Gastric cancer (GC) is the fifth most common cancer worldwide, following lung, breast, prostate and colon cancers. It accounts for about 8% of the total cancer cases and 10% of cancer related deaths.¹⁻³ The 5 year survival is low (≤20 %) except in countries like Korea (> 60%) and Japan where type of cancer is biologically different and early screening is in effect.⁴⁻⁶

Wide geographic variation exists in the incidence of GC, with a high incidence in the eastern parts of Asia and Europe, but rare in North America and Western Europe. Healthy dietary practices and effective Helicobacter pylori (H. pylori) eradication probably explains the decreasing incidence. Early diagnosis is a challenge with absence of classical symptoms and paucity of molecular markers.⁷ Endoscopy and target biopsies coupled with effective surgical procedures have improved outcomes marginally.⁸

A recent trend shows rise in GC in the cardia as opposed to non-cardia cancers, with a shift in the histology as well. The intestinal type of gastric adenocarcinoma is decreasing compared to the diffuse type.⁹ An increasing incidence has been reported among the indigenous populations (Maori in New Zealand and Inuit in North America) compared to others inhabiting the same geographical region.¹⁰,¹¹

GLOBAL EPIDEMIOLOGY

Distribution of GC is wide but occurs predominantly (>70%) in the developing countries¹² with Eastern Asia, Korea, Japan and China being highly endemic areas (Fig-1).¹ Incidence within a region/ country also varies as in China and India (higher in the North-eastern and Southern states). A different pattern of incidence exists in migrant populations compared to the natives living in endemic regions, pointing to environmental influences.

CHINA

Forty two percent of all cases worldwide are in China, partially attributed to its large population.¹³ GC is the second most frequently diagnosed cancer in China and

John F.,¹ Sekkah Veedu J.,¹ Pitchumoni, C.S.² ¹Department of Internal Medicine, Saint Peter's University Hospital/ Rutgers University, New Brunswick, N.J. and Drexel University College of Medicine, Philadelphia, P.A. ²Chief of Gastroenterology, Hepatology, and Clinical Nutrition, Saint Peter's University Hospital/Rutgers University, New Brunswick, N.J. Adjunct Professor of Medicine, New York Medical College Clinical Professor of Medicine, Rutgers University/Drexel University, Philadelphia, PA
the third leading cause of cancer related death. The incidence is declining both in rural and urban areas but slower than in the Western world. There is an increased prevalence among adolescents and young adults in Shanghai, which is postulated to be related to consumption of food rich in salted pork and to H. pylori and genetic polymorphisms. In Shandong province, nutritional deficiencies from childhood to adolescence during the famine (1959–1961) might have played a role in the risk for GC. Famine exposure in early life caused gastric mucosal damage leading to intrusion of carcinogens (H. pylori, N-nitrosamines and acetaldehyde) coupled with mutations. The use of refrigerators, improved hygiene and antibiotics are factors in the drastic reduction in chronic H. pylori infection, which is the strongest risk factor. A 50% increased risk for GC in those consuming pickled vegetables/foods suggests the existence of causes other than H. pylori. Higher intake of cruciferous vegetables was identified as protective against non-cardia GCs. However, the incidence has been projected to increase in the next 40 years as a consequence of population growth and aging.

**JAPAN**

GC is the second most frequently diagnosed cancer after colorectal cancer and the second leading cause of cancer death (15%) in Japan. The highest mortality rates were seen among those born towards the end of the nineteenth century and in females, risk being higher than that of USA, UK, France and Korea. Environmental factors, including diet, and H. pylori infection are the main risk factors. Protective role for green tea, the most commonly consumed beverage worldwide, is controversial. The prevalence of H. pylori negative GC in Japan is less than 1%. A synergistic effect of high dietary vitamin A intake and H. pylori infection on malignant alterations in the gastric mucosa through oxidative stress is postulated. Reduced intake of vitamin A together with H. pylori eradication may be an effective strategy to reduce the risk of GC.

