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Gastric cancer: An infectious disease

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Introduction

Although viral and parasitic agents have been implicated in human cancers, gastric cancer is at the present time the only malignant neoplasia recognized as causally associated in humans with a bacterium. In 1994 the International Agency for Research on Cancer (IARC) concluded: "there is sufficient evidence in humans for the carcinogenicity of infection with *Helicobacter pylori*" [1]. At that time they concluded that "there is inadequate evidence in experimental animals for the carcinogenicity of infection with *Helicobacter pylori*". Since then, experimental evidence of carcinogenicity has been documented, especially utilizing the Mongolian gerbil model [2]. In 2009 the evidence was reevaluated and confirmed by the IARC [3]. *H. pylori* is associated with causation of gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma [3]. Since gastric adenocarcinomas account for more than 90% of all gastric malignancies [4], this review will focus on adenocarcinomas.

Although gastric cancer rates have been decreasing in many countries, this disease is the second most common cause of death from cancer worldwide and ranks fourth worldwide in cancer incidence (Table 1) [5]. Approximately one million new cases were estimated in 2007 [6]. There are marked differences in gastric cancer rates among populations worldwide. The highest incidence rates are in Japan, Korea, China, Eastern Europe and the Andean portions of Latin America. Lower rates are seen in Africa, Oceania, North America, and Brazil (Fig. 1). Despite the low overall rates in gastric cancer incidence and mortality in the United States, there are some ethnic groups at increased risk, including African Americans, Native Americans, and immigrants from East Asia and Latin America [7–9]. In addition, although overall incidence rates of gastric cancer have been steadily declining in the United States, a recent observational study based on data from the National Cancer Institute's Surveillance, Epidemiology, and End

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Results identified increasing rates of non-cardia cancer in white U.S. residents aged 25 to 39 years in the past 3 decades [10]. The causes of this phenomenon are unclear.

Agent-host-environment interactions

Infection with *H. pylori* is the strongest known risk factor for gastric cancer [1,11–13]; however, only a small minority of people infected with *H. pylori* develops gastric cancer or gastric precancerous lesions. The epidemiologic triangle, a conceptual model that posits that the outcome depends on the complex interplay of the agent with environmental and host factors [14], can be applied to better understand the etiology of gastric cancer. Factors specific to the host, such as genetic background, diet, and smoking behavior, as well as factors related to the environment, including neighborhood socioeconomic status, parasites endemic to the region, and possibly even climate, play key roles in whether gastric cancer develops in a particular individual. There is clearly a strong environmental component that affects the cancer risk. Migrant populations from high-risk areas of the world show a decrease in risk in the second generation when they move to a lower-risk area [15]. Some of these factors work on both the individual and societal level, and can be viewed as factors associated with host, environment, or both, depending on the specific characteristic. A change in this precarious balance of agent, host, and environment – such as infection with a more virulent strain of *H. pylori* or increased salt intake – can affect the speed of the cascade of events that lead to the development of gastric cancer.

The infectious agent

H. pylori

H. pylori is a Gram-negative microaerophilic spiral bacterium that localizes mostly extracellular within the gastric lumen (Fig. 2). Identified and cultured for the first time in 1982 by Marshall and Warren [16], *H. pylori* is present in more than 50% of the human population [17] and is highly adapted to colonize the human stomach. It possesses a potent urease which allows it to live in the acid microenvironment of the gastric lumen. This is accomplished by hydrolyzing the urea which filters into the lumen resulting in an ammonium cloud that protects the bacterium from the acid pH. In the same reaction, carbon dioxide is produced and immediately eliminated with the exhaled air. Oral administration of ^{13}C-urea is used as a diagnostic test since $^{13}CO_2$ is exhaled if the infection is present. Other factors that contribute to the persistence of the bacterium in the stomach are certain characteristics of the lipopolysaccharide that reduce the intensity of the host immune response and the expression of adhesins that confer intimate adherence to the gastric epithelium [18,19].

H. pylori has been part of the native human flora since time immemorial. Both species migrated out of Africa some 60,000 years ago and have traveled together since then to other continents. Molecular microbiological studies have shown that the genome of the bacteria evolves frequently, mostly from recombination. Achtman and colleagues, using the multilocus sequence typing (MLST) of 7 housekeeping genes, have identified bacterial strains which traced their origin to specific populations of Africa (hpAfrica), Europe (hpEurope) and Asia (hpEAsia) [20–22]. The original Amerindian strains in the Americas, after being exposed to European strains, supposedly then acquired the *cag* pathogenicity island (*cag* PAI), a recognized virulence factor [23–26]. It is not clear if the Amerindian strains were totally replaced by European strains or if they acquired some of their genes by recombination [26]. Preliminary results from an ongoing study in Colombia show that *H. pylori* isolates from the high-gastric cancer-risk populations of the Andes Mountains, of mestizo extraction (mixed Amerindian and European ancestry), display European genotypes by MLST, presumably indicating the exposure of Amerindian strains to European strains. In contrast, inhabitants of the low-gastric cancer-risk area on the Pacific coast, of mixed African and European extraction,

display heterogeneity of their *H. pylori* strains: some harbor West African genotypes and some harbor European genotypes (data not published). These findings suggest that the ancestry of the bacterial strains may be linked to cancer risk.

