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• *REVIEW* •

Multidisciplinary approach to understand the pathogenesis of gastric cancer

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Abstract

Gastric carcinoma remains a common disease worldwide with a dismal prognosis. Therefore, it represents a very important health problem. It occurs with a high incidence in Asia and is one of the leading causes of cancer death in the world. Although the incidence and mortality of gastric carcinoma are decreasing in many countries, gastric cancer still represents the second most frequent malignancies in the world and the fourth in Europe. The 5-year survival rate of gastric carcinoma is low. The etiology and pathogenesis are not yet fully known. The study of gastric cancer is important in clinical medicine as well as in public health. Over the past 15 years, integrated research in molecular pathology has clarified the details of genetic and epigenetic abnormalities of cancer-related genes in the course of the development and progression of gastric cancer. Gastric cancer, as all cancers, is the end result of the interplay of many risk factors as well as protective factors. Although epidemiological evidence indicates that environmental factors play a major role in gastric carcinogenesis, the role of immunological, genetic, and immunogenetic factors are thought to contribute to the pathogenesis of gastric carcinoma. Among the environmental factors, diet and *Helicobacter pylori* are more amenable to intervention aimed at the prevention of gastric cancer. The aim of the present paper is to review and include the most recent published evidence to demonstrate that only a multidisciplinary approach will lead to the advancement of the pathogenesis and prevention of gastric cancer. On the immunogenetic research it is clear that evidence is accumulating to suggest that a genetic profile favoring the proinflammatory response increases the risk of gastric carcinoma.

Key words: Gastric cancer; *H pylori*; Immunogenetics; IL-1; Diet; Trefoil regulation; gp130

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DISEASE DEFINITION AND CLASSIFICATION

The stomach wall is divided into three major areas: fundus, corpus, or body, and antrum and it has five layers: the inner lining (the mucosa) contains glands. Underneath is the submucosa; then is the layer of muscle; next is the subserosa. The outer layer is the serosa. Gastric cancers are malignancies arising in any part of stomach. Most gastric cancers arise in the antrum, the distal third of the stomach. The predominant site of gastric cancer occurrence has changed over the last 30 years[1-6]. A large number of tumors involving the proximal stomach and gastro-esophageal junction have been found. The lesser curvature of the stomach is more frequently involved than the greater curvature.

Several different types of cancer can occur in the stomach. Adenocarcinoma, which starts in the glandular cells, is the most common cancer of the digestive tract and histology accounts for 90-95% of all gastric malignancies. It can spread to nearby lymph nodes (LN) and other areas of the body, such as the liver, pancreas, colon, lung, and ovaries. Other types of malignancy in the stomach are sarcoma arising from the cells of the muscle layer, and more common, lymphoma arising in the B and T cells of the lamina propria. The latter two types of malignancies have different prognosis and require different management than adenocarcinoma.

In this review we will concentrate in adenocarcinoma of the stomach mainly because other types have rarely been reported[7,8].

Several classification systems are used for gastric cancer. Borrmann types, developed by Borrmann in 1923, identify five different types. This tissue classification of gastric cancer is characterized by the shape of the tumor on gastric mucosa and its pervading style in gastric wall.

Lauren developed the DIO system of the histomorphological classification, which assumes two main biological groups: diffuse gastric cancer (D) and intestinal gastric cancer (I), and other (O)[9,10]. The former two groups account for 90% of all stomach cancers. The intestinal type is well differentiated and characterized by polypoid or fungating

lesions that may ulcerate centrally. Many evidences show that this type is strongly associated with *Helicobacter pylori* (*H pylori*), and usually arises on a backdrop of chronic gastritis, gastric atrophy, and intestinal metaplasia[11]. Clinically, the latter is present with diffuse thickening of the stomach wall, rather than a discernible mass. A genetic predisposition is presumed in young patients with a diffuse type of gastric cancer, in contrast to the intestinal type associated with older age[12,13]. The intestinal type of adenocarcinoma has a better prognosis than the diffuse variant, most of which have spread beyond the confines of the stomach at the time of diagnosis. As with other cancers, stage is the most important determinant of outcome[14].

