

Dietary habits and stomach cancer in Mizoram, India

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Background. An extremely high prevalence of stomach cancer was observed in Mizoram (India), where the population consumes uncommon food. The relation of food habits and stomach cancer was examined in this study. **Methods.** A hospital-based case-control study was conducted during 2001–2004 to determine the risk factors among 329 patients with histologically confirmed stomach cancer and 658 matched controls. Food habits were determined by personal interview. **Results.** An elevated risk of stomach cancer was observed with frequent consumption of sa-um [odds ratio (OR) 3.4] (sa-um is fermented pork fat, a traditional food) and with frequent consumption of smoked dried salted meat (OR 2.8) and fish (OR 2.5). Soda (alkali), used as a food additive, increased the risk of stomach cancer (OR 2.9). *Helicobacter pylori* infection was not found to be an independent risk factor for carcinogenesis of stomach cancer in this study. However, when *H. pylori* infection interacted with consumption of sa-um or smoked dried meat, it showed a significant association. **Conclusion.** Peculiar food habits in Mizoram might be associated with the high prevalence of stomach cancer in Mizoram along with other factors. *H. pylori* infection might increase the risk of stomach cancer, or it may play a role as a promoter of stomach cancer in Mizoram.

Key words: stomach cancer, smoked dried fish and meat, dietary habits, sa-um, Mizoram

Introduction

Stomach cancer is the most frequent cancer in Mizoram, and the prevalence is high [age-adjusted rate (AAR)

39.1/10⁵ for men and 14.4/10⁵ for women].¹ A high prevalence of stomach cancer among men has been reported from Changle, China and among women in Yamagata, Japan.² India is grouped among countries with a low prevalence.³ Among Indian states⁴ the highest incidence was reported in Chennai (AAR 13.2/10⁵ for men and AAR 7.0/10⁵ for women), but this has been negated by the findings in Mizoram.

Diet has been implicated as a cofactor in the progression from gastritis to gastric cancer; accordingly, the incidence of stomach cancer varies around the world depending on dietary patterns.^{5–7} Diets low in vegetables and fruit^{8–11} and high in salt-preserved foods or salt-processed meat increase the risk of stomach cancer.^{7–9,12–15} Mizoram is situated between 92.15' and 93.29'E longitude and 21.58' to 24.35'N latitude; it is a virtually land-locked area situated between Myanmar in the east and Bangladesh in the west. The people of this region are culturally and ethnically distinct from the other tribes and communities of northeastern India. The Mizo people have their ancestral origin in China.¹⁶ Fish, pork, beef, and other meats are popular nonvegetarian foods in Mizoram. They preserve them by smoke-drying and salting for future consumption. Sa-um (fermented pork fat) and bekang (fermented soya bean) are two other unusual foods in Mizoram. Because of the peculiar food habits along with the high prevalence of stomach cancer in Mizoram, a hospital-based case-control study was undertaken at Aizawl Civil Hospital, Aizawl, Mizoram to investigate the role of diet and other peculiar food habits in the development of stomach cancer.

Commonly used food items and their methods of preparation in Mizoram are as follows.

Smoked salted fish: Locally available fresh fish are salted, dried over fire for a few days, and stored in containers for months for future use. They are consumed after boiling or frying.

Smoked salted meat: Fresh red meat (pork or beef) are cut into small pieces, mixed with salt, and dried over fire for varying periods and stored either at room temperature or are frozen. This stored meat is boiled before consumption.

Sa-um (fermented pork fat): Pork fat is boiled in water and stored in a special container called an um (a container made from a gourd shell) for 3–4 days or until it gives off a peculiar smell. The final product is called sa-um. Sa-um is eaten mixed with vegetables or chilies.

Bekang (fermented soya bean): Soya beans are boiled and kept in a warm, airtight environment under the sun or near fire for about 3 days to ferment. They are eaten directly or with chilies.

