Helicobacter Pylori Infection and Gastric Cancer

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Introduction

The role played by infectious diseases in cancer causation is a timely subject. Infections are associated with some of the most prevalent cancers in the world, such as carcinomas of the stomach, liver, and cervix. Pisani *et al.* (1) estimates that ~15% of malignant neoplasms that occur worldwide are attributable to infections that may be preventable. It is important that we share the gift of good health and long life with all segments of our society. The professionals represented in this forum may have an opportunity to direct future actions in this area, especially for minorities and underprivileged communities.

We are familiar with old enemies that affect the health of our society, such as chemical carcinogens, radiation, and smoking. Carcinogenic influences caused by chronic infections have only recently been emphasized. Although it has long been suspected that some chronic infections may cause cancer, we now have a major opportunity to address the issue scientifically by exploring mechanistic questions and designing prevention strategies.

More than a century ago, Bizzozero (2) described "spiral bacteria" that colonized the human stomach. Infections with these bacteria ("helicobacters") have only recently been proposed as pathogens and recognized as human carcinogens (3, 4). Although mechanisms of action are unknown, the carcinogenic role of the bacterium might be mediated by resulting chronic active inflammation. It appears that the bacterium has been evolving for centuries. Some strains have gained virulence and capacity to induce tissue damage after acquiring "pathogenicity islands" from other bacteria through interchange of DNA sequences (5).

Magnitude of the Gastric Cancer Burden

Table 1 shows the incident cases for the most prevalent cancers worldwide (6, 7). Stomach cancer is the second commonest cancer in the world, with 750,000 incident cases per year. Fig. 1, published by the IARC (8), shows gastric cancer incidence among males worldwide. Japan and Korea have the highest incidence rates. Asia and Eastern Europe account for ~70% of gastric cancer cases worldwide. Another high-incidence area is South America, in particular the Andean region. However, marked contrasts can exist within certain countries. Maoris in New Zealand have much higher rates than Caucasians living in the same country (9). Similar contrasts exist in Hawaii and New Mexico, where Native-American Indians, Hispanic, and Japanese populations have much higher rates than Caucasians (9). Therefore, demographic and cultural characteristics play a more important role than geographic location.

Table 1 Estimated new cases for 1985 (both genders)

Lung	895,500
Stomach	754,800
Breast	719,100
Colon and Rectum	677,500
Cervix	473,300
Mouth and Pharynx	412,400
Lymphoma	316,000
Liver	314,900
Esophagus	303,500
Prostate	291,200
Leukemia	216,000
Pancreas	185,100
Bladder	181,700
All sites	7,623,600

In the United States during the past decade, the annual number of deaths from gastric cancer slightly exceeds 20,000. Overall, age-specific incidence and mortality rates for gastric cancer have been decreasing drastically. However, the steady increase in the United States population and immigration from high-risk countries has kept the annual number of deaths stable. Within the United States, marked contrasts exist among racial/ethnic groups. African-Americans have rates that are approximately double those for Caucasians and Hispanics in the United States. Native-Americans also have high mortality rates, but immigrants from Asia (particularly Japanese and Korean immigrants) have even higher death rates (9). It appears that decreasing mortality rates, first observed in affluent populations, are being observed in several minority populations.

Fig. 2 is a classical graph published by William Haenszel in 1958 (10). United States Caucasians born from 1865 to 1869 had higher mortality rates than each subsequent birth cohort, and the trend has persisted.

Cancer Etiology

Numerous international epidemiological studies have gradually defined the major risk factors for gastric cancer. Hirayama (11) first reported in 1963 that consumption of salted pickles was associated with cancer risk. Subsequently, studies in several countries have confirmed the risk-enhancing effect of excessive dietary salt (12). A less consistent risk-enhancing effect has been described for other factors, such as consumption of smoked pork products and tobacco smoking (13). Several studies have also shown that frequent consumption of fresh fruits and vegetables decreases gastric cancer risk by approximately one-third. These findings have been linked to dietary antioxidants, such as ascorbic acid (14).

A newly described, but potent, risk-enhancing factor is the infection of the stomach mucosa with *Helicobacter pylori*.

Accepted 1/6/03.

