Gastric cancer

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Background: Gastric cancer remains a major cause of mortality and morbidity worldwide, and the total number of gastric cancer cases is predicted to rise as a result of population growth. The pathogenesis of gastric cancer represents a paradigm for microbially induced and inflammation-driven malignancies, and understanding this will be the best means of defeating this cancer.

Sources of data: We reviewed the relevant English language literature in relation to gastric cancer with particular reference to the role of Helicobacter pylori. We summarize what is known of the epidemiology, aetiology and pathogenesis of gastric cancer. We also describe current approaches to the detection and management of early gastric cancer and discuss the prevention strategies.

Areas of agreement: H. pylori is the most important aetiologial risk factor for this cancer, and the pathogenesis involves the combined effects of host genetics, bacterial virulence and environmental factors.

Areas of disagreement: Although most accept that removing Helicobacter could prevent gastric cancer, there are still no definitive trials to prove this concept. There is also some anxiety about the long-term effects of removing such a prevalent chronic infection from large sections of the population.

Conclusions: Gastric cancer is now arguably one of the most understood malignancies, and real progress is being made towards eradicating this global killer. Much work still needs to be done to define the optimal approach for eradicating the causative agent, namely H. pylori infection.

Keywords: gastric cancer/helicobacter pylori/epidemiology/diet/host genetics/screening/endoscopic therapy/cancer prevention
Introduction

The earliest descriptions of gastric cancer can be found in ancient Egyptian medical papyri such as the Ebers papyrus dating to around 1550 BC. At the turn of the twentieth century, gastric cancer was the leading cause of cancer-related death in the UK. The incidence of gastric cancer has fallen dramatically in most countries over the past 70 years. Between 1975 and 2003, the incidence of gastric cancer in males in the UK halved, and it now represents the fifth and ninth most common cancer in males and females, respectively. Nonetheless, 8000 new cases of gastric cancer were registered in the UK in 2003, and gastric cancer deaths in 2004 totalled over 5800. Globally, gastric cancer is the second most common cause of cancer-related death and, as a result of population aging and growth, the predicted incidence for 2010 is 1.1 million with the majority of this health burden being borne by economically lesser-developed countries.

Although two-thirds of cases of gastric cancer occur in lesser-developed countries, the age-standardized incidence figures are in fact comparable with those of more developed countries. There are, however, geographical variations of up to 10-fold in gastric cancer incidence, even greater than those observed for oesophageal cancer. In general, incidence rates are lowest in Western Europe and North America and highest in Eastern Asia, South America and Eastern Europe. The prevalence of gastric cancer in Japan is around eight times higher than in the USA. This geographical distribution is not clear-cut with India, for example, having a relatively low incidence when compared with other Asian countries such as China, Japan and Indonesia. Even within individual countries, there are both regional and racial differences in incidence. Migrant populations from high-risk parts of the world can represent high-risk subgroups within low-risk populations, for example, Koreans living in the USA. With subsequent generations, the risk within migrant populations falls to assume the background risk in the host country.

In all populations for which data are available, the incidence of gastric cancer in males is around twice that of females. In the UK, this ratio is 5:3.

Pathological differentiation

The vast majority of malignant tumours of the stomach are adenocarcinomas. Historically gastric adenocarcinomas were subdivided by the Laurèn histological classification into intestinal and diffuse subtypes.
The intestinal type appears to arise from a background of chronic atrophic gastritis, with the development of intestinal metaplasia and transition through progressively increasing stages of dysplasia to carcinoma. The intestinal type is the predominant histological type in high-risk countries, more common in men, and increases significantly in incidence with age. The diffuse type does not show marked geographic variation, can arise in the absence of atrophic gastritis, is more common in females, and often occurs in younger patients with a positive family history. These epidemiological differences lead to the notion that the two histological subtypes had distinct aetiologies. There are, however, problems with this concept. Laurén himself was unable to classify a significant number of tumours as being either intestinal or diffuse, and some tumours show features of both histological subtypes. It has become apparent over the recent years that gastric adenocarcinoma can also be subdivided according to the anatomical site at which it arises. Tumours can be said to be proximal, arising in the cardia region of the stomach, or distal arising from non-cardia regions. As with the histological subtypes, there are aetiological and epidemiological differences between the two tumour sub-sites. Until recently, adenocarcinoma of the gastric cardia represented a small proportion of gastric cancers as a whole. The global trend of falling gastric cancer incidence therefore reflects non-cardia cancer incidence. The incidence of carcinoma of the gastric cardia actually appears to be rising. Whilst this may be partly due to more accurate reporting, the dramatic fall in the incidence of distal cancers has not been paralleled for cardia cancers. Gastric cardia cancer is now therefore relatively more common accounting for around 50% of cases of gastric cancer in developed countries.

