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Helicobacter pylori Infection and Gastric Adenocarcinoma

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Abstract

Gastric adenocarcinoma is the second leading cause of cancer-related mortality worldwide. Infection with *Helicobacter pylori* is the strongest recognized risk factor for gastric adenocarcinoma. This bacterial species colonizes the stomach of more than half of the world's population; however, only a very small proportion of infected subjects develop adenocarcinoma. *H. pylori* causes a chronic gastritis that may last decades, and a multistep precancerous process is recognized for the most frequent histologic type of gastric adenocarcinoma: the intestinal type. The severity and long-term outcome of this infection is modulated by an increasing list of bacterial, host, and environmental factors, which interplay in a complex manner. Identification of individuals at high risk for gastric cancer that may enter a surveillance program and intervention during the precancerous process is the most suitable strategy for decreasing mortality due to this malignancy.

Keywords

Gastric cancer; gastric adenocarcinoma; *Helicobacter pylori*; CagA; VacA; multifocal atrophic gastritis; intestinal metaplasia; dysplasia

Although gastric cancer incidence and mortality rates have been slowly decreasing in many countries over the last five decades, gastric cancer is still the second most common cause of cancer-related deaths and the fourth most common malignancy worldwide (see Table 1).[1] Approximately one million cases were estimated for 2008, 70% of them in less developed regions.[1]

Overall, gastric cancer has a poor prognosis. In the US, two-thirds of the cases are diagnosed when the tumor has reached some degree of dissemination through the gastric wall, and the overall five-year survival rate is 25%.[2]

For most of the 20th century the search for the causes of cancer emphasized the role of ionizing radiation and exposure to chemical carcinogens, especially tobacco smoke, which is a recognized risk factor for malignancy in multiple organs, including the stomach.[3] The 21st century has brought more attention to infectious agents and chronic active inflammation as primary causes of some cancers. Convincing evidence has become available for the oncogenic role of two virus families: papilloma viruses in carcinoma of the uterine cervix and hepatitis viruses in hepatocellular carcinoma. So far, only one bacterial species has been

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implicated: *Helicobacter pylori* (*H. pylori*) in gastric carcinoma.[4] It has been estimated that 17.8% of cancers worldwide are due to infectious agents, and *H. pylori* is estimated to be responsible for 5.5% of all cancer cases and more than 60% of gastric cancer cases.[5] Although *H. pylori* is also implicated as a causative agent in gastric mucosa-associated lymphoid tissue lymphoma, this article is focused on gastric adenocarcinomas, which account for more than 90% of gastric cancer cases. Other infectious agents classified as carcinogens by the International Agency for Research on Cancer (IARC) are: Epstein-Barr virus (EBV or HHV4) in lymphomas and nasopharyngeal carcinoma, herpes virus 8 (HHV8) in Kaposi's sarcoma, human T-cell lymphotropic virus type I (HTLV-1) in adult T-cell leukemialymphoma, *Schistosoma haematobium* in bladder carcinoma, and *Opistorchis viverrini* in cholangiocarcinoma.[6] Additionally, chronic inflammation is recognized as a risk factor for developing several types of cancer, including gastric, intestinal, esophageal, prostate, and others.[7] Macrophages, dendritic cells, and lymphocytes are effectors of the inflammatory role in the induction and promotion of the neoplastic process, mostly mediated by cytokines and chemokines.[8] This article briefly summarizes the main aspects concerning gastric adenocarcinomas and the carcinogenic effects of *H. pylori* infection.

Classification and Pathology of Gastric Adenocarcinomas

Gastric adenocarcinoma is a heterogeneous disease. The most commonly used classification system in the US is the Lauren classification,[9] which recognizes two main histologic types: intestinal and diffuse (see Figure 1). Ten to 15% of gastric adenocarcinomas are mixed, containing features of both types. Although these two types seem to follow different precancerous processes and show clinical and epidemiologic differences, *H. pylori* infection is the strongest risk factor for the development of most tumors of both types.

Intestinal adenocarcinoma is the predominant type in populations with high incidence rates of gastric cancer and is the type of tumor associated with the worldwide decline in gastric cancer rates. This tumor type shows a male predominance (male/female ratio of 2:1) and most cases are diagnosed during the sixth to eight decades of life. Microscopically, intestinal-type adenocarcinomas are composed of cohesive tumor cells forming irregular glandular or papillary structures, or they may be arranged in sheets in a solid pattern (see Figure 1A).

