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Helicobacter pylori infection and gastric cancer: evidence from a retrospective cohort study and nested case-control study in China

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Abstract

AIM: To explore the association between *Helicobacter pylori* (*Hp*) infection and risk of gastric cancer in China.

METHODS: Utilizing gastroendoscopic biospsy tissue banks accumulated from1980 to1988 in Shandong, Zhejiang, and Jiangsu, where stomach cancer incidence was high, during stomach cancer screening conducted by Health Science Center of Peking University, School of Medicine of Zhejiang University, and Zhongshan Hospital of Fudan University. Warthin Starry silver staining method was applied to determine *H. pylori* infection status of biopsies collected during gastroendoscopic examination. In the retrospective study, the subjects were divided into two cohorts, the exposure cohort was positive *H. pylori* infection, and the non-exposure cohort was negative. Death from stomach cancer was determined as the outcome of the study. Logistic regression and Cox regression were applied to analyze the association between *Helicobacter pylori* infection and gastric cancer risk. In the nested case-control study, there were 28 deaths from gastric cancer in the fields of Muping, Shandong province, and Zhoushan, Zhejiang provinces. 4 controls were matched to each case on the basis of age (±5 years old), sex, residential place at the same time entered into the study. Conditional logistic regression analysis was used to analyze the data.

RESULTS: There were a total of 2 719 subjects (male 1 399, female 1 320) with gastroendoscopic biopsies stored available treated as a cohort. *H. pylori* positive cohort included 1 671 subjects (61.5 %) and *H. pylori* negative cohort 1 048 subjects(38.5 %). These subjects were followed up for 1-19 years, averaged 10.88 years. The outcome of death from stomach cancer in the exposure cohort was 33, and in the non-exposure cohort 11. After adjustment for age and sex, RR=1.9850 (P=0.0491), 95 % CI was 1.0026, and 3.9301. The results of conditional logistic regression showed an OR of 4.467 and 95 % CI of 1.161, and 17.190 for the nested case control study.

CONCLUSION: The results from the retrospective cohort study and the nested-case control study on the association of *H. pylori* infection and gastric cancer in China suggested that *Helicobacter pylori* infection might increase the risk of stomach cancer.

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INTRODUCTION

Large volume of literature on the association of *H. pylori* infection and gastric cancer has been published since Warren and Marshall first isolated *Helicobacter pylori* from human gastric mucosa in 1983[1]. The first compelling evidence linking *H. pylori* infection to gastric cancer was obtained from seroepidemiologic studies using nested case-control study design in the United States and Britain[2-4]. Although there were discrepancy among epidemiological studies[5-22], some meta-analyses indicated the magnitude of the association *H. pylori* infection and risk of gastric cancer was ORs=2-6[23-27]. Most of the studies based on serological data; the status of whether the *H. pylori* harbored in gastric mucosa at the time of sample collection was uncertain and it only indicated past infection of *H. pylori*. Using the *H. pylori* detected by microscopy from biopsy had some limitations because only several specimens were taken during endoscopy underwent, which might lead to underestimation. However, the bacilli found under microscope might reveal actual status of *H. pylori* harbored in the gastric mucosa. Under the support of foundation of Chinese Medical Board of New York Inc., Health Science Center of Peking University, Medical School of Zhejiang University and Zhongshan Hospital of Fudan University cooperated in the study of the association of *H. pylori* infection and gastric cancer. The subjects of *H. pylori* infection was positive when there were bacilli found under the microscope, the outcome of the study was gastric cancer death. A nested case-control design was carried out using gastric cancer death from Muping, Shandong province and Zhoushan, Zhejiang province where most of the subjects resided in the rural areas.

MATERIALS AND METHODS

Field of investigation

The field of Health Science Center of Peking University is Gaoling town in Muping County of Yantai City of Shandong province (short for Muping below), the mortality rate of gastric cancer was averaging 40/100 000 population during the last two decades. Screening and early diagnosis program were undertaken for those over 35 years old in 1987 and 1988. 2200 subjects' biopsies were taken and underwent histopathological diagnosis The field of School of Medicine of Zhejiang University is Daishan county in Zhoushan archipelago of Zhejiang Province (short for Zhoushan below), the mortality rate of gastric cancer was about 50/100 000 population, gastric cancer screening had been conducted and gastroendoscopy and histological diagnosis had been done on about 1800 subjects from 1980 to 1983. The field of Zhongshan Hospital of Fudan University is Changzhou city in Jiangsu province (short for Changzhou below), the mortality rate of gastric cancer was about 40/100 000 population, gastroendoscopy had been carried out in 1500 subjects.

