cagA-seropositive strains of *Helicobacter pylori* increase the risk for gastric cancer more than the presence of *H pylori* alone

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ARTICLE

Huang JQ, Zheng GF, Sumanac K, Irvine EJ, Hunt RH. Meta-analysis of the relationship between cagA seropositivity and gastric cancer. *Gastroenterology* 2003;125:1636-44.

ARTICLE SUMMARY

Huang et al have performed a meta-analysis to determine the relationship between cagA seropositivity (by serology and polymerase chain reaction) and the risk of gastric cancer. An extensive review of the literature identified no previous systematic overviews. The authors identified 16 studies involving 2284 cases and 2770 controls. The overall prevalence of *Helicobacter pylori* was 77.7% in cases and 63.1% in controls. Tests for cagA were positive in 62.8% of cases and 37.5% of controls. Thus, *H pylori* and cagA seropositivity significantly increased the risk for gastric cancer, by 2.28 (95% CI 1.71 to 3.05) and 2.87 (95% CI 1.95 to 4.22), respectively. In patients with *H pylori*, those who were infected by a cagA-positive strain had a slightly higher risk of gastric cancer, with an odds ratio of 1.64 (95% CI 1.21 to 2.24). The authors also found that patients infected with *H pylori* with or without cagA seropositivity had an increased risk of noncardia gastric cancer, but not of cancer of the gastric cardia. They concluded that cagA-positive strains confer a greater risk of gastric cancer than does *H pylori* infection alone.

COMMENTARY

This study is to be applauded for its high methodological quality and for the fact that it provides interesting epidemiological data about the relationship between cagA seropositivity and gastric cancer. In a meta-analysis, the inclusion criteria for studies affect the overall results. Thus, a proper study protocol needs to be followed, the process of study selection needs to be well defined and the studies themselves should be described in detail. Validity criteria were used to evaluate the quality of the studies, but the results of this evaluation were unclear from Table 1.

The demographic characteristics of both cases and controls included in each study influence the overall results. Several questions arise from this meta-analysis. For example, how were cases identified? Was there any systematic bias in collecting the cases of gastric cancer, such as a regional referral bias? Were there more rigorous attempts to identify *H pylori* in cases because the investigators suspected an association between the infection and gastric cancer (1)? The authors themselves suggested that one study, by Chow, could have been excluded because 66% of the patients had esophageal or cardia cancer. Did the other studies also include patients with esophageal cancer?

The authors list the many different populations that were used as controls in the various studies. They must have considered a priori what they would accept as reasonable control groups when designing their meta-analysis protocol. Because all analyses depend on differences in the prevalence of either *H pylori* or cagA seropositivity between cases and controls, the characteristics of the control population are of crucial importance. The previous meta-analysis by the same authors (2) revealed a difference in risk between population- and hospital-based controls, but this distinction was not made in the current paper.

Despite the heterogeneous populations included in the meta-analysis, this work provided findings consistent with their earlier paper (2), in that there was a higher prevalence of *H pylori* in patients with gastric cancer compared with controls, and that there was no association between *H pylori* and cancer of the gastric cardia. Their previous meta-analysis (2) showed that there was a difference in the prevalence of *H pylori* between patients with early and advanced gastric cancer, so it is surprising that this association was not explored in this analysis. This study makes the additional finding that patients infected with cagA-positive strains of *H pylori* had a slightly greater risk of gastric cancer than patients infected with cagA-negative strains. An interesting finding was that a mean of 37% (range 0% to 75%) of patients with negative *H pylori* serology had positive cagA serology, implying that patients had previously been infected with *H pylori*. Why would the immune response be more robust for cagA than for *H pylori* antibodies? Perhaps cagA testing, where available, might be useful to verify infection in high-risk patients who test negative for *H pylori* (3).

This meta-analysis has demonstrated an epidemiological association between *cagA* strains and noncardia gastric cancer. This does not prove that the *cagA*-positive *H pylori* strains are more virulent, nor does it prove causation. As is often the case with meta-analyses, these results raise further questions about the clinical applicability of the data. The authors suggested that evaluating *cagA* status might help to identify populations at greatest risk for gastric cancer, but they did not discuss this further. From a practical perspective, the overall risk of developing gastric cancer in *H pylori*-infected individuals is very small (4), and there is some evidence that *H pylori* eradication might reduce this risk (5).

