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Prediagnostic *Helicobacter pylori* Antibodies and Colorectal Cancer Risk in an Elderly, Caucasian Population

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Abstract

Background: Study results on overall seroprevalence of *Helicobacter pylori* and colorectal cancer risk have been inconsistent. However, one study found positive associations with antibodies to specific *H. pylori* proteins. To follow up on those findings, we assessed associations of 15 *H. pylori* specific proteins with colorectal cancer incidence in the prospective Cancer Prevention Study-II Nutrition Cohort.

Materials and Methods: Participants in this nested case–control study included 392 cases and 774 controls who were predominantly elderly (median age at blood draw: 71 years) and Caucasian (98%). Seroreactivity against 15 *H. pylori* proteins was assessed by fluorescent bead-based multiplex serology and associations with colorectal cancer were estimated using conditional logistic regression.

Results: *Helicobacter pylori* serostatus was not associated with colorectal cancer incidence (odds ratio (OR), 1.17, 95% confidence interval (95% CI), 0.91–1.50). Among individual antigens, GroEl serostatus was associated with colorectal cancer risk (OR, 1.32, 95% CI: 1.03–1.70), whereas CagM was associated with colon cancer risk only (OR, 1.35, 95% CI: 1.01–1.80). No dose–response relationships were observed for any of the antigens, including GroEl and CagM.

Conclusions: The results of our study do not support an association between *H. pylori* infection and colorectal cancer risk in this elderly, mostly Caucasian population.

Approximately half of the worlds' population is infected with *Helicobacter pylori* (*H. pylori*). Infection usually occurs in childhood and persists unless treated [1]. *H. pylori* is an established cause of gastric cancer [1] and may promote tumorigenesis in other organs in the gastrointestinal tract, such as the colon. Unlike in the stomach, *H. pylori* does not take up residence in the colon, however it may move through the colonic lumen and activate a local chain of events that can lead to cancer [2]. Some studies support this via evidence of *H. pylori* presence in the tumor, but other studies have found no evidence of this pathogen in colon tumors [2]. Even if *H. pylori* does not act on the colon directly, indirect mechanisms of colon carcinogenesis have been hypothesized. One hypothesis is through increased production of the peptide hormone gastrin. Gastrin has been shown to be mitogenic to the colon both in vitro [3,4] and in mice [5,6]; and two prospective studies [7,8] reported positive associations between higher serum/plasma gastrin levels and risk of colorectal cancer. Another leading hypothesis is that reduced gastric acid secretion (as a result of *H. pylori* infection) promotes changes in colorectal microflora that may also contribute to colorectal carcinogenesis [2,9]. Other possible mechanisms of colorectal carcinogenesis for *H. pylori* include induction of inflammation [10] and production of mutagenic toxins [11]. The complex interplay between bacterial inflammation, toxin production, and subsequent cellular responses can create a procarcinogenic environment—increasing cell proliferation and angiogenesis and inhibiting apoptosis [11]. In vitro, *H. pylori* is capable of transforming colorectal cells

leading to abnormal cell proliferation and tumorigenesis. In particular, the *H. pylori* strains harboring the cag pathogenicity island and the vacuolating cytotoxin (vac)A gene are known to be more virulent than others, and may be especially carcinogenic [13,14].

Results of studies on overall seroprevalence of *H. pylori* and colorectal cancer risk have been inconsistent, but recent studies suggest that there may be a positive association. A review of 150,000 surgical pathology reports among patients who had both a colonoscopy and esophago-gastro-duodenoscopy between 2008 and 2011, showed a higher frequency of *H. pylori*-positive gastritis (but not *H. pylori*-negative gastritis) among patients whose colonoscopy revealed colon cancer [15]. Furthermore, a recent meta-analysis reported a statistically significant positive summary odds ratio (odds ratio (OR) = 1.30, 95% confidence interval (CI) = 1.07–1.59) for the association between *H. pylori* and colon cancer [16]. In a 2013 prospective analysis from the Southern Community Cohort Study (SCCS), there were strong positive associations for specific strains of *H. pylori* and risk of colorectal cancer [17]. In that analysis, Epplein et al. found that seropositivity for antibodies to VacA, HP231, HP305, NapA, HcpC were associated with a 60–80% higher risk of colorectal cancer, and an almost 2-fold risk of colon cancer specifically. Previous research supports these findings showing the toxins CagA and VacA, produced by some strains of *H. pylori,* modulate cell proliferation and apoptosis by altering the signaling of mitogen-activated protein kinase and epidermal growth factor pathways [18]. In addition, studies of gastric cancer show that cag-positive strains are more likely to cause inflammation and malignancy than cag-negative strains [13].

