

# *Helicobacter pylori* Seropositivity and Subsite-Specific Gastric Cancer Risks in Linxian, China

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**Background:** *Helicobacter pylori* carriage (i.e., persistent exposure to the organism without gastric epithelial cell invasion) is an established risk factor for noncardia gastric cancer. However, its association with the risk of cancer of the gastric cardia is controversial. Consequently, we designed this prospective, nested case-control study to further explore the subsite-specific gastric cancer risks associated with *H. pylori* seropositivity (a surrogate marker for persistent exposure). **Methods:** A total of 99 patients with gastric cardia cancer, 82 patients with noncardia gastric cancer, and 192 cancer-free subjects were selected from among the participants (n = 29 584) of a nutrition intervention trial previously conducted in Linxian, China. *H. pylori* seropositivity was determined by assaying for the presence of *H. pylori* whole cell and CagA antibodies in baseline serum samples from all subjects. Seropositivity was defined as one or both serum assays being positive. Odds ratios (ORs) for subsite-specific gastric cancer were estimated by multivariate logistic regression analyses. All statistical comparisons were two-sided ( $\alpha = .05$ ). **Results:** *H. pylori* seropositivity rates for subjects with gastric cardia cancer, noncardia gastric cancer, and gastric cardia and noncardia cancers combined were 70% ( $P = .02$ ), 72% ( $P = .01$ ), and 71% ( $P = .003$ ) compared with 56% for cancer-free control subjects. OR estimates for *H. pylori* seropositivity were 1.87 (95% confidence interval [CI] = 1.10 to 3.17) for gastric cardia cancer, 2.29 (95% CI = 1.26 to 4.14) for noncardia gastric cancer, and 2.04 (95% CI = 1.31 to 3.18) for gastric cardia and noncardia cancers combined. **Conclusions:** *H. py-*

*lori* seropositivity was associated with increased risks for both gastric cardia cancer and noncardia gastric cancer in this well-characterized cohort. Thus, *H. pylori* carriage may increase the risk of cancer throughout the stomach. [J Natl Cancer Inst 2001;93:226-33]

*Helicobacter pylori* colonizes approximately one half of the world's population (1). Since its initial isolation in 1983 (2), *H. pylori* has been associated with a broad spectrum of gastrointestinal diseases. A large body of evidence supports a causative role for *H. pylori* in chronic gastritis (3). According to one widely accepted model of gastric carcinogenesis, chronic gastritis is an early-stage precursor lesion for gastric adenocarcinoma (4). Extensive data support an association between *H. pylori* seropositivity and an increased risk of gastric cancer (5-7). In 1994, the International Agency for Research on Cancer recognized *H. pylori* as a class I human carcinogen (8). Additional support for this classification has since been demonstrated in animal model systems (9,10).

Several groups have attempted to clarify the magnitude of the association between *H. pylori* carriage (persistent exposure to the organism without gastric epithelial cell invasion) and gastric cancer risk by conducting meta-analyses of existing data. In one report of 19 cohort and case-control studies (2491 case patients and 3959 control subjects), Huang et al. (5) calculated a pooled odds ratio (OR) of 1.9 (95% confidence interval [CI] = 1.3 to 2.8) for seropositive subjects relative to seronegative subjects. With the use of slightly different study selection criteria, Danesh (6) derived a risk ratio of 2.5 (95% CI = 1.9 to 3.4) from 10 prospective investigations. Eslick et al. (7) analyzed 42 studies, in which a variety of *H. pylori* detection methods were used, and found an overall OR of 2.0 (95% CI = 1.7 to 2.5). With regard to attributable rather than relative risk, Parkin et al. (11) have suggested that 42% of the global gastric cancer burden may be ascribed to *H. pylori*.

Although the procarcinogenic potential of *H. pylori* carriage is seemingly well established, its relationship with gastric cardia cancer risk is controversial. The purpose of this study was to investigate further the subsite-specific risks between *H. pylori* seropositivity, as a surrogate marker for persistent exposure, and gastric cancer in a well-characterized, pro-

spectively followed population. In addition, we sought to determine whether certain strains of *H. pylori* are more strongly associated with gastric cancer risk in this subject cohort by measuring both whole-cell antibodies (referred to as *H. pylori* immunoglobulin G [IgG] antibodies) and CagA antibodies for all study participants.

## SUBJECTS AND METHODS

All phases of this study were approved by the appropriate Institutional Review Boards at the U.S. National Cancer Institute (Bethesda, MD) and the Cancer Institute of the Chinese Academy of Medical Sciences (Beijing, Peoples' Republic of China), and subjects provided written informed consent.

