W, Cuello C, et al. A model for gastric cancer epidemiology. Lancet 1975;2:58–60.
5. Malaty HM, El-Kasabany A, Graham DY, et al. Age at acquisition of *Helicobacter pylori* infection: a follow-up study from infancy to adulthood. Lancet 2002; 359:931–935.
6. Correa P. A human model of gastric carcinogenesis. Cancer Res 1988;48:3554–3560.
7. Haenszel W, Kurihara M, Segi M, et al. Stomach cancer among Japanese in Hawaii. J Natl Cancer Inst 1972; 49:969–988.
8. Staszewski J. Migrant studies in alimentary tract cancer. Recent Results Cancer Res 1972;39:85–97.
9. Parsonnet J. Clinician-discoverers–Marshall, Warren, and *H. pylori*. N Engl J Med 2005;353:2421–2423.
10. Moss SF. The rediscovery of *H. pylori* bacteria in the gastric mucosa by Robin Warren, and implications of this finding for human biology and disease. Dig Dis Sci 2013; 58:3072–3078.
11. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984;1:1311–1315.
12. Warren JR, Marshall BJ. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983;1:1273–1275.
13. Marshall BJ, Goodwin CS, Warren JR, et al. Prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*. Lancet 1988; 2:1437–1442.
14. Marshall BJ, Armstrong JA, McGechie DB, et al. Attempt to fulfil Koch's postulates for pyloric Campylobacter. Med J Aust 1985;142:436–439.
15. Palmer ED. Investigation of the gastric mucosa spirochetes of the human. Gastroenterology 1954; 27:218–220.
16. An international association between *Helicobacter pylori* infection and gastric cancer. The EUROGAST Study Group. Lancet 1993;341:1359–1362.
17. Correa P, Fox J, Fontham E, et al. *Helicobacter pylori* and gastric carcinoma. Serum antibody prevalence in populations with contrasting cancer risks. Cancer 1990; 66:2569–2574.
18. Forman D, Sitas F, Newell DG, et al. Geographic association of *Helicobacter pylori* antibody prevalence and gastric cancer mortality in rural China. Int J Cancer 1990; 46:608–611.
19. Sierra R, Munoz N, Pena AS, et al. Antibodies to *Helicobacter pylori* and pepsinogen levels in children from Costa Rica: comparison of two areas with different risks for stomach cancer. Cancer Epidemiol Biomarkers Prev 1992;1:449–454.
20. Palli D, Decarli A, Cipriani F, et al. *Helicobacter pylori* antibodies in areas of Italy at varying gastric cancer risk. Cancer Epidemiol Biomarkers Prev 1993;2:37–40.
21. Fukao A, Komatsu S, Tsubono Y, et al. *Helicobacter pylori* infection and chronic atrophic gastritis among Japanese blood donors: a cross-sectional study. Cancer Causes Control 1993;4:307–312.
22. Tsugane S, Kabuto M, Imai H, et al. *Helicobacter pylori*, dietary factors, and atrophic gastritis in five Japanese populations with different gastric cancer mortality. Cancer Causes Control 1993;4:297–305.
23. Siurala M, Sipponen P, Kekki M. *Campylobacter pylori* in a sample of Finnish population: relations to morphology and functions of the gastric mucosa. Gut 1988; 29:909–915.
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;302:1302–1305.
25. Parsonnet J, Friedman GD, Vandersteen DP, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. N Engl J Med 1991;325:1127–1131.
26. Nomura A, Stemmermann GN, Chyou PH, et al. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. N Engl J Med 1991; 325:1132–1136.
27. Forman D, Webb P, Parsonnet J. *H pylori* and gastric cancer. Lancet 1994;343:243–244.

28. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes, liver flukes and *Helicobacter pylori*. Lyon, June 7-14, 1994. IARC Monogr Eval Carcinog Risks Hum 1994;61:1–241.
29. Huang J-Q, Sridhar S, Chen, et al. Meta-analysis of the relationship between *Helicobacter pylori* seropositivity and gastric cancer. Gastroenterology 1998;114: 1169–1179.
