Original Article

Stomach cancer in 67 Chinese counties: evidence of interaction between salt consumption and helicobacter pylori infection

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Objective: To examine the interaction between salt-intake and *helicobacter pylori* (*H. pylori)* infection in the development of stomach cancer in an ecological study of 67 Chinese rural counties. Methods: Stomach cancer mortality data of 67 counties were derived from a national survey conducted in China between 1986 and1988. Information regarding the prevalence of *H. pylori* infection and urinary sodium excretion were collected from the same individuals during a subsequent dietary survey in 1989. Results: In these 67 counties, *H. pylori* prevalence and urinary sodium were correlated with stomach cancer mortality, with r=0.31 (p=0.01) and r=0.28 (p=0.03), respectively. After stratification, the significant correlation between *H. pylori* prevalence and stomach cancer mortality only existed in counties with high levels (≥5.0 mg/mg creatinine/12-hour) of urinary sodium (r=0.5; p=0.002). Similarly, the significant correlation between urinary sodium and stomach cancer mortality was only presented in counties with high (≥71.6%) *H. pylori* prevalence (r=0.4; p=0.017). Multivariate regression analysis showed results consistent with the correlation analysis. Conclusion: These findings suggest that there may be an interaction between high salt consumption and *H .pylori* infection in the development of stomach cancer. Corroborating data from epidemiological, clinical, and experimental studies are needed.

Key Words: helicobacter pylori, stomach cancer, mortality, urinary nitrate, urinary sodium

INTRODUCTION

Stomach cancer ranks third among the most common cancers in China,[1] and it is the first and second leading cause of cancer deaths in rural and urban China, respectively.[2] The mortality rate of stomach cancer in China doubles the average rate in the world, with an overall five-year relative survival rate of approximately 20% or less.[3] It was estimated that there were approximately 400,000 new cases diagnosed in China, and 300,000 deaths from this malignancy in 2005.[3] Thus, an increased understanding of factors relevant to stomach cancer etiology and prevention remains an important public health goal in China and elsewhere. *Helicobacter pylori (H. pylori)* infection has been shown to be a major risk factor for stomach cancer in ecological,[4,5] case-control[6-9] and cohort[8,10] studies. In 1994, the International Agency for Research on Cancer (IARC) designated *H. pylori* as carcinogenic to humans (Class 1).[11] However, high *H. pylori* prevalence in areas with concomitantly low stomach cancer incidence, e.g., certain parts of Africa[12] and Asia,[13] suggests that *H. pylori* infection alone cannot fully explain the worldwide distribution of stomach cancer. Indeed, several-fold differences in stomach cancer incidence rates across geographic regions,[14] and within regions temporally, [15] suggest that the association between *H. pylori* and stomach cancer may be modified by other environmental, lifestyle or dietary factors. Among these latter, dietary salt has been a suspected risk factor for stomach cancer for decades. Numerous experimental[16,17] and epidemiological studies[18-23] have examined the association between salt intake and stomach cancer risk, with some finding positive associations,[16-21] and others finding no clear association.[22,23] One possible reason for the discrepant findings to date may be related to biological interaction between *H. pylori* infection and salt consumption. Such interaction has been examined in a few animal experiments, where high-salt diet was shown to enhance the effects of *H. pylori* on gastric carcinogenesis. [24-26] Three epidemiological studies on this issue have been reported in the literature.[7, 21, 27] One case-control study in Korea demonstrated that subjects with *H. pylori* infection and high-salt consumption had a significantly increased risk of developing stomach cancer than subjects without

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Manuscript received 18 March 2008. Initial review completed 28 September 2008. Revision accepted 13 October 2008.

H. pylori infection and with low-salt consumption.[21] Another case-control studies found no clear synergistic interaction between *H. pylori* infection and salt consumption in stomach cancer.[7] A prospective study of Japanese subjects revealed that high salt intake had a strong association with stomach cancer only in the subjects with *H. pylori* infection.[27] Thus, whether salt intake interacts with *H. pylori* infection in the development of stomach cancer remains unclear. The primary aim of the present study was to provide additional evidence regarding this potential interaction by examining stomach cancer mortality (SCM) variation according to regional salt-intake and *H. pylori* infection rates in 67 Chinese rural counties.