**KOREA**

GC has been the most frequently diagnosed cancer in men and ranks fourth in women, after thyroid, breast and colorectal cancer. Incidence increases with age and is rare below 30 years; the crude mortality rate was 28.5 in men and 15.7 in women (per 100,000) in 2012. The 5-year survival rates have however dramatically increased from 43.0% to 63.8% in men and 42.6% to 61.6% in women since 1995. The prevalence of the more aggressive H. pylori negative cancers is 5.4% in South Korea. There is an increased prevalence of obesity among patients with gastric cardia cancers. Renal transplant patients had a higher risk for GC and Epstein- Barr virus (EBV) was the principal etiologic agent than H. pylori. High prevalence of autoimmune gastritis (40.7%) with intestinal metaplasia (12.5%) was one major histological risk factor. Autoimmune gastritis, the host and environmental factors such as increased consumption of dairy products were identified as risk factors for intestinal metaplasia.

**INDIA**

In India, GC is the most fatal cancer in men after lung with a mortality rate of 11.4%. The highest incidence rate is in the Northeastern areas. The age attributable risk (AAR) among the Bhutia population in Sikkim (60.4 in men and 29.4 in women per 100000) was the highest among the Population Based Cancer Registries in India in 2010 which was the highest in the world. The age-adjusted incidence rate in men was the highest in the Chennai registry in South India (11.1 per 100000) during 2003-2005. The state of Jammu and Kashmir has a high incidence of gastrointestinal tract cancers which accounts for about 50% of all cancers. GC is one of the top five cancers in the valley, with a 3.1:1 male: female ratio.

Although the prevalence of H. pylori is very high, the incidence of GC is low in India and Africa which is a paradox, often referred to as the Indian/ African enigma. The protective role of diet (curcumin in turmeric powder), host inflammatory polymorphisms (IL-1), dissimilarity in bacterial strain and the predominant immune response (protective Th 2 vs Th 1) are suggested explanations.

Although H. pylori infection is the cause of at-least 80% of cases and other factors including diet, lifestyle, especially tobacco use, genetic and socioeconomic conditions, have a considerable role. Other suspected etiologies include excessive consumption of pickles, rice, high-temperature foods, smoke-dried salted meat and fish and overuse of baking soda, spices and chilies. Certain occupations with exposure to high temperature and dusty environments (miners, farmers, cooks, machine operators in timber and rubber industry)
increased the risk of GC especially diffuse type of adenocarcinoma.\textsuperscript{7} There is a decreasing trend in the incidence over the past decades which is in concordance with the global scenario.\textsuperscript{39}

**EUROPE**

GC is the fifth most common cancer in males and seventh in females with a male: female ratio 1.5:1.\textsuperscript{1,47} There is a fourfold difference in incidence across countries in the European Union with the highest incidence and mortality rates in Belarus, Albania and Russian Federation.\textsuperscript{1} Belarus for males and Albania for females mark the areas of highest incidence.\textsuperscript{1,48} Central and Eastern European countries have higher incidence rates when compared to Western or Northern European countries. Sweden was the country with the lowest incidence and the rate in UK was below EU average.\textsuperscript{48}

A significant association between alcohol consumption and risk of GC was seen in Lithuania and accounted for about 8\% of the total cases. The possible explanation was the presence of contaminants like acetaldehyde, a human carcinogen.\textsuperscript{49}

Similar to the trend worldwide, the incidence of gastric non-cardia cancers has decreased attributed to the improvement in socioeconomic conditions and consequent decrease in H. Pylori prevalence in the younger population.\textsuperscript{43,50} Furthermore, H. pylori eradication therapy has augmented the decline in incidence and mortality rates.\textsuperscript{51}

**FINLAND**

Finland has a higher incidence of GC compared to other Scandinavian countries. It is the sixth common cause of cancer death in men and seventh in women.\textsuperscript{1} Increased intake of salt, decreased consumption of fruits and vegetables and alcoholism are notable associations with no association with high coffee consumption.\textsuperscript{52-54} The high prevalence of H. pylori infection in the lower socioeconomic strata is a strong association for the increased incidence of distal tumors.\textsuperscript{55} The need for prompt eradication of H. pylori with proper follow-up in patients with precancerous lesions is stressed.\textsuperscript{56} This endogenous infection, heavy drinking and smoking along with ALDH2 deficiency posed the greatest risk for GC.\textsuperscript{57,58}

**USA**

GC in US ranks fifteenth in incidence and fourteenth in mortality.\textsuperscript{1} There is a rising trend in the incidence of reflux related gastric cardia and gastro-esophageal cancers in the past 50 years.\textsuperscript{59,60}

