Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.5465

World J Gastroenterol 2009 November 21; 15(43): 5465-5471
World Journal of Gastroenterology ISSN 1007-9327

BRIEF ARTICLE

Association between *Helicobacter pylori* seropositivity and digestive tract cancers

I-Chen Wu, Deng-Chyang Wu, Fang-Jung Yu, Jaw-Yuan Wang, Chao-Hung Kuo, Sheau-Fang Yang, Chao-Ling Wang, Ming-Tsang Wu

I-Chen Wu, Deng-Chyang Wu, Fang-Jung Yu, Chao-Hung Kuo, Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan, China
Deng-Chyang Wu, Jaw-Yuan Wang, Chao-Hung Kuo, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan, China
Jaw-Yuan Wang, Division of Gastrointestinal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan, China
Sheau-Fang Yang, Department of Pathology, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan, China
Chao-Ling Wang, Ming-Tsang Wu, Graduate Institute of Occupational Safety and Health, Kaohsiung Medical University, Kaohsiung 807, Taiwan, China
Chao-Ling Wang, Department of Preventive Medicine, Kaohsiung Medical University Hospital, Kaoshiung 807, Taiwan, China
Ming-Tsang Wu, Department of Family Medicine, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan, China
Author contributions: Wu IC, Wu DC and Wu MT participated in the analysis of data, designed and conducted the research and wrote the manuscript; Yang SF participated in the laboratory analysis; Yu FJ, Wang JY, Kuo CH and Wang CL participated in the collection of study subjects.
Supported by Grants From Kaohsiung Medical University Hospital, 97-ND-006, the National Science Council, NSC 97-2314-B-037-018, NSC 98-2314-B-037-004, and the Department of Health, Taiwan
Correspondence to: Ming-Tsang Wu, MD, ScD, Department of Family Medicine, Kaohsiung Medical University Hospital, 100 Shih-Chuan 1st Road, Kaohsiung 807, Taiwan, China. 960021@ms.kmuh.org.tw
Telephone: +886-7-3121101-2315 Fax: +886-7-3221806
Received: September 1, 2009 Revised: October 9, 2009
Accepted: October 16, 2009
Published online: November 21, 2009

Abstract

AIM: To explore the role of *Helicobacter pylori* (*H pylori*) infection on the risk of digestive tract cancers.

METHODS: In total, 199 oral squamous-cell carcinoma (SCC), 317 esophageal SCC, 196 gastric cardia and non-cardia adenocarcinoma and 240 colon adenocarcinoma patients were recruited for serum tests of *H pylori* infection. Two hospital- and one community-based control groups were used for the comparisons. *H pylori* seropositivity was determined by an enzyme linked immunosorbent assay method against *H pylori* IgG.

RESULTS: Presence of *H pylori* infection was significantly inversely associated with esophageal SCC [adjusted odds ratio (AOR): 0.315-0.472, all *P*-value < 0.05] but positively associated with gastric adenocarcinoma (both cardia and non-cardia) (AOR: 1.636-3.060, all *P*-value < 0.05) in comparison to the three control groups. Similar results were not found in cancers of the oral cavity and colon.

CONCLUSION: Our findings support the finding that *H pylori* seropositivity is inversely associated with esophageal SCC risk, but increases the risk of gastric cardia adenocarcinoma.

Key words: *Helicobacter pylori* infection; Oral cancer; Esophageal squamous cell carcinoma; Gastric cardia adenocarcinoma; Colon cancer

Peer reviewer: Mark Bloomston, MD, FACS, Assistant Professor of Surgery, Division of Surgical Oncology, The Ohio State University, N924 Doan Hall,410W.10th Avenue, Columbus, OH 43082, United States

Wu IC, Wu DC, Yu FJ, Wang JY, Kuo CH, Yang SF, Wang CL, Wu MT. Association between *Helicobacter pylori* seropositivity and digestive tract cancers. *World J Gastroenterol* 2009; 15(43): 5465-5471 Available from: URL: http://www.wjgnet.com/1007-9327/15/5465.asp DOI: http://dx.doi.org/10.3748/wjg.15.5465

INTRODUCTION

It is widely accepted that chronic *Helicobacter pylori* (*H pylori*) infection, especially cytotoxin-associated gene A (CagA)-positive strains, causes non-cardiac gastric carcinoma *via* the intestinal metaplasia-carcinoma sequence[1,2]. However, there is debate in regard to the association between *H pylori* infection and gastric cardia adenocarcinoma. Most studies in Asian countries[3-5] have indicated an increased risk of cardia cancer in *H pylori*-infected subjects, while those in Western countries have reported a protective role

of *H pylori*[6] or a negative association[7-9] between these two.