MATERIALS AND METHODS

From 1986 to 1988, a national stomach cancer mortality survey was performed in 69 counties. These 69 counties were randomly chosen from the total of about 2400 largely rural counties in China to represent the full range of mortality rates (in the previous 1973-75 nationwide survey) for seven major types of cancer: nasopharynx, oesophagus, stomach, liver, lung, colorectal and leukaemia.[28] There counties are distributed throughout China and are in aggregate, reasonably representative of rural mainland China as a whole. In majority of the counties, population numbers were around 300,000. Stomach cancer mortality (SCM) is a cumulative mortality aged 35-69 in 1986-1988. Age standardized mortality rates (aged 35-69) were calculated by the standard age structure (aged 35-44, 45-54 and 55-69). Two counties unable to generate complete data were deleted from the final database; hence, this study analyzed complete data from 67 rural Chinese counties. The present study focused on the relationship between stomach cancer mortality and the interaction between sodium intakes and *H. pylori*. However, female urinary samples were not available in these 67 counties in the 1989 survey. Therefore, we focused on male stomach cancer mortality in the present study.

H. pylori prevalence, urinary sodium excretion and urinary nitrate excretion were derived from a subsequent dietary survey conducted in 1989 in the same 69 counties.[28] Within each county, an age- and sex-stratified sample of 60 residents aged 35-64 was chosen from two randomly selected Xiangs (township), thus there were roughly equal numbers of males and females in each of three age groups: 35-44, 45-54 and 55-64. Simultaneously, 10 ml fasting venous blood were collected from selected subjects in trace-mineral-free heparinized vacutainers, which were placed on ice in light-free vacuum jars. Samples we transported to the county laboratory within about four hours of the last blood draw of the day, stored temporarily at -15 to -20 °C there, and then shipped on dry ice to the Chinese Academy of Preventive Medicine (CAPM) in Beijing, where they were again stored at –20°C. In 1990, *H. pylori* antibody was tested by ELISA with analyzer Dade Behring ELISA Processor III in Chinese Academy of Preventive Medicine. The number of samples tested in this study was 8,280. A detailed description of the *H. pylori* antibody assays is provided elsewhere.[29] A 12-hour urine collection was to be done from males only on two separate days, once after a small (500mg) oral dose of praline and once after the same dose of praline together with enough ascorbate (200mg) to inhibit virtually all gastric nitrosation of amino acids for as long as the praline was still in the stomach. Samples of the collected urine were frozen at –15 to –20 °C prior to transport on dry ice to Beijing, and urinary sodium was tested in Beijing CAPM. Compared with other traditional urinary sodium indices, sodium to creatinine ratio, which is not affected by circadian excretion rhythms and is considered reasonably valid,[30,31] was tested. The test results of *H. pylori* (serum antibody percentage), urinary sodium (mg/ mg.creatinine/ 12-hour) and urinary nitrate (g/ 12-hour) were computerized for data analysis.

