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World J Gastroentero, 2000; 6(5):671-675
World Journal of Gastroenterology
 ISSN 1007-9327

# Fish sauce and gastric cancer: an ecological study in Fujian Province, China

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**Subject headings** stomach neoplasm/etiology; food habits; risk factors; nitrosamines; epidemiology; fish products; fish sauce; carcinogens

Cai L, Yu SZ, Ye WM, Yi YN. Fish sauce and gastric cancer: an ecological study in Fujian Province, China. ***World J Gastroentero***, 2000;6 (5): 671-675

## Abstract

**AIM To explore the relationship between consumption of fish sauce and the risk of gastric cancer in Fujian Province.**

**METHODS An ecological study was carried out. A total of 11 000 subjects from 55 townships were randomly selected from 10 counties within Fujian Province. All subjects were local residents who had been living in Fujian Province for more than 20 years, within the age group of 45-74 years. Trained interviewers conducted face-to-face interviews with a standardized questionnaire, which covered the frequency and amount of food intake, dietary habit, tobacco and alcohol consumption and history of chronic gastric diseases. Univariate and multivariate analyses were performed using Epi-info and SAS statistical packages, respectively.**

**RESULTS A significant correlation between monthly consumption of fish sauce and mortality of gastric cancer was found. Pearson's coefficient of correlation was statistically significant with $r = 0.7356$ for males, $r = 0.5246$ for females ($P<0.01$). In the multivariate analysis, consumption of fish sauce still showed an association with the risk of gastric cancer. No significant positive correlation between esophagus cancer, liver cancer, colon cancer and consumption of fish sauce were observed.**

**CONCLUSION Long-term intake of fish sauce may be related to high mortality of gastric cancer. Consumption of fish sauce might be one of important and unique etiologic factors of gastric cancer in Fujian Province. Further studies are needed to confirm this ecological study.**

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**Project supported by Natural Science Foundation of Fujian Province, China, No. K98036**
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**Received** 2000-05-06 **Accepted** 2000-06-02

## INTRODUCTION

Fujian Province is a high-risk area of gastric cancer in China[1]. The standardized mortalities of gastric cancer during 1986-1988 were 37-72 per 100 000 for men and 14-90 per 100 000 for women, accounting for 25.31% of total cancer mortality. In certain areas, the annual incidence of gastric cancer is more than 50 per 100 000 persons[2]. The health of general population in Fujian Province is most seriously threatened by gastric cancer.

A number of potential risk factors for gastric cancer have been examined in previous studies[3]. Among these, the dietary hypotheses are of particular interest[4,5]. N-nitroso compounds derived from the consumption of preserved food may be associated with the risk of the disease[6].

In the investigation of dietary factors, we have reported the relationship between high salt intake and gastric cancer in the high-risk area of Fujian Province[7-9]. The salted food includes fish sauce, which is particularly favored by Fujian local residents. Fish sauce is usually produced from several kinds of sea fishes after prolonged fermentation processes. Its mutagenicity has been reported by several experimental studies[10-12]. However, there have been few reports from population-based epidemiological study on the relationship between fish sauce and risk of gastric cancer. Therefore, this ecological study was carried out to explore the relationship between them in the area of Fujian Province.

## MATERIALS AND METHODS

### *Study areas, subjects and methods*

Gastric cancer is the most common cancer among the major types of cancer in Fuji an Province. However, even within the province the death rate distribution of gastric cancer varies greatly among different areas. This ecological study included 55 townships in 10 counties. The retrospective investigations of death cause, which was a part of a national program, had been concluded in these areas.

In reference to the national gastric cancer death rate of 17.30/100 000 (95% confidence interval: 9.15/100 000-25.45/100 000, calculated by Poisson-normal-approximation method), the death rate among these 10 counties can be divided into three groups: ① High incidence area: Changle, Putian, and Fuzhou; ② Medium incidence area: Changtai, Huian, Shaxian, Sanming, Yongding, and Zhangpu; ③ Low incidence area: Fuan (Figure 1).

