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 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 examination 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, lung, liver, 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...
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 quintile 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 quintile. 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 allatoxin metabolites, nitrate, N-nitroso-proline, N-nitroso-sarcosine, and N-nitroso-thiazolidine-4-carboxylic acid.
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, \(\beta\)-carotene, and hemoglobin as the significant determinants for women. Combining these variables, plus \(\alpha\)-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 \(R = 0.44, P \leq 0.05\) for females.

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

<table>
<thead>
<tr>
<th>Plasma variables</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>0.11 (0.0127)*</td>
<td>0.11 (0.0127)*</td>
</tr>
<tr>
<td>(\beta)-Carotene (\mu g/dl)</td>
<td>-0.24 (0.089)</td>
<td>-0.20 (0.118)</td>
</tr>
<tr>
<td>Retinol (\mu g/dl)</td>
<td>-0.15 (0.01)</td>
<td>0.01 (0.421)</td>
</tr>
<tr>
<td>Vitamin D (\mu g/dl)</td>
<td>0.23 (0.067)</td>
<td>0.13 (0.173)</td>
</tr>
<tr>
<td>Vitamin C (\mu g/dl)</td>
<td>-0.26 (0.011)</td>
<td>-0.06 (0.13)</td>
</tr>
<tr>
<td>Selenium (\mu g/dl)</td>
<td>-0.33 (0.082)</td>
<td>-0.39 (0.79)</td>
</tr>
<tr>
<td>Zinc (\mu g/dl)</td>
<td>0.16 (0.119)</td>
<td>0.09 (0.120)</td>
</tr>
<tr>
<td>Copper (\mu g/dl)</td>
<td>0.30 (0.99)</td>
<td>0.17 (1.06)</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>0.12 (0.71)</td>
<td>0.25 (4.6)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>0.30 (0.30)</td>
<td>0.47 (3.1)</td>
</tr>
<tr>
<td>Cotinine (ng/ml)</td>
<td>-0.44 (150)</td>
<td>-0.11 (20)</td>
</tr>
<tr>
<td>H. pylori IgG Ab (% positive, 46 counties)</td>
<td>0.28 (60)</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Independent dietary variables</th>
<th>All counties</th>
<th>46 counties with H. Pylori antibody titer*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>RC, SRC, P</td>
<td>RC, SRC, P</td>
</tr>
<tr>
<td>Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green vegetables (times/year)</td>
<td>-0.00420</td>
<td>-0.418 0.0003</td>
</tr>
<tr>
<td>Salted vegetables (times/year)</td>
<td>0.00169</td>
<td>0.177 0.09</td>
</tr>
<tr>
<td>Fruit (times/year)</td>
<td>-0.00397</td>
<td>-0.076 NS</td>
</tr>
<tr>
<td>Potatoes (times/year)</td>
<td>0.00041</td>
<td>0.035 NS</td>
</tr>
<tr>
<td>Eggs (times/year)</td>
<td>0.01080</td>
<td>0.378 0.0008</td>
</tr>
<tr>
<td>Meat (times/year)</td>
<td>-0.00296</td>
<td>-0.185 0.08</td>
</tr>
<tr>
<td>H. Pylori (% IgG positive)</td>
<td>-0.00298</td>
<td>-0.169 NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Females</th>
<th>RC, SRC, P</th>
<th>RC, SRC, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All counties</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Refers to the independent variable.

**Refers to the regression coefficient; SRC, standardized regression coefficient; NS, not significant \((P > 0.10)\).
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 no previous reports linking egg consumption to increased risk of 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).

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-nitrosopropylene 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 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 future etiological investigations.

Acknowledgments

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References


Risk factors for stomach cancer in sixty-five Chinese counties.

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