The incidence of GC among Caucasians is only half of that among Asian Americans, Pacific Islanders, African Americans, and Hispanics.\textsuperscript{12} This ethnic disparity could be due to migration from endemic regions.\textsuperscript{3} The increased incidence in the Hispanic population has been attributed to a high prevalence of H. pylori.\textsuperscript{59} Increasing age, non-white ethnicity, poor education and low-income groups are the factors other than H. pylori causing distal tumors.\textsuperscript{61,62} Distal tumors were common in the eastern coast, large urban centers and teaching hospitals.\textsuperscript{63} The overall incidence of GC is decreasing. The reason for a slight rise among the younger population (25-39 years) is not well understood.\textsuperscript{3}

(continued on page 36)
The geographical distribution varies between regions with a high prevalence in the northern and north-western parts (along the border of Caspian Sea) compared to the Persian Gulf and the desert areas.87 The Persian and Arabs with better socioeconomic conditions occupy the deserts including the Persian gulf which explain the decreased prevalence in these areas.80 Consumption of smoked fish in coastal areas, smoking, high salt intake, increased prevalence of H. pylori infection, poor socioeconomic background and genetic predisposition is responsible for the high rates.88,89 Selenium levels were much lower in inhabitants of endemic areas with an inverse association with GC.87,90 Unlike other parts of the world, endemic regions in Iran have predominance of gastric cardia cancers.87,91 Overall, the incidence is decreasing.92

**ETIOLOGICAL FACTORS FOR GASTRIC CANCER**

**H. pylori**

The association of this ancient bacterium with GC came into light only since its discovery in 1982.93 H. pylori have been documented to produce gastritis, peptic ulcer, gastric carcinoma and lymphoma including the MALT type. The infection was found more among people with lower socioeconomic status, poor educational background and higher BMI. H. pylori prevalence is higher among foreign-born Hispanics compared to non-Hispanic whites.94 Infection with virulent H. pylori strains (CagA positive) together with a permissive environment in a genetically susceptible host is essential for the occurrence of GC.7 H. pylori breach the gastric barrier and trigger a sequence of events starting from acute gastritis, chronic gastritis, atrophic gastritis, intestinal metaplasia and dysplasia finally leading to carcinoma.18 But only about 5% of people infected with H. pylori develop cancer highlighting the need for a permissive environment for the organism. H. pylori eradication strategies have resulted in a drastic reduction in prevalence among subsequent generations.94

**DIETARY FACTORS**

Most of the observations about diet and GC are speculative. A high consumption of salted food, red meat and starch based low in protein diet increases the risk for GC while consumption of fruits and vegetables
decreases the risk. High salt intake, alcohol consumption and smoking induced mucosal damage is proposed as a facilitating factor for H. pylori that lead to epithelial cell proliferation, parietal cell loss and progression to premalignancy. Other dietary risk factors are given in Table 1.

Scientific explanation for the role of diet is a relationship between N-nitroso compounds (NOC) and GC. NOC can be found in some vegetables (cabbage, cauliflower, carrot, celery, radish, beets, spinach), cereals and beer. Preformed NOC is seen in cured meat, dried milk, dried coffee and instant soups. Broiling meat, grilling and baking in open furnaces, sun drying, salting and pickling increase the formation of NOC which increase proximal gastric tumors and esophageal squamous cell carcinoma in men. Endogenous production by bacteria/activated macrophages and conversion of dietary nitrates in the acidic gastric environment are other sources for NOC. Heme-iron content of the meat influences the endogenous formation of NOC in the lower GI tract. Refrigeration was found to decrease the bacterial burden in food thereby decreasing the formation of nitrates. Improved methods of food preservation have dramatically decreased the dietary risk and mortality from GC.