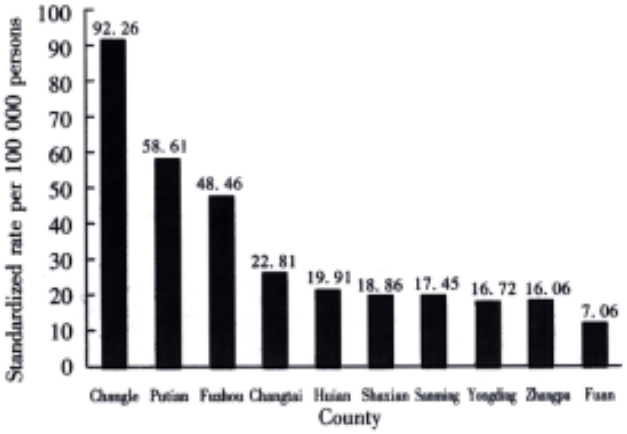
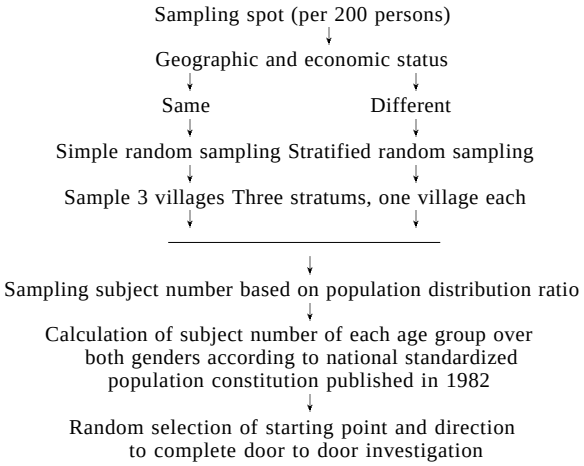



**Figure 1** Gastric cancer mortality in 10 counties, Fujian, China, 1991.

A total of 200 subjects in each town (sampling spot) were interviewed. The 55 townships were randomly selected from 10 counties which include 11 000 subjects in this study.




All subjects of this study are local resident of more than 20 years, within the age of 45-74 years, who can clearly answer the questions asked by the interviewers. Specially trained interviewers conducted face-to-face interviews according to a standardized questionnaire, which covers the frequency and amount of food intake. The investigations also include demographic factors, dietary habit, smoking and alcohol consumption, and history of chroni c gastric diseases.

### *Statistical analysis*

The database was established using Epi-info, and the gastric cancer mortality for 45-74 age group was calculated based on world truncated standardized population constitution. The correlation coefficient and multiple regression analysis were carried out using SAS software.

## RESULTS

### *Univariate analysis*

The highest Pearson's correlation coefficient was found between gastric cancer mortality and average monthly consumption of uncooked fish sauce. Similar results were observed for both males and females, with Pearson's correlation coefficient for males of 0.7356 and 0.5246 for females ($P<0.01$) (Table 1) . Positive correlation were found between gastric death rate and fish sauce-related variables (Fish sauce consumption, population ratio who consume fish sauce, population ratio who consume uncooked fish sauce, and uncooked fish sauce consumption). Further, compared with other factors, larger Pearson's correlation coefficients were observed for all 4 variables ($\chi^1$-$\chi^4$) .

**Table 1 Correlation analysis between exposure factors and standardized truncated mortality of gastric cancer (55 townships)**

| Factors | Pearson's coefficient of correlation | |
|---|---|---|
| | Male | Female |
| $\chi^1$ Fish sauce average consumption (0.5kg/month) | 0.5170[a] | 0.4261[a] |
| $\chi^2$ Population ratio who consume fish sauce | 0.3576[a] | 0.2720[a] |
| $\chi^3$ Population ratio who consume uncooked fish sauce | 0.6904[a] | 0.5086[a] |
| $\chi^4$ Uncooked Fish sauce average consumption (0.5kg/month) | 0.7356[a] | 0.5246[a] |
| $\chi^5$ Salted fermented sea foods average consumption (0.5kg/year) | 0.4863[a] | 0.3653[a] |
| $\chi^6$ Population ratio of crapulence | 0.4887[a] | 0.3198[a] |
| $\chi^7$ Population ratio of taking moldy foods | 0.5538[a] | 0.2582 |
| $\chi^8$ Fresh vegetables consumption (0.5kg/year) | -0.4742[a] | -0.2307 |
| $\chi^9$ Fresh meat, fish, egg average consumption (0.5kg/year) | 0.4254[a] | 0.1298 |
| $\chi^{10}$ Average ratio of coarse food grain to grain ration | 0.3900[a] | 0.2107 |
| $\chi^{11}$ Prevalence of chronic gastric diseases | 0.2973[b] | 0.1107 |
| $\chi^{12}$ Average index of smoking | -0.2158 | 0.1737 |
| $\chi^{13}$ Average cumulative alcohol consumption (0.05kg) | 0.1703 | -0.1942 |
| $\chi^{14}$ Population ratio of taking irregular dinners | 0.2172 | 0.1443 |
| $\chi^{15}$ Average salted vegetables consumption (0.5kg/year) | -0.1488 | -0.0079 |
| $\chi^{16}$ average salt consumption (0.5kg/month) | -0.2455 | -0.2160 |
| $\chi^{17}$ Average fresh fruit consumption (0.5kg/year) | 0.0978 | -0.0581 |
| $\chi^{18}$ Average bean products consumption (0.5kg/year) | -0.1475 | -0.0422 |