According to the standard of WHO, the cellular classification in gastric carcinoma has these subtypes: papillary adenocarcinoma, tubular adenocarcinoma, mucinous adenocarcinoma, signet-ring cell carcinoma, squamous cell carcinoma, adenoacanthoma, undifferentiated carcinoma, unclassified carcinoma and carcinoid tumor.

The Fifth International Union Against Cancer tumor node metastasis (UICC TNM) classification, which was published in 1997, based on the number of metastatic LN, has proved to be a reliable and objective method as the principal assessing the extent and severity of disease and determining the prognosis of cancer patients[15]. The new TNM classification not only is an objective, simple and reproducible system, but also a significant prognostic index for gastric cancer superior to the old classification. The new TNM classification represents a prognostic factor equally powerful to the old classification. Especially, the new N-classification is superior to the old N-classification in terms of the homogeneity of each N group[16,17].

X-ray examination after taking barium meal may eventually contribute to detecting delayed gastric emptying quantitatively and indicates the degree of tumor infiltration. Similarly and more accurately, spiral CT is of help in the identification of the gross type, invasion to serous layer and adjacent organs of gastric cancer in its stage of progression. The CT scan is also valuable in detecting metastatic as hepatic, splenic, and abdominal apart from the involvement of LN near the lesion. Enhanced dynamic CT scan plays a significant role in the diagnosis of gastric carcinoma; early enhancing phase scanning is the technique of choice nowadays for demonstrating tumor lesions. Sophisticated scanning technique is mandatory in improving the diagnostic accuracy of gastric carcinoma[18,19].

The ultrasound examination of stomach so far has been still a difficult technique that requires expertize. It can be used to observe the infiltration of the tumor into the lower layer of the mucous membrane. Endoscopic ultrasonography is very accurate in assessing the depth of tumor infiltration and the lymph node metastasis. It also can be used to determine the progress and prognosis of gastric carcinoma[20].

DISEASE CHARACTERISTICS

Precancerous lesions of stomach

Six different pathological disorders have been described as increasing the risk for malignancy in the stomach. The following processes have been implicated as precancerous lesions.

Chronic atrophic gastritis There is evidence from animal model that nitrosamine plays a role in developing malignancy. Achlorhydria in atrophic gastritis allows bacterial colonization of the stomach, most extremely in places where overgrowth may cause nitrate reduction and transform the nitrate, which exist in many foods to potentially develop carcinogenic *N*-nitroso compounds[21]. This occurs more often in antrum gastritis with intestinal metaplasia and non-typical proliferation. The course of gastritis is rather long and gastric cancer is believed to develop slowly over many years. Some patients present dyspepsia, vague abdominal fullness (after meal), irregular pain, belching, nausea, and vomiting, but not specific. Severe cardiac gastritis may produce glossitis and anemia.

Gastric polyps Familial adenomatous polyps are associated with upper gastrointestinal adenomas and adenocarcinoma. Based on Nakamura's classification[22,23], hyperplastic polyps were further classified into the following subtypes: the foveolar epithelial type, fundic glandular hyperplastic type, and pyloric glandular hyperplastic type. It was found that atypical hyperplastic foci usually appear in the foveolar epithelial subtype, indicating a close relationship to cancer. This finding suggests that the subclassification of hyperplastic gastric polyp has a higher practical value in clinical application[24].

Gastric ulcer Some gastric cancers are considered to transform from gastric ulcers, but with a low rate, 1-5% in China. Cancerous degeneration of ulcer was small and the epithelial regeneration at the ulcer's edge and benign fusion of the muscularis mucosa with the muscularis propria were very common. The cancerous tissue extending to node metastasis was rare. Therefore, the cancerous tissue down to the submucosa was found at the margin but not at the base of the ulcer. These patients should be thought seriously, specially if they are more than 45 years old, the symptoms of gastric ulcer are persistent 1 mo after treatment. These findings that conform well to Hauser's criteria blood test are positive. These results suggest that multiple biopsies should be taken from the edge of chronic ulcers. The most distinct feature of malignant ulcer was the lack of cancerous infiltration and muscular residue in the scar tissue of ulcer base. The existence of this type of ulcer clinically and pathomorphologically supports the viewpoint that gastric cancer ulcer can undergo malignant change[25].

