

Opposing Risks of Gastric Cardia and Noncardia Gastric Adenocarcinomas Associated With *Helicobacter pylori* Seropositivity

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Background: Colonization with *Helicobacter pylori* is a risk factor for gastric adenocarcinoma, but the magnitude of this association and its relationship to anatomic location of the cancer, duration of follow-up, age at diagnosis, histologic subtype, and *H. pylori* strain differences are less clear. We conducted a prospective nested case-control study of *H. pylori* serology to address these questions. **Methods:** Case and control subjects were selected from the 29 133 50- to 69-year-old males recruited into the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. At baseline, detailed demographic data and a serum sample were collected. From 1985 to 1999, 243 incident cases of gastric adenocarcinoma were diagnosed in cohort members. Serum samples from 234 case subjects (173 with noncardia gastric cancers and 61 with gastric cardia cancers) and 234 age-matched control subjects were assayed for antibodies against *H. pylori* whole-cell and CagA antigens. We fit conditional logistic regression models to estimate the unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association of *H. pylori* seropositivity, defined as seropositivity to either whole-cell or CagA antigens, with noncardia gastric and gastric cardia cancers. All statistical tests were two-sided. **Results:** *H. pylori* seropositivity was strongly associated with the risk of noncardia gastric cancer (adjusted OR = 7.9, 95% CI = 3.0 to 20.9) but was inversely associated with the risk of gastric cardia cancer (adjusted OR = 0.31, 95% CI = 0.11 to 0.89). *H. pylori* seropositivity rates did not vary statistically significantly by length of follow-up, age at diagnosis, or histologic subtype. A calculation of rates showed that the absolute risks of noncardia gastric and cardia gastric adenocarcinomas in the *H. pylori*-positive participants of this cohort would be 63 and 12 per 100 000 person-years, respectively, whereas corresponding rates in *H. pylori*-negative participants would be 8 and 37 per 100 000 person-years, respectively. **Conclusion:** *H. pylori* is a strong risk factor for noncardia gastric cancer but is inversely associated with the risk of gastric cardia cancer. These findings bolster the hypothesis that decreasing *H. pylori* prevalence during the past century may have contributed to lower rates of noncardia cancer and higher rates of cardia cancer in Western countries. [J Natl Cancer Inst 2006;98:1445-52]

Colonization of the human stomach with *Helicobacter pylori* is an important risk factor for gastric adenocarcinomas (1-13), but this association varies by anatomic subsite (5,8). A combined

analysis of 12 prospective studies found a strong positive association between seropositivity against *H. pylori* antigens at study entry and subsequent risk of noncardia gastric adenocarcinoma (8). However, this analysis found no association between anti-*H. pylori* seropositivity and risk of gastric cardia adenocarcinoma (8).

Although the association between *H. pylori* colonization and gastric noncardia adenocarcinoma is strong (8), estimates of the magnitude of the association vary, presumably because of differences in study design (8), length of follow-up (8), patient age at diagnosis (1,8,11,14), histologic subtype of cancer (6), *H. pylori* strain (15,16), and host characteristics (16-18). Long-term prospective studies are probably more accurate than retrospective studies in assessing the association between anti-*H. pylori* seropositivity and risk of gastric cancer. *H. pylori* does not colonize areas of stomach with malignant or premalignant changes (19), so after the development of advanced gastric disease the *H. pylori* population may decline, resulting in lower levels of circulating anti-*H. pylori* antibodies. Such reductions in the levels of circulating antibodies could limit the accuracy of retrospective case-control studies and short-term prospective studies in estimating the association between *H. pylori* infection and the risk of noncardia gastric cancer, whereas prospective studies with long-term follow-up and in which serum collection was done before the development of premalignant disease would provide more valid estimates of risk (8).

Several other factors could affect the risk estimates. Results of several studies suggest that *H. pylori* infection is more strongly associated with the risk of noncardia gastric cancer risk in younger individuals than in older individuals (1,8,14). It remains unclear whether *H. pylori* is a stronger risk factor for gastric cancers with intestinal histology than for gastric cancers with

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diffuse-type histology (8,20–22). Risk variation may also reflect differences between CagA-positive and CagA-negative *H. pylori* strains (12,23,24). CagA-positive strains increase the turnover of gastric epithelium by delivering CagA protein into the epithelial cells (23) and may further increase risk of noncardia gastric cancer. Most, but not all, studies have observed a higher risk of noncardia gastric cancer associated with CagA-positive strains than with CagA-negative strains (25).