A randomized, placebo-controlled, population-based, primary prevention study has recently been reported from China (6). In this study, 1630 healthy subjects were randomized to *H pylori* eradication or placebo, then offered follow-up gastroscopy five years later. Of their subjects, 988 did not exhibit gastric atrophy, intestinal metaplasia or gastric dysplasia on study entry. Therefore, the majority of their subjects were at a relatively low baseline risk of gastric cancer. The authors discovered only 18 gastric cancers during a total of 7.5 years of follow-up, with no significant benefit from *H pylori* eradication. They did find, however, that, of patients without precancerous gastric mucosal changes, gastric cancer did not develop in any patient given *H pylori* eradication treatment, but that six of the patients given placebo developed cancer ($P=0.02$). While the numbers were small, this study provides the first prospective, randomized trial data that eradication of *H pylori* might prevent cancer in some patients. This study did not explore the role of *cagA*.

Some patients will undergo screening gastroscopy if they have a family history of gastric cancer or if they live in high-risk areas, such as Japan. Currently, if *H pylori* infection is found, the standard of care is to eradicate the organism, regardless of *cagA* status. Therefore, it seems that even if *cagA* testing were available, it is unlikely to be done routinely. While the data from this meta-analysis have academic value, the usefulness of this information in everyday practice remains to be determined.

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The authors respond:

We thank Dr Chiba for his comments on our paper. He has raised several issues regarding the selection of studies for analysis, identification of gastric cancer patients, reporting of study results, handling of heterogeneity in control groups and the practical value of recommending testing for *cagA* to identify patients at high risk for gastric cancer.

Firstly, he questioned whether a proper study protocol had been followed. This was clearly detailed in the Methods section and included the literature search, the definition of eligibility criteria, methods for identifying primary studies, assessment of study quality, data extraction and statistical analyses. We also reported how studies were selected, in the first paragraph of the Results section, where it was deemed most appropriate. We consider his suggestion that we provide detailed information on included studies is neither practical nor necessary, given the space limitations for articles in *Gastroenterology* and that a strict study protocol had been followed to select and evaluate studies.

He also questioned how cases were selected and whether there was any systematic bias in identifying cases and in determining *Helicobacter pylori* status of the cases. During the process of selecting primary studies, the methodology used by original investigators to identify cases and controls was considered as one important element of study quality, which was assessed carefully and independently by two reviewers according to guidelines for reading case-control studies proposed by Lichtenstein et al (1). All patients with gastric cancer were required to have histological confirmation. In order to increase the accuracy of detecting *H pylori* infection, we also specifically defined that all cases and controls had undergone serologic testing. There was no evidence to suggest that the original investigators used differing methods to search for *H pylori* infection in cases and controls.

Dr Chiba questioned whether patients with esophageal cancer could have been included in studies other than that by Chow and colleagues. In fact, no patients with esophageal cancer were included in the remaining studies.

We agree with Dr Chiba's comment on the potential impact of various types of controls on the results of analysis.

Dr Chiba suggests that patients with early gastric cancer should have been separated from those with advanced cancer. However, he must be aware that the stage of gastric cancer was not given in these studies and, hence, such subgroup analysis was not possible.

Lastly, Dr Chiba questioned the clinical value of testing for *cagA* strains of *H pylori* in the prevention of gastric cancer. At least three studies have shown unequivocally that current serological testing for *H pylori* infection, without testing for antibodies to *cagA*, is not sensitive enough to detect all patients who were previously infected (2-4). Therefore, relying on *H pylori* serology alone would miss about 37% of patients who had been infected previously. There is no evidence at this time to suggest that, in patients with antibodies to *cagA* but not to *H pylori*, eradication treatment could slow the progression of gastric atrophy and/or intestinal metaplasia. Nevertheless, anti-*Helicobacter* eradication treatment reduces gastric inflammation and intestinal metaplasia and could prevent the development of gastric cancer in a subgroup of patients (5). Thus,

patients who are seropositive for *cagA* but negative for *H pylori* may also benefit from eradication treatment. Moreover, our evidence shows that if *cagA* strains of *H pylori* are not sought, these patients would be classified as non-infected and, therefore, would not benefit from *H pylori* eradication and would remain at increased risk for gastric cancer (5,6).

Furthermore, it seems likely that serological testing for *H pylori* and *cagA*, as we suggest, could be combined with serological testing for gastrin-17 and pepsinogen-1 (7), which are markers for atrophic gastritis in the antrum and fundus. Such an approach should be evaluated, since it would be relatively simple and cheap to develop a combination serological test. This strategy could provide valuable information for risk

assessment with respect to the presence of *H pylori* infection and strain virulence and their impact on atrophic gastritis.

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