Pathological and laboratory examination criteria

The histologic sections stained by H&E was according to the National Gastric Cancer Prevention Study Pathological Diagnostic Criteria, and gastric cancer was confirmed by pathological diagnosis. The *H. pylori* infection was determined by histologic assessment. Warthin Starry silver staining was applied to the histologic section of endoscopic biopsies and to determine the status of *H. pylori* infection of the subjects. The diagnostic criteria followed the Criteria for diagnosis on histologic sections on the first meeting of experts when an agreement was reached in April 1999[28].

Subjects of retrospective cohort study

Biopsies were available for histologic sections and Warrthin Starry silver staining from Muping, Zhoushan and Changzhou comprised the cohort. There were 1055, 875 and 793 subjects' biopsies available, respectively. The pathologic diagnosis was retrieved according to the record of diagnosis, and gastric cancer patients were excluded either for those diagnosed at the time of screening or diagnosed within one year after screening program. The histologic assessment of *H. pylori* infection was conducted by pathologists well trained on diagnosing *H. pylori* infection with Warrthin Starry silver staining slides. The exposure cohort was *H. pylori* infection positive after the histologic section assessment, and the non-exposure cohort was negative.

Subjects of nested case-control study

The cases were those who died from gastric cancer during the following period after the screening program and met the criteria set forth above in Muping and Zhoushan. For each case of gastric cancer death, we matched 4 controls on the basis of age (not ±5years), sex, date of biopsy specimen sampling and residential place, who were gastric cancer-free at the end of 1999.

Questionnaire survey

All subjects whose biopsies for histologic assessment were given a questionnaire interview, which included demographic data, family history of gastric cancer, life style such as smoking habit etc., and diagnosis and treatment of *H. pylori* infection in the past. The interviewers were village doctors trained on the interviewing skills. The interviews started from 1998 to the end of 1999. The subjects died and those who could not answer the questions while interviewing, was helped by their relatives familiar with them.

Statistical analysis

A database was established by the EPI info package, was put in according to standard procedure after the questionnaires evaluation and met the requirements. The SPSS package was used to conduct logistic regression analysis of the cohort and the Egret package (A Commercial System for Advanced Epidemiologic Statistics 1999) was applied to conduct Cox regression analysis of the survival data of the cohort, conditional logistic regression was used to compute the asymptotic ORs for the nested case control data.

RESULTS

General information of the cohort

The total subjects of the cohort were 2 719. There were 1 055 subjects from Muping, 875 subjects from Zhoushan and 793 subjects form Changzhou.

1 399 (51.5 %) subjects were male, and 1 320 (48.5 %) female. 1 671 (61.5 %) subjects were *H. pylori* positive; 1 048 (38.5 %) were *H. pylori* negative. Table 1 listed the general information of the three cohorts.

Table 1 The general information of the *H. pylori* positive and *H. pylori* negative cohorts

	H. pylori positive cohort	*H. pylori* negative cohort	Total	*P*
Gender (male/female)	1671(881/790)*	1048(520/528)	2719 (1399/1320)	>0.05
Muping	675(424/251)	380(239/141)		=1.000
Zhoushan	501(285/216)	370(183/187)		=0.033*
Changzhou	495(172/323)	298(98/200)		=0.643
Age (<50, 50-60, ≥60)	1671 (604,505,562)	1048 (366,310,372)	2719 (970,815,934)	>0.05
Muping	675(216,189,270)	380(102,110,168)		0.082,0.096
Zhoushan	501(221,138,142)	370(142,109,119)		0.097,0.224
Changzhou	495(167,178,150)	298(112,91,85)		0.108,0.131
Economic Status (well,poor)	1612 (1513,99)	1007 (949,58)	2619 (2462,157)	>0.05 (0.719-0.734)
Smoking (yes, no)	1610 (877,733)	1006 (566,450)	2616 (1433,1183)	>0.05 (0.123-1.0)
Alcohol drinking (yes, no)	1610 (624,986)	1006 (384,622)	2616 (1008,1608)	>0.05 (0.07-0.814)
Family history of gastric cancer (yes, no)	1670 (167,1503)	1046 (98,948)	2716 (265,2451)	>0.05 (0.277-0.948)

*The number in the parenthesis indicated the relevant number of each category defined in the first column.