Although the overall association between anti-*H. pylori* seropositivity and gastric cardia cancer has been reported to be null (8), there is substantial geographic variation with respect to this association; most studies of East Asian populations have shown an increased risk, whereas most studies of Western populations have shown either no association or reduced risk (26). The direction of the association by geographic region may be important because, since the 1970s, both a substantial reduction in *H. pylori* prevalence and a substantial increase in the incidence of gastric cardia adenocarcinoma have been observed in the Western world (27–29) and in Japan (30,31) but not in other East Asian countries (32,33). Variations in risk estimates for gastric cardia adenocarcinomas, like those for noncardia gastric adenocarcinomas, may also reflect differences in study design, the length of follow-up, age at diagnosis, histology, and *H. pylori* strain. However, the small number of cardia cancers in prospective studies has made it difficult to examine subgroup-stratified associations (8,26).

We conducted a long-term prospective case-control study to estimate the magnitudes of the associations between *H. pylori* seropositivity and the risks of gastric cardia and noncardia gastric cancers among Finnish males who participated in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a randomized cancer prevention trial conducted in Southern Finland. We also examined the magnitude of these associations by time from serum collection to cancer diagnosis, age at diagnosis, histologic subtype, and CagA positivity.

SUBJECTS AND METHODS

Study Population

The case and control subjects included in this study were identified from among the participants in the ATBC study, a randomized, double-blind, placebo-controlled, primary prevention trial that was conducted to determine whether daily supplementation with alpha-tocopherol, beta-carotene, or both would reduce the incidence of lung or other cancers among male smokers. Between 1985 and 1988, 29 133 eligible Finnish male smokers between the ages of 50 and 69 years were recruited to the ATBC study. The trial ended in 1993, but the participants are still being followed as a cohort. Details of the study design and methods have been published (34). This study was approved by the institutional review boards of both the National Public Health Institutes in Finland and the National Institutes of Health in the United States. All participants provided written informed consent.

All case subjects had incident gastric adenocarcinoma that was diagnosed through April 30, 1999. Cancer cases were identified primarily via the Finnish Cancer Registry, which provides nearly 100% coverage of all cancer cases in Finland (35). Diagnosis of gastric cancer cases defined according to the International Classification of Diseases, 9th Revision [ICD-9; (36)] code 151 was confirmed by review of hospital records and histopathologic specimens. Cases were classified as gastric cardia cancer if

they involved the esophagogastric junction and as noncardia gastric cancer if they did not.

Of the 243 case subjects diagnosed with gastric adenocarcinoma, 234 (96%) had adequate serum samples for *H. pylori* analysis. We used a computer program written in SAS (SAS Institute Inc, Cary, NC) that randomly selected an equal number of control subjects (N = 234) from among those ATBC study participants who remained cancer free through April 30, 1999, so that each control subject was matched with one of the cases for age (± 3 months).

Demographic and Dietary Data Collection

At ATBC study entry, all participants completed a questionnaire on demographic characteristics and lifestyle and provided a fasting serum sample that was stored in aliquots at -70°C . Diet was assessed with the use of a self-administered food frequency questionnaire that contained 276 food items (37). The food frequency questionnaire was satisfactorily completed by 27 110 participants (93%) at ATBC study entry.

Serum Assays

Serum was evaluated for immunoglobulin G antibodies against *H. pylori* whole-cell and CagA antigens by enzyme-linked immunosorbent assays, as previously described (38). The results were expressed as optical density ratios relative to simultaneously analyzed laboratory standards. Results were considered positive if the optical density ratio was greater than or equal to 1.0 for the whole-cell antigen assay and greater than or equal to 0.35 for the CagA antigen assay. Individuals who were seronegative for both types of antibodies (whole cell and CagA) were classified as *H. pylori* negative, whereas individuals who were seropositive for either whole-cell or CagA antibodies were classified as *H. pylori* positive. This classification system was used because a study comparing serology with gastric biopsy culture has shown that the stomachs of individuals who are negative for *H. pylori* whole-cell antibodies but positive for CagA antibodies are in fact colonized with CagA-positive strains of *H. pylori* (39). Therefore, *H. pylori*-positive individuals were further classified according to whether they carried CagA-negative strains (whole-cell seropositive, CagA seronegative) or CagA-positive strains (whole-cell seropositive, CagA seropositive or whole-cell seronegative, CagA seropositive) (39).

