HELICOBACTER PYLORI INFECTION AND THE RISK OF GASTRIC CARCINOMA

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Abstract *Background.* Infection with *Helicobacter pylori* has been linked with chronic atrophic gastritis, an inflammatory precursor of gastric adenocarcinoma. In a nested case–control study, we explored whether *H. pylori* infection increases the risk of gastric carcinoma.

Methods. From a cohort of 128,992 persons followed since the mid-1960s at a health maintenance organization, 186 patients with gastric carcinoma were selected as case patients and were matched according to age, sex, and race with 186 control subjects without gastric carcinoma. Stored serum samples collected during the 1960s were tested for IgG antibodies to *H. pylori* by enzyme-linked immunosorbent assay. Data on cigarette use, blood group, ulcer disease, and gastric surgery were obtained from questionnaires administered at enrollment. Tissue sections and pathology reports were reviewed to confirm the histologic results.

Results. The mean time between serum collection and the diagnosis of gastric carcinoma was 14.2 years. Of the 109 patients with confirmed gastric adenocarcinoma (excluding tumors of the gastroesophageal junction), 84 percent had been infected previously with *H. pylori*, as compared with 61 percent of the matched control subjects (odds ratio, 3.6; 95 percent confidence interval, 1.8 to 7.3). Tumors of the gastroesophageal junction were not linked to *H. pylori* infection, nor were tumors in the gastric cardia. *H. pylori* was a particularly strong risk factor for stomach cancer in women (odds ratio, 18) and blacks (odds ratio, 9). A history of gastric surgery was independently associated with the development of cancer (odds ratio, 17; $P = 0.03$), but a history of peptic ulcer disease was negatively associated with subsequent gastric carcinoma (odds ratio, 0.2; $P = 0.02$). Neither blood group nor smoking history affected risk.

Conclusions. Infection with *H. pylori* is associated with an increased risk of gastric adenocarcinoma and may be a cofactor in the pathogenesis of this malignant condition. (N Engl J Med 1991;325:1127-31.)

GASTRIC carcinoma is estimated to be the world's second most common cancer.[1] Although the dramatic decline in the incidence of gastric carcinoma in the United States and Western Europe over the past 50 years has led some to proclaim an "unplanned triumph,"[2] in much of Latin America and Asia the incidence remains very high.[3,4]

Because the incidence of gastric carcinoma can change dramatically from place to place and from one generation to the next, it has been hypothesized that its incidence is determined largely by environmental rather than genetic factors.[5] From studies of migrants, it has further been inferred that the risk is increased by exposure to environmental factors in childhood.[6-8] One specific histologic type of gastric adenocarcinoma, the so-called intestinal type, is particularly prone to the regional and temporal variations of an environmentally related malignant condition[5,9]; the decrease in the incidence of stomach cancer in the United States has resulted primarily from a decline in the intestinal type of disease.[10] The incidence of the less common histologic type of adenocarcinoma, the diffuse type, varies less over time and according to geographic location, although it too has decreased in recent years.[11] Association of the diffuse type with blood-group A has suggested a genetic component to its genesis.

Until recently, research on environmental causes of gastric carcinoma focused primarily on diet. The recent identification of *Helicobacter pylori* (formerly *Campylobacter pylori*[12]) in chronic inflammatory conditions of the stomach, however, has stimulated interest in its potential role in carcinogenesis.[13-17] *H. pylori* has been linked to chronic atrophic gastritis, an established precursor of the intestinal type of gastric carcinoma.[18,19] It is not surprising then that several areas in the United States and other parts of the world that are associated with a high risk of gastric carcinoma also have a high prevalence of *H. pylori* infection, even among young children.[13-15] High rates of infection have also been found in patients with cancer or precancerous conditions,[17] and a case–control study found that patients with gastric carcinoma had a relative risk of *H. pylori* infection of 2.7 relative to healthy control subjects.[16] One study linked *H. pylori* with the intestinal type of disease more specifically.[20] These cross-sectional and retrospective investigations, however, provide only circumstantial evidence for a causal association between *H. pylori* and gastric carcinoma. A sequence more consistent with cause and effect — i.e., infection preceding cancer — has not been established.

