Journal of Carcinogenesis

Review Article

Gastric cancer review

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Published: 19 December, 2014
Journal of Carcinogenesis 2014,13:14
This article is available from: http://www.carcinogenesis.com/content/13/1/14

Received: 17 July, 2014
Accepted: 14 October, 2014

Abstract

Gastric cancer is an aggressive disease that continues to have a daunting impact on global health. Despite an overall decline in incidence over the last several decades, gastric cancer remains the fourth most common type of cancer and is the second leading cause of cancer-related death worldwide. This review aims to discuss the global distribution of the disease and the trend of decreasing incidence of disease, delineate the different pathologic subtypes and their immunohistochemical (IHC) staining patterns and molecular signatures and mutations, explore the role of the pathogen *H. pylori* in tumorgenesis, discuss the increasing incidence of the disease in the young, western populations and define the role of biologic agents in the treatment of the disease.

Keywords: Biologic targeted therapy, diffuse subtype, gastric cancer, *Helicobacter pylori*, intestinal subtype

INTRODUCTION

Gastric cancer is an aggressive disease that continues to have a daunting impact on global health. Despite an overall decline in incidence over the last several decades, gastric cancer remains the fourth most common type of cancer and is the second leading cause of cancer-related death worldwide.[1,2] Although the incidence is declining due to improved nutrition, food preservation, better prevention, earlier diagnosis and treatment, the disease still carries a poor prognosis. Gastric cancer is often diagnosed at an advanced stage. The cornerstone of therapy is surgical resection with adjuvant chemotherapy or chemoradiation in appropriate cases. Such an approach has led to improved survival.[3,4] Unfortunately, treatment of advanced or metastatic gastric cancer has seen little progress and median overall survival (OS) in this group remains <1 year.[5] Gastric cancer is a heterogeneous disease that demands continued attention and research with regard to prevention, early detection and novel therapeutic options.

Access this article online

Quick Response Code:

Website: www.carcinogenesis.com

DOI: 10.4103/1477-3163.146506

The global distribution of gastric cancer varies substantially across geographical regions which illustrate the multitude of factors that are associated with the incidence, survival and mortality of the disease. The Asian countries account for the majority of the world's cases while Europe and the Americas combined makeup less than a quarter of the world disease burden.[6,7] Even within the highly affected areas, certain populations are more commonly afflicted; particularly the lower socioeconomic classes, and within the United States, the African American population.[6,8]

The two main histologic subtypes of the disease, intestinal and diffuse type, as classified by Lauren,[9] define two distinct entities that have different epidemiology, etiology, pathogenesis and behavior. The last several decades have demonstrated a gradual decline in the rates of gastric cancer in most populations and across subtypes. Perhaps, the decline can be attributed in part to improved food preservation with

the advent of electric refrigeration,[10] increased accessibility to fresh fruits and vegetables year round, lower salt diets (less salt preservation), the decreased use of tobacco[11] and eradication of *Helicobacter pylori* infections in endemic areas. However, whereas most gastric tumors are declining in incidence, tumors of the gastric cardia and gastroesophageal junction are becoming more frequent and there is a trend of rising incidence of noncardia gastric cancer among American whites between 25 and 39 years of age[12] and in the same age group in other western countries.[13,14]

Environmental and nutritional factors have been implicated in the development of the disease. Consumption of salt and salt-preserved food, nitrates, and smoked or pickled foods have been associated with increased risk of developing gastric cancer.[10] Much of the evidence about salt and food preservation, however, is indirect and is based on time trend comparisons.[10] While tumors of the cardia and the gastroesophageal junction may be related to gastroesophageal reflux, a clear causal relationship exists between noncardia gastric cancers and chronic mucosal infection by the Class I human carcinogen, *H. pylori*.[15] This review aims to discuss the global distribution of the disease and the trend of decreasing incidence of disease, delineate the different pathologic subtypes and their immunohistochemical (IHC) staining patterns and molecular signatures and mutations, explore the role of the pathogen *H. pylori* in tumorgenesis, discuss the increasing incidence of the disease in the young, western populations and define the role of biologic agents in the treatment of the disease.

GLOBAL IMPACT

Seventy-three percent of gastric cancer cases are diagnosed in Asia; almost 50% of the world's cases are diagnosed in China alone.[6,7] Europe accounts for an additional 15% and Central and South America contribute 7% of the global burden.[6,16] Within these global regions, there is further variability as to which populations are more greatly affected. The incidence rate in men is double that of women and incidence increases with age. Even within the same geographic region certain ethnic groups have significantly higher risk of disease. Within the United States, Hispanics, African Americans, and Native Americans are more frequently affected than Caucasian Americans.[6,11] However, ethnic predisposition cannot be considered alone since socioeconomic status also impacts disease incidence.