Despite the widespread dissemination of *H. pylori* infection, it is estimated that only a minute fraction of infected subjects will ever develop gastric adenocarcinoma. However, it is also estimated that 77% of the world's non-cardia gastric cancer is attributable to *H. pylori* infection [17]. Several components of the *H. pylori* genome are linked to carcinogenicity. *cag* PAI, a major determinant of virulence, is a cluster of genes present in about 60% of *H. pylori* isolates from Western countries and in almost all of the isolates from East Asian countries [27]. One gene (*cagA*) in the *H. pylori cag* PAI encodes an effector protein (CagA) and others encode proteins for a type IV secretion apparatus that translocates CagA into gastric epithelial cells [23,24]. Infection with *cagA*-positive *H. pylori* strains has been associated with increased risk for development of peptic ulcer [24,28], gastric precancerous lesions and gastric adenocarcinoma [29–31]. *cagA*-positive strains are more prevalent in high-cancer-risk than in low-risk populations: approximately 90% in the Andes Mountains and 70% in the Pacific coast of Colombia [32]. The CagA protein is polymorphic, as shown by the sequences flanking the so-called EPIYA motifs. Most strains have EPIYA-A and EPIYA-B motifs. The EPIYA-C motif is characteristic of the Western strains while the EPIYA-D segment characterizes East Asian strains. These motifs become tyrosine phosphorylated when they enter the epithelial cells of the host, presumably starting the chain of events that may eventually result in neoplastic transformation [27]. Another virulence factor is a protein known as VacA, a multifunctional cytotoxin which causes intracellular vacuoles and form membrane channels in epithelial cells [33]. The *vacA* gene is present in all *H. pylori* strains, and comprises several variable loci (designed s, i, m). The combination of different alleles determines the production of cytotoxin and is associated with the pathogenicity of the bacterium [18,33].

Despite the fact that both types of peptic ulcers (gastric and duodenal) are causally linked to *H. pylori* infection, it has been recognized that gastric peptic ulcer is associated with a high risk of gastric cancer, whereas duodenal ulcer is associated with a low risk when compared to the general population [13,34]. Patients with gastric ulcers typically have multifocal atrophic gastritis. Patients with duodenal ulcers have antrum-predominant gastritis but none of the atrophic changes.

Epstein-Barr virus (EBV)

Increasing evidence indicates the possibility of a role of EBV in the etiology of some gastric cancers. Multiple studies around the world have found the presence of the EBV in 5–16% of gastric adenocarcinomas. A recent meta-analysis including 70 articles estimated that the overall EBV positivity was 8.7% among gastric cancer cases and that EBV-associated adenocarcinomas are more frequent in males than females, in gastric cardia or corpus than in antrum, and in tumors of postsurgical gastric stump/remnants [35]. In addition, a strong association (>90%) was confirmed between EBV and the uncommon histologic type lymphoepithelioma-like gastric carcinoma [35]. Several observations support the etiological involvement of EBV in some gastric cancers, including the uniform presence of clonal EBV in all malignant cells of EBV-positive tumors but not in surrounding normal epithelial cells [36]. However, the precise role of EBV in gastric carcinogenesis is still unclear.

The environment

Diet

In 2007 an expert panel from the World Cancer Research Fund released a report declaring that high intakes of vegetables and fruit probably decrease risk of gastric cancer, and that high

intakes of salt and salty food probably increase risk of gastric cancer [37]. The majority of the evidence for these associations comes from case-control studies; cohort studies have been more inconsistent and have primarily found weaker, non-significant associations. The mechanism for the inverse association of gastric cancer risk with high vegetable and fruit intake has been hypothesized to be related to the presence of antioxidants, which protect against oxidative damage. The positive association with salt has been more clearly delineated, as salt acts directly on the stomach lining, destroying the mucosal barrier and causing gastritis, increasing epithelial proliferation [38]. A synergistic interaction between diet and *H. pylori* infection with risk of gastric cancer has been proposed [39], and studies on this topic have generally suggested a stronger effect among *H. pylori*-positive individuals [40,41].