Cancer of gastric remnant Patients after gastrectomy have more opportunity to get vicious tumor than normal people, and the course from remnant stomach to gastric cancer is nearly 15-30 years. Refluxing of intragastric and bile after gastrectomy became the base of gastritis. Furthermore the pH is increased and is beneficial to the abnormal proliferation of cell, carcinogen such as nitrite transfer to nitrosamine. Bile salt, a carcinogen, sometimes can lead to cancer.

Cholecystitis It was found that both the content of various kinds of biliary acid salt and pH value of gastric juice were much higher in patients with gastric cancer, gastric ulcer, and chronic atrophic gastritis than in normal controls. Bile acid salt is known to be harmful to gastric mucosa and the damage becomes more severe with the increase of bile acid salt concentration and prolongation of exposure. Therefore,

our results suggest that the bile acid salt in the gastric juice is one of the carcinogenic factors[26].

Pernicious anemia Pernicious anemia can lead to atrophic gastritis and is well known to be associated with gastric cancer. Pernicious anemia and autoimmune disease in general is rare in Chinese patients. There are few reports of pernicious anemia in Chinese patients and does not play a significant role as a predisposing cause of gastric cancer in China[27,28].

Gastric schistosomiasis Gastric carcinoma has been found arising from schistosomiasis in the epidemic area of south China and this chronic inflammation has been linked to development of gastric cancer in this area of China[29].

Early gastric cancer

The designation early gastric cancer (EGC) refers to a gastric carcinoma, which does not infiltrate beyond the submucosa. This definition is not influenced by absence or presence of metastases or by the diameter of the tumor. The 5-year survival of EGC is 90% or more. The diagnosis can regularly be made if, in the case of persistent vague upper abdominal complaints, an optimal radiological examination of the stomach is done. At even the slightest radiological suspicion, or if complaints persist in spite of negative radiological findings, gastroscopic examination and multiple-aimed biopsies should follow. Attention should be focused on the gastric angular incisure, antrum and lesser curvature to perform site-directed biopsy. Final diagnosis depended on the pathological diagnosis of the biopsy material. Pathologic diagnosis would be correct, provided the biopsy material was taken from the proper site[30,31].

An investigation from Liaoning Province reported pathological characteristics of EGC in Chinese patients. The peak age of the patients was between 50 and 59 years. The incidence in female before 50 years was higher than that in male but reverse after this age. The most common site was in lower part of the stomach. Highly differentiated carcinomas were more frequently found in those cancer foci of no larger than 0.5 cm in diameter. More signet ring cell carcinomas were found. Lymphatic metastasis was more in type IIc+III and the least in type I. Comparing with the Japanese cases, it was found that the peak age of EGC patients in Japanese was 10 years older than that in Chinese patients and most of the tumor occurred in middle part of the stomach. Type III and mucinous adenocarcinoma was hardly found[32].

The recurrence rate was higher in submucosal tumors than in mucosal tumors, in lymphatic and vascular vessel invasion-positive cases than in negative cases, in synchronous multiple gastric cancer than in solitary tumors, in tumors of 1.5 cm or more in diameter than in tumors of less than 1.5 cm. The rate of hematogenic metastasis to the liver or lung was 45.5%, and the recurrence in the residual stomach was 27.3% and in lymph node was 27.3%[33].

Advanced gastric cancer

Because of the elusive nature of gastric disorders, gastric cancer usually is advanced when symptoms first appear. There are several characteristic routes by which gastric carcinoma will progress and metastasize: (1) by extension and infiltration along the mucosal surface and stomach wall or lymphatic vessels, (2) via lymphatic or vascular embolism, probably to regional LN, (3) by direct extension into adjacent structures such as the pancreas, liver, or esophagus, and (4) by blood-borne spread. The pattern of metastatic spread of gastric cancer correlates with the size and the location of tumor. Lesions of the distal portion of the stomach usually metastasize to infra-pyloric, inferior gastric, and celiac LN. Tumors in the proximal portion often metastasize to pancreatic, pericardial, and gastric LN. With advanced gastric cancer, involvement of the left supraclavicular nodes may occur. Distant metastatic sites are the lung, adrenal glands, bone, liver, pancreas, and peritoneal cavity[34].

