Gastric cancer and *Helicobacter pylori* infection

K S Clarkson, K P West

Abstract

**Aims**—To identify differences in the prevalence of *Helicobacter pylori* infection in different groups of patients with gastric cancer.

**Methods**—In total 224 cases of gastric cancer were studied: 120 (53·6%) intestinal; 69 (30·8%) diffuse; and 35 (15·6%) unclassified. Site of tumour, presence and severity of gastritis, presence and extent of intestinal metaplasia, and age and sex were also recorded. Infection by *H pylori* was assessed using modified Giemsa staining.

**Results**—*H pylori* infection was found in 96 (43%) cases. There was no significant association between infection and histological type of tumour, nor was there any significant association between infection and site of tumour, the presence of intestinal metaplasia, age, or sex. The only significant association identified was between infection and gastritis.

**Conclusions**—These results are in broad agreement with those of other similar studies, although the overall prevalence of infection, at 43%, was lower than has been reported in some series. The findings do not support a role for *H pylori* in any particular subgroup of patients with gastric cancer but do not exclude a role for the organism in the pathogenesis of gastric cancer as a whole.

(J Clin Pathol 1993; 46: 997–999)

There are wide geographical variations in the incidence of gastric cancer. This has led to speculation about environmental factors that may be important in its pathogenesis.1 2 Atrophic gastritis and intestinal metaplasia have been accepted as pre-cancerous conditions for some years, at least in relation to the intestinal type of gastric cancer.

*Helicobacter pylori* has been closely linked with chronic gastritis and there is considerable support for a causal association.3 Infection with this organism is very common and this is especially so in certain countries with a high incidence of gastric cancer, such as Columbia. This has led to speculation about the role of the organism in the pathogenesis of gastric cancer and previous work has reported a link between infection and cancer.4 The purpose of this study was to examine the prevalence of the organism in a large series of gastric cancer cases in a British population and to identify any subgroups amongst which there were significant differences in prevalence.

**Methods**

All cases of gastric carcinoma diagnosed at Leicester Royal Infirmary between 1982 and 1986 were identified and the histopathological blocks retrieved. The tissues had all been fixed in 10% formol-saline. When possible, resection specimens were used but biopsy material was included if it contained sufficient non-tumour tissue. Sections were stained with haematoxylin and eosin, alcin blue-periodic-acid Schiff, and modified Giemsa for assessment of tumour type, the presence and degree of gastritis, intestinal metaplasia and *H pylori* infection. No attempt was made to differentiate the various subtypes of intestinal metaplasia. Tumours were typed using the Lauren classification.5 Gastritis was graded mild, moderate, or severe according to the intensity of the neutrophil polymorph and mononuclear infiltrate in accordance with previous studies.6 7 Cases were not separated by topographical sites as we were concerned with the overall prevalence of gastritis rather than its distribution within the stomach. Intestinal metaplasia was scored as follows: 0 = none, 1 = focal; 2 = affecting less than half of the epithelium present, 3 = affecting more than half of the epithelium present. *H pylori* colonisation was recorded simply as present or absent. All sections were examined independently by the authors and disagreements resolved by discussion. The semiquantitative scoring system used for metaplasia has been described by Loffeld et al.8 Statistical analysis of the results was performed using the $\chi^2$ test.

**Results**

In total, 224 cases of gastric carcinoma were identified. In 156 cases resection specimens were available; in the remaining 65 cases multiple biopsy specimens were studied. There were 156 men (69·6%) and 68 women (30·4%), giving a male:female ratio of 2:3:1. The mean age at diagnosis was 68·6 years with a range of 35 to 91 years. There was no significant age difference between the men and women studied.

