

BMJ Open Association between *Helicobacter pylori* infection and tumor markers: an observational retrospective study

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ABSTRACT

Objective *Helicobacter pylori* infection is a major cause of several cancers such as gastric, pancreatic and lung. The relationship between *H. pylori* and tumour markers continues to remain unclear. The primary goal of this study is to clarify the associations between *H. pylori* infection and six tumour markers (ie, carcinoembryonic antigen (CEA), cancer antigen (CA) 153, CA199, CA724, CA125 and alpha-fetoprotein (AFP)). The secondary goal is to provide understanding for further research about *H. pylori* infection and gastrointestinal cancer.

Design Observational retrospective study.

Setting The study was performed in Beijing, China, where enrolled subjects had all passed health examinations during the period of 2012–2016. Subjects were categorised into *H. pylori* (+) and *H. pylori* (–) group according to their infection status and the measured six biomarkers. We used logistic regression models and generalised linear models to explore the associations between *H. pylori* infection and six tumour markers (ie, CEA, CA153, CA199, CA724, CA125 and AFP).

Participants A total of 14 689 subjects were included and 6493 (44.2%) subjects were infected by *H. pylori*. The subjects had a mean age (1SD) of 45 (18) years. There were 4530 (31.0%) female subjects.

Results After adjusting for the confounding factors, infections with *H. pylori* were found to be significantly associated with abnormal ratios in CEA, AFP and CA724 of *H. pylori* (+) to *H. pylori* (–) groups. Significant positive correlation was found between *H. pylori* infection and CEA values (adjusted $\beta=0.056$; 95% CI 0.005 to 0.107; $p=0.033$).

Conclusions In this observational retrospective study, we observed the *H. pylori* infections in a Chinese population and found higher CEA level in *H. pylori*-infected subjects and abnormal ratios in CEA, AFP and CA724 in infected subjects to uninfected subjects. These findings may provide a basis for future exploration with *H. pylori* and tumour markers.

INTRODUCTION

As one of the leading causes of morbidity and mortality globally, cancer represents a major detrimental public health problem worldwide.¹ Cancer not only causes a tremendous socioeconomic burden, it negatively impacts patients' quality of life resulting in physical

Strengths and limitations of this study

- This is an observational retrospective study in a large sample size-based Chinese population.
- All data are based on highly reliable hospital records.
- However, we cannot confirm the actual causality between *Helicobacter pylori* infection and changes of tumour markers from an observational study conducted in a single centre.
- The serological testing for the presence of two antibodies against *H. pylori*, IgG and IgM, indicate a past exposure to this bacterium rather than a current exposure.

and emotional distress in not only their life, but their families as well.^{2,3} According to the WHO, a recent report stated there was an estimated 14.1 million new cancer cases worldwide in 2012, mostly occurring in low/middle-income countries.⁴ In China, cancers of the stomach, oesophagus and liver are commonly diagnosed and identified as leading causes of cancer death.⁵ According to the Cancer Statistics in China, the morbidity of gastric cancer is 498.0/100 000, the morbidity of pancreatic cancer is 79.4/100 000 and the morbidity of lung cancer is 610.2/100 000, respectively.⁵ WHO announced that many patients would have a higher chance of survival if they were diagnosed earlier on during the course of illness and received proper treatment and care. Therefore, significant improvements need to be made to alleviate burdens through early methods of cancer detection.⁴

There are various known important tumour biomarkers in cancer progression such as carcinoembryonic antigen (CEA), cancer antigen (CA) 153, CA199, CA724, CA125 and alpha-fetoprotein (AFP) which have been shown in the past literature to have various evidence in diagnostic modalities.^{6,7} These tumour markers were reported to have a close relationship with specific cancers. For example, CEA and colorectal cancer, CA199

and colon cancer,⁸ CA724 and gastric cancer⁹ and AFP and hepatocellular carcinoma,¹⁰ to name a few. Although the roles of these tumour markers in screening, diagnosis and oncological treatment remain poorly standardised, they are still invaluable assets to medical practice and are commonly used.⁶