Serologic tests for *H. pylori* have been developed by many investigators worldwide and have proved to be excellent tools for studies of the epidemiology of *H. pylori*.[21-23] As compared with endoscopy (in which infection is defined by either a positive culture or histologic staining), enzyme-linked immunosorbent assays (ELISAs) have proved to be sensitive and specific for the detection of active disease. These assays do not detect cross-reacting antibodies to *C. jejuni*, *Escherichia coli*, or *C. fetus*.[24,25] Although the concern remains that serologic results may reflect past rather than concurrent infection, there is no evidence to date that positive titers indicate anything but ongoing disease; persons

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with positive serologic results, including asymptomatic control subjects, have been confirmed to have active infections when gastric biopsy has been performed simultaneously. Serologic testing has proved so successful in identifying ongoing infection that it has been suggested that serologic analysis rather than biopsy be considered the gold standard for diagnosis.[26,27]

In the mid-1960s, the Kaiser Permanente Medical Care Program collected and froze serum from a large cohort of patients who received multiphasic health checkups. Using this cohort, we performed a nested case–control study to evaluate the association of the different types of gastric carcinoma with antecedent *H. pylori* infection as determined by ELISA.

Methods

Study Population

Between 1964 and 1969, serum for frozen storage was collected from 128,992 adult subscribers to the Kaiser Permanente Medical Care Program who had participated in the multiphasic health checkup, a comprehensive health examination.[28] Subsequently, the serum samples were shipped to and catalogued and maintained by the Orentreich Foundation for the Advancement of Science, as described previously.[29] Instances of hospitalization and tumor-registry reports of the participants in the multiphasic health checkup were monitored routinely, and cancer outcomes were recorded and usually verified by record review.

Between enrollment and October 1989, 246 participants were given a diagnosis of gastric carcinoma. Of these patients 200 were randomly selected as case patients. Each patient was matched according to age at serum donation (±12 months), sex, race, date of serum donation (±6 months), and site at which the multiphasic health checkup was performed (Oakland or San Francisco) to one of the participants in the multiphasic health checkup who did not have gastric carcinoma (the control subjects). History of cigarette use, ulcer disease, and gastric surgery before serum donation was obtained from questionnaires answered at the time of enrollment in the multiphasic health checkup. Gastric and duodenal ulcers were not distinguished on the questionnaire but were included together in the category "ulcer disease." Questionnaire data concerning cigarette use and ulcers have been validated previously.[30] Blood-group data were also obtained from records compiled for the multiphasic health checkup.

ELISA

Serum samples were tested by ELISA for *H. pylori* IgG. The high-molecular-weight cell-associated proteins from three strains of *H. pylori* eluted on an agarose A-5m column were used as the ELISA antigen, as described previously.[31] One microliter of serum, diluted 1:100, was used for each assay; peroxidase conjugate of antihuman IgG was diluted 1:1000. The threshold for a positive ELISA was set at twice the mean value obtained for 15 known negative controls. These 15 negative controls and 1 positive control were used to calibrate each run. In our laboratory, the assay had a sensitivity of 91 percent and a specificity of 98 percent for active gastric infection when tested on 74 control samples (22 positive and 52 negative) with biopsy-proved infection. All assays were done in duplicate on three separate days and were performed without knowledge of the case–control status or histologic results.

Histopathological Analysis

All biopsy reports and tissue specimens from the patients were reviewed for histologic features suggestive of tumor. If possible, the location of the tumor in the stomach was categorized into one of three groups: body or fundus, antrum or pylorus, or cardia. Because of their association with Barrett's esophagus,[32] adenocarcinomas of the gastroesophageal junction were categorized separately. Gastric adenocarcinomas were classified as either intestinal type or diffuse type according to the criteria of Lauren.[33] Tissue sections from metastases were assumed to have the same histologic features as the primary gastric tumor. Biopsy sections were not examined for *H. pylori* infection.

Statistical Analysis

After the serum analysis, epidemiologic, pathological, and serologic data were entered and analyzed with the EpiInfo (Centers for Disease Control, Atlanta) and Egret (Statistics and Epidemiology Research Corporation, Seattle) computer programs. Pairs of patients and control subjects were excluded from analysis if serum was not available from both members of the pair. Matched analysis was done with McNemar's chi-square test with 95 percent confidence intervals as described previously,[34] the paired t-test, and conditional logistic regression. Unmatched analyses among case patients were done with the chi-square test, the t-test, and logistic regression.

