How does H. Pylori infection cause gastric cancer?

Kenneth E.L. McColl1 and Emad El-Omar2

1University Department of Medicine & Therapeutics, Western Infirmary, Glasgow,
2University Department of Medicine & Therapeutics, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen, UK.

Abstract. H. pylori is now recognised to be an important co-factor in the aetiology of non-cardia gastric cancer of both the diffuse and intestinal histological type. The latter type develops via a complex multistage and multifactorial process. The first stage involves progression from superficial gastritis to atrophic pangastritis with intestinal metaplasia and associated hypochlorhydria. This gastric phenotype may then progress to dysplasia and cancer. Many co-factors are involved in this progression including the strain of H. pylori, host genetic factors, such as interleukin-1 polymorphisms and gender, plus environmental factors such as smoking and diet. Intestinal colonisation with helminthic infection may retard the progression by altering the immune and inflammatory response to H. pylori and colonisation of the achlorhydric stomach with nitrosating bacteria may promote progression to cancer. H. pylori appears to be an obligatory co-factor in the aetiology of most gastric cancers. Consequently, prevention of the infection or its eradication in early life should reduce the incidence of this common and usually fatal tumour.

Key words: H. pylori, cancer, gastric, mechanism

Introduction

Helicobacter pylori infection is associated with an increased risk of cancer throughout the stomach except for the most proximal cardia region. Meta-analysis of case-controlled studies within prospective cohorts indicate that H. pylori seropositivity confers a six-fold increased risk of non-cardia gastric cancer. In a population with a 50% prevalence of H. pylori, approximately 75% of non-cardia gastric cancers can be attributed to the infection. The risk of both the intestinal and diffuse histological subtypes of non-cardia gastric cancer are increased in the presence of H. pylori infection.

Between 1 and 3% of patients with H. pylori infection will go on to develop gastric cancer and this compares with 5–15% developing peptic ulcer disease. However, approximately 80% of H. pylori infected subjects will not develop any significant disease outcome. There has been considerable interest in the mechanism by which H. pylori infection increases the risk of non-cardia gastric cancer in this subgroup of subjects. The mechanism is most fully understood with respect to the development of the intestinal histological type of cancer.

It is now recognised that the infection induces a spectrum of histological and physiological phenotypes within the stomach. In some subjects, the infection induces an antral predominant non-atrophic pattern of gastritis and this results in increased gastrin release and increased acid secretion (Fig. 1). This phenotype is associated with an increased risk of duodenal ulcer disease but little, if any, increased risk of gastric cancer. In other subjects, the infection induces an atrophic pan-gastritis or body predominant gastritis with intestinal metaplasia and this histological picture is associated with increased gastrin release but markedly reduced or absent acid secretion. It is this latter phenotype which is associated with a markedly increased risk of developing gastric cancer. The marked reduction in gastric acid secretion in the latter phenotype seems to be associated with both the atrophy and the inflammation of the body region of the stomach. Eradicating the infection results in rapid resolution of the inflammatory infiltrate and this is associated with a significant return of gastric acid secretion. The atrophy shows little early resolution following eradication of the infection and this may prevent full recovery of gastric acid secretion. The mechanism by which the inflammatory infiltrate produces this reversible inhibition of gastric acid secretion is not fully understood. However, the infection is known to stimulate increased mucosal production of interleukin-1 and this cytokine is known to be a very powerful inhibitor of acid secretion.
has been shown to inhibit the release of histamine from ECL cells and to inhibit the parietal cell response to stimulation by both histamine and acetylcholine.\(^7, 8\)

There has been considerable interest in the factors that determine the particular histological and physiological phenotype induced in the stomach by \textit{H. pylori} infection. It has focused on three potential influencing factors, namely (i) different strains of \textit{H. pylori} infection, (ii) host genetic factors and (iii) environment co-factors. Each of these will be discussed in turn.

In patients infected with the more virulent CagA positive strain, there is a more intense inflammatory infiltrate in both the antral and body region of the stomach.\(^9\) CagA positive infection is also associated with an increased prevalence of atrophy. However, the distribution of the inflammation between the antral and body region of the stomach and the associated disturbance in gastric secretion is unrelated to the strain of the infection.\(^9\) Infection with the more virulent CagA positive strain of \textit{H. pylori} infection thus increases the risk of developing either gastric cancer or duodenal ulcer disease but does not in itself determine which of these two outcomes is more likely. This is consistent with the observation that CagA positive infection is associated with an increased risk of both gastric cancer and duodenal ulcer disease.

