Association between *Helicobacter pylori* seropositivity and digestive tract cancers

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**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

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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. How- ever, there is debate in regard to the association between *H pylori* infection and gastric cardia adenocarcinoma. Most studies in Asian countries have indicated an increased risk of cardia cancer in *H pylori*-infected subjects, while those in Western countries have reported a protective role.
of \textit{H pylori} or a negative association between these two.

Recently, cumulative evidence has indicated that \textit{H pylori} infection plays a protective role in the development of reflux esophagitis and esophageal adenocarcinoma (EA). In contrast, the relationship between \textit{H pylori} infection and esophageal squamous cell carcinoma (SCC) is still inconclusive. Very few studies have examined the role of \textit{H pylori} infection on colon and oral cancers. Therefore, we aim to expand our esophageal SCC cases and to examine the relationship between \textit{H pylori} infection and the risk of oral SCC, gastric cancer, especially gastric cardia adenocarcinoma and colon cancer, in a Taiwanese population.

\section*{Materials and Methods}

\subsection*{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. 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 (casecontrol = 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 \textit{H pylori} infection. Twelve cases did not have suitable controls. In order to examine the different prevalence of \textit{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. They were cancer-free, had visited for a health check-up in NTUH, and had enough stored serum specimens for testing \textit{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. 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 \textit{H pylori} seropositivity. For those with positive \textit{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.

\subsection*{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. 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. Cardia adenocarcinoma was classified as being of gastric origin, if Barrett’s esophagus was not detected in the adjacent tissue.

\subsection*{H pylori serology and CagA status}
Non-heparinized whole blood was collected and serum was isolated and stored at -70°C for subsequent analysis. A commercially available immunochromatographic screening test (Chembio \textit{H pylori} STAT-PAK, Chembio Diagnostic System, Inc., Medford, NY, USA) utilizing a combination of \textit{H pylori} antigen coated particles and anti-human IgG was used to qualitatively and selectively detect \textit{H pylori} antibodies in serum. 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 \(\geq 5\) units, respectively. The research technicians were also blinded to the status of cases and controls.

\subsection*{Statistical analysis}
Multiple logistic regression models were used to examine the association between \textit{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 (\(\leq\) primary school, junior high and high school, and > high school), cigarette
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 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 1  Demographic characteristics of digestive tract cancer patients and controls n (%)

|          | Oral SCC | Esophageal SCC | Gastric adenocarcinoma | Gastric non-cardia adenocarcinoma | Colon adenocarcinoma | 1st hospital-based control | 2nd hospital-based control | Community-based control |
|----------|----------|----------------|------------------------|-----------------------------------|----------------------|---------------------------|---------------------------|-------------------------|
| n        | 199      | 317            | 196                    | 240                               |                     |                           |                           |                         |
| Age mean ± SD | 50.6 ± 9.9 | 58.3 ± 11.6   | 63.2 ± 15.5            | 64.5 ± 12.7                       |                     |                           |                           |                         |
| (min, med, max) | (26, 30, 78) | (34, 58, 86) | (22, 65, 91)           | (24, 66, 89)                      |                     |                           |                           |                         |
| Sex      |           |                |                        |                                   |                     |                           |                           |                         |
| Male     | 188 (90.5)| 301 (95.0)    | 123 (62.8)             | 139 (57.9)                        |                     |                           |                           |                         |
| Female   | 11 (5.5)  | 16 (5.0)      | 73 (37.2)              | 101 (42.1)                        |                     |                           |                           |                         |
| Educational level |           |                |                        |                                   |                     |                           |                           |                         |
| % primary school | 117 (58.8)| 176 (55.5)   | 118 (60.2)             | 133 (55.4)                        |                     |                           |                           |                         |
| Junior high & high school | 76 (38.2)| 120 (37.9)   | 53 (27.0)              | 72 (30.0)                        |                     |                           |                           |                         |
| > high school | 6 (3.0)  | 21 (6.6)      | 25 (12.8)              | 35 (14.6)                        |                     |                           |                           |                         |
| Cigarette smoking |          |                |                        |                                   |                     |                           |                           |                         |
| No       | 32 (16.1)| 39 (12.3)     | 101 (51.5)             | 143 (59.6)                        |                     |                           |                           |                         |
| Yes      | 167 (83.9)| 278 (87.7)    | 95 (48.5)              | 97 (40.4)                        |                     |                           |                           |                         |
| Alcohol consumption |          |                |                        |                                   |                     |                           |                           |                         |
| No       | 64 (32.2)| 60 (18.9)     | 145 (74.0)             | 193 (80.4)                        |                     |                           |                           |                         |
| Yes      | 135 (67.8)| 257 (81.1)    | 51 (26.0)              | 47 (19.6)                        |                     |                           |                           |                         |
| Betel quid chewing |          |                |                        |                                   |                     |                           |                           |                         |
| No       | 29 (14.6)| 149 (47.0)    | 171 (87.2)             | 213 (88.8)                        |                     |                           |                           |                         |
| Yes      | 170 (85.4)| 168 (53.0)    | 25 (12.8)              | 27 (11.2)                        |                     |                           |                           |                         |

