Genetic predisposition to gastric cancer

S. BEVAN and R.S. HOULSTON

From the Section of Cancer Genetics, Institute of Cancer Research, Sutton, UK

Introduction

Wide variations exist in the incidence of gastric cancer between populations. In Japan, the incidence is as high as 80 per 100,000 males, whilst in most African states the overall incidence is only 5 per 100,000. In Europe, incidence rates are between 20 and 40 per 100,000, and females have about half the male gastric cancer risk.1

Approximately 90% of gastric cancers are adenocarcinomas. These can be classified according to their differentiation or according to the histomorphological classification of Lauren, which divides the tumours into ‘intestinal’ and ‘diffuse’.2 Intestinal tumours are usually exophytic, often ulcerating, and are associated with intestinal metaplasia of the stomach. Diffuse tumours are poorly differentiated infiltrating lesions which lead to thickening of the stomach (limitis plastica). Patients with diffuse-type tumours have a worse prognosis than those with an intestinal type. Intestinal cancers appear to be more common in proximal (fundus) localized tumours than in distal lesions, while diffuse, poorly differentiated tumours predominate in younger patients.3 Interestingly, the diffuse type of gastric carcinoma demonstrates a nearly equal sex ratio, compared with a male preponderance in the intestinal form.

The varying rates in different populations, coupled with studies of migrants, strongly implicate environmental factors in the aetiology of gastric cancer. These factors include the level of antioxidants such as vitamin E and ascorbic acid in the diet, and the role of Helicobacter pylori.4–6 In addition to environmental factors, there is increasing evidence that some gastric cancers are caused by an inherited predisposition. Identification of these predisposition genes should be useful for identifying those at high risk, as well as helping to provide a model for gastric carcinogenesis in general.

Evidence for a genetic predisposition to gastric cancer

Evidence for a genetic predisposition to gastric cancer comes from both epidemiological studies and case reports of gastric cancer families. Systematic case-control and cohort analyses of gastric cancer patients have shown that the risk of gastric cancer in first-degree relatives is increased 2–3-fold.7–16 An association between gastric cancer and other cancers (colorectal and CNS tumours) has been observed in some of these studies.12,16 These associations suggest the presence of predisposition genes with pleiotropic effects. The risk of gastric cancer in relatives of patients has been shown to be dependent upon histology.15 Relatives of patients with intestinal disease have a 1.4-fold increase in risk, compared with a 7.0-fold increase in risk in relatives of patients with diffuse disease.15 This suggests that differences in histology reflect, in part, a greater hereditary basis in diffuse gastric cancer.

There are many reports in the literature of families exhibiting striking clustering of gastric cancer compatible with an autosomal dominant pattern of inheritance,7 with one of the most celebrated gastric cancer families being that of Napoleon Bonaparte (Figure 1).17 Napoleon, his father and grandfather, four sisters and a brother all died of stomach cancer, many at early age. It has often been suggested that even very striking familial clusters of a common cancer can be ascribed to ascertainment bias. This is however, a statistical fallacy. For example, a family consisting of three affected siblings with stomach cancer (such as Napoleon’s family) would be expected to occur by chance less than once every 1000 years. Familial clustering of disease can, however, result from shared environmental...
risk factors acting independently or in conjunction with genetic factors. There is no evidence that dietary factors are significantly different between familial and sporadic forms of the disease, although the significant trend of increasing gastric cancer risk with increasing numbers of siblings is consistent with the hypothesis that domestic crowding and deprivation in childhood is a covariant of subsequent gastric cancer risk. H. pylori infection is the most likely reason for this observation, and infection confers an increased risk of both atrophic gastritis and gastric cancer. Although H. pylori infection might theoretically account for some familial aggregation of gastric cancers, the prevalence of infection and associated risks make it unlikely to be responsible for most familial cases.

### Predisposition syndromes

Gastric cancer is a manifestation of a number of inherited cancer predisposition syndromes. These include hereditary non-polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), Cowden syndrome (CS) and Peutz-Jeghers syndrome (PJS). Until recently, evidence to support the existence of a distinct ‘gastric cancer syndrome’ was only indirect, based upon clinical observations. Direct proof has come from the demonstration of co-segregation of mutations within the E-cadherin gene and gastric cancer in two large families. Some cases of gastric cancer are found in association with colorectal cancer in families. It is probable that a proportion of these can be ascribed to HNPCC, which is characterized by dominantly-inherited early-onset of colorectal cancer. In addition to the high risk of colorectal cancer, gene carriers are at increased risk of both uterine and gastric adenocarcinomas, with the risk of gastric cancer being increased 4-fold in mutation carriers.