## Study Design

Details of the Linxian General Population Trial have been described previously (12). Briefly, 29 584 subjects were recruited from March through May 1985. Individuals with a known history of cancer were excluded. All enrolled study participants provided a 10-mL venipuncture sample 9-12 months before they started taking nutritional supplements (March 1986). After collection, serum specimens were separated, distributed into aliquots, and stored frozen for future analyses. Local healthcare providers recorded cancer incidence and mortality data at monthly intervals throughout the intervention period. Periodic surveys were conducted to verify completeness and accuracy of the medical information. Outcomes for the present study were based on follow-up data through May 1991 (6-6.25 years after baseline blood was drawn; 5.25 years after the start of the nutritional supplements). Demographic and lifestyle variables of interest, including height, weight, tobacco use, alcohol consumption, family cancer history, and primary water supply, were obtained from a preintervention questionnaire and physical examination. Intervention groups were categorized by randomized assignments from the General Population Trial: group A = retinol and zinc; group B = riboflavin and niacin; group C = ascorbic acid and molybdenum; and group D =  $\beta$ -carotene,  $\alpha$ -tocopherol, and selenium.

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## Case and Control Subjects

Details regarding case ascertainment for the Linxian General Population Trial have been reported previously (12). By the end of the 5.25-year intervention period, in the General Population Trial, 435 subjects had been diagnosed with incident gastric cardia cancer, 104 had developed noncardia gastric cancer, and 26 951 were alive and cancer free (of the original 29 584 enrolled subjects, there were 1335 deaths unrelated to cancer and 1298 incident cancers diagnosed). Of the 435 subjects with gastric cardia cancer, 100 were randomly selected, within six strata defined by sex and age ( $\leq 50$ , 51–60, and  $>60$  years). One selected gastric cancer case patient had inadequate serum, so 99 patients with gastric cancer were used for these analyses. Of the 104 patients with noncardia gastric cancer, all 82 with adequate serum samples were analyzed. From among the 26 951 subjects alive and cancer free at the end of the intervention period, 200 control subjects who were frequency matched within the six age and sex strata to the gastric cardia cancer case patients were selected randomly. Of these, 192 had adequate serum and their data were analyzed. Demographic, lifestyle, and intervention group variables did not show a statistically significant difference between the selected and nonselected case patients with gastric cardia cancer, the selected and nonselected control subjects, or the selected subjects with adequate and inadequate serum (data not shown).

A committee of experienced gastrointestinal pathologists, cytopathologists, and radiologists from the United States and China reviewed the diagnostic tissue specimens, cytology samples, and x-rays from all clinically suspected malignancies and confirmed or refuted each diagnosis by consensus opinion. Histologic diagnoses of adenocarcinoma were available for the large majority of case patients with gastric cancer (70%). The remaining gastric cancers were diagnosed as adenocarcinomas based on balloon cytology specimens. Adenocarcinoma subtype (intestinal or diffuse) was not recorded routinely. Cancers were localized to the gastric cardia, which was defined as the most proximal 3 cm of the stomach (13), by barium x-ray, esophagogastroduodenoscopy, or surgical resection in 97 (98%) case patients. Two case patients with adenocarcinoma diagnosed by balloon cytology were ascribed to the gastric cardia, because this screening method samples the proximal but not the distal gastric mucosa (14). Noncardia gastric cancers were defined as adenocarcinomas originating from mucosal regions outside of the cardia and were typically localized from surgically resected tissues. Gastric cancer staging information was not routinely recorded as part of the Linxian General Population Trial, so these data were not available for analysis in the present study.

The mean ( $\pm$  standard deviation), median, and range for time to gastric cancer diagnosis from the start of the intervention trial was 2.94 ( $\pm 1.56$ ), 2.84, and 0.93–5.24 years for patients with gastric cardia adenocarcinoma and 2.08 ( $\pm 1.48$ ), 1.81, and 0.04–5.13 years for patients with noncardia gastric adenocarcinoma. Patients with gastric cardia cancer and cancer-free control subjects had similar age and sex distributions, as expected from the matching criteria used. Patients with noncardia gastric cancer were slightly older (median age, 60 years) than control subjects (55 years;  $P = .02$ ), and there was a higher

percentage of men (77%) with noncardia gastric cancer than among control subjects (51%;  $P < .001$ ). Tobacco use and alcohol consumption were reported by 0% and 10% of women, respectively. Therefore, subsequent analyses on the basis of these two variables were restricted to men only.