Results

Of the 200 eligible pairs of patients and control subjects, 186 (93 percent) had banked serum samples available from both members of the pair and were included in the analysis. As can be seen in Table 1, the patients and control subjects were closely matched. Gastric carcinoma was diagnosed a mean of 14.2 years after serum collection (range, 1 to 24).

Tissue sections and pathology reports were reviewed for 149 of the 186 patients (80.1 percent), and reports alone were reviewed for 13 (7.0 percent); 24 patients (12.9 percent) had no pathological confirmation of cancer (Table 2). Of the 162 cases for which some pathological information was available, 109 were adenocarcinomas of the stomach. Of the adenocarcinomas of the stomach, 74.3 percent were of the intestinal type. Sixty-eight occurred at a specific gastric site: 34 in the antrum or pylorus, 30 in the body or fundus, and 4 in the cardia. The remaining 41 tumors either were extensive and involved multiple sites or involved sites that could not be determined from the available data.

The epidemiologic features of cases of intestinal-type and diffuse-type cancers suggested that the likelihood of misclassification was low. The mean age of the patients with intestinal-type adenocarcinoma was 68.7 years, as compared with 65.6 years for patients with diffuse-type adenocarcinoma (P = 0.2). Seventy-three percent of the cases of intestinal-type cancer occurred in men, as compared with 61 percent of the cases of diffuse-type adenocarcinoma (P = 0.2). The matched odds ratio for type A blood in patients with intestinal-type adenocarcinoma was 1.1 (95 percent

Table 1. Demographic Characteristics of Patients and Control Subjects.

Characteristic	Patients (N = 186)	Controls (N = 186)
Mean age at enrollment — yr	53.7	53.7
Female — no. (%)	64 (34.4)	64 (34.4)
Race — no. (%)		
Asian	4 (2.2)	4 (2.2)
Black	35 (18.8)	35 (18.8)
White	147 (79.0)	147 (79.0)
H. pylori infection* — no. (%)	149 (80.1)	111 (59.7)

*Matched odds ratio, 2.65; 95 percent confidence interval, 1.64 to 4.28.

Table 2. Histologic Diagnoses of Cases.

TYPE OF TUMOR	NO. OF CASES (%)
Adenocarcinoma of stomach	109 (58.6)
Intestinal type	81 (43.5)
Diffuse type	28 (15.1)
Gastroesophageal-junction adenocarcinoma	27 (14.5)
Gastric lymphoma	11 (5.9)
Other*	7 (3.8)
Undetermined	8 (4.3)
No pathological results reviewed	24 (12.9)

*Includes two squamous-cell tumors of the esophagus, two leiomyomas, one ovarian cancer, one case of Ménétrier's disease, and one benign adenoma.

confidence interval, 0.6 to 2.2); the matched odds ratio in patients with diffuse-type disease was 2.0 (95 percent confidence interval, 0.6 to 6.6). The older age of the patients with intestinal cancer and the higher proportion of men are consistent with known epidemiologic features of intestinal-type disease, whereas the slight predominance of men and the association with type A blood are typical of diffuse disease.[2,9]

H. pylori infection was a risk factor for the development of both types of adenocarcinomas of the stomach (Table 3). The odds ratio for *H. pylori* infection was elevated considerably in adenocarcinomas of the antrum or pylorus (odds ratio, 7.0; 95 percent confidence interval, 0.9 to 56.9) and those of the body or fundus (odds ratio, 4.7; 95 percent confidence interval, 1.3 to 16.2). Only one of the four patients with adenocarcinoma in the cardia and one of the four matched control subjects were infected with *H. pylori*. *H. pylori* infection was not associated with tumors of the gastroesophageal junction. Although the elevated odds ratio in gastric lymphoma suggested a possible association with *H. pylori* infection, the number of cases was too small for an accurate analysis. Among the 32 pairs for whom histologic diagnosis could not be confirmed (because the results were indeterminate or no specimen was available for review), *H. pylori* infection was also significantly more common in the patients than in the control subjects (odds ratio, 5.5; 95 percent confidence interval, 1.2 to 24.8).

