Human Gastric Carcinogenesis: A Multistep and Multifactorial Process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention

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Abstract

Evidence from pathology and epidemiology studies has been provided for a human model of gastric carcinogenesis with the following sequential stages: chronic gastritis; atrophy; intestinal metaplasia; and dysplasia. The initial stages of gastritis and atrophy have been linked to excessive salt intake and infection with Helicobacter pylori. The intermediate stages have been associated with the ingestion of ascorbic acid and nitrate, determinants of intragastric nitrosation. The final stages have been linked with the supply of β-carotene and with excessive salt intake. Nitrosating agents are candidate carcinogens and could originate in the gastric cavity or in the inflammatory infiltrate.

Introduction

Although gastric cancer rates have been declining in recent decades, it remains one of the most serious health burdens throughout the world. Understanding its causation is important for the primary and secondary prevention of the disease. The highest death rates for many decades were registered in Japan, followed by northern Europe and the Andean populations of Latin America. The recent decline has been more marked in Japan and northern Europe. Fig. 1 shows the latest published death rates which are highest in Costa Rica and relatively high in eastern Europe (1). Data for China are not available in this series but gastric cancer accounts for the highest cancer mortality in that country. As of 1980, gastric cancer was the most frequent neoplasm registered in the world (2). In the United States, American Indians, Hispanics, Blacks, and immigrants from northern Europe, Asia, and Latin America display risks that are considerably higher than those of native White Americans. Some of the available incidence rates are shown in Table 1 (3). The absolute number of gastric cancer deaths has been increasing recently (4). The American Cancer Society estimated 20,000 cases in 1989 and 23,800 in 1991. The reasons for this increase are not entirely clear; it may be related to population growth and immigration of high-risk groups. A sharp increase of carcinomas localized in the gastric cardia has been recently registered in white males of the United States and western Europe, thus far unexplained on etiological grounds (5).

The recent decline has been observed mainly for the so-called intestinal type of gastric carcinoma, in contrast with the diffuse type which has declined less notoriously (6). A series of changes have been identified as precursors to the intestinal type of gastric carcinoma, representing apparently sequential steps in the precancerous process, namely superficial gastritis, chronic atrophic gastritis (gland loss), small intestinal metaplasia, colonic metaplasia, and dysplasia (7, 8).

An etiological hypothesis, depicted in Fig. 2, has been proposed to explain the progressive tissular and cellular changes and to identify the etiological forces acting at different points in the chain of causation (9, 10). Research on the hypothesis has continued on several fronts and produced new information which will be reviewed briefly in this article. We will address the phenotypic markers, the etiological factors, and the pathways of carcinogenesis and conclude with remarks about the implications for cancer prevention.

Phenotypic Markers

Hematoxylin and eosin stain remains the basic tool to assess the gastric cancer precursors and the gold standard against which other markers are compared. Studies of mucin histochemistry have confirmed that as the precancerous process advances, the normal neutral mucin of the superficial (foveolar) epithelium is gradually replaced by acid sialomucins of the type which characterize the small intestine and in later phases by sulfated mucins seen normally in the large intestine (11).

A second abnormality detectable in the mucin secretions is the anomalous appearance of blood group antigens, especially the Lewis antigens (12). The abnormal expression of both markers (sulfomucins and Lewis antigens) in the mucin moiety is a powerful predictor of risk, as shown in Table 2 which explores the relative risk of the most advanced precancerous lesions, based on studies of a Colombian population at high gastric cancer risk (13). Both cross-sectional tabulations and cohort follow-up studies coincide in assigning a very high risk to the concomitant expression of both phenotypic abnormalities. It appears that at this point this combination of markers may offer an excellent opportunity to identify subjects at the highest risk of neoplastic transformation.

Other markers with potential prognostic significance have been described. The pepsinogens secreted by the gastric epithelium can be detected in biopsy material and also have the great advantage of being detectable in the blood. Low serum pepsinogen I levels and low ratio of pepsinogen I to pepsinogen II are associated with high risk of dysplasia and cancer (14). The possible utilization of these markers in screening of high risk populations is being actively investigated at the present time (15-17).

Etiological Factors

The original hypothesis published in 1975 considered 3 major etiological factors, namely excessively salty foods and low intake of ascorbic acid and carotenoids (18). Since then, a new major factor has been added, infection with Helicobacter pylori.
plausibility is added when the effects of concentrated salt intake on the gastric mucosa are considered. It causes excessive cell replication, an event well known to increase cancer risk because of potentiation of the action of carcinogens and the possibility of increased rate of endogenous mutations (30, 31). The acute effects of concentrated salt solutions lead to mucosal damage and its repair is associated with inflammatory changes. An excessively salty diet induces atrophy in experimental animals (32) and is associated with atrophic changes in the human gastric mucosa (18). For these reasons it probably has a dual effect at the initial stages of the chain of causation, inducing both gastritis and atrophy, as depicted in Fig. 3. Excessive salt may also increase the mutagenicity of nitrosated foods (33). The recent decline in gastric cancer rates may be related to lower salt intake, made possible by refrigeration. In Japan, a strong and effective public health effort to reduce salt intake aimed at reducing hypertensive cerebrovascular accidents antedated by more than 10 years the marked decline in gastric cancer rates (27). Salt intake may also play a role in the late stages of carcinogenesis, as discussed below.

