EDITORIAL

Helicobacter pylori Infection: A Novel Risk Factor in the Etiology of Gastric Cancer

David Forman*

The study reported by Talley et al. (1) in this issue of the Journal shows that the prevalence of infection with the bacterium Helicobacter pylori was significantly higher in a group of gastric cancer patients than in a matched control group. This study now brings to four the number of case-control studies on this subject; all of these studies have reported a statistically significant positive result (2-4). The odds ratios in the studies ranged from 2.7 (1) to 6.0 (4). The remarkable degree of consistency between these studies, which have been carried out in British (2), American (1,3), and Japanese-American (4) populations, now puts forth beyond a reasonable doubt the conclusion that there is an association between H. pylori infection and gastric cancer.

In the 8 years since H. pylori was first cultured and characterized (5), this bacterium has become the subject of intense clinical research concentrating predominantly on its involvement in gastrointestinal disease. There is now broad agreement that, following infection, bacteria colonize in the stomach and induce an acute inflammatory response (6). Because infections rarely resolve spontaneously, bacteria will remain active in the gastric epithelium for years (or probably decades), giving rise to chronic gastritis and eventually to chronic gastritis with atrophy (7). This condition has been viewed as a critical step in the progression of events that lead to gastric cancer (8,9). Although antibiotic therapy can eradicate H. pylori (6), chronic infections are frequently asymptomatic (10) and most infected individuals will, therefore, be neither diagnosed nor treated.

The involvement of H. pylori goes some considerable way toward features of the descriptive epidemiology of gastric cancer. Several populations with extremely high rates of gastric cancer, notably in South America, have endemic H. pylori infection at a young age (11,12). Within rural China, there was a significant geographical correlation between gastric cancer mortality and H. pylori prevalence (13). The long-established association between poor socioeconomic conditions and gastric cancer (14) has been reflected in a similar association with H. pylori infection (10,15), and it is plausible that the worldwide decline in gastric cancer mortality (16) could, at least partly, be due to secular changes in bacterial infection rates (17).

In addition to these epidemiological findings, evidence suggests that several of the pathogenic consequences of H. pylori infection may be relevant to carcinogenesis. Apart from the prolonged inflammatory stimulus giving rise to gastritis with atrophy and apart from the microbiological and biochemical events associated with the subsequent hypochlorhydria (8), H. pylori also induces tissue monocytes to produce reactive oxygen intermediates (18), which can act as potent genotoxic carcinogens (19). At the same time, preliminary evidence indicates that infection dramatically reduces the concentration of gastric juice ascorbic acid (20), thus impairing an important defense against oxidative DNA damage (21).

There is, therefore, impressive background evidence compatible with the findings of the case-control studies. Talley et al. (1) have added to this evidence the observation that H. pylori infection has a specific association with gastric cancer insofar as other groups of patients with colorectal, esophageal, and lung cancers did not have significantly elevated infection rates. The specificity can be taken one step further in that both of the studies in American populations (1,3) clearly showed that the association was with noncardia gastric cancer. Patients with cancers of the cardia and the gastroesophageal junction did not have higher infection rates than their controls. There was, however, no difference in risk between patients with cancers in the gastric antrum or corpus or, despite previous pathological evidence to the contrary (22), between patients with intestinal or diffuse forms of the cancer.

The fact that an epidemiological association has been established does not, of course, prove that there is a causal relationship. A number of unanswered questions still stand in the way of a direct cause-effect interpretation of the evidence. First, why are the odds ratios, despite statistical significance, still relatively low and considerably less than, say, the odds ratio for the association of the hepatitis B virus and hepatocellular carcinoma (23)? Second, why are there several population groups with a high H. pylori infection rate but a low risk of gastric cancer, e.g., in China (13) and Africa (24)? Third, if, as many now believe, H. pylori is a contributory cause of duodenal ulceration, why is it that the descriptive epidemiology of this disease is so different from that of gastric cancer?

Several explanations can be offered to address these questions: different bacterial strains may have different pathogenic consequences, individuals infected early in life may show a response different from that of individuals infected at an older age, and host variability in acid output may affect the response to infection. It is also probable that, by itself, bacterial infection is unlikely to cause either an ulcer or a cancer and that dietary and other cofactors in combination with H. pylori will determine the overall risk of disease. Future studies looking at these issues may help define whether there are infected subgroups at particular high risk of developing disease.

A further question relevant to causality is whether the time sequence of events is in the correct order. In the study by Talley et
al. (1), blood samples were taken after the cancers had been diagnosed; one cannot, therefore, exclude the possibility that the stomach becomes more susceptible to \textit{H. pylori} infection as a consequence of cancer development. This criticism is much less pertinent to the other three studies (2–4), which were all prospective in design and in which blood was collected many years prior to diagnosis. In two of these studies (2,4), exclusion of case patients diagnosed soon after providing blood samples did not cause any reduction in the odds ratio, which adds further support to the hypothesis that infection precedes cancer development. In addition, the precancerous conditions gastritis with atrophy and intestinal metaplasia are associated with a loss of \textit{H. pylori} colonization rather than with an increase in susceptibility (25,26).

Definitive proof of causality will depend on randomized intervention trials of the long-term effects of \textit{H. pylori} eradication on the risk of gastric cancer or precancerous lesions. This situation implies the existence of a safe and effective antibacterial therapy suitable for widespread use in asymptomatic populations. In this context, there would be justifiable concern about the use of current anti-\textit{H. pylori} therapeutic protocols, given their known side effects, notably colitis and antibiotic resistance (6).

The issue of therapy raises a general public health problem of whether asymptomatic infections should be treated at all. There will certainly be a rise in demand for treatment, and it is likely to become more acute in view of the cancer association. Clinicians will have to make judgments about the benefit of this treatment; but, even with a satisfactory therapy, the high prevalence of infection in most populations—the control subjects in the four case-control studies had infection rates that ranged from 38% to 76%—as well as the relatively small increase in risk means that it is unlikely that bacterial eradication will be a cost-effective approach to reducing the risk of gastric cancer. Primary prevention is likely to be the most efficacious approach to controlling infection, but this approach presupposes an understanding of the major mode of transmission, which is still far from established.

Worldwide rates of gastric cancer are declining but, outside the United States, it is still a common and fatal cancer (27). If \textit{H. pylori} is involved in the etiology of the disease, then the attributable risk is likely to be high, despite a low absolute risk subsequent to infection. Perhaps as many as 60% of all gastric cancers could be prevented by control of the bacteria (3,4). No other single agent has yet been identified that could play as important a role in the etiology of gastric cancer, and further research in this area should become an important priority.

References


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