Recently, cumulative evidence has indicated that *H pylori* infection plays a protective role in the development of reflux esophagitis[10,11] and esophageal adenocarcinoma (EA)[6,8,12,13]. In contrast, the relationship between *H pylori* infection and esophageal squamous cell carcinoma (SCC) is still inconclusive[8,14-17]. Very few studies have examined the role of *H pylori* infection on colon and oral cancers. Therefore, we aim to expand our esophageal SCC cases and to examine the relationship between *H pylori* infection and the risk of oral SCC, gastric cancer, especially gastric cardia adenocarcinoma and colon cancer, in a Taiwanese population.

MATERIALS AND METHODS

Selection of cases and controls

This was a hospital-based case-control study design. Three hundred and seventeen newly pathologically proven ESCC patients (301 males and 16 females) were recruited from two medical centers in the Kaohsiung metropolitan area in southern Taiwan, including the Kaohsiung Medical University Hospital (KMUH) and the Kaohsiung Veterans General Hospital (KVGH) between 2000 and 2007. The detailed information was described elsewhere[18]. Patients with newly pathologically proven oral SCC (n = 199), gastric (n = 196) and colon adenocarcinoma (n = 240) were recruited from the KMUH in the same period.

The first hospital-based control group was recruited from the Department of Preventive Medicine in these two hospitals and matched with each esophageal SCC patient (case:control = 1:1-4) by gender, age (within a 4 year age difference) and hospitalization (within 4 wk after each case was identified). In this study, we randomly selected 1 out of 1-4 matched controls (n = 305, 289 males and 16 females) for each case to investigate the status of *H pylori* infection[19]. Twelve cases did not have suitable controls. In order to examine the different prevalence of *H pylori* infection from different areas or different sources of selection, we included another two comparison groups, defined as the second hospital-based control group and the community-based control group, in this study. The second hospital-based control group (n = 403, 374 males and 29 females) were originally used for the esophageal cancer study in National Taiwan University Hospital (NTUH) in Taipei[20]. They were cancer-free, had visited for a health check-up in NTUH, and had enough stored serum specimens for testing *H pylori* status during the same period of this study. The community-based control group (n = 395, 204 males and 191 females) consisted of healthy subjects living in Kaohsiung who voluntarily participated in one large multi-year study of childhood neoplasms at the same period of this study[14,21]. The second hospital-based and the community-based control groups were not matched by age and gender with our esophageal SCC patients.

All subjects provided blood samples before any treatment or blood transfusion for *H pylori* seropositivity. For those with positive *H pylori* antibodies, CagA status was further examined using an enzyme immunoassay. The institutional review boards at NTUH and KMUH reviewed and approved this study, and all participants signed written sheets of informed consent.

Location of esophageal SCC and gastric adenocarcinoma

Lesions were classified with respect to their location in the upper, middle or lower third of the esophagus, described previously[22,23]. Gastric cardia adenocarcinomas were defined as a tumor centered within 3 cm distal to the gastroesophageal junction. There was no difficulty in distinguishing lower third esophageal cancer with cardia invasion from gastric cardia cancer extending to the lower esophagus, because SCC comprise more than 95% of esophageal cancers in Taiwan[24]. Cardia adenocarcinoma was classified as being of gastric origin, if Barrett's esophagus was not detected in the adjacent tissue.

H pylori serology and CagA status

Non-heparinized whole blood was collected and serum was isolated and stored at -70℃ for subsequent analysis. A commercially available immunochromatographic screening test (Chembio *H pylori* STAT-PAK, Chembio Diagnostic System, Inc., Medford, NY, USA) utilizing a combination of *H pylori* antigen coated particles and anti-human IgG was used to qualitatively and selectively detect *H pylori* antibodies in serum[14]. According to the manufacturer's instructions, the sensitivity and specificity of STAT-PAK were 94% and 98%, respectively. Final readings were recorded after verification by at least two research technicians blinded to the status of cases and controls.

A commercial kit, Helori CTX IgG (ravo Diagnostika GmbH, Freiburg, Germany), was used to detect the IgG antibodies against serum CagA by enzyme immunoassay. The average optical density (A) values of subject specimens, blank, negative and positive controls were calculated. The A of negative and positive controls must be always < 0.100 and > 0.800, respectively, in each set of samples. The concentration of each sample was expressed as units obtained from the formula: sample $A \times$ calibrator value (units)/calibrator A Based on guidelines set forth by the manufacturer, we set negative and positive cutoff points for each concentration as $<$ 5 and $\geqslant$ 5 units, respectively. The research technicians were also blinded to the status of cases and controls.