Survival

Outside of Japan, survival rates for gastric cancer remain poor. Estimated 5 year survival in Europe is only 24–27%. The survival rates in North America are somewhat better perhaps as a result of earlier detection as a result of the overall larger number of diagnostic endoscopic procedures performed. In Japan, where population-based endoscopic screening was introduced in the 1960s, the 5-year survival is greater than 50%.

Helicobacter pylori as a risk factor for gastric cancer

The discovery of *H. pylori* in 1983 has proved to be pivotal in our understanding of the aetiology of gastric cancer. *H. pylori* is a
gram-negative bacillus capable of colonizing the gastric mucosa. Countries with high rates of gastric cancer, such as China and Japan, tend to have a high prevalence of *H. pylori* infection.  

In 1994, the World Health Organization and the International Agency for Research on Cancer consensus group stated that there was sufficient evidence to classify *H. pylori* as a Class I (i.e. definite) human carcinogen. The evidence as it stood at that time comprised epidemiological studies only, many of which were poorly controlled for confounding risk factors for gastric cancer. Over the subsequent 10 years, numerous cohort and case-control studies were published demonstrating an association between serological evidence of *H. pylori* infection and increased risk of gastric cancer. Much of these data have been subjected to meta-analysis with the conclusion that *H. pylori* infection carries around a 2-fold increased risk for the development of gastric cancer. This association is strongest for non-cardia cancer, but holds for both intestinal and diffuse histological types.

The most compelling epidemiological evidence comes from a large prospective series from Japan. A total of 1526 patients who had been found to have duodenal ulcers, gastric ulcers, gastric hyperplasia or non-ulcer dyspepsia were recruited. Endoscopy and biopsy were performed at enrolment and *H. pylori* status established by histological, enzymatic (urease test) or serological methods. A total of 1246 patients had evidence of *H. pylori* infection, the remainder did not. The participants underwent endoscopic follow-up for the detection of early gastric cancer (EGC) over a mean follow-up period of 7.8 years. Gastric cancers developed in 36 (2.9%) of infected patients, but in none of the uninfected patients. Among patients with *H pylori*, those with severe atrophic gastritis, corpus predominant gastritis and intestinal metaplasia were found to be at highest risk of developing gastric cancer. Interestingly, 4.7% of infected patients with non-ulcer dyspepsia went on to develop gastric cancer, but none of the 275 patients with duodenal ulcer developed gastric cancer. The latter observation is in keeping with previous studies that have shown a negative association between history of duodenal ulcer and the risk of gastric cancer.

Since the vast majority of individuals infected with *H. pylori* do not develop gastric cancer, there must be additional factors that determine which individuals will go on to develop malignancy. One potential factor is bacterial virulence. The most widely studied *H. pylori* virulence factor is the cytotoxin-associated gene A antigen (CagA). One meta-analysis has specifically addressed the association between infection with CagA harbouring strains of *H. pylori* and gastric cancer risk. Among *H pylori*-infected populations, seropositivity for CagA increases the risk of developing non-cardia gastric cancer by around an additional 2-fold. In the West, around 60% of *H. pylori* isolates possess CagA...
compared with virtually all isolates in Japan. In addition to CagA, there are other bacterial virulence factors that have been associated with increased risk of gastric cancer. These include the vacuolating cytotoxin VacA and some outer membrane proteins such as OipA and BabA.