We examined the correlation of urinary sodium, *H. pylori* prevalence, and other risk factors and stomach cancer mortality using Pearson correlation statistics. To select variables for linear regression analysis, stepwise linear regression was performed on dietary factors and life-style variables with significant univariate correlations and on those associated in other reports with the risk of stomach cancer. Due to interest in nitrate as a possible cause of gastric cancer and the finding that the urinary nitrate were significantly correlated with the stomach cancer mortality rate and with urinary sodium,[32] this variable was added separately to the model to determine its effect in combination with other risk factors. Finally, multivariate regression analysis was performed with SCM as the dependent variable and *H. pylori*, sodium, nitrate, and body mass index as independent variables. To determine whether the association between *H. pylori* prevalence and SCM was modified by urinary sodium levels, an interaction term of salt-*H. pylori* was introduced into the multivariate regression model. In order to further observe the association of SCM and its risk factors, we repeated the analyses after dichotomizing salt consumption to low and high (cut-off: median of urinary sodium, 5.0 mg/mg creatinine/12-hour), dichotomized the *H. pylori* to low and high (cut-off: median of *H. pylori* prevalence, 71.6%). Since unequal probability sampling was used in the diet survey, the design effects were estimated for *H.plori* prevalence, urinary sodium excretion in each county. The design effect is basically the ratio of the actual variance, under the sampling method actually used, to the variance computed under the assumption of simple random sampling. Statistical Analysis Software (SAS) version 9. 0 was used for all above analysis. All statistical tests were two-sided.

RESULTS

Table 1 shows the mean urinary sodium levels, mean *H. pylori* prevalence rates, urinary nitrate average levels, and SCM mortality rates in the selected 67 Chinese counties. The average (range) urinary sodium, *H. pylori* (serum antibody percentage), urinary nitrate and SCM were 5.2 mg/mg·creatinine/12-hour (2.6-10.7), 71.4% (25.6%-96.5%), 0.17 g/12-hour (0.05-0.36) and 185 per 100,000 (14-656), respectively. We observed a relative high variation for each of these variables, particularly for SCM with a 45-fold difference between the highest and the lowest counties.

The correlation between urinary sodium and SCM was statistically significant in 67 counties. Similar results were obtained between *H. pylori* infection and SCM (Table 2). After stratification, positively significant correlations were observed between sodium and SCM in coun

Table 1. Mean urinary sodium, serum helicobacter pylori antibody, urinary nitrate, and stomach cancer mortality in males from 67 Chinese counties

County	U-na†	H.p‡	U-nitro§	M-SCM¶
Wudu	10.7	74.9	0.14	350
Huguan	8.5	92.3	0.07	389
Cixian	8.0	69.6	0.11	145
Zaoyang	7.9	66.3	0.25	163
Yinjiang	7.7	63.2	0.20	80
Zongyang	7.5	79.8	0.20	261
Changling	7.1	72.1	0.09	160
Linxian	7.0	51.9	0.10	189
Shanyang	6.8	59.9	0.17	114
Xiuyan	6.8	59.5	0.14	167
Daishan	6.5	85.3	0.25	241
Jiaxian	6.5	68.3	0.09	385
Huaian	6.3	77.8	0.23	333
Jingxing	6.3	62.9	0.15	207
Quxian	6.2	69.7	0.17	94
Longde	6.1	90.5	0.08	413
Shangshui	6.0	77.1	0.14	70
Tuoli	5.9	77.4	0.05	226
Cangxi	5.9	59.2	0.11	264
Tianzhu	5.8	87.0	0.09	456
Xiajiang	5.8	86.4	0.22	110
Nancheng	5.8	82.2	0.13	322
Longxian	5.8	61.5	0.06	149
Echeng	5.7	75.0	0.18	356
Qianshan	5.7	70.3	0.24	151
Songxian	5.6	58.9	0.21	289
Qingzhen	5.6	53.7	0.17	53
Baoqing	5.4	62.6	0.16	119
Jiexiu	5.4	44.7	0.14	72
Qidong	5.3	87.5	0.23	125
Jiangxian	5.3	56.3	0.13	207
Jianhu	5.2	70.1	0.26	553
Taixing	5.1	85.2	0.22	391
Xinyuan	5.1	80.6	0.06	151
Xianghuangqi	5.0	71.2	0.19	204
huanghua	5.0	63.5	0.12	49
Xuanwei	5.0	42.9	0.24	19
Huishui	4.8	67.8	0.19	18
Yang-zhong	4.7	91.0	0.18	543
Haimen	4.7	74.5	0.32	83
Shuyang	4.7	53.7	0.21	144
Lean	4.6	85.0	0.14	77
Qiyang	4.5	81.2	0.13	100
Songjiang	4.5	76.7	0.27	136
Qingpu	4.5	72.1	0.14	166
Mayang	4.4	64.9	0.27	60
Shanghai	4.3	77.6	0.20	167
Tulufan	4.3	77.3	0.09	89
Wuhua	4.2	96.5	0.26	33
Yuanjiang	4.1	56.7	0.15	43
Dunhuang	4.0	67.7	0.09	345
Rongxian	4.0	25.6	0.30	14
Wenjiang	3.9	75.0	0.18	145
Nanan	3.8	87.7	0.24	182
Changle	3.8	86.0	0.36	656
Laoshan	3.7	60.4	0.10	161
Wuchuan	3.6	89.0	0.15	121
Chongzuo	3.4	89.0	0.06	58
Jiashan	3.4	64.0	0.27	127
Yongning	3.4	50.5	0.08	356
Zhangpu	3.3	72.3	0.19	124
Linwu	3.2	78.8	0.15	105
Cangwu	3.2	70.1	0.29	20
Huain	3.0	83.5	0.20	161
Fushui	2.9	87.3	0.14	57
Panyu	2.9	56.0	0.32	24
Sihui	2.6	71.6	0.15	29
Mean (SD)	5.2 (1.5)	71.4 (13.6)	0.17 (0.07)	185 (142)