Statistical analysis

Multiple logistic regression models were used to examine the association between *H pylori* infection (seropositivity by STAT-PAK) and esophageal SCC risk using each of three control groups as a basis of comparison before and after adjusting for other covariates, including age (continuous), gender, educational levels ($\leqslant$ primary school, junior high and high school, and $>$ high school), cigarette

Table 1 Demographic characteristics of digestive tract cancer patients and controls *n* (%)

	Cancer				Control		
	Oral SCC	Esophageal SCC	Gastric adenocarcinoma	Colon adenocarcinoma	1st hospital-based control	2nd hospital-based control	Community-based control
n	199	317	196	240	305	403	395
Age mean ± SD	50.6 ± 9.9	58.3 ± 11.6	63.2 ± 13.5	64.5 ± 12.7	57.1 ± 11.4	60.0 ± 10.2	40.2 ± 6.2
(min, med, max)	(26, 50, 78)	(34, 58, 86)	(22, 65, 91)	(24, 66, 89)	(34, 57, 82)	(39, 60, 84)	(30, 40, 58)
Sex							
Male	188 (90.5)	301 (95.0)	123 (62.8)	139 (57.9)	289 (94.8)	374 (92.8)	204 (51.6)
Female	11 (5.5)	16 (5.0)	73 (37.2)	101 (42.1)	16 (5.2)	29 (7.2)	191 (48.4)
Educational level							
≤ primary school	117 (58.8)	176 (55.5)	118 (60.2)	133 (55.4)	78 (25.6)	162 (40.2)	41 (10.4)
Junior high & high school	76 (38.2)	120 (37.9)	53 (27.0)	72 (30.0)	93 (30.5)	76 (18.9)	241 (61.0)
> high school	6 (3.0)	21 (6.6)	25 (12.8)	35 (14.6)	134 (43.9)	165 (40.9)	113 (28.6)
Cigarette smoking							
No	32 (16.1)	39 (12.3)	101 (51.5)	143 (59.6)	168 (55.1)	248 (61.5)	283 (71.6)
Yes	167 (83.9)	278 (87.7)	95 (48.5)	97 (40.4)	137 (44.9)	155 (38.5)	112 (28.4)
Alcohol consumption							
No	64 (32.2)	60 (18.9)	145 (74.0)	193 (80.4)	215 (70.5)	288 (71.5)	298 (75.4)
Yes	135 (67.8)	257 (81.1)	51 (26.0)	47 (19.6)	90 (29.5)	115 (28.5)	97 (24.6)
Betel quid chewing							
No	29 (14.6)	149 (47.0)	171 (87.2)	213 (88.8)	280 (91.8)	381 (94.5)	-
Yes	170 (85.4)	168 (53.0)	25 (12.8)	27 (11.2)	25 (8.2)	22 (5.5)	-

SCC: Squamous cell carcinoma.

Table 2 Serum status of *H pylori* and CagA in cancer patients and control *n* (%)

	Cancer					Control		
	Oral SCC	Esophageal SCC	Gastric cardia adenocarcinoma	Gastric non-cardia adenocarcinoma	Colon adenocarcinoma	1st hospital-based control	2nd hospital-based control	Community-based control
n	199	317	29	167	240	305	403	395
H pylori								
-	104 (52.3)	205 (64.7)	8 (27.6)	48 (28.7)	105 (43.8)	141 (46.2)	164 (40.7)	235 (59.5)
+	95 (47.7)	112 (35.3)	21 (72.4)	119 (71.3)	135 (56.3)	164 (53.8)	239 (59.3)	160 (40.5)
CagA[1]								
-	14 (14.7)	8 (7.3)	1 (4.8)	9 (7.6)	12 (8.9)	24 (14.6)	-	11 (6.9)
±	13 (13.7)	10 (9.2)	3 (14.3)	8 (6.8)	7 (5.2)	14 (8.5)	-	6 (3.8)
+	68 (71.6)	91 (83.5)	17 (81.0)	101 (85.6)	116 (85.9)	126 (76.8)	-	142 (89.0)

[1]CagA status was determined among the subjects with *H pylori* seropositivity (No CagA data was available in 3 esophageal SCC, 1 gastric non-cardia adenocarcinoma and 1 community-based control).

smoking, alcohol drinking and betel nut chewing. Information about betel nut chewing was not available in the community control, so it was not evaluated in the regression models when the community control was used as the control group. The data were analyzed using the SAS statistical package; all *P*-values were two-sided.

RESULTS

Distribution of demographic variables and substance use for cancer cases and controls is summarized in Table 1. The majority of oral and esophageal SCC patients were male, and more than half of all cancer patients had an educational level of primary school or below. The ratio of women to men among the esophageal SCC was 3.5% (6/173) in KVGH, which is slightly lower, but not significantly different, than that in KMUH (6.9%, 10/144, *P*-value = 0.18). The mean age of the community control group (40.2 ± 6.2 years) was about 20 years younger than the other two control groups.