**Helicobacter and cancer of the gastric cardia**

The association between *H. pylori* infection, atrophic gastritis and cancer of the cardia region of the stomach is less clear than it is for distal cancers. In Western countries, there appears to be a negative association between *H. pylori* infection and cardia cancer, whereas there is a trend towards positive association in Eastern Asia.5

A recent nested case–control study based in Norway has helped elucidate the aetiology of cardia cancer.12 The study set out to compare the premorbid state of the gastric mucosa between individuals with cardia and non-cardia gastric cancer. Out of an original cohort of 101,601 individuals, 129 non-cardia and 44 cardia cancers were included and matched with three controls each. Serum samples had been collected a median of 11.9 years before the diagnosis of cancer. The serum samples were analysed for *H. pylori* serology, and the ratio of pepsinogen 1:2, which is a marker of *H pylori*-induced atrophic gastritis. As expected, there was a strong association between *H. pylori* seropositivity and non-cardia cancer; however, there was a negative association between *H. pylori* infection and cardia cancer. The predominant histological subtype of cardia cancer was intestinal and was not associated with gastric atrophy. In persons with cardia cancer plus serological evidence of atrophic gastritis, however, there was a strong association with *H. pylori* infection, and the intestinal:diffuse ratio was 1:1, similar to non-cardia cancer. These findings indicate that there are two aetiologically distinct types of cardia cancer: one associated with *H pylori*-induced atrophic gastritis, similar to non-cardia cancer, and the other associated with non-atrophic gastric mucosa and resembling oesophageal adenocarcinoma.12

**The role of host genetics**

*Helicobacter pylori* is responsible for three separate phenotypes in the infected host. The first is corpus-predominant gastritis leading to atrophic gastritis, hypochlorhydria and to the development of gastric cancer. The second is the benign phenotype where *H. pylori* infection results in a mild mixed gastritis that has minimal effect on the physiology of gastric acid production. The third phenotype is the duodenal...
ulcer phenotype where an antrum-predominant gastritis leads to increased gastric acid secretion and duodenal ulceration. Therein lies the paradox that *H. pylori* infection can predispose to two mutually exclusive conditions.

Individual differences in the host response to *H. pylori* infection, determined by host genetic polymorphisms, might, in part, explain why some individuals are more likely to develop the gastric cancer phenotype than others. Evidence for the importance of host genetic factors initially came from the finding of an increased incidence of atrophic gastritis and hypochlorhydria in *H. pylori*-infected relatives of gastric cancer patients when compared with matched controls.13

Interleukin-1 beta (IL-1β) is a pro-inflammatory cytokine and also a potent inhibitor of gastric acid secretion. The *IL-1* gene was therefore a potential candidate for host genetic polymorphisms that may influence gastric cancer risk. Individuals with pro-inflammatory *IL-1* gene cluster polymorphisms are at increased risk of developing mucosal atrophy and hypochlorhydria in response to *H. pylori* infection, and this is reflected in a 2–3-fold increase in the risk of non-cardia cancer.14,15 Following the identification of pro-inflammatory *IL-1* gene cluster polymorphisms, pro-inflammatory genotypes of tumour necrosis factor-α (TNF-α) and interleukin-10 (IL-10) were described as independent risk factors for non-cardia cancer.14 TNF-α is another pro-inflammatory cytokine whose expression is upregulated in the gastric mucosa in response to *H. pylori* infection. IL-10, on the other hand, is an anti-inflammatory cytokine that suppresses expression of pro-inflammatory cytokines including IL-1β, TNF-α and interferon-γ. The risk of developing gastric cancer has been studied with respect to the inheritance of multiple pro-inflammatory polymorphisms in the aforementioned genes. The risk increases progressively such that an individual with three or four polymorphisms who is infected with *H. pylori* has 27-fold increased risk of developing non-cardia cancer.16 This clearly demonstrates that gene–environment interactions are important in the aetiology of gastric cancer, and that inflammation and the adaptive immune response play a pivotal role in driving gastric carcinogenesis.

**Familial gastric cancer**

Approximately 10–15% of gastric cancers arise in individuals with a significant family history of the condition.17,18 An increased risk of gastric cancer is associated with several of the recognized dominantly inherited cancer predisposition syndromes, such as familial adenomatous polyposis, hereditary non-polyposis colon cancer and
Peutz-Jeghers syndrome. Hereditary diffuse gastric cancer (HDGC) is also inherited as a dominant trait, and in around a third of affected kindred is caused by inactivating mutations in the \textit{CDH1} gene, which encodes the epithelial cell adhesion protein E-cadherin.\textsuperscript{18} HDGC is highly penetrant and the average age at diagnosis is 38 years.

