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Gastric Cancer: Overview

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Keywords

Gastric cancer; *Helicobacter pylori*; Etiology; Epidemiology; Host factors; Precancerous cascade; Prevention; Early detection

INTRODUCTION

Gastric cancer is a major health burden worldwide. It is the second cause of cancer deaths after lung cancer.[1,2] More than 90% of the tumors are adenocarcinomas, the main focus of this review. The prognosis is dismal, with an average 5-year survival rate of less than 20%, mainly because of late diagnosis, because the early stages are clinically silent. Only a few countries, especially Japan, have set up extensive programs of early detection. If the tumor is detected and treated before it invades the muscular layer of the stomach, the 5-year survival rate can reach 90%.[3] The highest incidence rates are reported for East Asia (Korea, Mongolia, Japan, and China) with annual incidence rates between 40 and 60 per 100,000 inhabitants. In Latin America, pockets of high risk are reported in the Andes Mountains, with rates between 20 and 30 per 100,000,[1] in contrast to the much lower rates reported for the coastal and river valley regions.[4] Lower rates are found in Africa (~0.3 to 3 per 100,000, and in affluent populations of North America). The incidence rate in African Americans is about double that seen in white American. In general, the incidence rate for men is double that for women.[1]

In recent decades, there has been a gradual decrease in gastric cancer rates in many populations. It has been proposed that this decrease reflects trends in food handling, especially refrigeration and the abundance of fresh fruit and vegetables in the diet, as well as a decrease in the use of tobacco and dietary salt. However, not all types of gastric cancer are declining; tumors of the cardia and esophagogastric junction are becoming more frequent. Recently, an unexplained increase in gastric cancer incidence in younger individuals, mostly less than 40 years of age, has been reported.[5]

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ETIOLOGY

The cause of gastric cancer is multifactorial, although infection with *Helicobacter pylori* is considered to be the primary cause; its effects are modulated by microbial, environmental, and host factors.

Gastric cancer is one of a few types of neoplasms directly linked to an infectious agent. In 1994, the International Agency for Research on Cancer (IARC) classified infection with *H pylori* as a class I human carcinogen for gastric cancer.[6] The same infectious agent is recognized as the primary cause of gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

H pylori is a gram-negative bacterium capable of colonizing the gastric mucosa and eliciting an immune response in the host. The infection is predominantly acquired in early infancy and remains present for life if not treated with antibiotics. One type of gastritis associated with the infection, namely multifocal atrophic gastritis, may be linked to the precancerous process. Nonatrophic antral gastritis is not associated with the precancerous process but may be linked to duodenal ulcer. Reactive oxygen species (ROS) may be generated by the infection and may induce DNA mutations. *H pylori* is also able to induce hypermethylation of DNA, especially the CpG islands, thereby silencing genes associated with tumor suppression. A study on subjects infected with *H pylori* reported that a population at high risk for gastric cancer from the Colombian Andes (Tuquerres) had significantly greater hypermethylation of the *RPRM* gene (a tumor suppressor gene) in the gastric mucosa compared with those in a low-risk population on the Pacific coast (Tumaco).[7]

H pylori strains vary considerably in their pathogenicity and carcinogenicity. More virulent strains carry the cytotoxic-associated gene *cagA*, encoding an oncogenic protein that can be injected directly into gastric epithelial cells by a type IV secretion system.[8,9] Most strains in East Asia and in the high-risk area of the Colombian Andes are *cagA* positive. After entering the cytoplasm of the gastric epithelial cells, CagA becomes phosphorylated in motifs that contain the EPIYA sequences and starts a chain of molecular events linked to carcinogenesis. The EPIYA sequences are classified as A, B, C, or D according to the amino acids flanking them. The number and type of EPIYA motifs vary in different *H pylori* strains. In western countries, *H pylori* strains contain EPIYA motifs A, B, and C. In East Asia, the strains contain the D motif instead of the C motif.[10] Strains with more than 3 EPIYA motifs induce significantly more gastric atrophy, intestinal metaplasia, and gastric cancer. In vivo and in vitro studies have shown that CagA induces disruption of intercellular junctions, loss of epithelial polarity, increased proliferation, reduced apoptosis, and eventually carcinogenicity.[11] Another virulence-associated gene is *vacA*, which induces cytoplasmic vacuoles, pores in the cell membrane, and apoptosis.[12] Although all *H pylori* strains contain the *vacA* gene, genetic variations determine its functional activity and cancer risk. The *vacA* gene has genetic variations in the *s* (signal) region, which can be s1a, s1b, s1c, or s2. The middle region shows alleles that can be m1 or m2 and the intermediate region can be i1 or i2. Strains *vacA* s1/m1 or *vacA*s1/m1/i1 convey a higher risk of progression and cancer than strains vacA s2/m2 or vacA s2/m2/i2.

