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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