Data were stratified according to sex and race. *H. pylori* infection was a significant risk factor for adenocarcinoma in women but not in men (Table 4). In blacks, *H. pylori* infection appeared to be a more important risk factor for adenocarcinoma than in whites, but the wide confidence intervals overlapped. Neither blood group nor smoking history affected risk in conditional logistic-regression models.

Seven patients had undergone gastric surgery before serum samples were obtained, and a total of 22 participants (8 patients and 14 control subjects) (matched odds ratio, 0.4; 95 percent confidence interval, 0.1 to 1.3) had a history of peptic ulcer disease before their initial multiphasic health checkup, although the sites of the ulcers were not ascertained. All 7 patients who had undergone gastric surgery and 21 of the 22 subjects with ulcers (95.5 percent) were seropositive for *H. pylori*. In a conditional logistic-regression model of all pairs of participants except the seven containing patients with nongastric cancers, *H. pylori* infection (odds ratio, 2.7; $P<0.001$) and gastric surgery (odds ratio, 16.8; $P = 0.03$) were independent risk factors for cancer, whereas peptic ulcer disease was negatively associated with the subsequent development of cancer (odds ratio, 0.2; $P = 0.02$). For adenocarcinoma, ulcer disease ($n = 21$) remained negatively associated with cancer (odds ratio, 0.2; $P = 0.05$) whereas *H. pylori* infection remained a risk factor (odds ratio, 3.8; $P<0.001$). For adenocarcinoma, the number of patients who had undergone gastric surgery was small ($n = 4$), and the increased odds ratio was not significant (odds ratio, 7.9; $P = 0.1$).

DISCUSSION

Chronic inflammation, with or without infection, has been causally linked to the development of cancer. Examples include vesicular schistosomiasis and bladder cancer, inflammation caused by draining sinus tracts and squamous-cell carcinoma, and ulcerative colitis and colon cancer. Our study demonstrated a strong association between infection with *H. pylori* — an organism that uniformly causes gastric inflammation — and gastric adenocarcinoma. Persons seropositive for *H. pylori* were approximately three times more likely to have gastric adenocarcinoma in the ensuing 1 to 24 years of follow-up than were control subjects matched for age, sex, and race.

On the basis of previous studies[20,35] and the known epidemiologic features of gastric adenocarcinoma,[2,5,9-11] we suspected that intestinal-type cancer but not the diffuse type would be linked to *H. pylori*. This proved not to be the case: *H. pylori* was associated with an increased risk for all adenocarcinomas, whether diffuse or intestinal, and whether located in the body of the stomach or in the antrum. Although it is possible that some misclassification of the type of tumor led to this finding, the characteristics of the patients with these two histologic types of cancer were consistent with previously described epidemiologic features and did not suggest misclassification. In contrast, tumors of the gastroesophageal junction, which frequently arise from the abnormal mucosa in Barrett's esopha-

Table 3. Association of *H. pylori* with Different Types of Gastric Tumor.

TYPE OF TUMOR	NO. OF PAIRS*	PATIENTS INFECTED	CONTROLS INFECTED	MATCHED ODDS RATIO	95% CONFIDENCE INTERVAL
		percent			
Adenocarcinoma	109	84.4	60.6	3.6	1.8–7.3
Intestinal type	81	82.7	59.3	3.1	1.5–6.6
Diffuse type	28	89.2	64.3	8.0	1.0–64.0
Gastroesophageal-junction tumor	27	63.0	70.4	0.8	0.3–2.1
Gastric lymphoma	11	90.9	63.6	4.0	0.5–35.8

*Each pair consisted of a patient and a control subject.

