Risk Factors for Stomach Cancer in Sixty-Five Chinese Counties[1]

Robert W. Kneller, Wan-De Guo,[2] Ann W. Hsing,[2] Jun-Shi Chen, William J. Blot, Jun-Yao Li, David Forman, and Joseph F. Fraumeni, Jr.

National Cancer Institute, Bethesda, Maryland 20892 [R. W. K., A. W. H., W. J. B., J. F. F.]; Institute of Nutrition and Food Hygiene, Chinese Academy of Prevention Medicine [J-S. C.], and Cancer Institute, Chinese Academy of Medical Sciences [W-D. G., J-Y. L.], Beijing, People's Republic of China; and Imperial Cancer Research Fund, Cancer Epidemiology Unit, Oxford OX2 6HE, England [D. F.]

Abstract

Stomach cancer mortality data were compared with dietary and biochemical data from 65 Chinese counties to provide clues to reasons for the marked geographic variation of stomach cancer mortality rates in China. Sex-specific correlation and multivariate regression analyses showed significant positive associations with consumption of salted vegetables and eggs, prevalence of antibodies to *Helicobacter pylori*, and levels of plasma albumin; and significant negative associations with intake of green vegetables and levels of plasma selenium and β-carotene. Limitations of ecological data preclude causal inferences, but these findings suggest factors that may contribute to making stomach cancer the leading cause of cancer death in China and other countries.

Introduction

Stomach cancer is the leading cause of cancer mortality in China (1). It remains one of the most common causes of cancer worldwide (2), although its incidence has been declining in many industrialized countries (3). In China, mortality rates vary considerably by region, with low rates in the south and pockets of high mortality in the west-central, northeastern, and coastal areas (4). Reasons for these variations are not well understood, although dietary factors are suspected to be important (5–7). We correlated stomach cancer mortality data with results from a survey of diet, life-style, and biochemical markers to provide clues to these geographic variations.

Materials and Methods

Stomach cancer mortality rates from a nationwide survey conducted in the mid-1970s were correlated with ecological data collected in autumn 1983 on diet, life-style, and biochemical markers in 65 rural counties (1). Details of both surveys are reported elsewhere (1, 4). The nationwide mortality survey attempted to ascertain all cancer deaths from 1973 through 1975 in an area encompassing 96% of the total Chinese population (1). Overall, 70% of the stomach cancer cases were diagnosed on the basis of pathology examinations, surgery, gross tissue specimens, gastroscopy, ultrasound, or radiological examinations; 23% on the basis of physical exam and history; and 7% on the basis of inference, by professionals, from reports by decedent's next of kin (1). Male and female cumulative mortality rates to age 65 per 1000 were calculated for each county (1).

The 65 counties in the ecological survey were selected on the basis of the 1973–1975 cancer mortality rates to represent a cross-section of mortality rates for the seven most prevalent cancers in China (*i.e.*, stomach, esophageal, liver, lung, colorectal, and nasopharyngeal cancer, and leukemia) (1). An age- and sex-stratified sample of 100 residents aged 35 through 64 was chosen from two randomly selected townships in each county, so that there were approximately equal numbers of men and women in each of three age groups: 35–44, 45–54, and 55–64. Ten ml of fasting blood were collected from each participant. At blood collection, survey team members administered a questionnaire to obtain demographic, smoking, and dietary information (1).

Mean responses (for continuous questionnaire variables) and percentage of positive answers (for dichotomous variables) were calculated by sex for each county. Over 60 biochemical assays were conducted on sex- and township-specific pooled plasma samples. Mean values of the plasma analytes were calculated by sex for each county. However, the assays for red cell hemoglobin and antibodies against *Helicobacter pylori* (formerly known as *Campylobacter pylori*) were conducted on individual samples, and plasma from male subjects in only 46 counties was available for the *H. pylori* assays (1, 8). A detailed description of the individual assays is provided elsewhere (1). In 64 of the 65 counties, subjects in one of the two townships also gave a urine sample collected over 4 h. Most urine analytes were assayed in age- and sex-specific pooled samples. In 1984, urine was collected from male subjects in 26 of the original 65 counties for analysis of nitrosamines (1).