Smoking

Tobacco smoking is the risk factor associated with the largest number of cancer cases worldwide and the causal link with stomach cancer is recognized [42]. A recent meta-analysis of 32 studies, including 18 cohort studies, found significant positive associations of smoking with risk of both cardia and non-cardia gastric cancer among the majority of studies, overall increasing risk by 62% for male current smokers (95% CI: 1.50–1.75) and 20% for female current smokers (95% CI: 1.01–1.43) [43]. Tobacco smoke contains multiple well-known chemical carcinogens [44]. While the mechanisms by which smoking increases the risk of gastric cancer are not completely understood, it is possible that tobacco smoke carcinogens affect gastric cancer risk directly through contact with the stomach mucosa or indirectly through the blood flow [45].

Non-steroidal anti-inflammatory drugs

Observational studies have consistently found a protective effect of regular use of non-steroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, on risk of gastric cancer. Specifically, a 2009 meta-analysis found that regular NSAID users had an 18%–20% reduced risk of gastric cardia adenocarcinoma and a 32%–36% reduced risk of distal gastric adenocarcinoma [46]. NSAIDs are seen as chemopreventive agents as they suppress the production of cyclooxygenase enzymes, which are involved in prostaglandin biosynthesis [47]. While clinical trials of NSAIDs and risk of colorectal adenoma among high-risk populations have mostly met with success [48], there has been only one clinical trial with gastric cancer or a gastric cancer precursor. In this randomized trial of the COX-2 inhibitor rofecoxib, the drug did not reduce risk of gastric intestinal metaplasia after a 2-year period [49]. It is possible, however, that the duration of drug use was not long enough, and/or that intervention with NSAIDs may be effective at a later stage of the carcinogenesis process. A recent international consensus statement on aspirin and cancer prevention concluded that future research should focus on high-risk individuals and aim to resolve the questions of optimal dose, age to begin therapy, and treatment duration [50].

Socioeconomic status

Lower socioeconomic status, whether measured by education and/or income, has been consistently associated with an at least two-fold greater risk of gastric cancer [51]. This gradient has been observed within both high-risk countries (such as Japan) and low-risk countries (including the United States) [52]. The actual factors creating this association are most likely characteristics related to low socioeconomic status that increase likelihood of transmission and re-infection with *H. pylori*, such as household crowding, large family size, poor household sanitation, and less frequent use of antibiotics. Additionally, low socioeconomic status could be an indicator of a diet lower in fresh fruits and vegetables. The high gastric cancer risk seen in a few countries with overall high socioeconomic status, such as Japan and South Korea, is

not completely understood, but it is possibly due to the prevalence of highly virulent strains of *H. pylori* in these countries [53].

The African enigma

H. pylori infects more than half of the world's population, with variable rates of prevalence across countries and among ethnic groups [17]. However, discordance between the high prevalence of *H. pylori* infection and the low rates of gastric cancer has been observed in some areas, especially in the African continent. This phenomenon has been called the "African enigma" [54]. Studies carried out in different regions of Africa have shown that the majority of populations are infected with *H. pylori*, with 61–80% showing evidence of antibodies to *H. pylori*, and that acquisition of the infection occurs at an early age [54,55]. In sub-Saharan Africa, despite overall high *H. pylori* infection prevalence, gastric cancer incidence rates are relatively low [55]. A similar pattern has been found in other geographic regions. In Colombia, our group has identified a high-risk area for gastric cancer in the Andes Mountains and a low-risk area on the Pacific coast [56]. The two populations have similar prevalence of *H. pylori* infection in adult population (74% and 80%) [32] and a common pattern of very early age at infection [57]. In Costa Rica, marked regional heterogeneity in cancer incidence has been observed in spite of no significant variation in *H. pylori* infection prevalence [58]. In both Colombia and Costa Rica, greater prevalence of more virulent strains have been observed in the high-risk areas [32,59,60]. However, it is unlikely that these differences are large enough to completely explain the differences in gastric cancer risk.

The lack of correlation between gastric cancer incidence and *H. pylori* infection prevalence indicates that other factors, such as environmental factors, host genetic background, and co-infections, may modulate the outcome of the infection. One important factor is diet. High-risk populations tend to have excessive salt intake, while low-risk communities on the coastal regions of Colombia more frequently consume fish and seafood and fruits. Another factor is the type of immune response of the host to the *H. pylori* infection. Intestinal parasites, especially helminths, are more frequent in tropical climates and they tend to modulate the immune response towards a Th2 anti-inflammatory type [61,62]. In Colombia, we observed that children in the low-risk area (on the coast) were more than twice as likely to be infected with helminths and both adults and children had serum IgE levels several times higher than those in the high-risk area (mountains) [62]. In addition, significantly greater eosinophilic infiltration of the gastric mucosa was observed in infected adult subjects of the low-risk area compared to subjects of the high-risk area [63]. In an animal model, supporting this hypothesis, concurrent helminth infection considerably reduced *Helicobacter*-associated gastric inflammatory cytokines and chemokines associated with a Th1 response and gastric atrophy [64]. Similar evidence from a Chinese population indicates that a concurrent helminth infection modifies the immune response to *H. pylori* and reduces the probability of developing gastric corpus atrophy [65]. These results suggest that early acquisition of the parasite induces an anti-inflammatory Th2 immune response against the *H. pylori* infection. This anti-inflammatory response may aid in ameliorating the chronic damage to the gastric mucosa, subsequently decreasing the risk of gastric cancer.

