Helicobacter pylori and Gastric Cancer: A New Paradigm for Inflammation-Associated Epithelial Cancers

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Although gastric cancer has been investigated for centuries, the association with *Helicobacter pylori* infection has been recognized for only the past few decades. Although the disease has been declining in most industrialized countries, it remains the second most common cause of cancer death worldwide and is, in theory, a largely preventable disease. We have gained many new insights and advances from studies of *Helicobacter*-infected mouse models. These models corroborate findings in human patients, in whom disease outcome is largely determined by the expression of host proinflammatory cytokines. Studies of the cellular origins of cancer in the *Helicobacter*-infected mouse model has led to the surprising insight that gastric cancer may originate from circulating bone marrow-derived stem cells (BMDC) and not from resident tissue stem cells as previously believed. It is likely that this new BMDC paradigm of epithelial cancer will prove useful in future investigations of gastrointestinal metaplasia and gastrointestinal cancers associated with chronic inflammation.

I. History of Gastric Cancer and Discovery of *Helicobacter pylori*

Stomach cancer has been recognized for several millennia. As early as 400 BC, Hippocrates first described cancer (which he named *karkinos* or *karkinoma*). Among his first descriptions was that of a patient with associated *melaina* or black vomiting,[1] who likely had cancer of the stomach. In 1867, Waldeyer began intensive histologic investigations of mammary and gastric carcinoma. He believed that microscopic analysis strongly suggested that gastric cancer had its origins in the "pepsin and mucous glands" of the stomach, which led to his formulation of the *epithelial theory of cancer*. This theory, which states that all carcinomas are derived originally from epithelial cells, eventually became the central dogma of cancer biology, despite numerous competing theories over the years. Waldeyer was firmly convinced that "the development of cancer cells always originates in the preexisting, genuine epithelia of the organism. . . ."[1]

In the early 20th century, interest grew in determining the cause of cancer. In 1913, Johannes Andreas Grib Fibiger developed the first rodent model of stomach cancer, which suggested a link between chronic irritation and cancer.[2] By 1940, gastric cancer was recognized as the second leading cause of cancer death in the United States, and attention turned to epidemiologic associations. Studies of migrant populations suggested that stomach cancer was associated with an environmental exposure occurring early in life.[3] In the early 1970s, Correa formulated a multistep model of gastric cancer, which postulated a temporal sequence of pathologic changes that led from chronic (type B) gastritis to atrophic gastritis, intestinal metaplasia, and dysplasia and the eventual development of gastric cancer[4] (Figure 1). Based on epidemiologic studies of dietary histories, the first step in the Correa pathway—the development of gastric inflammation—was believed to be initiated by a diet rich in salt and nitrates/nitrites as well as deficiencies in fresh fruits and vegetables. Dietary factors and continued effects of chronic inflammation were felt to be responsible for the orderly progression from gastritis to atrophy, metaplasia, dysplasia, and, in a subset of patients, carcinoma.

Our understanding of gastric cancer underwent a marked shift with the rediscovery of *Helicobacter pylori*. Human gastric bacteria were first recognized in the early 19th century, but their identity and clinical significance were not appreciated until they were isolated and cultured from a human gastric biopsy by Marshall and Warren in 1982.[5] Originally named *Campylobacter pyloridis*, the organism was shown to be a spiral-shaped, gram-negative, microaerophilic rod strongly associated with gastritis and peptic ulcer disease. It was recognized as a separate genus and renamed *Helicobacter pylori* in 1989. A causal relationship between *H pylori* and gastric cancer was first postulated by Marshall and Warren in 1983.[5] The firm association between *H pylori* and gastric

Abbreviation used in this paper: BMDC, bone marrow-derived stem cells.

