Helicobacter pylori Infection: Mainly Foe but Also Friend?

Olof Nyrén, William J. Blot

The discovery of *Helicobacter pylori* revolutionized peptic ulcer treatment and justifiably led to the awarding of last year's Nobel Prize to Robin Warren and Barry Marshall. *H. pylori* eradication therapy is associated with three- to fivefold higher success rates in preventing duodenal and gastric ulcer recurrences compared with placebo and is superior to pharmacologic acid suppression in duodenal ulcer healing *(1)*. Consequently, elimination of *H. pylori* infection in peptic ulcer patients is by no means controversial.

During the past 15 years, numerous observational studies of various designs have also demonstrated a positive association between the presence of anti–*H. pylori* antibodies and the risk of stomach cancer. The literature on this association has become so extensive that the first review of published meta-analyses is now available *(2)*. Each of the six meta-analyses included in that review showed that serologic evidence of *H. pylori* infection is associated with increased stomach cancer risk, with pooled odds ratios (ORs) of stomach cancer that ranged from 1.92 to 2.56 and with little heterogeneity. In other words, individuals who carry antibodies to *H. pylori* purportedly have a two to three times higher risk of stomach cancer than people who do not carry such antibodies. Some of the more recent studies, however, have reported a stronger association when the outcome was restricted to noncardia gastric cancer and when measures were taken to deal with the fairly frequent occurrence of "false-negative" tests for *H. pylori* antibodies resulting from the infection's tendency to disappear from the precancerous or cancerous stomach without leaving behind any measurable antibodies.

One of the reviewed meta-analyses also indicated that the risk of stomach cancer varies according to the type of *H. pylori* strain a person is infected with *(3)*. Approximately 60% of all *H. pylori* strains isolated in Western countries have the cagA gene, which is located in a variable 40-kb locus (termed the cag pathogenecity island). Strains that carry this locus (cagA-positive strains) are particularly virulent and have consistently been found to be more strongly linked to stomach cancer than cagA-negative strains. It has been shown that some patients with noncardia stomach cancer have antibodies to the CagA protein but no *H. pylori* antibodies according to conventional immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA) serologic tests based on mixed surface antigens from whole cell preparations and that the use of a broader criterion of *H. pylori* seropositivity that involves evidence of either mixed surface antibodies or antibodies to CagA dramatically increased the strength of the observed association between the infection and noncardia gastric cancer in case–control study settings *(4)*. Antibodies against CagA seem to persist in serum for longer times after *H. pylori* eradication than antibodies to the mixed surface antigens captured by conventional IgG ELISA *(5)* and are thus more likely to signal burned-out infections from the past. The stronger association with stomach cancer typically observed when seropositivity to CagA is used as marker of *H. pylori* infection could therefore be explained not only by the higher virulence of CagA-positive strains but also conceivably by a reduction in the assumed differential exposure misclassification that is due to the gradual suppression and/or loss of the infection with the increasingly inhospitable precancerous intragastric environment. This presumed misclassification is also one strong reason why prospective cohort studies with sera collected well before clinical development of stomach cancer have been considered preferable to case–control studies that involve serotesting of case subjects with already prevalent cancers. Although the summary effect estimate in one meta-analysis that was restricted to prospective studies *(6)* did not differ materially from those in meta-analyses that included case–control studies, there is some evidence that the *H. pylori*–cancer association strengthens with increasing time between serotesting and cancer diagnosis *(7)*.

In this issue of the *Journal*, Kamangar et al. *(8)* provide yet another important piece of information on the *H. pylori*–cancer link from a carefully conducted and analyzed prospective cohort study. In this study, the authors distinguished—correctly, as it turns out—between cardia and noncardia gastric cancers and analyzed these two outcomes separately. They also used the broader criterion for *H. pylori* seropositivity (i.e., a positive test for antibodies to mixed surface antigens only, to CagA only, or both) to classify every subject with respect to their *H. pylori* serostatus and found a strong positive association between *H. pylori* seropositivity and the risk of noncardia cancer (OR = 7.9). A substantial positive association was evident also when the serologic pattern indicated a CagA-negative infection (i.e., a positive test for antibodies to mixed surface antigens but not to CagA). The positive association pertained to both major histologic types of noncardia stomach cancer and was essentially independent of age at diagnosis (although a non–statistically significant trend toward higher relative risks among younger patients was noted).

Although these findings, on the whole, fit nicely with current dogma, some details differ. First, Kamangar et al. found no evidence of higher relative risks with increasing time between serotesting and cancer diagnosis (in fact the trend was in the opposite direction), arguing against the importance of the hypothesized preferential *H. pylori* disappearance in cases with developing cancers. However, the power of their study to evaluate differential effects

Affiliations of authors: Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (ON); International Epidemiology Institute, Rockville, MD (WJB); Department of Medicine, Vanderbilt University Medical Center, Nashville, TN (WJB).