## Serologic Assays

*H. pylori* serum antibodies were measured by experienced laboratory technicians who were unaware of the subjects' case-control status. Antibodies to the whole-cell antigen preparation (IgG immunoglobulin class) were detected with an *H. pylori*-specific enzyme-linked immunosorbent assay (ELISA), as described previously (15). Antibodies to the CagA antigen (IgG immunoglobulin class) were measured with an ELISA based on a purified recombinant truncated protein (16). Both of these assays have been validated previously by use of Chinese sera (17–19). Serum samples were assayed in duplicate, with the results expressed as optical density ratios relative to simultaneously analyzed laboratory standards. Positive results were interpreted as an optical density ratio greater than or equal to 1.0 for the whole-cell antigen assay and an optical density ratio greater than or equal to 0.35 for the CagA antigen assay. When two assayed aliquots provided an indeterminate result (i.e., the values straddled the seropositivity threshold), additional aliquots were analyzed and the average of all results (excluding obvious outliers) was used to determine serologic status. Both serum assays were performed for all subjects to allow independent assessments of whole-cell antibodies and CagA antibodies in association with the gastric cancer outcomes. Serum samples were analyzed in a sequence designed to minimize potential biases introduced by variation in the assay measurements over time and across batches. Specifically, within every 10 samples, each case sample was grouped with a control sample from the same sex-age stratum. Samples from cardia and noncardia cancer patients from all six strata were intermixed throughout the total serum set. One of 42 quality-control specimens, which consisted of pooled serum from Linxian residents, was also included randomly within every group of 10 subject samples. On the basis of the quality-control specimens, the mean, standard deviation, and coefficient of variation were 1.83%, 0.26%, and 14.2%, respectively, for the whole-cell assay and 0.15%, 0.04%, and 26.7% for the CagA assay.

## Statistical Analyses

Demographic and serologic variables, including age at onset of the intervention trial ( $\leq 50$ , 51–60, or  $>60$  years), sex, body mass index [(weight in kg)/(height in m)<sup>2</sup>] (in quartiles), educational level (no formal schooling, primary school, or middle school or beyond), tobacco use (never smoker or ever smoker for at least 6 months), alcohol consumption (never or rarely, only occasionally, or at least monthly), family cancer history (none or any), primary water supply (central village source or piped into home), intervention group assignment (A, B, C, and D as dichotomous but nonmutually exclusive variables), and *H. pylori* antibody status (positive or negative, based on the whole-cell assay and CagA assay results individually or combined), were compared between and across subject subgroups by use of the  $\chi^2$  test. Ordinal variables were compared be-

tween subject subgroups by using a Wilcoxon rank-sum test modified to test for trend (20). Logistic regression models were fit to estimate ORs as a measure of risk of gastric adenocarcinoma by anatomic subsite based on the predictor variables listed above. Terms for the sampling variables (age and sex) were included in all logistic regression models. When added separately to the age- and sex-adjusted risk models for gastric cardia and noncardia gastric cancer, respectively, none of the baseline demographic or lifestyle variables, including body mass index ( $P = .45$ ;  $P = .41$ ), educational level ( $P = .22$ ;  $P = .52$ ), tobacco use ( $P = .14$ ;  $P = .35$ ), alcohol consumption ( $P = .60$ ;  $P = .88$ ), family history of cancer ( $P = .68$ ;  $P = .52$ ), and primary water supply ( $P = .52$ ;  $P = .96$ ), were statistically significant. With reference to intervention group assignment, subjects randomly assigned to group D had a borderline statistically significant reduction in gastric cardia cancer risk ( $P = .06$ ), and subjects randomly assigned to group A had a statistically significant reduction in noncardia gastric cancer risk ( $P = .02$ ), in keeping with the overall results from the General Population Trial (12). Statistical calculations were performed with STATA computer software, version 5.0 (Stata Corporation, College Station, TX). All  $P$  values reported are from two-sided tests ( $\alpha = .05$ ).

## RESULTS

In total, 212 (57%) subjects had whole-cell *H. pylori* antibodies and 125 (34%) had CagA antibodies. On the basis of the four strata of assay result combinations, 102 (27%) subjects had both whole-cell antibodies and CagA antibodies, 110 (29%) had whole-cell antibodies without CagA antibodies, 23 (6%) had CagA antibodies without whole-cell antibodies, and 138 (37%) did not have either whole-cell or CagA antibodies. Defined as either or both assay results positive versus both assay results negative, *H. pylori* serum antibodies were detected in 235 (63%) subjects. None of the demographic, lifestyle, or intervention group assignment variables were statistically significantly associated with *H. pylori* exposure status, with the exception of sex and CagA antibodies ( $P = .001$ ; Table 1). Whole-cell seropositivity and CagA seropositivity were each more prevalent among case patients than among control subjects (Table 2). Whole-cell seropositivity rates were 63% for case patients with gastric cardia cancer ( $P = .07$ ), 62% for case patients with noncardia gastric cancer ( $P = .11$ ), and 62% for case patients with gastric cardia and noncardia cancer combined ( $P = .03$ ) versus 52% for control subjects. CagA seropositivity rates were 39% for case patients with gastric cardia cancer ( $P = .08$ ), 37% for case patients with noncardia gastric cancer ( $P = .23$ ), and 38% for case patients with gastric cardia and