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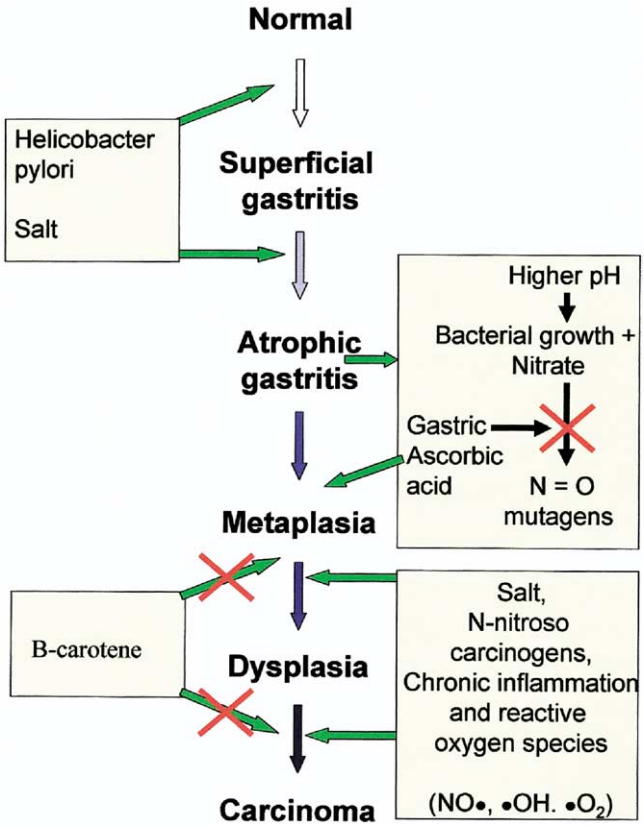

Figure 1. Multistep model for the progression of gastric cancer (adapted from Fox JG, Wang TC. N Engl J Med 2001;345:829–832).

cancer has been demonstrated by a number of case control studies, which have retrospectively examined the *Helicobacter* infection status of gastric cancer patients.[6–11] This association has begun to approach that shown for smoking and lung cancer, and *H pylori* was classified as a definite (type I) carcinogen in 1994 by the IARC, a branch of the World Health Organization.[12] Although it is clear that most infected patients will remain asymptomatic and will not go on to develop peptic ulcer disease or gastric cancer from their infection, the causal link between *H pylori* and gastric cancer is now quite clear and includes not only epidemiologic associations but also animal model and interventional data (Table 1).

II. Histologic Classification and Recent Epidemiology

Gastric adenocarcinoma is generally subdivided into 2 main histologic types based on a classification scheme devised by Lauren in 1965. The Lauren classification recognizes 2 categories: the intestinal (well-differentiated) type and the diffuse type. Intestinal type cancer is more common, tends to occur in older patients, and is more closely linked to environmental and dietary factors. Histologically, it is characterized by gland-like tubular structures mimicking intestinal glands. In contrast, the diffuse type of gastric cancer is less common, affects younger patients, and carries a worse prognosis. Occasional cases of diffuse-type gastric cancer may be primarily genetic in origin, such as familiar diffuse gastric cancers associated with mutations in the E-cadherin gene.[13] The diffuse type of cancer is more poorly differentiated, lacks glandular structure, and tends to be more aggressive. Recent studies indicate that both intestinal and diffuse types of gastric cancer are strongly associated with *H pylori* infection.[9] Nevertheless, over the last 60 years, there has been a marked decline in the incidence of the intestinal-type gastric cancer but not diffuse type. The decline in intestinal-type cancer is largely responsible for the overall decline in the incidence of gastric carcinoma in most industrialized nations and can be attributed to (at least in part) the decline in *H pylori* prevalence in developed nations. In general, *H pylori* infection is acquired early in life through a fecal-oral or oral-oral mode of transmission, and many years of infection are required for cancer development. In the United States, the rate of new *H pylori* infection is declining rapidly because of improved hygiene (cleaner water, sanitation, and improved food storage), resulting in a birth-cohort effect of which older generations are more likely to be infected with *H pylori* relative to younger patients and are at a higher risk for gastric cancer in their later decades of life. Gastric adenocarcinoma is currently the 14th leading cause of death in the world. Because of the aging of the world's population, it has been predicted by some that gastric cancer incidence will rise to become the 8th leading cause of death in the world by the year 2010.[14] Over the next century however, the prevalence of *H pylori* is expected to plummet further, resulting in additional declines in gastric cancer incidence rates in industrialized nations because the new "aging" population has lower infection rates and is therefore at lower

Table 1. Evidence Supporting *H pylori* as a Causal Factor in Gastric Cancer

1. Epidemiologic data indicate a geographic association between prevalence of *H pylori* and prevalence of gastric cancer.
2. Epidemiologic trends show declining incidence of gastric cancer in countries with falling rates of *H pylori* infection.
3. Inoculation of *H pylori* into (2) humans resulted in chronic active gastritis, an early precursor lesion for gastric cancer.
4. Evidence that *Helicobacter* infection in animal models results in progression to atrophy and metaplasia, which are accepted as preneoplastic lesions.
5. Animal models, including ferrets, gerbils, and mice, show that gastric *Helicobacter* infection can lead to experimentally induced gastric cancer.
6. Eradication of *Helicobacter* in animal models and humans appears to lower the risk of developing gastric cancer.