The *H pylori* seropositivity in esophageal SCC patients was 35.3%, which was consistently lower than those in the three controls (40.5%-59.3%) (Table 2). The seropositivity of *H pylori* among the ESCC patients was similar in those two hospitals: 36.1% (KMUH 53/147) and 34.7% (KVGH 59/170) (data not shown). In contrast, *H pylori* seropositivity in gastric adenocarcinoma patients (71.4%) was higher than that in all three control groups. *H pylori* seropositivity in gastric cardia and non-cardia adenocarcinoma patients was similar (Table 2). In addition, the prevalence of CagA-positive subjects among *H pylori*-infected cancer cases was 71.6%-85.9%, similar to that among *H pylori*-infected controls (76.8%-89.0%).

In multivariate analyses, there was still a significantly inverse association between *H pylori* seropositivity and esophageal SCC (AOR: 0.315-0.472, all *P*-values < 0.05).

Table 3 Association between *H pylori* infection and cancer risks

		Odds ratio (95% CI)	*P*-value	Adjusted odds ratio (95% CI)[1]	*P*-value
Oral SCC *vs*	1st hospital control	0.105 (0.787-1.553)	0.5640	0.961 (0.637-1.449)	0.8494
	2nd hospital control	0.627 (0.445-0.882)	0.0074	0.378 (0.190-0.751)	0.0055
	community control	1.342 (0.952-1.891)	0.0932	1.064 (0.622-1.820)	0.8211
Esophageal SCC *vs*	1st hospital control	0.470 (0.340-0.648)	< 0.0001	0.454 (0.290-0.710)	0.0005
	2nd hospital control	0.375 (0.277-0.508)	< 0.0001	0.315 (0.203-0.489)	< 0.0001
	community control	0.802 (0.591-1.089)	0.1581	0.472 (0.257-0.865)	0.0151
Gastric	1st hospital control	2.149 (1.465-3.152)	< 0.0001	2.015 (1.278-3.174)	0.0025
adenocarcinoma *vs*	2nd hospital control	1.715 (1.187-2.479)	0.0041	1.636 (1.071-2.501)	0.0228
	community control	3.672 (2.538-5.312)	< 0.0001	3.060 (1.650-5.674)	0.0004
Colon	1st hospital control	0.785 (0.549-1.123)	0.1857	0.595 (0.319-1.113)	0.1040
adenocarcinoma *vs*	2nd hospital control	0.882 (0.639-1.219)	0.4476	0.851 (0.581-1.245)	0.4055
	community control	1.888 (1.365-2.613)	0.0001	1.117 (0.612-2.039)	0.7177

[1]Compared to KMUH or NTUH controls: adjusting for age (continuous), gender (female *vs* male), educational levels (≤ primary school *vs* > high school; junior and high schools *vs* > high school), cigarette smoking (yes *vs* no), alcohol consumption (yes *vs* no) and betel nut chewing (yes *vs* no); Compared to community controls: Adjusting for the above factors except for betel nut chewing.

In the multivariate analyses of esophageal SCC and 1st hospital control, besides the significant protective effect of *H pylori*, we found that cigarette smoking (AOR = 2.608, 95% CI: 1.540-4.414), alcohol consumption (AOR = 5.078, 95% CI: 3.130-8.240), and betel nut chewing (AOR = 5.142, 95% CI: 2.916-9.065) are still the significant risk factors for esophageal SCC. However, we did not see any significant interaction between *H pylori* and any of those substances (tobacco, alcohol, and betel nut) in the multivariate analyses.

H pylori infection was positively related to gastric adenocarcinoma, including the cardia (AOR: 1.636-3.060; all *P*-values < 0.05), in comparison to all three control groups, after adjusting for other co-variates (Table 3). Oral SCC was found to have a significantly inverse association with *H pylori* infection (AOR = 0.378, 95% CI: 0.190-0.751), when compared with the 2nd hospital-based control group, but not the other two. *H pylori* infection was not significantly associated with colon cancer, compared with all three control groups.