Serum samples from each case subject and the matched control subject were assayed in duplicate in the same batch by experienced technicians who were unaware of the case-control status of the samples. When the duplicate samples provided indeterminate results (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. Thirty-five quality control serum samples, aliquoted from a single large pool, were equally distributed among different batches. On the basis of these samples, average within-batch coefficients of variation for the whole-cell and CagA antigen assays were 15% and 20%, respectively.

Statistical Analysis

All *P* values are two-sided, and *P* values less than .05 were considered statistically significant. We used the Wilcoxon

matched-pairs test to compare demographic characteristics between case subjects and the matched control subjects, including education level (primary school or lower versus high school or higher) and residence (urban versus rural), and potential confounders, including smoking duration (years), body mass index ($[\text{weight in kg}]/[\text{height in m}]^2$), and intakes of nitrates (mg/day) and of fruits, vegetables, starch, and sodium (all in g/day). All dietary intake data were adjusted for calorie intake using the method of residuals (40). We fit conditional logistic regression models to estimate unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for cancer by anatomic subsite. Adjustment was done for demographic characteristics and the potential confounders mentioned above. We also estimated the crude and adjusted odds ratios by duration of case subject follow-up (0.0–6.9 versus 7.0 years or more), by age at diagnosis (younger than 65 years versus 65 years or older), by histologic subtype (diffuse, intestinal, or not specified), and by *H. pylori* strain (CagA positive versus CagA negative). Cut points for age and follow-up were chosen so that there would be sufficient numbers of noncardia gastric cancer case subjects and gastric cardia cancer case subjects (40%–60% of cancer subjects) on each side of the cut point. Odds ratio point estimates varied by strata of follow-up, age at diagnosis, histology, and *H. pylori* strain, but none of the differences between these strata were statistically significant; 95% confidence intervals for the estimate in each group included the point estimates in other groups. We also repeated all the analyses using unconditional logistic regression analysis. No qualitative differences were observed between conditional and unconditional models. Therefore, we report only the results from unconditional logistic regression models for the associations by anatomic location. Only four diffuse-type cardia adenocarcinomas were diagnosed, which did not allow a meaningful subgroup analysis by histology for cardia adenocarcinomas. However, all descriptive data were reported for these four cases.

RESULTS

In total, 220 subjects (47%) were positive for antibodies to both *H. pylori* whole-cell and CagA antigens, 130 (28%) were

positive for whole-cell antibodies only, 23 (5%) were positive for CagA antibodies only, and 95 (20%) were positive for neither. Thus, 80% of the studied population (197 [84%] of the gastric cancer case subjects and 176 [75%] of the control subjects) had serologic evidence of *H. pylori* infection. The median time from serum collection to cancer diagnosis was 5.8 years (interquartile range [IQR] = 3.4–8.6 years) for noncardia gastric cancer case subjects and 6.7 years (IQR = 4.4–9.0 years) for cardia cancer case subjects.

Demographic Characteristics and Potential Confounders

Table 1 shows the distributions of the case and control subjects by demographic characteristics and potential confounders. Fruit consumption was statistically significantly lower among the noncardia gastric cancer case subjects than among the matched control subjects ($P = .03$). All other variables showed nonstatistically significant differences between the noncardia gastric cancer case subjects and the matched control subjects. Results for fruits, vegetables, and other potential confounders in our nested study were similar to those obtained for the full cohort (41).

Anatomic Subsite

The prevalence of whole-cell antibody seropositivity was nearly identical among the control subjects matched to the noncardia gastric cancer case subjects and those matched to the gastric cardia cancer case subjects (71% and 72%, respectively; Table 2). Whole-cell antibody seropositivity was more common in the noncardia cancer case subjects than in the matched control subjects (86% versus 71%; adjusted OR = 3.32, 95% CI = 1.72 to 6.42) but less common in cardia cancer case subjects than in the matched control subjects (57% versus 72%; adjusted OR = 0.28, 95% CI = 0.09 to 0.86). *H. pylori* seropositivity rates were identical (75%) in the two groups of control subjects when we used the broader criterion for *H. pylori* seropositivity (i.e., positive for either whole-cell or CagA antigens). *H. pylori* seropositivity was more common in noncardia gastric cancer case subjects (93%; adjusted OR = 7.92, 95% CI = 3.02 to 20.9) but

Table 1. Demographic characteristics and potential confounders in gastric adenocarcinoma case subjects and matched control subjects*