Clinical syndromes

In the early stage, GC seldom showed significant symptoms, some of which are common to other, less serious gastrointestinal disorders (bloating, gas, and a sense of fullness). Some degrees of dysplasia occur, appetite loss, heartburn, vague abdominal fullness, flatus, excessive belching, and breath odor, mild or severe, were similar as in the presentation of chronic gastritis or gastric ulcer previously reported. Soon afterwards the difficulty in swallowing, particularly difficulty that increases over time, nausea and vomiting, abdominal pain and weight loss were on the rise. In the late stage some patients might vomit blood; have blood in the stools or black stools, tiredness due to anemia, abdominal pain and weight loss are aggravated, a decline in general health.

As other malignancies, early detection, early diagnosis, and early treatment remain the key to improve the survival of patients with resected cancer of the gastric cardia. Why residual tumor left at the resection edge and the presence of tumor thrombi do not influence survival needs to be further studied.

EPIDEMIOLOGY

The epidemiology of gastric cancer involves many features, since there are significant geographical, ethnical, and cultural factors influencing the prevalence of GC. It is more frequent in the developing world than in the developed world, more common in Asia than in Europe, and more in Latin America than in North America and Africa[35]. Stomach cancer in China has distinct geographically different distribution. The morbidity in urban areas is higher than in rural areas, giving a difference of 1.9 times[36]. According to an investigation between 1989 and 1999, in Linqu County of China, no reduction in GC mortality was observed in the highest risk population worldwide[37].

The most recent estimates indicate that gastric cancer is the second most common cancer in the world after lung cancer. It represents 11% of all cancers in men and 7% of all cancers in women. In developing countries, lung cancer ranks first, representing 13% of all cancers and gastric cancer second (12%). In developed countries gastric cancer ranks fifth, representing 7% of all cancers, three-fourth of which occur in Asia. About 80% of the cases diagnosed in Asia occur in China and Japan. Steady decline in the rates of gastric cancer has been observed everywhere in the last few decades. However, the total number of new cases

diagnosed worldwide is increasing mainly because of increasing and aging of the population. It was estimated that there were 700 000 new cases in 1980, 755 000 in 1985, 900 000 in 1990, 1 013 000 in 1995, and 1 000 000 in 2000. This indicates that the impact of gastric cancer in public health is not decreasing[4].

ETIOLOGY

Gastric cancer, of all cancers, is the end result of the interplay of many risk factors as well as protective factors. Genetic and environmental factors are likely to play a role in the etiology of the disease. Several factors are suspected to play a role in gastric carcinogenesis, including the effects of diet, exogenous chemicals, intragastric synthesis of carcinogens, genetic factors, infectious agents, and pathological conditions in the stomach (such as gastritis). According to Correa, there is evidence from pathology and epidemiology studies that gastric carcinogenesis develops with the following sequential stages: chronic gastritis; atrophy; intestinal metaplasia; and dysplasia. The initial stages of gastritis and atrophy have been linked to excessive salt intake and infection with *H pylori*[38].

Environmental factors and gene polymorphisms involved in the susceptibility of gastric cancer

Several epidemiological evidences indicate that environmental factors play an important role in gastric carcinogenesis. The fact that immigrants exhibit incidence rates similar to those of their country of origin has led researchers to accept exogenous influences such as environment and diet. The investigation from China showed that the risk factors of gastric cancer were living in high incidence area for a long period, low economic income, low consumption of fresh vegetables and fruits and animal protein, high intake of sweet potato and ink fish and salted meat, eating and drinking too much at one meal and mental injury, and a family history of gastric cancer. High intake of grains and low intake of animal fat and proteins appear to be associated with a decreased risk. Diets rich in vitamins A and C are associated with low risk for gastric cancer. Controversy exists over the role of nitrates found in soil-grown foods, drinking water, and prepared foods. Because refrigeration and a high intake of ascorbic acid inhibit the formation of nitrates, it is postulated that the presence of these factors may account for decreasing gastric cancer. Neither smoking tobacco nor drinking alcohol has been demonstrated to increase the risk of gastric carcinoma[32,39-44].

