Helicobacter pylori Antibodies in Areas of Italy at Varying Gastric Cancer Risk[1]

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Abstract

In a survey of 930 adults aged 35–74 years randomly sampled from the general population of four areas of Italy, two at low and two at high risk for gastric cancer, plasma levels of *Helicobacter pylori* IgG antibodies were assayed in order to investigate associations with the geographical distribution of gastric cancer and other dietary and life-style factors, as assessed by personal interview. *H. pylori* positivity (antibody titer above or equal to 10 μg/ml), 45% overall, increased with age and was inversely associated with social class but showed little geographical variation or association with dietary variables and blood nutrients. *H. pylori* positivity was also associated with increased blood levels of pepsinogens, particularly pepsinogen II. The authors discuss these findings in relation to those from a previous case-control study of gastric cancer in the same areas.

Introduction

Recently, infection with the bacterium *Helicobacter pylori* has been associated both with gastritis (1, 2) and with an increased risk of gastric cancer (3–6). Few studies, however, have been conducted to evaluate the determinants of the infection. In a previous paper (7), using blood pepsinogen (PG I and PG II)[3] levels as markers of CAG, we reported associations between food consumption, nutrient intake, plasma nutrient levels, and CAG among a representative sample of the adult population in four areas of Italy who participated in an epidemiological study to evaluate reasons for the marked geographic variation in GC within the country (8, 9). Herein we describe the relationship between these factors and *H. pylori* infection status, as assessed by IgG antibody levels, in the same random population sample.

Materials and Methods

Details of the study population, dietary and other interview data, and blood collection and analysis have been published elsewhere (10). Briefly, during 1985–1988, 1469 adults aged 35–74 years and randomly selected from the populations of four areas of Italy participated as controls in a multicenter epidemiological study to evaluate GC risk factors. The study areas included two with high death rates for GC Forlì/Imola and Florence, in central and northern Italy; and two with low death rates, Genoa in northern Italy and Cagliari in Sardinia. Among those contacted, 83% agreed to participate and were interviewed using a structured questionnaire seeking dietary and other information, and 73% also donated a blood sample. The mean age of the study population was 58.9 years, and 58% were males. The questionnaire recorded demographic, socioeconomic, residential, occupational, smoking, medical, family, and dietary information. Blood samples were collected and processed according to a rigid protocol, described elsewhere (7). One set of plasma aliquots was air-shipped on dry ice to the laboratory of University Diagnostics, Ltd. (London), where enzyme-linked immunosorbent assays for *H. pylori* IgG antibodies were carried out in duplicate according to the method of Newell *et al.* (11). Another was tested by radioimmunoassay at the Veterans Administration Medical Center (Sepulveda, CA) for plasma concentrations of PG I and PG II (12). Finally, a set of aliquots was assayed at Hoffmann-La Roche (Basel, Switzerland) for concentrations of carotene, retinol and α-tocopherol using a high-performance liquid chromatography method (13). In total, results of assays for fat-soluble vitamins, carotene, cholesterol, *H. pylori* antibodies, and pepsinogens were available for 930 who donated blood, together with the information from the questionnaire.

Received 3/31/92.

[1] Supported by the Consiglio Nazionale delle Ricerche Applied Project "Oncologia," Contracts 87.01506.44, 87.01581.44, and 87.1344.44; the U.S. National Cancer Institute, contract N01-CP-51019; the Instituto Oncologico Romagnolo, Forlì, Italy; Regione Emilia-Romagna, Italy; Osservatorio Epidemiologico Regione Toscana, Italy; the Imperial Cancer Research Fund, England; and the Lega Italiana per la Lotta Contro i Tumori, Rome, Italy. Presented in part at the Fourth Workshop on Gastroduodenal Pathology and *Helicobacter pylori*, Bologna, Italy, on November 28–30, 1991.

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[3] The abbreviations used are: PG I, PG II, pepsinogens I and II; CAG, chronic atrophic gastritis; GC, gastric cancer; OR, odds ratio; CI, confidence interval.