[a]$P<0.01$, [b]$P<0.05$.

Smoking index: (amount of smoking/day×years of smoking)/age of starting smoking.

Gastric cancer mortality for 45-74 age group was calculated based on world truncated standardized population constitution.

### *Multi-variables analysis*

Considering the possible confounding effects among factors, multivariate regression analyses were performed on other factors ($\chi^5$-$\chi^{18}$) and each of fish sauce variables ($\chi^1$-$\chi^4$) respectively. MAXR method from REG of SAS package was used. The optimum subset of variables was established which also includes fish sauce as one of variables. The consumption of fish sauce still shows association with the risk of gastric cancer in analysis after controlling the possible confounding factors (Tables 2-5). The corresponding multiple correlation coefficients indicate that the goodness of fit tests was significant.

**Table 2 The results of multivariate regression analysis on $\chi^1$, $\chi^5$-$\chi^{18}$ and mortality of gastric cancer for men**

| Factor | β | Sβ | Standard error | *t* | *P* |
|---|---|---|---|---|---|
| $\chi^1$ | 187.363 9 | 0.467 8 | 43.167 4 | 4.340 | 0.000 1 |
| $\chi^{13}$ | 0.030 6 | 0.310 5 | 0.010 1 | 3.018 | 0.004 1 |
| $\chi^{11}$ | 861.782 4 | 0.571 3 | 241.989 1 | 3.561 | 0.000 8 |
| $\chi^7$ | 338.206 0 | 0.181 9 | 160.782 6 | 2.103 | 0.040 7 |
| $\chi^{14}$ | 421.516 6 | 0.332 9 | 132.587 1 | 3.179 | 0.002 6 |
| $\chi^8$ | -0.804 2 | -0.612 7 | 0.225 0 | -3.574 | 0.000 8 |
| $\chi^{17}$ | -2.633 9 | -0.252 7 | 1.103 6 | -2.387 | 0.021 0 |

| Source of variation | DF | Sum of squares | Mean Square | *F* value | *P* |
|---|---|---|---|---|---|
| Regression | 7 | 4 802 841.324 9 | 686 120.189 3 | 47.482 | 0.000 1 |
| Error | 48 | 693 599.320 9 | 14 449.985 9 | | |
| Total | 55 | 5 496 440.645 8 | | | |

$R^2$ = 0.873 8 Adjusted $R^2$ = 0.855 4

**Table 3 The results of multivariate regression analysis on $\chi^4$, $\chi^5$ -$\chi^{18}$ and mortality of gastric cancer for men**

| Factor | β | Sβ | Standard error | *t* | *P* |
|---|---|---|---|---|---|
| $\chi^4$ | 271.596 1 | 0.449 1 | 45.488 3 | 5.971 | 0.000 1 |
| $\chi^{13}$ | 0.024 8 | 0.252 1 | 0.009 2 | 2.696 | 0.009 6 |
| $\chi^{11}$ | 671.680 3 | 0.445 3 | 223.110 6 | 3.011 | 0.004 1 |
| $\chi^7$ | 285.953 7 | 0.153 8 | 143.870 8 | 1.988 | 0.052 6 |
| $\chi^{14}$ | 366.509 3 | 0.289 4 | 119.231 5 | 3.074 | 0.003 5 |
| $\chi^8$ | -0.539 4 | -0.410 9 | 0.212 4 | -2.539 | 0.014 4 |
| $\chi^{17}$ | -1.259 9 | -0.120 9 | 0.856 9 | -1.470 | 0.148 0 |

| Source of variation | DF | Sum of squares | Mean Square | *F* value | *P* |
|---|---|---|---|---|---|
| Regression | 7 | 4 942 225.615 6 | 706 052.230 8 | 61.149 | 0.000 1 |
| Error | 48 | 554 215.030 1 | 11 546.146 5 | | |
| Total | 55 | 5 496 440.645 6 | | | |

