Disappearing Microbiota: *Helicobacter pylori* Protection against Esophageal Adenocarcinoma

Martin J. Blaser

Once rare, esophageal adenocarcinoma (EAC) is the most rapidly increasing malignancy in many developed countries, such as the United States, United Kingdom, Australia, and Norway, and now is surpassing esophageal squamous cell carcinomas in certain populations (1, 2). EAC has very specific clinical and epidemiologic characteristics: It involves the distal but not proximal esophagus, preferentially affects males and people of higher socioeconomic status, and unlike esophageal squamous cell carcinoma, is not related to drinking alcohol or smoking (3). The rapid increase in EAC is not an artifact of surveillance or classification (4); it is real and frightening. A smaller increase in adenocarcinomas involving the gastric cardia is probably related to the increase in EAC (5); however, this relationship is unclear because the origin of cardia tumors, which frequently are advanced when diagnosed, could be esophageal or gastric.

In recent years, it has become clear that EAC is a consequence of long-term gastroesophageal reflux disease, an inflammatory condition of the distal esophagus (6), often through progression to Barrett's esophagus, a metaplastic malady that may become dysplastic (7, 8). The three progressive and related conditions—gastroesophageal reflux disease, Barrett's esophagus, and EAC—have been increasing over the past several decades in developed countries; their substantial increase is a late 20th century phenomenon; and they were essentially unknown before 1900 (9).

Numerous hypotheses have been raised to explain the origins of these maladies, which are not obvious (10). Nevertheless, reports going back more than 10 years have linked the rising tide of gastroesophageal reflux disease and its consequences with *Helicobacter* (*H.*) *pylori* (gram-negative bacteria that colonize the human stomach), especially the *cagA*$^+$ variety, but inversely (8, 11, 12). This inverse association raised an intriguing question: How could the lack of an organism predispose to a cancer?

Understanding the relationship between *H. pylori* and humans is necessary to begin addressing this question. Fortunately, much has been learned about *H. pylori* since its discovery and isolation in pure culture in 1982. It now is clear that *H. pylori* has colonized the human stomach probably since the beginning of the human species and certainly before prehistoric migrations out of Africa over 58,000 years ago (13). Acquired in young childhood, *H. pylori* persists in the stomach essentially for life unless eradicated by antibiotics (14, 15). *H. pylori* in humans was nearly omnipresent until recently. Clone libraries of 16S rRNA genes show that *H. pylori* is the most numerous organism in the human stomach (16), in contrast with most other human niches where no single organism dominates persistently. *H. pylori* strains can be subdivided on the basis of *cagA*, a marker gene for the presence of the *cag* island, a chromosomal region that encodes a type IV secretion system that injects *H. pylori* constituents (including the *cagA* protein) into human gastric mucosal epithelial cells (17, 18). In this and many other characteristics, *cagA*$^+$ *H. pylori* strains are more interactive with human hosts than are *cagA*-negative strains (15, 17–19). On the basis of history, numbers, and intimacy, *H. pylori* can be considered as having been the dominant microbe colonizing the human stomach.

In developed countries, however, *H. pylori* has been progressively disappearing over the course of the 20th century (20-22). This secular trend allows examination of the consequences of the presence or absence of *H. pylori* (Fig. 1). Numerous studies have made it clear that *H. pylori*–positive and *H. pylori*–negative persons have substantial differences in gastric physiology and in tissue and immune responses (15). It also has become clear that the presence of *H. pylori* increases the risks for peptic ulcer disease and noncardia gastric cancer (NCGC; NCGC is used synonymously with the term "gastric cancer" throughout this Perspective) and that removing *H. pylori* with antibiotics reduces these risks (23, 24). Therefore, there is biological cost to humans to carry *H. pylori*, the removal of which may improve public health in some areas of the world (25). Not surprisingly, the *cagA*$^+$ strains, which are more interactive, are associated with a greater risk of these diseases (26, 27). Nevertheless, it is important to examine whether there are disease contexts in which persistent gastric carriage of *H. pylori* could confer benefits.