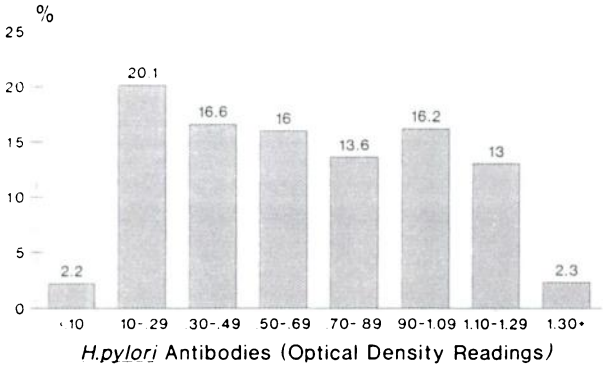

Fig. 1. Relative frequency distribution of *H. pylori* antibody titers as measured by absorbance readings.

H. pylori positivity was defined as an absorbance reading of 0.7 (corresponding to an IgG antibody titer of 10 μg/ml) or greater. This cutoff is consistent with that used in validation studies for this assay system and has been associated in other studies with high sensitivity and specificity for detecting individuals with *H. pylori* infection (14).

Stratified logistic regression models with *H. pylori* infection as the dependent variable were used to evaluate the odds ratios of *H. pylori* positivity (15, 16). All the models included terms for gender, age (in years), GC familial history (0, 1, or 2+ first-degree relatives affected), migration from southern Italy (yes/no), residence (urban/rural), body mass index (tertiles for Quetelet's index, weight (kg)/height (m^2), and social class (low, medium, and high). These variables had been used to adjust for potential confounding in the original case-control study of diet and GC (8, 9). CAG status (defined by PG levels) and previous gastric surgery (yes/no) were then added to the model, followed by the questionnaire-derived dietary variables. CAG status was estimated by plasma pepsinogen I and pepsinogen II values as: severe CAG, PG I ≤ 20 pg/liter; mild and moderate CAG, PG I > 20 pg/liter and a PG I:PG II ratio ≤ 2.9; and non-CAG, PG I > 20 pg/liter and PG I:PG II > 2.9.

Results

The distribution of *H. pylori* IgG antibody titers among the population sample is shown in Fig. 1. In 45% of the subjects, the values were equal to or greater than 10 μg/ml, which was defined as evidence of *H. pylori* infection. The distribution of antibody titers, however, was only weakly bimodal, with peaks at 0.10–0.29 and 0.90–1.09 absorbance reading units, and a sizable fraction had values close to the 0.70 cutoff point.

Table 1 presents the distribution of *H. pylori* positivity (antibody titer ≥ 10 μg/ml), according to sex, age, and other demographic variables. The infection rate was associated with increasing age. *H. pylori* did not vary significantly by sex, social class, urban/rural residence, or migration, although there was a mild gradient of lower risk with increasing social status and a higher prevalence among the minority of subjects who had migrated from southern to northern Italy. There was little difference in *H. pylori* prevalence between areas of high and low risk of GC. All 7 subjects who reported GC in at least two first-degree relatives were *H. pylori*-positive.

Table 1 Distribution of *H. pylori* positivity according to several demographic factors

Factor	*n*	*H. pylori* (*N*)	Positivity[a] (%)	OR[b]	95% CI
Gender					
Males	540	250	46.3	1.0	
Females	390	169	43.3	0.9	(0.7–1.2)
Age					
35–49	234	85	36.3	1.0	
50–64	335	156	46.6	1.5	(1.03–2.1)
65–74	361	178	49.3	1.6	(1.1–2.3)
Migration from south					
No	844	374	44.3	1.0	
Yes	86	45	52.3	1.5	(0.9–2.4)
Residence					
Urban	737	325	44.1	1.0	
Rural	193	94	48.7	1.1	(0.8–1.6)
Study area[c]					
Low GC risk	216	95	44.0	1.0	
High GC risk	714	324	45.4	1.1	(0.8–1.6)
Social class					
Low	561	269	47.9	1.0	
Medium	230	97	42.2	0.9	(0.6–1.2)
High	139	53	38.1	0.8	(0.5–1.2)
GC family history[d]					
0	831	373	44.9	1.0	
1	92	39	42.4	0.9	(0.6–1.4)
2+	7	7	100.0	∞	
Total	930	419	45.1		

[a] See text for definition of *H. pylori* positivity.
[b] ORs from logistic regression model including terms for each variable listed in the table.
[c] Low GC risk areas for Genoa and Cagliari; high GC risk areas for Florence, Imola, Forlì.
[d] The OR for all subjects with at least a first-degree relative affected by GC was 1.2 (0.8–1.7).