Helicobacter pylori is a pathogenic bacterium discovered in the human gastric mucosa for the first time in 1983 and reported in 1984.^{11 12} The prevalence of *H. pylori* infection still remains unacceptably high in many regions of the world^{13 14} with a reported range of 8.7% to 85.5%.¹³ In recent years, the prevalence of *H. pylori* infection continues to remain elevated in some low/middle-income countries and illustrates a decreasing trend in developed countries such as Canada and the USA.^{13 15} Unfortunately, in low/middle-income countries, *H. pylori* infection continues to play a major role in the incidence of various cancers, including but not limited to gastric cancer,^{16 17} pancreatic cancer¹⁸ and lung cancer.¹⁹ As reported in a synthetic analysis, *H. pylori* is the largest contributor to 2 million new infection-related cancer cases worldwide in 2012, and in addition, more than 40% infection-related cancer cases are attributable to *H. pylori* in China.²⁰

According to the evidence stated above, there seems to be a certain association between *H. pylori* and tumour markers and, to our knowledge, several previous research studies have pointed out higher levels of CEA²¹ and AFP²² in individuals with *H. pylori* infection. However, no published studies with large sample sizes have explored such an association. Therefore, we have conducted this observational retrospective study, based on the examination of a large sample size in an adult Chinese population using a health record database. The overarching aim is to clarify the association between *H. pylori* infection and tumour markers, as well as to provide more evidence for further research on cancer and *H. pylori* infection to reduce the occurrences of cancer and its resulting burdens.

METHODS

Study design and participants

This observational retrospective study was performed at the Aerospace Centre Hospital located in Beijing, China. All subjects recruited in this study underwent health examinations at least once at this hospital during the period of time between 2012 and 2016. The objective of annual health examination is to conduct the comprehensive examination in subjects in order to prevent the occurrence and development of disease at an early stage. According to the records of disease history and results of the health examination, no subjects recruited in our study have been diagnosed with cancer in the past and at present. A total of 14689 subjects were included in the study and 6493 (44.2%) subjects were infected by *H. pylori*. Subjects were excluded from the study if they did not have a detectable *H. pylori* infection inflammatory status (anti-*H. pylori* IgG and IgM) or one of the following

tumour markers: CEA, AFP, CA199, CA125, CA153 and CA724.

By conducting a chart review, we collected demographic information and physiological status of all recruited subjects, including underlying diseases (such as diabetes, hypertension and coronary heart disease), height, weight, low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC) and abdominal ultrasound examination results. Body mass index (BMI) was calculated by the weight (kg) divided by the square of height (m). A subject is categorised as obese if his BMI ≥ 28 kg/m², overweight if $24 \leq \text{BMI} < 28$ kg/m², normal if $18.5 \leq \text{BMI} < 24$ kg/m² and underweight if his BMI < 18.5 kg/m², according to the criteria of weight for adults in the health industry standard of China (WS/T 428–2013). *H. pylori* infection status was assessed by ELISA specific for anti-*H. pylori* antibodies, particularly IgG and IgM. If both serological testing results were positive, the subject was diagnosed as *H. pylori* infection. Subjects with *H. pylori* infection were divided into the *H. pylori* (+) group, while subjects without *H. pylori* infection were in *H. pylori* (–) group. The ratios of individual biomarkers were measured between the two groups. The ratio is defined according to the cut-off value. Abnormal ratio means the percentage of individuals with abnormal CEA (ie, CEA > 5 ng/mL) in total *H. pylori* (+) subjects or individuals with abnormal CEA in total *H. pylori* (–) subjects.

This study was performed with approval and all methods were carried out in accordance with the approved guidelines. Written informed consent was obtained from all subjects at the stage of recruitment.

Patient and public involvement

Since our study was a retrospective study, study participants were not involved in the recruitment to and conduct of our study design. In addition, no patient advisers were involved in our study. Although the results have not been published as a full journal article yet, they were disseminated to study participants as grey literature, with internal reports in Chinese characters.