Some adhesion proteins of the membrane have been linked to higher virulence. One of them is BabA (blood-group antigen-binding adhesin) encoded by the gene *babA*, not present in all strains. BabA adheres to the antigen Lewis[b], present in the epithelial cell membrane. Infections with *H pylori* strains *babA2*-positive are associated with greater cancer risk.

The Infectious Agent

Infection with *H pylori* is very prevalent; it has been estimated that at least 50% of adults worldwide harbor the infection. However, a small minority (less than 1%) ever develop gastric cancer. *H pylori* has been a member of the human microbiota since time immemorial. Both species, *Homo sapiens* and *H pylori*, migrated together out of Africa approximately 60,000 years ago and populated most of the world. Throughout millennia, gradual transformations of the bacterial genome have resulted in several prototypes, including hpEurope, hpAfrica1 (including hspWest Africa and hspSouth Africa), hpAfrica2 and hpSahul (Oceania).[13,14] In Colombia, the inhabitants who live at high altitude in the Andes Mountains (Tuquerres) are mestizos (admixture of Amerindian and European); they have a high risk of gastric cancer and are infected with *H pylori* of the European prototype. By contrast, inhabitants of the Pacific coast, who are predominantly of Africa origin, carry a prevalence of approximately 30% European and 70% African *H pylori* strains. Independent of geographic location, patients infected with European prototype strains have more severe gastric premalignant lesions and oxidative damage than those infected with African prototype strains.[15] These findings show that although *cagA* and *vacA* are associated with virulence, they are not the only genes linked to virulence and carcinogenicity. They also indicate that migrants from Europe and Africa brought with them their original *H pylori* strains.

Epstein-Barr Virus

The presence of Epstein-Barr virus (EBV) has been found in between 5% and 16% of gastric cancers, implying that it may possibly play a causative role. The virus is more frequently found in men than in women, in tumors of the cardia or gastric body and in tumors found in gastrectomy specimens. It is very prevalent (~90%) in gastric lymphoepitheliomas (carcinomas with lymphoid stroma).[16]

Environmental Factors

Tobacco use has been found to be a risk factor for gastric cancer and precancerous lesions.[17] High dietary salt consumption increases cancer risk.[18] Consumption of processed meat has also been associated with a high cancer risk.[19] No clear association has been found with alcohol consumption. Consumption of fresh fruits and vegetables has been associated with reduced cancer risk.

Host Factors

Several studies have reported an association between cancer risk and genetic polymorphisms of genes linked to the inflammatory response, such as the interleukins *IL1B*, *IL1RN*, *IL10*, and tumor necrosis factor-α, *TNF*.[20–22] Several of these are tumor suppressors of gastric

acid secretion, which may facilitate bacterial colonization of the gastric corpus. The *IL1B-511T* allele is a risk factor for gastric adenocarcinoma.

CLINICAL CHARACTERISTICS

The early stages of gastric cancer are usually asymptomatic or associated with nonspecific symptoms such as dyspepsia. Advanced stages may be accompanied by persistent abdominal pain, anorexia, and weight loss. Ulcerated tumors may be associated with hematemesis. Persistent vomiting may be a sign of pyloric stenosis. The lack of specific symptoms may lead to a delayed diagnosis. Approximately 80% of patients are diagnosed at advanced stages in most countries where no early detection programs are in place.

CLASSIFICATION SYSTEMS

The location of the tumor dictates the anatomic classification: (1) cardial, (2) distal. It is frequently difficult to assign the location of origin in tumors of the gastroesophageal junction as esophageal or gastric, especially when the tumor has reached a considerable size. The occurrence of distal tumors has decreased in recent decades; in contrast, the occurrence of proximal tumors has increased, especially in industrialized countries, apparently related to gastroesophageal reflux. Adenocarcinomas of the cardia display aggressive behavior, invading the gastric and esophageal walls and metastasizing to local lymph nodes; the 5-year survival rate is around 14% in the United Sates. The American Joint Commission on Cancer Classification (AJCC) decided to classify tumors of the gastroesophageal junction and those involving the proximal 5 cm of the stomach as esophageal carcinomas.[23]

The degree of invasion dictates the classification of gastric cancer as early or advanced. Early cancers are limited to the mucosa and submucosa, irrespective of lymph node metastasis. Beyond those layers, tumors are classified as advanced. Five year survival rates are 85% to 100% for early cancers and 5% to 20% for advanced cancers. Advanced cancer cases are classified according to the gross morphology as Bormann groups: (1) polypoid, (2) ulcerated with well-defined borders, (3) ulcerated with ill-defined borders, (4) infiltrating diffuse without evidence of mass or ulceration, which is frequently called linitis plastica.