Of the 224 cases, 120 (53·6%) were classified as intestinal type carcinomas and 69 (30·8%) as diffuse type. The remaining 35...
Table 1 Helicobacter pylori infection and histological type and site of gastric cancer

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal</td>
<td>56 (45.7%)</td>
<td>64 (53.3%)</td>
<td>120</td>
</tr>
<tr>
<td>Diffuse</td>
<td>24 (34.8%)</td>
<td>45 (65.2%)</td>
<td>69</td>
</tr>
<tr>
<td>Site of tumour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>23 (40.4%)</td>
<td>34 (59.6%)</td>
<td>57</td>
</tr>
<tr>
<td>Body</td>
<td>26 (48.1%)</td>
<td>28 (51.9%)</td>
<td>54</td>
</tr>
<tr>
<td>Distal</td>
<td>31 (51.7%)</td>
<td>29 (48.3%)</td>
<td>60</td>
</tr>
</tbody>
</table>

Cancer type $\chi^2 = 2.97; 1 df; not significant.

Cancer site $\chi^2 = 1.56; 2 df; not significant.

(15.6%) were unclassified. There were no significant differences in the ages of the patients with the different tumours types, but intestinal carcinoma was proportionately more common in men.

H pylori was identified in 96 (43%) cases and no difference was observed in prevalence between biopsy and resection specimens. Prevalence of infection for the main tumour types is shown in table 1. There was no significant difference between intestinal and diffuse carcinomas.

Where possible tumours were also categorised according to their location within the stomach. They were recorded as proximal (close to the cardia), body, or distal (antrum/pylorus). The prevalence of infection according to tumour site is shown in table 1. No significant association was seen.

The well known association between H pylori and gastritis was confirmed in this study. Intestinal metaplasia was identified in 115 (51.3%) cases and there was no significant association with infection (table 2).

The possibility of an association between infection and early onset of gastric cancer was investigated (table 2). No significant association was found between age and infection.

Table 2 Helicobacter pylori infection and gastritis, intestinal metaplasia and age in patients gastric cancer

<table>
<thead>
<tr>
<th>Age</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1 (7.1%)</td>
<td>13 (92.9%)</td>
<td>14</td>
</tr>
<tr>
<td>Mild</td>
<td>14 (25%)</td>
<td>42 (75%)</td>
<td>56</td>
</tr>
<tr>
<td>Moderate</td>
<td>54 (50.9%)</td>
<td>52 (49.1%)</td>
<td>106</td>
</tr>
<tr>
<td>Severe</td>
<td>28 (58.3%)</td>
<td>20 (41.7%)</td>
<td>48</td>
</tr>
<tr>
<td>Metaplasia</td>
<td>Present</td>
<td>46 (40%)</td>
<td>69 (60%)</td>
</tr>
<tr>
<td>Absent</td>
<td>44 (40.4%)</td>
<td>65 (59.6%)</td>
<td>119</td>
</tr>
</tbody>
</table>

Gastritis: $\chi^2 = 22.03; 3 df; p < 0.001$.

Metaplasia: $\chi^2 = 0.01; 1 df; not significant.

Age: $\chi^2 = 4.72; 3 df; not significant.$

Discussion

Studies of the prevalence of H pylori infection in gastric cancer have been conducted in several countries and produced widely varying results ranging from 59–84%. The well known association between H pylori and gastritis was confirmed in this study. Intestinal metaplasia was identified in 115 (51.3%) cases and there was no significant association with infection (table 2).

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<table>
<thead>
<tr>
<th>Age</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-70 years</td>
<td>38 (53.5%)</td>
<td>33 (46.5%)</td>
<td>71</td>
</tr>
<tr>
<td>70+ years</td>
<td>33 (56.7%)</td>
<td>57 (43.3%)</td>
<td>90</td>
</tr>
</tbody>
</table>

Gastritis: $\chi^2 = 22.03; 3 df; p < 0.001$.

Metaplasia: $\chi^2 = 0.01; 1 df; not significant.$

Age: $\chi^2 = 4.72; 3 df; not significant.$

patients, in terms of age, sex and the proportion of intestinal and diffuse cancers is fairly typical for Britain and it should be borne in mind, when looking at our results, that some of the published studies come from parts of the world with a much higher prevalence of gastric cancer.