Risks for males and females were analyzed separately because of the 2-fold excess in male mortality rates (1) and in order to compare the consistency of risk factors between sexes. The stomach cancer rates were transformed to their natural log values so that their distribution was closer to normal. Sex-specific Pearson correlation coefficients (R) were calculated between the transformed

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[2] Correspondence: From China, to Wan-De Guo, Cancer Institute of Chinese Academy of Medical Sciences, Langtan Lake, Zhuoanmenwai, Department of Epidemiology, Beijing, People's Republic of China; from other countries, to A. W. Hsing, Room 415, Executive Plaza North, National Cancer Institute, Bethesda, MD 20892. (To whom requests for reprints should be addressed.)

Table 1 Pearson correlation coefficients for the association between geographic conditions[a] and socioeconomic status[a] and stomach cancer mortality rates (log-transformed) in 65 Chinese counties

Variables	Men	Women
Aridity (zones 1–4, increasing order) (1.5)[b]	0.27[c]	0.28[c]
Heat zone (zones 1–10, increasing order) (4.1)	−0.56[d]	−0.59[d]
Elevation (m) (370)	0.12	0.19
Latitude (degrees north) (31)	0.53[e]	0.55[d]
Per capita commercial output (yuan) (638)	0.05	0.02
Literacy rate (% 12 years and older) (68)	−0.06	−0.07
% population employed in agriculture (79)	−0.28[c]	−0.23[f]

[a] From Refs. 1 and 4.
[b] Numbers in parentheses, means over the 65 counties.
[c] $P < 0.05$.
[d] $P < 0.001$.
[e] $P < 0.01$.
[f] $P < 0.10$.

county-specific mortality rates and 285 dietary, biochemical, life-style, and geographic indices. To select variables for linear regression analysis, stepwise linear regression was performed on dietary variables with significant univariate correlations for either males or females and on those associated in other reports with risk of stomach cancer. A final regression model included variables selected by the stepwise regression procedures for either males or females, plus those reported in other studies to have significant associations with risk. This same procedure was used to create a final regression model for risks associated with blood micronutrients. Plasma cotinine was excluded from this model because of inconsistent correlations between cotinine levels and questionnaire indices of smoking prevalence and because of other issues concerning its reliability as an indicator of exposure to tobacco smoke (9). Due to interest in *H. pylori* as a possible cause of gastric cancer precursor lesions and the finding that rates of seropositivity to *H. pylori* were significantly correlated with the untransformed stomach cancer mortality rates (8, 10), this variable was added separately to both models to determine its effect in combination with other risk factors. A standard statistical package (11) was used for these regression procedures and to calculate standardized regression coefficients.

Table 2 Pearson correlation coefficients for the association between selected dietary and smoking questionnaire variables and stomach cancer mortality rates (log-transformed) in 65 Chinese counties