Diffuse-type adenocarcinomas do not show gender predominance, tend to develop in younger subjects, have a poorer prognosis than the intestinal-type tumors, and are more frequently located in proximal stomach than in distal stomach. Although environmental factors seem to play a less important role than in the intestinal-type tumors, *H. pylori* infection is also associated with the development of diffuse-type adenocarcinomas.[10,11] Despite the overall decline in gastric cancer rates, the proportion of diffuse-type carcinomas has been increasing in several countries.[12,13]

Microscopically, diffuse-type gastric adenocarcinomas are composed of non-cohesive, poorly differentiated, tumor cells that disseminate individually or in small clusters infiltrating the stroma. A subtype, the signet-ring cell adenocarcinoma, is formed by characteristically round tumor cells containing abundant intracytoplasmic mucin and nuclei flattened against the periphery of the cells (see Figure 1B).

Approximately 10% of gastric adenocarcinomas have familial clustering. Hereditary diffuse gastric cancer is a cancer predisposition syndrome associated with germline mutations and with methylation of the gene encoding for E-cadherin (*CDH1*), a protein for cell-to-cell adhesion that plays an important role in the maintenance of cell polarity in epithelial tissues.[14,15] Although gastric cancer cases related to this syndrome account for less than 1%

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of the total cases of gastric cancer, it is of great clinical importance due to the early onset (mean age at diagnosis 40 years) and high penetrance.

The syndrome is dominated by the development of multiple independent foci of diffuse-type gastric adenocarcinoma, often with signet-ring cell morphology. Prophylactic total gastrectomy is the recommended treatment for patients with germline *CDH1* mutations to eliminate the risk for developing gastric adenocarcinoma.[16]

The Infectious Agent

H. pylori is a gram-negative, spiral-shaped microaerophilic bacterium with 4–6 polar flagella that allow for motility in the mucus layer of the gastric lumen. *H. pylori* infection is the main cause of gastritis, peptic ulcers, and gastric adenocarcinoma. Although *H. pylori* is found mainly extracellular (see Figure 2), some studies show evidence of invasion to gastric mucosa and gastric lymph nodes.[17–19] It is believed that *H. pylori* contributes to gastric cancer development by direct action of its virulence factors and indirectly by initiation and maintenance of a chronic inflammation in the gastric mucosa.

H. pylori strains are extremely diverse and the severity of the clinical outcome is largely influenced by the presence of virulence factors. The most recognized virulence markers for *H. pylori* are the cytotoxin-associated gene *cagA* and the vacuolating cytotoxin gene *vacA*. The *cagA* gene is present in about 60% of strains isolated in developed countries and in almost all strains from East Asian countries,[20] and is a marker of the cag pathogenicity island.[21] This island is a 40kb locus that encodes a type IV secretion system and several proteins, including CagA, an oncoprotein. On contact with host epithelial cells, *H. pylori* utilizes the type IV secretion system to inject CagA into epithelial cells, beginning a series of changes that lead to morphologic alterations of the host cells, disruption of intercellular junctions, and loss of cell polarity. Infection with *cagA*-positive strains increase cancer risk compared with infection with *cagA*-negative strains.[10,22]

The gene *vacA* is present in all *H. pylori* strains and encodes VacA, a bacterial toxin that induces vacuolation in epithelial cells. The gene presents three regions of great diversity (s, signal terminus; m, mid-region; i, intermediate region) and the combination of different alleles determines the vacuolating activity.[23,24]

Our studies in Colombia, a country with high rates of gastric cancer, show that *H. pylori* isolates from the high altitude Andes Mountains population have ~90% prevalence of such markers (*cagA*-positive *vacA* s1m1), compared with ~70% in isolates from the Pacific coast.[25] Such difference is significant but may not fully explain the big difference in cancer rates, 25-times higher in the mountains than on the coast. Recently developed techniques of multi-locus sequence typing have allowed us to trace the ancestral origin of Colombian *cagA*-positive, *vacA* s1m1 *H. pylori* isolates. All isolates analyzed from the high-risk area (Andes Mountains) population (n=35) display European ancestry. Other investigators have shown that when populations of European ancestry are mixed with populations of Asian ancestry, the original *H. pylori* strains of Amerindian genotype are replaced by European strains.[26] In our study in Colombia, isolates analyzed from the coastal region (n=29) have a heterogeneous ancestry. Approximately one-third have European ancestry, probably reflecting the same phenomenon just described for the high-risk area isolates. The rest have African ancestral markers.[27] It would appear that the low virulence *H. pylori* strains in Africa prevailed in the Colombian Pacific coastal inhabitants after their ancestors migrated several centuries ago. Our preliminary results in Colombia indicate that the ancestral origin of the *H. pylori* strains may, at least partially, determine their carcinogenicity potential, independently of the classical virulence markers *cagA* and *vacA*. Other investigators have