Histologic Classification

The most frequently used classification is the Lauren classification,[24] which recognizes 2 types: intestinal (with intercellular junctions) and diffuse (without intercellular junctions), representing 2 different nosologic entities. Both types are associated with *H pylori* infection. Other classifications, more complex and of limited use, are proposed by the World Health Organization and the Japanese Endoscopic Society.[25,26] The intestinal type adenocarcinoma is so named because it forms glands or tubules lined by epithelium resembling the intestinal mucosa. It is the most frequent type found in all high incidence populations and its incidence has decreased in recent decades. It displays cohesion among tumor cells. Diffuse carcinoma cells lack cohesion and invade tissues independently or in small clusters. Signet ring cell carcinomas are classified as diffuse. Their tumor cells contain abundant cytoplasmic mucin that displaces the nucleus toward the periphery. Some classifications include the term colloid carcinomas for tumors with excessive mucus secretion, intracellular and/or

extracellular. A small proportion of tumors are mixed, with intestinal and diffuse components. For statistical purposes, they are included in the intestinal type category.

The Precancerous Cascade

Before cancer becomes clinically apparent, a prolonged precancerous process takes place, with well-defined sequential stages: chronic active gastritis → chronic atrophic gastritis → intestinal metaplasia, first complete or small intestinal type and then incomplete or colonic → dysplasia (also called intraepithelial neoplasia), and finally invasive carcinoma. The process is initiated and sustained by infection with *H pylori*. Although the bacterial colonies remain in the gastric lumen, they induce an inflammatory process in the gastric mucosa that usually lasts for decades and may lead to gland loss (atrophy). The process is multifocal and is first seen in the incisura angularis and extends with time to the anterior and posterior gastric walls. Subsequently, the gastric epithelium is replaced by cells with intestinal phenotype (intestinal metaplasia). The metaplastic cells first display a small intestinal complete phenotype but, with time, they have a tendency to develop focal areas of large intestinal (incomplete or colonic) phenotype. Complete metaplastic cells are eosinophilic absorptive enterocytes with a well-developed brush border alternating with well-developed goblet cells; colonic metaplastic cells lack a brush border and have multiple irregular intracytoplasmic mucus vacuoles. Dysplasia is first low-grade and later develops foci of high-grade with increasing degrees of nuclear polymorphism and irregular architecture, which increase the cancer risk. In Japan, high-grade dysplasia is classified as intramucosal carcinoma. As the process advances, genetic abnormalities accumulate, such as mutations in the *APC*, *TP53*, and *Kras* genes. Hypermethylation and microsatellites may also be observed.

PREVENTION AND EARLY DETECTION

Strategies addressing cancer prevention are based on eradication of *H pylori* infection, recommendations on dietary changes to increase the daily intake of fresh fruits and vegetables and reduce salt consumption. Patients with extensive atrophic or metaplastic changes in the gastric mucosa have increased cancer risk. In these patients, periodic endoscopic surveillance is recommended.[27] If incomplete metaplasia or dysplasia are diagnosed, such surveillance is necessary. If the lesions are clearly identified topographically, endoscopic resection is a valid strategy. In Japan, endoscopic resection of such lesions leads to 5-year survival rates up to 90%.[3] An active search for serologic markers of high cancer risk is under way in Japan. So far, besides low pepsinogen levels as markers of corpus atrophy, accepted markers are not generally are available.

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KEY POINTS

- Gastric cancer represents a major health burden worldwide.
- The cause of gastric cancer is multifactorial, although infection with *Helicobacter pylori* is considered to be the primary cause.
- Infection with *H pylori* is very prevalent; it has been estimated that at least 50% of adults worldwide harbor the infection.
- The early stages of gastric cancer are usually asymptomatic or associated with nonspe cific symptoms, such as dyspepsia.
- Strategies addressing cancer prevention are based on eradication of *H pylori* infection, recommendations on dietary changes to increase daily intake of fresh fruits and vegetables, and reduction in salt consumption.