In this issue of *Cancer Prevention Research*, Islami and Kamangar have deepened our understanding of one such potential benefit (28). To better characterize the relationship between *H. pylori* and esophageal cancers, they did a meta-analysis of 19 studies involving over 1,700 cases and 5,600 controls. Their careful studies confirm and extend the results of a prior meta-analysis that examined a group of publications that only partially overlapped theirs (29). The analysis of Islami and Kamangar led to four major observations. First, there is an inverse relationship between the presence of *H. pylori* and EAC. Second, this phenomenon was present in widely dispersed geographic regions. Third, the effect appears to be essentially exclusively related to *cagA*$^+$ strains. Last, there was no relationship of *H. pylori* with esophageal squamous cell carcinomas. Based on a variety of different definitions and analyses, the results showed

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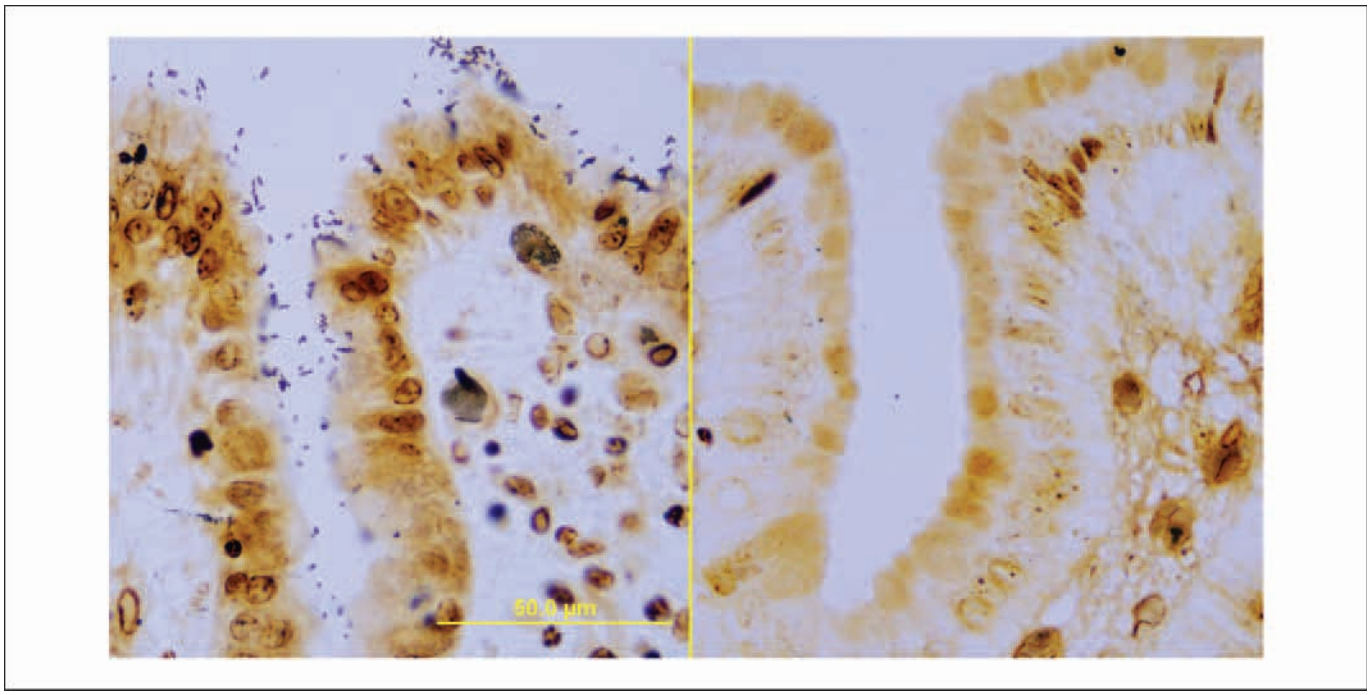

Fig. 1. Steiner stain of gastric antral biopsies from an *H. pylori*–positive patient (*left*) and an *H. pylori*–negative patient (*right*; photomicrographs courtesy of Zhiheng Pei, M.D., Ph.D.). *H pylori* positivity is associated with risk of gastric cancer, whereas *H. pylori* negativity is associated with risk of EAC. The presence of *H. pylori* (*left*) is indicated by the dark curved bacilli in the mucus layer adjacent to the epithelial cell surfaces. The *H. pylori*–positive biopsy shows deeper staining of the epithelial cells, indicating tissue reactivity, and the lamina propria shows increased mononuclear cell numbers (compared with the *H. pylori*–negative biopsy). The biopsies were formalin fixed and paraffin embedded, and both images have the same magnification (*bar,* 50 µm).

remarkable consistency in indicating that the absence of *H. pylori* is at least a marker of risk for EAC and may be partially responsible for these cancers. The specificity of the relationships (EAC but not esophageal squamous cell carcinoma; *cagA*$^+$ but not *cagA*-negative) provides further support for a causal relationship. These analyses tie the secular trend of the disappearance of *H. pylori* with that of the increase in incidence of EAC (Fig. 2) in a causal (rather than coincidental) relationship. Because *H. pylori* is a risk factor for NCGC (11), it is not surprising that the disappearance of an etiologic agent (*H. pylori*; refs. 20–22) has been followed by the gradual diminution in incidence of its sequelum (NCGC; ref. 30). The analyses of Islami and Kamangar provide evidence that just as *H. pylori* disappearance is reducing NCGC incidence, it may be fueling the increase of EAC incidence, linking the two known and opposing secular trends.