Variables	Males	Females
Tobacco use		
% ever smoked any tobacco regularly	−0.03 (81)[a]	−0.06 (13)[a]
No. manufactured cigs/day	−0.03 (7.0)	0.06 (0.4)
Other tobacco per day (g)	−0.15 (5.6)	−0.08 (0.7)
Alcohol consumption (g/day)	−0.15 (30)	−0.03 (2)
Fruits and nonstarchy vegetables (times/year)		
Salt-preserved vegetables	0.26[b] (134)	0.30[b] (135)
Moldy salt-preserved vegetables	0.13 (8.2)	0.15 (9.3)
Green vegetables	−0.44[c] (197)	−0.36[d] (196)
Fruit	0.06 (18)	−0.03 (16)
Starchy foods		
Potatoes (times/year)	0.24[e] (43)	0.32[d] (45)
Sweet potatoes (times/year)	−0.19 (40)	−0.15 (40)
Moldy sweet potatoes (times/year)	0.06 (1.5)	0.09 (1.5)
Corn (1982 ration, g/day)	0.20 (77)	0.18 (71)
Moldy corn (times/year)	−0.03 (0.67)	0.07 (0.61)
Wheat (1982 ration, g/day)	0.30[b] (127)	0.29[b] (112)
Millet (1982 ration, g/day)	0.24[e] (13)	0.25[b] (14)
Wheat + millet (1982 ration, g/day)	0.35[d] (141)	0.31[b] (125)
Wheat + millet + corn (g/day)	0.35[d] (221)	0.33[d] (198)
Rice (1982 ration, g/day)	−0.31[b] (357)	−0.34[d] (319)
Soybeans and other legumes (g/day)	−0.06 (11)	0.04 (9.3)
Other foods		
Meat (times/year)	−0.31[b] (74)	−0.26[b] (54)
Fish (times/year)	0.13 (42)	−0.25[b] (36)
Meat + fish (times/year)	−0.26[b] (115)	−0.32[b] (91)
Eggs (times/year)	0.38[d] (42)	0.12 (31)
Milk (times/year)	0.10 (13)	0.20 (13)
Oil and fat (1982 ration, g/day)	−0.18 (13)	−0.18 (11)
Water supply (%)		
Surface water (river, pond, rain)	0.09 (30)	0.12 (28)
Shallow well	0.04 (47)	0.08 (48)
Deep well	−0.15 (23)	−0.23[e] (24)

[a] Numbers in parentheses, sex-specific means over the 65 counties.
[b] $P < 0.05$.
[c] $P < 0.001$.
[d] $P < 0.01$.
[e] $P < 0.1$.

Results

Cumulative stomach cancer mortality rates in the 65 counties varied over 70-fold, from 1.8 to 132.6 (median, 25.6) per 1000 for men and from 0.6 to 49.9 (median, 10.8) per 1000 for women.

Table 1 shows that stomach cancer mortality is higher in cold, northerly, arid regions. There were no significant correlations between mortality and available indicators of socioeconomic status, although there was an inverse association with the percentage of the population employed in agriculture.

As indicated in Table 2, tobacco and alcohol consumption were not associated with elevated risk. Consumption of green vegetables, rice, meat, and fish was associated with reduced mortality. Counties in the lowest consumption quartile for green vegetables had cumulative mortality rates 2.3 and 1.9 times higher among men and women, respectively, compared to counties in the highest consumption quartile. On the other hand, salt-preserved vegetables, potatoes, wheat, and millet, plus combinations of wheat, corn, and millet, were correlated with significantly increased mortality. Among men but not women, eggs were significantly associated with risk. No clear associations were found for fruit or various sources of drinking water.

Among blood analytes (Table 3), significant protective effects were found for plasma selenium and, among men, vitamin C. β-Carotene showed a protective association of borderline significance among men. Significant risk associations were found for plasma albumin, red cell hemoglobin, plasma copper (men only), and plasma ferritin (women only). The prevalence of antibodies to *H. pylori* was associated with a borderline significant risk ($P = 0.06$). No significant positive associations were found for urinary metabolites, including aflatoxin metabolites, nitrate, *N*-nitroso-proline, *N*-nitroso-sarcosine, and *N*-nitroso-thiazolidine-4-carboxylic acid.

Table 3 Pearson correlation coefficients for the association between selected blood variables and stomach cancer mortality rates (log-transformed) in 65 Chinese counties

Biochemical variables	Males	Females
Plasma variables		
Total cholesterol (mg/dl)	0.11 (127)[a]	0.11 (127)[a]
β-Carotene (μg/dl)	−0.24[b] (8.9)	−0.20 (11.8)
Retinol (μg/dl)	−0.15 (51)	0.01 (41.2)
α-Tocopherol (μg/dl)	0.23[b] (687)	0.13 (735)
Vitamin C (mg/dl)	−0.26[c] (1.1)	−0.06 (1.3)
Selenium (μg/dl)	−0.33[d] (8.2)	−0.39[d] (7.9)
Zinc (μg/dl)	0.16 (119)	0.09 (120)
Copper (μg/dl)	0.30[c] (99)	0.17 (106)
Ferritin (ng/ml)	0.12 (71)	0.25[c] (46)
Albumin (g/dl)	0.30[c] (3.0)	0.47[e] (3.1)
Cotinine (ng/ml)	−0.44[e] (150)	−0.11 (20)
H. pylori IgG Ab (% positive, 46 counties)	0.28[b] (60)	
Red cell analytes		
Hemoglobin (g/dl whole blood)	0.30[c] (13.8)	0.30[c] (12.9)

[a] Means over all counties with available data.
[b] $P < 0.10$.
[c] $P < 0.05$.
[d] $P < 0.01$.
[e] $P < 0.001$.