Average follow-up duration of the subjects (Table 2)

Table 2 Follow-up duration of the cohort

Fields	*n*	Average follow-up duration(yrs)	Standard devisiom
Muping	1055	11.1496	2.8798
Zhoushan	871	14.1883	2.5603
Changzhou	793	6.5596	2.1343
Total	2719	10.8805	4.0358

There were 2 719 subjects' biopsies available for histologic assessment of *H. pylori* infection in the three fields where the prevalence rate of gastric cancer was high in China and were followed up to observe the outcome. The average follow-up duration was 10.88 years.

Number of gastric cancer deaths observed in cohort

The number of gastric cancer deaths observed in each field in *H. pylori* positive and *H. pylori* negative cohorts was listed in Table 3.

Table 3 The distribution of gastric cancer deaths observed in the follow-up period of the cohorts

Field	*H. pylori* positive cohort		*H. pylori* positive cohort		Total	
	n	No. of gastric cancer death	*n*	No. of gastric cancer death	*n*	No. of gastric cancer death
Muping	675	9	380	3	1055	12
Zhoushan	501	10	370	6	871	16
Changzhou	495	14	298	2	793	16
Total	1671	33	1048	11	2719	44

There were 1 671 subjects in the exposure cohort and 1 048 subjects in the non-exposure cohort, 33 and 11 cases respectively died from gastric cancer during the follow-up period.

The results of cohort study

The average age of gastric cancer death cases of the *H. pylori* positive and *H. pylori* negative cohorts was 60.41 and 69.18, respectively. The *t* test showed that there was significant difference between the two cohorts (t=2.494, P=0.017). The results of logistic regression analysis of association of *H. pylori* infection and gastric cancer death of different age groups were shown in Table 4. The results of Cox regression analysis was shown in Table 5.

Table 4 Result of logistic regression analysis of different age groups

Variables	OR	95 %
<50 years old	4.601	1.885,11.229
50-60 years old	1.916	0.961,3.822
⩾60 years old	Do not convergence	

Table 5 The results of Cox regression analysis with adjustment of age and sex

Variable	β	S.E	Wald	df	*P*	RR	95%CI	
							lower	upper
H. pylori	0.6856	0.3485	3.8705	1	0.0491	1.9850	1.0026	3.9301
Age	0.9062	0.5005	3.2773	1	0.0702	2.4748	0.9278	6.6010
Sex	-0.3237	0.3203	1.0215	1	0.3122	0.7234	0.3861	1.3554

The RR=1.9850, P=0.0491, 95 % CI is 1.0026 to 3.9301 for exposure of *H. pylori* infection cohort to non-exposure cohort with adjustment of age and sex.

The cumulative hazard function for positive and negative *H. pylori* infection and gastric cancer death adjusted age and sex was shown in Figure 1: a higher hazard for subjects with positive *H. pylori* infection, the difference was statistically different.

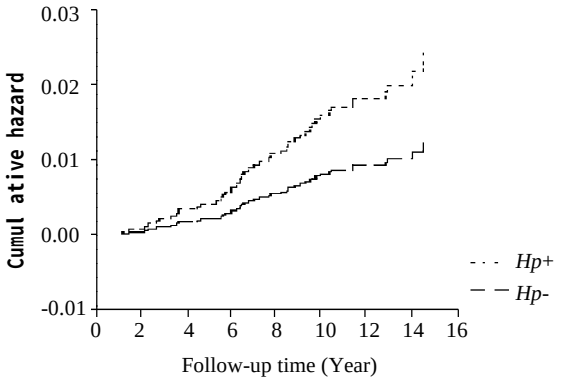

Figure 1 Cumulative hazard funtion for subjects with positive and negative *H. pylori* infection

The results of nested case-control study

The total number of gastric cancer death within the cohort of Muping and Zhoushan was 28, and 21 were male, 7 female. The average age of the subjects of cases and controls was 65.89 and 65.21, and the statistical analysis showed no difference between the two cohorts.

After univariate analysis, the result of multivariate analysis with adjustment of potential confounding factors was shown in Table 6.