**Table 1.** *Helicobacter pylori* serum assay results by baseline characteristics of the study population

Characteristic	No.*	Serum assay results		
		Whole-cell seropositive, No. (%)	CagA seropositive, No. (%)	Whole-cell and/or CagA seropositive, No. (%)
Age, y				
≤50	106	63 (59)	35 (33)	68 (64)
51–60	124	73 (59)	43 (35)	83 (67)
>60	143	76 (53)	47 (33)	84 (59)
Sex				
Women	164	97 (59)	70 (43)	109 (66)
Men	209	115 (55)	55 (26)†	126 (60)
Body mass index‡				
Quartile 1 (median = 19.3 kg/m <sup>2</sup> )	93	53 (57)	29 (31)	59 (63)
Quartile 2 (median = 20.7 kg/m <sup>2</sup> )	93	55 (59)	33 (35)	60 (65)
Quartile 3 (median = 22.0 kg/m <sup>2</sup> )	95	57 (60)	37 (39)	66 (69)
Quartile 4 (median = 24.7 kg/m <sup>2</sup> )	91	46 (51)	26 (29)	49 (54)
Educational level				
No formal schooling	158	93 (59)	62 (39)	105 (66)
Primary school	174	93 (53)	46 (26)	102 (59)
Middle school or beyond	12	7 (58)	5 (42)	7 (58)
Tobacco use				
Nonsmoker	62	33 (53)	20 (32)	36 (58)
Smoker	146	81 (55)	35 (24)	89 (61)
Alcohol consumption				
Never or rarely	137	76 (55)	38 (28)	84 (61)
Only occasionally	64	34 (53)	15 (23)	37 (58)
At least monthly	7	4 (57)	2 (29)	4 (57)
Family history of cancer				
No	252	144 (57)	85 (34)	159 (63)
Yes	121	68 (56)	40 (33)	76 (63)
Primary water supply				
Central village source	290	165 (57)	100 (34)	184 (63)
Piped into home	82	46 (56)	25 (30)	50 (61)
Intervention group§				
A (retinol and zinc)	192	107 (56)	64 (33)	116 (60)
B (riboflavin and niacin)	190	112 (59)	65 (34)	124 (65)
C (ascorbic acid and molybdenum)	195	114 (58)	69 (35)	130 (67)
D (β-carotene, α-tocopherol, and selenium)	161	83 (52)	50 (31)	96 (60)

\*Total number of subjects = 373; lower values represent missing data or limitation of the analyses to men only (for tobacco use and alcohol consumption).

† $P = .001$  by two-sided  $\chi^2$  test.

‡Body mass index = (weight in kg)/(height in m)<sup>2</sup>.

§Randomized assignment from the General Population Trial (note that groups A–D are not mutually exclusive).

**Table 2.** *Helicobacter pylori* serum assay results by case–control status

	No.	Serum assay results		
		Whole-cell seropositive, No. (%)	CagA seropositive, No. (%)	Whole-cell and/or CagA seropositive, No. (%)
Control subjects	192	99 (52)	56 (29)	107 (56)
Case patients with gastric cancer				
Cardia	99	62 (63)	39 (39)	69 (70)*
Noncardia	82	51 (62)	30 (37)	59 (72)†
Combined	181	113 (62)‡	69 (38)	128 (71)§

\* $P = .02$  by two-sided  $\chi^2$  test compared with control subjects.

† $P = .01$  by two-sided  $\chi^2$  test compared with control subjects.

‡ $P = .03$  by two-sided  $\chi^2$  test compared with control subjects.

§ $P = .003$  by two-sided  $\chi^2$  test compared with control subjects.

noncardia cancer combined ( $P = .07$ ) versus 29% for control subjects. On the basis of the composite serologic variable, *H. pylori* seropositivity rates were 70% for case patients with gastric cardia cancer ( $P = .02$ ), 72% for case patients with noncardia gastric cancer ( $P = .01$ ), and 71% for case patients with gastric cardia and noncardia cancer combined ( $P = .003$ ) versus 56% for control subjects.