Characteristic or confounder	Gastric noncardia cancer case–control pairs (N = 173)			Cardia gastric cancer case–control pairs (N = 61)		
	Case subjects	Control subjects	<i>P</i> †	Case subjects	Control subjects	<i>P</i> †
Mean age at enrollment, y (SD)	58.8 (5.0)	58.8 (5.0)	n/a	59.4 (4.7)	59.5 (4.8)	n/a
Education level, no. (%)						
Primary school or lower	147 (85)	147 (85)	1.00	47 (77)	46 (75)	.82
High school or higher	26 (15)	26 (15)		14 (23)	15 (25)	
Area of residence, no. (%)						
Urban	103 (60)	115 (66)	.16	43 (70)	36 (59)	.11
Rural	70 (40)	58 (34)		18 (30)	25 (41)	
Mean smoking duration, y (SD)	37.1 (9.9)	37.3 (8.3)	.84	37.9 (6.7)	37.2 (9.1)	.85
Mean body mass index, kg/m ² (SD)	26.0 (4.0)	26.2 (3.5)	.36	27.1 (4.2)	26.4 (4.3)	.18
Mean dietary intake‡ (SD)						
Nitrate, mg/day	58.5 (27)	60.1 (26)	.58	60.8 (28)	60.9 (36)	.83
Fruit, g/day	116 (100)	129 (81)	.03	127 (81)	140 (115)	.98
Vegetable, g/day	105 (61)	108 (56)	.55	109 (73)	114 (87)	.60
Starch, g/day	146 (57)	149 (55)	.37	148 (63)	152 (47)	1.00
Sodium, g/day	5.00 (0.78)	4.97 (0.75)	.41	4.93 (0.71)	4.89 (0.65)	.81

*SD = standard deviation; n/a = not applicable.

†*P* values were obtained from Wilcoxon matched-pairs test (two-sided).

‡All dietary intakes were adjusted for calorie intake using the method of residuals. Nutritional data were available for 159 noncardia cancer case subjects, 54 cardia cancer case subjects, and 229 control subjects.

Table 2. Association between *Helicobacter pylori* seropositivity status and the risks of gastric noncardia and cardia adenocarcinomas among participants of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study*

Cancer type	No. of case-control pairs	Whole-cell antibody positive†, N (%)	<i>H. pylori</i> positive†, N (%)	Unadjusted matched OR (95% CI)	Adjusted matched OR‡ (95% CI)
Noncardia gastric adenocarcinoma	173				
Case subjects		149 (86)	161 (93)	5.43 (2.42 to 12.16)	7.92 (3.02 to 20.90)
Control subjects		122 (71)	130 (75)		
Gastric cardia adenocarcinoma	61				
Case subjects		35 (57)	36 (59)	0.54 (0.27 to 1.10)	0.31 (0.11 to 0.89)
Control subjects		44 (72)	46 (75)		

*Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for seropositivity to *H. pylori*, as defined by positive serum results for either whole-cell antibody or CagA antibody.

†Whole-cell positive indicates seropositivity to whole-cell group antigen. *H. pylori* positive indicates seropositivity to either whole-cell or CagA antigens.

‡Adjusted for age at enrollment, education level, area of residence, smoking duration, body mass index, and intakes of nitrates, fruits, vegetables, salt, and starch. Nutritional data were available for 153 noncardia case-control pairs and 51 cardia case-control pairs.

less common in gastric cardia cancer case subjects (59%; adjusted OR = 0.31, 95% CI = 0.11 to 0.89) compared with the respective control subjects. Thus, we observed opposing associations between *H. pylori* seropositivity and either noncardia or cardia gastric cancers, regardless of which definition of seropositivity was used. On the basis of these adjusted odds ratios, a calculation of rates showed that the absolute risks of noncardia gastric and cardia gastric adenocarcinomas in the *H. pylori*-positive participants of this cohort would be 63 and 12 per 100 000 person-years, respectively, whereas corresponding rates in the *H. pylori*-negative participants would be 8 and 37 per 100 000 person-years, respectively.

We also observed opposing associations when we used unconditional logistic models. The crude and adjusted odds ratios for the association between the risk of noncardia gastric cancer and *H. pylori* seropositivity were 4.50 (95% CI = 2.34 to 8.65) and 5.11 (95% CI = 2.51 to 10.43), respectively. The crude and adjusted odds ratios for the association between the risk of gastric cardia cancer and *H. pylori* seropositivity were 0.49 (95% CI = 0.28 to 0.88) and 0.47 (95% CI = 0.25 to 0.89), respectively.