30. Olefson S, Moss SF. Obesity and related risk factors in gastric cardia adenocarcinoma. Gastric Cancer 2015; 18:23–32.
31. *Helicobacter* and Gastric Cancer Collaborative Group. Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. Gut 2001;49:347–353.
32. Ekstrom AM, Held M, Hansson LE, et al. Helicobacter pylori in gastric cancer established by CagA immunoblot as a marker of past infection. Gastroenterology 2001; 121:784–791.
33. Huang JQ, Zheng GF, Sumanac K, et al. Meta-analysis of the relationship between cagA seropositivity and gastric cancer. Gastroenterology 2003;125:1636–1644.
34. Backert S, Tegtmeyer N, Fischer W. Composition, structure and function of the *Helicobacter pylori* cag pathogenicity island encoded type IV secretion system. Future Microbiol 2015;10:955–965.
35. Uemura N, Okamoto S, Yamamoto S, et al. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med 2001;345:784–789.
36. Ford AC, Forman D, Hunt R, et al. *Helicobacter pylori* eradication for the prevention of gastric neoplasia. Cochrane Database Syst Rev 2015;7:CD005583.
37. 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;150:1113–1124.
38. International Agency for Research on Cancer. Cancer fact sheets: stomach cancer. Available from: http://gco.iarc.fr/today/data/pdf/fact-sheets/cancers/cancer-fact-sheets-5.pdf. Accessed: November 11, 2016.
39. Herrero R, Park JY, Forman D. The fight against gastric cancer - the IARC Working Group report. Best Pract Res Clin Gastroenterol 2014;28:1107–1114.
40. Asaka M, Mabe K, Matsushima R, et al. *Helicobacter pylori* eradication to eliminate gastric cancer: the Japanese strategy. Gastroenterol Clin North Am 2015; 44:639–648.
41. IARC Helicobacter pylori Working Group. Helicobacter pylori eradication as a strategy for preventing gastric cancer. IARC Working Group reports, number 8. 2014. Lyon, France: International Agency for Research on Cancer. Available from: http://publications.iarc.fr/Book-And-Report-Series/Iarc-Working-Group-Reports/Helicobacter-Pylori-Eradication-As-A-Strategy-For-Preventing-Gastric-Cancer-2014. Accessed January 11, 2017
42. Lee YC, Chen TH, Chiu HM, et al. The benefit of mass eradication of *Helicobacter pylori* infection: a community-based study of gastric cancer prevention. Gut 2013; 62:676–682.
43. Pan KF, Zhang L, Gerhard M, et al. A large randomised controlled intervention trial to prevent gastric cancer by eradication of *Helicobacter pylori* in Linqu County, China: baseline results and factors affecting the eradication. Gut 2016;65:9–18.
44. Ford AC, Forman D, Hunt RH, et al. *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.
45. Zeng M, Mao XH, Li JX, et al. Efficacy, safety, and immunogenicity of an oral recombinant *Helicobacter pylori* vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015; 386:1457–1464.
46. Blanchard TG, Czinn SJ. Current status and prospects for a *Helicobacter pylori* vaccine. Gastroenterol Clin North Am 2015;44:677–689.
47. Islami F, Kamangar F. *Helicobacter pylori* and esophageal cancer risk: a meta-analysis. Cancer Prev Res (Phila) 2008;1:329–338.
48. Xie FJ, Zhang YP, Zheng QQ, et al. *Helicobacter pylori* infection and esophageal cancer risk: an updated meta-analysis. World J Gastroenterol 2013;19:6098–6107.
49. IARC monographs on the evaluation of carcinogenic risks to humans. "Biological Agents," a review of human carcinogens. 100B. Lyon, France: IARC, 2012:385–435.
50. Gatenby P, Soon Y. Barrett's oesophagus: evidence from the current meta-analyses. World J Gastrointest Pathophysiol 2014;5:178–187.
51. El-Omar EM, Oien K, El-Nujumi A, Gillen D, et al. *Helicobacter pylori* infection and chronic gastric acid hyposecretion. Gastroenterology 1997;113:15–24.