Whole-cell seropositivity and CagA seropositivity were associated with similarly increased ORs for gastric cardia cancer and noncardia gastric cancer (Table 3). Relative to either of the individual assay results, *H. pylori* seropositivity was associated with greater risks of gastric cardia cancer (OR = 1.87; 95% CI = 1.10 to 3.17), noncardia gastric cancer (OR = 2.29; 95% CI = 1.26 to 4.14), and both gastric cancer subsites combined (OR = 2.04; 95% CI = 1.31 to 3.18). Cross-product terms for age category by serology result ( $P = .15$ ,  $P = .24$ , and  $P = .11$ , respectively) and sex by serology result ( $P = .54$ ,  $P = .51$ , and  $P = .36$ , respectively) were not statistically significant in any of the logistic regression models. Limiting our analyses to patients with histologically confirmed gastric cardia cancer did not appreciably affect the OR estimates for whole-cell seropositivity (OR = 1.74; 95% CI = 0.97 to 3.11), CagA seropositivity (OR = 1.61; 95% CI = 0.88 to 2.96), or *H. pylori* seropositivity (OR = 2.11; 95% CI = 1.14 to 3.89). Exclusion of case patients with gastric cardia cancer diagnosed during the first 2 years of the intervention trial also minimally altered the risk estimates for whole-cell seropositivity (OR = 1.51; 95% CI = 0.85 to 2.68), CagA seropositivity (OR = 1.68; 95% CI = 0.91 to 3.08), and *H. pylori* seropositivity (OR = 1.94; 95% CI = 1.05 to 3.56). Adjusting for intervention group assignment changed the gastric cancer risk estimates by less than 10% for each serology variable at both anatomic subsites (data not shown).

To further assess the effects of *H. pylori* strain type on gastric cancer risk, ORs were estimated for CagA seropositivity among those subjects who expressed one or both types of serum antibodies. In this subgroup, the presence of CagA antibodies in serum was associated with modest, nonstatistically significant risk elevations for gastric cardia cancer (OR = 1.35; 95% CI = 0.71 to 2.55), noncardia gastric cancer (OR = 1.33; 95% CI = 0.66 to 2.69), and gastric cancer at both sub-

**Table 3.** Multivariate odds ratio estimates for gastric adenocarcinoma by serology results

	Gastric adenocarcinoma					
	Cardia		Noncardia		Combined	
	No. of case/No. of control subjects	OR (95% CI)*	No. of case/No. of control subjects	OR (95% CI)	No. of case/No. of control subjects	OR (95% CI)
Whole-cell seropositive						
No (referent)	37/93	1.00	31/93	1.00	68/93	1.00
Yes	62/99	1.58 (0.95 to 2.62)	51/99	1.68 (0.96 to 2.95)	113/99	1.60 (1.05 to 2.45)
CagA seropositive						
No (referent)	60/136	1.00	52/136	1.00	112/136	1.00
Yes	39/56	1.79 (1.05 to 3.06)	30/56	1.84 (1.01 to 3.34)	69/56	1.83 (1.15 to 2.89)
Whole-cell and/or CagA seropositive						
No (referent)	30/85	1.00	23/85	1.00	53/85	1.00
Yes	69/107	1.87 (1.10 to 3.17)	59/107	2.29 (1.26 to 4.14)	128/107	2.04 (1.31 to 3.18)

\*OR = odds ratio (CI = 95% confidence interval), adjusted for age and sex.

sites combined (OR = 1.39; 95% CI = 0.80 to 2.42). Further restriction of the study sample to include only subjects seropositive for whole-cell antibodies (i.e., excluding the 23 subjects who were whole-cell seronegative and CagA seropositive) minimally changed the OR estimates for CagA seropositivity, which were 1.32 (95% CI = 0.68 to 2.56) for case patients with gastric cardia cancer, 1.18 (95% CI = 0.56 to 2.53) for case patients with noncardia gastric cancer, and 1.30 (95% CI = 0.72 to 2.32) for case patients with gastric cancer at both subsites combined.

A statistically significant interaction between the two serum assay results (defined as whole-cell assay result  $\times$  CagA assay result) was noted in the noncardia gastric cancer risk model ( $P = .04$ ). With whole-cell-seronegative/CagA-seronegative subjects as the referent, whole-cell-seronegative/CagA-seropositive subjects had the highest estimated risk (OR = 4.51; 95% CI = 1.39 to 14.64), and whole-cell-seropositive/CagA-seropositive subjects (OR = 2.22; 95% CI = 1.07 to 4.63) and whole-cell-seropositive/CagA-seronegative subjects (OR = 2.04; 95% CI = 1.03 to 4.05) had intermediate risks. Although the interaction between serum assay results was not statistically significant in the gastric cardia cancer risk model ( $P = .26$ ), a similar OR pattern was observed when these same assay result combinations were compared (data not shown).