† U-na: urinary sodium (mg/mg creatinine)

‡ H.p: serum H.pylori antibody (%)

§ U-nitro: urinary nitrate (g/12hrs)

¶ M-SCM: male age standardized stomach cancer mortality (/100,000)

ties with high *H. pylori* prevalence (≥71.6%), and between *H. pylori* and SCM in counties with high urinary sodium (≥5.0 mg/mg.creatinine/12-hour). No correlation was found between *H. pylori* and SCM in counties with low urinary sodium (<5.0 mg/mg.creatinine/12-hour) and between sodium and SCM in counties with low *H. pylori* prevalence (<71.6%).

H. pylori prevalence and urinary sodium was positively and significantly associated with SCM after adjustment for BMI and urinary nitrate (Table 3). The cross-product term measuring the interaction of urinary salt with *H. pylori* was statistically significant with *p* value 0.22. After stratification of urinary sodium levels, a statistically significant positive association between *H. pylori* prevalence and SCM only existed at high urinary sodium levels. Similarly, a statistically significant positive association between urinary sodium and SCM was only present in regions with high *H. pylori* prevalence.

Design effect ranged from 1.03-2.69 for *H.plori* prevalence and 1.02-1.95 for urinary sodium excretion in 67 counties.

DISCUSSION

Our results demonstrated that a significant positive association between *H. pylori* infection and the risk of stomach cancer was observed in the counties with high urinary sodium excretion, but not in the counties with low urinary sodium excretion. Accordingly, a positive significant association between urinary sodium and SCM was found in the counties with high *H. pylori* prevalence, but not in the

Table 2. Pearson correlation coefficients between helicobacter pylori infection, urinary sodium, and stomach cancer mortality in males from 67 Chinese counties

	All counties		H.p[†,‡]		U-na[†,§]	
	U-na[†]	H.p[†]	U-na[†] <5.0	U-na[†] ≥ 5.0	H.p[†] < 71.6	H.p[†] ≥ 71.6
n	67	67	30	37	32	35
r	0.28	0.31	0.20	0.50	0.13	0.40
p	0.025	0.011	0.280	0.002	0.490	0.017

[†] U-na: urinary sodium (mg/mg creatinine); H.p: Helicobacter pylori antibody (%)
[‡] stratified by the median of 12-hour urinary excretion of sodium
[§] stratified by the median of prevalence of helicobacter pylori antibody

Table 3. Multivariate regression analysis of stomach cancer mortality in males associated with urinary excretion of sodium and prevalence of serum helicobacter pylori in 67 counties