DISCUSSION

After expanding the case number of esophageal SCC patients, we still found an inverse association between *H pylori* seropositivity and esophageal SCC when compared to different control groups. Conflicting results were reported in the previous two prevalence studies about the relationship between the two in Sweden[8,17]. One nationwide case-control study conducted by Ye *et al*[8] used enzyme-linked immunosorbent assay (ELISA) to detect both serum *H pylori* and CagA antibodies in 85 esophageal SCC patients and 499 controls in Sweden. Initially, they did not find any significant association between *H pylori* seropositivity and esophageal SCC risk (AOR = 0.9, 95% CI: 0.5-1.6). Thus, the authors further categorized the study subjects based on both statuses of *H pylori* and CagA seropositivity. They found subjects with negative *H pylori* but positive CagA, to have a significant 3.0-fold risk of developing esophageal SCC, compared with those who were found to be negative for both[8]. But the insignificant finding was noted in the group of both positive *H pylori* and CagA patients (AOR = 1.6, 95% CI: 0.8-3.3). That was a post-hoc statistical analysis, so the preliminary finding is a warranty for further confirmation. Siman *et al*[17] updated their nested case-control study and found neither *H pylori* (OR = 0.44, 95% CI: 0.15-1.2) nor CagA seropositivity (OR = 2.0, 95% CI: 0.24-infinity) was significantly associated with esophageal SCC risk (n = 37). Recently, two studies were conducted in two major endemic areas in China-Huaian City[15] and Linxian[16]. The population-based case-control study in Huaian (case number 107) showed those with positive findings for *H pylori* antibody to be at 3-fold risk of developing esophageal SCC (AOR = 3.19, 95% CI: 1.11-9.15)[15]. But, in the case-cohort study including 335 ESCC patients in Linxian, no association was found between esophageal SCC risk and positive finding for antibodies to either *H pylori* (Hazard ratio = 1.17, 95% CI: 0.88-1.57) or CagA (Hazard ratio = 1.08, 95% CI: 0.80-1.47)[16]. In these two areas, the predominant risk factors for ESCC were diet and nutrition, instead of cigarette smoking and alcohol consumption mostly found in Western countries and Taiwan. The Linxian research group suggested the difference in risk factors for esophageal SCC in different areas may affect the relationship between *H pylori* and esophageal SCC[16].

In Taiwan, about 95% *H pylori* strain is CagA positive[25]. This study has shown that subjects with positive *H pylori* serology have > 85% $CagA^+$ strains in both esophageal SCC patients and controls, suggesting using IgG serology to measure *H pylori* infection can represent the $CagA^+$ strains in Taiwan. The relatively low seroprevalence of *H pylori* infection in the community control group may be due to younger age (average age = 40.2 years), compared to those in the two hospital-based control groups (average age = 57.1 and 60.0 years).

The exact mechanism by which *H pylori* infection affects the development of EA and esophageal SCC is still puzzling. The strongest risk factor of distal EA is Barrett's esophagus, a condition secondary to long-term gastroesophageal reflux disease, and *H pylori* colonization may protect against Barrett's esophagus[11,13,26]. Rich-

ter *et al*[27] also hypothesized that *H pylori* can prevent EA development through gastric atrophy and possibly by increased intragastric ammonia production. Ye *et al*[8] challenged this hypothesis by demonstrating an unaffected protective effect for EA after adjusting for gastric atrophy. However, they hypothesized that $CagA^+$ *H pylori* infection caused esophageal SCC through the pathway of gastric atrophy[8]. An atrophic stomach might enhance the overgrowth of bacteria and increase endogenous nitrosamines production, which causes esophageal SCC[28]. In contrast, another hypothesis is *H pylori*-induced gastric atrophy, which decreases intragastric acidity[14], might protect the lower esophageal mucosa from repeated injury by acid exposure, and thus decrease the esophageal SCC risk in an Asian population[29]. Another mechanism concerning the protective effect of *H pylori* infection on esophageal cancer risk directly involves apoptosis[30,31]. Jones *et al*[30] found significantly increasing apoptosis in OE33 Barrett's-derived EA cells, but not in normal esophageal cells, after being treated with intact *H pylori* wild-type strains. Our *in vitro* study demonstrated similar apoptosis effect on esophageal SCC cells, but not in AGS cells, after being co-cultured with *H pylori*[31]. However, this proposed mechanism is still speculative and needs to be further verified.

The prevalence of *H pylori* infection in patients with cardia and non-cardia adenocarcinoma was about 70%, significantly higher than control subjects (about 56%), which was similar to the previous study done in China[4]. Fewer cardia cancer patients (n = 29) were noted in our study, but the prevalence of *H pylori* and CagA seropositivity was similar to that in non-cardia cancer patients. Previous studies have linked *H pylori* colonization to carditis and intestinal metaplasia in the cardia, indicating a role distinct from Barrett's esophagus[32,33]. The subsites of gastric cancer were not well defined in some of the previous studies, but most researchers in Asian countries[3-5,34] supported at least a trend of positive association between *H pylori* seropositivity and proximal gastric cancer. On the contrary, observational studies in Western countries indicated no association[7-9] or inverse association[6] between *H pylori* seropositivity and cardia cancer. Further studies are needed to investigate the discrepancy of findings between Asian and Caucasian populations.

H pylori infection was not significantly associated with the risk of colon adenocarcinoma in this study. Hartwich *et al*[35] found a positive association between colon adenocarcinoma risk and *H pylori* seropositivity, especially $CagA^+$ strains. However, there are also reports indicating no association between *H pylori* seroprevalence and colorectal neoplasia[36,37]. In addition, a recent report from Taiwan did not find any association between *H pylori* infection by the ^{13}C-urea breath test and the risk of colon adenomatous polyp, which is the pre-cancer of colon adenocarcinoma[38].

