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Review article

The future of gastric cancer prevention

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Abstract

Despite advances in surgical treatment and chemotherapy, gastric cancer remains a major global health burden. The most recent estimates show that it is the fourth most common cancer and the second most common cause of cancer deaths worldwide. Various etiologic factors have been linked with the disease. It is widely accepted that *Helicobacter pylori* infection and high salt intake are positively associated with this neoplastic process. Controversial associations have been found with smoking or drinking habits. In contrast, there is convincing evidence that the adequate consumption of fresh fruits and vegetables reduces the risk of gastric cancer. Prevention intervention trials involving antioxidant supplements and anti-*H. pylori* treatment have shown beneficial effects in preventing the progression of pathologic changes in the gastric mucosa. On the other hand, recent advances related to differences in the genotypes of the bacteria and in human cytokine polymorphisms would allow the design and implementation of large-scale screening programs to identify subjects at the highest risk of gastric cancer. Curing the infection in such subjects and supplying adequate amounts of antioxidants should prevent a neoplastic outcome, and this intervention should be monitored by endoscopic surveillance.

Key words *Helicobacter pylori* · Gastric cancer · Prevention · Genetic polymorphisms · Bacterial genotypes

Introduction

Approximately 90% of gastric cancers are adenocarcinomas [1], which may be further distinguished as intestinal and diffuse subtypes [2]. Intestinal-type adenocarcinoma predominates in the high-incidence areas [3]. The early stages of the disease are often clinically silent, and in most countries, patients have advanced stages at diagnosis. Once the neoplastic cells invade the muscularis propria, the prognosis is dismal, with reported 5-year survival rates of around 20% in the United States [4].

Preventive strategies offer the best opportunities for control of the disease, for several reasons. (1) The precancerous process usually takes decades and its different precancerous stages have been well characterized. (2) The decline of gastric cancer incidence indicates its preventability, and the main etiologic factors known are amenable to control measures. (3) Descendants of populations that migrated from high- to low-incidence countries have shown reduction of their risk of cancer compared with their homeland risk [5,6]. (4) Recent advances in molecular biology have identified polymorphisms in bacterial virulence genes, as well as in host susceptibility genes, that, when combined, carry a very high risk of the disease [7,8]. The theoretical framework to develop successful preventive strategies has been clarified; a multidisciplinary approach should combine population screening with molecular biological techniques that are being developed.

Magnitude of the gastric cancer burden

Although the gastric cancer incidence rates have been declining in many countries [9,10], the most recent estimates show that it is the fourth most common cancer and the second most common cause of cancer deaths worldwide (Tables 1 and 2) [11,12]. The geographic distribution of gastric cancer is characterized by wide international variations. High-risk areas include Japan, Korea, and China, as well as Central and South America. Incidence rates are low in southern Asia, North America, and Africa [11].

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Table 1. Estimated new cancer cases. Ten most common sites, world 2000 [11]

Cancer	Male	Female	Both sexes	Percentage
Lung	902000	337000	1239000	12.3
Breast	0	1050000	1050000	10.4
Colon/Rectum	499000	446000	945000	9.4
Stomach	558000	318000	876000	8.7
Liver	398000	166000	564000	5.6
Prostate	543000	0	543000	5.4
Cervix uteri	0	471000	471000	4.7
Esophagus	279000	133000	412000	4.1
Bladder	260000	76000	336000	3.3
Non-Hodgkin's lymphoma	167000	121000	287000	2.9

Table 2. Estimated cancer deaths. Ten most common sites, world 2000 [11]

Cancer	Male	Female	Both sexes	Percentage
Lung	810000	293000	1103000	17.8
Stomach	405000	241000	647000	10.4
Liver	384000	165000	549000	8.8
Colon/Rectum	255000	238000	492000	7.9
Breast	0	373000	373000	6.0
Esophagus	227000	111000	338000	5.4
Cervix uteri	0	233000	233000	3.8
Pancreas	112000	101000	213000	3.4
Prostate	204000	0	204000	3.3
Leukemia	109000	86000	195000	3.1

Etiological hypotheses

Gastric carcinogenesis is a multifactorial process. Following the classical epidemiological model, it could be proposed that the process represents the interaction of three major sets of factors: the agent (*Helicobacter pylori*), the host, and the external environment. The target tissue for this interaction is the gastric mucosa (Fig. 1).