H pylori

Gastric carcinogenesis is a multistep and multifactorial process beginning with *H pylori*-associated gastritis in most cases. *H pylori* infection, together with other environmental factors and individual susceptibility, determine the final risk for the development of gastric cancer. The discovery of *H pylori* in the early 1980s has proved a turning point in understanding the pathogenicity of this malignancy. *H pylori* infection is common worldwide and about half of the human population believed to be infected. But only a small fraction of infected individuals develop gastric cancer. Additional factors must be involved in the progression toward cancer[45,46,50].

H pylori are highly host-adapted bacterial pathogens that establish a chronic infection in the human stomach and have no known animal or environmental reservoirs. It shows a high degree of genetic heterogeneity due to mutations and frequent recombination. In the past, specific genes have been identified which are associated with bacterial virulence. These genes (e.g., *vacA*, cytotoxin associated gene A (*cagA*), and *iceA*) have been studied individually, and distinct genotypes have been defined. There is accumulating evidence that the different genotypes of *H pylori* show a particular geographic distribution[51]. *H pylori* strains containing the cagA protein are associated with more severe disease and harbor a 40-kb pathogenicity island (PAI) induce NF-κB activation and interleukin (IL)-8 secretion in gastric epithelial cells. *H pylori* changes the expression of genes encoding growth factors and cytokine/chemokines and their receptors, apoptosis proteins, transcription factors, and metalloprotease-disintegrin proteins, and tissue inhibitors of metalloproteinases[47].

H pylori stimulate endothelial cells to upregulate adhesion molecule expression and to increase the production of neutrophil-recruiting chemokines. The PAI encodes a bacterial type IV secretory system that secretes and translocates the cagA protein into host cells, where it is phosphorylated by a host-cell kinase and causes morphological changes. Innocenti *et al*., found that several, but not all, *H pylori* strains are able to activate endothelial cells to express the adhesion molecules VCAM-1, ICAM-1, and E-selectin and to secrete neutrophil-recruiting chemokines, and therefore contribute to tissue damage and ulcer formation[48,49]. Among people infected with *H pylori*, the virulence of the infecting strain is a major determinant which develops disease. Strains producing vacuolating cytotoxin activity are more commonly isolated from people with peptic ulcers than without. The gene encoding the toxin, *vacA*, varies between strains, especially in its signal sequence and mid regions. *vacA* genotype influence cytotoxin activity, and signal sequence type correlates closely with peptic ulceration. Infection with strains possessing *cagA* is more common among people with peptic ulceration or gastric adenocarcinoma than without. CagA+ *H pylori* infection is more closely associated with gastric cancers and peptic ulcers than cagA-infection. Because cagA+ infection may be associated with the development of atrophic gastritis, cagA infection is believed to be a risk factor for intestinal-type gastric cancer. But Deguchi *et al*., reported that cagA infection is also associated with diffuse-type gastric cancer in Japan. They also found that all p53 alteration were in *H pylori*-positive gastric cancer and their mutations were more frequent in the cagA group, although the correlation between p53 mutation and *H pylori* infection did not reach statistical significance. p53 abnormality was clinically correlated with prognostic factors (e.g., tumor size, depth, lymph node metastasis) of gastric cancer. These findings indicated that cagA+ *H pylori* infection might have an important role in the development of gastric cancer with p53 mutation[52].

The p53 tumor suppressor gene, located on chromosome

17p13, is one of the most commonly mutated genes in all types of human cancer. p53 codon 72, which produces variant proteins with an arginine (Arg) or proline (Pro), has been reported to be associated with cancers of the lung, esophagus, and cervix. Recently, studies in Japan suggested that the Pro/Pro genotype at p53 codon 72 contributes to susceptibility of diffuse-type gastric cancer patient with *H pylori*-CG[53]. The mutation of p53 and inactivation of p21WAF1 and p16 play an important role in carcinogenesis of stomach. However, *H pylori* infection was not associated with the abnormal expression of these three genes in China[54].