**SMOKING AND ALCOHOL**

Smoking is attributed to about 11-29% of GC. The highest occurrence of cancer is seen among current as well as former smokers in males while only among current smokers in females. A dose-response

---

**Table 2. Summary of Etiologic Factors**

<table>
<thead>
<tr>
<th><strong>Helicobacter pylori infection</strong></th>
<th>Virulent strains are Cag A positive; association with non-cardia cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet</strong></td>
<td>smoked foods, salted fish and meat, and pickled vegetables; reduced fruits and vegetable consumption</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>Attributable to ~28% of GC cases; N Nitroso compounds in smoke carcinogenic; Association with proximal tumors</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>Association with distal tumors; Acetaldehyde is the carcinogen</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>Related to gastric cardia cancer; GERD probable cause</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td>More in indigenous population, Hispanics in US, Black Caribbean community in UK</td>
</tr>
<tr>
<td><strong>Epstein-Barr virus infection</strong></td>
<td>~9% of GC, smoking increases the risk</td>
</tr>
<tr>
<td><strong>Certain occupations</strong></td>
<td>Mining, Refining, Farming, Processing wood, rubber, asbestos</td>
</tr>
<tr>
<td><strong>Hereditary Cancers</strong></td>
<td>Hereditary non-polyposis colorectal cancer, Familial adenomatous polyposis, Li-Fraumeni syndrome</td>
</tr>
<tr>
<td><strong>Pernicious anemia</strong></td>
<td>GC is a long-term complication and risk proportional to duration</td>
</tr>
<tr>
<td><strong>Gender and Age</strong></td>
<td>Common in males and risk increases with age</td>
</tr>
<tr>
<td><strong>Common variable immune deficiency</strong></td>
<td>Increased frequency of H.Pylori, 10% have pernicious anemia</td>
</tr>
</tbody>
</table>
relationship has not been established so far.\textsuperscript{105} But there is a risk reduction after abstinence, which is related to the duration since quitting. The risk is much less in those who quit smoking ≥21 years (17% higher than non-smokers) compared to those who quit within the last 10 years (69% more than non-smokers).\textsuperscript{108} A greater association of smoking with proximal tumors than distal ones was noted.\textsuperscript{108} Cigarette smoke, which contains many carcinogens such as N-nitroso-compounds, can directly damage the gastric mucosa and affect gastric prostaglandin synthesis.\textsuperscript{7,108,109} It was also found to decrease the efficacy of \textit{H. pylori} eradication leading to persistence of the bacteria resulting in dysplasia/metaplasia of the gastric mucosa.\textsuperscript{110} Studies have shown that smoking reactivates EBV-positive cell lines (Akata and B95-8).\textsuperscript{110}

Alcohol use has a strong association with gastric noncardia cancer.\textsuperscript{111} Unlike smoking, abstinence from drinking has not shown to reduce the risk, which could be due to the chronic histological damage caused by heavy drinking and intestinal metaplasia. Beer consumption had the highest association for cancer in one study, which was explained by the presence of nitrosamines (N-nitrosodimethylamine), a potent animal carcinogen.\textsuperscript{112} Acetaldehyde, the metabolite of alcohol metabolism is a carcinogen.\textsuperscript{112} \textit{H. pylori} strains possessing aldehyde dehydrogenase activity produce acetaldehyde from ethanol under micro-aerobic conditions.\textsuperscript{113} Alcohol also induces cytochrome P4502E1 that could play an important role in carcinogenesis by formation of reactive oxygen species.\textsuperscript{112}

**OBESITY**

Obesity is emerging as a risk factor for GC, in particular proximal gastric lesions.\textsuperscript{94,114} The increased incidence of gastro-esophageal reflux could be a possible cause. Adiponectin, leptin, insulin resistance, insulin-like growth factors and obesity-related inflammatory markers are also incriminated in the etiology of cancer.\textsuperscript{114}

**ETHNICITY**

The incidence of GC tends to vary among ethnicities. In US, the incidence among Caucasians is about half when compared to the rest (Hispanics, African Americans and Asian Pacific islanders).\textsuperscript{3,7,115} A higher incidence of GC among blacks of Caribbean descent compared to other races was recently reported from UK.\textsuperscript{116,117} Despite these strong ethnic factors, environmental factors play a major role in gastric carcinogenesis. Japanese settled in the US have a much lower incidence compared to native Japanese and an inverse trend among African-Americans compared to the native African population provide evidence for this.\textsuperscript{3,7}