Due to the limited number of prospective studies on this topic, particularly for specific *H. pylori* strains, we examined the association between *H. pylori* antibodies and colorectal cancer risk in the Cancer Prevention Study-II Nutrition Cohort.

Materials and Methods

The present prospective analysis is a case–control study nested within the American Cancer Society Cancer Prevention Study-II Nutrition Cohort (CPS-II Nutrition). CPS-II Nutrition (n = 184,185) is a prospective study of cancer incidence in 21 states in the United States initiated in 1992. The recruitment, characteristics, and follow-up of the cohort are described in greater detail elsewhere [19]. Participants in this nested case–control study were among the subgroup of CPS-II Nutrition Cohort participants provided a blood sample between 1998 and 2001 and were cancer-free at blood draw (n = 39,371). Colorectal cancer cases diagnosed before June 30, 2009 (n = 392) were identified by self-report on biennial questionnaires and subsequently verified through medical records (n = 277) or registry linkage (n = 92). An additional 23 cases were obtained through National Death Index records. These cases died between survey cycles and, therefore, did not have the opportunity to report their colorectal cancer. For each case, two controls were individually matched on sex, race, birth date, and blood draw date (±6 months). The race criteria had to be relaxed for 6 (2%) cases.

Seroreactivity against 15 *H. pylori* antigenic proteins: Cad, HomB, CagM, CagA, Catalase, HcpC, HP0231, HP0305, HpaA, HyuA, GroEL, NapA, Omp, VacA, and UreA were assessed by fluorescent bead-based multiplex serology (serum dilution 1 : 1000) at the German Cancer Research Center [20]. In this method, each antigen is carried by a uniquely-colored bead. Bead sets carrying different antigens are mixed with plasma and are evaluated with a Luminex 200 analyzer to quantify the antibody reactivity to each antigen in the sample. The level of antibody reactivity to each antigen is measured as median fluorescence intensity (MFI) [20]. Coefficients of variation for quality control samples ranged from 7 to 17%; intraclass correlation coefficients ranged from 79 to 99%. Antigen-specific serostatus cutpoints were calculated from the MFI values from 30 additional sera previously classified for *H. pylori* status [20]. Consistent with earlier studies, overall *H. pylori* seropositivity was defined as reactivity to at least four proteins [17,20]. For dose–response analyses, cutpoints for antibody levels were calculated from MFI tertiles among seropositive control participants. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for associations of overall *H. pylori* serostatus, antigen-specific serostatus, and antibody levels with risk of colorectal cancer. Serostatus associations were also examined stratified by cancer site (colon, rectal), stage (local, regional, distant), and age at diagnosis (tertiles). Analyses by stage were further adjusted for education (<high school, high school/missing, some college/vocational school, college and above) and for a history of colorectal screening in the past 2 years (ever vs never).

Results

The study population included 392 cases and 774 controls. Participants were aged 56–87 years (median: 71) at blood draw and cases had a median age of 76 years at colorectal cancer diagnosis. Controls were significantly more likely than cases to be non-obese and report colorectal cancer screening within 2 years of

blood draw. *H. pylori*-negative participants were significantly more likely to have higher educational attainment, to be non-obese and to be regular aspirin users. This mostly Caucasian cohort (98%) had an overall *H. pylori* seroprevalence of 36.8% (39.3% cases, 35.5% controls).

In this study, overall *H. pylori* serostatus was not associated with colorectal cancer (OR, 1.17, 95% CI, 0.91–1.50), colon cancer (OR, 1.21, 95% CI, 0.92–1.59), or rectal cancer incidence (OR, 1.00, 95% CI, 0.57–1.77). Among individual antigens, GroEl seropositivity was associated with colorectal cancer risk (OR, 1.32, 95% CI: 1.03–1.70, Table 1), whereas CagM seropositivity was associated with colon, but not rectal, cancer risk (OR, 1.35, 95% CI: 1.01–1.80). No association was found between other antigens and colorectal cancer risk. When analyses were stratified by cancer site, age and stage-at-diagnosis, there was no clear evidence of effect modification. No dose–response associations were observed for any antigens, including GroEl and CagM (Table 2).