The host

Host genetics in H. pylori-induced gastric cancer

The association between chronic inflammation and cancer is well established and gastric adenocarcinoma is usually accompanied by an evident inflammatory infiltrate. The long-standing inflammatory response against *H. pylori* in the gastric mucosa may cause sustained tissue injury leading to the development of distal gastric cancer. Host genetic factors may influence the nature and intensity of the immune response to *H. pylori*. Polymorphisms in

cytokine genes have shown to be associated with risk for gastric cancer. Biologically, the genetic polymorphisms are thought to modulate risk by increasing expression of pro-inflammatory factors that enhance and prolong the inflammatory response in gastric mucosa. El-Omar *et al*. [66,67] were the first to show that polymorphisms in *IL1B* and *IL1RN* genes (*IL1B* encoding interleukin (IL)-1β and *IL1RN* encoding its naturally occurring receptor antagonist) were associated with elevated risk for hypochlorhydria and gastric cancer in subjects with *H. pylori* infection. IL-1β is a pro-inflammatory cytokine and a potent inhibitor of gastric acid secretion. It has been hypothesized that a profound acid secretion suppression promotes proliferation and dissemination of *H. pylori* from the antrum to the corpus, leading to a severe and more extensive gastritis that favors the development of atrophy and subsequently adenocarcinoma [68]. A meta-analysis concluded that *IL1B-511T* and *IL1RN*2* polymorphisms are associated with gastric cancer in Caucasians but not in Asians, and that the association of *IL1B-511T* in Caucasians was stronger when intestinal-type and noncardia gastric cancer cases were examined [69]. Polymorphisms in other cytokine genes have also been associated with cancer risk, including tumor necrosis factor alpha [70–72] and IL-10 [70]. Studies combining host susceptibility and bacterial virulence factors have shown that gastric cancer risk is highest among those with both host and bacterial high-risk genotypes [73,74]. An increasing amount of evidence shows the possible role of multiple other polymorphisms in genes mainly related to processes involved in carcinogenesis and/or cell defense and repair [75].

Pathology

Gastric adenocarcinomas are classified anatomically as proximal (cardia) and distal (non-cardia). Distal adenocarcinomas are commonly associated with *H. pylori* infection, but the association of this infection with cardia adenocarcinomas is less well defined. Gastric cardia adenocarcinomas are associated with gastroesophageal reflux disease [76]. Due to unclear reasons, the incidence of gastric cardia adenocarcinoma has been increasing during the last decades in conjunction with increase in esophageal adenocarcinoma, especially among white males [76–79]. In the United States, gastric cardia adenocarcinomas have lower overall 5-year survival rates than distal adenocarcinomas (14% vs. 26%) [76]. In addition to the problem of distinguishing gastric cardia from non-cardia adenocarcinomas, there is the difficulty in separating true cardia tumors from adenocarcinomas of the distal esophagus, frequently involving the gastroesophageal junction (GEJ). Thus, according to the Siewert and Stein classification, three types of carcinomas develop around the GEJ: 1) adenocarcinomas of the distal esophagus; 2) true cardia carcinomas, extending 1 cm above and 2 cm below the anatomic GEJ; and 3) subcardiac gastric cancers, tumors located more than 2 cm below the anatomic GEJ that may infiltrate the GEJ from below [80].

Carcinoma of the stomach may be detected either in an early stage or in an advanced stage. Early gastric cancer is defined as an adenocarcinoma confined to the gastric mucosa or submucosa regardless of lymph node metastasis [81]. The majority of patients with early gastric cancer are asymptomatic. Among symptomatic patients, dyspepsia and epigastric pain are the most common symptoms. The macroscopic appearance of advanced carcinomas may be polypoid, fungating, ulcerated or infiltrative (Borrmann's classification), with occasional combination of types. Histologically, there are several classifications for gastric adenocarcinomas. The most widely used in the United States is the Lauren's classification [82], which recognizes two main types: intestinal and diffuse (Fig. 3). Intestinal-type tumors predominate in geographic areas with a high incidence of gastric cancer, whereas diffuse-type tumors are found more uniformly throughout the world.