Stepwise linear regression selected green vegetables, eggs, and meat as the significant dietary determinants of risk among men. For women, this procedure selected green vegetables and salted vegetables as the significant determinants of risk. Fruit, which has been frequently associated with lowered risk (5, 10), and potatoes, a carbohydrate source associated with increased risk in one report (7), were then added to create the final regression model for dietary variables (Table 4). This shows a strong protective association with green vegetables and elevated risk associated with salted vegetables and eggs, as well as a significant independent risk for *H. pylori* when that variable is added to the model.

The stepwise regression procedure using blood micronutrients selected selenium, albumin, and copper as the significant determinants of risk among men, and selenium, albumin, β-carotene, and hemoglobin as the significant determinants for women. Combining these variables, plus α-tocopherol and vitamin C (previously associated with decreased risk; Refs. 10, 12–14), in the final regression model yielded the results shown in Table 5. The strongest association was with selenium, with stomach cancer mortality rates falling as plasma selenium levels rose. *H. pylori* was associated with elevated risk, but not significantly so ($P = 0.26$), when added to this model. In both the dietary and micronutrient models, risk factors for men and women tended to be similar.

Discussion

The opposite effects associated with green and salted vegetables are key findings of this study. Stomach cancer mortality tended to be low in counties with high consumption of fresh green vegetables and elevated in counties where salted vegetables were eaten more frequently. Numerous case-control studies in China and other countries (5–7, 15) have reported a protective effect for green vegetables, although only a few studies have reported an elevated risk associated with salted vegetables (5). In addition to salt, which itself may increase risk (5, 6, 15), Chinese salted vegetables have been reported to contain nitrosamines and other compounds that may be carcinogenic (16, 17). Green vegetable consumption was strongly correlated with warm, moist, and southerly geographic conditions, while salted vegetable intake tended to be higher in cool northern regions where pickling is an important means of preserving vegetables for winter and spring consumption. This may partly explain the higher rates of stomach cancer in northern counties and the other geographic correlations shown in Table 1.

In contrast to previous reports (5), we did not find an inverse relationship between stomach cancer risk and indices of socioeconomic well-being. Nevertheless, it may be that economic development reduces stomach cancer rates through specific changes, such as improved transportation and access to refrigeration, that permit substitution of fresh for salt-preserved foods. These changes still had not occurred in rural China at the time of the 1983 survey.

Our finding of a significant inverse association for meat is consistent with a recent case-control report from Turkey (18). Meat is a common source of selenium (19), which showed the strongest protective effect among all the plasma micronutrients; and the correlations between meat consumption and plasma selenium levels were strong ($R = 0.50$, $P < 0.0001$ for males; and $R = 0.44$, P

Table 4 Regression coefficients and standardized regression coefficients, by sex, for a linear regression model relating dietary factors with stomach cancer mortality rates (natural log-transformed) in 65 Chinese counties

Independent dietary variables	Males						Females		
	All counties			46 counties with *H. Pylori* antibody titers[a]			All counties		
	RC[b]	SRC	*P*	RC	SRC	*P*	RC	SRC	*P*
Green vegetables (times/year)	−0.00420	−0.418	0.0003	−0.00467	−0.455	0.001	−0.00286	−0.341	0.006
Salted vegetables (times/year)	0.00169	0.177	0.09	0.00209	0.214	0.07	0.00219	0.262	0.02
Fruit (times/year)	−0.00397	−0.076	NS	0.00224	0.047	NS	−0.00731	−0.152	NS
Potatoes (times/year)	0.00041	0.035	NS	−0.00039	−0.034	NS	0.00172	0.169	NS
Eggs (times/year)	0.01080	0.378	0.0008	0.01060	0.346	0.007	0.00731	0.250	0.05
Meat (times/year)	−0.00296	−0.185	0.08	−0.00298	−0.169	NS	−0.00215	−0.149	NS
H. pylori (% IgG positive)				0.01233	0.268	0.03			