Benign neoplasms of the gastric mucosa have malignant potential, but are uncommon in the population. A number of inherited cancer syndromes are characterized by a high frequency of these lesions which mediate an increased risk of gastric cancer. Gastric polyps are a manifestation of FAP (approximately 60% of gene carriers develop multiple gastric polyps and 12% have true gastric adenomas), Cowden’s syndrome and Peutz-Jeghers syndrome. Polyposis limited to the stomach has also been reported in a single three-generation family. Hyperplastic gastric polyps are five times as common as true gastric polyps, but confer a smaller risk of malignancy. They are also found in increased frequency in both FAP and Peutz-Jeghers syndrome.

An increased incidence of gastric cancer has been reported in relatives of medullary or tubular breast cancer cases. This association may reflect in part the increased risk of gastric cancer seen in some families with the Li-Fraumeni syndrome (characterized by the association of soft-tissue sarcomas, leukaemia, and brain and breast tumours). Gastric cancer has also been anecdotally reported in association with ataxia telangiectasia and in patients with IgA immune deficiency, although it is conceivable that the association between IgA deficiency and
gastric cancer is a consequence of the gastritis seen in some IgA-deficient patients.\textsuperscript{35}

**Predisposition genes**

Molecular studies of neoplastic disease have shown that multiple genetic alterations are an essential feature of tumorgenesis. These alterations involve two classes of genes: tumour suppressor genes—the products of which normally inhibit neoplastic development by negatively regulating growth and differentiation; and oncogenes—which when activated positively contribute to neoplastic transformation. Inactivation of tumour suppressor genes, coupled with activation of oncogenes, leads to malignancy. Genetic alterations involved in the transformation of normal cells to the malignant state can be both inherited in the germline and arise somatically in the tissue in which the cancer develops. The genetics of stomach cancer are likely to be similar to breast and colon cancers, in which a subset of the disease occurs in individuals who possess one or more of the causal genetic alterations required for neoplastic transformation in their germline. In the majority of cases, these genes are altered at the tissue level by random errors in cellular processes. According to the multi-step model of carcinogenesis, the development of the full neoplastic phenotype in both inherited and non-inherited forms of gastric cancer depends upon multiple genetic alterations.

Studies have shown that the calcium-dependent cell adhesion molecule E-cadherin plays a role in gastric carcinogenesis.\textsuperscript{36} Mutations in E-cadherin can cause downregulation of gene expression, resulting in loss of cell–cell adhesion and an increase in invasiveness. Unsurprisingly, therefore, mutations are more common in undifferentiated diffuse-type cancers.\textsuperscript{37} As well as playing a role in the development of sporadic gastric cancers, germline mutations in E-cadherin are responsible for some dominantly inherited forms of gastric cancer in two large Maori families.\textsuperscript{23} Further studies are now needed to determine what contribution mutations within this gene make to familial gastric cancer.

Microsatellite instability (MI), a form of DNA replication error (RER), is seen in 20–30% of gastric cancers,\textsuperscript{38} with a higher frequency seen in familial cases. Germline mutations in the mismatch repair (MMR) genes hMSH2 on chromosome 2p, and hMLH1 on chromosome 3p, cause 90% of the MI observed in colorectal cancers from HNPPC families. Germline and somatic mutations in these MMR genes are rarely seen in sporadic or familial, non-HNPPC gastric cancers however, suggesting that alternative genes are involved in RER in these cases.\textsuperscript{29}

The association of gastric polyps and cancers in FAP implicates the APC gene in gastric carcinogenesis. Inactivation of the APC gene on chromosome 5q is seen in about 20% of early sporadic gastric cancers,\textsuperscript{40,41} but is predominately associated with the differentiated diffuse disease. The APC gene therefore appears to play a key role in initiation of a subset of sporadic gastric as well as colonic cancers.