The precancerous process

It is currently accepted that intestinal-type adenocarcinomas develop through a series of sequential lesions in the gastric mucosa (Fig. 4). This multistep precancerous process was described in 1975 [83,84] based on observations in Colombian populations with high risk of gastric cancer [56,85,86], and before the identification of *H. pylori* infection as a carcinogen. The process starts when *H. pylori* colonizes the gastric mucosa, initially in the antropyloric region, avoiding the lower pH in the acid-producing areas (fundus and corpus) of the stomach. The immune response induced by the bacterium may vary in severity, but usually causes a non-atrophic chronic gastritis that may last decades, unless treatment eradicates the bacterium. Over time, the infection may spread proximally to the oxyntic mucosa, mainly in patients taking proton pump inhibitors. Prolonged and severe infection may eventually result in loss of glandular tissue (multifocal atrophic gastritis) and sometimes in gastric ulcers. The atrophic changes usually start in the incisura angularis and may extend to the antrum and the corpus mucosa, as the foci become progressively larger and coalesce. In some patients with multifocal atrophic gastritis, the lost glands are then replaced by glandular structures with intestinal phenotype, displaying characteristics of small intestine (complete intestinal metaplasia) or colonic epithelium (incomplete intestinal metaplasia). The complete type displays absorptive enterocytes with brush border, well-developed goblet cells, and Paneth cells. In incomplete intestinal metaplasia, there are goblet cells of variable size, absence of brush border and sometimes presence of sulfomucins. Evidence has supported that intestinal metaplasia of the incomplete type is associated with increased risk of gastric cancer [87,88]. A small proportion of subjects with intestinal metaplasia eventually will progress further to dysplasia (synonyms: intraepithelial neoplasia, non-invasive neoplasia, adenoma), which is classified as low grade or high grade. A fraction of subjects with dysplasia will develop adenocarcinoma, defined as invasion of the lamina propria or beyond. *H. pylori* tends to disappear as intestinal metaplasia develops. Therefore, previous or current *H. pylori* infection may be underestimated in subjects with intestinal metaplasia or more advanced lesions.

Intestinal-type adenocarcinoma

Besides *H. pylori* infection, other environmental factors including diet and smoking are recognized risk factors for intestinal-type adenocarcinoma. More recently (as described above), the etiopathogenic role of host genetic factors is increasingly recognized in this type of carcinoma. Most cases of intestinal-type adenocarcinomas are diagnosed between the ages of 50 and 70 years, and the incidence rate is approximately double in men compared to women. Microscopically, intestinal-type adenocarcinomas are formed by tumor cells arranged cohesively in irregular tubular or papillary structures infiltrating the stroma. Epithelium with intestinal metaplasia is frequently seen in neighboring mucosa (Fig. 3A). Based on architectural and cellular characteristics, the tumors have variable degree of differentiation. In the better differentiated adenocarcinomas, most of the cells are columnar and contain cytoplasmic mucin. Poorly differentiated adenocarcinomas have a predominantly solid pattern.

Diffuse type adenocarcinoma

Diffuse-type adenocarcinoma is relatively more frequent in populations at low risk for gastric cancer, in younger subjects, and environmental factors have been thought to play a less important role than genetic factors. Since atrophic changes are not severe in diffuse-type gastric cancer, it was previously considered to have little relation to *H. pylori* infection. However, epidemiologic and histopathological studies [30,89] have shown that the development of diffuse-type cancer is also related to *H. pylori* infection. Gross alterations include thickening and rigidity of the gastric wall, a condition known as linitis plastica. Microscopically, the tumoral cells of the diffuse type are usually round and rather small, and are arranged as single cells with minimal or absence of intercellular cohesion (Fig. 3B).

Hereditary diffuse gastric cancer is an autosomal dominant disorder that accounts for less than 1% of all cases of gastric cancer. Mutations in E-cadherin gene (*CDH1*) are germline defects associated with this syndrome [90–92]. *CDH1* encodes E-cadherin, a cell-to-cell adhesion molecule that plays a fundamental role in the maintenance of the normal architecture of epithelial tissues. Diffuse gastric cancer is the most important cause of cancer mortality in these families [93]. In addition to mutation, epigenetic inactivation of E-cadherin by promoter hypermethylation has been frequently reported in sporadic diffuse gastric cancer [94,95].