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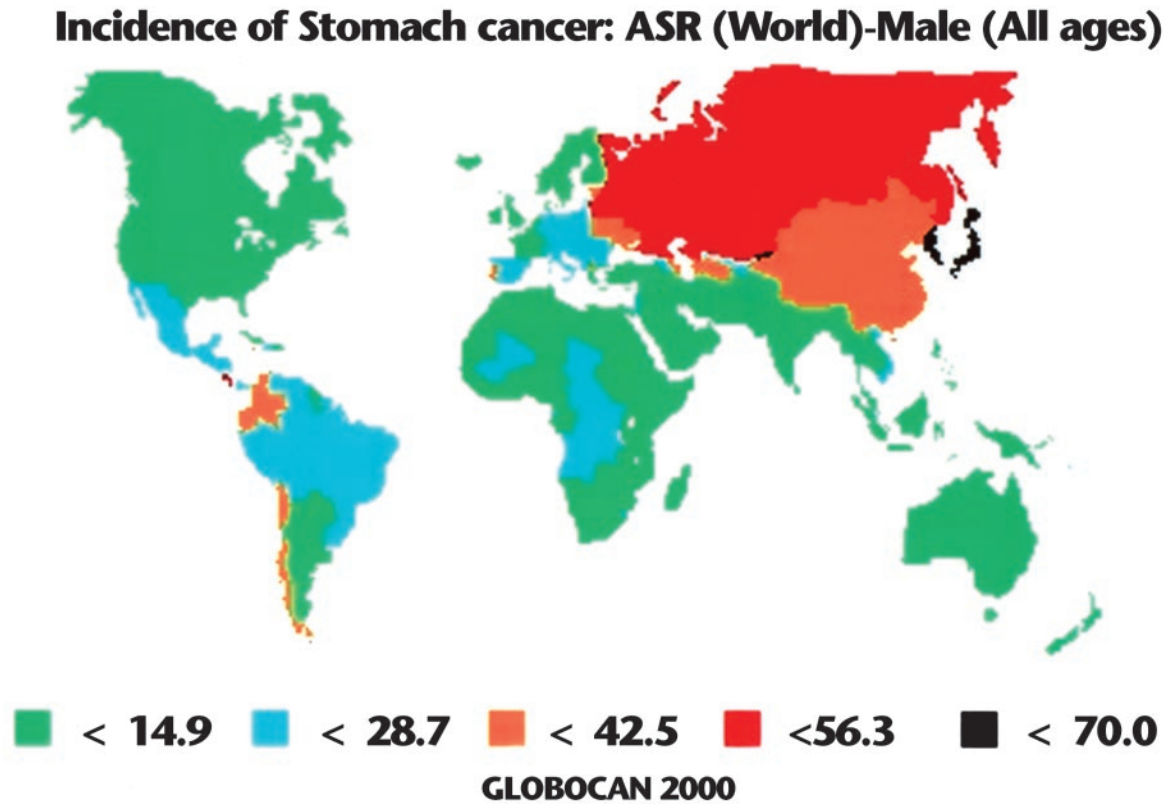

Fig. 1. Worldwide gastric cancer incidence rates in males (8).

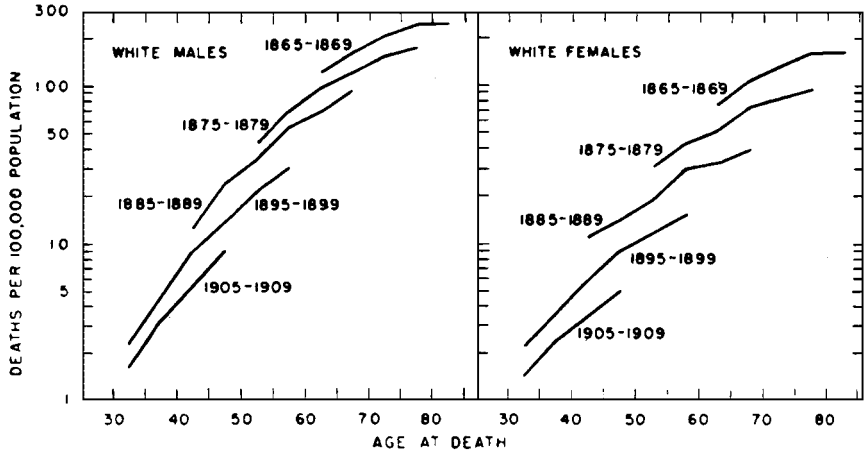

Fig. 2. Age-specific mortality rates from stomach cancer in successive cohorts of United States Caucasians (10).