Table 2 shows mean PG levels according to *H. pylori* positivity. Mean levels of plasma PG I and PG II were significantly ($P < 0.01$) higher among those with positive *H. pylori* antibody titers. The excess was more evident for PG II levels than for PG I. The mean PG I:PG II ratio was 25% lower among those positive for *H. pylori*. Table 3 shows moderate and severe CAG prevalence (defined by PG levels) according to *H. pylori* positivity. Despite the lower average PG I:PG II ratios, severe CAG was somewhat less frequent in *H. pylori*-positive *versus* *H. pylori*-negative subjects (4.5% *versus* 6.9%). Moderate CAG, however, was more frequent in *H. pylori*-positive subjects (9.5% *versus* 3.7%). The adjusted ORs and 95% CI for severe and moderate CAG were 0.6 (0.3–1.04) and 2.5 (1.4–4.6), respectively, for *H. pylori*-positive subjects. Gastric surgery showed little relation to *H. pylori* positivity (43% of 21 resected *versus* 45% of 909 nonresected subjects).

Availability of freezers, use of frozen foods, and preference for salt and other diet-related variables, previously shown to be associated with gastric cancer, were not related to *H. pylori* positivity. The frequency of consumption of 17 food groups was not significantly associated with *H. pylori* positivity. There was no de-

Table 2 Mean plasma PG I, PG II, and PG I:PG II ratios according to *H. pylori* positivity

Helicobacter pylori[a]	*n*	%	PG I (pg/liter)	PG II (pg/liter)	PG I:PG II
Negative	511	54.9	75.2	10.9	8.1
Positive	419	45.1	82.3	15.7	6.1
Total	930	100.0	78.4	13.1	7.2

[a] See text for definition of *H. pylori* positivity.

Table 3 Prevalence of severe and moderate CAG according to *H. pylori* positivity

Helicobacter pylori	Severe CAG[a]		Moderate CAG[a]		Non-CAG[a]		Total	
	n	%	*n*	%	*n*	%	*n*	%
Negative	35	6.9	19	3.7	457	89.4	511	100.0
Positive	19	4.5	40	9.5	360	85.9	419	100.0
Total	54	5.8	59	6.3	817	87.9	930	100.0

[a] See text for definition of severe and moderate CAG and non-CAG and *H. pylori* positivity.

creasing trend with increasing fruit intake and only a mild increase with consumption of salted/dried fish.

The dietary intake of 13 nutrients was also evaluated, but only the index of vitamin C intake showed a positive association with *H. pylori* positivity, while no relationship was seen for the other nutrients, including alcohol (highest *versus* lowest tertile of intake: OR = 0.7; 95% CI, 0.5–1.4). No significant association with any plasma nutrient was found for *H. pylori* positivity.

Discussion

This study of 930 randomly selected subjects, representative of middle-aged adults of both sexes in several areas of Italy, revealed that age is a strong independent determinant of *H. pylori* infection, with prevalence rising with advancing years. *H. pylori* positivity was also more common among adults in lower social classes, although the effect was not as strong as reported by others (17, 18). In Peru, the prevalence of infection among children was also higher among those of lower social status and varied by source of drinking water (19). We found no strong dietary associations, except for an unexpected positive trend with vitamin C intake, which in view of the multiple comparisons made may be due to chance. The lack of association with diet has also been reported in a study comparing *H. pylori* seroprevalence in strict vegetarian Seventh-Day Adventists and other groups in the United States (20). Alcohol consumption has been associated with *H. pylori* infection of the gastric mucosa, in patients with or without liver cirrhosis (21), but we could not confirm this finding.