**Table 1**

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<td>Hawaii</td>
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<td>31 (Hawaiian)</td>
<td>28 (Japanese)</td>
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The current status of these factors in gastric cancer causation is described below.

**H. pylori**

This bacterium is not found in normal stomachs but is very frequently found in chronic gastritis. Several facts strongly support its role as a causative agent, such as the disappearance of the inflammatory reaction after elimination of the bacteria with antibiotic treatment (19). It is therefore suspected that *H. pylori* infection plays a causative role at the early phases of the chain, as outlined in Fig. 3. It has been proposed that infection during childhood may be a factor which distinguishes high-risk from low-risk populations (20). In some low-risk populations, the infection is very prevalent since childhood (21). It thus appears that *H. pylori* infection is a contributory but not a sufficient factor in gastric carcinogenesis.

The role of this chronic gastric infection has received strong support from 4 independent cohort studies which found that infection with *H. pylori*, detected many years before, increases the risk of gastric cancer (20–24). Since this infection typically remains active for life if not eradicated with adequate therapy, *H. pylori* is probably a source of active inflammation lasting for decades. The effects of *H. pylori* on the microenvironment of the gastric cavity and the gastric mucosa are poorly understood but an increase in cell replication and a constant attraction of polymorphonuclear leukocytes are events with suspected carcinogenic potential (25, 26).

**Excessive Salt (NaCl) Intake**

The epidemiological and experimental evidence for this etiological factor is strong and consistent (9, 27–29). Biological
Ascorbic Acid

The next segment in the chain of causation, namely the transition from atrophic to metaplastic mucosa, represents a morphological mutation that is easily detected histologically. The mutat(s) are unknown, but it has been proposed that at least some of them may be N-nitroso compounds as illustrated in Fig. 4. Chronic atrophic gastritis, because of the loss of acid-secreting parietal cells, leads to higher gastric pH and proliferation of anaerobic bacteria which reduce nitrate, abundant in many foods, to nitrite. The latter molecule has a propensity to react with other nitrogen-containing compounds to form N-nitroso mutagens and carcinogens. These processes may be inhibited by naturally occurring antioxidants, as shown by multiple epidemiological studies which find an inverse association between gastric cancer and the ingestion of fresh fruits and vegetables. Allium vegetables are associated with lower cancer rates and may contain natural inhibitors (34). A natural inhibitor abundant in fresh fruits and vegetables is ascorbic acid. The protective effect of this vitamin continues to receive strong support from epidemiological and laboratory research. All independent case-control studies which addressed the subject have reported significant reductions of gastric cancer risk associated with ascorbic acid intake. This has been found in populations of diverse ethnicity (35). Lower blood levels of ascorbic acid have been reported in patients with intestinal metaplasia as compared to controls (36). Ascorbic acid is actively secreted into the gastric cavity. It has been shown that ascorbic acid may be oxidized to dehydroascorbic acid in the gastric cavity, losing in that way its potential to block nitrosation reactions (37).

Ascorbic acid is markedly decreased in the gastric juice in the presence of chronic gastritis, elevated pH, and infection with *H. pylori* (37). More research is needed to better understand the physiopathology of ascorbic acid in the gastric microenvironment. The findings up to the present time point to a strong antioxidant function of ascorbic acid in the gastric microenvironment.

Carotenoids

The role of β-carotene has been linked to late events in the gastric precancerous process, especially in dysplasia and early invasive carcinoma (38, 39). Although the mechanism of its protective action has not been elucidated, its role as free-radical scavenger and its capacity to open intercellular gap junction communications have been pointed out (40, 41). In this late stage of carcinogenesis, carotenoids may have the opposite effects of dietary salt, which potentiates the effects of gastric carcinogens (42). Fig. 5 outlines the postulated enhancing role of salt and the inhibiting role of β-carotene in the late steps of the carcinogenesis model (10).

Pathways of Gastric Carcinogenesis

Although our knowledge of the modulation of the gastric carcinogenesis process has advanced, the identification of the carcinogen(s) remains elusive. Two leading hypotheses have emerged, luminal synthesis of carcinogen(s) and intramucosal carcinogenesis, outlined in Fig. 6, which depicts the last stages of the carcinogenesis model (10). Recently a new source of carcinogens has been postulated. Two studies have shown that tobacco smoking increases the risk of transformation from metaplasia to dysplasia (43, 44).