$R^2$ = 0.899 2 Adjusted $R^2$ = 0.884 5

**Table 4 The results of multivariate regression analysis on $\chi^1$, $\chi^5$ -$\chi^{18}$ and mortality of gastric cancer for women**

| Factor | β | Sβ | Standard error | *t* | *P* |
|---|---|---|---|---|---|
| $\chi^1$ | 81.232 7 | 0.502 0 | 24.717 9 | 3.286 | 0.001 9 |
| $\chi^{11}$ | 417.192 2 | 0.432 8 | 122.121 2 | 3.416 | 0.001 3 |
| $\chi^{14}$ | 132.182 7 | 0.258 2 | 44.083 4 | 2.998 | 0.001 5 |
| $\chi^5$ | 1.270 2 | 0.163 9 | 0.920 9 | 1.379 | 0.173 9 |
| $\chi^{17}$ | -1.855 8 | -0.404 5 | 0.595 8 | -3.115 | 0.003 0 |

| Source of variation | DF | Sum of squares | Mean Square | *F* value | *P* |
|---|---|---|---|---|---|
| Regression | 5 | 646 897.444 8 | 129 379.489 0 | 34.871 | 0.000 1 |
| Error | 50 | 185 511.738 5 | 3 710.234 8 | | |
| Total | 55 | 832 409.183 3 | | | |

$R^2$ = 0.777 1 Adjusted $R^2$ = 0.754 9

**Table 5 The results of multivariate regression analysis on $\chi^4$, $\chi^5$ -$\chi^{18}$ and mortality of gastric cancer for women**

| Factor | β | Sβ | Standard error | *t* | *P* |
|---|---|---|---|---|---|
| $\chi^4$ | 100.238 2 | 0.409 0 | 26.013 2 | 3.853 | 0.000 3 |
| $\chi^{11}$ | 448.485 9 | 0.465 8 | 124.452 2 | 3.604 | 0.000 7 |
| $\chi^{14}$ | 153.932 8 | 0.300 7 | 43.506 8 | 3.538 | 0.000 9 |
| $\chi^{15}$ | 2.382 6 | 0.307 4 | 0.956 5 | 2.491 | 0.016 1 |
| $\chi^{18}$ | -0.934 3 | -0.407 8 | 0.385 3 | -2.425 | 0.019 0 |

| Source of variation | DF | Sum of squares | Mean Square | *F* value | *P* |
|---|---|---|---|---|---|
| Regression | 5 | 657 252.078 6 | 31 450.415 7 | 37.52 | 0.0001 |
| Error | 50 | 175 157.104 7 | 3 503.142 1 | | |
| Total | 55 | 832 409.183 3 | | | |

$R^2$ = 0.789 6 Adjusted $R^2$ = 0.768 5

### *Correlation analysis between exposure factor and other digestive tract cancers*

The Pearson's correlation coefficients between each factor and truncated standardized mortality for esophagus cancer, liver cancer, and colon cancer were calculated separately and results are shown in Tables 6 - 8. There are no signifi cant positive correlation among 4 variables for fish sauce consumption and any of the mortality rates among three other digestive tract cancers. In multivariate regression analysis, the variables that reflect fish sauce consumption were not selected into the model when analyzing relationship between fish sauce and mortality of the other three cancers.