	All counties		H.p[†,‡]		U-na[†,§]	
	U-na[†]	H.p[†]	U-na[†]<5.0	U-na[†]≥5.0	H.p[†]<71.6	H.p[†]≥71.6
β	22.07	3.59	3.32	5.17	6.28	34.70
SE	10.54	1.15	1.66	1.55	16.40	15.34
p	0.040	0.003	0.056	0.002	0.705	0.031
R^2	0.26	0.26	0.33	0.26	0.20	0.24

[†]U-na: urinary sodium (mg/mg creatinine); H.p: Helicobacter pylori antibody (%)
[‡] stratified by the median of 12-hour urinary excretion of sodium
[§]stratified by the median of prevalence of helicobacter pylori antibody

counties with low *H. pylori* prevalence. Thus, our results suggest that there may be an interaction between high salt intake and *H. pylori* infection in the development of stomach cancer.

Two previous case-control studies and one prospective study have examined the relationship among salt consumption and *H. pylori* infection in the development of stomach cancer, and the results of these studies are inconsistent.[7,21,27,33] In a multicenter case-control study with 122 non-cardiac stomach cancer cases and 235 controls in Japan,[7] subjects with *H. pylori* infection and high-salt intake had an increased risk compared with subjects with *H. pylori* infection and low salt-intake. However, perhaps due to the small number of *H. pylori* negative cases, this difference did not reach statistical significance. A hospital-based case-control study[21] reported that subjects with *H. pylori* infection and high-salt consumption had a 10-fold risk of early stomach cancer than subjects without *H. pylori* infection and with a low-salt consumption (p=0.047). The sample size of that study (n=69) was also prohibitively small. In a cohort study conducted in the Japanese Hisayama population, the risk of gastric cancer was analyse with respect to high salt intake (≥10 g/day) relative to low salt intake (<10 g/day), according to the status of atrophic gastritis and *H. pylori* infection at baseline.[27] The HR of gastric cancer significantly increased with high salt intake in the subjects who had *H. pylori* infection, whereas this effect was not significant in those who did not have *H. pylori* infection. Because this study only had 2,476 subjects and 93 incident cases over 14 years of follow-up, the study was limited in their ability to stratify by salt intake, as compared with our data. Consistent with these previous studies,[21,27] our ecological study found a statistically significant interaction between regional salt intake and *H. pylori* infection in their correlation with regional stomach cancer mortality.

Valid quantification of sodium intake remains difficult in epidemiological studies. Because tight homeostatic control mechanisms minimize variation in blood sodium level,[34] and food frequency questionnaires cannot measure salt intake reliably, urinary sodium is considered to be the best measure of habitual salt intake.[34, 35] An estimated 86%[36] to 93%[37] of sodium intake can be detected in the excreted urine. We used urinary sodium excretion as a measure of regional salt intake in our study.

The present study has several other strengths. The entire procedure of SCM and nutrition survey in the present study was closely supervised by a national research quality control group from the Chinese Ministry of Health. To assess the reproducibility of the 1989 survey results, 13 out of 69 counties were selected in 1993 using a stratified sampling method and the survey was carried out exactly as the 1989 survey.[28] The 1993 survey (data not shown) showed a good reproducibility compared with the 1989 survey; the Pearson correlation was 0.95 for the prevalence of *H. pylori* between two surveys. In addition, random sample selection in this study helped ensure results that were representative of the Chinese rural population, although limiting ourselves to 67 counties may have resulted in limited ranges of exposure of our variables of interest.

The interpretation of our findings, as well as those of the few analytical studies, should be tempered by the fact that the mechanism by which salt interacts with *H. pylori* in the development of stomach cancer has not been well elucidated. A high-salt diet appeared to enhance the colonization of *H. pylori* in C57BL/6 mice; the increase in *H. pylori* gastric colonization implicated a possible synergistic mechanism.[38] Kato proposed that salt exacerbates *H. pylori* infection through up-regulation of surface mucous cell mucin and down-regulation of gland mucous cell mucin.[26] Surface mucous cell mucin and gland mucous

cell mucin are two different types of mucin in gastric mucus.[39] *H. pylori* was only discovered in surface mucous gel layer and mucins from gland mucous cells may disturb the movement of *H. pylori* within the mucous gel layer.[40] Recent study results indicated that high salt concentrations may up-regulate CagA (*H. pylori* gene) expression, which then may lead to increased CagA translocation in gastric epithelial cells and an enhanced ability of *H.pyori* to alter gastric epithelial cell function.[17] Taken together, these experimental findings tend to support our own.

