The evolving epidemiology of *Helicobacter pylori* infection and gastric cancer

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The relationship between *Helicobacter pylori* infection and the risk of gastric cancer has been well established in the last decade. Four meta-analyses have found that the infection increases the risk of noncardia gastric cancer by 2- to 6-fold compared with noninfected control populations. However, the role of *cagA* strains of *H pylori* in relation to gastric cancer has not been evaluated systematically. We undertook a meta-analysis of epidemiological studies examining the relationship between infection with *cagA*-positive strains of *H pylori* and the risk of gastric cancer, and found that patients who are seropositive for *cagA* strains of *H pylori* are at an increased risk for developing noncardia gastric cancer compared with those with *H pylori* infection alone. Therefore, searching for *cagA*-positive strains of *H pylori* may help identify populations at a greater risk for developing gastric cancer.

Key Words: *cagA* strains; Gastric cancer; *Helicobacter pylori*; Meta-analysis

L'épidémiologie évolutive de l'infection à *Helicobacter pylori* et du cancer gastrique

Le lien entre l'infection à *Helicobacter pylori* et le risque de cancer gastrique a bien été établi depuis dix ans. Quatre méta-analyses ont permis de découvrir que l'infection accroît le risque de cancer gastrique hors cardia de deux à six fois par rapport aux populations témoin non infectées. Cependant, le rôle des souches *cagA* de *H pylori* n'a pas été évalué de manière systématique dans le cancer gastrique. Nous avons entrepris une méta-analyse des études épidémiologiques sur le lien entre l'infection par des souches positives au *cagA* de *H pylori* et le risque de cancer gastrique, et nous avons découvert que les patients séropositifs aux souches *cagA* de *H pylori* présentent un risque plus élevé de développer un cancer gastrique hors cardia que ceux qui sont atteints d'une simple infection à *H pylori*. Par conséquent, la recherche des souches positives au *cagA* de *H pylori* peut contribuer à repérer les populations les plus vulnérables au cancer gastrique.

There is now overwhelming epidemiological evidence that populations infected with *Helicobacter pylori* have an increased risk of noncardiac gastric cancer when compared with uninfected control populations (1-4), and that the magnitude of the risk increases significantly with the duration of the infection. A recent meta-analysis of 12 nested case-control studies (4) within prospective cohorts reports that *H pylori* infection increases the risk of noncardiac gastric cancer six-fold in populations who have been infected for 10 years or longer before the diagnosis of gastric cancer, suggesting that the younger the acquisition of the infection, the higher the life-time risk for developing gastric cancer.

Although approximately half of the world's adult population is infected with *H pylori*, only a small minority (less than 3%) develop gastric cancer (5). Several factors, in concert, determine the final risk of gastric cancer. They include *H pylori* infection and virulent strains of the bacteria, environmental factors, host susceptibility and interactions between the host and the environmental factors, and the resultant patterns of chronic gastritis.

Recent research into the association between genetic factors and gastric cancer has provided promising results. The most consistent reports are the increased risk of gastric cancer

associated with interleukin-1 beta and N-acetyltransferase 1 polymorphisms, which may account for up to 48% of attributable risk of gastric cancer (6,7). Therefore, host genetic factors may determine why some individuals develop gastric cancer when exposed to gastric carcinogens, while others do not.

Epidemiological studies suggest that patients harbouring *cagA*-positive strains of *H pylori* are at a greater risk for gastric cancer than those without the strains (8-11), although conflicting reports exist (12-18). Nevertheless, many important questions remain unanswered, such as, what is the magnitude of risk of gastric cancer associated with infection with *cagA*-positive strains of *H pylori*? Do *cagA*-positive strains increase the risk of gastric cancer over and above the risk associated with *H pylori* infection alone? Is the risk of gastric cancer increased if a patient is negative for *H pylori*, but positive for *cagA* strains? Does *cagA* positivity protect the patient from gastric cancer at the cardia?

To answer these important questions, we undertook a systematic review of the relevant literature to comprehensively examine the totality of evidence and potential sources of heterogeneity between studies investigating the relationship between infection with *cagA*-positive strains of *H pylori* and the development of gastric cancer.