As exciting as these results are, they raise important questions needing to be addressed. For example, is the absence of *H. pylori* just a marker for another causal phenomenon? Why do only some *H. pylori*–negative persons develop EAC? Why does EAC develop sometimes in *H. pylori*–positive persons? The path toward answering such questions lies in both prospective and mechanistic studies.

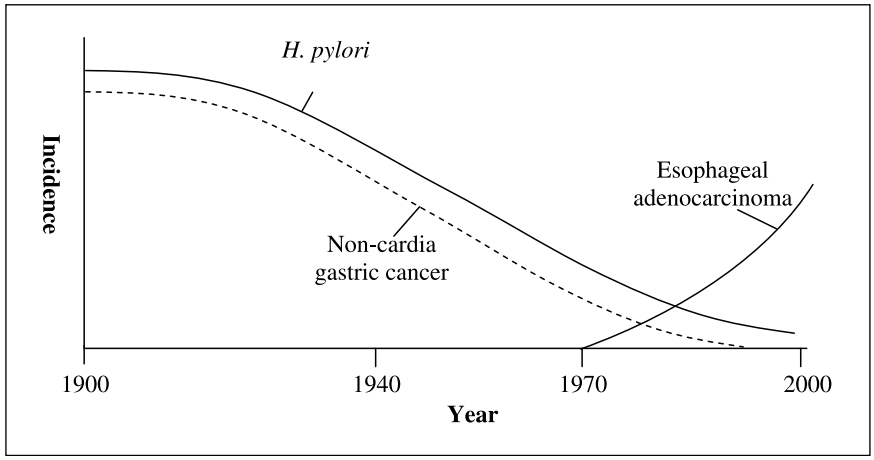

Fig. 2. Relative incidences of gastric *H. pylori* colonization, NCGC, and EAC during the 20th century in the United States and other now-developed countries. After a relatively short latency, the incidence of NCGC began to decrease in parallel with the declining incidence of *H. pylori*. However, the increase in EAC did not begin until many decades after both *H. pylori* and noncardia gastric cancer had begun to decrease.

Several mechanisms could be relevant to the potential protective effect of *H. pylori* gastric colonization against EAC and its precursor lesions. First, gastric acidity begins to diminish after decades of carriage of *H. pylori* and the gradual age-related development of atrophic gastritis (15, 31). Therefore, the *H. pylori*–positive stomach produces a lower acid load and less damage to the distal esophagus when reflux arises. Second, a role of *H. pylori* in regulating gastric secretion of leptin could affect the propensity for gastroesophageal reflux disease and sequelae because leptin would be present in the refluxate and the esophagus possesses leptin receptors (32). A similar mechanism could also be at play for gastric ghrelin (33). Third, *H. pylori*, by its effects on the gastric T-cell compartments (34, 35), may skew immune and cytokine responses in ways that affect the adjacent esophageal compartment. Fourth, the presence of *H. pylori* may affect the other constituent organisms within the gastric (16) and esophageal (36) microbiota, and such effects in the lumen may affect microbiota interactions with tissues (37). Last, effects on esophageal-gastric motility, including those mediated by vagal innervation, may also influence *H. pylori* effects in the esophagus (38). At present, there is insufficient direct evidence for determinant roles of any of these proposed mechanisms, making them critical directions for future research.

Another interesting question is illustrated in Fig. 2. NCGC incidence began to decrease in the early 20th century, and we now know that *H. pylori* incidence fell as well; both trends began well before the discovery of *H. pylori* (30) and physician attempts to eradicate it (23, 24). However, the increase in EAC did not begin until decades after gastric cancer rates began to decrease—*Why?*