[a] *H. pylori* included to test its independence as a risk factor.
[b] RC, regression coefficient; SRC, standardized regression coefficient; NS, not significant ($P > 0.10$).

Table 5 Regression coefficients and standardized regression coefficients, by sex, for a linear regression model relating blood micronutrient with the stomach cancer mortality rates (natural log-transformed) in 65 Chinese counties

Independent plasma micronutrient variables	Males						Females		
	All counties			46 Counties with *H. Pylori* antibody titers[a]			All counties		
	RC[b]	SRC	*P*	RC	SRC	*P*	RC	SRC	*P*
β-Carotene (μg/dl)	−0.04186	−0.209	0.08	−0.04833	−0.263	0.08	−0.04157	−0.259	0.01
α-Tocopherol (μg/dl)	0.00036	0.051	NS	0.00070	0.104	NS	−0.00018	−0.028	NS
Vitamin C (mg/dl)	−0.11355	−0.055	NS	0.21826	0.098	NS	0.00317	0.002	NS
Selenium (μg/dl)	−0.12261	−0.360	0.002	−0.13499	−0.396	0.006	−0.15726	−0.478	<0.0001
Copper (μg/dl)	17.019	0.144	NS	30.074	0.253	NS	4.4869	0.061	NS
Albumin (g/dl)	1.4432	0.223	0.07	1.5171	0.243	NS	2.6954	0.398	0.0002
Hemoglobin (g/dl blood)	0.14754	0.151	NS	−0.02285	−0.023	NS	0.17369	0.214	0.08
H. pylori (% IgG positive)				0.00716	0.149	NS			

[a] *H. pylori* included to test its independence as a risk factor.
[b] RC, regression coefficient; SRC, standardized regression coefficient; NS, not significant ($P > 0.10$).

= 0.0003 for females). Whether these findings are coincidental or indicate an etiological connection between meat consumption, high plasma selenium, and reduced risk of stomach cancer remains to be answered. Case-control findings for consumption of grains and other starches have been contradictory (5–7, 15). We found mild positive associations with wheat and potatoes but no strong evidence of an independent risk. We know of no previous reports linking egg consumption to increased risk. Counties with high egg consumption tended to be in coastal areas, to have higher percentages of their populations employed in industry, and to have significantly higher indexes of socioeconomic status.

The key finding in the analysis of plasma micronutrients was the strong association between elevated selenium and areas of low mortality. Several studies have suggested that serum selenium levels may be associated with reduced cancer risk (20). Two ecological studies have linked serum selenium specifically to reduced stomach cancer risk (21, 22), and in Finland, levels of selenium in stored sera were significantly decreased among persons who subsequently developed stomach cancer (23). It has been proposed that selenium has antioxidant properties that can inhibit the development of gastric carcinomas (20).

Our findings suggesting a protective effect for β-carotene are in agreement with several case-control studies, including one from a high-incidence rural area of China (6), although others have failed to find an independent protective effect (14). Our regression analysis did not show strong independent associations for vitamin C or α-tocopherol, despite protective effects detected by some case-control studies including (for vitamin C) one in a high-risk rural area of China (6, 10, 12–14). Also, we did not find a synergistic protective effect of selenium and vitamin E reported elsewhere for overall cancer risk (20). Since fruit consumption was low in most of the 65 counties, green vegetables probably were the major source for carotenes as well as vitamin C (24). Green vegetables may contain other protective compounds besides β-carotene, vitamin C, and α-tocopherol (24, 25). Furthermore, most case-control studies of stomach cancer that have found protective associations with vitamin C or α-tocopherol have examined dietary intake, rather than blood levels, which are influenced by factors in addition to diet (26, 27).

