COMMENTARY

Are There any Real *Helicobacter pylori* Infection-negative Gastric Cancers in Asia?

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Abstract

The great variability in gastric cancer rates across Asia, with very high incidences in Japan and Korea, and exceedingly low incidences in ethnic Malays, whether in Malaysia or Indonesia, appears largely due to variation in *Helicobacter pylori* infection rates. While between 2% and 10.6% of gastric cancers in a recent Japanese survey were considered to be negative for bacterial infection on the basis of seropositivity and *H. pylori*-dependent mucosal atrophy, it is notoriously difficult to preclude past infection. The situation is greatly complicated by reported differences in the etiology of gastric cardia and non-cardia cancers. In the Western world there do appear to be tumours arising close to the esophageal-gastric junction which are not related to *H. pylori* and associated inflammation, but in most Asian populations these appear to be very rare. Therefore preventive efforts, and particularly screening, should be focused on markers of bacterial infection, with avoidance of unnecessary exposure to X-ray radiation.

Key words: Gastric cancer - cardia - non-cardia - *H. pylori* - inflammation

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Introduction

Although the incidence of stomach cancer is steadily declining in Japan, it is still a major cause of malignancy-associated death. Its prevention and control remain crucial. Recently, Kato et al. (2007) presented an important article indicating that the percentage of *Helicobacter pylori* (*H. pylori*) infection-negative gastric cancer ranged from 2.0% (minimum) to 10.6% (maximum), indicating that the bacterium is a major etiologic factor. The results seem compatible with our finding that the very low incidence of stomach malignancy in Yogyakarta (Tokudome et al., 2005) and Semarang (Tokudome et al., 2006), Indonesia, appears to be due to the rarity of infection. Similar results have been reported in Malaysia, whereby the incidence of gastric carcinoma was found to be much higher in Chinese in Penang compared to Malays in Kelantan, where the *H. pylori* infection rate is exceptionally low (Gurjeet et al., 2005).

A complicating factor is the existence of cardia and non-cardia cancers in the body of the stomach with differing etiologies (Palli et al. 2007). Furthermore, the current evidence indicates that cardia cancers are also of at least two distinct types in Western populations (Jonkers et al., 1999; Gonzalez et al., 2006), one resembling cancer of the more distal stomach (Type A), being a consequence of atrophic gastritis due to bacterial infection or more rarely autoimmune atrophic gastritis. The other type (Type B) resembles oesophageal adenocarcinoma and is likely to be a consequence of short-segment gastro-oesophageal reflux disease. Type A occurs in patients with evidence of atrophic gastritis whereas Type B is found in subjects with healthy acid-secreting stomachs (McColl, 2006). *H. pylori* appears to be a strong risk factor for non-cardia gastric cancer but is inversely associated with the risk of gastric cardia cancer. These findings bolster the hypothesis that decreasing *H. pylori* prevalence during the past century may have contributed to lower rates of non-cardia cancer and higher rates of cardia cancer in Western countries (Kamangar et al., 2006). In contrast, associations between *H. pylori* exposure and gastric cardia and non-cardia adenocarcinoma development in Linxian, China, were equally strong, in contrast to Western countries, perhaps due to the absence of Barrett's oesophagus and oesophageal adenocarcinomas , making all cardia tumours of gastric origin, rather than a mixture of gastric and oesophageal malignancies (Kamangar et al., 2007).

As has been suggested (Ekstrom et al., 2001; Huang et al., 1998; Malfertheiner et al., 2002), *H. pylori* may disappear from the stomach along with the progressive changes of gastric milieu from chronic inflammation/ atrophic gastritis, intestinal metaplasia, dysplasia to cancer. However, Kato et al (2007) found that the level of gastric atrophy detected by pepsinogen test (Miki et

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al.,1993) did not necessarily correlate well with that diagnosed by Updated Sydney System Scores. Furthermore, testing of serum anti-*H. pylori* IgG antibodies according to ELISA would invariably yield false negative test, particularly in case-control study settings (Ekstrom et al., 2001; Huang et al., 1998). Thus, the maximum proportion (10.6%) of *H. pylori* infection-negative stomach malignancy appears to have been overestimated. The final judgment on the percentage of *H. pylori* infection-positive or -negative stomach cancer should be made according to prospective approaches, in which no gastric malignancy occurred among *H. pylori* infection-negative subjects and randomized controlled trials of the *H. pylori* eradication program (Ohata et al., 2004; Uemura et al., 2001).

Stomach cancer indeed appears to be an infectious disease caused by *H. pylori* infection (Kikuchi et al., 1995; Huang et al., 1998; Ekstrom et al., 2001; Uemura et al., 2001; Ohata et al., 2004; Tokudome et al., 2005; Tokudome et al., 2006; Egi et al., 2007). Thus, infection prevention, control and eradication of the bacterium seem crucial for primary prevention of gastric malignancy. For secondary prevention, instead of immediate application of photofluography/X-ray examination, we propose that non-invasive examinations for *H. pylori* infection, including urea breath test and assays for the bacterial antigen and antibodies, together with pepsinogen test should be first adopted to screen high-risk subjects. This will assure more effective use of personnel and monetary resources and reduce unnecessary exposure to X-ray radiation.

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