Gastric Carcinoma: A Review of Current Trends

INTRODUCTION

It is quite surprising to learn that the second leading cause of death due to cancer worldwide is the result of stomach cancer.\(^1,2\) In 1990, there were 900,000 new cases of gastric carcinoma (GC) diagnosed throughout the world.\(^1\) In the 1930s, GC was the leading cause of cancer and cancer-related deaths in the United States and since then the incidence of GC has decreased dramatically.\(^2\) However, this has not been the case for Japan and many developing countries. In fact, some developing countries such as Mexico have shown an increase in the incidence of GC over the last ten years. As a result, GC is the most common type of gastrointestinal cancer in Mexico and the second most common cause of cancer-related mortality in that country.\(^3\)

EPIDEMIOLOGY

According to US studies, caucasians are less susceptible to GC than Hispanic Americans, Native Americans, and African Americans.\(^5,6\) The gender ratio is 2:1 favoring males over females in the acquisition of the disease.\(^2\) In the United States, the incidence of GC has dropped dramatically in the last 50 years. In men, the number of cases per 100,000 has dropped from 30 to 10.\(^2\) In women, the number of cases per 100,000 declined from 30 to 5.2. The disease is uncommon in persons younger than 40 years of age and the peak incidence of the disease occurs in the seventh decade.\(^2,4\) Despite declining trends, there are approximately 25,000 new cases of GC diagnosed each year.\(^6,7\) Therefore, GC poses a large obstacle for the U.S. to overcome.

In Mexico, incidence rates were shown to increase between 1980-1997. During this period it was estimated that 76,315 people died from GC. The male to female ratio was shown to be 1.2 to 1.0. Some of the most interesting epidemiological data can be retrieved from statistics describing the location trends of these cancers within the stomach. In 1930, most gastric carcinomas arose from the distal stomach, which is anatomically defined as the body and antrum.\(^2\) The worldwide decline in gastric carcinoma is believed to result from a reduction of lesions in the distal stomach. However, some studies have shown an increase in adenocarcinoma of the proximal stomach and the gastroesophageal junction.\(^8\)

AETIOLOGY

Numerous factors are believed to contribute to the development of gastric cancer, including the examples listed in Table 1.\(^9,10\)

Of these, dietary factors are considered the most important in terms of their contribution to GC. Consumption of both processed and fresh meat is linked with an increased risk for gastric cancer while consumption of vegetables and fruits lowers the risk for disease.\(^11,12\) Refrigeration of foods has played a key role in the decline of GC in most developed countries.\(^2\) Refrigeration makes fruits and vegetables more readily available and decreases the need for salt preservation of meats.

However, recent studies continue to place an increasing emphasis on the relationship between \textit{Helicobacter pylori} infection and the risk of gastric cancer. In a study by Uemuria and colleagues, 1246 of 1526 Japanese patients who developed duodenal ulcers, gastric ulcers, gastric hyperplasia, or nonulcer dyspepsia were infected with \textit{H. pylori}.\(^13\) Of the patients followed (over 7 years), only patients who were infected with \textit{H. pylori} developed gastric cancer (36 cases). While only 2.9% of the infected group developed cancer, it is significant that this was the only group to develop GC.

Additionally, some data indicates certain strains of \textit{H. pylori} may be more likely to cause GC than others. In 1998, workers found that strains possessing Cag pathogenicity (CagA+) were linked to increased rates of GC. The study showed that 2775 individuals, with CagA+ strains, from three different regions of Mexico were at an increased risk of developing GC proportionally in each of the populations.\(^14\) Therefore, in Mexico, it may be a unique strain or genetic susceptibility to such a strain that has lead to the continued increase in the number of new cases of GC each year. Resistance of \textit{H. pylori} to antibiotics, such as metronidazole, supports the possibility that a unique strain may be responsible for the development of GC. Rates of resistance to this drug are estimated to be as high as 70% throughout Mexico.\(^15\)

Also, new data supports the notion
Is Gastric Carcinoma a Problem of the Past or Future?

that iatrogenic causes may be involved secondary to the administration of parietal cell histamine receptor antagonists and gastric proton-pump inhibitors. This is of particular interest because it shows that there may be an increase in the overall incidence of GC with a shift in tumour location from the antrum toward the body and gastroesophageal junction.

PATHOLOGY

Ninety percent or more of stomach cancers are described as adenocarcinomas. The remaining few are either lymphomas or leiomyomas. Of the adenocarcinomas, there are two key subtypes: the intestinal-type and the diffuse type. The intestinal type is described as a bulky tumour consisting of glandular structures. This type of GC is believed to make up the majority of the cases seen worldwide. The incidence in the intestinal type has fallen over the last several years and may be responsible for the overall decline in gastric carcinomas throughout the world. In the diffuse type, cell cohesion is not present. Individual cells infiltrate and thicken the wall of the stomach so that no discrete masses are formed. Generally, this type can occur anywhere throughout the stomach but its tendency is to occur in the cardia region. The prognosis of the diffuse type is poor. The relationship between the intestinal and diffuse types remains unclear.