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shown that *H. pylori* isolates from modern African-Americans retain traces of African roots, despite the multiple generations since their ancestors were taken from West Africa.[28]

Among the mechanisms of carcinogenesis associated with inflammation, one hypothesis postulates that oxidative and nitrosative stress alter permanently the DNA molecules of the gastric epithelial cells. This mechanism is supported by our preliminary findings studying gastric mucosa biopsy samples of Colombian subjects. *H. pylori* isolates from inhabitants of the Andes Mountains (with high risk for gastric cancer) induce higher levels of inducible nitric oxide synthase and spermine oxidase, enzymes involved in nitrosative and oxidative stress, than isolates from the coastal region.[29] These experiments were conducted with *cagA*-positive, *vacA* s1m1 *H. pylori* isolates from both regions, indicating that other components of the *H. pylori* genome, not yet elucidated, may have carcinogenic potential.

In addition, preliminary findings indicate that *cagA*-positive, *vacA* s1m1 *H. pylori* isolates from the mountains increase the expression of the CagA protein when cultured in a broth medium with high-salt concentration (John T Loh, unpublished data, 2010).

Another hypothesis postulates that bone marrow-derived cells contribute to the development of gastric cancer in *Helicobacter*-infected gastric mucosa. Experiments in mice reconstituted with labeled bone marrow and infected with *H. felis* (the mouse-adapted *Helicobacter* species) demonstrated that bone marrow-derived cells travel to, and engraft in, gastric mucosa with chronic inflammation and progress to adenocarcinoma.[30]

Epidemiologic Studies

Classic case-control studies have yielded inconsistent messages about causation. It seems clear now that these discrepancies can be explained by the temporality bias: the infection is mostly acquired during childhood and persists for years, but it tends to disappear when advanced atrophy and intestinal metaplasia extend, creating an unfavorable environment for *H. pylori* colonization, but increasing the cancer risk. Several studies have supported the role of this temporality bias. Fukuda et al.[31] conducted a case-control study to evaluate the role of *H. pylori* infection in gastric cancer. No overall association was detected, but when the comparisons were limited to younger patients, early cancers, or small tumors, significant associations were found. Also, when the degree of atrophy was evaluated by serum pepsinogen (PG) levels (PGI/PGII ratio) the association with *H. pylori* infection was significantly elevated.[31] Similar results were reported by Ohata et al.[32] in a cohort study of 4,655 subjects followed up by an average of 7.7 years. Patients with negative serology for *H. pylori* but with extensive atrophy (evaluated by serum pepsinogen levels) had higher gastric cancer risk than those who remained infected. It does appear that the oncogenic potential of the *H. pylori* infection persists after the infection is lost.[32]

The outcome of most human infections is determined by the interaction of the infectious agent with two other major sets of factors: the susceptibility of the host and the external environmental forces. The effects of these factors have been explored in the two populations of contrasting cancer risk in Colombia.

The Geographic Enigmas

The overall estimate of *H. pylori* prevalence in adults is 76% in developing countries and 58% in developed countries.[33] However, the association between gastric cancer and *H. pylori* infection is challenged by the contrasting geographic distribution of the two nosologic entities in some areas. In Africa, the prevalence of *H. pylori* infection is very high, but the gastric cancer rates are very low.[34] This ‘African enigma’ and similar enigmas have given rise to epidemiologic investigations into the causes of the phenomenon.[35]

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Epidemiologic investigations in Colombia describe marked variation in gastric cancer risk among different regions. Very high gastric cancer rates, estimated to be 150 per 100,000 in 1976[36] and high prevalence of *H. pylori* infection is found in inhabitants of the high-altitude Andes Mountains. They are predominantly 'mestizos', a mixture of Amerindian and European migrants. By contrast, residents of the Pacific coast, only about 100 miles apart, have very low cancer rates (estimated at six per 100,000),[36] but also very high prevalence of the infection. Residents of the Pacific coast are predominantly from African ancestry. This phenomenon in Colombia is similar to the fact described by the African enigma. The striking differences in gastric cancer rates in these two Colombian populations may be associated with differences in multiple factors, including pathogenicity of the infecting *H. pylori* strains, genetic background of the populations, nutritional factors, and the type of inflammatory response against *H. pylori* infection.