Among the main external environmental factors are: low socioeconomic status, crowding, poor hygienic conditions, and diet. Diet has been linked to the etiology of gastric cancer in numerous international studies [13]. High salt intake has been considered an important causative factor for many years [14,15]. However, salt consumption has been reduced in many countries, probably as a result of public health campaigns and improvements in food preservation (refrigeration), leading to the decreased consumption of salty preserved foods [16,17]. Most consistently, adequate intake of fresh fruits and vegetables is associated with decreased risk [18,19]. Alcohol and tobacco use is associated with a modest increase in risk; however, this relation is controversial [20,21].

H. pylori infection has been recognized as having a prominent causative role [22]. A combined analysis of prospective and case-control studies reported a significant association between prior *H. pylori* infection and gastric cancer overall, but no association with cancer of the cardia [23]. The bacterial infection is usually acquired during childhood, and persists for many decades unless treated with antibiotics [7]. It is widely accepted that the bacteria do not penetrate the epithelial cells but reside in the gastric lumen and may adhere to the cell surface [24,25]. The infection induces a chronic gastritis with dense mononuclear inflammatory infiltrate, but is frequently accompanied by acute (active) inflammation characterized by the presence of polymorphonuclear neutrophils [26].

The clinical outcome of *H. pylori* infection varies according to the interrelation of bacterial, host, and environmental factors [27–29]. In most subjects the inflammation is mild and does not lead to recognizable clinical signs or symptoms [24]. Patients who develop clinical symptoms usually fall into one of two distinct categories. In one of them, the individuals exhibit gastritis mostly localized in the gastric antrum and often associated with hyperacidity. They tend to develop duodenal ulcers, which persist in time. The antral inflammation is not accompanied by loss of glands (nonatrophic gastritis), as represented by the microphotograph on the lower left side of Fig. 1. Several studies have concluded that this syndrome does not lead to increased cancer risk [30,31]. In contrast, the other category is predominant in populations at high risk of gas-

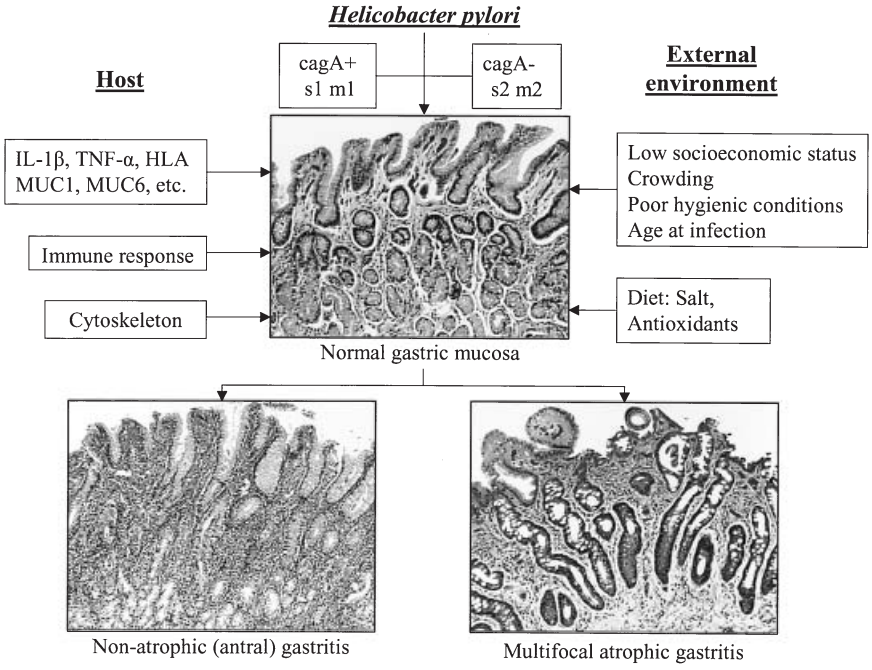

Fig. 1. Schematic representation of factors which interact to determine the clinical outcome of *Helicobacter pylori* infection. *IL-1*β, interleukin-1β; *TNF-*α, tumor necrosis factor-α

tric cancer, in whom the chronic gastritis involves the antrum and the corpus in multiple foci characterized by loss of glands (atrophy), usually leading to their replacement by glands with intestinal phenotype (intestinal metaplasia). This type of gastritis has received the name of multifocal atrophic gastritis or pangastritis, and is represented by the microphotograph on the lower right side of Fig. 1 [26,32].