Time From Serum Collection to Diagnosis

Identical proportions (93%) of *H. pylori*-seropositive noncardia gastric cancer case subjects were observed among those diagnosed within the 7 years after serum collection and those diagnosed 7 or more years after serum collection (Table 3). Compared with the control subjects, noncardia gastric cancer case subjects diagnosed within the 7 years after serum collection and those diagnosed 7 years or more after serum collection had adjusted odds ratios of cancer in association with *H. pylori* seropositivity of 12.97 (95% CI = 2.79 to 60.23) and 6.15 (95% CI = 1.42 to 26.56), respectively. The *H. pylori* seropositivity rates among gastric cardia cancer case subjects diagnosed in these two periods were close (55% and 64%, respectively), and both rates were less than the average rate among the matched control subjects (75%).

Age at Diagnosis

We used the median age at diagnosis (65 years) to stratify case subjects (and the age-matched control subjects) into two groups. Overall, the *H. pylori* seropositivity rate among control subjects younger than 65 years was lower than that among control subjects aged 65 years or older (72% versus 79%), reflecting a decline in *H. pylori* carriage in younger cohorts. *H. pylori* seropositivity was

strongly associated with the risk of noncardia gastric cancer in both age groups. The adjusted odds ratio was 14.54 (95% CI = 3.04 to 69.64) for the younger cohort and 8.57 (95% CI = 1.73 to 45.54) for the older cohort (Table 3). However, the 95% confidence interval for the odds ratio in each cohort included the odds ratio point estimate for the other cohort. Therefore, the difference in odds ratios between the two age groups was not statistically significant. *H. pylori* seropositivity rates were lower among the gastric cardia cancer case subjects than among the control subjects, and the matched odds ratio point estimates were less than 1.0 in both age groups (Table 3).

Histologic Subtype

Among the noncardia gastric cancer case subjects, 94% of those with diffuse histology and 94% of those with intestinal histology were seropositive for anti-*H. pylori* antibodies; the *H. pylori* seropositivity rates among the corresponding matched control subjects were 79% and 77%, respectively (Table 3). The adjusted odds ratios for diffuse- and intestinal-type cancers were 5.70 (95% CI = 0.85 to 38.86) and 9.77 (95% CI = 2.21 to 45.60), respectively.

Among the gastric cardia cancer case subjects, only four (6%) had diffuse histology and 40 (66%) had intestinal histology. Because of the small number of diffuse-type cases, meaningful statistical comparisons with respect to histology were not possible.

CagA-Positive Versus CagA-Negative *H. pylori* Strains

Both CagA-negative and CagA-positive *H. pylori* strains were more common in the noncardia gastric cancer case subjects than in the matched control subjects, with respective adjusted odds ratios of noncardia gastric cancer associated with *H. pylori* seropositivity of 6.55 (95% CI = 2.31 to 18.53) and 8.93 (95% CI = 3.27 to 24.40), respectively (Table 4). By contrast, both CagA-negative and CagA-positive *H. pylori* strains were less common in cardia gastric cancer case subjects than in the matched control subjects, but the difference was statistically significant only for CagA-negative strains (adjusted OR = 0.21, 95% CI = 0.06 to 0.81) (Table 4).

DISCUSSION

The results of this study show opposing associations between *H. pylori* with risk of noncardia gastric and gastric cardia

Table 3. Association between *Helicobacter pylori* seropositivity and the risks of gastric noncardia and cardia adenocarcinomas stratified by time to cancer diagnosis, age at diagnosis, and histologic subtype among participants of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study*