Precancerous Cascade

Observational studies in Colombia in the 1970s[37,38] led to the identification of a sequence of precancerous lesions in the gastric mucosa.[39] After *H. pylori* was recognized as a causative agent for gastritis in 1983,[40] it is known that the precancerous process starts with the colonization of the gastric mucosa. Although *H. pylori* remains mainly in the gastric lumen, the contact with the epithelium initiates an inflammatory response with increase in production of cytokines and chemokines that attract inflammatory cells to the mucosa. The immune response is not effective in eliminating the infecting agent, and may last decades, unless the bacterium is eradicated. Persistent, long-term inflammation may cause damage to the epithelial cells and, over time, loss of glands. These gastric glands may then be replaced by glands lined by epithelium with intestinal phenotype. If sustained injury to the gastric mucosa persists, dysplastic changes and malignant transformation may develop. Thus, it is believed that gastric adenocarcinomas of the intestinal type[9] are preceded by a precancerous process with the following well-recognized steps: chronic active inflammation → multifocal atrophy (gland loss) → intestinal metaplasia, complete type → intestinal metaplasia, incomplete type → dysplasia.[39,41] (see Figure 3). It is generally recognized that the process starts during childhood, triggered by the infection with *H. pylori*, and advances slowly through the years, eventually leading in a few patients, after several decades, to invasive carcinoma.

In terms of the mechanisms of gastric carcinogenesis, recent studies identifying mitochondrial DNA mutations in human gastric mucosa have demonstrated the presence of multiple stem cells in a gastric unit (defined by the gastric glands associated with a single neck and foveolus) and the process of monoclonal conversion and clonal derivation from a single stem cell.[42] In these studies, McDonald et al. demonstrated that human gastric units are able to divide by fission into clonal patches, leading to fields of mutated gastric units.[42] It is highly probable that a bud forms from the stem cell zone in the neck of the gland, giving origin to a new gastric unit. These studies have also shown that crypts with intestinal metaplasia within the human stomach are clonal (incorporating all the major differentiated intestinal lineages), contain multiple multipotential stem cells, and can spread by crypt fission. Such expansion has important implications for gastric carcinogenesis.

Intervention Trials and Use of Non-steroidal Anti-inflammatory Drugs for Prevention of Gastric Cancer and Precancerous Lesions

Several reports have confirmed the benefit of *H. pylori* eradication as a measure to decrease gastric cancer risk.[43–45] Our experience with a chemoprevention trial of gastric dysplasia in Colombia[46,47] led us to emphasize the underestimated role of time free of exposure to *H. pylori*, the putative carcinogenic agent, on the outcome of the intervention. Using a detailed histopathology score that recognizes the type and extension of precancerous lesions of the

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gastric mucosa, our results at 12 years of follow-up showed that curing the *H. pylori* infection heals the mucosal damage, expressed as an exponential sigmoid curve, representing the anti-carcinogenic dynamics, the mirror image of the cancerous process. No detectable healing effect was observed for the first three years of infection-free time, and at six years, the healing effect was modest.[48] Our findings indicate that regression of the precancerous lesions is more complete in patients with less-advanced (absence of intestinal metaplasia) diagnoses at baseline than in patients with more advanced lesions, such as intestinal metaplasia and dysplasia. This healing process eventually may prevent cancer development.

In terms of the use of non-steroidal anti-inflammatory drugs (NSAIDs), results of a recent meta-analysis showed that use of aspirin or other NSAIDs was associated with a significant reduction in the risk for gastric and esophageal adenocarcinomas.[49] Clinical trials using long-term use of cyclooxygenase 2 (COX-2) inhibitors have been suspended because of cardiovascular complications. A randomized controlled study investigated the effects of long-term treatment with the COX-2 inhibitor rofecoxib in patients with gastric intestinal metaplasia after *H. pylori* eradication.[50] The trial was suspended after two years, and no regression of the intestinal metaplasia was observed. More recently, a clinical trial using the less cardiotoxic COX-2 inhibitor etodolac has reported to effectively reduce metachronous carcinomas in Japanese subjects after endoscopic mucosal resection of early gastric adenocarcinomas.[51]

Host Genetic Susceptibility

Host factors modulating the outcome of the *H. pylori* infection have been widely explored by investigators in several countries during the last decade. Important advances include investigations of polymorphisms in genes associated with the immune response to *H. pylori* infection, mainly in interleukin *(IL)-1B*, *IL1RN*, *TNF*, and *IL10*. IL-1β is a proinflammatory cytokine and a potent inhibitor of gastric acid secretion.[52] It has been hypothesized that a profound acid secretion suppression promotes dissemination of *H. pylori* proximally to the corpus, leading to a more extensive and severe gastritis that may favor the development of atrophy and subsequently cancer.[52] Carriers of the *IL1B-511T* allele are higher producers of IL-1β and have an increased risk for gastric cancer.[53,54] However, two meta-analyses concluded that the risk effect is ethnicity-specific: it is seen in Caucasians but not in most Asian populations.[55,56] This contrast may be explained by the relative frequency of the high-risk allele in the population: ~35% in Caucasians and ~50% in Asians, Africans, and Hispanics. The low prevalence of this allele in the Caucasian population makes it easier to detect a significantly increased risk compared with cancer patients, with over 50% prevalence of the allele. High prevalence in other populations may indicate biological cancer susceptibility, even though it becomes harder to detect a statistically significant elevation of the relative risk.