Outcomes

Cut-off values were administered to distinguish whether tumour marker levels were normal or abnormal. According to previous studies, the cut-off values of serum CEA, AFP, CA199, CA724, CA153 and CA125 were set to 5 ng/mL, 10 ng/mL, 37 U/mL, 10 U/mL, 25 U/mL and 35 U/mL, respectively, which we adapted for our study as well.^{23–26}

Statistical analysis

Descriptive statistics were performed by summarising continuous variables as mean \pm 1 SD, or median \pm IQR. Categorical variables were summarised as frequencies and proportions. We used Mann-Whitney U test to evaluate the statistical significant levels among continuous variables, and χ^2 test along with the Fisher exact test among categorical variables. In addition, we used logistic

regression models and generalised linear models to explore the relationships and associations between *H. pylori* infection and tumour marker groups (ie, CEA, AFP, CA199, CA724, CA125 and CA153).

We adjusted the variables of age, sex, diabetes, hypertension, coronary heart disease, LDL, HDL, TC and BMI in the models above. ORs, β values and their 95% CIs were estimated using maximum likelihood methods. A difference is considered statistically significant if it showed a two-sided $p < 0.05$. All statistical analyses were performed using Stata V.14.0 (Stata Corp LP, College Station, Texas, USA).

RESULTS

Demographic information of subjects and physiological status

Among the 14 689 subjects in the current study, there were 6493 (44.2%) with *H. pylori* infection. The subjects had a mean age (1SD) of 45 (18) years old with a range from 18 to 92 years old. There were 4530 (31.0%) female subjects. 10.7% of subjects were diagnosed with diabetes, 24.2% with hypertension and 4.2% with coronary heart disease. The overall prevalence of the abovementioned underlying diseases was 28.9% (4521/14 689). Significant differences were found in both LDL and HDL levels between *H. pylori* (+) and *H. pylori* (-) groups. As for BMI, 37.0% of the subjects were overweight and 12.8% were obese. Subjects in the *H. pylori* (+) group generally had a higher BMI than subjects in the *H. pylori* (-) group

($p < 0.05$). All basic characteristics of subjects included in the study are demonstrated in table 1.

Associations between *H. pylori* infection and tumour markers

The levels of CEA, AFP, CA199, CA724, CA153, CA125 and tumour marker categories with authoritative cut-off value are presented in table 2. Mann-Whitney U tests were performed to analyse the difference of tumour marker levels between the *H. pylori* (+) and *H. pylori* (-) groups. The levels of CEA, AFP and CA724 in subjects in the *H. pylori* infection group were significantly higher than those in the *H. pylori* (-) group (all $p < 0.05$). Subjects showed no significant differences in the levels of the other three tumour markers (CA199, CA153 and CA125) between two groups ($p > 0.05$). Based on the cut-off values of CEA at 5.0 ng/mL and AFP at 10.0 ng/mL, significant difference was found between the two groups for these two tumour markers ($p < 0.05$).

Multinomial logistic regression and generalised linear models were used in this study to further analyse the association between *H. pylori* infection and tumour markers (tables 3 and 4). After adjusting for the potential confounders, including age, sex, underlying diseases, LDL, HDL, TC and BMI, a significant direct association was found for CEA (OR 1.242; 95% CI 1.004 to 1.485; $p = 0.018$), a very significant negative association for AFP (OR 0.556; 95% CI 0.360 to 0.860; $p = 0.008$) and a significant inverse association for CA724 (OR 0.345; 95% CI 0.145 to 0.821; $p = 0.016$) between *H. pylori* infection and

Table 1 The basic characteristics of the subjects and the prevalence of *Helicobacter pylori* infection in the study