In this ecological study, data from each county are in an aggregated form that represents the overall population level in this county, and individual level data are not available. Therefore, causal inference is limited by the possibility that our observations may differ from what is true among individuals within any given population, i.e., "ecological fallacy".[41] Although BMI and nitrate were adjusted in multivariate regression analysis, the influence of other potential confounders cannot be excluded.

The mortality rates of stomach cancer were derived from a survey performed between 1986 and 1988 but the risk factors (*H. pylori* infection and salt consumption) were obtained from a survey in 1989. We assume that mortality rates of stomach cancer have not substantially changed in these counties between the two surveys, which would result in misclassification and consequent bias towards the null. Our assumption is supported by the fact that various lifestyle and nutritional factors did not change dramatically in China during the study period.[3] In addition, two Chinese national surveys indicated that the SCM rates between 1973-1975 and 1990-1992 were 19.8 and 21.8 per 100,000 person-years, respectively,[3] indicating that the mortality rates of stomach cancer have been relatively stable. Nonetheless, some misclassification of the outcome is possible. The design effect for *H.plori* prevalence, urinary sodium excretion in the present study ranged from 1 to 3, which indicates a well designed study. Therefore, the sampling method in the diet survey had few effects on the results.

In summary, although limited by design, the results of this ecological study lend support to the hypothesis that *H. pylori* and salt intake may interact in the development of stomach cancer. If confirmed in other studies, this information would be useful in targeted efforts at prevention, both within China and in other areas with high endemic incidence.

ACKNOWLEDGEMENT

The authors gratefully acknowledge Dr. Fred Kadlubar for his generous assistance and Michele Whitworth for her technical assistance in the preparation of this manuscript.

AUTHOR DISCLOSURES

All authors declare that there isn't any conflict of interest in this manuscript.

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Original Article

Stomach cancer in 67 Chinese counties: evidence of interaction between salt consumption and helicobacter pylori infection

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食盐的摄入与幽门螺旋杆菌感染在胃癌发生过程中的交互作用—中国 67 个农村县的生态学研究

目的：通过一项 67 个中国农村县的生态学研究，评价食盐的摄入与幽门螺旋杆菌感染在胃癌发生过程中的交互作用。方法：1986 年至 1989 年，中国开展了一次全国性癌症死亡率的调查，本次研究的 67 个县的胃癌死亡率资料来源于该全国调查；1989 年中国在相同人群中展开了一次全国膳食调查，本研究的幽门螺旋杆菌感染流行率和尿钠的资料则来源于此。结果：幽门螺旋杆菌流行率和尿钠与胃癌死亡率显著相关，相关系数分别为 0.31 (p=0.01) 和 0.28 (p=0.03)。对尿钠水平分层后，幽门螺旋杆菌流行率与胃癌死亡率的显著相关仅存在于尿钠≥5.0 mg/mg 肌苷/12 小时的组，相关系数为 0.5，p=0.002；同样对幽门螺旋杆菌流行率水平分层后，尿钠与胃癌死亡率的显著相关仅存在于幽门螺旋杆菌流行率≥71.6%的组，相关系数为 0.4，p=0.017。多元回归结果与相关分析一致。结論：提示食盐的摄入与幽门螺旋杆菌感染在胃癌发生过程中可能有交互作用。这还需要其他流行病、临床和实验性确证研究资料的支持。

關鍵字： 幽门螺旋杆菌、胃癌、死亡率、尿硝酸塩、尿钠