Because the relationship of *H. pylori* with NCGC is direct and with EAC is inverse, it is necessary to consider several hypotheses to explain the timing dichotomy between decreasing gastric cancer rates and increasing EAC rates. First hypothesis: The age of acquiring a substantial *H. pylori*–associated risk differs between NCGC and EAC. *H. pylori*–associated risk may begin early (before age 10 years) for NCGC and later (after the age of 50 years) for EAC. Studies of migrants to the United States conducted 50 years ago support the critical importance of early age in acquiring risk for gastric cancer (39); as yet, there is no direct such evidence with regard to EAC. Second hypothesis: The risk of EAC requires a cofactor (in addition to lack of *cagA*$^+$ *H. pylori*) that has been acquired in recent years. Possible candidates for a cofactor acquired after 1950 include antibiotic use that not only affected *H. pylori* but also altered the other microbiota (37, 40); iron fortification of foods, especially bread and cereals (ref. 41; beginning in the 1940s), because high iron levels increase risk of EAC and other cancers (42); and the relatively recent explosive rise in obesity (43, 44). The differing time courses of the rates of *H. pylori* disappearance in the West and in East Asia may provide clues about the candidate cofactors for this hypothesis. Third hypothesis: A change in the microecology of the stomach affects the esophagus. *H. pylori* may suppress competing microbiota, which bloom in its absence. Although we generally consider individuals to be *H. pylori*–positive or *H. pylori*–negative—an "either/or" proposition—the reality is more complex. *H. pylori*–positive persons may harbor several different *H. pylori* strains, including *cagA*$^+$ or *cagA*-negative ones (45). There is evidence that *cagA*$^+$ strains are declining more rapidly than are *cagA*-negative strains in developed country populations (21). It is possible that the particular balance of *cagA*$^+$ and *cagA*-negative strains in a host's stomach is critical to the types of pathophysiologic interactions that occur (46). Furthermore, *H. pylori* can be detected by PCR in persons who are negative for *H. pylori* by all conventional methods (including histologic examination, specific culture, and serologic responses; refs. 16, 47). We do not fully understand this phenomenon of low-level colonization and so do not have the tools to link it either to disease or to disease protection. Our knowledge of overall gastric microecology is still sparse (16). Fourth hypothesis: A change in the microecology of the esophagus could induce esophageal inflammation. It only recently has become clear that the distal esophagus has residential microbiota (36); just as the stomach once was considered "sterile," the idea of residential esophageal microbiota had not been considered (until recently). Preliminary studies suggest that changes in esophageal microecology occur before premalignant changes (48). In addition to having changes secondary to the absence of *H. pylori*, microecology may have independent differences reflecting other factors as well. This is an area needing much greater examination.

In 1998, I began using the term *acagia* to describe the status of a person with no evidence for the gastric carriage of a *cagA*$^+$ *H. pylori* strain and I hypothesized that *acagia* may predispose individuals to the risk of esophageal diseases, including gastroesophageal reflux disease, Barrett's esophagus, and EAC (49). A decade later, we now have a sufficient number of relevant observations to address this hypothesis, and the analysis by Islami and Kamangar (28) provides strong supporting evidence. In light of the Bradford Hill (50) criteria for understanding questions of causality, the consistency, coherence, secular trends, and biological plausibility of *H. pylori* protecting against esophageal carcinogenesis all point toward a true relationship.

However, we are just at the beginning of the story. As medical scientists, we must learn to understand *H. pylori* as a human organism that evolved in the gastric niche and whose elimination must have consequences (46, 49). *H. pylori* increases risk for one major form of cancer (NCGC) and yet appears to protect against a less common but rapidly increasing malignancy (EAC), and inversely correlates with (and so may protect against) other important diseases (e.g., allergic asthma, rhinitis, and atopy) that have been increasing (especially in children) as *H. pylori* has been disappearing (22). We must learn how to optimize public health not only where *H. pylori* and NCGC are too prevalent but also where the disappearance of *H. pylori* is possibly leading to the emergence of diseases that were not common previously. The solutions to these divergent problems likely will differ. Elimination of *H. pylori* is beneficial for elderly persons who already have had NCGC or have gastric premalignant changes (24). However, finding the optimal age (and population) for *H. pylori* eradication in light of the potential benefits of colonization in earlier life will require a balanced strategy. We are just beginning to understand the critical factors involved with *H. pylori* or other microbiota that drive the risk of or protection from disease (46).

H. pylori colonization is an exciting and critically important area of human biology not only because of the medical significance of *H. pylori* per se but also as a model of changing

microbiota (37) in body compartments barely yet assessed molecularly for their microbial contents. Microbial species and their gene content, as well as transcripts expressed and the proteins produced, will all likely affect the ultimate oncogenic drama. Stay tuned.

Disclosure of Potential Conflicts of Interest

Martin J. Blaser is one of the codiscoverers of *cagA* based on studies conducted at Vanderbilt University. He could potentially receive royalties based on commercialization of his inventions; no applications of this technology are currently licensed.

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