**Table 6 Correlation analysis between exposure factors and truncate d standardized mortality of esophagus cancer**

| Factors | Male | | Female | |
|---|---|---|---|---|
| | Pearson's *r* | *P* | Pearson's *r* | *P* |
| $\chi^1$ | -0.251 1 | 0.064 4 | -0.307 9 | 0.022 2 |
| $\chi^2$ | -0.253 8 | 0.061 5 | -0.364 7 | 0.006 2 |
| $\chi^3$ | -0.217 0 | 0.111 5 | -0.251 9 | 0.063 6 |
| $\chi^4$ | -0.171 4 | 0.210 9 | -0.221 8 | 0.103 7 |
| $\chi^5$ | -0.039 0 | 0.777 8 | -0.098 8 | 0.473 0 |
| $\chi^6$ | -0.071 5 | 0.604 2 | 0.036 0 | 0.793 9 |
| $\chi^7$ | 0.302 5 | 0.024 8 | 0.213 0 | 0.118 4 |
| $\chi^8$ | -0.361 8 | 0.006 6 | -0.227 4 | 0.095 0 |
| $\chi^9$ | 0.060 9 | 0.659 0 | -0.175 1 | 0.201 0 |
| $\chi^{10}$ | 0.357 1 | 0.007 4 | 0.173 1 | 0.206 2 |
| $\chi^{11}$ | -0.349 3 | 0.009 0 | 0.125 2 | 0.362 5 |
| $\chi^{12}$ | 0.533 0 | 0.000 1 | 0.059 2 | 0.667 7 |
| $\chi^{13}$ | -0.068 6 | 0.618 7 | 0.372 5 | 0.005 1 |
| $\chi^{14}$ | 0.329 2 | 0.014 1 | 0.277 1 | 0.040 6 |
| $\chi^{15}$ | 0.260 6 | 0.054 6 | 0.474 0 | 0.000 3 |
| $\chi^{16}$ | 0.638 4 | 0.000 1 | 0.374 3 | 0.004 9 |
| $\chi^{17}$ | -0.256 9 | 0.058 4 | -0.275 9 | 0.041 5 |

Esophagus cancer mortality for 45-74 age group was calculated based on world truncated standardized population constitution.

**Table 7 Correlation analysis between exposure factors and truncated standardized mortality of liver cancer**

| Factors | Male | | Female | |
|---|---|---|---|---|
| | Pearson's *r* | *P* | Pearson's *r* | *P* |
| $\chi^1$ | -0.091 3 | 0.507 4 | -0.140 7 | 0.305 5 |
| $\chi^2$ | -0.142 0 | 0.301 0 | -0.180 8 | 0.186 5 |
| $\chi^3$ | -0.023 7 | 0.863 9 | -0.101 7 | 0.459 9 |
| $\chi^4$ | 0.006 1 | 0.964 8 | -0.097 0 | 0.481 3 |
| $\chi^5$ | 0.222 6 | 0.102 8 | 0.191 5 | 0.161 4 |
| $\chi^6$ | 0.067 9 | 0.622 1 | 0.254 6 | 0.060 7 |
| $\chi^7$ | 0.411 3 | 0.001 8 | 0.214 1 | 0.116 6 |
| $\chi^8$ | -0.328 0 | 0.014 5 | -0.168 1 | 0.219 9 |
| $\chi^9$ | 0.120 0 | 0.383 0 | 0.073 7 | 0.592 7 |
| $\chi^{10}$ | 0.362 7 | 0.006 5 | 0.160 9 | 0.240 7 |
| $\chi^{11}$ | 0.057 0 | 0.679 4 | 0.159 4 | 0.245 1 |
| $\chi^{12}$ | 0.135 2 | 0.324 9 | 0.059 5 | 0.666 1 |
| $\chi^{13}$ | -0.012 0 | 0.941 2 | -0.245 3 | 0.071 0 |
| $\chi^{14}$ | -0.002 4 | 0.986 3 | 0.156 9 | 0.252 7 |
| $\chi^{15}$ | 0.063 0 | 0.647 7 | 0.293 6 | 0.029 6 |
| $\chi^{16}$ | 0.196 7 | 0.150 1 | 0.094 6 | 0.492 2 |
| $\chi^{17}$ | -0.106 5 | 0.438 9 | -0.005 3 | 0.969 3 |

Liver cancer mortality for 45-74 age group was calculated based on world truncated standardized population constitution.