PATHOPHYSIOLOGY

Hyposcretion and Its Relationship to GC

A recent clinical review proposed that hyposcretion of acid in the stomach may be the culprit for the development of GC. It is known that H. pylori infections are associated with distal carcinomas of the stomach. Patients who develop this type of cancer have an H. pylori-associated decrease in acid secretion as well. Originally, it was believed that the hyposcretion was due to atrophy and destruction of parietal cells. The current trend is that hyposcretion results from an H. pylori-induced inflammation because eradication of H. pylori partially reverses such hyposcretion. Reduced acid secretion may lead to gastric cancer by impairing the absorption of vitamin C or promoting the overgrowth of certain salivary and intestinal bacteria. If this information is combined with the information on high salt diets, we can conclude that a cumulative effect occurs in those persons who have such diets and are colonized with H. pylori. High salt diets are known to suppress parietal cells and cause gastric atrophy. Such a hypothesis is supported by Uemuria and colleagues. These studies showed that patients infected with H. pylori are at a higher risk for the development of GC, especially those individuals with severe corpus-predominant gastritis.

Gastritis and Its Relationship to GC

There is some indication that acid secretion may be protective against GC. It has been shown that suppression of acid with a proton pump inhibitor (PPI) reduces gastritis in the antrum, although it allows H. pylori to colonise the body of the stomach. This may indicate that a low acid secretion causes a positive feedback cycle leading to increased corpus gastritis and causing a decrease in acid secretion. A recent study showed that PPIs may mask the symptoms of early GC and mislead physicians as to the source of dyspepsia. These researchers suggest that dyspepsia is experienced in a significant number of patients with early GC and that they are often given PPIs because their symptoms are mistaken for benign ulcer disease. Inevitably, this leads to the immediate resolution of symptoms since

<p>| Table 1: Causes of Gastric Carcinoma |</p>
<table>
<thead>
<tr>
<th>ENVIRONMENTAL</th>
<th>HOST FACTORS</th>
<th>GENETIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary: Nitrites</td>
<td>Age</td>
<td>Family history of gastric cancer</td>
</tr>
<tr>
<td>Salted foods</td>
<td>Infection by H.pylori, EBV</td>
<td>HNPP *</td>
</tr>
<tr>
<td>Smoked foods</td>
<td>Partial gastrectomy</td>
<td>Group A blood type</td>
</tr>
<tr>
<td>Pickled vegetables</td>
<td>Gastric adenomas</td>
<td></td>
</tr>
<tr>
<td>High meat diet</td>
<td>Barrett Oesophagus</td>
<td></td>
</tr>
<tr>
<td>Low fruit and vegetable diet</td>
<td>Chronic gastritis</td>
<td></td>
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<tr>
<td>Saturated fats</td>
<td>Pernicious anaemia</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Menetrier's disease</td>
<td></td>
</tr>
<tr>
<td>Low Socioeconomic Status</td>
<td>Smoking</td>
<td></td>
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</tbody>
</table>

* Hereditary nonpolyposis colon cancer syndrome
the drugs tend to offer immediate relief. Also, mucosal irritation may be diminished and mask early GC sites on endoscopy.\textsuperscript{16} The impact of this information on future treatment strategies remains uncertain. Patients tend to prefer PPIs because they offer immediate pain relief. However, it seems from the data provided above that these drugs may provide too much relief and may actually hinder the long-term health of the patient. Comparative studies of triple therapy regimens that include H\textsubscript{2} antagonists versus PPIs are necessary to establish the overall effect in the development of GC.

**CLINICAL FEATURES**

**Symptoms and Signs**

There are very few symptoms in the earliest (and most treatable) forms of gastric carcinoma. Symptoms at the time of diagnosis include abdominal pain, nausea, anorexia, dysphagia, early satiety, and ulcer-type pain. Signs, such as weight loss, melena, and lower-extremity edema, are not usually present until the disease has advanced well beyond curative treatment. The lack of significant physical findings makes the diagnosis quite difficult. The presence of an abdominal mass tends to be an ominous sign and indicates extensive growth and regional spread of the cancer.

**Diagnosis**

Unfortunately, modern technology has little benefit in terms of early stage identification of GC. Computed tomography (CT) has only proven to be useful in establishing widespread disease. Therefore, if GC is seen on a CT image, the added benefit of improving diagnosis is questionable. Some studies have shown that CT even underestimates the spread of disease compared to open laparotomy.\textsuperscript{20} Currently, the imaging method of choice is fibreoptic endoscopy, which has an estimated diagnostic accuracy of approximately 95 percent.\textsuperscript{21} Also, it should be noted that recent advances in pharmacotherapy may mask early GC, which can make detection of earlier forms even less effective.