A recent meta-analysis including 203 relevant studies (assessing 225 polymorphisms across 95 genes) found a total of 37 polymorphisms across 27 genes to be significantly associated with gastric cancer in Asians, and 12 polymorphisms across 11 genes in Caucasians.[56] In Asian populations, polymorphisms associated with gastric cancer were: *IL1B+3954T, IL8-251A, IL10-592C, IL10-1082G*, and *IL4-590T*, among others. In Caucasian populations, polymorphisms associated with increased gastric cancer risk were: *IL1B-511T, ILRN-86bp-VNTR, MTHFR-667T, and TNF-308A*, among others.[46] Other less well-documented factors that may increase susceptibility to gastric cancer are polymorphisms in genes encoding DNA repair enzymes such as *XRCC* and *OGG1*; detoxifying enzymes such as *GTSTM, GST1, NAT1, NAT2*; and protective mucin glycoproteins such as *MUC6* and *MUC5AC*.[57] Hereditary gastric cancer predisposition syndromes, usually associated with E-cadherin

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mutations (previously mentioned), contribute very little to the overall incidence of gastric cancer.[58]

Environmental Factors

Low socioeconomic status, poor home sanitation, and home crowding during childhood increase the frequency and severity of *H. pylori* infection and increase cancer risk. Tobacco smoking is a recognized risk factor for several types of cancer including gastric adenocarcinomas. It has been estimated that 17% of the gastric cancer cases are attributable to smoking.[3,59] Dietary factors also play an important role. Excessive salt intake increases cancer risk, while adequate intake of fresh fruits and vegetables decreases the risk.[60–62] In terms of salt consumption, studies *in vitro* have shown that several *H. pylori* genes associated with virulence (including *cagA*) were upregulated when the bacterium was cultured in a medium with high salt concentration. As a result, increased expression of CagA was observed, leading to alteration of gastric epithelial cell morphology and function.[63] Another relevant factor is the habitat. Subjects living in low-altitude, tropical humid regions are more frequently infected with intestinal parasites, especially helminthes, which modulate the immune response against *H. pylori* toward a Th2 type (anti-inflammatory),[64,65] and may decrease the cancer risk. By contrast, high-altitude mountain dwellers have lower prevalence of infection with intestinal parasites and display a Th1 (pro-inflammatory) immune response which increases cancer risk.[66]

The Perfect Storm

It would appear that the gastric cancer risk in a given population is influenced by more than one etiologic factor. The very high cancer risk for the high-altitude Andes Mountains' dwellers in Colombia may be related by a combination of the following etiologic forces: low socioeconomic status; high frequency of host genetic susceptibility markers; high salt intake and low consumption of fresh fruits and vegetables; highly virulent *H. pylori* strains: *cag*-positive *vacA* s1m1 of European ancestry; increased CagA protein expression by *H. pylori* induced by high salt consumption; and Th1 (pro-inflammatory) immune response against *H. pylori* infection, not modulated by intestinal parasites.

Cancer Screening and Prevention

In Japan, where gastric cancer is the most common cause of cancer-related deaths, mass screening programs for gastric cancer are well developed. As a result, between 45 and 70% of gastric cancers are diagnosed at an early stage (tumor limited to the mucosa or submucosa), providing five-year survival rates between 45 and 90%.[13,67] One of the screening tools for detection of subjects at risk for gastric cancer is the assessment of serum levels of pepsinogens (PGs), which reflect the extension of atrophic or metaplastic changes of the gastric mucosa.[68,69] Serum PGI levels lower than 70μg/l and PGI/PGII ratio lower than 3.0 are associated with severe atrophy of the corpus mucosa. Serum PG tests have proven to be very useful for cancer screening in populations at high risk for gastric cancer due to their low cost and minimal invasiveness. Individuals with low PG levels will then undergo gastric endoscopy and topographic mapping.

In the US, a country with overall low gastric cancer rates, there are some ethnic groups with increased risk, such as African-Americans, Hispanics, and American-Asians/Pacific Islanders. Another risk factor is the presence of extensive gastric intestinal metaplasia or intestinal metaplasia of the incomplete type. We proposed an algorithm for the management and surveillance of gastric intestinal metaplasia[70] that includes assessment of *H. pylori* infection (test with serology if biopsy is negative) and treatment when present. While the management for low-grade dysplasia is not well defined, subjects with high-grade dysplasia

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should undergo surgical or endoscopic resection due to the high probability of harboring a prevalent or incident invasive carcinoma.[71]

The strategy for gastric cancer prevention is to identify subjects at high risk and offer them intervention and surveillance whenever possible. General recommendations include avoiding smoking and excessive salt intake, and consuming adequate amounts of fresh fruits and vegetables.