Table 4. Stratified Analysis of the Association of *H. pylori* with Adenocarcinoma.*

Stratification Group	No. of Pairs†	Patients Infected	Controls Infected	Matched Odds Ratio	95% Confidence Interval
		percent			
Sex					
Female	33	90.9	39.4	18.0	2.4–134.8
Male	76	81.6	69.7	2.0	0.9–4.5
Race‡					
Black	27	96.3	66.7	9.0	1.1–71.0
White	79	79.7	58.2	2.9	1.4–6.2

*Includes intestinal-type and diffuse-type adenocarcinomas of the stomach.
†Each pair consisted of a patient and a control subject.
‡Excludes three Asians with adenocarcinoma.

gus, were not linked to *H. pylori* infection. Therefore, we conclude that *H. pylori* infection is associated with an increased risk of all gastric adenocarcinomas that occur distal to the cardia.

It is possible that an unidentified factor increases susceptibility both to *H. pylori* infection and to gastric carcinoma and that *H. pylori* might just be a marker for an increased risk of cancer. *H. pylori*, however, is a plausible pathophysiologic cofactor for cancer. Several potential mechanisms can be postulated: metabolic products of the organisms directly transform the mucosa; rapid turnover of cells resulting from infection-related injury increases the risk of DNA damage, predisposing the mucosa to transformation by ingested or endogenous mutagens; and endogenous byproducts of inflammation, such as superoxide and hydroxyl ions, cause oxidative damage, mutation, and malignant transformation.[36] These mechanisms are not mutually exclusive, and a combination of mechanisms is likely.

It is clear, however, that infection with *H. pylori* alone cannot explain the pathogenesis of gastric carcinoma. *H. pylori* infection is extraordinarily common, affecting approximately 50 percent of North American adults who are older than 50 years, and in some developing nations it affects almost all adults.[37] Only a very small percentage of infected persons will ever have gastric carcinoma. There must be other critical cofactors affecting risk, cofactors that may also explain the difference in risk between blacks and whites and between men and women. Possible cofactors are age at the onset of infection, diet, and differences in gastric acidity.

We hypothesize that in order to increase the risk of cancer, *H. pylori* infection must begin in childhood. Spontaneous cures of *H. pylori* infection have not been documented, and it is likely that infection acquired early persists throughout life.[38] Studies of migrants have reported that the risk of gastric carcinoma is determined in childhood.[6-8] There are few other environmental factors, besides *H. pylori* infection, that can retain their effect over a lifetime. Decades of inflammation and exposure of dividing stem cells to inflammatory or exogenous mutagens might provide sufficient time for multiple mutations and malignant transformation.

Diet may also have an important effect on the risk of cancer. Dietary factors that have been suspected to increase risk, such as nitrates, carbohydrates, and salt, could potentially amplify the risk of mutation beyond that due to inflammation alone. Proposed protective dietary components, such as fresh vegetables and fruits,[7,39,40] probably exert their effects through vitamins A, C, and E, dietary antioxidants that might limit inflammation-related oxidative damage.[7,27]

As has been previously reported,[41] gastric surgery was an independent risk factor for cancer. The negative association with peptic ulcer disease, however, was unanticipated. In the light of the close association of *H. pylori* infection with both ulcer disease and gastric carcinoma, one would expect ulcer disease and gastric carcinoma to be directly, rather than inversely, related. It is possible that cofactors in the pathogenesis of *H. pylori*–related ulcer disease protect against the subsequent development of gastric carcinoma. For example, acid might be necessary for peptic ulcer disease to occur but might inhibit gastric carcinogenesis. Similarly, ulcer disease might reflect the occurrence of an acute infection in adulthood and the absence of a chronic infection in childhood. Alternatively, treatment of ulcer disease may impart protection against gastric carcinoma. If the inverse relation between ulcer disease and cancer is corroborated, important clues to the pathogenesis of carcinoma may be uncovered.

Gastric carcinoma remains a major killer worldwide. Crude etiologic-fraction calculations of data from this study suggest that 60 percent of gastric adenocarcinomas are attributable to infection with *H. pylori;* this implies that 60 percent of the cases of cancer would disappear if *H. pylori* did not exist. *H. pylori* infection is both readily diagnosed and curable. Whether eradication of gastric infection would actually decrease the risk of cancer, however, remains to be seen. Even if elimination of the organism is found to affect the risk of cancer, indiscriminate treatment of all infected persons is unlikely to be a practical, cost-effective approach to reducing the incidence of this uncommon cancer. Populations considered to be at particularly high risk, however, might benefit from screening for *H. pylori* infection, treatment, palliation (e.g., with antioxidant vitamins), or preventive measures. To define high-risk populations further, epidemiologic and laboratory studies are needed to explore interactions of *H. pylori* infection with potential cofactors for cancer.