Variable	No. of case-control pairs	<i>H. pylori</i> -positive case subjects, N (%)	<i>H. pylori</i> -positive control subjects, N (%)	Unadjusted matched OR (95% CI)	Adjusted matched OR (95% CI)†
Noncardia gastric cancer					
Time to diagnosis, y					
0.0–6.9	100	93 (93)	74 (74)	7.33 (2.19 to 24.50)	12.97 (2.79 to 60.23)
≥7.0	73	68 (93)	56 (77)	4.00 (1.34 to 11.96)	6.15 (1.42 to 26.56)
Age at diagnosis, y					
<65	95	90 (95)	69 (73)	8.00 (2.42 to 25.57)	14.54 (3.04 to 69.46)
≥65	78	71 (91)	61 (78)	3.50 (1.15 to 10.63)	8.57 (1.73 to 45.54)
Histology					
Diffuse	52	49 (94)	41 (79)	5.00 (1.10 to 22.80)	5.70 (0.85 to 38.86)
Intestinal	90	85 (94)	69 (77)	5.00 (1.71 to 14.59)	9.77 (2.12 to 45.60)
Not specified	31	27 (87)	20 (65)	8.00 (1.00 to 64.07)	16.77 (0.45 to 639.06)
Cardia gastric cancer					
Time to diagnosis, y					
0.0–6.9	33	18 (55)	27 (81)	0.30 (0.10 to 0.94)	<0.01 (<0.01 to 2.64)
≥7.0	28	18 (64)	19 (68)	0.89 (0.34 to 2.30)	0.70 (0.16 to 3.00)
Age at diagnosis, y					
<65	27	17 (63)	19 (70)	0.75 (0.26 to 2.16)	–‡
≥65	34	19 (56)	27 (79)	0.43 (0.16 to 1.11)	0.07 (0.01 to 0.84)
Histology					
Diffuse	4	1 (25)	4 (100)	–‡	–
Intestinal	40	22 (55)	30 (75)	–	–
Not specified	17	13 (76)	12 (71)	–	–

*Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for seropositivity to *H. pylori*, as defined by positive serum results for either whole-cell antibody or CagA antibody.

†Adjusted for age at enrollment, education level, area of residence, smoking duration, body mass index, and intakes of nitrates, fruits, vegetables, salt, and starch. Nutritional data were available for 153 noncardia case-control pairs and 51 cardia case-control pairs.

‡Due to small number of diffuse cardia cancer cases, meaningful statistical comparison was not possible.

adenocarcinomas. Our results confirm that there is a strong association between *H. pylori* seropositivity and risk of noncardia gastric cancer. A combined analysis of prospective studies of the association between *H. pylori* seropositivity and the risk of gastric cancer produced summary odds ratios of 3.0 for noncardia gastric adenocarcinomas (8). However, because it has been suggested that *H. pylori* does not colonize premalignant lesions of the stomach (19), serum antibodies to *H. pylori* may decline by the time gastric cancer develops. Therefore, the authors of the combined analysis suggested that the best estimate of the magnitude of odds ratio for noncardia adenocarcinomas was close to 6.0, the estimate obtained from case subjects with more than

10 years of follow-up. The adjusted odds ratio of 7.92 that we observed is close to that predicted by the combined analysis. However, we found no evidence for changes in *H. pylori* antibody levels over time; about 93% of noncardia cancer case subjects were positive for *H. pylori* antibodies, regardless of the length of time from serum collection to diagnosis. Because the prevalence of *H. pylori* seropositivity remained constant among the case subjects over time, any non-statistically significant variation in odds ratios is likely to be due to the small variation in *H. pylori* seropositivity among the control subjects over time.

The strength of association between *H. pylori* seropositivity and the risk of gastric cancer did not vary statistically significantly

Table 4. Association of CagA-positive and CagA-negative *Helicobacter pylori* strains with the risks of cardia and noncardia adenocarcinomas among participants of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study*

Serologic test results†	Case subjects, N (%)	Control subjects, N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)‡
Noncardia gastric cancer				
<i>H. pylori</i> negative	12 (7)	43 (25)	1.00 (referent)	1.00 (referent)
<i>H. pylori</i> positive				
CagA-negative strains	51 (29)	44 (25)	5.05 (2.11 to 12.07)	6.55 (2.31 to 18.53)
CagA-positive strains	110 (64)	86 (50)	5.64 (2.47 to 12.88)	8.93 (3.27 to 24.40)
Gastric cardia cancer				
<i>H. pylori</i> negative	25 (41)	15 (25)	1.00 (referent)	1.00 (referent)
<i>H. pylori</i> positive				
CagA-negative strains	11 (18)	24 (39)	0.34 (0.14 to 0.85)	0.21 (0.06 to 0.81)
CaA-positive strains	25 (41)	22 (36)	0.81 (0.35 to 1.85)	0.43 (0.12 to 1.52)

*OR = odds ratio; CI = confidence interval.

†*H. pylori* negative = negative for both whole-cell and CagA antibodies; *H. pylori* positive, CagA-negative strains = positive for whole-cell antibodies and negative for CagA antibodies; *H. pylori* positive, CagA-positive strains = positive or negative for whole-cell antibodies and positive for CagA antibodies.

