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Relationship between the birth cohort pattern of *Helicobacter pylori* infection and the epidemiology of duodenal ulcer

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Summary

**Background:** *Helicobacter-pylori*-related duodenal ulcer (DU) is an important cause of dyspepsia.

**Aim:** To determine the relationship between the pattern of *H. pylori* infection and the epidemiology of duodenal ulcer in a single population.

**Design:** Prospective two-part study of (i) patients with DU referred for endoscopy because of dyspepsia, and (ii) the incidence of *H. pylori* infection in the general population of the same area.

**Methods:** Details of 533 DU patients were recorded, and related to the pattern of *H. pylori* infection among 10,537 adults in the same community, determined by the 13C-urea breath test.

**Results:** In patients with DU, birth year was more important than age in determining the rate of presentation for endoscopy (the 'birth cohort' effect). *H. pylori* infection showed a similar birth cohort effect, and the prevalence decreased steadily in those born in successive years, from 28.8% in the 1930s to 3.5% in the 1970s. The proportion of dyspeptic patients who had duodenal ulcers also fell progressively, from 22.2% in 1979 to 5.7% in 1998. *H. pylori* prevalence and duodenal ulcer incidence were closely correlated at all ages.

**Discussion:** Duodenal ulcer prevalence (as judged by the rate of referral of duodenal ulcer patients for endoscopy) is determined principally by the distribution of *H. pylori* infection in the local population. The birth cohort effect seen in adult duodenal ulcer patients reflects the acquisition of *H. pylori* in childhood. In Bristol, *H. pylori* prevalence and duodenal ulcer incidence are both declining to very low levels.

Introduction

At least 25% of the adult population in the UK have dyspepsia, and about 2% of the population per year consult their general practitioner for this reason.1 Duodenal ulcer has been recognized as a common cause of dyspepsia, which is a major and costly public health problem. Large amounts of money are spent on medications and investigations for dyspepsia, with substantial further costs incurred as a result of hospitalization, time lost from work and the payment of sickness benefit.2,3

The management of patients presenting with dyspepsia due to a duodenal ulcer has been revolutionized by the discovery that nearly all duodenal ulcers occurring in patients who are not taking non-steroidal anti-inflammatory drugs (NSAIDs) are associated with chronic *Helicobacter pylori* infection,4–8 which is usually acquired in childhood.9,10 Eradication of the *H. pylori* infection cures the ulcer,5–8,11 usually permanently, since reacquisition of *H. pylori* infection is rare.12 Various...
strategies have been developed that aim to identify patients whose dyspepsia is due to a duodenal ulcer resulting from chronic *H. pylori* infection. These include performing early endoscopy in all dyspeptic patients\(^{13,14}\) testing for *H. pylori* infection and treating any infected patients to eradicate the organism,\(^{15}\) testing for *H. pylori* infection and referring for endoscopy only those who are infected,\(^{16}\) or treating dyspeptic patients symptomatically and investigating only if the symptoms are severe or persistent.\(^{17}\) It is not easy to compare the cost-effectiveness of such strategies, since this depends not only on the costs of the investigations and treatment, but also on the prevalence of *H. pylori* infection in the local community and on the incidence of *H. pylori*-related duodenal ulcer among patients from that community presenting with dyspepsia. This information is rarely available, and the exact relationship between *H. pylori* infection and duodenal ulcer incidence in a single population has not been described previously.

We have studied the incidence of Helicobacter-related duodenal ulcer as a cause of dyspepsia over a period of 20 years in a single health district, and compared this with the *H. pylori* prevalence in different age groups in the same population, obtained as part of the community-based Bristol Helicobacter Project.

**Methods**

The study consisted of two separate parts, one based in the district general hospital responsible for providing a diagnostic service for all dyspeptic patients living in the defined catchment area of Frenchay Health District, and one based in the community served by that hospital.

In part 1, patients with undiagnosed dyspepsia (defined as intermittent epigastric pain or discomfort) who lived in Frenchay Health District and were referred to the medical gastroenterology service at Frenchay Hospital, Bristol, for diagnostic endoscopy during the 20-year period 1979–1998 were studied. An open-access endoscopy service was available throughout this period, with a waiting time usually of about 4–6 weeks. Patients with chest pain, heartburn or reflux, and any patients with a previously diagnosed ulcer or who were taking NSAIDs, were excluded. Age, sex, indications for endoscopy and findings were recorded prospectively for all patients. Duodenal ulcer was defined conventionally, as an ulcer > 5 mm in diameter, situated in the duodenum and/or pyloric channel. Acid-suppressant medication was discontinued in all patients for a period of at least 2 weeks before their endoscopy.

