
The Individual and Joint Contributions of Helicobacter pylori Infection and Family History to the Risk for Peptic Ulcer Disease

Hermann Brenner, Dietrich Rothenbacher, Günter Bode, and Guido Adler

Family history of peptic ulcer and infection with Helicobacter pylori have been identified as major risk factors for peptic ulcer disease. It is unclear, however, to what degree their impacts are independent of each other. This question was addressed in a cross-sectional study among 299 consecutive out-patients (25–54 years old) of a general practitioner. Adjusted odds ratios (95% confidence intervals) for gastroscopically verified peptic ulcer disease were 3.8 (1.4–10.1) for persons with H. pylori infection, 8.4 (2.9–24.1) for persons with a family history of ulcer, and 29.5 (6.1–143.9) for persons with both risk factors compared with persons without these risk factors. These results suggest strong, multiplicative contributions of both factors to the risk for peptic ulcer disease.

It has long been noted, that gastric and duodenal ulcers cluster within families. Studies of twins suggest that the observed familial aggregation is largely due to genetic factors, but common environmental factors also seem to play a major role [1].

Other well-known risk factors for peptic ulcer include smoking and use of nonsteroidal antiinflammatory drugs [2]. In recent years, infection with Helicobacter pylori has been identified as another strong risk factor [2–4]. Like peptic ulcer disease, H. pylori infection, which is typically acquired in early childhood, has been found to cluster within families [5–6]. Familial aggregation of infection may again be due to various pathways, including common genetic or environmental factors that increase susceptibility to infection [7–8], but also to intrafamilial transmission of the agent [9]. It is unclear, however, to what degree H. pylori infection may explain intrafamilial clustering of peptic ulcer disease. Furthermore, the joint contributions of H. pylori infection and family history of ulcer to the risk for peptic ulcer disease are unknown.

Herein, we assess the independent and joint contributions of H. pylori infection and family history of ulcer to the risk for peptic ulcer disease in an unselected sample of out-patients of a general practitioner in southern Germany.
Material and Methods

Study design and study population. A cross-sectional study was done among consecutive 15- to 79-year-old outpatients who visited the office of a general practitioner in Blaustein, a community of ~15,000 inhabitants located in southern Germany. Patients were recruited 3 days a week during usual office hours between June and September 1996. Patients were recruited without regard to the reason for their visit.

Of 531 eligible subjects, 501 (94.4%) agreed to participate in the study. The study was designed to address several questions, including the prevalence and risk factors for H. pylori infection, which are reported elsewhere [10], and the consequences of H. pylori infection. The current analysis concerning the impact of H. pylori infection and of family history on the risk for peptic ulcer is restricted to 299 adults who were 25–54 years of age. Patients <25 years old (n = 60) were excluded because none of these patients had a gastroscopically verified gastric or duodenal ulcer (GVU). Patients >55 years old (n = 142) were excluded to minimize eventual bias due to incomplete or inaccurate recall or ascertainment of family history of ulcer. In particular, parents of these patients would typically have been born between 1873 and 1923, and it is likely that diagnostic verification of peptic ulcers has been very poor throughout most of their lifetime.

Data collection. The field work was done by trained research assistants in a separate room in the general practice. Active infection with H. pylori was determined by use of the 13C-urea breath test. First, an initial breath sample was collected in a plastic bag. The patients then received 200 mL of apple juice (pH 2.2–2.4), which contained 75 mg of 13C-urea (Mass Trace, Woburn, MA). Thirty minutes later, a second breath sample was collected. The breath samples were analyzed using an isotope-selective, nondispersive infrared spectrometer (Wagner-Analytical Systems, Worpswede, Germany). A change of the 13CO2/12CO2 ratio over baseline of >5% was considered to indicate active infection. Sensitivities and specificities of the 13C-urea breath test close to 100% have consistently been reported, suggesting the test to be the reference standard in patients in whom endoscopy is not indicated [11, 12]. Although urea breath test results among H. pylori-positive patients are affected to some extent by food intake, the distinction between infected and uninfected patients is highly accurate even under nonfasting conditions [13].

Patients filled out a standardized questionnaire between collection of the first and second breath samples. They were asked if they ever had a GVU and whether their mother or father had a history of ulcer. The questionnaire also contained questions on sociodemographic factors and on other potential risk factors for peptic ulcer, such as cigarette smoking.

Statistical analysis. We compared the frequency of GVU among persons with a currently or previously treated H. pylori infection with the frequency among other persons, and we compared the frequency of GVU among persons with a family history of ulcer with the frequency among other persons. The individual and joint relationships of H. pylori infection and family history of ulcer with subjects’ lifetime history of GVU were quantified by crude and adjusted odds ratios (OR) and their 95% confidence intervals (CI). Adjustment was made for age, sex, and smoking by conditional multiple logistic regression. All analyses were done with the SAS statistical software package [14].

Results

The study sample included 191 women and 108 men with a mean age of 38.1 years. About one-third of the subjects were current smokers (33.6%), and about one-quarter were former smokers (25.2%).

Nineteen patients (6.4%) reported a lifetime history of GVU. Seventy-nine patients (26.4%) were either infected with H. pylori at the time of the examination (n = 70) or had been successfully treated for H. pylori infection in the past (n = 9). Forty-one patients (13.7%) reported that their father (n = 26), their mother (n = 12), or both (n = 3) had a physician-diagnosed gastric or duodenal ulcer.