Since this discovery, research on gastric cancer etiology has changed dramatically. In 1983, Marshall and Warren (3) published their finding of the association of *H. pylori* infection with chronic gastritis and peptic ulcer. The authors also suggested that *H. pylori* infection might be linked to gastric cancer. Warren examined gastric biopsies obtained by use of fiber optic technology and documented the association between the presence of the bacteria and chronic active gastritis. To overcome the skepticism of their colleagues, Marshall *et al.* (15) ingested a culture of the bacteria and subsequently developed chronic active gastritis. In 1994, the IARC (WHO) classified *H. pylori* infection as a human carcinogen based on epidemiological evidence (4). Experimental evidence was subsequently provided by investigators who induced gastric cancer in Mongolian gerbils with *H. pylori* strains of human origin (16, 17). Notably, the bacterium does not invade gastric tissue but remains in the gastric lumen. The search continues for mechanisms by which the bacteria cause profound changes in cells of the gastric mucosa without invading them.

Case control studies of the association between *H. pylori* infection and gastric cancer have yielded inconsistent findings. The matter appears to have been settled by the case control

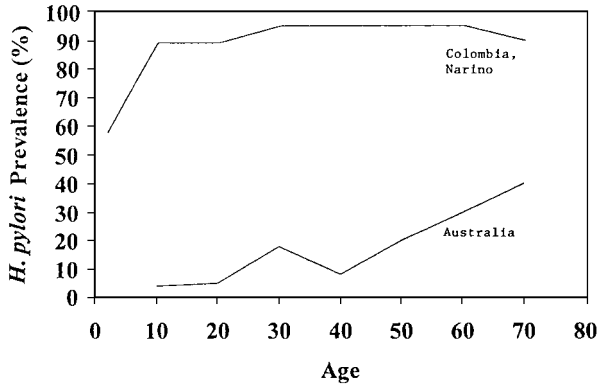

Fig. 3. Age-specific prevalence rate of *H. pylori* infection in Aldana, Nariño, Colombia (23), and Australia (24, 25).

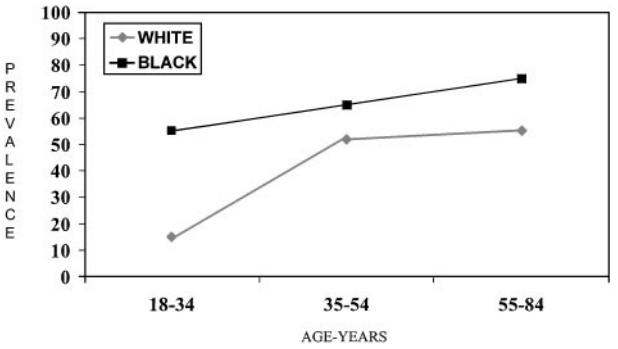

Fig. 4. Prevalence of *H. pylori* infection in healthy volunteers in New Orleans (26).

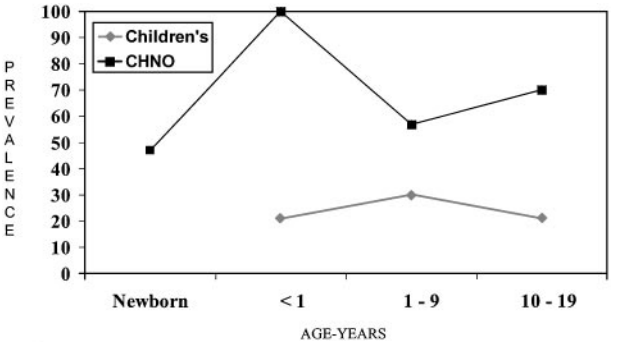

Fig. 5. Prevalence of *H. pylori* infection in New Orleans African-American children of low social economic status (Charity Hospital) compared with middle-class (Children's Hospital; Ref. 26).

study of Fukuda *et al.* (18) that showed elevated cancer risk associated with infection in younger patients with early stage cancers. Thereafter, it was realized that several previous studies had temporal bias related to the age at infection (mostly in childhood) rather than age at cancer diagnosis (mostly after age 50). Some precancerous gastric lesions originally induced by the infection later resulted in a microenvironment hostile to the *H. pylori* colonization. An example is precancerous changes of gastric atrophy and intestinal metaplasia, which reduce gastric acid secretion and provide a favorable environment for the growth of other anaerobic bacteria that compete successfully for colonization of the gastric mucosa.