The effect of *H pylori* infection on oral SCC risk has not yet been determined. Our study found conflicting results when *H pylori* infection status in three comparison controls was compared to that in oral cancer patients. Previous studies have shown that *H pylori* was detectable in the oral cavity by histopathologic diagnosis or polymerase chain reaction[39,40], but this bacterium may be present as a transient organism because of the difficulty of surviving in the oral cavity[41]. Thus, further studies are necessary to elucidate the relationship between *H pylori* infection and oral cancer risk.

Several limitations were present in this study: (1) The control group is mainly for the comparison of esophageal SCC, but not for other digestive cancers; (2) This is a cross-sectional case-control study design; the causal relationship may be not clearly elucidated; (3) Like other epidemiological studies[8,15-17], we only measured *H pylori* antibodies in human serum, which may not be representative for actual *H pylori* infection.

In summary, our study supports an inverse relationship between *H pylori* prevalence and esophageal SCC risk in Taiwan. In contrast, *H pylori* infection increases gastric adenocarcinoma risk, including the cardia and non-cardia. There is an inconsistent or negative association between *H pylori* infection and the risks of oral and colon cancers. The choice of the control groups in this study were mainly for the comparison of esophageal SCC, but not for other patient groups. Thus, the role of *H pylori* in digestive tract cancers, except esophageal SCC, in this study still requires further examination.

COMMENTS

Background

There is debate in regard to the association between *Helicobacter pylori* (*H pylori*) infection and gastric cardia adenocarcinoma. Recently, cumulative evidence has indicated that *H pylori* infection plays a protective role in the development of esophageal adenocarcinoma. In contrast, the relationship between *H pylori* infection and esophageal squamous cell carcinoma (SCC) is still inconclusive. Very few studies have examined the role of *H pylori* on colon and oral cancers.

Research frontiers

This study aimed to explore the role of *H pylori* infection on the risk of digestive tract cancers, including cancers of the oral cavity, esophagus, stomach, and colon.

Innovations and breakthroughs

H pylori seropositivity is inversely associated with esophageal SCC risk, but increases the risk of gastric non-cardia and cardia adenocarcinoma.

Applications

Eradication of *H pylori* in all infected subjects should be cautious because *H pylori* might protect against other diseases, such as esophageal cancer.

Terminology

STAT-PAK assay for *H pylori* is an immunochromatographic screening test to detect *H pylori* IgG antibodies in serum; Helori CTX IgG kit is an enzyme immunoassay to detect CagA (the virulent protein of *H pylori*) IgG antibodies in serum.

Peer review

This is an important clinical observational study, indicating *H pylori* is not always a bad bug. Although *H pylori* can cause gastric non-cardia and cardia adenocarcinoma, it may protect against esophageal cancer.

REFERENCES

1 **Watanabe** T, Tada M, Nagai H, Sasaki S, Nakao M. Helicobacter pylori infection induces gastric cancer in mongolian gerbils. *Gastroenterology* 1998; **115**: 642-648

2 **Parsonnet J**, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, Sibley RK. Helicobacter pylori

infection and the risk of gastric carcinoma. *N Engl J Med* 1991; **325**: 1127-1131

3 **Komoto K**, Haruma K, Kamada T, Tanaka S, Yoshihara M, Sumii K, Kajiyama G, Talley NJ. Helicobacter pylori infection and gastric neoplasia: correlations with histological gastritis and tumor histology. *Am J Gastroenterol* 1998; **93**: 1271-1276

4 **Limburg P**, Qiao Y, Mark S, Wang G, Perez-Perez G, Blaser M, Wu Y, Zou X, Dong Z, Taylor P, Dawsey S. Helicobacter pylori seropositivity and subsite-specific gastric cancer risks in Linxian, China. *J Natl Cancer Inst* 2001; **93**: 226-233

5 **Kikuchi S**, Wada O, Nakajima T, Nishi T, Kobayashi O, Konishi T, Inaba Y. Serum anti-Helicobacter pylori antibody and gastric carcinoma among young adults. Research Group on Prevention of Gastric Carcinoma among Young Adults. *Cancer* 1995; **75**: 2789-2793

6 **Chow WH**, Blaser MJ, Blot WJ, Gammon MD, Vaughan TL, Risch HA, Perez-Perez GI, Schoenberg JB, Stanford JL, Rotterdam H, West AB, Fraumeni JF Jr. An inverse relation between cagA+ strains of Helicobacter pylori infection and risk of esophageal and gastric cardia adenocarcinoma. *Cancer Res* 1998; **58**: 588-590

7 **Wu AH**, Crabtree JE, Bernstein L, Hawtin P, Cockburn M, Tseng CC, Forman D. Role of Helicobacter pylori CagA+ strains and risk of adenocarcinoma of the stomach and esophagus. *Int J Cancer* 2003; **103**: 815-821