Cancer control

The high mortality rate from gastric cancer is believed to be primarily due to late-stage diagnoses. In the United States, two thirds of gastric cancer cases are diagnosed when the tumor has invaded the muscularis propria and the overall 5-year survival rate is about 25% [96]. Early gastric cancer is generally small and asymptomatic, and surgery or endoscopic resection can offer the chance of a cure. In Japan, a country with one of the highest incidence rates of gastric cancer, over 50% of cases are diagnosed at an early stage due to a massive screening program. The 5-year survival rate in this group is over 90% [97]. A recent review article authored by gastric cancer experts from the Asia Pacific Working Group on Gastric Cancer recommended multistage screening using serum-pepsinogen testing (to determine the presence and extension of atrophic gastritis) and *H. pylori* serology to identify patients at high risk, who should then go on to endoscopic surveillance [98]. *H. pylori* eradication has also been proposed as a method of gastric cancer prevention. In studies of precancerous gastric lesions, *H. pylori* eradication generally reduced the rate of progression [99]. While individual randomized, controlled trials of *H. pylori* eradication on gastric cancer risk have generally found non-statistically significant suggestions of protection, a recent meta-analysis of these trials found that when considering these trials together (and thus increasing the power to observe an association), *H. pylori* eradication treatment does significantly reduce risk of gastric cancer [100]. Additionally, a recent retrospective cohort study in Taiwan concluded that for patients with peptic ulcers, early *H. pylori* eradication – defined as within one year of hospitalization for the ulcer – decreased the risk of gastric cancer [101]. However, large scale *H. pylori* eradication strategies face challenges such as development of antibiotic resistant strains. In the United States, due to the low incidence rates of gastric cancer, endoscopic surveillance is recommended only in subjects with low-grade dysplasia. Patients with high-grade dysplasia need to undergo endoscopic or surgical resection [102]. However, surveillance of subjects with gastric intestinal metaplasia should be considered in presence of risk factors for gastric cancer such as family history of gastric cancer, ethnicity, and extensive or incomplete-type intestinal metaplasia [88,103,104].

An *H. pylori* vaccine has been in development for years, but there has been little success and currently an efficacious human vaccine does not exist. Both *H. pylori* strategies of eradication and vaccine development have also been criticized due to the potential unexpected effects of *H. pylori* eradication, including increased risk of esophageal adenocarcinoma, gastro-esophageal reflux-related diseases, and possibly allergic and autoimmune diseases [105–108].

Epilogue

The role of infectious agents and chronic inflammation in carcinogenesis is being increasingly recognized. It has been estimated that about 18% of cancers are directly linked to infections, particularly gastric adenocarcinoma (*H. pylori*), cervical carcinoma (human papilloma viruses) and hepatocarcinoma (hepatitis B and C viruses) [17]. Multiple clinical trials of COX-2 inhibitors and anti-inflammatory agents have shown a beneficial effect on the development of very diverse tumors, such as those of the colon, prostate and breast [50]. However, their

mechanism of action is not completely understood and may differ among the infectious agents and tumor types.

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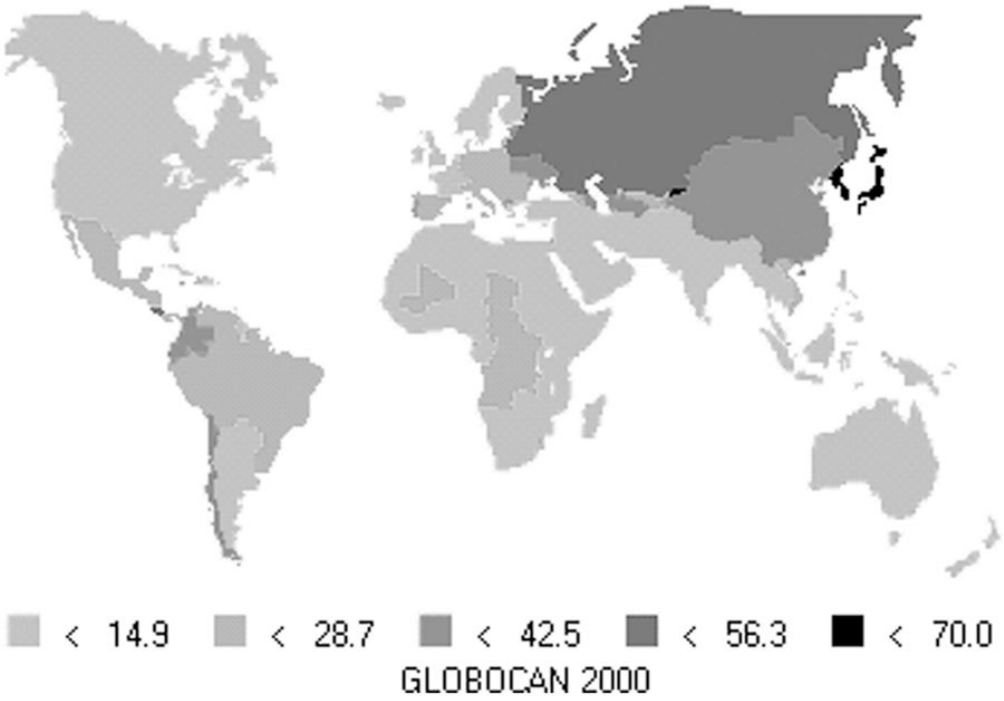

Figure 1.
Incidence of stomach cancer in males, worldwide (age-standardized rates). GLOBOCAN, 2000 (http://www-dep.iarc.fr/).