Variable*	Total (n=14689)	<i>H. pylori</i> (+) (n=6493)	<i>H. pylori</i> (-) (n=8196)	P value
Age (year)	45±18	46±18	44±18	<0.001
≤30	4099 (27.9)	1657 (40.4)	2442 (59.6)	<0.001
31–60	7218 (49.1)	3225 (44.7)	3993 (55.3)	
>60	3372 (23.0)	1161 (47.8)	1761 (52.2)	
Sex, female	4530 (31.0)	1774 (39.2)	2756 (60.8)	<0.001
Underlying diseases	4521 (28.9)	1968 (46.3)	2283 (53.7)	0.001
Diabetes	1575 (10.7)	710 (45.1)	865 (54.9)	0.459
Hypertension	3550 (24.2)	1656 (46.7)	1894 (53.4)	0.001
Coronary heart disease	612 (4.2)	260 (42.5)	352 (57.5)	0.382
LDL>3.1 mmol/L	3882 (26.4)	1839 (47.4)	2043 (52.6)	<0.001
HDL<0.83 mmol/L	4392 (29.9)	2044 (46.5)	2348 (53.5)	<0.001
TC>5.7 mmol/L	2724 (18.5)	1233 (45.3)	1491 (54.7)	0.217
BMI (kg/m ²)	24.2±3.5	24.4±3.5	24.0±3.5	<0.001
Underweight	400 (3.4)	153 (38.3)	247 (61.8)	<0.001
Normal	5561 (46.8)	2318 (41.7)	3243 (58.4)	
Overweight	4396 (37.0)	2056 (46.8)	2340 (53.2)	
Obesity	1518 (12.8)	724 (47.7)	794 (52.3)	

*Continuous variables were summarised as mean±1 SD. Categorical variables were summarised as frequencies and proportions. BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol.

Table 2 The distribution of tumour marker parameters

Variable*	Total (n=14 689)	<i>Helicobacter pylori</i> (+) (n=6493)	<i>H. pylori</i> (-) (n=8196)	P value
CEA (ng/mL)	1.8 (1.2–2.7)	1.9 (1.3–2.8)	1.8 (1.2–2.6)	<0.001
≥5	516 (3.9)	267 (4.5)	249 (3.4)	0.001
<5	12 695 (96.1)	5591 (95.4)	7104 (96.6)	
AFP (ng/mL)	4.5 (3.2–5.8)	4.6 (3.3–5.8)	4.4 (3.1–5.8)	0.004
≥10	98 (0.8)	30 (0.5)	68 (0.9)	0.007
<10	12 956 (99.3)	5738 (99.5)	7218 (99.1)	
CA199 (U/mL)	6.1 (3.0–11.4)	6.1 (3.1–11.4)	6.1 (3.1–11.9)	0.883
≥37	142 (2.2)	57 (2.0)	85 (2.5)	0.151
<37	6190 (97.8)	2861 (98.1)	3329 (97.5)	
CA724 (U/mL)	1.2 (0.9–3.0)	1.4 (0.9–3.4)	1.2 (0.9–2.8)	0.017
≥10	31 (3.1)	7 (1.8)	24 (4.0)	0.062
<10	958 (96.9)	375 (98.2)	583 (96.1)	
CA153 (U/mL)	6.7 (5.3–9.1)	7.6 (6.5–10.9)	6.2 (5.1–8.4)	0.098
≥25	0	0	0	
<25	79 (100.0)	26 (100.0)	53 (100.0)	—
CA125 (U/mL)	11.7 (8.7–16.8)	11.5 (8.9–19.5)	11.9 (7.5–16.0)	0.468
≥35	9 (5.5)	4 (7.8)	5 (4.4)	0.366
<35	156 (94.5)	47 (92.2)	109 (95.6)	

*Continuous variables were summarised as mean±IQR. Categorical variables were summarised as frequencies and proportions. AFP, alpha-fetoprotein; CA, cancer antigen; CEA, carcinoembryonic antigen.

the corresponding abnormal levels of tumour markers. We did not find any association between *H. pylori* infection and abnormal levels of the remaining two tumour markers, CA 199 (OR 0.791; 95% CI 0.560 to 1.116; $p=0.182$) and CA 125 (OR 0.265; 95% CI 0.547 to 8.970; $p=0.265$) (table 3).

The results of continuous tumour marker analyses are shown in table 4. Significant positive correlation was found between *H. pylori* infection and CEA values (adjusted $\beta=0.056$; 95% CI 0.005 to 0.107; $p=0.033$). No correlation was found between *H. pylori* infection and

other five tumour marker values after adjusting for the potential confounders (all $p>0.05$).