|                                  | Oral SCC | Esophageal SCC | Gastric adenocarcinoma | Gastric non-cardia adenocarcinoma | Colon adenocarcinoma | 1st hospital-based control | 2nd hospital-based control | Community-based control |
|----------------------------------|----------|----------------|------------------------|-----------------------------------|----------------------|---------------------------|---------------------------|-------------------------|
| n                                  | 199      | 317            | 196                    | 240                               |                     |                           |                           |                         |
| H pylori                          |          |                |                        |                                   |                     |                           |                           |                         |
| -                                 | 104 (52.3)| 205 (64.7)   | 8 (27.6)               | 48 (28.7)                         | 105 (43.8)          | 141 (46.2)                | 164 (53.8)                | 160 (40.5)              |
| +                                 | 95 (47.7)| 112 (35.3)    | 21 (72.4)              | 119 (71.3)                        | 135 (56.3)          | 141 (46.2)                | 164 (53.8)                | 160 (40.5)              |
| CagA1                             |          |                |                        |                                   |                     |                           |                           |                         |
| -                                 | 14 (14.7)| 8 (7.3)       | 1 (4.8)                | 9 (7.6)                           | 12 (8.9)            | 24 (14.6)                 | -                         | 11 (6.9)               |
| ±                                 | 33 (17.7)| 10 (9.2)      | 3 (14.3)               | 8 (6.8)                           | 7 (5.2)             | 14 (6.5)                  | -                         | 6 (3.8)                |
| +                                 | 68 (71.6)| 91 (83.5)     | 17 (81.0)              | 101 (85.6)                        | 116 (85.9)          | 126 (76.8)                | -                         | 142 (89.0)             |

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

|          | Oral SCC | Esophageal SCC | Gastric adenocarcinoma | Gastric non-cardia adenocarcinoma | Colon adenocarcinoma | 1st hospital-based control | 2nd hospital-based control | Community-based control |
|----------|----------|----------------|------------------------|-----------------------------------|----------------------|---------------------------|---------------------------|-------------------------|
| n        | 199      | 317            | 196                    | 240                               |                     |                           |                           |                         |
| H pylori |          |                |                        |                                   |                     |                           |                           |                         |
| -        | 104 (52.3)| 205 (64.7)   | 8 (27.6)               | 48 (28.7)                         | 105 (43.8)          | 141 (46.2)                | 164 (53.8)                | 160 (40.5)              |
| +        | 95 (47.7)| 112 (35.3)    | 21 (72.4)              | 119 (71.3)                        | 135 (56.3)          | 141 (46.2)                | 164 (53.8)                | 160 (40.5)              |
| CagA1    |          |                |                        |                                   |                     |                           |                           |                         |
| -        | 14 (14.7)| 8 (7.3)       | 1 (4.8)                | 9 (7.6)                           | 12 (8.9)            | 24 (14.6)                 | -                         | 11 (6.9)               |
| ±        | 33 (17.7)| 10 (9.2)      | 3 (14.3)               | 8 (6.8)                           | 7 (5.2)             | 14 (6.5)                  | -                         | 6 (3.8)                |
| +        | 68 (71.6)| 91 (83.5)     | 17 (81.0)              | 101 (85.6)                        | 116 (85.9)          | 126 (76.8)                | -                         | 142 (89.0)             |

1CagA 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).
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-variables (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[13,17]. 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[11] 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[13] and Lixinian[8]. 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)[16]. But, in the case-cohort study including 335 ESCC patients in Lixinian, 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)[26]. 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 Lixinian research group suggested the difference in risk factors for esophageal SCC in different areas may affect the relationship between H pylori and ESCC[8].