The incidence of gastric cancer can be further divided according to its location within the stomach with a distinction between the distal portion of the stomach (noncardia) and cancers arising from the proximal cardia region.[17] The distinction for cardia versus noncardia disease is important because there is evidence that the two entities have different etiologies and because several reports indicate that gastric cardia cancer and gastroesphageal junction tumor are increasing in incidence and there is a parallel increased incidence in noncardia cases in the young western populations.[12-14,17]

In general, the less developed nations carry a greater gastric cancer disease burden than developed countries. Within all afflicted nations, noncardia gastric cancer is more likely to affect persons of lower socioecomonic groups.[8] Similarly, risk of *H. pylori* infection is associated with lower socioeconomic status, overcrowding and unsanitary conditions.[17] Interestingly, wealth and education have an inverse relationship to noncardia tumors but are associated with cardia gastric cancer.[8] In making such observations, it is important to note that other risk factors, including *H. pylori* infection, tobacco use and diet, may confound the data related to socioeconomic status.[17] The impact of environmental factors is further supported by the fact that first-generation migrants coming from countries of the high incidence to a country of low incidence maintain the risk of the country of origin. The incidence rate decreases in the subsequent generations implicating environmental influences early in life.[18]

PATHOLOGIC SUBTYPES AND CHARACTERISTICS

Several classification systems exist to define gastric cancer but the most frequently used is the Lauren classification. The Lauren classification defines two main histologic subtypes: Intestinal type and diffuse type.[9] Each subtype represents distinct clinical and epidemiologic characteristics. There are rare cases of gastric carcinomas that display features of both histologic subtypes. The morphologic differences between the two subtypes are related to intercellular adhesion molecules, which are preserved in intestinal type disease and defective in diffuse gastric carcinoma. Both subsets can have targetable protein expressions such has human epidermal growth factor receptor 2 (HER2) expression.

Gene amplification is a frequent mode of gene alteration in gastric cancer. Such protein overexpression can be detected by IHC. Amplification of HER2 has been observed in colorectal, lung, gastric and ovarian tumors.[19] In gastric cancer, HER2 overexpression is reported in 7–34% of tumors, particularly at the G-E junction and in the intestinal type lesions.[20] Epidermal growth factor receptor (EGFR) overexpression has been shown to be a marker for poor prognosis in gastric cancer.[21] Expression of the both vascular endothelial growth

factor A (VEGFA) and its receptor is reported in about 40% of gastric cancer cases and increased expression of VEGFA is associated with a poor prognosis and advanced disease.[22] All the above proteins are targets for biologic therapeutic options and have been studied for impact on survival. The details of the therapeutic trials will be discussed later in this review. New biomarkers for targeted therapy are being explored, such as fibroblast growth factor receptor (FGFR), hepatocyte growth factor receptor, and the mammalian target of rapamycin. Some of the new targets are in clinical trials.

INTESTINAL SUBTYPE

The intestinal subtype is the most frequently diagnosed histology in high-risk populations and is more likely to be sporadic than inherited.[23] It is diagnosed in older individuals, males more than females, and the tumors tend to have the gross appearance of ulcerated masses.[24] Tumor genesis is strongly associated with *H. pylori* infection. As such, the intestinal subtype is linked to the decreasing incidence in gastric cancer seen globally over the last several decades.[24]

Chronic infection with *H. pylori* bacterium leads to a sequence of histologic changes that result in a malignant lesion. The cascade of events begins with sustained bacterial infection with *H. pylori* that leads to nonatrophic gastritis that transforms into multifocal atrophic gastritis without metaplasia then into intestinal metaplasia and finally dysplasia develops.[25,26] The prolonged gastric inflammation resulting from chronic *H. pylori* infection may cause epithelial damage that leads to gastric atrophy characterized by loss of parietal cells and chief cells and glandular atrophy.[24] The gastric epithelium is replaced by intestinal metaplasia, particularly in the lesser curvature of the stomach, but it can be seen anywhere in the stomach.[24] Eventually, foci of dysplasia can develop in the areas of metaplasia. Overtime the areas of dysplasia can invade the lamina propria defining them as invasive carcinoma by western standards. In Japan, severe nuclear and architectural abnormalities in the absence of invasion are considered carcinoma.[27]

Several oncogenes are overexpressed in intestinal type tumors; however none have been consistently present in any particular stage of disease. The c-met oncogene is involved with the development of about 20% of intestinal type gastric cancers and expression of the c-met transcript is associated with more advanced disease.[28] In fact, certain virulent strains of *H. pylori* form an effector protein that appears to modulate c-met receptor signal transduction pathways, which may lead to tumor initiation and progression.[29] K-ras mutations have also been found in intestinal metaplasia, dysplasia and invasive carcinomas.[30]

Alterations in tumor suppressor genes are found in many intestinal type gastric cancers. The P53 tumor suppressor gene (TP53) is an important regulator of the cell cycle. Loss of heterozygosity or mutational inactivation of TP53 expression occurs in more than 60% of invasive gastric cancers.[31] Abnormalities in TP53 expression have also been observed in *H. pylori*-associated chronic gastritis, metaplasia and dysplasia; however the relationship between TP53 and *H. pylori* remains unclear.[32,33] Mutations in the adenomatous polyposis coli gene have also been identified in intestinal and diffuse type gastric tumors and are also linked to *H. pylori* and gastric tumor initiation and proliferation.[34] Hypermethylation and microsatellites are also observed.