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TABLE 1

Studies comparing the prevalence of *H pylori* infection in gastric cancer patients and controls.

Reference	Age (years)*	Cases (n)	Controls (n)	Matching	OR (95% CI)
Ekström et al (19)	68/67	279	238 population-based	Age, sex	2.07 (1.44-2.98)
Chow et al (17) (range)	30-79	196	223 population-based cohort	Age, sex and race	0.91 (0.61-1.35)
Yamaoka et al (14)	65/65	110	110 asymptomatic subjects	Age, sex	2.19 (1.17-4.1)
Limburg et al (18)	age strata	181	192 cancer-free cohort	Age, sex and region	1.56 (1.03-2.36)
Parsonnet et al (8)	50-56/56	103	139 noncancer cohort	Age, sex and race	3.89 (1.98-7.65)
Blaser et al (16)	59/59	109	109 noncancer cohort	Age, sex and race	5.38 (2.11-13.68)
Kikuchi et al (15)	<40/<43	103	201 noncancer patients and screening subjects	Age, sex adjusted	12.92 (6.5-25.66)
Maeda et al (20)	63/61	80	80 asymptomatic subjects	Age, sex	2.42 (1.22-4.81)
Rudi et al (13)	63/63	90	90 patients with cardiovascular disease	Age, sex	1.59 (0.73-3.44)
Enroth et al (12)	73/71	72	114 normal endoscopies	Age, sex and hospital	2.3 (1.16-4.56)
Shimoyama et al (11)	63/62	81	81 normal endoscopies or with atrophic gastritis	Age, sex	1.39 (0.63-3.09)
Brenner et al (9)	61/64	68	239 patients with colorectal cancer	Age, sex	1.65 (0.87-3.11)
Queiroz et al (10)	62/61	119	119 dyspeptic patients	Age, sex	Not available

*Mean age: cases/controls; All cases were diagnosed by histology

SYSTEMATIC REVIEW OF EPIDEMIOLOGICAL STUDIES

Prevalence of *H pylori* infection and risk of gastric cancer

A comprehensive literature search was conducted in the Medline and PubMed databases for relevant studies in all languages from January 1990 to September 2002. Of 200 potentially relevant citations, the screening of citation titles and abstracts identified 18 case-control studies for full article review (8-21). However, five studies were subsequently excluded for the following reasons: two studies (21,22) did not use serological testing for *H pylori* infection, two studies (23,24) did not have matched controls and one was a duplicate study (25).

Table 1 lists the major characteristics of 13 individual studies comparing the prevalence of *H pylori* infection in cases with that in controls, and their odds ratios (ORs) and 95% CI. These studies met the eligibility criteria and provided raw data on the seroprevalence of *cagA*-positive strains of *H pylori* and, therefore, were subject to analysis. The overall prevalence of *H pylori* infection was 73.1% (1076 of 1472) in cases and 58.2% (1057 of 1816) in controls, yielding an OR of 2.31 (95% CI 1.58 to 3.39) in a random effects statistical model. However, the test of homogeneity was statistically significant, suggesting the existence of possible methodological or biological heterogeneity. By exploring the sources of heterogeneity, two studies were identified to account for most of the between-study heterogeneity (15,17). Thus, a sensitivity analysis was performed by excluding these two studies, yielding an OR of 2.1 (95% CI 1.7 to 2.6). Further analysis revealed that the characteristics of these two study populations were different from the remaining studies, with one study consisting of significantly younger subjects (15) and the other including patients with esophageal carcinoma (17).