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References

1. Parkin DM, Laara E, Muir CS. Estimates of the worldwide frequency of sixteen major cancers in 1980. Int J Cancer 1988;41:184-97.
2. Howson CP, Hiyama T, Wynder EL. The decline in gastric cancer: epidemiology of an unplanned triumph. Epidemiol Rev 1986;8:1-27.
3. Parkin DM. Cancer occurrence in developing countries. Lyon, France: International Agency for Research on Cancer, 1986. (IARC scientific publications no. 75.)
4. Muir C, Waterhouse J, Mack T, Powell J, Whelan S, eds. Cancer incidence in five continents. Vol. 5. Lyon, France: International Agency for Research on Cancer, 1987. (IARC scientific publications no. 88.)

5. Correa P, Haenszel W. Epidemiology of gastric cancer. In: Correa P, Haenszel W, eds. Epidemiology of cancer of the digestive tract. The Hague, the Netherlands: Martinus Nijhoff, 1982:58-84.
6. Correa P, Cuello C, Duque E. Carcinoma and intestinal metaplasia of the stomach in Colombian migrants. J Natl Cancer Inst 1970;44:297-306.
7. Haenszel W, Kurihara M, Segi M, Lee RKC. Stomach cancer among Japanese in Hawaii. J Natl Cancer Inst 1972;49:969-88.
8. Armijo R, Orellana M, Medina E, Coulson AH, Sayre JW, Detels R. Epidemiology of gastric cancer in Chile. I — case-control study. Int J Epidemiol 1981;10:53-6.
9. Munoz N, Correa P, Cuello C, Duque E. Histologic types of gastric cancer in high- and low-risk areas. Int J Cancer 1968;3:809-18.
10. Munoz N, Connelly R. Time trends of intestinal and diffuse types of gastric cancer in the United States. Int J Cancer 1971;81:58-64.
11. Sipponen P, Jarvi O, Kekki M, Siurala M. Decreased incidences of intestinal and diffuse types of gastric cancer in Finland during a 20-year period. Scand J Gastroenterol 1987;22:865-71.
12. Goodwin CS, Armstrong JA, Chilvers T, et al. Transfer of *Campylobacter pylori* and *Campylobacter mustelae* to *Helicobacter* gen. nov. as *Helicobacter pylori* comb. nov. and *Helicobacter mustelae* comb. nov., respectively. Int J Syst Bacteriol 1989;39:397-405.
13. Forman D, Sitas F, Newell DG, et al. Geographic association of *Helicobacter pylori* antibody prevalence and gastric cancer mortality in rural China. Int J Cancer 1990;46:608-11.
14. Fox JG, Correa P, Taylor NS, et al. *Campylobacter pylori*-associated gastritis and immune response in a population at increased risk of gastric carcinoma. Am J Gastroenterol 1989;84:775-81.
15. Jaskiewicz K, Louwrens HD, Woodroof CW, van Wyk MJ, Price SK. The association of *Campylobacter pylori* with mucosal pathological changes in a population at risk for gastric cancer. S Afr Med J 1989;75:417-9.
16. Talley NJ, Zinsmeister AR, DiMagno EP, et al. Gastric adenocarcinoma and *Helicobacter pylori* infection. J Natl Cancer Inst (in press).
17. Scott N, Lansdown M, Diament R, et al. *Helicobacter* gastritis and intestinal metaplasia in a gastric cancer family. Lancet 1990;335:728.
18. Correa P, Haenszel W, Cuello C, et al. Gastric precancerous process in a high risk population: cohort follow-up. Cancer Res 1990;50:4737-40.
19. Correa P, Cuello C, Duque E, et al. Gastric cancer in Colombia. III. Natural history of precursor lesions. J Natl Cancer Inst 1976;57:1027-35.
20. Parsonnet J, Vandersteen D, Goates J, Sibley RK, Pritikin J, Chang Y. *Helicobacter pylori* in intestinal- and diffuse-type gastric adenocarcinomas. J Natl Cancer Inst 1991;83:640-3.