The role of host genetic factors in determining the response to \textit{H. pylori} infection and subsequent outcome has received considerable attention over the last few years. We recently studied 100 first-degree relatives of patients with non-cardia gastric cancer and compared them with 100 control subjects with family history of gastric cancer.\(^{10}\) The \textit{H. pylori} status of each subject was determined and gastric biopsies were taken to determine the pattern of \textit{H. pylori}-induced gastritis. In addition, we measured their gastric secretory function. These studies showed that there is a very high incidence of body predominant gastritis, atrophy and hypochlorhydria in \textit{H. pylori}-infected subjects with a family history of gastric cancer. In contrast, prevalence of this phenotype was very rare in the subjects with a family history of gastric cancer but with no evidence of \textit{H. pylori} infection and in \textit{H. pylori} uninfected subjects with or without a history of gastric cancer. This observation was consistent with interaction between the infection and a host genetic factor, resulting in a histological and physiological phenotype known to lead to gastric cancer.

The above studies stimulated our interest in identifying a potential host genetic factor which could interact with the infection and result in gastric cancer. The interleukin-1 gene appeared a likely candidate. It is known that if the infection induces increased production of interleukin-1 by the gastric mucosa and that this cytokine is a powerful inhibitor of acid secretion and could therefore induce hypochlorhydria in response to the infection.\(^5, 6\) In addition, the gene is recognised to have polymorphisms with differing inflammatory activity. We found that the pro-inflammatory genotypes were twelve times more common in \textit{H. pylori} infected subjects with hypochlorhydria and achlorhydria than in infected subjects without this phenotype (Table 1). In further studies we were able to show that subjects with the pro-inflammatory interleukin-1 genotype had an increased risk of going on to develop actual gastric cancer.\(^{11}\)

The above studies suggest that host genetic polymorphisms affecting the interleukin-1 gene can markedly affect the response to \textit{H. pylori} infection and disease outcome. When subjects with the pro-inflammatory genotype are infected with \textit{H. pylori}, the increased production of interleukin-1 will induce hypochlorhydria. The pro-inflammatory genotype and associated interleukin-1 production can also explain the pangastritis or body predominant gastritis. It is known that the pattern of gastritis is influenced by gastric acid secretory status. For example, marked inhibition of gastric acid secretion by proton pump inhibitors will transform an antral predominant non-atrophic gastritis to a body predominant gastritis and also accelerate the

### Table 1: IL-1 Genotype Frequencies in Gastric Cancer Relatives with Normal vs Low Acid Output\(^1\)

<table>
<thead>
<tr>
<th>Locus</th>
<th>Genotype</th>
<th>Low acid (n = 45)</th>
<th>Normal (n = 58)</th>
<th>OR (95% Cl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{IL-1B-31}</td>
<td>T/T</td>
<td>5</td>
<td>30</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>C/T</td>
<td>28</td>
<td>21</td>
<td>8.1 (2.0–33)</td>
</tr>
<tr>
<td></td>
<td>C/C</td>
<td>12</td>
<td>7</td>
<td>13.6 (2.6–71)</td>
</tr>
<tr>
<td></td>
<td>1/1</td>
<td>17</td>
<td>35</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>1/2</td>
<td>14</td>
<td>14</td>
<td>2.4 (0.9–6.2)</td>
</tr>
<tr>
<td></td>
<td>1/3, 4, 5</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2/2</td>
<td>14</td>
<td>7</td>
<td>5.6 (1.8–17)</td>
</tr>
</tbody>
</table>
development of atrophy. Consequently, the reduction in acid secretion induced by the increased interleukin-1 production will also lead to pangastritis or body predominant gastritis and atrophy.