Our positive findings for hemoglobin and ferritin, more notable for women than men, are consistent with a few reports suggesting that increased body iron stores may be associated with elevated cancer risk (28). Stomach cancer, however, has not been previously associated with indices of increased body iron. In fact, increased risk associated with low prediagnostic levels of serum ferritin has recently been reported (29). Blood copper levels have been reported to increase as stomach cancer progresses (30), but we know of no studies suggesting an etiological role, and our analysis of copper does not suggest that it is an independent risk factor. We cannot explain the strong positive association with plasma albumin, which has been reported to be negatively associated with overall cancer risk (28, 31, 32).

Ecological associations in China and elsewhere between the prevalence of *H. pylori* infection and elevated risk of stomach cancer have been reported previously, but without controlling for the effects of other associations (8, 33). Our regression results suggest that infection with *H. pylori* may be a determinant of geographic variations in stomach cancer risk, independent of diet. The association with *H. pylori* was diminished somewhat when controlling for levels of blood micronutrients, although *H. pylori* titers were not highly correlated with the other variables in the regression models. Serological evidence of *H. pylori* infection was relatively common, with prevalence rates from 27% to 96% in the counties for which data were available. Among all the major cancers in China, seropositive prevalence was significantly correlated only with stomach cancer mortality (1, 8). This apparent specificity, combined with the regression findings, suggests that the bacteria, which can thrive at low pH in the gastric mucosa and induce gastric inflammation (34), may play a role in gastric carcinogenesis (8, 10).

We did not find significant positive associations with urine output of sodium, nitrate, or nitrosamines, although elevated urinary excretion of *N*-nitrosoproline and other nitrosamines has been reported in Chinese peasants with advanced precancerous stomach lesions (35). Unlike some studies, we did not find an association with smoking (36). The meaning of the significant negative correlation between plasma cotinine and male stomach cancer mortality is not clear. We also found significant or borderline significant negative correlations between plasma cotinine and several other cancers, including male lung cancer; and there is uncertainty over whether serum cotinine is a reliable indicator of exposure to tobacco smoke (9). In agreement with the bulk of epidemiological evidence, we did not find significant associations with alcohol consumption (37).

In interpreting our results, several caveats should be considered. In particular, the findings are based on average exposure values and on countywide mortality rates, not on individual data. Because we used ecological data, it was difficult to analyze interactions between exposure variables, and any conclusions as to causal associations must be regarded with extra caution. Since we examined correlations between stomach cancer mortality and over 200 variables, some of our significant findings will arise by chance alone. As in any multivariate analysis, the regression results depend upon what variables are included in our models, although associations with several variables (green and salted vegetables and plasma selenium) were robust. We used mortality rates since incidence rates were unavailable, but in urban Shanghai, where access to well-equipped medical facilities is among the best in China, stomach cancer mortality:incidence ratios from 1973 through 1977 were 0.91 for males and 0.93 for females (38). In rural areas, these ratios almost certainly were higher. Thus, we probably can derive conclusions about cancer incidence from the mortality rates. Finally, since mortality data are for 1973-1975, while exposure data are for 1983, our findings assume stability of exposure levels and mortality rates between these two periods. Although we cannot conclusively validate this assumption, data from a rural county where stomach cancer rates are high suggest that diet did not change substantially between 1965 and 1980 (6), nor did stomach cancer mortality from 1973-1975 to 1979-1983 (39).

In summary, despite the limitations of ecological analysis, this unique data set allowed us to assess the relationship between stomach cancer risk and diet, serological evidence of *H. pylori* infection, and various blood micronutrients. The wide variation in stomach cancer rates and exposure variables in China probably facilitated the detection of strong protective effects for green vegetables and plasma selenium, as well as decreased risk associated with plasma β-carotene and increased risks associated with salted vegetables and *H. pylori* infection. These relationships, which were similar for men and women, may contribute to the striking patterns of stomach cancer mortality in China and provide clues for further etiological investigations.

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