Correspondence to: Olof Nyrén, MD, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, SE-171 77 Stockholm, Sweden (e-mail: olof.nyren@ki.se).

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with respect to time since serotesting was limited and chance could have played a role, as indicated by the wide confidence intervals for the relative risk estimates for each time period considered.

Second, the most important deviation from the current literature is their finding of a strong inverse association between *H. pylori* seropositivity and the risk of cancer of the gastric cardia. Although only 61 cardia cancers were studied, Kamangar et al. found that *H. pylori* seropositivity was associated with a statistically significant threefold lower risk of cardia cancer. A statistically significant inverse association between *H. pylori* seropositivity and the risk of cardia cancer has been reported only once before *(9)*; the majority of studies in Western populations have been unable to confirm an association in any direction *(7)*. By contrast, a growing and fairly consistent literature *(10–14)* has reported a markedly reduced risk of esophageal adenocarcinoma (up to fivefold) among individuals with serologic evidence of *H. pylori* infection. This inverse association, unlike that reported by Kamangar et al., was driven mainly by CagA-positive infections *(10,12)*.

Given the absence of a generally accepted definition of what constitutes cardia cancer, the apparent disagreement among the published studies with respect to the association between *H. pylori* seropositivity and the risk of cardia cancer might be explained by differences in site classifications. It is reasonable to assume that the cardia cancer category consists of a mixture of distal esophageal adenocarcinomas, genuine cardia cancers, and some subcardial gastric cancers. The definition of cardia cancer used by Kamangar et al. is pragmatic but differs from that used in most other studies in that it included all cancers that involved the cardia region, regardless of the location of the center of the tumor. Hence, large tumors in areas adjacent to the cardia region, such as those in the distal esophagus, were probably overrepresented compared to site classification that is based on the location of the tumor center. Given the increasing evidence that *H. pylori* infection is inversely related to esophageal adenocarcinoma, part of the explanation for the reduced risk of cardia cancers reported by Kamangar et al. could be the inclusion in their case series of cancers of the lower esophagus. It is unfortunate that Kamangar et al. did not investigate the risk of esophageal adenocarcinoma or, for that matter, of squamous cell esophageal carcinomas, which were positively associated with *H. pylori* seropositivity in a recent Swedish case–control study *(12)*. However, given the lack of anatomic and/or morphologic markers of cancers that arise in genuine cardia epithelium that render the site classification biologically relevant, the question of whether the inverse association pertains only to esophageal adenocarcinoma or to both esophageal and cardia adenocarcinoma remains academic. The important bottom-line message is that there may be cancers against which *H. pylori* infection might be protective.

Although the ultimate proof of causality is still missing, few would challenge the existence of a clear relationship between *H. pylori* infection and the increased risk of noncardia gastric cancer. Moreover, a growing number of randomized trials of *H. pylori* eradication have shown trends toward a reduced incidence of stomach cancer or indications of slowing progression of precancerous lesions after appropriate antibiotic treatment *(15–20)*, thus building our confidence in a causal inference. Hence, it has become increasingly difficult to remain indifferent to the possibility that we might have the means to eliminate a large proportion of all stomach cancers by using a relatively simple chemopreventive approach.

Because some opinion leaders *(21,22)* have voiced an eagerness to begin systematic eradication of all detected *H. pylori* infections with the sole purpose of preventing future stomach cancers, Kamangar et al. have a point when they caution against decisions that do not take the preventative potential of *H. pylori* into account. Clearly, unlike the positive *H. pylori*–noncardia gastric cancer relationship, the causality of the inverse *H. pylori*–cardia/esophageal adenocarcinoma association appears much less certain. The protective mechanisms remain conjectural because case–control data *(12)* suggest that atrophic gastritis, hypoacidity, and reduced occurrence of acid reflux may not be in the causal pathway. In addition, it cannot automatically be taken for granted that *H. pylori* eradication in adult life will affect esophageal/cardia adenocarcinoma risk. However, despite this uncertainty, it seems prudent to include the putative protective effect of *H. pylori* against adenocarcinoma of the esophagus or cardia in the equation when drawing up prevention plans for gastric cancer. A complete picture of the health outcomes potentially affected by *H. pylori* eradication is necessary to produce a fair balance sheet of the net effects. This balance sheet will undoubtedly vary between areas of the world where noncardia gastric cancer is common and esophageal junction adenocarcinoma is rare, such as in parts of China, and areas where rates of gastric cardia cancer and esophageal adenocarcinoma now are much greater than the rates of distal gastric cancer, such as in a growing number of Western nations. In the former situation, the number of stomach cancers averted may far exceed the number of esophageal cancers induced by *H. pylori* eradication, while the opposite may hold true for the United States and most parts of Europe if the infection does indeed help prevent cardia or esophageal cancers.

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