**Other risk factors**

Although \textit{H. pylori} plays a crucial role in the pathogenesis of gastric cancer, it cannot be considered the sole causative agent in this malignancy. There are other factors that clearly contribute and perhaps the strongest are diet and smoking.

**Diet**

The marked geographic variation in gastric cancer incidence suggests that environmental influences play an important aetiological role, and much attention has, therefore, focussed on the association between diet and gastric cancer risk. It has been postulated that the downward trend in gastric cancer incidence may in part be due to the advent of widespread refrigeration of food, hence increased intake of fresh produce, and less reliance on food preservation. Numerous studies have suggested a protective effect from diets rich in fresh fruit and vegetables; however, when one considers case-control and prospective data only, the evidence is less robust.\textsuperscript{3} Data from a recent large European prospective study (EPIC-EURGAST) failed to show an overall association between fruit or vegetable consumption and gastric cancer risk.\textsuperscript{19} There was, however, a statistically significant association between total dietary vegetable content (and onion and garlic intake) and the intestinal histological subtype. A non-significant negative association was observed between cardia cancer risk and citrus fruit consumption. Interestingly, the effect of fruit and vegetable intake appeared to be independent of \textit{H. pylori} status.

Vitamin C and other anti-oxidant nutrients have attracted a lot of attention as the potential mediators of any dietary influence on gastric cancer risk. Vitamin C seems a promising candidate since its levels are reduced in the serum of \textit{H. pylori}-infected individuals, and, as well as being a free radical scavenger, it reduces the formation of potentially carcinogenic \textit{N}-nitroso compounds.\textsuperscript{20} Furthermore, there is evidence from case-control studies of a negative association between dietary vitamin C and gastric cancer risk.\textsuperscript{21} Data from the EPIC cohort show a negative correlation between gastric cancer risk and serum vitamin C,
but not dietary vitamin C, intake, and this was unaffected by *H. pylori* status.\(^\text{22}\)

A review by the Cochrane Collaboration, which included a number of high-quality randomized trials, has concluded that there is no evidence that dietary supplementation with anti-oxidants, including vitamin C, reduces gastric cancer risk.\(^\text{23}\)

Salt and nitrite are other dietary components that have been implicated in gastric cancer risk. Both are frequently used in food preservation. Pickled and smoked foods may also contain potential carcinogens such as N-nitroso compounds and benzapyrene. Of note is the fact that the Japanese diet is particularly rich in salted fish and pickled vegetables. Dietary nitrate, of which a significant portion may come from water depending on the source, can be converted to nitrite by nitrate reductase-synthesizing bacteria. *H. pylori* infection and hypochlorhydria facilitate the growth of such bacteria.

Dietary salt and nitroso compounds appear to exert a synergistic effect with *H. pylori* in animal models of gastric carcinogenesis. Several case–control studies in humans have shown a positive association between gastric cancer risk and both salt and dietary nitrate/nitrite intake, although data from prospective studies are conflicting.\(^\text{24–26}\)

**Smoking**

Smoking is an independent risk factor for gastric cancer. Prospective studies have demonstrated a significant dose-dependent association between tobacco smoke and gastric cancer risk.\(^\text{27,28}\) In the EPIC cohort, it was estimated that 17.6% of gastric cancer in this European population was attributable to cigarette smoking.\(^\text{29}\)

**Detection and treatment of EGC**

As stated previously, survival rates from gastric cancer outside of Japan remain dismal. The reason that gastric cancer carries such a poor prognosis is that the presentation is invariably late in the natural history of the disease, with local extension or metastatic disease rendering the condition inoperable. Whilst chemotherapy, both neo-adjuvant and palliative, has a demonstrated role in improving survival in patients with gastric cancer,\(^\text{30}\) resection with curative intent offers the only real chance of long-term survival in patients with operable disease. Around 90% of cases of gastric cancer in Western countries are inoperable at
presentation in contrast to Japan where EGCs comprise 50% of gastric cancers detected.31 Early gastric cancer is defined as gastric carcinoma confined to the mucosa or sub-mucosa irrespective of the presence or absence of lymph node metastases.31 In Japan, 5-year survival rates following resection of EGC exceed 90%.32 The detection of EGC has, therefore, become the focus of endoscopic screening programmes in Japan, and the impressive overall survival rates for gastric cancer attest to the success of this approach. Population-based endoscopic screening, such as that employed in Japan, is not in practice in most other countries, and it would, therefore, be immensely helpful to be able to identify individuals at risk of EGC so that screening endoscopy could be offered on a targeted basis.