## DISCUSSION

In this large, nested case-control study, *H. pylori* seropositivity was associated with an approximately twofold in-

crease in the risk of gastric cancer, regardless of the anatomic subsite. On the basis of the range of summary risk estimates (1.9–2.5) from three meta-analyses (5–7), our data are in keeping with earlier reports and support the classification of *H. pylori* as a gastric carcinogen. More strikingly, ours is the first prospective study, to our knowledge, to report a statistically significant positive risk association between *H. pylori* serum antibodies and adenocarcinoma of the gastric cardia. The inclusion of an ample number of case patients with gastric cardia cancer and measurement of both whole-cell and CagA antibodies for each study subject improved our ability to detect this subsite-specific risk association.

Most previous investigations (21–36) of the relationship between *H. pylori* seropositivity and proximal gastric cancer risk have been relatively small (Table 4). Eight of the 16 previous studies (22,24,25,29,30,33,35,36) included fewer than 20 case subjects, and only two (27,32) included more than 50 case subjects. Moreover, the available data are difficult to interpret because of a lack of uniformity in the anatomic subsite definitions used by different studies. Some reports (22,24,25,26,29,30,31,33,34,36) have apparently limited case subjects to patients with gastric cardia adenocarcinomas, whereas other reports (21,23,27,28,32,35) have included cancers from a larger segment of the upper stomach, the gastroesophageal junction, or the lower esophagus. Only two studies (21,28), one in an Asian population and one in a Western population, have reported statistically significant risk associations, and their results were qualita-

tively opposite. In a retrospective case-control study from Japan, Kikuchi et al. (28) observed a markedly increased risk of cancers in the upper one third of the stomach (OR = 11.3; 95% CI = 2.6 to 68.8). In a prospective nested case-control study from Norway, Hansen et al. (21) found a reduced risk of adenocarcinomas of the gastroesophageal junction (OR = 0.40; 95% CI = 0.20 to 0.77). However, this statistically significant risk reduction was only found when the authors used the *H. pylori* serology data to choose the threshold value that produced the most statistically significant effect and was not found when the assay manufacturer's recommended threshold value was used (OR = 0.58; 95% CI = 0.29 to 1.13). Despite the considerable heterogeneity across previously published reports, Huang et al. (5) and Eslick et al. (7) reported pooled OR estimates for the association between *H. pylori* and proximal gastric cancer risk. Although neither of the summary estimates was statistically significant, these studies found risk elevations of 23% and 54%, respectively.

Tumors that span the gastroesophageal junction are often difficult to classify as either gastric or esophageal in origin. Yet, the distinction may be relevant for epidemiologic assessments of adenocarcinoma risk factors. In Western countries, esophageal adenocarcinomas appear to develop through an ordered clinical sequence, beginning with reflux esophagitis, progressing to Barrett's metaplasia, and culminating in malignant transformation (37,38). Goldblum et al. (39) have demonstrated that recurrent exposure to refluxed stomach contents is more injurious to the esophageal squamous mucosa than the

**Table 4.** Previous studies of *Helicobacter pylori* seropositivity and proximal gastric cancer risk

Investigators, y (reference No.)	Study design	No. of case subjects	Subsite definition*	OR (95% CI)†
Parsonnet et al., 1991 (23)	Nested case-control	27	Gastroesophageal junction	0.8 (0.3 to 2.1)
Nomura et al., 1991 (25)	Nested case-control	5	Gastric cardia (NOS)	Not given
Aromaa et al., 1996 (36)	Nested case-control	9	Gastric cardiac (NOS)	Not given
Siman et al., 1997 (24)	Nested case-control	13	Gastric cardia (NOS)	0.9 (0.2 to 3.7)
Hansen et al., 1999 (21)	Nested case-control	45	Gastroesophageal junction	0.6 (0.3 to 1.1)‡
Yuan et al., 1999 (22)	Nested case-control	19	Gastric cardia (NOS)	4.3 (0.5 to 41.8)§
Talley et al., 1991 (31)	Case-control	32	Gastric cardia (NOS)	0.9 (0.3 to 2.6)
Hansson et al., 1993 (29)	Case-control	19	Gastric cardia (NOS)	1.4 (0.4 to 4.8)
Rudi et al., 1995 (26)	Case-control	36	Gastric cardia (NOS)	1.3 (0.5 to 3.2)
Fukuda et al., 1995 (27)	Case-control	52	Upper one third of stomach	0.9 (0.4 to 1.9)
Kikuchi et al., 1995 (28)	Case-control	35	Upper one third of stomach	11.3 (2.6 to 68.8)
Erkisi et al., 1997 (34)	Case-control	22	Gastric cardia (NOS)	Not given
Martin-de-Argila et al., 1997 (35)	Case-control	5	Gastric cardia and fundus	Not given
Komoto et al., 1998 (30)	Case-control	14	Gastric cardia (most proximal 2 cm of stomach)	5.2 (0.7 to 41.7)
Chow et al., 1998 (32)	Case-control	129	Gastric cardia and esophagus	0.7 (0.4 to 1.1)
Peek et al., 1999 (33)	Case-control	14	Gastric cardia, excluding the gastroesophageal junction	Not given

