Editorial

Helicobacter pylori eradication for the prevention of gastric carcinoma

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Although the incidence of gastric adenocarcinoma in the United States and Europe has steadily declined over the past 50 years, gastric cancer was the most common cancer in the early part of the 20th century and remains the second most frequent fatal cancer in the world. Even today, the lifetime risk of developing gastric cancer is 1% to 3% in the United States, and in many countries it remains the first or second most common cancer. The link to *H. pylori* infection was confirmed after the discovery of the pathogenic role of the organism in gastritis. In 1994, the World Health Organization's (WHO) International Agency for Research on Cancer classified *H. pylori* as a definite carcinogen among other putative environmental and biologic carcinogens. In recent years the role of *H. pylori* infection in gastric cancer and MALT lymphoma has been the focus of both basic and clinical research. This research focused on aspects such as epidemiology, histopathology, transmission to animal models, virulence factors, molecular alterations and host genetic factors.

The strongest epidemiologic evidence for a link between the infection and later development of gastric adenocarcinoma comes from serologic studies demonstrating that people infected with *H. pylori* have a higher incidence of gastric carcinoma. Serologic tests are appropriate because antibodies to *H. pylori* document even remote exposures, whereas biopsy-based studies of gastric adenocarcinoma may miss prior *H. pylori* infection,

as *H. pylori* is unable to colonize adenocarcinoma tissue. Thus, prospective studies have demonstrated a link between *H. pylori* and gastric cancer, with the time between diagnosis of the infection and discovery of the cancer ranging from 6 to 14 years with matched odds ratios from 2.2 to 6.0.

Polymorphisms in a wide variety of genes that are present in a significant proportion of the normal population may modify the effect of environmental exposures, such as *H. pylori* infection. These gene-environmental interactions could explain the high variation in the gastric cancer incidence observed around the world.

There is no single mechanism for development of gastric carcinoma after *H. pylori* infection and cancer is typically multifactorial. The proposed pathogenetic mechanisms offer plausible explanations for the role of *H. pylori* in the initiation and promotion of gastric cancer. Acute gastritis is the initial lesion, progressing in some to multifocal atrophic gastritis. The sequence of events leading to gastric cancer is *H. pylori* infection, superficial gastritis, atrophy, development of increasingly severe intestinal metaplasia, dysplasia, and finally invasive carcinoma. The role of increased cell turnover or elaboration of toxic oxygen free radicals in the damaging effects of chronic *H. pylori* infection is a subject of research.

First-degree relatives have a higher risk for developing gastric cancer compared to patients with no family history. Additional risk factors such as *H. pylori* infection further increase the risk. Thus, in a large study comparing gastric cancer relatives to controls, the prevalence of *H. pylori* infection was higher in first-degree relatives of cancer patients than in controls (adjusted OR: 2.1; 95% CI 1.5-2.9). Furthermore, patients with a family history of gastric cancer and additional infection with CagA-positive *H. pylori* strains showed a total 8-fold increased

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risk for gastric carcinoma, and, specifically, a 16-fold increased risk for noncardia gastric carcinoma. Studies on the genetic diversity of the *cagA* pathogenicity island, demonstrated that it plays an important role in IL-8 production.

Considering the universality of *H. pylori* infection and its attributable risk in cancer causation, the public health implications are profound. Thus the prevailing question is: What measures could be taken to aid cancer prevention? Possibilities include education on hygiene, which could help to prevent person-to-person bacterial spread, and education on nutrition. More radical forms of intervention could include population-based *H. pylori* eradication therapy or vaccination against *H. pylori*. The issue of whether to conduct population-based screening for *H. pylori* is unresolved, although some consider adopting such an approach. Given the costs of effective antimicrobial treatment, the difficulties with compliance, the possibility of side-effects and induction of resistance, and the potential for re-infection in developing countries, mass eradication programmes are currently impractical. In general, more scientific data is needed before any firm recommendation can be made. The development of a vaccine appears to offer the best hope for the elimination of the infection, but a useful vaccine is probably some years away from clinical introduction.

Under current evidence, physicians should consider screening and treatment in the following groups of individuals: a. Asymptomatic first-degree relatives of gastric cancer patients, as the risk of developing gastric cancer is significantly increased. Relatives should be tested for the presence of the infection, and those who prove to be infected should be treated. b. Individuals with established atrophic gastritis with or without intestinal metaplasia. c. Individuals in need of long-term suppression of gastric acidity. Although this topic is generally considered controversial, all currently available evidence favours the accelerated development of mucosal atrophy when suppressing intragastric acidity in *H. pylori* infected patients and therefore *H. pylori* eradication is recommended. d. Individuals with ethnic risk factors and, finally, e. Individuals with a strong wish to be tested and treated.

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