In part 2, the Bristol Helicobacter Project, all people aged 20–59 years who were registered with seven general practices within the Frenchay Hospital catchment area in North East Bristol (total 26 203) were invited to participate in a community-based prospective randomized controlled trial of the effects of *H. pylori* eradication on dyspepsia, quality of life, resource utilization and various other outcome measures. These practices serve about 20% of the population of the Frenchay Hospital catchment area. Overall, 10 537 (40.2%) gave informed consent to take part in the study, and had a \(^{13}\)C-urea breath test for active *H. pylori* infection, using a standard orange juice and citric acid test meal, with a cut-off of Δ3.5 per ml.\(^{18}\)

**Results**

**Part 1: Study population and changes over the 20-year period**

533 patients (354 men and 179 women) presenting with dyspepsia had active non-NSAID-related duodenal ulcers (Table 1). The age distribution was essentially the same for men and women, except for a small but significant increase in the proportion of women in the over-70 year age group (\(\chi^2 = 11.2, p<0.01\)). The distribution of birth years showed a peak in the 1930s, with nearly half (49.7%) of all the patients having been born in the 1920s and 1930s.

There was relatively little difference in the median year of birth between those patients diagnosed between 1979 and 1983 and those diagnosed between 1994 and 1998 (1933 and 1936, respectively) (Table 2), despite the 15-year difference in mean date of endoscopy (Figure 1). Consequently, patients in whom the diagnosis of duodenal ulcer

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt;20</th>
<th>20–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>70–79</th>
<th>80+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>1 (0.3)</td>
<td>27 (7.6)</td>
<td>50 (14.1)</td>
<td>63 (17.8)</td>
<td>91 (25.7)</td>
<td>68 (19.2)</td>
<td>40 (11.3)</td>
<td>14 (4.0)</td>
<td>354</td>
</tr>
<tr>
<td>Women (%)</td>
<td>3 (1.6)</td>
<td>5 (2.8)</td>
<td>18 (10.1)</td>
<td>37 (20.7)</td>
<td>37 (20.7)</td>
<td>30 (16.8)</td>
<td>30 (16.8)</td>
<td>19 (10.6)</td>
<td>179</td>
</tr>
<tr>
<td>Total (%)</td>
<td>4 (0.8)</td>
<td>32 (6.0)</td>
<td>68 (12.8)</td>
<td>100 (18.8)</td>
<td>128 (24.0)</td>
<td>98 (18.4)</td>
<td>70 (13.1)</td>
<td>33 (6.2)</td>
<td>533</td>
</tr>
</tbody>
</table>

Table 1 Prevalence vs. age of duodenal ulcer patients
was made more recently were an average of 8.4 years older (Table 2). The date of birth was thus more important than the age of the patients in determining their duodenal ulcer risk, indicating the existence of a birth cohort effect for duodenal ulcer in this population.

The proportion of patients whose dyspepsia was due to a duodenal ulcer declined steadily from 22.2% in 1979 to 5.7% in 1998 (Figure 2). If this decline in the proportion of dyspeptic patients with duodenal ulcers seen in 1989–1998 who were born in those same 5-year periods was recorded, and the duodenal ulcer incidence for each cohort was calculated (Table 3). The duodenal ulcer incidence (as reflected in referrals for diagnostic endoscopy) for each cohort was then compared with the corresponding H. pylori infection rate in the catchment population. An average of 0.78 ± 0.23 (SD) dyspeptic patients per 1000 helicobacter-positive subjects per year were diagnosed by the endoscopy service as having duodenal ulcers, a rate of incidence which was similar for all but the youngest age groups. A plot of the rate of presentation of duodenal ulcer patients born in each of these 5-year cohorts vs. the corresponding H. pylori prevalence found in the same cohorts (Figure 4), indicates that when H. pylori prevalence reaches zero,

Table 2  Changes in characteristics of duodenal ulcer patients seen in two 5-year periods 15 years apart