The individual relationships of infection with H. pylori and of family history of ulcer with subjects’ lifetime history of GVU are shown in table 1. H. pylori infection was associated with an almost 4-fold increase in risk for GVU (adjusted OR, 3.8; 95% CI, 1.4–10.1). An even stronger relationship was seen between family history of peptic ulcer and subjects’ lifetime history of GVU (adjusted OR, 8.4; 95% CI, 2.9–24.1).

Table 2 shows the joint relationship of infection with H. pylori and family history of ulcer with subjects’ lifetime history of GVU. Lifetime prevalence of GVU ranged from 2.6% among persons without H. pylori infection and without family history of ulcer to 31.3% among persons with both risk factors.

Table 1. Individual relationships of infection with H. pylori and of family history of ulcer with gastroscopically verified ulcer (GVU).

<table>
<thead>
<tr>
<th></th>
<th>GVU, no. (%)</th>
<th>Crude</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection with H. pylori</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 220)</td>
<td>9 (4.1)</td>
<td>1.0’</td>
<td>1.0’</td>
</tr>
<tr>
<td>Yes* (n = 79)</td>
<td>10 (12.7)</td>
<td>3.4 (1.3–8.6)</td>
<td>3.8 (1.4–10.1)</td>
</tr>
<tr>
<td>Family history of ulcer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 258)</td>
<td>10 (3.9)</td>
<td>1.0’</td>
<td>1.0’</td>
</tr>
<tr>
<td>Yes (n = 41)</td>
<td>9 (22.0)</td>
<td>6.9 (2.6–18.2)</td>
<td>8.4 (2.9–24.1)</td>
</tr>
</tbody>
</table>

* Adjusted for sex, age (in years), and smoking (ever vs. never) by multiple logistic regression.

Reference category.

Includes 9 patients with GVU among 70 currently infected patients and 1 patient with GVU among 9 who were currently uninfected but who were previously treated for H. pylori infection.
The differences between the adjusted and the crude OR were mainly due to removal of confounding by sex, which was strongly related to peptic ulcer in this sample (adjusted OR for women vs. men, 0.19; 95% CI, 0.06–0.59). After sex had been controlled for, additional control for age and smoking did not materially affect the results.

**Discussion**

This study demonstrates that *H. pylori* infection and family history of peptic ulcer disease are strong, independent risk factors for peptic ulcer. If both factors are present, the risk for gastric or duodenal ulcer is increased to very high levels in an almost multiplicative manner.

Our result concerning the individual effect of infection with *H. pylori* on the risk for peptic ulcer is in close agreement with findings in previous studies [2]. Our estimate of the impact of family history of ulcer is somewhat higher than that found in most previous studies [1]. This may be due to several reasons. First, previous studies have not controlled for potential confounders. In our study, we controlled for covariates by multiple logistic regression, which strengthened the association between family history of ulcer and peptic ulcer among study participants. Second, previous studies have included older patients, among whom ascertainment of parental ulcer is likely to be far from complete. To minimize this problem, we excluded patients >55 years of age from the analysis. We feel confident about this decision, given that only 2.8% of patients >55 years old, compared with 13.7% of patients 25–54 years old, reported a physician-diagnosed gastric or duodenal ulcer among their parents.

To address the impact of excluding patients >55 years old, we carried out additional analyses in which these patients were included. These analyses showed the same pattern of multiplicative, independent associations of both *H. pylori* infection and family history with patients’ lifetime history of ulcer, but the estimate of the impact of family history was somewhat lower. This pattern would be consistent with underestimation of the impact of family history due to its incomplete ascertainment in studies including older subjects [15].

To our knowledge, this is the first study that addresses the joint effects of *H. pylori* infection and family history of ulcer. This issue is of particular interest, given that the mechanisms by which family history of ulcer increases disease risk are not fully understood. It would appear plausible that familial clustering of peptic ulcer disease may at least partly be mediated by *H. pylori* infection. In this study, however, family history of ulcer was a very strong risk factor for GVU even in the absence of *H. pylori* infection. These results suggest that *H. pylori* infection accounts for, at best, a rather minor share of the strong familial clustering of peptic ulcer disease. Our results also illustrate that *H. pylori* infection is a major risk factor for peptic ulcer whether familial predisposition does or does not exist.

In our study, the individual relationship of family history of ulcer with peptic ulcer disease was about twice as strong as the individual relationship of *H. pylori* infection with peptic ulcer disease. However, because *H. pylori* infection was about twice as common as family history of ulcer, it accounts for as large a share of peptic ulcers in this population as does a family history of the disease. This is of important clinical relevance since *H. pylori* infection, in contrast to family history of ulcer, offers possibilities for preventive or therapeutic intervention. In particular, the very high risk for peptic ulcer among *H. pylori*–positive persons with a family history of ulcer suggests that treatment of *H. pylori* infection may be worthwhile in this group even before the development of peptic ulcer. In this context, family history of ulcer may serve as a useful screening tool in deciding who to test and eventually treat for *H. pylori* infection.

**Acknowledgment**

We appreciate the help of A. Behr and his staff (general medical practice, Blaustein) in the conduct of this study.

**References**

8. Go MF, Graham DY. How does Helicobacter pylori cause duodenal ulcer disease: the bug, the host, or both? J Gastroenterol 1994;9:S8–S12.