‡Adjusted for age at enrollment, education level, area of residence, smoking duration, body mass index, and intakes of nitrates, fruits, vegetables, salt, and starch. Nutritional data were available for 153 case-control pairs.

by age at case subject diagnosis. However, our finding of a higher point estimate for the association between *H. pylori* seropositivity and the risk of noncardia gastric cancer in younger (<65 years) men versus older (≥ 65 years) men was consistent with findings from previous studies (1,8,14). One explanation for this observation is that noncardia gastric cancer may occur in older people via mechanisms that are unrelated to *H. pylori* infection. An alternative explanation is that, in the younger cohort, there is lower prevalence of *H. pylori* seropositivity in control subjects (11) but cases subjects remain positive for *H. pylori*.

Some studies (20,21) have suggested that the association between *H. pylori* and intestinal-type noncardia gastric cancer is stronger than the association between *H. pylori* and diffuse-type noncardia gastric cancer. However, two meta-analyses examined the *H. pylori*-associated risk ratio for histopathologic subtypes of noncardia cancer and reported no difference in risk between histologic subtypes (5) or a slightly higher risk (OR = 1.14) for the intestinal type compared with diffuse type (6). The combined analysis of prospective studies (8) did not find a risk difference between intestinal and diffuse-type noncardia gastric cancers. Our finding of no difference in the prevalence of *H. pylori* antibodies between individuals with intestinal and diffuse noncardia cancers (94% in both types) is consistent with the results of most previous studies (8,11,42). Our results are also consistent with those of a Swedish study that reported a decline in the rates of both intestinal and diffuse types of noncardia adenocarcinoma from 1989 to 1994 (43).

Several studies have shown that, compared with CagA-negative strains, CagA-positive strains of *H. pylori* are associated with a higher risk of noncardia gastric cancer (25). The genomes of CagA-positive strain of *H. pylori* contain the *cag* pathogenicity island, which includes approximately 31 putative genes, including *cagA* (23). Once delivered into epithelial cells, CagA may increase the risk of gastric cancer by increasing the turnover of the gastric epithelium (23). CagA-positive strains are also more likely than CagA-negative strains to have the *s1* allele of *vacA*, which encodes a molecule that impairs epithelial cell proliferation (24) and may increase gastric cancer risk (16). CagA-positive strains are also more likely to express the *babA* gene product, which controls bacterial adherence to Lewis^b antigens on gastric epithelial cells (24). We also found that, compared with CagA-negative strains, CagA-positive strains had a stronger association with risk of noncardia gastric cancer, although this difference was not statistically significant.

CagA measurement enabled improved classification of *H. pylori*-positive subjects in our study. A study that compared seropositivity to *H. pylori* whole-cell and CagA antigens versus *H. pylori* culture of biopsy samples showed that individuals who were seronegative for whole-cell antibodies but seropositive for CagA antibodies were in fact *H. pylori* positive and carried CagA-positive strains (39). Approximately 5% of all tested individuals in our study were positive for CagA antibodies but negative for whole-cell antibodies, a frequency similar to that reported in previous studies (38,42). Had we defined *H. pylori*-positive cases solely on the basis of whole-cell antibody positivity rather than on the basis of either whole-cell or CagA antibody positivity, the adjusted odds ratio would have been 3.3 (rather than 7.9), probably because of nondifferential misclassification of individuals with respect to their prior exposure to *H. pylori*.

We found that *H. pylori* seropositivity was inversely associated with the risk of gastric cardia adenocarcinomas. Only one

other prospective study (44) has shown a statistically significant inverse association between *H. pylori* seropositivity and the risk of gastric cardia cancer. Other studies have reported conflicting results. For example, most studies of Asian populations have found a positive association between *H. pylori* seropositivity and this cancer, whereas most studies of Western populations have found no association or an inverse association (8,26). The present study, conducted in Finland, yielded results similar to those observed in most other Western studies (44,45).

One explanation for the different associations reported by Asian and Western studies may be that the latter studies (26), as well as the present study, might have included a number of esophageal adenocarcinoma subjects among cardia cancer subjects. It is not always possible to distinguish between adenocarcinomas that arise in the gastric cardia and those that arise in the lower esophagus or the body of the stomach. This issue is further complicated by the ambiguities in the definitions of cardia (46) and cardia cancer (47). We defined gastric cardia cancer cases as those that involved the esophagogastric junction. However, in some parts of Asia where Barrett's esophagus and adenocarcinomas of the lower esophagus are very rare or nonexistent [e.g., Linxian, China; (38)], tumors that are classified as cardia gastric cancers do not include any esophageal adenocarcinoma cases. Nevertheless, the results of this and other studies (44,45,48-50) provide evidence that *H. pylori* colonization in the stomach is associated with decreased risks of some forms of adenocarcinoma arising near the junction of the esophagus and the stomach.