Overall prevalence of *cagA* seropositivity and risk of gastric cancer

Of the 13 studies, seven (8,9,11,12,15,18,20) provided data on the seroprevalence of *cagA* positivity irrespective of *H pylori* status. The results of six studies (8,9,11,12,15,20) show that *cagA* seropositivity was significantly associated with an increased risk of gastric cancer, with ORs ranging from 1.91 to 10.1. The pooled prevalence of *cagA* seropositivity was 67.8% (607 of 895) in the cases and 38.5% (450 of 1170) in the con-

trols, with an estimated OR of 3.3 (95% CI 1.98 to 5.48). Although the test of homogeneity was statistically significant, further scrutiny of the characteristics of the study populations and methodologies of these studies did not find any clear clinically or biologically important differences between the studies.

cagA seropositivity in *H pylori*-infected or negative populations and risk of gastric cancer

Eleven studies provided raw data on *cagA* seroprevalence in *H pylori*-infected populations (8-18). The pooled prevalence of *cagA* positivity was 77.4% (834 of 1078) in cases and 64.1% (703 of 1097) in controls, giving an estimated OR of 1.79 (95% CI 1.22 to 2.64). The test of homogeneity was statistically significant ($P < 0.001$). Two studies were identified to be primarily responsible for the heterogeneity, with one study including patients with esophageal cancer (17) and the other having a significantly larger effect size than the remaining studies (14).

Five studies provided data on *cagA* seroprevalence in *H pylori*-negative cases and controls with *cagA* seropositivity ranging from 0% to 74.7% in gastric cancer patients (8,11,12,15,18). The pooled prevalence was 42.3% (77 of 182) of the cases and 9.1% (35 of 386) of the controls, respectively, yielding an OR of 3.37 (95% CI 0.75 to 15.12).

Prevalence of *cagA* seropositivity and risk of gastric cancer by site

Six (10,11,14,15,17,18) and nine (8-11,13-15,17,18) studies provided data on *cagA* seroprevalence in *H pylori*-infected patients with gastric cancer at the cardia and at noncardiac sites. The pooled prevalence of *cagA* seropositivity was 58.3% (95 of 163) in patients with gastric cancer at the cardia and 67.8% (288 of 425) in the controls, giving an OR of 0.82 (95% CI 0.51 to 1.31). In contrast, the seroprevalence of *cagA* positivity in patients with noncardiac gastric cancer was significantly higher than their controls (81% versus 63%), with an estimated OR of 2.01 (95% CI 1.21 to 3.32).

DISCUSSION AND CONCLUSIONS

The relationship between *H pylori* infection and gastric cancer has been extensively examined in many epidemiological studies. Four meta-analyses of these studies reported that the mag-

nitude of risk of gastric cancer associated with *H pylori* infection is approximately two- to six-fold compared with noninfected control populations (1-4). However, the role of *cagA* strains of *H pylori* in relation to gastric cancer has not been assessed in a systematic manner.

By using the technique of meta-analysis, we systematically evaluated the literature about infection with *cagA* strains of *H pylori* and the risk of development of gastric cancer. We have identified that patients harbouring *cagA*-positive strains of *H pylori* had an increased risk of gastric cancer over and above the risk associated with *H pylori* infection alone. The magnitude of increased risk was estimated to be two-fold for noncardiac gastric cancer, whereas no relationship was found for patients with gastric cancer at the cardia.

Interestingly, a significant proportion of patients (42.3%) were seropositive for *cagA* strains, but negative for *H pylori* serology, suggesting a high misclassification of *H pylori* infection if the diagnosis is based on *H pylori* serological testing alone. Several possible explanations should be considered for

the discordant testing results between *cagA* strains and *H pylori* serology. These include a false-positive *cagA* test, a false-negative *H pylori* serology or the spontaneous disappearance of *H pylori* immunoglobulin (IgG) antibodies (19). It is possible that *H pylori* infection may resolve spontaneously when severe atrophy or intestinal metaplasia occurs in the stomach. There is evidence to suggest that *cagA* antibodies remain positive for a longer period of time than *H pylori* IgG surface antibodies (26,27). Therefore, relying on *H pylori* IgG antibodies alone may misclassify a significant proportion of patients who once had the infection, leading to a substantial underestimation of the risk of gastric cancer associated with *H pylori* infection.

In conclusion, infection with *cagA* strains of *H pylori* significantly increases the risk of noncardiac gastric cancer over and above the risk associated with *H pylori* infection alone. Gastric cancer at the cardia is not associated with infection with *cagA* strains of *H pylori*. Searching for *cagA*-positive strains may reduce misclassification of *H pylori* infection and help identify populations at a greater risk for developing gastric cancer.

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