GC mortality rates differ between our study areas by about 3-fold, but *H. pylori* positivity did not correlate with GC risk. The percentage of positives was nearly the same in high-risk *versus* low-risk areas of Italy, in agreement with a recent survey in San Marino, reporting a high prevalence in subjects who had migrated from southern Italy (22). Areas in the southern part of the country show both lower GC rates and lower socioeconomic levels (23), but we found no appreciable difference in the prevalence of *H. pylori* positivity between regions, even after adjusting for social class. In contrast, in a recent survey in 65 rural counties in China, where GC mortality rates varied over 20-fold, there was a significant positive correlation between GC mortality and the prevalence of *H. pylori* positivity that remained after adjustment for other correlates of GC risk (24, 25). Furthermore, in Colombia the prevalence of *H. pylori* was 93% and 63% in areas with high and low GC incidence, respectively (17).

We found significantly elevated levels of plasma pepsinogens among those who were *H. pylori* antibody-positive. The relative increase was particularly evident for PG II. The finding is consistent with reports linking PG and *H. pylori* antibody levels among children in Costa Rica (26) and, with the marked reductions in PG II and minor declines in PG I, among patients whose *H. pylori* infection has been eradicated following therapy for the infection (27).

H. pylori infection of the gastric mucosa has been linked to the early stages of nonspecific chronic gastritis (2), but it is considered to be unrelated to the further progression of these lesions (28). Our findings of a higher prevalence of mild and moderate CAG and a lower prevalence of severe CAG among persons positive for *H. pylori* are consistent with these observations, despite our reliance on surrogate markers (plasma pepsinogen levels) as indicators of CAG. It may seem surprising that we could find no positive association between plasma antibodies to *H. pylori* and severe CAG, an important GC precursor that presumably evolves from mild or moderate CAG. It is possible, however, that extensive atrophy of the gastric mucosa, leading to low levels of PG I and low acidity, makes it difficult for *H. pylori* to survive in competition with other gastric-colonizing bacteria (29). In addition, *H. pylori* does not colonize areas of intestinal metaplasia in the stomach, a condition frequently associated with severe atrophy (30). Both of these factors could lead to a reduction of antibody titers over time. Thus, it is possible that some of the individuals we classified as *H. pylori*-negative may in fact have been infected in the past, but their current antibody titer was below the threshold value (10 μg/ml) we used to determine positivity. There is no doubt that serological assays for *H. pylori* IgG antibodies can be sensitive and specific tests for identifying infected individuals in most circumstances, but this might not be the case in subjects with severe CAG and low PG I. Others, however, have reported a strong correlation between *H. pylori* detection by morphological and/or culture techniques and presence of IgG antibodies, even among CAG patients, with a sensitivity higher than 90% (31). Our observed distribution of IgG antibody titers differed from the sharply bimodal distributions that might have been anticipated, where most values cluster around either very low or high values and few are in between. In contrast, we found a flatter bimodal distribution, with nearly one-third of the subjects having intermediate values.

For several years evidence has accumulated that *H. pylori* infection of the gastric mucosa is associated with risk of GC. A prospective study in Britain has shown that infection with *H. pylori* is related to a significant 3-fold increased risk of GC (3), while studies in California,

Hawaii, and Minnesota have indicated 3-6-fold increases of GC associated with elevated serum antibody levels (4-6). The causal nature of the relationship between *H. pylori* and GC requires clarification, but the strength and consistency of the association suggest that the infection may play an etiological role.

In summary, the prevalence of *H. pylori* positivity was not found to correlate with the geographic variation of GC in Italy, despite the growing suspicion that *H. pylori* is a risk factor for GC. However, our data provide evidence that age and to some extent social class, but not necessarily dietary factors, are determinants of *H. pylori* prevalence, and that *H. pylori* antibody and plasma pepsinogen II levels are highly correlated. Additional studies are needed to clarify risk factors for this common infection and its role in gastric carcinogenesis.

Acknowledgments

The authors would like to thank D. Newell for helpful comments, R. M. Salkeld for performing nutrient assays at Hoffmann-La Roche, Ltd. (Basel, Switzerland), and S. Pedley and K. Marks for performing *H. pylori* assays at University Diagnostics, Ltd. (London).

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