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal ulcer*</td>
<td>17.02%</td>
<td>5.76%</td>
<td>( \chi^2 = 97.5, p&lt;0.001 )</td>
</tr>
<tr>
<td>M:F ratio</td>
<td>1.85:1</td>
<td>1.85:1</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>48.6</td>
<td>57.0</td>
<td>8.4 years, ( p&lt;0.01^{**} )</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>48</td>
<td>60</td>
<td>12 years</td>
</tr>
<tr>
<td>Aged &lt;40 years</td>
<td>30.9%</td>
<td>16.8%</td>
<td>( \chi^2 = 5.00, p&lt;0.05 )</td>
</tr>
<tr>
<td>Aged &lt;50 years</td>
<td>54.4%</td>
<td>31.9%</td>
<td>( \chi^2 = 9.10, p&lt;0.01 )</td>
</tr>
<tr>
<td>Median birth year</td>
<td>1933</td>
<td>1936</td>
<td>3 years</td>
</tr>
</tbody>
</table>

*As percentage of all dyspepsia. **t test.

Part 2: H. pylori infection rates in the local community, and their relationship with duodenal ulcer incidence

Of the 10 537 subjects who had a \(^{13}\)C-urea breath test done, 1634 (15.5%) were positive for H. pylori infection. Infection rates correlated strongly with age and inversely with year of birth \( (r=0.99, p<0.001 \) for both correlations) (Figure 3). The population of the Frenchay Hospital catchment area (taken from Area Health Authority statistics for 1995) was subdivided by years of birth into 5-year cohorts. The numbers of dyspeptic patients with duodenal ulcers seen in 1989–1998 who were born in those same 5-year periods were recorded, and the duodenal ulcer incidence for each cohort was calculated (Table 3). The duodenal ulcer incidence (as reflected in referrals for diagnostic endoscopy) for each cohort was then compared with the corresponding H. pylori infection rate in the catchment population. An average of 0.78 ± 0.23 (SD) dyspeptic patients per 1000 helicobacter-positive subjects per year were diagnosed by the endoscopy service as having duodenal ulcers, a rate of incidence which was similar for all but the youngest age groups. A plot of the rate of presentation of duodenal ulcer patients born in each of these 5-year cohorts vs. the corresponding H. pylori prevalence found in the same cohorts (Figure 4), indicates that when H. pylori prevalence reaches zero,

Figure 1. These birth year distributions in two groups of the duodenal ulcer patients diagnosed an average of 15 years apart show little difference. In this population, the date of birth of a patient is therefore more important than age in determining their risk of developing a duodenal ulcer (‘birth cohort effect’).
the duodenal ulcer incidence will be negligible (0.005 per 1000 per year).

**Discussion**

In most of the UK, as in many other parts of the developed world, the incidence of duodenal ulcer has been falling steadily since the 1960s, probably as a result of a decline in *H. pylori* infection as living conditions in childhood have improved. However, in areas where the *H. pylori* prevalence remains high, such as Glasgow and Northern Ireland, there does not as yet appear to be much of a decline in duodenal ulcer incidence.

Susser was the first to note that peptic ulcer death rates correlated closely with years of birth, giving rise to a so-called ‘cohort effect’. The cause of such cohort effects was unknown at that time, but now can be explained by differences in the rates of acquisition of *H. pylori* infection in childhood, which show a similar cohort effect.

The figures obtained in this study need careful interpretation, because of several potential sources
of bias. Firstly, there would have been a change with time in the pattern of referral of dyspeptic patients for diagnosis. Differences in the overall referral rate over the years, and the steadily declining use of other methods of diagnosis such as barium meals, would have had an effect. Secondly, in recent years, the introduction of new policies for dyspepsia management in general practice, such as those involving testing dyspeptic patients for H. pylori infection and then either giving H. pylori eradication therapy (‘test and treat’) or else referring H. pylori positive patients for endoscopy (‘test and refer’), might be expected to have affected the rate of decline of duodenal ulcer as a cause of dyspepsia. In the population that we studied, these policies seem in to have had little effect up to 1998, since the decline in duodenal ulcer among dyspeptic patients was exactly the same in the second 10 years of the study (when such policies were being introduced) as it was in the first 10 years (before they had been developed) (Figure 2). This may have resulted from a slow take-up of such policies in this area, although there are no objective figures on this.

Thirdly, we have not included patients whose ulcers presented with complications such as haemorrhage, because it was not possible to record their details prospectively, and the quality of the hospital records is inadequate for any retrospective study. These sources of bias will have resulted in a significant underestimate of the total incidence of duodenal ulcers, but should have had only a minor effect on the proportional figures that we calculated. Any study of this type can never give a true total incidence for duodenal ulcer, since some are asymptomatic, some do not present to their general practitioners, some are never referred for accurate diagnosis, and some are referred elsewhere.