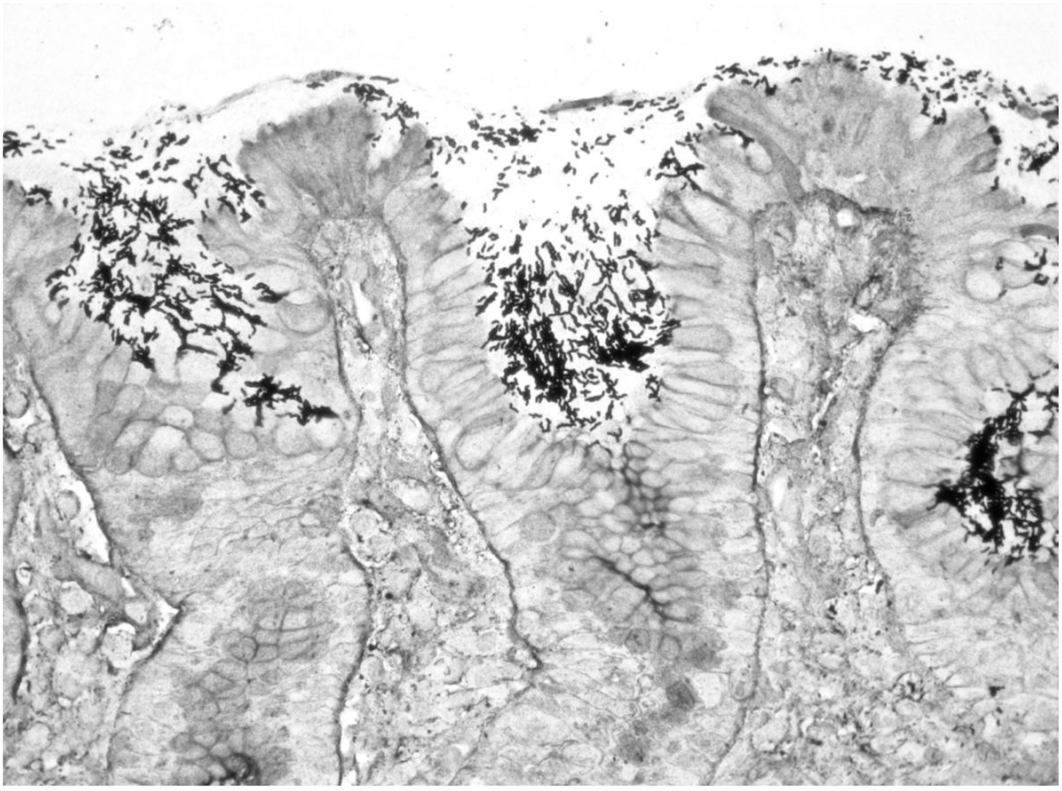

Figure 2.
Microphotograph of gastric mucosa colonized by abundant *H. pylori* organisms (modified Steiner silver stain, ×400).