Human Chk1 and Chk2 are DNA damage-activated protein kinases that function as downstream mediators of ataxia-telangiectasia mutated, which are involved in G_2/M cell-cycle arrest. A study from Japan found a significant correlation between the levels of expression of Chk1 and p53 proteins in gastric carcinomas. Chk2 might be important in the checkpoint function in human gastric carcinomas with p53 mutation[56]. Mutations of an oncogene, K-ras, may be involved in the early stage of carcinogenesis of the intestinal types. The incidence of K-ras mutations in gastric cancer is only 10%. However, by histological classifications, the incidence of K-ras mutation was more frequent in intestinal types than in diffuse types of gastric adenocarcinoma. In addition, K-ras mutations in *H pylori*-associated chronic gastritis were significantly more frequent in gastric cancer patients than in cancer-free patients (50% *vs* 3.7%, $P = 0.037$)[57].

No evidence for the involvement of antigastric antibodies in the stimulation of apoptosis was found. Therefore, host factors may be at least as important as bacterial factors in determining gastric mucosal responses to *H pylori*[55].

Interleukin gene polymorphisms and gastric cancer

The presence of *H pylori* in gastric antrum is, in most cases, associated with mucosal inflammatory changes consisting of infiltration of a large number of polymorphonuclear and mononuclear phagocytes. *H pylori* reside in the mucus layer overlying the epithelium and do not invade epithelial cells. However, accumulating evidence indicates that gastric infection with *H pylori* induces the expression of several proinflammatory cytokines, including IL-1β, IL-6, IL-8, IL-18 and TNF-α in gastric mucosa.

IL-1β is a potent proinflammatory cytokine and powerful inhibitor of gastric acid secretion that is upregulated in the presence of *H pylori* and is important in initiating and amplifying the inflammatory response to this infection. El-Omar *et al*., reported that gene polymorphisms in the interleukin gene family of cytokines (IL-1β-31C, IL-1β-511T, and IL-1RN*2 alleles) are associated with an increased risk of both hypochlorhydria, in *H pylori* negative infected first-degree relatives of gastric carcinoma[58,59]. A study from Portugal supported the hypothesis that host genetic factors that affect IL-1 gene determine why some individuals infected with *H pylori* develop gastric cancer while others do not[60,61]. The polymorphism of promoter region -31C/T of IL-1β gene and the polymorphism of IL-1RN genes 1/2 and 2/2 are associated with the susceptibility of gastric cancer in Chinese. Carrying -31T allele increases the risk of gastric cancer. Polymorphism of IL-1RN and IL-1β gene may be used as indicators of susceptibility of gastric carcinogenesis[62]. A study from Japan investigated the polymorphism of -511 T-to-C located in the IL-1β gene. According to these authors in view of the results for the IM or CAG without *H pylori* group, the presence of the C allele may also indicate a risk of mucosal atrophy of the stomach in the Japanese population[63].

Serum levels of IL-8 and nitrogen monoxide (NO) are correlated with CagA+*H pylori* strain infection. Combined detection of serum level of IL-8, NO, and HP-CagA will contribute to the early diagnosis of precancerous lesion in the stomach[64]. Secretion of IL-8 by gastric epithelial cell upon *H pylori* infection is dependent on activation of NF-κB[65].

IL-18 is a recently identified cytokine (originally termed interferon γ-inducing factor) and is related to the IL-1 family both structurally and functionally. Recently research has showed that IL-18 was increased in a variety of human inflammatory conditions, including Crohn's disease, rheumatoid arthritis, and tuberculoid leprosy with pleiotropic immunomodulatory functions. It has been found that IL-18 mRNA expression was greater in *H pylori*-positive than in *H pylori*-negative patients with normal mucosa. But mature IL-18 protein and active caspase-1 p20 are present in mucosa of both *H pylori*-infected and -uninfected subjects. The presence of the mature form of IL-18 in both normal and gastric mucosa suggests that gastric IL-18 has an important role in promoting local production of interferon-N and cell-mediated responses in the gastric mucosa[47].