The relatively low prevalence of H pylori infection in this study may be genuine, but it may represent an underestimate for a number of reasons. Histological examination can only detect current infection; serology can, in theory, detect both past and present infection. Furthermore, the patchy distribution of the organism may mean that it is missed by histological examination, especially in a retrospective study where sampling cannot be controlled. Other possible techniques for detection include $^{13}$C or $^{14}$C urea breath test, culture, immunocytochemistry and molecular biological methods. Histological analysis, however, remains a useful and inexpensive means of detection which has been shown by some authors to have a sensitivity of 95% and a specificity of 97%. It was therefore regarded as a suitable technique for this study.

At the outset we were concerned that delayed fixation of gastrectomy specimens might have an adverse effect on detection of H pylori. In particular we were concerned about the difficulty of identifying coccoid forms of the organism. This fear seems to have been unfounded, however, because we showed a similar prevalence in both biopsy and resection specimens. It seems reasonable to assume that any factors which might have been responsible for an underestimate of infection would have acted in the same manner on all cancers regardless of histological type, so our observations concerning the relative prevalence in intestinal and diffuse cancers remain valid.

The association between H pylori infection and gastritis is well known and was clearly shown in this study. There remained a considerable number of cases, however, in which there was inflammation without infection. This could have been due to a failure to identify the organism for the reasons described above. Alternatively, inflammation in some cases may occur as a reaction to the presence of a tumour. For example, the aberrant expression of MHC class II antigens, which has been shown in some gastric cancers, could provoke an inflammatory response in the vicinity of a tumour. Ulceration might also lead to local inflammation and, of course, some of the cases might be autoimmune (type A) gastritis. Extensive intestinal metaplasia could lead to a failure to detect H pylori as the bacterium cannot adhere to metaplastic epithelium. Loffeld et al found a significant reduction in the prevalence of infection in cases showing moderate to severe (grade 2/3) intestinal metaplasia compared with those cases in which metaplasia was absent or focal (grade 0/1). We were unable to confirm this observation.

The exact relation, if any, between H pylori
infection and gastric cancer cannot be deduced from this study because of the absence of a control group without gastric cancer. We are able to confirm from this large series, however, that infection is not confined to, or significantly associated with, any particular histological type of gastric cancer, nor, in our experience, is it significantly associated with age at presentation or gender. We were, unfortunately, unable to investigate the influence of social class due to lack of relevant data.

Correa et al. proposed a sequence for the pathogenesis of the intestinal type of gastric cancer. This begins with chronic gastritis followed by atrophy and intestinal metaplasia, the development of dysplasia and, finally, adenocarcinoma. Because *H. pylori* is now widely accepted as a cause of chronic gastritis, it is reasonable to postulate that it may have a role in the pathogenesis of gastric cancer, at least the intestinal type. Parsonnet et al. found a significant association between infection and histological findings, with a prevalence of 89% in intestinal cases compared with 32% in diffuse cases. Most other studies, however, including ours, have failed to confirm this observation, showing no significant difference between the different histological types. Such results could be taken to indicate that the organism has no role in the pathogenesis of gastric cancer and that it is merely a fortuitous occurrence. This assertion is not, however, supported by one large study that identified *H. pylori* infection as a risk factor for all types of gastric cancer.

The model described above does not address the problem of how *H. pylori* might contribute to the pathogenesis of diffuse type gastric cancer. There are several possible mechanisms that could have a role in the absence of gastric atrophy or intestinal metaplasia. These include the generation of free radicals which may damage DNA and reduced antioxidant secretion associated with infection. Some strains of *H. pylori* elaborate a 120 kilodalton protein that acts as a toxin. This protein is associated with more severe epithelial degenerative changes and an increased risk of peptic ulceration. Whether this protein is of relevance in carcinogenesis is not known. It is possible that other, as yet unidentified, molecules might be produced by certain strains of *H. pylori*, however, and that these might have a role in the pathogenesis of gastric cancer.

Further studies in this field might concentrate on strain differences within the species *H. pylori* and, in particular, on the effects of bacterial products, including the 120 kilodalton protein already described. In this way it might be possible to detect certain subtypes of the organism which are of greater relevance in gastric carcinogenesis.

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