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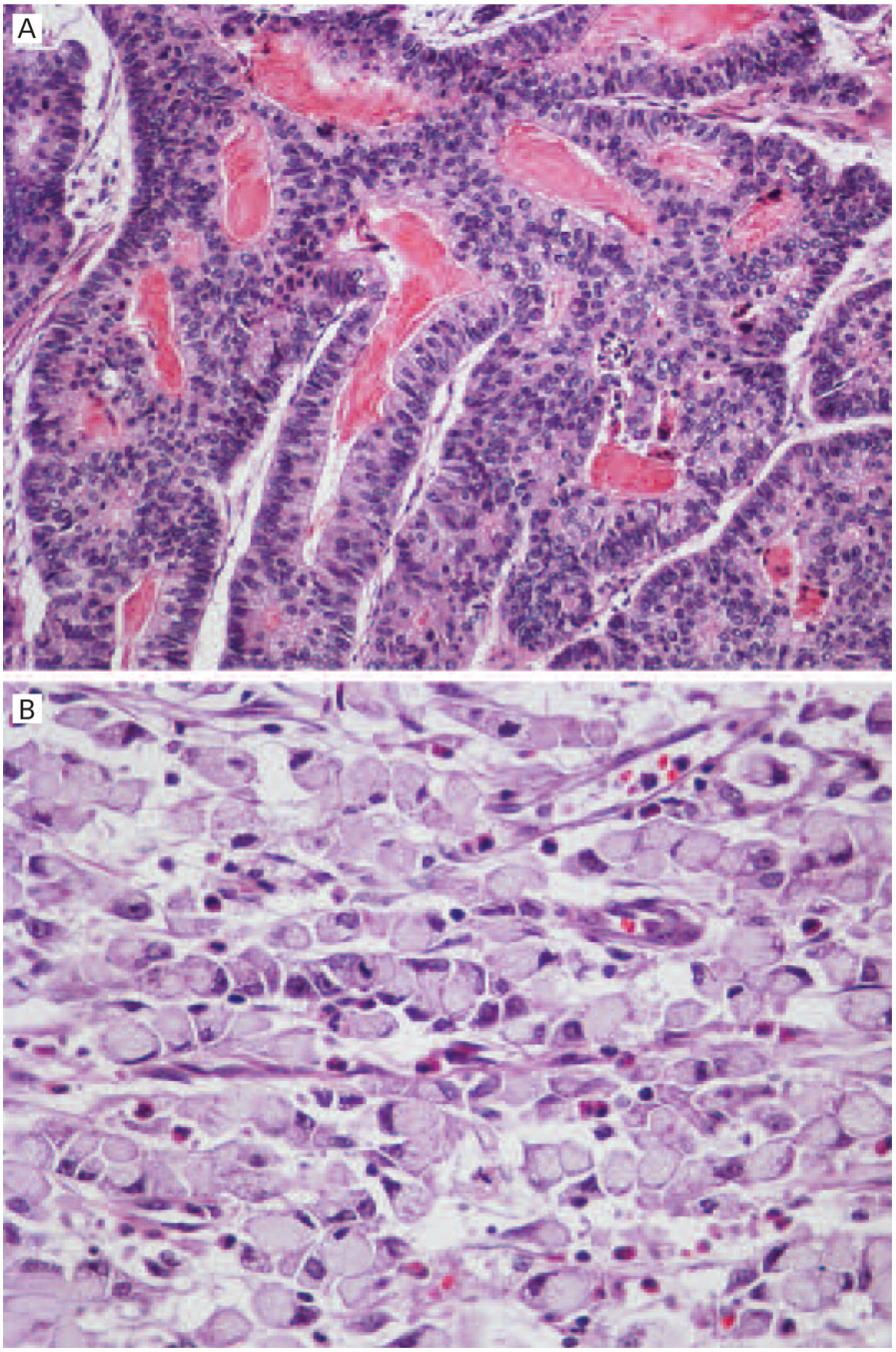

Figure 1. Photomicrographs of Gastric Adenocarcinoma of the Intestinal and Diffuse Types (Lauren Classification)

A: Intestinal type. The tumor cells are cohesively arranged, forming irregular glandular structures infiltrating the stroma (H&E, ×200). B: Diffuse type. Single tumor cells infiltrate diffusely the stroma. In this subtype, the signet-ring cell adenocarcinoma, the intracytoplasmic mucin compresses the nucleus against the periphery of the cell, giving it its characteristic signet-ring appearance (H&E, ×400).