H pylori induces the production of tumor necrosis factor-α (TNF-α), which is closely related to epithelial injury. TNF-α plays a crucial role in host defense against infection, but a high concentration of TNF-α may cause severe pathology. The gene for TNF-α is located within the class III region of the major histocompatibility complex, which is a highly polymorphic region. The most common exchanges are G to A transitions in the TNF-α promoter at positions -308 (-308A) and -238 (-238A), and these genetic changes have been reported to influence TNF-α concentrations. It is possible that increased TNF-α concentrations, as a result of -308A polymorphism, alter the immune response, which confers susceptibility to gastric disease with *H pylori*-cagA subtype infection[66]. In a study in Spain, these results suggest that TNF and LTA gene polymorphisms are related to the development of gastric and duodenal ulcer and may determine disease outcome in *H pylori* infection[67].

Wu *et al*., have reported that no association was noted between gastric cancer and the distribution of IL-1 and TNF-α genotypes in Taiwanese Chinese. Logistic regression analysis revealed that *H pylori* infection, cigarette smoking, and IL-10 genotype are independent risks for gastric cancer in the Taiwanese. Similar studies should be carried out in different populations and as Wu *et al*., have correctly performed the risk of genotypes should be adjusted with confounding environmental risks[68].

Genetic polymorphisms of some metabolizing enzymes

Environmental genotoxic chemical agents arising from the

diet, smoking, and air pollution are responsible for carcinogenesis in humans. It is generally accepted that the majority of carcinogenic chemical do not produce their biological effects *per se*, but require metabolic activation by host enzymes: phase I enzymes including cytochrome P450 enzyme and phase II enzymes including epoxide hydroxylase, *N*-acetyltransferase 2 (NAT2), and glutathione *S*-transferase (GSTs). Genetic polymorphisms have been recently shown in many of these enzymes, indicating that there are genetic differences among individuals in the ability to metabolize chemicals. Such genetic polymorphisms may affect the individual susceptibility to chemical carcinogenesis. From this point of view, the relationship between the genetic polymorphisms and carcinogenicity has been extensively examined to determine which polymorphic enzymes are highly associated with the susceptibility to cancers. Japanese researchers suggested that a combination of GSTM1 and NAT2 decreases the risk of gastric cancer in Japanese patients[69]. A population-based case-control study in China suggested that the GSTP1 genotype seems not to be associated with the risk of gastric cancer and chronic gastritis in a high-risk Chinese population[70]. The polymorphic genes of cytochrome P450, CYP2A6, and CYP2E1 have been implicated in increased susceptibility to certain malignancies. The CYP2A6 deletion was associated with gastric adenocarcinoma among Japanese population[72].

KILLER/death receptor DR5

The KILLER/death receptor DR5 has been identified as a potent inducer of apoptosis, and mapped to chromosome 8p21-22, showing frequent allelic loss in gastric cancer. As stated before, the p53-induced apoptosis is an important biological process to prevent the development of cancer, and is mediated in part by expression of KILLER/DR5 only in cells with wild-type p53 protein, but not in those lacking p53 function. A report from Japan suspected that inactivation of KILLER/DR5 caused by mutations of KILLER/DR5 may be one of the possible escaping mechanisms against KILLER/DR5-mediated apoptosis and that inactivating mutation of KILLER/DR5 may contribute to the promotion or progression of a subset of gastric cancers[71]. In Japan, another cancer registry-based study found that the incidence of gastric cancer was increased up to 5-fold in male relatives of early-onset prostate cancer patients. Currently unknown genes might contribute to the observed link between prostate and gastric cancer[73].

E-cadherin

E-cadherin is a member of the cadherin family of calcium-dependent cell adhesion molecules. These molecules are localized in lateral cell-cell contacts of the epithelial cells and regulate the process of homophilic/homotypic adhesion between epithelial cells and play a role as a tumor suppressor gene. E-cadherin associates with α-catenin, β-catenin, and γ-catenin to form a complex that is essential for cell–cell communication and cell adhesion. Indeed, abnormal E-cadherin expression (characterized by loss, reduced, and/or cytoplasmic expression) has been observed in several types of carcinoma, and is frequently associated with poor differentiated/undifferentiated carcinomas and/or invasive tumors. A co-operative study among Portugal, Germany, and Belgium reported that E-cadherin inactivation is significantly related with the diffuse histotype in gastric carcinoma, not only in "pure" diffuse carcinomas but also in the diffuse component of mixed tumors, β-catenin mRNA levels are increased in the vast majority of intestinal-type gastric cancers and this overexpression is independent of *H pylori* infection[74,75].