**Tumour Markers**

Although earlier studies provided hope about the effectiveness of tumour markers as aids in diagnosis, their use has proven ineffective in diagnosing gastric carcinoma at earlier stages of the disease.\textsuperscript{22}

**TREATMENTS**

**Surgery**

It is unfortunate that relatively few developments have occurred over the last several years in the treatment of GC. Surgical resection remains the mainstay of therapy. Complete excision of the tumour and associated lymph nodes is the only possible way to cure the disease, however cure rates are quite poor. Between 1982 and 1987, studies in the United States indicated that 5-year survival rates were as high as 60\% for patients who developed tumours that were limited only to the mucosa.\textsuperscript{23} However, these made up only 10\% of the patients with GC. Patients do not typically present for surgical therapy until their lesions have progressed well beyond the resectable stages.

Despite the many advances in surgery made throughout the past 20 years, there has been little change in the basic approach to GC. Endoscopic technology may play a small role in terms of its ability to minimize trauma during surgery and the change in prognosis is minimal.

It has been suggested that surgery followed by chemoradiotherapy may yield better results compared with surgical resection alone. In one study, the median survival time after surgery was 27 months as opposed to 36 months when treated with surgery followed by chemoradiotherapy.\textsuperscript{24} Although nine extra months might seem statistically significant, one must consider the quality of life during postoperative chemoradiotherapy.

**Radiotherapy**

Radiotherapy has not proven to be very useful in the treatment of GC. Doses of external-beam irradiation required to control the primary tumour are too harmful to the surrounding tissue. Therefore, radiation therapy is considered a palliative therapy rather than curative.\textsuperscript{25}

**Chemotherapy**

While a number of chemotherapeutic regimens have been studied, the results have shown little benefit in extending life. The most promising data have come from studies using chemotherapy alone or in combination with radiotherapy in patients who have undergone surgical resection.\textsuperscript{2} The addition of chemotherapy or combination therapy has been suggested to prevent proliferation of micrometastases not visibly detected at the time of surgery. However, this data has been equivocal at best. A 1993 meta-analysis was performed on studies that examined these parameters and the results showed no benefit in combination therapy versus surgical resection alone.\textsuperscript{26}
studies have been performed compared to the rest of the world. Therefore, a distinct possibility may exist in using combination therapy in this particular population.3

PROGNOSIS

There is little doubt that prognosis is improved by detecting the disease early in its course. Several studies have shown that 5-year survival rates are significantly improved when the early stages of GC are diagnosed.27,29 Additionally, once patients survive beyond five years, the Lauren histologic type becomes the main predictor of outcome.7 That is, those patients with the diffuse type of GC will benefit less when compared to those with the intestinal type.2,7,27

Interestingly, age does not influence the prognosis of a patient diagnosed with GC. Researchers in Mexico City studied all young and elderly patients treated for GC over a period of 6 years and found no significant difference between the two age groups in terms of clinicopathological characteristics and outcome.28

Quijano-Orvananos, studied eleven patients, 35 years of age or younger, in an attempt to support the prognostic data above.29 Ten of these patients presented with advanced disease. At follow-up, only one patient was still alive. The median survival was 15.3 months.

FUTURE OUTLOOK

It is clear that dietary factors play a dramatic role in decreasing GC worldwide and food preservation methods, such as refrigeration, may be equally beneficial. Both of these factors are often interrelated. The current trend in Mexico may be a reflection of cultural habits that tend to minimize the ingestion of fruits and vegetables and maximize ingestion of heavily salted meats. However, lack of refrigeration may be a reflection of the country’s economic status.

Worldwide eradication of H. pylori may lead to a decrease in the development of GC, especially in the antral region. The current trend of corpus GC in the United States in rising and the trend in Mexico may depend heavily on economic improvements as well as making triple therapy more readily available. However, since 70% of the Mexican population may be resistant to metronidazole, it is important that therapies include drugs that are effective within specific populations. Obviously, a quick economic solution in this country is unlikely. Therefore, encouragement and education is necessary in the interim period to promote healthier diets consisting of more fruits and vegetables and less meat. While the distinct possibility remains that unique strains of H. pylori may be responsible for GC in the Mexico, investigations will only prove useful once the socioeconomic and environmental factors have been improved.

REFERENCES


30. Lauren PA, Nevalainen JT. Epidemiology of intestinal and diffuse types of gastric carcinoma: a time-trend study in Finland with comparison between studies from high-and low-risk areas. *Cancer* 1993; 71:2923-33