Foreign-born Hispanics (>60\%) had a higher incidence of GC than those born in the US.\textsuperscript{115} The intestinal type of adenocarcinoma decreased among foreign-born Hispanics with an increase in the incidence of diffuse-type.\textsuperscript{115} Hispanics were younger (P < .01) and had greater proportion of distal tumors compared to whites at the time of diagnosis.\textsuperscript{94,118} Hispanics and African-Americans often presented with advanced disease compared to Asia/Pacific Islanders (P < .01).\textsuperscript{35,118} Asian race, female sex, distal tumors and care at a teaching hospital had favorable outcomes.\textsuperscript{118} The overall

(continued on page 40)
median survival was over 1 year among patients with Asian descent while all other ethnicities had less than a year.\textsuperscript{118}

**GENETICS**

Multiple genetic and epigenetic alterations are involved in the gastric carcinogenesis. Microsatellite instability (MSI), chromosomal instability (CIN), activation/suppression of oncogenes and tumor suppressor genes as well as cell cycle regulators are implicated in the etiology.\textsuperscript{7}

MSI, a genomic defect that represents defects in DNA replication (hMLH 1 – mismatch repair gene) accounts for about 13-44\% of GCs, which are of intestinal type, distally located with better prognostic factors.\textsuperscript{119} MSI is also implicated in intestinal metaplasia, a premalignant condition.\textsuperscript{120} A decreased tendency for invasion and nodal metastasis is seen in MSI due to mutations in TGF-\(\beta\), IGF II and BAX genes.\textsuperscript{7,119} CIN plays a major role in sporadic GCs. Several factors from N-nitroso compounds, smoking and H. pylori to DNA repair mechanisms and defects in cell cycle regulation contribute towards CIN. Erb-B2 oncogene activation has a role in intestinal-type of gastric adenocarcinoma while c-met (proto-oncogene that codes HGFR) and FGFR2 gene amplification (via Erb-B3/PI3 over-expression) plays a role in diffuse type of cancer.\textsuperscript{7,121} Inactivation of p53 gene has been found in about 60\% of the cancers while APC gene mutations are seen only in a small proportion of early cancers. Kras gene mutations are rare and seen only in stage 4

---

**Figure 2. Countries with the Highest Incidence of Gastric Cancer**

Source: http://globocan.iarc.fr

(continued on page 42)
Gastric Cancer

EPIDEMIOLOGY OF GASTROINTESTINAL CANCERS, #3

(continued from page 40)

Key Points

- Gastric cancer is still endemic in many Asian and Central American countries
- GC, the distal type is related to chronic H. pylori infection
- Intestinal metaplasia is the histological premalignant lesion
- The global trend shows a decrease in GC along with eradication of H. pylori
- The proximal or cardia cancers are increasing for reasons not clear

PERNICIOUS ANEMIA AND EBV

GC is a rare complication of Pernicious Anemia (PA). Multifocal atrophic gastritis not confined to the body of stomach has a higher risk. Intestinal type of adenocarcinoma and distal tumors are common, with the risk proportional to the duration of the disease. The increased pH that allows chronic H. pylori infection could be a possible cause. In Common Variable Immune Deficiency, seen in 10% of patients with PA, the normal mucosal defense mechanisms are weak to contain H. pylori infection aggravating the risk for GC.

EBV could be a possible etiology for GC in PA attributable to about 9% of cases. The lack of acidic environment coupled with damaged gastric mucosa (due to chronic inflammation) favour EBV colonozation. EBV is known to involve in the earlier stages of mucosal transformation based on the presence of monoclonal viral episomes in EBV positive tumor cells. An increased risk for EBV induced GC is seen in smokers (RR=2.4). EBV positive tumors tend to occur in the gastric cardia and more frequently in postsurgical patients.

CONCLUSION

(See the Key Points Table)

The overall incidence of GC is decreasing but the incidence of gastric cardia cancer is increasing with a noted association with obesity. The screening strategies adopted by countries like Japan and Korea helped to bring down the burden of this disease to a great extent and reduce the mortality. H. pylori prevalence in developing countries need to be tackled with adequate eradication measures coupled with early screening together with healthy dietary practices.

References

5. Choi JI. Current evidence of effects of Helicobacter pylori eradi-


Gastric Cancer

EPIDEMIOLOGY OF GASTROINTESTINAL CANCERS, #3


Derakhshan MH, Yazdianbod A, Sadjadi AR, Shokoohi B, McColl KE, Malekzadeh R. High incidence of adenocarcinoma arising (continued on page 46)