21. Goodwin CS, Blincow E, Peterson G, et al. Enzyme-linked immunosorbent assay for *Campylobacter pyloridis*: correlation with presence of *C. pyloridis* in the gastric mucosa. J Infect Dis 1987;155:488-94.
22. Hirschl AM, Pletschette M, Hirschl MH, Berger J, Stanek G, Rotter ML. Comparison of different antigen preparations in an evaluation of the immune response to *Campylobacter pylori*. Eur J Clin Microbiol Infect Dis 1988; 7:570-5.
23. Perez-Perez GI, Dworkin BM, Chodos JE, Blaser MJ. *Campylobacter pylori* antibodies in humans. Ann Intern Med 1988;109:11-7.
24. Perez-Perez GI, Taylor DN, Bodhidatta L, et al. Seroprevalence of *Helicobacter pylori* infections in Thailand. J Infect Dis 1990;161:1237-41.
25. Faulde M, Putzker M, Mertes T, Sobe D. Evaluation of an immunofluorescence assay for specific detection of immunoglobulin G antibodies directed against *Helicobacter pylori* and antigenic cross-reactivity between *H. pylori* and *Campylobacter jejuni*. J Clin Microbiol 1991;29:323-7.
26. Morris A, Ali MR, Brown P, Lane M, Patton K. *Campylobacter pylori* infection in biopsy specimens of gastric antrum: laboratory diagnosis and estimation of sampling error. J Clin Pathol 1989;42:727-32.
27. Strauss RM, Wang TC, Kelsey PB, et al. Association of *Campylobacter pylori* infection with dyspeptic symptoms in patients undergoing gastroduodenoscopy. Am J Med 1990;89:464-9.
28. Collen JF, Davis LF. The multitest laboratory in health care. J Occup Med 1969;11:355-60.
29. Friedman GD, Blaner WS, Goodman DS, et al. Serum retinol and retinol-binding protein levels do not predict subsequent lung cancer. Am J Epidemiol 1986;123:781-9.
30. Friedman GD, Siegelaub AB, Selzer CC. Cigarettes, alcohol, coffee and peptic ulcer. N Engl J Med 1974;290:469-73.
31. Evans DJ, Evans DG, Graham DY, Klein PD. A sensitive and specific serologic test for detection of *Campylobacter pylori* infection. Gastroenterology 1989;96:1004-8.
32. Garewal HS, Sampliner R. Barrett's esophagus: a model premalignant lesion for adenocarcinoma. Prev Med 1989;18:749-56.
33. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. Acta Pathol Microbiol Scand 1965; 64:31-49.
34. Robins J, Greenland S, Breslow NE. A general estimator for the variance of the Mantel-Haenszel odds ratio. Am J Epidemiol 1986;124:719-23.
35. Loffeld RJLF, Willems I, Flendrig JA, Arends JW. *Helicobacter pylori* and gastric carcinoma. Histopathology 1990;17:537-41.
36. Ames BN, Gold LS. Too many rodent carcinogens: mitogenesis increases mutagenesis. Science 1990;249:970-1.
37. Parsonnet J. The epidemiology of *C. pylori*. In: Blaser MJ, ed. *Campylobacter pylori* in gastritis and peptic ulcer disease. New York: Igaku-Shoin, 1989:51-60.
38. Rauws EAJ, Tytgat GNJ. Natural history of *C. pylori* infection. In: Blaser M, ed. *Campylobacter pylori* in gastritis and peptic ulcer disease. New York: Igaku-Shoin, 1989:187-93.
39. Buiatti E, Palli D, Decarli A, et al. A case-control study of gastric cancer and diet in Italy. II. Association with nutrients. Int J Cancer 1990;45:896-901.
40. Correa P, Cuello C, Fajardo LF, Haenszel W, Bolanos O, de Ramirez B. Diet and gastric cancer: nutrition survey in a high-risk area. J Natl Cancer Inst 1983;70:673-8.
41. Correa P. Clinical implications of recent developments in gastric cancer pathology and epidemiology. Semin Oncol 1985;12:2-10.