Trefoil regulation, gp130, and gastric cancer

For a long time it was believed that the stomach and the intestine respond differently to inflammation. The immunological system of the stomach appears less fully developed than the intestine. This in part is due to the fact that nature has given the stomach a mechanism to protect itself with the production of hydrochloric acid and therefore an environment where only special bacteria, such as *H pylori* can survive. The intestine on the contrary is full of bacteria; however, seemingly ends in unrelated diseases. Inflammatory bowel disease and gastric cancer share in common an origin in chronic inflammation. An important and interesting finding that has arisen from research in mice with a "knock-in" mutation abrogating the Src-homology tyrosine phosphatase 2 (SHP2)-Ras-ERK signaling that developed gastric adenomas by 3 mo of age. Mice with a mutation eliminating the STAT1/3 signaling gp130 (Delta STAT)) showed impaired colonic mucosal wound healing[76]. As stated in an editorial in Nature Medicine[77], given the close interplay between the immune response and epithelial cells, it is not surprising that perturbations in signaling of immune system mediators play a key role in disease of the gut. It is the gp130 receptor, which binds the IL-6 family (IL-6 and IL-11) of cytokines that serve as an inflammation intersection between the stomach and the intestine. The homodimers of gp130, a transmembrane receptor β-chain, contain two discrete functional modules which signal through SHP-2/Erk and STAT1/3 that are responsible for the different behavior exhibited by the stomach and the intestine in response to inflammation. To understand the pathogenesis, it is necessary to understand the function of other family of genes called the trefoil factor (TFF) family that intimately appear to work with the gp130 molecule. Suemori *et al*.[78], discovered in 1991 a group of small proteins designated intestinal trefoil factor. These authors demonstrated that it is primarily expressed and secreted onto the intestinal surface by goblet cells, suggesting that it may be an important component of intrinsic mechanisms for defending mucosal integrity. They are upregulated around areas of epithelial damage, ulceration, and neoplasia[79].

IL-1 and IL-6 overexpression in chronic gastritis may lead to mucosal damage and gastric carcinogenesis through transcriptional repression of TFF1 and TFF2[80]. TFF1 knockout mice developed multiple gastric adenomas and carcinomas, suggesting that TFF1 is a gastric-specific tumor-suppressor gene[81]. The gp130 directly regulates the TFF genes. The trefoils are key downstream targets of the SHP2/Erk and STAT signaling pathways. The data also add to TFF1's credibility as a gastric-specific tumor-suppressor gene and TFF3's as a mediator of intestinal homeostasis. The hyperproliferative lesions was observed in the stomachs

of gp130 arise as a result of enhanced STAT3 activity in the absence of a counter-acting signal from the SHP2-Ras-Erk pathway rather than from the complete absence of (IL-6 and IL-11-mediated) gp130 signaling. IL-6 is likely to have an important role in the initial phase of intestinal wound healing. Furthermore, endogenous IL-11, unlike pharmacologically administered IL-11, seemed to have negligible effects on the intestinal epithelium.

In conclusion, although the incidence of gastric cancer is decreasing in some parts of the world, it still takes a significant toll among the inhabitants of Japan, China, Chile, Finland, Poland, Austria, Yugoslavia, and Costa Rica. The key to prevention of cancer of stomach lies in dietary intake. It is important to consume a balanced diet high in fresh fruits and vegetables and moderate amount of animal protein and fats. Salted, smoked, and pickled foods should be consumed in low quantities.

Screening and early detection programs are very useful. If detected at an early stage and treated aggressively, gastric cancer can be cured. As with all other forms of gastrointestinal cancers, gastric cancer is insidious in its onset and development. It usually infiltrates rapidly and can be disseminated throughout the body before overt signs of cancer are manifested. Overall 5-year survival rates are reported to range from about 8% to 16%. Gastric cancer mimics several other gastrointestinal maladies and diseases such as polyps, ulcers, dyspepsia, and gastritis. Some of the most difficult aspects of prevention and early detection are informing and motivating people at risk for the development of gastric cancer to seek medical attention for chronic "stomach problems". Inappropriate use of home remedies, self-medication, and misdiagnosis are major hurdles to overcome.

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