\*NOS = not otherwise specified; definition of the gastric cardia not provided by the authors.

†Reported odds ratio (OR) and 95% confidence interval (CI), except where noted.

‡On the basis of the serum assay manufacturer's recommended threshold value for *H. pylori* seropositivity.

§Case subjects diagnosed 5 years or more after cohort enrollment; for case subjects (n = 24) diagnosed less than 5 years after cohort enrollment, OR = 0.75 (0.17 to 3.25).

||99% CI.

gastric cardia columnar mucosa. Extending this observation, gastroesophageal reflux might be expected to increase distal esophageal and gastric cardia adenocarcinoma risks to greater and lesser degrees, respectively. Indeed, Lagergren et al. (40) described substantially different OR estimates for esophageal adenocarcinoma (OR = 7.7; 95% CI = 5.3 to 11.4) and gastric cardia adenocarcinoma (OR = 2.0; 95% CI = 1.4 to 2.9) among subjects with symptomatic gastroesophageal reflux disease. Conversely, the presence of *H. pylori* has been associated with the generally accepted precursor lesions for gastric but not esophageal adenocarcinoma (33,39,41-45). Thus, *H. pylori* seropositivity might be expected to be a stronger risk factor for gastric cardia than for distal esophageal adenocarcinoma.

In Linxian, China, the vast majority of gastroesophageal junction tumors are believed to originate in the gastric cardia, based on the rarity of reflux esophagitis, the extreme rarity of Barrett's metaplasia or early esophageal adenocarcinoma, and the relatively common finding of small, localized adenocarcinomas of the gastric cardia in this population. Since 1985, our group has evaluated endoscopically nearly 7000 adult residents of Linxian as part of collaborative intervention trials and early detection studies. Nearly all of these individuals have been asymptomatic. In these evaluations, macroscopic or

histologic evidence of reflux esophagitis has been uncommon. In one representative survey of 754 patients who had biopsy specimens taken from focal esophageal abnormalities, only eight (1%) had histologic findings consistent with reflux esophagitis (46). Furthermore, no cases of histologically confirmed Barrett's esophagus or adenocarcinoma of the lower esophagus have been identified in any of our surveys, despite focused attempts to detect these conditions (14,47). In contrast, more than 175 cases of early adenocarcinoma have been found in the gastric cardia (unpublished observation). The vast majority of these tumors have been small and confined to a 2- to 3-cm region below the squamocolumnar junction, making anatomic localization to the gastric cardia essentially certain. Consistent with our experience, other groups have reported that reflux esophagitis and its complications are uncommon among Chinese adults residing in communities outside of Linxian (48,49).

*H. pylori* cagA-positive strains appear to be more virulent than their cagA-negative counterparts. Although essentially all *H. pylori*-colonized hosts develop chronic gastritis, CagA seropositivity has been linked to a more aggressive inflammatory response and multifocal gastric atrophy at both the cardia and noncardia subsites (33,50,51). With respect to malignant disease, several studies (16,52,53) have reported that the presence

of cagA-positive strains (as detected by the presence of CagA antibodies) are associated with increased risk of distal gastric cancer. However, the relationship between serologic CagA status and gastric cardia cancer risk is less well defined. CagA seropositivity was associated with a more than sixfold elevation in risk for cancers in the upper one third of the stomach among subjects from Japan (OR = 6.2; 95% CI = 1.2 to 32.0) (54). In contrast, CagA seropositivity was associated with a 60% risk reduction for adenocarcinomas of the gastric cardia and esophagus combined among subjects from the United States (OR = 0.4; 95% CI = 0.2 to 0.8) (32). Conceivably, an overrepresentation of esophageal adenocarcinomas in the latter study may have driven the negative risk estimate. According to Blaser (55) and Richter et al. (56), the enhanced gastric corpus inflammation induced by cagA-positive *H. pylori* strains can result in reduced acid secretion and decreased risks for reflux esophagitis, Barrett's metaplasia, and distal esophageal adenocarcinoma (55,56).