DIFFUSE SUBTYPE

The diffuse subtype of gastric cancer appears to be more aggressive than the intestinal type. It is generally diagnosed in younger patients and no gender bias exists.[24] While it can be associated with *H. pylori* infection it is more frequently associated with loss of expression of E-cadherin and no precancerous lesions have been defined.[35] Diffuse gastric tumors tend to invade the gastric wall and into adjacent structures, including the duodenum and esophagus without gland formation. Some presentations reveal diffuse infiltration of the gastric wall resulting in linitis plastica. Within this subtype, signet ring cell histology is occasionally observed.

Diffuse gastric tumors have a clear mechanism of carcinogenesis through defective intercellular adhesions. The majority of cases result from loss of expression of the E-cadherin cell adhesion protein.[35] The E-cadherin gene (CDH1) encodes a homodimeric transmembrane cellular adhesion protein that aids in assembling the cell: Cell adhesion complex.[36] The gene appears to function as a tumor suppressor gene requiring a "two hit" model if inactivation.[37] The hereditary form of diffuse gastric cancer (HDGC) has an autosomal dominant pattern of inheritance. The disease presents early in life and has a lifetime cumulative risk of developing gastric cancer of more than 80% by age 80.[38] Patients with HDGC often present with multifocal tumors under an intact mucosal surface making diagnosis difficult. Patients with CDH1 germline mutations and family history of gastric cancer are referred for prophylactic gastrectomy.[39] Sporadic diffuse gastric carcinomas have also been linked to abnormalities in CDH1. Mutations and loss of heterogygosity in the CDH1 gene and promoter hypermethylation are observed in sporadic diffuse type gastric tumors.[37,40]

Helicobacter pylori

Gastric cancer is one of the few neoplasms that is directly linked to an infectious organism. *H. pylori* is a spiral Gram-negative bacterium that colonizes the stomach of

about half of the world's population and is associated with chronic gastritis, peptic ulcer disease, gastric lymphomas and noncardia adenocarcinomas and is Class I human carcinogen.[15,17,41] *H. pylori* infection is the strongest known risk factor for the development of gastric cancer, however only a small minority of the infected population develops malignancy. *H. pylori* infections are more strongly associated with intestinal-type adenocarcinoma than the diffuse subtype of gastric cancer but can be causal in either histology.[42] It is estimated that the infection with the bacterium is responsible for almost 80% of distal gastric cancer cases, but has little association with cardia gastric carcinoma.[42]

The infection is typically acquired during infancy and will remain present for life if left untreated. The inflammation caused by a chronic infection may generate reactive oxygen species which are capable of inducing DNA damage.[11] *H. pylori* is also capable of inducing hypermethylation, particularly of CpG islands, thereby inactivating tumor suppressor genes.[11] Different strains of the bacteria have variable carcinogenicity. The more aggressive strains carry the cytotoxic-associated gene A (CagA) which encodes an oncogenic protein that can be injected directly into gastric epithelial cells via type IV secretion precipitating a cascade of molecular events linked to carcinogenesis.[43,44] CagA appears to induce disruptions of intracellular junctions, loss of epithelial polarity, increased proliferation, reduced apoptosis leading to carcinogenesis.[45] Most strains in the high-risk areas of East Asia and the Colombian Andes are CagA positive, which helps to explain the increased incidence of the malignancy in these area.[11] The vacA protein is another virulence factor that causes intracellular vacuoles and membrane channels in epithelial cells.[46]

Trials of *H. pylori* eradication are logistically difficult since the carcinogenesis from the infection occurs over the course of decades. The current trials have looked at progression and regression of precancerous lesions with eradication of infection.[47] One trial shows a significant reduction in gastric cancer incidence in the group receiving *H. pylori* therapy after 15 years of follow-up.[48] A separate review of the eradiation trials concluded that there is a point of no return with respect to the development of *H. pylori* associated gastric cancer after which time treatment is ineffective at reducing the risk of malignancy.[49] Until date, the true impact of eradication of the bacteria is unknown.