Could symptoms help predict those individuals who are likely to have EGC? Referral guidelines for urgent endoscopy, at least in the UK, often include the so-called ‘alarm symptoms’ such as weight loss, anaemia, dysphagia and anorexia. Symptom analysis in patients aged <45 years diagnosed with gastric cancer has shown that fewer than a half described alarm symptoms.31 As one might imagine, alarm symptoms tend to indicate advanced disease and, therefore, urgent endoscopy frequently has little impact on the final outcome. Unfortunately, no symptom complex has been shown to predict EGC, and most patients with EGC are in fact asymptomatic or have non-specific dyspeptic symptoms.31

Since *H. pylori* infection is common (around half of the World’s population is infected with the organism), the magnitude of screening all infected individuals is also impractical. Serological analysis of pepsinogen I and II and gastrin levels has been employed in an attempt to non-invasively detect the presence of the atrophic gastritis. Several large studies from Japan have produced promising results using serological screening, although data demonstrating sufficient sensitivity and specificity in non-high risk populations are currently lacking.31,33

**Endoscopic identification of early gastric cancer**

As experience grew in the endoscopic detection of EGC in Japan, it was felt necessary to devise a new macroscopic classification for gastric cancers.34 This system was subsequently adopted internationally. A lesion that is felt endoscopically to represent an EGC is denoted as 0 rather than T1 as would be used in pathological staging. Lesions are then sub-classified as being protruding (>2.5 mm), flat or excavated. Flat lesions are further subdivided according to whether they are completely flat or slightly elevated or depressed. In the West, most EGCs
are identified because of the presence of an obvious mass or ulcer seen at endoscopy; flat lesions are likely to be easily overlooked.\textsuperscript{31} Indeed, there are data from the UK demonstrating that a significant proportion of patients presenting with gastric or oesophageal cancer have had an endoscopy within the preceding 3 years at which time the diagnosis had been missed.\textsuperscript{35} Endoscopist error may be partly explained by the use of acid-suppressing medications that may cause re-epithelialization and masking of an underlying malignancy. Another explanation is that our approach to diagnostic endoscopy in a patient with dyspeptic symptoms is to exclude peptic ulcer disease and not to examine the whole of the gastric mucosa in detail for subtle alterations in appearance.\textsuperscript{31} This is where our endoscopic practice differs from that of the Japanese.

The vast majority of diagnostic upper gastrointestinal (GI) procedures performed in the UK use standard white-light endoscopy (WLE). Standard WLE has its limitations when carrying out surveillance endoscopy for dysplastic pre-malignant lesions. This is clear from our experience of screening in Barrett’s oesophagus where repeated WLE with systematic biopsy is time-consuming both for the endoscopist and pathologist, and results in poor diagnostic yield. The Japanese have led the way in the adoption of technologies whereby the detection of EGC can be enhanced. There are numerous established and emerging diagnostic modalities including high-resolution and magnification endoscopy, chromoendoscopy, point spectroscopy, fluorescence imaging and confocal endoscopy. These techniques are reviewed in detail elsewhere.\textsuperscript{36} Chromoendoscopy is being increasingly employed in endoscopy units in the West. The technique involves the topical application of stains to aid the endoscopic visualization of lesions. The nature and mechanism of action of the stains varies. Methylene blue, for example, stains intestinal-type epithelium, but not normal gastric mucosa. Indigo carmine accentuates mucosal patterns helping identify distorted surface topography. Techniques such as point spectroscopy and confocal endoscopy allow the mucosa to be assessed \textit{in vivo} for spectroscopic or microscopic evidence of dysplasia or malignancy. Although these techniques do not replace conventional biopsy for histology, they allow biopsies to be targeted and thus increasing diagnostic yield.