For many years, environmental factors have been recognised to be associated with increased risk of gastric cancer. Recent studies have confirmed that *H. pylori* infected subjects with a low intake of fruit and vitamin C have an increased risk of developing gastric cancer compared to subjects with *H. pylori* infection and a high intake of fruit and vitamin C. In addition, *H. pylori* infected subjects who smoke have a three-fold increased risk of developing gastric cancer compared to *H. pylori* infected subjects who do not smoke. Both the diet deficient in antioxidants and the free radicals in cigarette smoke are likely to promote the development of atrophic gastritis in *H. pylori* infected subjects. Recently, it has been shown that concurrent Helminthic infection modulates the response to *H. pylori felis* in mice and reducing the risk of developing atrophy. This appears to be due to down-regulation of the TH1 cytokine response. This observation might explain the relatively low incidence of gastric cancer in African countries, despite the high prevalence of *H. pylori* infection.

It can therefore be seen that a variety of bacterial, host genetic and environmental factors influence the development of atrophic gastritis with intestinal metaplasia and hypochlorhydria. This gastric phenotype is associated with a marked increased risk of progressing to gastric cancer. The mechanism by which this gastric cancer phenotype leads to gastric cancer remains incompletely understood. The atrophic gastritis, the intestinal metaplasia and the hypochlorhydria may all be involved in progression to cancer. The hypochlorhydria results in an elevation of intragastric nitrite, a reduction in intragastric vitamin C and overgrowth with a variety of bacteria including nitrosating species. This alteration in the intragastric milieu may result in the bacterial generation of N-nitroso compounds within the lumen of the stomach. However, the demonstration of such compounds has proved to be difficult due to the complexities of their analyses. In atrophic gastritis, the inflammatory process damages and destroys epithelial stem cells. It therefore seems likely that the inflammatory process may also produce DNA damage leading to mutagenesis and neoplasia. The atrophic gastritis is nearly always associated with intestinal metaplasia and this latter phenotype may also play a role in the development of gastric cancer. The intestinal metaplasia which is most common in *H. pylori* associated atrophic gastritis is of the complete histological type. It has microvilli and is a functionally absorptive mucosa. Close examination indicates a significant amount of fat droplets within the intestinal metaplasia epithelium and submucosa. Normal gastric epithelium is non-absorptive and serves as a barrier between the mucosa and the lumen. When this is replaced with intestinal metaplasia, this barrier is lost and chemical substances which are both lipid and water soluble can traverse the epithelium. This alteration in the barrier function of the epithelium will facilitate the entry of N-nitroso compounds formed within the achlorhydric stomach or carcinogens ingested in the diet. It can therefore be seen that the atrophic pangastritis and hypochlorhydric phenotype may increase the risk of gastric cancer by altering the intragastric luminal environment and the epithelial barrier as well as generating free radicals associated with the mucosal inflammation (Fig. 2).

A number of other observations are also relevant to the mechanism of the development of gastric cancer. The incidence of gastric cancer is substantially higher in males than females. This difference is due to an increased incidence of the intestinal type of cancer in the males. Interestingly, the incidence of gastric cancer phenotype i.e. atrophy, hypochlorhydria and metaplasia is not higher in males than females. The mechanism by which male gender increases progression to cancer or, alternatively, female gender protects against the progression is unknown. It is possible that there is a protective effect of female hormones and/or a promoting effect of male hormones. In addition, the lower levels of iron present in females throughout their reproductive years may reduce their propensity to free radical generation.

There has been recent interest in the possible role of gastrin in the development of gastric cancer in *H. pylori* infected subjects. It has been shown that the serum gastrin level correlates with the risk of gastric cancer in *H. pylori* infected subjects. This may simply be due to the hypochlorhydria causing reflex hypergastrinaemia and the cancer risk being associated with the atrophic gastritis rather than to the hypergastrinaemia. However, recent studies with hypergastrinaemia transgenic mice indicate that they have a markedly increased incidence of gastric cancer when infected by *Helicobacter felis* than wild-type mice. This raises the possibility that hypergastrinaemia may play a role in the progression to gastric cancer.
In conclusion, it can be seen that the development of gastric cancer is a complex, multistage and multifactorial process. The various stages involve the progression from *H. pylori* superficial gastritis to atrophic gastritis with intestinal metaplasia and hypochlorhydria and then the further progression to development of dysplasia and cancer. Numerous co-factors are involved in promoting or inhibiting this progression (Fig. 3). However, *H. pylori* infection does appear to be an obligatory co-factor in most cases of non-cardia gastric cancer. Consequently, prevention of *H. pylori* infection or its eradication at an early stage should markedly reduce the incidence of this common and usually fatal cancer.

**References**