In Taiwan, about 95% H pylori strain is CagA positive[23]. 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[16,13,26]. Rich-

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

| Cancer Type | Odds ratio (95% CI) | P-value | Adjusted odds ratio (95% CI) | P-value |
|-------------|-------------------|---------|-----------------------------|---------|
| Oral SCC vs community control | 0.627 (0.445-0.882) | 0.0074 | 0.378 (0.190-0.751) | 0.0055 |
| Esophageal SCC vs 1st hospital control | 0.470 (0.340-0.668) | < 0.0001 | 0.454 (0.290-0.710) | 0.0005 |
| Gastric adenocarcinoma vs 1st hospital control | 0.375 (0.277-0.508) | < 0.0001 | 0.315 (0.203-0.489) | < 0.0001 |
| Colon adenocarcinoma vs 2nd hospital control | 0.802 (0.591-1.089) | 0.1581 | 0.472 (0.257-0.865) | 0.0151 |

1. Compared to KMUH or NTUH controls: adjusting for age (continuous), gender (female vs male), educational levels (≤ 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.

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

The prevalence of \textit{H pylori} infection in patients with cardia and non-cardia adenocarcinoma was about 70%, significantly higher than control subjects (about 50%), which was similar to the previous study done in China.\textsuperscript{32} Fewer cardia cancer patients (\(n = 29\)) were noted in our study, but the prevalence of \textit{H pylori} and Caga seropositivity was similar to that in non-cardia cancer patients. Previous studies have linked \textit{H pylori} colonization to carditis and intestinal metaplasia in the cardia, indicating a role distinct from Barrett’s esophagus.\textsuperscript{32,33} The subites of gastric cancer were not well defined in some of the previous studies, but most researchers in Asian countries supported at least a trend of positive association between \textit{H pylori} seropositivity and proximal gastric cancer. On the contrary, observational studies in Western countries indicated no association\textsuperscript{34} or inverse association\textsuperscript{35} between \textit{H pylori} seropositivity and cardia cancer. Further studies are needed to investigate the discrepancy of findings between Asian and Caucasian populations.

\textit{H pylori} infection was not significantly associated with the risk of colon adenocarcinoma in this study. Hartwich et al.\textsuperscript{33} found a positive association between colon adenocarcinoma risk and \textit{H pylori} seropositivity, especially Caga strains. However, there are also reports indicating no association between \textit{H pylori} seroprevalence and colorectal neoplasia. In addition, a recent report from Taiwan did not find any association between \textit{H pylori} infection by the \textsuperscript{14}C-urea breath test and the risk of colon adenomatous polyph, which is the pre-cancer of colon adenocarcinoma.\textsuperscript{34}

The effect of \textit{H pylori} infection on oral SCC risk has not yet been determined. Our study found conflicting results when \textit{H pylori} infection status in three comparison controls was compared to that in oral cancer patients. Previous studies have shown that \textit{H pylori} was detectable in the oral cavity by histopathologic diagnosis or polymerase chain reaction,\textsuperscript{39,40} but this bacterium may be present as a transient organism because of the difficulty of surviving in the oral cavity.\textsuperscript{41} Thus, further studies are necessary to elucidate the relationship between \textit{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 not be clearly elucidated; (3) Like other epidemiological studies, we only measured \textit{H pylori} antibodies in human serum, which may not be representative for actual \textit{H pylori} infection.

In summary, our study supports an inverse relationship between \textit{H pylori} prevalence and esophageal SCC risk in Taiwan. In contrast, \textit{H pylori} infection increases gastric adenocarcinoma risk, including the cardia and non-cardia. There is an inconsistent or negative association between \textit{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 \textit{H pylori} in digestive tract cancers, except esophageal SCC, in this study still requires further examination.

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3. Hartwich et al.\textsuperscript{33} found a positive association between colon adenocarcinoma risk and \textit{H pylori} seropositivity, especially Caga strains. However, there are also reports indicating no association between \textit{H pylori} seroprevalence and colorectal neoplasia. In addition, a recent report from Taiwan did not find any association between \textit{H pylori} infection by the \textsuperscript{14}C-urea breath test and the risk of colon adenomatous polyph, which is the pre-cancer of colon adenocarcinoma.

**COMMENTS**

**Background**

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

**Research frontiers**

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

**Innovations and breakthroughs**

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

**Applications**

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

**Terminology**

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

**Peer review**

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