8 **Ye W**, Held M, Lagergren J, Engstrand L, Blot WJ, McLaughlin JK, Nyren O. Helicobacter pylori infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. *J Natl Cancer Inst* 2004; **96**: 388-396

9 **Huang JQ**, Zheng GF, Sumanac K, Irvine EJ, Hunt RH. Meta-analysis of the relationship between cagA seropositivity and gastric cancer. *Gastroenterology* 2003; **125**: 1636-1644

10 **Labenz J**, Blum AL, Bayerdorffer E, Meining A, Stolte M, Borsch G. Curing Helicobacter pylori infection in patients with duodenal ulcer may provoke reflux esophagitis. *Gastroenterology* 1997; **112**: 1442-1447

11 **Corley DA**, Kubo A, Levin TR, Block G, Habel L, Zhao W, Leighton P, Rumore G, Quesenberry C, Buffler P, Parsonnet J. Helicobacter pylori infection and the risk of Barrett's oesophagus: a community-based study. *Gut* 2008; **57**: 727-733

12 **Weston AP**, Badr AS, Topalovski M, Cherian R, Dixon A, Hassanein RS. Prospective evaluation of the prevalence of gastric Helicobacter pylori infection in patients with GERD, Barrett's esophagus, Barrett's dysplasia, and Barrett's adenocarcinoma. *Am J Gastroenterol* 2000; **95**: 387-394

13 **de Martel C**, Llosa AE, Farr SM, Friedman GD, Vogelman JH, Orentreich N, Corley DA, Parsonnet J. Helicobacter pylori infection and the risk of development of esophageal adenocarcinoma. *J Infect Dis* 2005; **191**: 761-767

14 **Wu DC**, Wu IC, Lee JM, Hsu HK, Kao EL, Chou SH, Wu MT. Helicobacter pylori infection: a protective factor for esophageal squamous cell carcinoma in a Taiwanese population. *Am J Gastroenterol* 2005; **100**: 588-593

15 **Wang Z**, Tang L, Sun G, Tang Y, Xie Y, Wang S, Hu X, Gao W, Cox SB, Wang JS. Etiological study of esophageal squamous cell carcinoma in an endemic region: a population-based case control study in Huaian, China. *BMC Cancer* 2006; **6**: 287

16 **Kamangar F**, Qiao YL, Blaser MJ, Sun XD, Katki H, Fan JH, Perez-Perez GI, Abnet CC, Zhao P, Mark SD, Taylor PR, Dawsey SM. Helicobacter pylori and oesophageal and gastric cancers in a prospective study in China. *Br J Cancer* 2007; **96**: 172-176

17 **Siman JH**, Engstrand L, Berglund G, Forsgren A, Floren CH. Helicobacter pylori and CagA seropositivity and its association with gastric and oesophageal carcinoma. *Scand J Gastroenterol* 2007; **42**: 933-940

18 **Lee CH**, Wu DC, Lee JM, Wu IC, Goan YG, Kao EL, Huang HL, Chan TF, Chou SH, Chou YP, Lee CY, Chen PS, Ho CK, He J, Wu MT. Carcinogenetic impact of alcohol intake on squamous cell carcinoma risk of the oesophagus in relation to tobacco smoking. *Eur J Cancer* 2007; **43**: 1188-1199

19 **Chen YJ**, Chen C, Wu DC, Lee CH, Wu CI, Lee JM, Goan YG, Huang SP, Lin CC, Li TC, Chou YP, Wu MT. Interactive effects of lifetime alcohol consumption and alcohol and aldehyde dehydrogenase polymorphisms on esophageal cancer risks. *Int J Cancer* 2006; **119**: 2827-2831

20 **Wu MT**, Lee YC, Chen CJ, Yang PW, Lee CJ, Wu DC, Hsu HK, Ho CK, Kao EL, Lee JM. Risk of betel chewing for oesophageal cancer in Taiwan. *Br J Cancer* 2001; **85**: 658-660

21 **Yu CL**, Wang SF, Pan PC, Wu MT, Ho CK, Smith TJ, Li Y, Pothier L, Christiani DC. Residential exposure to petrochemicals and the risk of leukemia: using geographic information system tools to estimate individual-level residential exposure. *Am J Epidemiol* 2006; **164**: 200-207

22 **Wu MT**, Wu DC, Hsu HK, Kao EL, Lee JM. Relationship between site of oesophageal cancer and areca chewing and smoking in Taiwan. *Br J Cancer* 2003; **89**: 1202-1204

23 **Lee CH**, Lee JM, Wu DC, Hsu HK, Kao EL, Huang HL, Wang TN, Huang MC, Wu MT. Independent and combined effects of alcohol intake, tobacco smoking and betel quid chewing on the risk of esophageal cancer in Taiwan. *Int J Cancer* 2005; **113**: 475-482

24 **Cancer Registry Annual Report**. National Department of Health, Taiwan, Republic of China, 2006