Several lines of evidence argue that our finding of an inverse association between *H. pylori* seropositivity and the risk of gastric cardia cancer is real and not due to chance. First, an association of similar direction was found when serum samples from a subgroup of these case subjects and a different set of control subjects from the ATBC study were tested in a different laboratory. The results of this smaller study have not been published as an independent paper, but summary statistics are shown in the combined analysis of the prospective studies (8). Second, using unconditional models, the point estimate for this association remained around 0.5, and the association remained statistically significant regardless of other variables included in the model. Third, inverse associations between *H. pylori* seropositivity and risks of gastroesophageal junctional cancers (i.e., esophageal or cardia cancers) have been shown in other Western studies (44, 45,48-50). The reasons for the observed inverse association between *H. pylori* seropositivity and the increased risk of gastroesophageal junctional adenocarcinomas are not entirely clear (48). However, one hypothesis is that *H. pylori* colonization induces gastric atrophy, which results in reduced gastric acidity, less acid reflux into the esophagus, and a reduced risk of Barrett's esophagus and junctional cancers (51,52).

H. pylori seropositivity was inversely associated with the risk of gastric cardia cancer for both shorter (0.0-6.9 years) and longer (7.0 years or more) follow-ups and in both younger and older cohorts, although the modest number of cardia cancer cases made it difficult to obtain stable estimates of odds ratios by subgroup, especially when using conditional models. Similarly, in this and prior studies (8), there were insufficient numbers of diffuse-type cardia cancer cases to reach meaningful conclusions about the effect of tumor histologic subtype on the association. The inverse association observed was more pronounced and statistically significant for CagA-negative strains than for CagA-positive strains, which contrasts with the results of an earlier retrospective study (48)

that suggested that CagA-positive strains were more strongly associated with a decreased risk of gastric cardia cancers.

The results of this study suggest that caution is warranted against mass treatment to eradicate *H. pylori*. Because *H. pylori* has been consistently associated with higher risk of gastric non-cardia cancer, several large clinical trials are ongoing to examine the effect of *H. pylori* eradication on gastric cancer incidence. The inverse association of *H. pylori* with gastric cardia cancer or esophageal adenocarcinoma, shown in this study and several other studies on Western populations (44,45,48–50), collectively suggests that *H. pylori* eradication may increase risk for gastroesophageal junctional cancers, at least in some Western populations. This hypothesis is supported by the substantial increase in the incidence of gastroesophageal junctional cancers in Western countries in the past few decades, possibly because of the lack of acquisition of *H. pylori* due to improved sanitation or the coincidental elimination of *H. pylori* due to widespread antibiotic use. Therefore, mass treatment to eradicate *H. pylori* may be justified in parts of the world where the incidence of distal gastric cancers far exceeds that of junctional cancers. However, in Western countries, where rates of gastroesophageal junctional cancer are now high, a mass eradication policy should be considered with caution. Future studies with stratifications based on *H. pylori* strains and careful anatomic classification should help clarify these issues.

The strengths of this study include the large sample size, the prospective design, the long-term follow-up, the availability of data on the location and histopathologic classification of tumors, the availability of extensive data on potential confounders, and the measurement of both *H. pylori* whole-cell and CagA antibodies. The most important limitation of this study, the possible misclassification in distinguishing cardia cancers from adenocarcinomas of the proximal noncardia stomach or lower esophagus, is a limitation inherent to all studies of gastric cardia cancers and does not refute our finding that *H. pylori* seropositivity is associated with reduced risks of some forms of gastroesophageal junctional cancer. The relatively small number of gastric cardia cancer cases limited our ability to perform subgroup analyses.

In summary, in this prospective study, *H. pylori* seropositivity was a strong risk factor for noncardia gastric cancer but was inversely associated with the risk of gastric cardia cancer. Moreover, *H. pylori* was a strong risk factor for noncardia gastric cancer regardless of the length of the interval between serum collection and diagnosis or the tumor histologic subtype. Our findings bolster the hypothesis that the decreasing prevalence of *H. pylori* infection during the past century may have contributed to the lower rates of noncardia gastric cancer and to the higher rates of cardia/junctional gastric cancers observed in Western countries (53,54).

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NOTES

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