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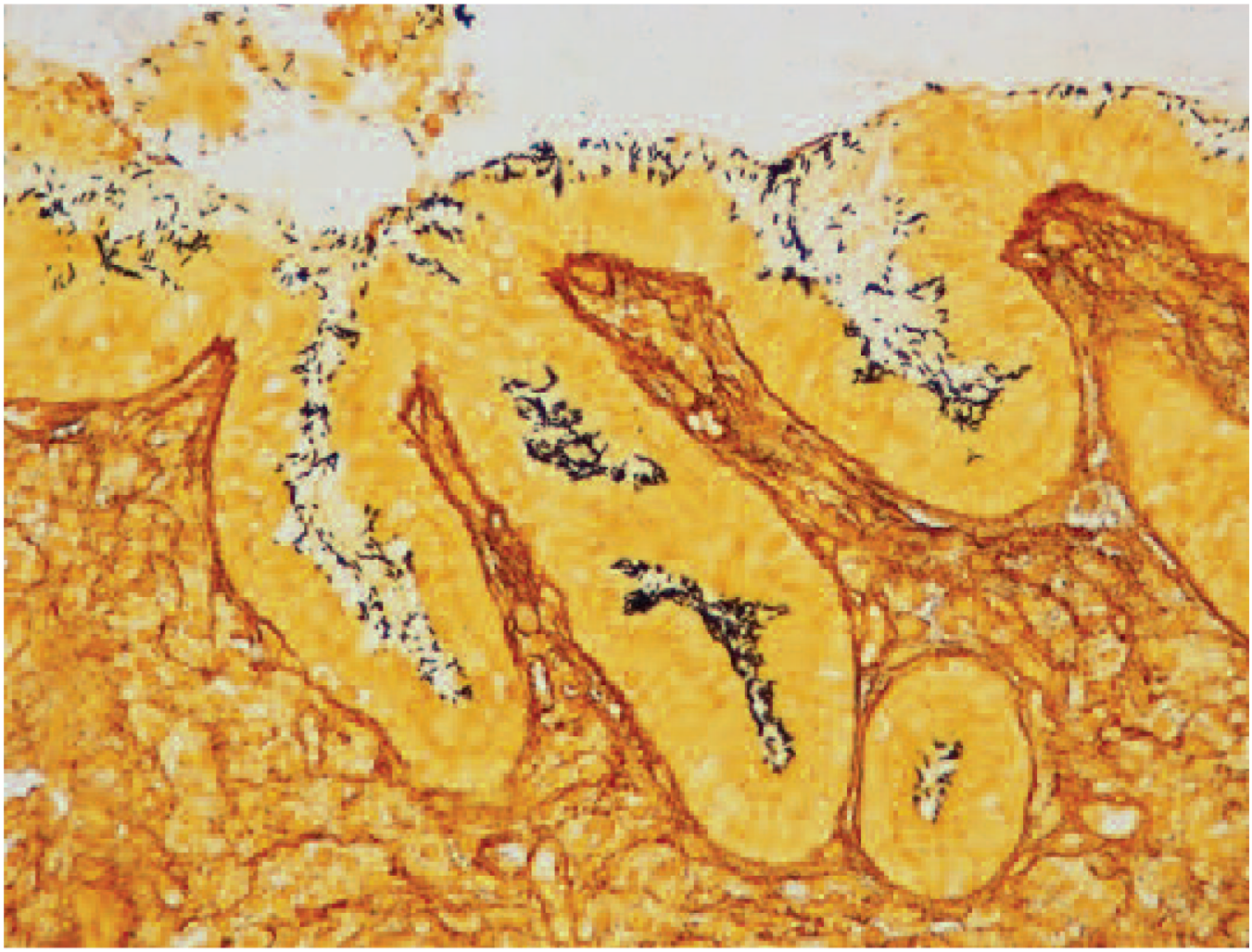

Figure 2. Histologic Section of Human Gastric Mucosa Colonized by *Helicobacter pylori*
Abundant microorganisms (black staining) are seen attached to the epithelial cells and surrounding mucus layer (modified Steiner silver stain, ×400).