52. Blaser MJ, Chen Y, Reibman J. Does *Helicobacter pylori* protect against asthma and allergy? Gut 2008; 57:561–567.
53. Blaser MJ. Missing microbes: how the overuse of antibiotics is fueling our modern plagues. 1st ed. New York: Henry Holt & Co., LLC, 2014.
54. Oertli M, Sundquist M, Hitzler I, et al. DC-derived IL-18 drives Treg differentiation, murine *Helicobacter pylori*-specific immune tolerance, and asthma protection. J Clin Invest 2012;122:1082–1096.
55. Castano-Rodriguez N, Kaakoush NO, Lee WS, et al. Dual role of *Helicobacter* and *Campylobacter* species in IBD: a systematic review and meta-analysis. Gut 2017;66: 235–249.
56. Lender N, Talley NJ, Enck P, et al. Review article: associations between *Helicobacter pylori* and obesity–an ecological study. Aliment Pharmacol Ther 2014; 40:24–31.
57. Wang Y, Bi Y, Zhang L, et al. Is *Helicobacter pylori* infection associated with asthma risk? A meta-analysis based on 770 cases and 785 controls. Int J Med Sci 2012;9:603–610.
58. Howson CP, Hiyama T, Wynder EL. The decline in gastric cancer: epidemiology of an unplanned triumph. Epidemiol Rev 1986;8:1–27.

59. Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. Semin Radiat Oncol 2013;23:3–9.
60. McLean MH, El-Omar EM. Genetics of gastric cancer. Nat Rev Gastroenterol Hepatol 2014;11:664–674.
61. Wang MY, Liu XF, Gao XZ. *Helicobacter pylori* virulence factors in development of gastric carcinoma. Future Microbiol 2015;10:1505–1516.
62. Gaddy JA, Radin JN, Loh JT, et al. High dietary salt intake exacerbates Helicobacter pylori-induced gastric carcinogenesis. Infect Immun 2013;81: 2258–2267.
63. Lertpiriyapong K, Whary MT, Muthupalani S, et al. Gastric colonisation with a restricted commensal microbiota replicates the promotion of neoplastic lesions by diverse intestinal microbiota in the Helicobacter pylori INS-GAS mouse model of gastric carcinogenesis. Gut 2014;63:54–63.
64. Figueiredo C, Machado JC, Pharoah P, et al. *Helicobacter pylori* and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. J Natl Cancer Inst 2002; 94:1680–1687.
65. Tsukamoto T, Toyoda T, Mizoshita T, et al. *Helicobacter pylori* infection and gastric carcinogenesis in rodent models. Semin Immunopathol 2013;35:177–190.
66. Krueger S, Roessner A, Kuester D. Murine models of *H. pylori*-induced gastritis and gastric adenocarcinoma. Pathol Res Pract 2011;207:599–607.
67. Eguchi H, Carpentier S, Kim SS, et al. $P27^{kip1}$ regulates the apoptotic response of gastric epithelial cells to *Helicobacter pylori*. Gut 2004;53:797–804.
68. Eguchi H, Herschenhous N, Kuzushita N, et al. *Helicobacter pylori* increases proteasome-mediated degradation of p27(kip1) in gastric epithelial cells. Cancer Res 2003;63:4739–4746.
69. Kuzushita N, Rogers AB, Monti NA, et al. $p27^{kip1}$ deficiency confers susceptibility to gastric carcinogenesis in *Helicobacter pylori*-infected mice. Gastroenterology 2005;129:1544–1556.
70. Zhang S, Kim W, Pham TT, et al. Native and bone marrow-derived cell mosaicism in gastric carcinoma in *H. pylori*-infected p27-deficient mice. Oncotarget 2016; 7:69136–69148.
71. Zhang S, Lee DS, Morrissey R, et al. Early or late antibiotic intervention prevents *Helicobacter pylori*-induced gastric cancer in a mouse model. Cancer Lett 2014; 355:106–112.

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Conflicts of interest
The author discloses no conflicts.