DISCUSSION

Our retrospective study evaluated the relationships between *H. pylori* infection and six tumour markers within a large sample size from a Chinese population. The main finding of our study is that the subjects with *H. pylori* infection may have a higher CEA level and an abnormal CEA ratio between the *H. pylori* (+) group to the *H. pylori*

Table 3 The associations between *Helicobacter pylori* infection and tumour marker groups by the logistic regression models

Variables	Crude			Adjusted*		
	OR	95% CI	P value	OR	95% CI	P value
Model 1 single variable model						
CEA	1.362	1.142 to 1.624	0.001	1.242	1.039 to 1.485	0.018
AFP	0.555	0.361 to 0.854	0.007	0.556	0.360 to 0.860	0.008
CA199	0.78	0.556 to 1.095	0.152	0.791	0.560 to 1.116	0.182
CA724	0.453	0.193 to 1.063	0.069	0.345	0.145 to 0.821	0.016
CA125	1.855	0.477 to 7.218	0.373	2.215	0.547 to 8.970	0.265
Model 2 any one of the tumour markers model						
CEA/AFP/CA199/CA724/CA125	1.077	0.931 to 1.246	0.319	0.963	0.830 to 1.118	0.628

*Adjusted OR and 95% CI were calculated by adjusting for the potential confounders, including age, sex, hypertension, hyperlipidaemia, coronary heart disease, diabetes, low-density lipoprotein, high-density lipoprotein, total cholesterol and body mass index. AFP, alpha-fetoprotein; CA, cancer antigen; CEA, carcinoembryonic antigen.

Table 4 The associations between *Helicobacter pylori* infection and tumour marker levels by the generalised linear models

Variables	Crude			Adjusted*		
	β	95% CI	P value	β	95% CI	P value
CEA	0.154	0.010 to 0.208	<0.001	0.056	0.005 to 0.107	0.033
AFP	-0.094	-0.296 to 0.109	0.364	-0.115	-0.318 to -0.089	0.268
CA199	-0.101	-0.966 to 0.764	0.819	-0.084	-0.954 to 0.785	0.849
CA724	0.115	-0.443 to 0.673	0.685	-0.109	-0.669 to 0.451	0.702
CA125	2.002	-0.625 to 10.219	0.633	2.772	-5.572 to 11.116	0.515
CA153	1.4742	-0.100 to 3.045	0.067	1.380	-0.291 to 3.052	0.124

*Adjusted β and 95% CI were calculated by adjusting for the potential confounders, including age, sex, hypertension, hyperlipidaemia, coronary heart disease, diabetes, low-density lipoprotein, high-density lipoprotein, total cholesterol and body mass index. AFP, alpha-fetoprotein; CA, cancer antigen; CEA, carcinoembryonic antigen.

(-) group. To our knowledge, this issue has not been addressed in previous animal or epidemiological studies of this sample size.

The prevalence of *H. pylori* infection in our study was 44.2%, which is lower than the results of Chinese adult population in another systematic review, which reported the weighted mean prevalence of *H. pylori* infection to be 66% for rural Chinese populations and 47% for urban Chinese populations.²⁷ The exploration regarding the relationship between *H. pylori* infection and several varieties of cancer has started decades ago. Positive associations have been previously reported between *H. pylori* infection and the development of colorectal, hepatocellular and lung cancers, and a negative association has been found with oesophageal cancer in several previous meta-analyses.²⁸⁻³¹ A recent nationwide population-based retrospective cohort study in Taiwan, focusing on the relationships between *H. pylori* infection and cancer risks, illustrated that *H. pylori* infection might be an independent carcinogenic risk factor. This research group put forward one of the possible mechanisms of oncogenic transformation, which is that *H. pylori* infection triggers inflammation resulting in interactions between the bacteria and host cells in local and distant microenvironments.³² However, we cannot conclude the association between *H. pylori* infection and cancer risk from the current analysis because all recruited subjects have undergone the annual health examinations instead of cancer diagnosis examinations, although none of the recruited subjects have been diagnosed with cancer. We analysed the association between six tumour markers and *H. pylori* infection with the intention to provide potential evidence and early clues for the clinical intervention studies in preventing different types of cancers. With certain tumour markers indicating a higher risk of cancer, our study hopes to arouse the public's attention to take more initiative to prevent or treat *H. pylori* infection.