It is clear that mutations in other genes can initiate gastric carcinogenesis through alternative pathways. The frequent association of gastric polyps in dominantly inherited Cowden’s and Peutz-Jeghers syndromes undoubtedly implicates the Pten gene on chromosome 10p\textsuperscript{42} and the PJS1 gene on chromosome 19p,\textsuperscript{43} respectively, although the role of these genes as initiators of gastric cancer overall is small. Among the tumour suppressor genes, TP53 is the best understood, and its mutation is associated with many types of cancers (DNA damage results in TP53-mediated arrest followed by repair or apoptosis).\textsuperscript{44} Although mutations in TP53 occur in gastric cancer, its role as a predisposition gene appears to be confined to the Li-Fraumeni syndrome.

Possible sites of other predisposition genes, such as tumour suppressor genes, can be identified from sites of chromosomal loss. These can be detected either cytogenetically or by loss of heterozygosity (LOH) using microsatellite markers. LOH at chromosomes 1p, 5q, 7q, 11p, 13q, 17p and 18p among others has been observed in a high percentage of gastric cancers.\textsuperscript{45–50}

Although highly penetrant genes such as E-cadherin may cause a substantial proportion of gastric cancers at a young age, they are unlikely to be responsible for a high proportion of all gastric cancers. By comparison, low-penetrance susceptibility genes will rarely produce large familial clusters of disease, but could potentially account for a significant proportion of all gastric cancer cases. Since the genetic effects of these genes are undetectable by linkage, their identification is dependent on association studies. One of the earliest associations between a polymorphism and the risk of cancer was observed between the ABO blood group system and gastric cancer risk. Patients with blood group A have a 1.01-fold increase in risk of gastric cancer compared with individuals with blood group O.\textsuperscript{51} A relationship between expression of sulfomucins in gastric intestinal metaplasia (a marker of pre-neoplastic progression) and expression of ABO, Lewis and secretor has been reported,\textsuperscript{52} indicating that the closely interrelated ABO, Lewis and secretor phenotypes may therefore modulate the interaction between \textit{H. pylori} and the gastric surface epithelium. Similarly, pernicious anaemia is associated with a 3-fold increase in gastric cancer risk,\textsuperscript{53,54} possibly because of a reduction in intra-luminal acid secretion and bacterial overgrowth leading to increased nitrite
formation. The HLA-DR5 genotype is associated with a 6-fold increase in risk of pernicious anaemia, indicating that events leading to gastric cancer do indeed have a significant genetic component.

Other genes which may confer susceptibility to gastric cancer include those involved in the biochemical breakdown pathways of carcinogens. Many of these show polymorphic variation, although studies of cytochrome p450 2E1 and glutatatione-S-transferase have not found any evidence for polymorphism being a gastric cancer risk factor. There have been few studies on the possible role of polymorphic variation in oncogenes as a causative factor in gastric carcinogenesis, and most of them have been negative. However, one study has shown that polymorphic variation in L-myc is associated with a 1.6-fold increase in gastric cancer risk (95% CI 1.03–2.34). The study was based upon small numbers however, and the results should therefore be interpreted with caution.

Pepsinogens have been shown to be markers of terminal differentiation in gastric mucosa, as well as indicators of pre-neoplastic and neoplastic change. It has recently been shown that circulating levels of these pepsinogens and the PGI/PGII ratio is influenced by polymorphic variation in the PGC gene on chromosome 6p11-21.3, and it is therefore conceivable that a relationship between polymorphic variation in the PGC gene and the onset of gastric cancer may exist.

Understanding the genetic epidemiology of gastric cancer is clearly an essential prerequisite for identifying those placed at risk because of family history, although unfortunately our present knowledge of this is limited.

Conclusions

There can be little doubt that the current treatment of gastric cancer is essentially a damage-limitation exercise. An attractive proposition to reduce the incidence of the disease is to identify individuals who are at high risk, and who may benefit from targeted screening and other prophylactic measures to prevent the onset of frank malignancy. There is now evidence that mutations in a number of genes are associated with an increased risk. Whilst information on the genetic epidemiology of gastric cancer is clearly limited, there is an opportunity to identify certain high-risk groups, for example the high frequency of gastric polyps seen in FAP and Peutz-Jeghers syndrome would justify 2-yearly gastro-duodenoscopy, and in HNPCC families featuring gastric cancer screening for upper gastro-intestinal malignancies may be appropriate as an early screening protocol.

References