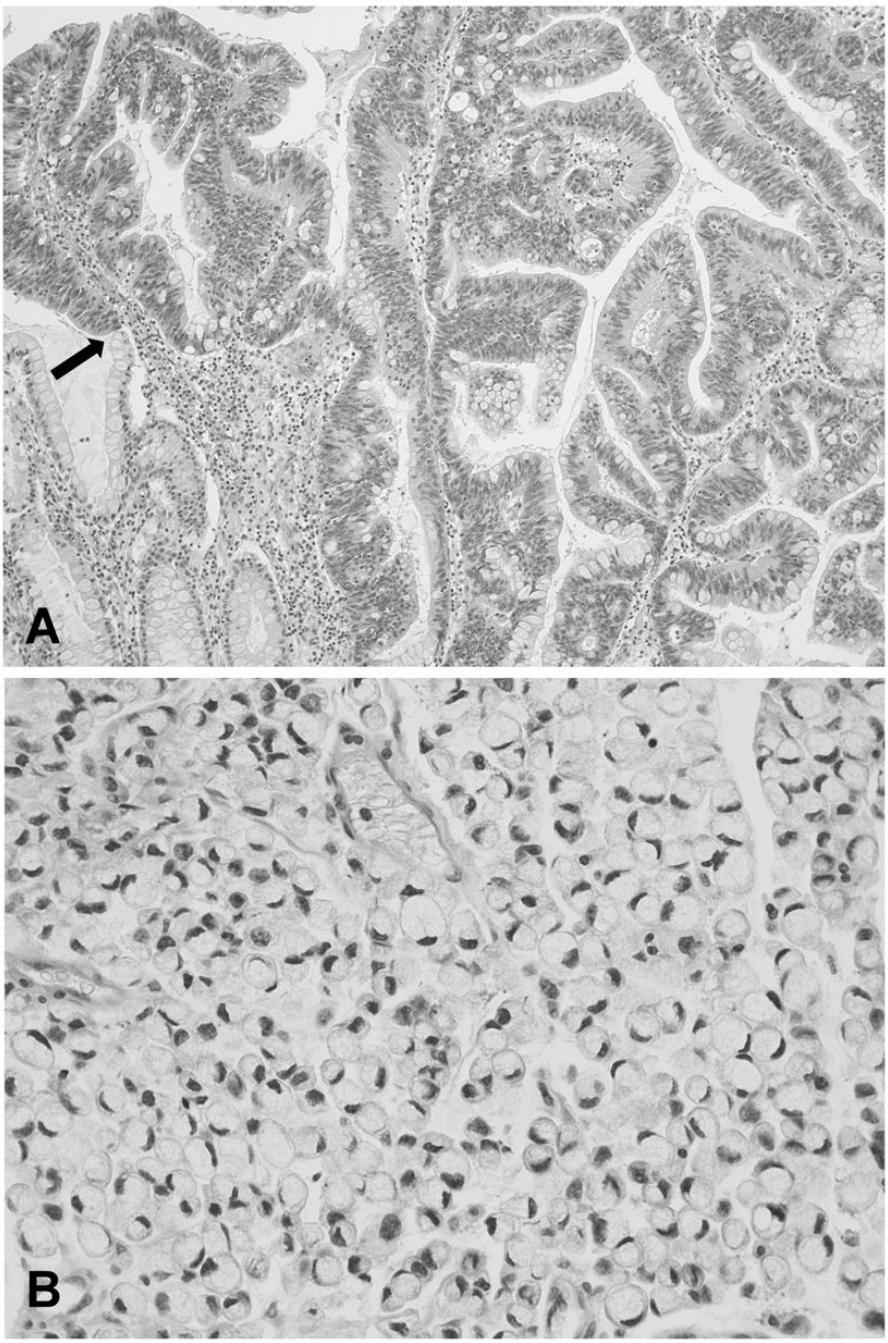

Figure 3.
Microphotographs of gastric adenocarcinoma. A) Intestinal type, showing tumor cells cohesively arranged forming irregular glandular structures. On the left lower corner there are few glands with intestinal metaplasia. An arrow shows the transition zone between intestinal metaplasia and adenocarcinoma (×100). B) Diffuse type, with tumor cells that show lack of cohesiveness infiltrating diffusely. In this subtype, the signet-ring adenocarcinoma, the nuclei are pushed to the periphery due to the abundant mucinous cytoplasmic content (×400).

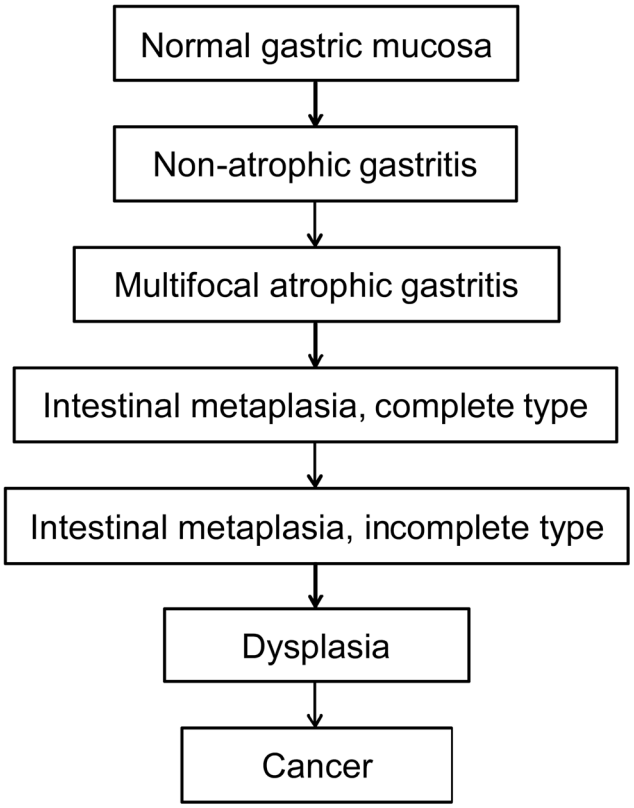

Figure 4.
Model of sequential steps in the gastric precancerous process. Adapted from Correa P., *et al.* [83].

Table 1

New cases and deaths by cancer site worldwide, 2002 [5].

	New cases	Deaths
Lung	1,352,132	1,178,918
Breast	1,151,298	410,712
Colon and rectum	1,023,152	528,978
Stomach	**933,937**	**700,349**
Liver	626,162	598,321
Prostate	679,023	221,002
Cervix uteri	493,243	273,505
Esophagus	462,117	385,892
Bladder	356,557	145,009
Non-Hodgkin lymphoma	300,571	171,820
Leukemia	300,522	222,506
Pancreas	232,306	227,023
All sites but skin	**10,862,496**	**6,723,887**