**Table 8 Correlation analysis between exposure factors and truncated standardized mortality of colon cancer**

| Factors | Male | | Female | |
|---|---|---|---|---|
| | Pearson's *r* | *P* | Pearson's *r* | *P* |
| $\chi^1$ | 0.246 1 | 0.070 1 | 0.107 7 | 0.434 1 |
| $\chi^2$ | 0.235 6 | 0.083 3 | 0.105 5 | 0.443 3 |
| $\chi^3$ | 0.242 8 | 0.074 1 | 0.053 5 | 0.698 2 |
| $\chi^4$ | 0.225 0 | 0.098 6 | 0.010 3 | 0.940 8 |
| $\chi^5$ | 0.003 5 | 0.979 6 | -0.022 3 | 0.871 8 |
| $\chi^6$ | -0.050 4 | 0.714 8 | -0.012 7 | 0.926 6 |
| $\chi^7$ | 0.096 4 | 0.483 8 | -0.124 2 | 0.366 2 |
| $\chi^8$ | -0.160 5 | 0.241 8 | 0.127 4 | 0.353 9 |
| $\chi^9$ | 0.083 3 | 0.521 5 | 0.065 2 | 0.636 2 |
| $\chi^{10}$ | -0.097 4 | 0.491 5 | -0.248 2 | 0.067 7 |
| $\chi^{11}$ | 0.384 3 | 0.003 8 | 0.225 1 | 0.098 5 |
| $\chi^{12}$ | -0.281 5 | 0.037 4 | 0.027 7 | 0.841 2 |
| $\chi^{13}$ | -0.189 5 | 0.165 9 | -0.181 9 | 0.183 9 |
| $\chi^{14}$ | 0.218 5 | 0.109 1 | -0.061 1 | 0.657 9 |
| $\chi^{15}$ | -0.289 9 | 0.031 8 | -0.055 4 | 0.687 9 |
| $\chi^{16}$ | -0.165 4 | 0.227 4 | -0.224 7 | 0.099 0 |
| $\chi^{17}$ | 0.205 3 | 0.132 7 | 0.178 7 | 0.191 9 |

Colon cancer mortality for 45-74 age group was calculated based on world truncated standardized population constitution.

## DISCUSSION

Gastric cancer is the second common cancer in the world today[13]. It remains the leading cause of cancer death in China[14]. In the studies of etiology and epidemiology on gastric cancer, the associations between gastric cancer risk and *Helicobacter pylori* (Hp) infection[15-18], occupational exposures[19], diet and life factors[20-25], lack of essential trace elements[26] have been observed. The most widely reported protective factors are dietary factor[27-33]. It has been reported that a large amount of nitrite exists in most salted fishes and smoking meat, and may be related to the high gastric cancer incidence along coastal area and among Japanese or Chinese population.

Each local resident in Fujian Province consumed daily about 30mL fish sauce as one kind of condiments. Fish sauce is a liquid product of small marine fish and table salt (7:3). The fishes are completely liquefied after fermentation for 1-2 years. The salted fermented fish products may contain many precursors of N-nitroso compound derived from the proteins content of the fishes, which could synthesize N-nitrosamides under simulated human stomach conditions[34]. N-nitrosamides is suggested as a major initial cause of gastric cancer[35]. Zhang *et al*[36] had analyzed the N-nitroso compound precursors from 49 fish sauce samples obtained from high risk area of gastric cancer in Fujian Province, and detected 630μM/mL of 17 free amino acids. After nitrosifiction the total amount of N-nitroso compound in samples was as high as 2.95μM/mL. The concentration of N-nitrosylamine from ethyl acetate extraction solution was 0.06μM/mL. Fish sauce is rich in creatinine and other nitrosamide precursors. It was mutagenic and carcinogenic for the glandular stomach of Wistar rats, after it was nitrosified under simulated human stomach condition[37]. All these experiments have shown that fish sauce is potentially carcinogenic.

High incidence of gastric cancer may be attributed, to some extent, to some unique dietary habits in the high-risk area. This ecological study showed the positive correlationship between gastric cancer mortality and fish sauce favored by Fujian residents. The relationship between gastric cancer and uncooked fish sauce intake is particularly obvious. Among four digestive tract cancers, only gastric cancer had a positive correlation with fish sauce consumption, which suggests that the association may be specific to gastric cancer. This study indicates that long-term use of fish sauce may be related to high gastric cancer mortality in the Fujian area.

This ecological comparison study may provide a possible hypothesis for the etiology of gastric cancer. Fish sauce has both N-nitroso compounds and a high salt content, which might partially explain the high gastric cancer mortality along the Fujian coast. Further studies are needed to confirm our results. Recently, a population-based case-control study was conducted in Changle County, Fujian Province. The residents in Changle County had a high prevalence of *H. pylori* infection. However, no statistical significant difference was found in respect to presence of *H. pylori* infection between gastric cancer patients and controls. The results showed that fish sauce intake, deficiency in fresh vegetables were risk factors in gastric cancer[38].

The development of human gastric cancer is a multistep and multifactorial process[39]. A number of molecular events are involved in gastric carcinogenesis[40]. Coordinate prevention and treatment measures must be taken, including changing the habit of taking fish sauce, nutrition guidance and cancer prevention education for general public. This would undoubtedly have positive effect on reducing the risk of gastric cancer in Fujian Province.

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Edited by You DY
Proofread by Zhu LH and Ma JY