Genetic polymorphisms

Genetic susceptibility has been proposed as another important determinant in the carcinogenic process. Several human allelic variants (polymorphisms) have shown an increased risk of gastric cancer. A recent review groups the principal polymorphisms studied according to the processes in which their encoded proteins intervene: MUC1 and MUC6, related to mucosa protection; interleukin 1-beta (IL-1β), interleukin 1-receptor antagonist (IL-1-RN), tumor necrosis factor-alpha (TNF-α), and human leukocyte antigen (HLA) molecules, associated with the inflammatory response; and glutathione S-transferases (GSTs) and N-acetyl transferases (NATs), associated with detoxification processes. Other polymorphisms associated with an increased risk have been found in genes encoding proteins that are involved in antioxidant processes, DNA repair, and cell proliferation [33].

The more extensively explored polymorphisms associated with gastric atrophy and gastric cancer are those related to IL-1β and TNF-α [34–36]. Recent studies in the United States and Portugal reported a significantly increased risk of gastric cancer in IL-1β-511T carriers, IL-1-RN 2/2 genotype, and TNF-α-308A carriers [37,38]. One of these studies associated noncardia cancer with IL-1β-511 T/T (odds ratio [OR], 9.5; 95% confidence interval [CI], 4.0–22.7), IL-1-RN 2/2 (OR, 5.4; 95% CI, 2.6–11.1), and TNF-α-308 A/A (OR, 4.8; 95% CI, 1.8–12.8) [37]. Gastric cancer risk increased progressively with an increasing number of high-risk polymorphisms [37,38].

On the other hand, it has been recently shown that variants of *H. pylori* genes determine its virulence [39]. *H. pylori* strains show a high grade of genetic diversity [40] and broad geographic variation in the genotypes [41]. Two main bacterial genes, *cagA* and *vacA*, are generally recognized as determining virulence. Strains with *vacA* m1 alleles are more toxigenic than those with m2 alleles, which are mildly or nontoxigenic, and, within the m1 group, strains with s1a/m1 alleles are more toxigenic than those with s1b/m1 alleles [42]. *vacA* s1 and m1 genotypes are related to gastric cancer risk [8]. The presence of the *cagA* gene is associated with a more severe proinflammatory response and with increased oxidative and nitrative stress in gastric mucosa than its absence [43]. *cagA*-positive genotypes predominate in gastric cancer patients [44] and in populations at high gastric cancer risk [45].

Several combinations of high-virulence bacterial genotypes with high-risk host genetic polymorphisms result in a remarkable increase in cancer risk. For instance, the combination of the *vacA* s1 genotype with

IL-1β-511/T carriers results in an OR of 87 (95% CI, 11–679) [8]. Benefits that may derive from such knowledge could not only advance the field of carcinogenesis studies but could also point the way to cancer prevention.

Oxidative damage

Although the exact mechanisms of the carcinogenic process remain largely unknown, recent focus has been directed to the possibility that "oxidative stress" may be a crucial mechanism in the chain of events that may finally result in neoplastic cell transformation. Figure 2 is a schematic representation of such a hypothesis [46]. *H. pylori* infection leads to gastric mucosal inflammation, with infiltration by macrophages and polymorphonuclear neutrophils, which contain inducible nitric oxide synthase (iNOS) [47–49]. This enzyme drives the formation of large amounts of nitric oxide (NO), a highly reactive molecule that has been broadly implicated in carcinogenic processes [50,51]. Reactive nitrogen oxide species (including peroxynitrite, $ONOO^-$) may damage DNA [52,53] and impair DNA repair mechanisms [54,55], as well as inhibit mitochondrial function of the target epithelial cells. In addition, they may induce changes in the cell cycle (depressed apoptosis and increased proliferation) of actively replicating epithelial cells [56]. As the precancerous process advances, iNOS is seen in the cytoplasm of dysplastic and neoplastic epithelial cells [48,57,58]. Simultaneously with these changes, the inflammatory cells also synthesize antioxidant enzymes, such as catalase and superoxide dismutase, which may prevent the cellular damage induced by the oxidative stress [48,59]. It thus appears that, during the many years of evolution of the precancerous process, opposing forces of oxidation and anti-oxidation operate and interact to either induce or prevent neoplastic cell transformation.

Therefore, it appears that antioxidants may contribute to the prevention of carcinogenesis in the stomach by neutralizing reactive oxygen species.