PARADOXICAL INCREASED INCIDENCE OF GASTRIC CANCER IN A GLOBAL SUBPOPULATION

Although the overall incidence of gastric cancer is declining both globally and in the United States, a recent observational analysis from the SEER Program reveals increasing rates of noncardia, intestinal type gastric cancer in white US residents ages 25–39 over the last three decades.[12] The same trend has been observed in Spain and six other European countries.[13,14] The cause of this trend is unclear. The frequent use and possibly abuse, of H2 blockers and proton pump inhibitor, has been implicated as a precipitating factor but is also unlikely given the young age of the affected population. Another possible hypothesis is the increased frequency of antibiotic use during childhood.[50] The cause of this concerning trend warrants further epidemiologic evaluations in order to prevent further increase in disease burden.

THERAPEUTIC OPTIONS

Depending on the size and location of the primary tumor, the preferred means of therapy is surgical resection with total or subtotal gastrectomy. Chemotherapeutic interventions have been evaluated in the neoadjuvant, adjuvant, and metastatic settings. The SWOG 9008 trial evaluated postoperative chemoradiation after resection of gastric or G-E junction tumors. Patients were randomized to observation versus 5-FU/leucovorin and radiation up to 45 Gy. The 10 year follow-up revealed significant improvement in OS in the treatment arm; however, postoperative chemotherapy is generally poorly tolerated in this population.[51] The MAGIC trial evaluated perioperative chemotherapy with epirubicin, cisplatin, and 5-FU (ECF) in adenocarcinoma of the G-E junction or lower esophagus and found that the chemotherapy group had significantly higher OS and progression-free survival (PFS) than those who received surgery alone.[52] In the metastatic or recurrent setting any of the combination chemotherapy regimens such as ECF, DCF, FOLFIRI or best supportive care are reasonable options.[53-55]

While several targeted therapies have been studied, only two targeted treatments have been approved for use in the United States based on positive clinical trials. Inhibition of HER2 has been tested as a targeted therapy for several cancers. Trastuzumab is a monoclonal antibody that targets HER2 and thereby inhibits HER2 mediated signaling and prevents cleavage of its extracellular domain.[56] A Phase III international study (ToGA trial) evaluated the efficacy of trastuzumab in combination with conventional therapy (cisplatin plus 5-FU or capcitabine). Patients were stratified by HER2 overexpression. Patients treated with trastuzumab and chemotherapy had improved OS compared with chemotherapy alone.[57]

Ramucirumab, a monoclonal antibody against vascular endothelial growth factor receptors 2, is the first Food and Drug Administration approved biologic therapy used as a single agent that demonstrates survival benefit in patients

with advanced gastric cancer or gastroesophageal cancer who have progressed after first-line treatment.[20,58] Although the addition of bevacizumab, a monoclonal antibody against VEGFA, in combination with cisplatin and capecitabine in the treatment of gastric cancer in the AVAGAST trial demonstrated improved overall response rate and PFS, OS was not significantly improved, indicating that bevacizumab does not have a role in the treatment of gastric cancer.[59] Both the EXPAND and REAL3 studies which evaluated the monoclonal antibodies against EGFR, cetuximab and panitumumab, respectively, revealed that the addition of the anti-EGFR antibodies to chemotherapy does not improve survival in advanced gastric cancer. In fact, the addition resulted in inferior OS.[60,61] A clinical trial is underway to evaluate the role of the anti-EGFR antibody, nimotuzumab as an adjunct to irinotecan in the second-line treatment of gastric cancer (Clinicaltrials.gov identifier: NCT01813253). Similar studies are evaluating the benefit of adding biologic agents targeting FGFR (Clinicaltrials.gov identifier: NCT01457846), as well as, the anti-MET antibody, onartuzumab in selected patients (Clinicaltrials.gov identifier: NCT01662869).

FOCUS OF FUTURE ENDEAVORS

Gastric cancer remains a significant threat to global health. Although there has been a consistent and measureable decline in the incidence of the disease over the last several decades, there is still significant room for improvement with regard to prevention, early detection and intervention and life extending therapies. Clear recommendations for screening and intervention exist in the high-risk populations like those with CDH1 mutations and a family history of gastric cancer.[39] It is less clear whether all high-risk areas should undergo routine screening and treatment of the infectious and carcinogenic organism, *H. pylori.* No clear recommendations have been made in support of screening for atrophic or dysplastic changes in asymptomatic patients in high-risk regions. It is known that patients found to have atrophic or dysplastic changes in the gastric mucosa are at an increased risk of developing invasive cancer. In this population of patients, endoscopic surveillance is recommended.[62] In Japan, any lesions that are clearly identified are endoscopically resected, which has yielded a 5-year survival rate up to 90% in this population.[63] The encouraging results from the Japanese observational analysis serve as a foundation upon which screening guidelines could be established for high-risk patient populations around the world.

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How to cite this article: Carcas LP. Gastric cancer review. J Carcinog 2014;13:14.

Source and Support: Nil. **Conflict of Interest:** None declared.

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