Discussion

Our study provides little support for a strong connection between *H. pylori* serostatus and colorectal cancer risk. Associations were observed for serostatus of two (of 15) antigens, but there were no dose–response associations, and chance may explain these observations given the high number of analyses performed. Our null results for overall *H. pylori* serostatus were consistent with other prospective studies [17,21,22], but we did

Table 1 Seroprevalence for antibodies to *H. pylori* proteins in relation to colorectal cancer in the Cancer Prevention Study-II[a]

	Risk of colorectal cancer			Risk of colon cancer		Risk of rectal cancer	
Antigen	Controls n (%)	Cases n (%)	OR (95% CI)	Cases n (%)	OR (95% CI)	Cases n (%)	OR (95% CI)
GroEl−	527 (68.1)	241 (61.5)	1.00 (ref.)	196 (62.0)	1.00 (ref.)	45 (59.2)	1.00 (ref.)
GroEl+	247 (31.9)	151 (38.5)	**1.32 (1.03–1.70)**	120 (38.0)	1.30 (0.98–1.72)	31 (40.8)	1.42 (0.81–2.46)
Urea−	485 (62.7)	245 (62.5)	1.00 (ref.)	201 (63.6)	1.00 (ref.)	44 (57.9)	1.00 (ref.)
Urea+	289 (37.3)	147 (37.5)	0.99 (0.77–1.28)	115 (36.4)	0.97 (0.73–1.29)	32 (42.1)	1.09 (0.61–1.95)
HP231−	614 (79.3)	298 (76.0)	1.00 (ref.)	240 (75.9)	1.00 (ref.)	58 (76.3)	1.00 (ref.)
HP231+	160 (20.7)	94 (24.0)	1.21 (0.90–1.62)	76 (24.1)	1.19 (0.86–1.64)	18 (23.7)	1.31 (0.68–2.55)
NapA−	570 (73.6)	282 (71.9)	1.00 (ref.)	227 (71.8)	1.00 (ref.)	55 (72.4)	1.00 (ref.)
NapA+	204 (26.4)	110 (28.0)	1.09 (0.83–1.44)	89 (28.2)	1.12 (0.82–1.51)	21 (27.6)	1.00 (0.52–1.91)
HP305−	614 (79.3)	317 (80.9)	1.00 (ref.)	252 (79.7)	1.00 (ref.)	65 (85.5)	1.00 (ref.)
HP305+	160 (20.7)	75 (19.1)	0.90 (0.66–1.22)	64 (20.3)	0.95 (0.68–1.33)	11 (14.5)	0.69 (0.33–1.46)
HpaA−	580 (74.9)	299 (76.3)	1.00 (ref.)	241 (76.3)	1.00 (ref.)	58 (76.3)	1.00 (ref.)
HpaA+	194 (25.1)	93 (23.7)	0.93 (0.70–1.24)	75 (23.7)	0.90 (0.66–1.23)	18 (23.7)	1.08 (0.55–2.12)
CagM−	539 (69.6)	256 (65.3)	1.00 (ref.)	203 (64.2)	1.00 (ref.)	53 (69.7)	1.00 (ref.)
CagM+	235 (30.4)	136 (34.7)	1.21 (0.94–1.58)	113 (35.8)	**1.35 (1.01–1.80)**	23 (30.3)	0.77 (0.42–1.43)
CagA−	569 (73.5)	279 (71.2)	1.00 (ref.)	222 (70.3)	1.00 (ref.)	57 (75.0)	1.00 (ref.)
CagA+	205 (26.5)	113 (28.8)	1.14 (0.86–1.49)	94 (29.7)	1.22 (0.90–1.65)	19 (25.0)	0.85 (0.45–1.58)
HyuA−	549 (70.9)	283 (72.2)	1.00 (ref.)	231 (73.1)	1.00 (ref.)	52 (68.4)	1.00 (ref.)
HyuA+	225 (29.1)	109 (27.8)	0.93 (0.71–1.21)	85 (26.9)	0.88 (0.65–1.18)	24 (31.6)	1.16 (0.65–2.07)
Catalase−	625 (80.8)	325 (82.9)	1.00 (ref.)	260 (82.3)	1.00 (ref.)	65 (85.5)	1.00 (ref.)
Catalase+	149 (19.2)	67 (17.1)	0.86 (0.62–1.18)	56 (17.7)	0.92 (0.65–1.32)	11 (14.5)	0.62 (0.28–1.34)
VacA−	534 (69.0)	261 (66.6)	1.00 (ref.)	212 (67.1)	1.00 (ref.)	49 (64.5)	1.00 (ref.)
VacA+	240 (31.0)	131 (33.4)	1.12 (0.86–1.46)	104 (32.9)	1.10 (0.82–1.48)	27 (35.5)	1.19 (0.63–2.25)
HpcC−	616 (79.6)	300 (76.5)	1.00 (ref.)	241 (76.3)	1.00 (ref.)	59 (77.6)	1.00 (ref.)
HpcC+	158 (20.4)	92 (23.5)	1.19 (0.89–1.60)	75 (23.7)	1.25 (0.90–1.74)	17 (22.4)	1.00 (0.53–1.90)
Cad−	662 (85.5)	326 (83.2)	1.00 (ref.)	265 (83.9)	1.00 (ref.)	61 (80.3)	1.00 (ref.)
Cad+	112 (14.5)	66 (16.8)	1.18 (0.85–1.64)	51 (16.1)	1.16 (0.80–1.67)	15 (19.7)	1.29 (0.65–2.60)
Omp−	561 (72.5)	271 (69.1)	1.00 (ref.)	222 (70.3)	1.00 (ref.)	49 (64.5)	1.00 (ref.)
Omp+	213 (27.5)	121 (30.1)	1.17 (0.90–1.53)	94 (29.7)	1.14 (0.84–1.54)	27 (35.5)	1.29 (0.73–2.27)
HOMB−	557 (72.0)	269 (68.6)	1.00 (ref.)	217 (68.7)	1.00 (ref.)	52 (68.4)	1.00 (ref.)
HOMB+	217 (28.0)	123 (31.4)	1.18 (0.90–1.56)	99 (31.3)	1.30 (0.95–1.77)	24 (31.6)	0.86 (0.47–1.56)