The precancerous process

It has long been recognized that multiple sequential changes of the gastric mucosa take place before invasive neoplasia develops [60]. Figure 3 depicts the well-recognized steps in the process: gastritis → atrophy → intestinal metaplasia → dysplasia. Each of these lesions has been well characterized, but each of them may display different degrees of severity, as well as some different phenotypic varieties. Subjects who develop multifocal atrophic gastritis frequently progress to intestinal metaplasia. The metaplasia, at the beginning of the process, phenotypically resembles the small-intestinal mucosa with absorptive enterocytes alternating with well-developed goblet cells. Such metaplasia is usually called "type I" or "complete" [61,62], because it displays the "complete" set of digestive enzymes seen in the normal small intestine. In more advanced stages,

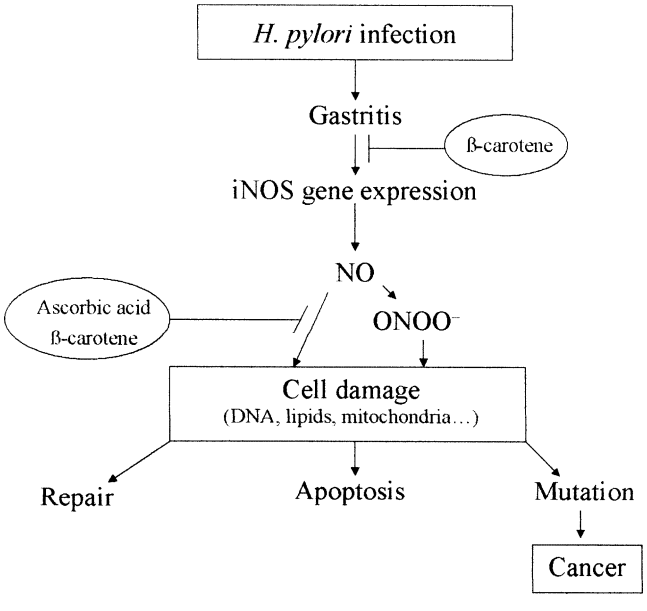

Fig. 2. Hypothetical events in oxidative damage in gastric carcinogenesis. *iNOS*, inducible nitric oxide synthase. Adapted from reference [46] (Correa and Miller, 1998), with permission

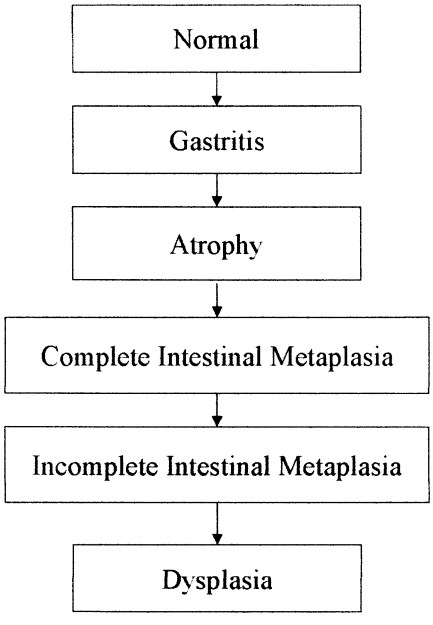

Fig. 3. Multistep model of gastric precancerous process. Adapted from reference [60] (Correa et al., 1975), with permission

usually seen in older patients, the metaplastic cells display a "colonic" phenotype, which is called "type III" or "incomplete", because it lacks some of the normal digestive enzymes of the small intestine. It is phenotypically characterized by columnar cells without a clear brush border and with many cytoplasmic mucous vacuoles of varying sizes. Such metaplasia is frequently seen in the vicinity of areas of dysplasia, or in patients with "early" carcinomas [62], and has been associated with a higher risk for gastric cancer when compared to complete metaplasia [63]. Incomplete metaplasia may represent a mild form of dysplasia, which may require more frequent follow-up of the patient, because it may be followed by overt dysplasia or early carcinoma [64].

Prolonged follow-up of patients with different stages of the precancerous process has shown a slow general progression, with apparent episodes of "progression" to more advanced lesions, as well as instances in which the most recent biopsies display less advanced lesions than those observed in previous biopsies, apparently suggesting that some lesions may "regress" to less advanced stages [65].