The most compelling reason for the classification of *H. pylori* infection as a human carcinogen was provided by three independent retrospective (historical) cohort studies. Populations in Hawaii, California, and Great Britain (19–21) were recruited for cohort studies in the 1960s. At that time, *H. pylori* infection was unknown in the medical community. Frozen serum samples were preserved for each member of the cohort. Almost 20 years later, some subjects from these cohorts developed gastric cancer. Their stored serum samples ("cases") were assayed for antibodies against *H. pylori*. These results were compared with the sera of subjects ("controls") who did not develop gastric cancer. The relative risk of cancer in infected subjects was significantly greater than the risk in the subjects who were not infected. The risk increased in magnitude with the time interval between initial blood collection and cancer diagnosis (22). This study design essentially rules out selective recall as an important bias.

Major differences in the prevalence and age at first infection with *H. pylori* are found between countries with high and low gastric cancer rates. This is illustrated in Fig. 3, which contrasts the populations at high risk of gastric cancer in a rural area of Colombia to the lower risk population of Australia (23–25). In the rural Colombian community, ~50% of children are infected by age 2, and 90% are infected by age 9. In adults, the prevalence rates of infection remain >90% (26). In contrast, recently born Australian children have very low rates of *H. pylori* infection, and the prevalence of infection among adults increases with age (25). Because new infections in adults are rare, the increase in incidence with age is probably attributable to a decline in infection during childhood among successive birth cohorts. Therefore, Australian adults at age 50 with high rates of *H. pylori* infection (~50%) were more likely to have been infected during their childhood. In general, the infection tends to stay active unless treated with antibiotics.

A discrepancy exists between *H. pylori* infection prevalence and cancer rates in certain populations in Africa, India, and the coastal areas of Latin America. These populations have high rates of infection but low gastric cancer rates (Fig. 1). This phenomenon has been called the "African enigma" and remains largely unexplained (27).

Fig. 4 shows infection prevalence rates of *H. pylori* in apparently healthy individuals attending the University Dental Clinic in New Orleans. African-Americans have higher prevalence of infection than Caucasians. Because *H. pylori* infections tend to occur in childhood, African-American children of low socioeconomic status seen at Charity Hospital were compared with middle class at Children's Hospital in New Orleans. Fig. 5 shows that the prevalence of infection is associated with socioeconomic status rather than with ethnic background (26). Low socioeconomic situations, such as overcrowded housing, poor nutrition, and other factors, have been linked to higher infection prevalence.

Cancer Prevention

In most countries, the 5-year survival rate for gastric cancer is ≤20%. Early detection can reduce cancer mortality, but cost-efficient, noninvasive methods are not available to screen populations for early cancer. In Colombia, subjects with atrophic gastritis were consented and randomized to treatment of *Helicobacter* infection with either triple drug combinations or dietary supplementation with ascorbic acid and/or β-carotene for 6

years (28). Progression, no change, or regression of the precancerous lesions constituted the end points. Cure of infection was associated with a significantly higher likelihood of regression of precancerous lesions in patients with intestinal metaplasia and/or multifocal atrophic gastritis (relative risk of regression = 8.7; 95% confidence interval, 2.7–28.2). Supplementation with antioxidants resulted in a smaller, but statistically significant, likelihood of regression of lesions (28). Other chemoprevention trials are in progress. However, the classification of *Helicobacter* infection as a cause of cancer in 1994 (4) has made it difficult to recruit infected subjects into a randomized trial.

Prevention is clearly the optimal approach to the control of gastric cancer, the best long-term strategy for the elimination of the disease, including improvement of nutrition and housing sanitation. For individuals infected with *H. pylori*, cancer prevention strategies include curing infection, reducing salt intake, and improving intake of fresh fruits and vegetables. There is no available vaccine against the infection at the present time. However, several consensus statements regarding treatment of *H. pylori* infection have recommended therapy for infected persons because of their high risk of gastric cancer (29, 30).

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