Bold indicates statistically significant at $p < .05$.

[a]Results are from a conditional logistic regression model with cases and controls matched on age, race, sex, and blood draw date.

Table 2 Risk of colorectal cancer by antibody level tertiles of *H. pylori* proteins in the Cancer Prevention Study-II[a]

Risk of colorectal cancer							
Antigen Level	Controls n (%)	Cases n (%)	OR (95% CI)	Antigen level	Controls n (%)	Cases n (%)	OR (95% CI)
GroEl−	527 (68.1)	241 (61.5)	1.00 (ref)	CagA−	569 (73.5)	279 (71.2)	1.00 (ref)
T1	81 (10.5)	59 (15.1)	**1.58 (1.10–2.27)**	T1	68 (8.8)	29 (7.4)	0.87 (0.55–1.37)
T2	85 (11.0)	56 (14.3)	1.42 (0.98–2.06)	T2	69 (8.9)	40 (10.2)	1.23 (0.82–1.84)
T3	81 (10.5)	36 (9.2)	0.96 (0.63–1.45)	T3	68 (8.8)	44 (11.2)	1.31 (0.88–1.97)
Urea−	485 (62.7)	245 (62.5)	1.00 (ref)	HyuA−	549 (70.9)	283 (72.2)	1.00 (ref)
T1	96 (12.4)	48 (12.2)	0.98 (0.67–1.43)	T1	75 (9.7)	33 (8.4)	0.85 (0.55–1.30)
T2	98 (12.7)	52 (13.3)	1.05 (0.73–1.52)	T2	76 (9.8)	38 (9.7)	0.95 (0.63–1.44)
T3	95 (12.3)	47 (12.0)	0.95 (0.65–1.39)	T3	74 (9.6)	38 (9.7)	0.99 (0.65–1.50)
HP231−	614 (79.3)	298 (76.0)	1.00 (ref)	Catalase−	625 (80.7)	325 (82.9)	1.00 (ref)
T1	53 (6.8)	29 (7.4)	1.19 (0.74–1.90)	T1	50 (6.5)	19 (4.8)	0.62 (0.35–1.11)
T2	55 (7.1)	31 (7.9)	1.11 (0.69–1.78)	T2	50 (6.5)	25 (6.4)	1.05 (0.64–1.71)
T3	52 (6.7)	34 (8.7)	1.34 (0.84–2.13)	T3	49 (6.3)	23 (5.9)	0.89 (0.53–1.48)
NapA−	570 (73.6)	282 (71.9)	1.00 (ref)	VacA−	534 (69.0)	261 (66.6)	1.00 (ref)
T1	67 (8.7)	33 (8.4)	1.00 (0.64–1.56)	T1	80 (10.3)	45 (11.5)	1.16 (0.78–1.73)
T2	69 (8.9)	40 (10.2)	1.18 (0.78–1.79)	T2	81 (10.5)	42 (10.7)	1.05 (0.70–1.57)
T3	68 (8.8)	37 (9.4)	1.10 (0.72–1.68)	T3	79 (10.2)	44 (11.2)	1.15 (0.77–1.72)
HP305−	614 (79.3)	317 (80.9)	1.00 (ref)	HpcC−	616 (79.6)	300 (76.5)	1.00 (ref)
T1	53 (6.8)	15 (3.8)	**0.53 (0.30–0.97)**	T1	53 (6.8)	23 (5.9)	0.90 (0.54–1.52)
T2	54 (7.0)	31 (7.9)	1.11 (0.70–1.77)	T2	53 (6.8)	32 (8.2)	1.24 (0.78–1.96)
T3	53 (6.8)	29 (7.4)	1.04 (0.65–1.67)	T3	52 (6.7)	37 (9.4)	1.42 (0.90–2.23)
HpaA−	580 (74.9)	299 (76.3)	1.00 (ref)	Cad−	662 (85.5)	326 (83.2)	1.00 (ref)
T1	64 (8.3)	30 (7.7)	0.89 (0.56–1.40)	T1	36 (4.7)	20 (5.1)	1.13 (0.64–1.99)
T2	65 (8.4)	26 (6.6)	0.79 (0.50–1.27)	T2	40 (5.2)	29 (7.4)	1.47 (0.90–2.40)
T3	65 (8.4)	37 (9.4)	1.10 (0.72–1.67)	T3	36 (4.7)	17 (4.3)	0.92 (0.51–1.67)