Chemoprevention trials

Clinical chemoprevention trials can be separated into two types according to their end-points: cancer or intermediate (precancerous) stages. Some intervention trials have been concluded that involved nutrient supplements and examining gastric cancer as an endpoint. One of them was carried out in China; the authors report reductions in gastric cancer mortality and incidence after 5 years of follow-up in the group that received daily supplements containing beta-carotene, vitamin E, and selenium [66]. Another study, in the low-risk population of United States male physicians, showed no statistically significant benefit due to beta-carotene, after an average follow-up of 12 years [67]. Several studies evaluating precancerous lesions as an endpoint and using *H. pylori* treatment [68,69] and antioxidant supplements have been published [70]. They report that *H. pylori* eradication is beneficial in preventing the progression of preneoplastic lesions in the gastric mucosa. Wong et al. [69] published preliminary results of a trial in China after 5 years of *H. pylori* eradication, showing a significantly lower proportion with progression of gastric atrophy in the intervention group compared to placebo. A 6-year trial in Colombia tested the effect of anti-*H. pylori* treatment and dietary supplementation with antioxidants, following a factorial design [70]. Disease progression/regression was evaluated by comparing pre- and postintervention gastric biopsies. Eradication of the infection resulted in significant regression of lesions, with a relative risk (RR) of 8.7 (95% CI, 2.7–28.2) for patients with atrophy and an RR of 5.4 (95% CI, 1.7–17.6) for patients with intestinal metaplasia. Dietary supplementation with beta-carotene, ascorbic acid, or both agents, resulted in an increased risk of regression of lesions compared with placebo: RR, 5.1 (95% CI, 1.7–15.0); RR, 5.0 (95% CI, 1.7–14.4); and RR, 8.3 (95% CI, 2.2–31.5); respectively. Differences among these groups were not significant. The combined effect of anti-*H. pylori* treatment and antioxidant supplements led to results similar to those for each agent. No additive effects were found for any of the combinations.

These results give support to the hypothesis that oxidative stress may represent the final common path of *H. pylori* carcinogenesis. It would appear that the damage could be prevented either by curing the infection or by avoiding the oxidative damage by the use of antioxidant agents.

Future directions

Our present knowledge has advanced on several fronts. To formulate preventive strategies, the main aspects to be considered can be summarized in the following points:

1. The gastric cancer burden is very considerable.
2. Although a multifactorial etiology is acknowledged, the main factors are infection with *H. pylori* and the inadequate intake of antioxidant micronutrients, which are especially abundant in fresh fruits and vegetables. Both factors can be controlled.
3. An etiologic hypothesis suggests that oxidative damage may be the final common path leading to neoplastic transformation.
4. The precancerous process is very prolonged, usually lasting several decades. Its intermediate steps are well-characterized histopathologically and may be reversible.
5. Recently studied polymorphisms in the bacterial and host genes have been shown to be associated with increase in the cancer risk. Virulent bacteria infecting susceptible subjects is an event that identifies individuals at very high risk of gastric cancer.
6. Chemoprevention trials have demonstrated effectiveness in inhibiting the progression or promoting the regression of precancerous lesions.

The current understanding of the complex interaction between host and *H. pylori* permits the formulation of new preventive strategies in gastric cancer. What is needed at the present time is to develop rapid and inexpensive tests to detect the bacterial and host polymorphisms that considerably increase the risk of cancer. Once such techniques are developed, clinicians and

Table 3. Incidence rates and estimates of the number of subjects needing screening to find one case of gastric cancer in males 45 years of age and older. Selected cancer registries as examples [71]

Registry	Crude incidence rate, males (≥45 years)[a]		Number of subjects[b]	
	Total[c]	Infected[d]	Total[c]	Infected[d]
California, Los Angeles — NonHispanic White, USA	34.8	49.7	2877	2014
California, Los Angeles — Black, USA	51.2	73.1	1955	1368
Cali, Colombia	110.5	157.9	905	633
Quito, Ecuador	110.8	158.4	902	632
Kangwha County, Republic of Korea	237.2	338.9	422	295
Hiroshima, Japan	293.8	419.7	340	238
Yamagata, Japan	396.0	565.7	253	177

[a] Annual incidence per 100000 persons
[b] Number of subjects needed to find one case of gastric cancer
[c] Estimated data for total population in the age stratum
[d] Estimated data for infected population in the age stratum, assuming 70% *Helicobacter pylori* infection

epidemiologists should design screening programs to identify, in the general population, subjects with a very high risk of developing gastric cancer. Such individuals should receive effective anti-*H. pylori* treatments and should be prescribed adequate amounts of antioxidant micronutrients. Endoscopic follow-up will be needed to monitor the efficiency of the intervention.

Strategies for prevention may differ according to the risk level of populations. As an example, Table 3 shows an estimate of the number of males 45 years of age and older that would need to be screened to find one case of gastric cancer for six registries of cancer from different areas of the world, based on the crude incidence rates. Our estimates were done using the total male population, by area, for this age stratum; additional estimates were done assuming 70% *H. pylori* infection. The higher the incidence rate, the lower the number of persons required for the screening process. It would appear that the cost-benefit ratio of screening is economically justifiable in high-risk populations.

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