In this study, OR estimates for CagA seropositivity and whole-cell seropositivity were nearly equivalent at each gastric cancer subsite. In addition, CagA seropositivity was not associated with statistically significant risk elevations among *H. pylori*-seropositive subjects. Nonetheless, measurement of CagA antibodies for each subject improved our ability to ap-

appropriately classify *H. pylori* status. Similar to at least three other studies (52,54,57), we observed a small group of subjects (6%) who were seronegative by the whole-cell assay and seropositive by the CagA assay. Solely on the basis of the whole-cell assay results, these subjects would have been misclassified as *H. pylori* seronegative. When *H. pylori* seropositivity was defined as one or both assay results positive, greater separation was observed between case patients with gastric cancer and control subjects, and the subsite-specific OR estimates were further from unity. Of interest, comparison of the four possible assay result combinations revealed that subjects who were whole-cell seronegative and CagA seropositive had the highest risk estimates for both gastric cardia and noncardia gastric cancer. This result should be interpreted with caution because of the small number of subjects within this cell. However, Torres et al. (57) also reported a strong association between this mixed seropositivity pattern and increased risk of gastric cancer in a large study from Mexico. One possible explanation is that CagA seropositivity is a better marker of *H. pylori* exposure among patients with advanced premalignant lesions, such as atrophic gastritis. Severe disruption of the normal gastric mucosa can lead to clearance of *H. pylori*. However, CagA antibodies appear to persist longer than other *H. pylori* antibodies (58). Therefore, subjects with the highest short-term risk of developing gastric cancer might be found to express CagA but not whole-cell antibodies. The reason for the lower rate of CagA seropositivity among men in this study is unknown. To our knowledge, statistically significant differences in CagA seropositivity by sex have not been reported previously but may be worthy of further investigation.

Certain weaknesses of our study merit further discussion. First, the period from serum collection to case diagnosis was relatively short for most subjects. Forman et al. (59) have demonstrated that the duration of follow-up is an important determinant of *H. pylori*-associated gastric cancer risk, with extended surveillance corresponding to an increase in the OR estimate. Thus, our study may have underestimated the true subsite-specific gastric cancer risks associated with *H. pylori* seropositivity. We intend to address this possibility as additional longitudinal data from the parent intervention trial cohort

become available. Second, we were unable to analyze gastric adenocarcinomas by histologic subtype because of a lack of routinely recorded information for this variable. Nonetheless, the existing data are inconclusive as to whether or not histologic subtype modifies the association between *H. pylori* exposure and gastric cancer risk (5,7), so this factor should not have appreciably influenced our OR estimates. Third, we used educational level as a single surrogate marker for socioeconomic status. Both the presence of *H. pylori* and gastric cancer have been associated with lower socioeconomic levels (60–62). However, nearly all of the participants in the General Population Trial were recruited from Linxian communes with similar economic infrastructures. Thus, from the uniformity of occupational and housing conditions in this region, it seems unlikely that consideration of additional socioeconomic parameters would have meaningfully altered our observations.

In summary, we found that *H. pylori* seropositivity was associated with similarly increased risks of gastric cardia and noncardia gastric cancer among residents of Linxian. Our study included the largest number of prospectively identified case patients with gastric cardia cancer assembled to date, and our data are in keeping with current models of gastric carcinogenesis. In most studies from Western populations, where gastroesophageal reflux disease and its sequelae are relatively common, tumors classified as gastric cardia adenocarcinomas appear to include a substantial number of distal esophageal adenocarcinomas. Conversely, among the residents of Linxian, where gastroesophageal reflux disease and its sequelae are rare or nonexistent, essentially all gastric cardia adenocarcinomas appear to originate from the proximal stomach. The overwhelming majority of observational studies have supported a positive association between *H. pylori* seropositivity and the risk of noncardia gastric cancer. It seems biologically plausible that a similar risk association would apply to the gastric cardia, as observed in this study. Confirmation of our results in carefully designed studies conducted among non-Asian populations would lend further support to this theory. Extended follow-up of the Linxian General Population Trial cohort is ongoing and should provide valuable information as to whether or not *H. pylori* eradication represents a logical cancer

prevention strategy in this high-risk population.

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## NOTES

Martin Blaser, a discoverer of CagA, may receive royalties from licenses from Vanderbilt University. Manuscript received May 15, 2000; revised November 6, 2000; accepted November 21, 2000.