CagM−	539 (69.6)	256 (65.3)	1.00 (ref)	Omp−	561 (72.5)	271 (69.1)	1.00 (ref)
T1	78 (10.1)	45 (11.5)	1.20 (0.80–1.79)	T1	70 (9.0)	35 (8.9)	1.06 (0.69–1.65)
T2	80 (10.3)	61 (15.6)	**1.59 (1.11–2.28)**	T2	73 (9.4)	47 (12.0)	1.31 (0.88–1.95)
T3	77 (9.9)	30 (7.7)	0.82 (0.52–1.28)	T3	70 (9.0)	39 (9.9)	1.13 (0.74–1.73)
				HOMB−	557 (72.0)	269 (68.6)	1.00 (ref)
				T1	72 (9.3)	35 (8.9)	1.00 (0.64–1.55)
				T2	73 (9.4)	36 (9.2)	1.04 (0.68–1.59)
				T3	72 (9.3)	52 (13.3)	**1.50 (1.02–2.23)**

Bold indicates statistically significant at $p < .05$.

[a]Results are from a conditional logistic regression model with cases and controls matched on age, race, sex, and blood draw date.

not observe the strong, positive associations for VacA and the other antigens found by Epplein et al. [17], including when results were stratified by subsite, cancer stage, and age at diagnosis.

This is the largest prospective study on *H. pylori* antigens to date. Despite a sizable sample and sufficient power to examine *H. pylori* serostatus, we did have a limited sample size for certain antigens. Although the sample size was twice that of the SCCS, seroprevalence of specific antigens, especially the more virulent strains, VacA and CagA, were lower than in the SCCS (31.8 vs 71.7% and 27.3 vs 68.8%, respectively). These differences in prevalence are likely explained by socioeconomic factors since *H. pylori* is much more common in low-income and minority populations [23] that are more common in the SCCS [17] than in the CPS-II Nutrition Cohort. These differences in population characteristics may explain, at least in part, the discrepancies between our results and those of Epplein et al. [17]. Previous studies support the idea of differences by study population in the association between *H. pylori* and colorectal cancer [21,24–26] as well as precursors such as polyps and adenomas [24,27–30].

In summary, the results of our study do not support an association between *H. pylori* antibodies and colorectal cancer risk in an elderly, educated, Caucasian population. More research is needed to investigate whether the differences observed between our results and Epplein et al. can be explained by differences in popu-

lation characteristics or if other factors, including chance, explain these findings.

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