Intramural Synthesis of Carcinogens

The original hypothesis postulated the synthesis of carcinogens in the gastric cavity via nitrosation reactions induced by the high nitrite content of gastric juice (18). A potent mutagen has been identified after nitrosation of the precursor 4-chloro-6-methoxyindole found in fava beans, the staple food of some high-risk populations (45). It has been further reported that nitrosoindoles are genotoxic, inducing sister chromatid exchanges, and have tumor-promoting functions significantly inducing ornithine decarboxylase and inhibiting gap junction intercellular communications (46). Nitrosoindoles have also been found in other foods, such as Chinese cabbage, frequently consumed by high-risk populations (47).

The urinary excretion of nitrosoproline, an indicator of endogenous nitrosation, was higher in children of a high gastric cancer risk area of Costa Rica as compared to children of a
low-risk area. The same high-risk children had high levels of nitrosamine acids in their urine (48). Colombian patients with intestinal metaplasia and dysplasia had higher excretion of nitrosopropylene (adjusted for nitrate) than subjects without such lesions (49). Anaerobic bacteria, which frequently colonize stomachs with intestinal metaplasia, induce endogenous formation of nitroso compounds (50). These findings point to a role for bacterially catalyzed (as opposed to acid-catalyzed) nitrosation in the gastric cavity.

Intramucosal Carcinogens

Intramucosal nitrosation was reported by Stemmermann and Mower (51) in 1981. They detected nitroso compounds, derived from hydroxyzine and diazepam given by i.m. injection as pre-anesthetic agents, in homogenates of gastric antral biopsies with intestinal metaplasia. The rapidity of the reaction and the subsite specificity suggested that the nitrosation reaction took place in the mucosa itself rather than in the lumen.

While studying urinary excretion of nitrate, Tannenbaum et al. (52) confirmed old reports of in vivo nitrate synthesis and went on to demonstrate that it was the product of chemical reactions stimulated by bacterial lipopolysaccharides. Cellular components of inflammatory infiltrate, namely activated macrophages and polymorphonuclear leukocytes, are directly involved in these reactions through a biochemical pathway in which NO is produced (53). The same investigators have shown that NO induces mutations in human cells. These could alter the p53 suppressor gene in different ways. The p53 mutations reported in colon cancer could be induced by NO-related deamination of thymine while those reported in liver and lung cancers could be induced by NO via depurination (53). Polymorphonuclear leukocytes attracted by H. pylori are seen in the immediate vicinity of replicating cells, some of which stain positive for mutant p53 protein as shown in Fig. 7. The TRP-MET translocation (chromosome 7→1), a mutation reported in gastric carcinomas, has been detected at earlier points in the chain of events, such as intestinal metaplasia and even superficial gastritis (54).

Prevention of Gastric Carcinoma

The accumulated knowledge on gastric carcinogenesis in humans can be used to adopt prevention measures. Primary prevention should be achieved by intervention on the etiological factors already identified, namely excessive salt intake, deficient intake of fresh fruits and vegetables (containing micronutrient antioxidants), and H. pylori infection. The diet of wealthy western societies seems to have been doing just that in an unplanned way for several decades. One or more of these factors is still...
present in the communities which today continue to display very high rates of gastric cancer and efforts should be made to achieve primary prevention by correcting them.

For those subjects who already have the precursor lesions, a different strategy may be indicated. The first need is to identify patients with advanced precursors or with neoplasia in the “early” or “superficial” stage. If a small malignant lesion is identified, surgical resection is indicated. Excellent results in terms of survival have been reported (55). In the absence of neoplastic lesions, markers of progression of the precancerous process are needed. In terms of histological markers, our results indicate a high degree of efficiency of the combined expression of sulfomucins and Lewis antigen abnormalities, two easily accessible histological techniques. Screening populations at high risk could identify the individuals who need special attention. One screening method tested in Japan is based on double-contrast X-ray techniques administered to the general population and followed by endoscopy in those subjects with X-ray abnormalities. The efficiency of this methodology has been only partially evaluated (56). The cost of the procedures involved precludes their application to large populations of low economic potential.

Screening with pepsinogen serum levels has been attempted but still requires more thorough evaluation. Low pepsinogen I levels indicate loss of chief cells in the corpus (atrophy), an indirect marker of advanced cancer precursor lesions. Pepsinogen II, the only type normally secreted in antral glands, is abnormally synthesized by some preneoplastic and neoplastic cells. The ratio of pepsinogen I to pepsinogen II may therefore reflect the risk with more fidelity. Research on this subject is in progress in populations with different profiles of risk factors.

The “spontaneous” decline in gastric cancer rates observed in many countries could be generalized to the populations experiencing high risk at the present time by applying primary and secondary prevention strategies based on the progress made in elucidating the carcinogenic mechanisms. Chemoprevention trials using micronutrient antioxidants and anti-Helicobacter therapy are under way. Human gastric carcinogenesis may be useful as a model in elucidating the carcinogenic process in other organs.

Acknowledgments

I am especially grateful to William Haenszel for his support, guidance, encouragement, and constructive critique since 1962 and to Steven R. Tannenbaum for helping us bridge epidemiology with laboratory science.

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