Table 6 The result of conditional logistic analysis of *H. pylori* and gastric cancer risk

	β	P	OR	95% CI (lower)	95% CI(upper)
H. pylori infection	1.497	0.0295	4.467	1.1610	17.1900
Non-farmer	-1.415	0.0669	0.243	0.0535	1.1040
Poor economic condition	1.287	0.2022	3.620	0.5011	26.1600
Usually drank unboiled water	1.099	0.1565	3.000	0.6564	13.710
Wash hands before meals	-1.896	0.0241	0.150	0.0289	0.7798
Like to eat smoked food	0.913	0.2102	2.492	0.5974	10.3900
Lower vegetables intake	0.5153	0.4542	1.674	0.4342	6.4550
Smoking	5.808	0.0037	332.800	6.5840	1.683e+004
Older age started to smoke	-0.145	0.0137	0.865	0.7707	0.9707
Lower fruits intake	-0.524	0.4836	0.592	0.1367	2.5660
History of upper addominal pain	0.678	0.3027	1.970	0.5425	7.1530

After adjusted some potential confounding factors, it showed that *H. pylori* infection was significantly associated with gastric cancer death, the OR was 4.467, 95 % CI was 161-17.19, P<0.05.

DISCUSSION

The aim of this study was to explore the association between *H. pylori* infection and gastric cancer risk. The average follow up duration was 10.8 years. The results of retrospective analysis showed that the risk of death from gastric cancer in the *H. pylori*

positive cohort was 1.985 times to *H. pylori* negative cohort (95 % CI (1.0026, 3.9301)); the results of the nested case-control showed the association between *H. pylori* infection and gastric cancer risk increased after adjustment of some potential confounding factor, the OR was 4.467, 95 % CI was 1.161 to 17.190. The result suggested that the *H. pylori* infection was associated with gastric cancer death. The results were in accordance with those retrospective and nested case control studies[2-4,10,12,14,18,19, 21,22] and meta-analyses of *H. pylori* infection and gastric cancer risk published recently[23-27]. It was also similar to the magnitude of association between *H. pylori* infection and non-cardia gastric cancer 2.29[29] in Linxian of China reported by Limburg *et al* in a nested case control study and the results of Hansen *et al*[14]. The average age of gastric death in the *H. pylori* infection cohort was younger than that of negative cohort, the difference was statistically significant, the ORs of different age groups were in favor of that *H. pylori* infection was risk factor for the young[10,30,31]. Because the carcinogenesis of gastric cancer was of multiple stages and multiple factors involvement, *H. pylori* infection is not an independent risk factors on the carcinogenesis of gastric cancer. The prevalence of *H. pylori* infection is high in developing counties, only a small proportion of people infected with the bacteria develop gastric cancer. The biological mechanism of gastric carcinogenesis remains unclear. Our results suggested that *H. pylori* infection played different role at different ages of life.

The gastric cancer death in this study was those histologically confirmed cases and excluding those followed after gastroendoscopic screening within one year in each field and cardia gastric cancer, all these limitations might strengthen the virtual epidemiological evidence generated by this study.

There are several methods to determine the *H. pylori* infection of the stomach; the sensitivity and specificity are approximate[32-34]. The application of these methods would render different results' false negative results in different population[7,13,33,34], and the use of multiple tests may help to provide a more accurate diagnosis of *H. pylori* infection[35]. Although the seroconversion rate was a bit lower[36,37]. The loss of *H. pylori* infection may occur earlier in those using serological assessment of *H. pylori* infection than using histological assessment of *H. pylori* infection, because sera *H. pylori* IgG can be detected after the eradication of *H. pylori*. Histologic assessment of biopsies was more reliable and with less information bias. The data of this study was a combined analysis in high gastric cancer prevalence areas in China. The recent mortality rate of gastric cancer was about 40-50/100 000 persons by screening and early diagnostic program carried out in the three regions and the biopsies reserved made such a study feasible. Although the subjects screened could not represent the natural population and some biopsies used by other studies, there might be selection bias, which could result some bias in the estimation the association between *H. pylori* infection and gastric cancer risk. Since strict quality control and the confounding factors controlled during the analysis were conducted, the chance of misclassification of diagnosis and exposure was minimized, and the overall result was reliable.

Although we had provided evidence for positive association between *H. pylori* infection and gastric cancer risk based on histologic assessment of *H. pylori* infection by limited cohort subjects, it needs to expand the study in a natural population to minimize the selection bias. The association between *H. pylori Cag A* positive strain, which is considered more virulent than others, and gastric cancer should be further investigated. More convincing evidence of *H. pylori* infection and gastric cancer risk would be gained by *H. pylori* eradication interventional study.

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