Our finding of a relatively constant rate of presentation of duodenal ulcers with dyspepsia at different ages (except in the youngest age group, in whom the rate was lower), when corrected for H. pylori prevalence, is consistent with previous observations on duodenal ulcer.30–32 Doll, Avery Jones and Buckatzsch in 1951,31 at a time when H. pylori prevalence was probably high in all age groups of their study population, calculated a total annual incidence of duodenal ulcer in men in the UK of 3.2 per 1000, which was almost constant between the ages of 35 and 64 years. The reason for the lower rate of duodenal ulcer presentation in the youngest cohort that we studied, those born in 1970–1974, may be that many of those in this cohort who were destined to develop ulcers were still too young to have presented. They would have been aged 15–19 at the beginning of the 10-year period of observation and 25–29 at the end: according to previous studies31,32 fewer than half of all duodenal ulcer patients would have presented by those ages.

We have assumed for the purposes of this study that the Helicobacter Project participants and the duodenal ulcer patients were representative of the population of Frenchay Health District (the catchment area of Frenchay Hospital). The General Practices participating in the Bristol Helicobacter Project are all within the catchment area of Frenchay Hospital, and serve about 20% of its population. The population characteristics of the different practices differ slightly from each other and from those of the whole of the district, mainly in the relative proportion of elderly people in each. This should not have had any effect on our results, since we confined our analysis to the age range 20–59. Markers of social deprivation in childhood or in adulthood showed non-significant differences between the individual general practices, and were similar to the figures for the district as a whole. The H. pylori infection rates and the changes in these between successive birth cohorts did not differ significantly between individual general practices, and are therefore likely to be representative of those throughout the whole of the district.

The duodenal ulcer population was derived solely from the Frenchay Hospital catchment area, since we only included patients living there. The most significant source of error in our figures is probably related to our confining our analysis to the well-documented patients seen by the medical.

Figure 4. Patients seen for endoscopy 1989–1998 because of dyspepsia due to a duodenal ulcer, analysed by birth cohorts and compared with H. pylori prevalence in the same birth cohorts in the catchment population (data derived from Table 3). Each point represents one 5-year birth cohort, from 1970–1974 on the left to 1940–1944 on the right. The formula for the relationship (y = 0.0077x + 0.0054, r = 0.93, p < 0.01) indicates that when the prevalence of H. pylori infection in the local population reaches zero, virtually no duodenal ulcers will be seen (0.0054 per 1000 per year) in that age group.
endoscopy service, and excluding those diagnosed elsewhere (e.g. by radiology). This would have reduced the total number of duodenal ulcer patients available for analysis, and thus would have underestimated the figures for total incidence, but should not materially have affected the relative changes in the proportion of dyspeptic patients with duodenal ulcers that we demonstrated, nor the relationship with *H. pylori* prevalence in individual birth cohorts.

Our findings are all consistent with the suggestion that the community prevalence of *H. pylori* infection is the most important determinant of non-NSAID-related duodenal ulcer incidence. The decline in duodenal ulcer incidence in Bristol in recent years is largely accounted for by the progressive decline in the number of younger people who are infected by *H. pylori*. This is happening at such a rate that, in this area, duodenal ulcer will probably become of minor importance as a cause of dyspepsia in the near future. In this part of North-East Bristol, the cost-effectiveness of any policies for dyspepsia management that include testing for *H. pylori* infection is already borderline for younger patients who were born in this area.

Accurate knowledge of the age-related *H. pylori* prevalence in any area increases the accuracy of estimates of the cost-effectiveness of different strategies (such as ‘test and treat’ or ‘test and refer’) for the management of dyspeptic patients in that area. The costs of such strategies will vary greatly between different parts of the UK, depending on the local pattern of *H. pylori* infection, which is still known accurately for only a few areas. For example, the *H. pylori* infection rate in adults aged 40–49 years found in community-based studies in the UK varies from 15% in Bristol to 28% in Leeds and 60% in Glasgow. The contribution of duodenal ulcers to the burden of dyspepsia in Bristol is already very small, whereas in Glasgow it remains large, and in Leeds it is intermediate. A public health policy for the management of dyspepsia needs to be tailored to suit the location, and to be based on accurate knowledge of the local prevalence of *H. pylori* infection.

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References