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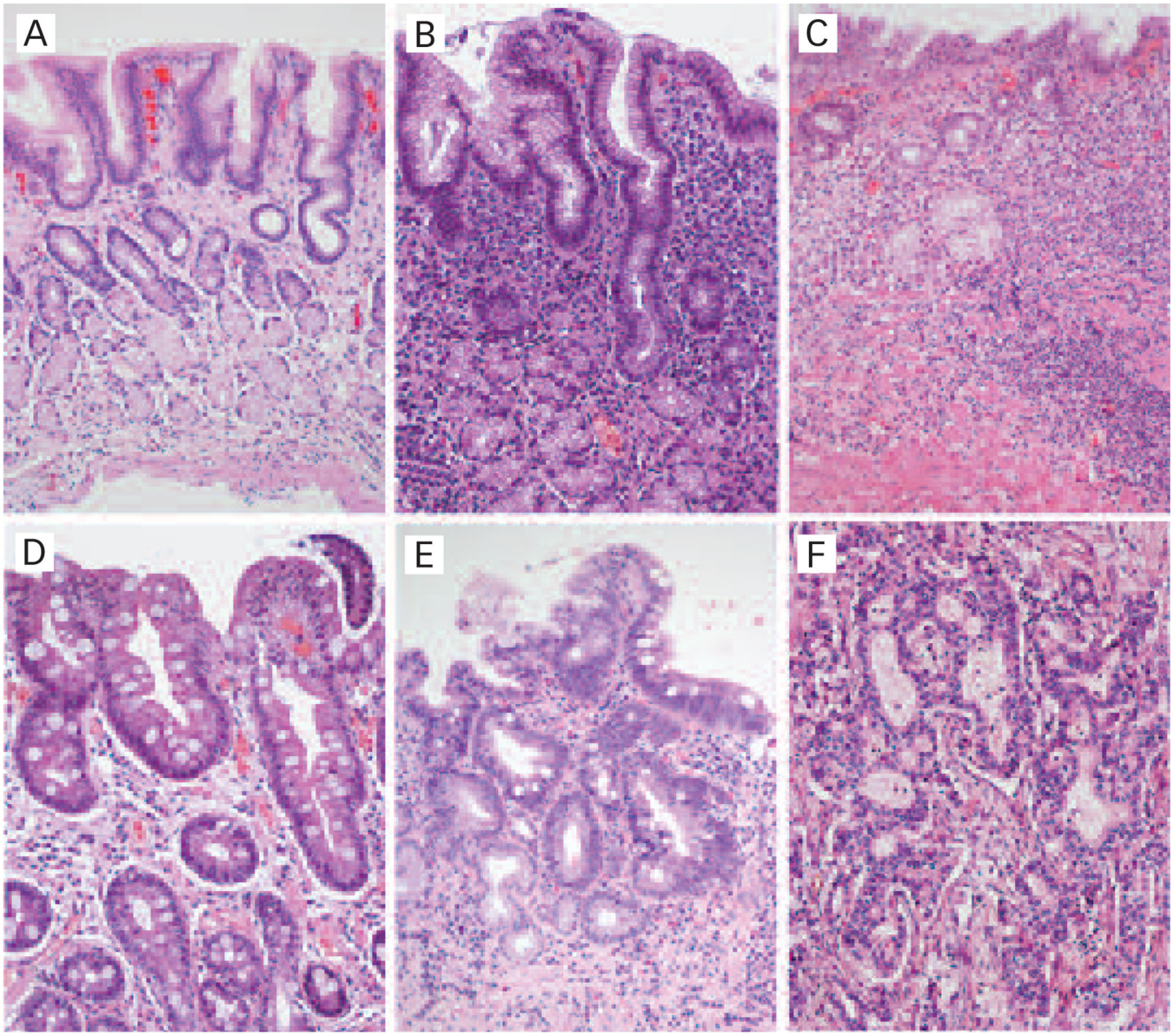

Figure 3. Photomicrographs of Sequential Steps in the Gastric Mucosa for the Development of Adenocarcinoma

A) Normal gastric antral mucosa. B) Non-atrophic gastritis. Abundant inflammatory cells are seen in the lamina propria and the glands are well conserved. C) Multifocal atrophic gastritis, with prominent loss of deep glands. D) Intestinal metaplasia of the complete type, with well-formed goblet cells and brush border. E) Dysplasia, low-grade. Epithelial cells with enlarged, hyperchromatic and pseudostratified nuclei that maintain the polarity respect to the basement membrane. F) Adenocarcinoma of the intestinal type (H&E, ×200).

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Table 1

New Cases and Deaths from Cancer by Site Worldwide (Both Sexes) 2008[1]

	New Cases	Deaths
Lung	1,608,800	1,378,400
Breast	1,383,500	458,400
Colon and rectum	1,233,700	608,600
Stomach	989,600	738,000
Liver	748,300	695,900
Prostate	913,800	258,400
Cervix uteri	529,400	274,900
Esophagus	482,300	406,800
All cancers (excluding non-melanoma skin cancer)	12,677,900	7,571,500