25 **Yang JC**, Wang TH, Wang HJ, Kuo CH, Wang JT, Wang WC. Genetic analysis of the cytotoxin-associated gene and the vacuolating toxin gene in Helicobacter pylori strains isolated from Taiwanese patients. *Am J Gastroenterol* 1997; **92**: 1316-1321

26 **Lagergren J**. Adenocarcinoma of oesophagus: what exactly is the size of the problem and who is at risk? *Gut* 2005; **54** Suppl 1: i1-i5

27 **Richter JE**, Falk GW, Vaezi MF. Helicobacter pylori and gastroesophageal reflux disease: the bug may not be all bad. *Am J Gastroenterol* 1998; **93**: 1800-1802

28 **Houben GM**, Stockbrugger RW. Bacteria in the aetiopathogenesis of gastric cancer: a review. *Scand J Gastroenterol Suppl* 1995; **212**: 13-18

29 **Fujimori T**, Kawamata H, Ichikawa K, Ono Y, Okura Y, Tomita S, Imura J. Pathological issues of gastric and lower esophageal cancer: helicobacter pylori infection and its eradication. *J Gastroenterol* 2002; **37** Suppl 13: 28-33

30 **Jones AD**, Bacon KD, Jobe BA, Sheppard BC, Deveney CW, Rutten MJ. Helicobacter pylori induces apoptosis in Barrett's-derived esophageal adenocarcinoma cells. *J Gastrointest Surg* 2003; **7**: 68-76

31 **Wu IC**, Wu MT, Chen YK, Hsu MC, Chou SH, Lee CH, Shiea JT, Wu IL, Huang CT, Wu DC. Apoptotic effect of Helicobacter pylori on oesophageal squamous-cell carcinoma cells in vitro. *Eur J Clin Invest* 2008; **38**: 760-765

32 **Peek RM Jr**, Vaezi MF, Falk GW, Goldblum JR, Perez-Perez GI, Richter JE, Blaser MJ. Role of Helicobacter pylori cagA(+) strains and specific host immune responses on the development of premalignant and malignant lesions in the gastric cardia. *Int J Cancer* 1999; **82**: 520-524

33 **Goldblum JR**, Vicari JJ, Falk GW, Rice TW, Peek RM, Easley K, Richter JE. Inflammation and intestinal metaplasia of the gastric cardia: the role of gastroesophageal reflux and H. pylori infection. *Gastroenterology* 1998; **114**: 633-639

34 **Yuan JM**, Yu MC, Xu WW, Cockburn M, Gao YT, Ross RK. Helicobacter pylori infection and risk of gastric cancer in Shanghai, China: updated results based upon a locally developed and validated assay and further follow-up of the cohort. *Cancer Epidemiol Biomarkers Prev* 1999; **8**: 621-624

35 **Hartwich A**, Konturek SJ, Pierzchalski P, Zuchowicz M, Labza H, Konturek PC, Karczewska E, Bielanski W, Marlicz K, Starzynska T, Lawniczak M, Hahn EG. Helicobacter pylori infection, gastrin, cyclooxygenase-2, and apoptosis in

colorectal cancer. *Int J Colorectal Dis* 2001; **16**: 202-210
36 **Siddheshwar RK**, Muhammad KB, Gray JC, Kelly SB. Seroprevalence of Helicobacter pylori in patients with colorectal polyps and colorectal carcinoma. *Am J Gastroenterol* 2001; **96**: 84-88
37 **Moss SF**, Neugut AI, Garbowski GC, Wang S, Treat MR, Forde KA. Helicobacter pylori seroprevalence and colorectal neoplasia: evidence against an association. *J Natl Cancer Inst* 1995; **87**: 762-763
38 **Liou JM**, Lin JW, Huang SP, Lin JT, Wu MS. Helicobacter pylori infection is not associated with increased risk of colorectal polyps in Taiwanese. *Int J Cancer* 2006; **119**: 1999-2000
39 **Umeda M**, Kobayashi H, Takeuchi Y, Hayashi J, Morotome-Hayashi Y, Yano K, Aoki A, Ohkusa T, Ishikawa I. High prevalence of Helicobacter pylori detected by PCR in the oral cavities of periodontitis patients. *J Periodontol* 2003; **74**: 129-134
40 **Adler I**, Denninghoff VC, Alvarez MI, Avagnina A, Yoshida R, Elsner B. Helicobacter pylori associated with glossitis and halitosis. *Helicobacter* 2005; **10**: 312-317
41 **Okuda K**, Kimizuka R, Katakura A, Nakagawa T, Ishihara K. Ecological and immunopathological implications of oral bacteria in Helicobacter pylori-infected disease. *J Periodontol* 2003; **74**: 123-128

S- Editor Wang YR **L- Editor** O'Neill M **E- Editor** Ma WH