\textbf{Endoscopic therapy for early gastric cancer}

As a result of the increasing numbers of EGCs that have been detected in Japan over the past 15 years, techniques have evolved that allow EGCs to be treated endoscopically, thus reducing the morbidity and mortality associated with traditional gastric surgery. The completeness
of resection must not be compromised by the decision to utilize therapeutic endoscopy, and patients must, therefore, be carefully selected with adherence to treatment guidelines. Lymph node metastases are a contraindication to endoscopic resection since formal surgical lymph node dissection is required. The presence of lymph node metastases correlates with the depth of tumour invasion, and endoscopic ultrasonography (EUS) in combination with endoscopy is helpful in staging tumour depth and detecting perigastric nodal metastases.

The two endoscopic techniques most widely used in the treatment of EGC are endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Both therapies are tissue preserving, allowing the specimen to be retrieved and sent for histology, this is in contrast to ablative techniques. There are a variety of different EMR techniques; however, these all tend to involve the use of a snare to remove the affected mucosa, often following injection of saline into the submucosa to elevate the lesion. EMR is generally limited to lesions <2 cm in diameter. Larger areas of mucosa can be removed by ESD where more extensive submucosal injection is carried out followed by dissection of the submucosa from the muscularis propria using specialized endoscopic cutting devices. ESD is claimed to have higher en bloc resection rates (over 90%) and lower local recurrence rates than EMR.

Prevention of gastric cancer by H. pylori eradication

Screening for EGC is not feasible in most populations, and therefore, the prevention represents the most promising approach to reducing gastric cancer mortality on a global scale. Although the exact mechanisms by which H. pylori promotes gastric carcinogenesis remain unclear, it is the single most important aetiological agent in gastric cancer and therefore the target of preventative strategies. H. pylori is believed to be acquired in infancy or childhood. There is therefore a long latency period before the development of malignancy during which H. pylori eradication may be effective in preventing gastric carcinogenesis. Despite what appears to be a logical assumption—that H. pylori eradication in infected individuals will prevent the development of gastric cancer—there is minimal supporting clinical evidence from controlled trials. This is partly due to the difficulty faced in recruiting infected individuals who may be randomized to placebo, and the consequent ethical issues this generates. In addition, the follow-up period required for such studies is often prohibitively lengthy. The largest randomized controlled trial, conducted in a high-risk region of China, was published by Wong et al. In this study, 1630 healthy H. Pylori carriers were randomized to receive either eradication...
therapy or placebo. There was no overall difference in the incidence of gastric cancer between the two groups over a follow-up period of 7.5 years. Within the subgroup of patients who had no endoscopic evidence of atrophy or intestinal metaplasia at recruitment, there was, however, a significant reduction in the risk of gastric cancer in the active treatment group. This suggests that there is likely to be a ‘point of no return’ in gastric carcinogenesis, beyond which *H. pylori* eradication is ineffective in preventing the progression to carcinoma. The evidence that eradicating *H. pylori* leads to regression of premalignant mucosal changes is conflicting, although it appears that, at least in some individuals, both atrophic gastritis and, to a lesser extent, intestinal metaplasia can regress following eradication of *H. pylori*, but this remains highly controversial. It is likely that not all gastric cancers will be prevented by *H. pylori* eradication since some individuals will already have developed premalignant mucosal changes that may no longer be dependent on *H. pylori* for driving the progression to carcinoma.

**Summary**

Our understanding of the mechanisms by which gastric cancer arises is more advanced than for the majority of other solid tumours. *H. pylori* is the single most important environmental risk factor for the development of non-cardia gastric cancer as well as for at least a proportion of cardia cancers. Prevention of gastric cancer will only be achievable through prevention of acquisition of *H pylori*, or eradication of the infection before an as yet undetermined critical committal stage in the gastric carcinogenesis. Further studies are required to determine the efficacy of *H. pylori* eradication as a preventative strategy in gastric cancer. The evidence implicating dietary factors, and the potential for dietary modification to reduce gastric cancer risk, is conflicting and merits further investigation.

Screening for EGC in high-risk populations reduces gastric cancer mortality and facilitates endoscopic therapy, thus reducing the morbidity associated with the condition. It may eventually be possible to target screening to those individuals most at risk of developing gastric cancer within non-high-risk populations. Risk estimation is likely to incorporate factors such as age, family history and *H. pylori* status combined with serological testing for gastric atrophy, and possibly molecular genetic analysis for predisposing polymorphisms and bacterial virulence factors.
References