In our study, we found that subjects in the *H. pylori* infection group have significantly higher levels of CEA, AFP and CA724 than those in the *H. pylori* (-) group, which proved to be consistent with previous research results.^{21 22} Our results further illustrate that abnormal

CEA ratios were also higher in the *H. pylori* infection group. Researchers have pointed out that rising CEA level might indicate cancer progression or recurrence; therefore, it is considered one of the helpful tumour markers in monitoring of many cancers,³³ such as adenocarcinoma,³⁴ gastric cancer^{33 35} and breast, lung, oesophagus, pancreas and skeletal metastases cancers.^{7 26 36} In our study, we found a higher level and abnormal ratio of CEA in subjects with *H. pylori* infection; the results indicated that *H. pylori* infection may play a role in the progression of specific cancer and has the potential to regard as a useful marker for cancer. Therefore, with this information, the appropriate screening modalities such as imaging and biopsies could be considered earlier on and could have therapeutic benefits. More laboratory and cohort research are needed to confirm our hypothesis.

An interesting phenomenon demonstrated was that after categorising the cut-off values according to previous references, the abnormal ratios of AFP and CA724 were lower in the *H. pylori* infection group than those of the *H. pylori* (-) group. This was inconsistent with the results of continuous variable analysis. To our knowledge, there is no globally accepted standard cut-off value of tumour markers for cancer screening at present, although previous research has indicated that AFP is commonly used as a tumour marker to help to detect and diagnose cancers of the liver, testicles and ovaries^{37 38} and CA724 has a potential in diagnosis of gastric cancer.⁹ We cannot provide strong evidence to determine that *H. pylori* infection plays a role in the cancer process with our limited results. Further studies are needed to provide definitive information about the association of *H. pylori* infection and the two tumour markers found to be significant and to establish standard cut-off values of these tumour markers.

The strength of this study is its large sample size-based population, which increases the generalisability of the results. All the data are based on highly reliable hospital records. However, several limitations in our study must be addressed. First, as an observational study, we cannot confirm the actual causality between *H. pylori* infection and changes of tumour markers. In the future, cohort

studies would be best to analyse the causality. Second, all subjects were from Aerospace Centre Hospital in Beijing that underwent health examinations and many of the subjects were from an urban area, which is not sufficiently representative of the whole population and may lead to selection bias. Individuals from multiple centres with different backgrounds are needed. Another limitation is that serological testing for the presence of anti-*H. pylori* IgG and IgM does not indicate a current infection and only shows past exposure to this bacterium, which may have added bias to the detection of *H. pylori* infection. Moreover, our analyses were limited to the available data of subjects' health examination and only a few of the subjects had willingness for the detection of tumour markers CA724, CA153 and CA125. Individuals in China can choose their physical examination contents from a variety of packages, and due to costs, most individuals opt out of certain unnecessary tumour markers. Another important point that needs to be considered is that none of the patients diagnosed with cancer were recruited in our study. However, we cannot rule out the possibility that a very small proportion (even none) of the recruited subjects may develop cancer, which has not been diagnosed yet. In addition, the reported results in our study provide rationale to explore the association between *H. pylori* infection and tumour markers, which encourage researchers to perform further studies in large sample cohorts with longer longitudinal durations on topic about intervention on *H. pylori* infection, in order to prevent the prevalence of cancer.

CONCLUSION

In conclusion, our observational retrospective study illustrated that higher abnormal ratios of CEA, AFP and CA724 were observed in infected to uninfected subjects. Higher level of CEA was also found to be related to *H. pylori* infection after controlling confounders. These new findings provide a basis for further research regarding the mechanism of action of these tumour markers. Specifically, not only exploring tumour markers, but also finding their relationships with *H. pylori* infection and cancer, especially gastrointestinal cancer, will help researchers with meaningful pre-diagnosis of early stage cancer. These findings could aid in the earlier diagnosis and intervention provided to better patient's quality of life.

Contributors Conceived and designed the experiments: Q-BL, M-YX, LL and BC. Collected data and performed the experiments: M-YX, JY and LL. Analysed the data: Q-BL, M-YX and BC. Contributed reagents/materials/analysis tools: Q-BL, SW, YC, M-YX and LL. Wrote the paper: Q-BL, M-YX, BC, YC, LL and NM.

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Competing interests None declared.

Patient consent Obtained.

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