Methods

We conducted a hospital-based matched case-control study at Aizawl Civil Hospital, Mizoram. This is a tertiary health-care facility and is the only hospital at which cancer patients are treated in the state with a population of 891 058 (2001 census). In the study, conducted from August 2001 to August 2004, a total of 372 newly diagnosed stomach cancers (all Mizos) were registered. Among them, 43 cases were excluded for various reasons. Stomach cancer represented 35.1% of all cancer cases registered in this hospital during the study period ($n = 1060$).

The inclusion criteria for this study are as follows.

- Newly diagnosed (between August 2001 and August 2004) stomach cancer confirmed by histopathology
- Mizo indigenous person

The exclusion criteria for the study are as follows.

- Patients with advanced disease ($n = 19$) with an obscure primary site
- Patients with recurrent cancer ($n = 13$)
- Patients too old to be interviewed ($n = 8$)
- Patients who refused to be interviewed ($n = 3$)

Patients

A total of 329 patients were finally included (253 men, 76 women) with a male/female ratio of 3.3:1.0. The mean ages of the patients (cases) and controls were 56.8 and 57.1 years, respectively. Age-matched (± 5 years) and sex-matched controls were also selected from the Mizo indigenous population coming from the same locality as the study cases who visited the hospital for nonmalignant minor ailments such as a minor injury, eye ailments, infections, or osteomuscular disease. Two

controls were selected ($n = 665$) for each case. All patients were directed to the social investigator(s) of the project for interviews. Every effort was made to collect the information from the controls simultaneously. However, in case of nonavailability of the controls, efforts were continued for 1 month. Each patient and the two controls were informed about the project, and written consent was obtained before inclusion in the study.

Trained social investigators were employed for interviewing both the patients and the controls at the hospital using a structured pretested questionnaire. The patient's disease status and the object of the study were hidden from the interviewer to minimize bias. Diets and the dietary history of patients and controls were recorded based on 6 months of recall. The main items included in the questionnaire were age, sex, present and past occupation, income, medical history, family history of cancer, and details of their habits including smoking, alcohol drinking, and chewing. A food frequency questionnaire that contained details of dietary practices prevalent in Mizoram were used. The frequencies of consumption were classified as follows: (1) never eaten; (2) occasionally; (3) once a week; (4) twice or more a week.

A spot urease test was done with endoscopic biopsy sample from all suspected stomach cancer cases to detect *Helicobacter pylori* infection. Results of cases confirmed on histopathology were recorded. An enzyme-linked immunosorbent assay (ELISA) test kit (Monobind, Costa Mesa, CA, USA) was used to detect any anti-*H. pylori* immunoglobulin G (IgG), IgM, and IgA in the serum of patients and controls. Blood serum of 252 patients and 540 controls was tested against IgG antibody, 144 patients and 372 controls were tested against IgA antibody, and 108 patients and 168 controls were tested against IgM antibody.

The institutional ethical committee of the Regional Medical Research Centre, Dibrugarh, cleared the study.

Statistical analysis

Univariate and multiple logistic regression analyses were used to analyze data. The conditional maximum likelihood method¹⁷ was used to estimate the parameters of the regression model because of the matched design, and significance was taken at $P \leq 0.05$ (two-tailed). Initially, a univariate analysis was performed. The crude measure of association between single putative dietary risk factors and stomach cancer was expressed as the odds ratio (OR), and its 95% confidence interval (CI) was calculated from the standard error of the regression coefficient. To control for confounding variables and other covariates such as associated habits

of smoking and alcohol drinking, the data were analyzed by conditional multiple logistic regression to evaluate the extent of risk association. The statistical packages used for the analysis were Epi-info-2002 and SPSS version 12.

Results

Stomach cancer strongly related to education (OR 1.85, 95%CI 1.0–7.5 for the illiterate; OR 1.18, 95%CI 0.08–5.20 for those at high-school level education or more). A nonsignificant inverse relation was also associated with higher-income individuals (OR 0.27, 95%CI 0.007–4.200) (Table 1).

Table 1. Social characteristics and risk factors

Social characteristics	Cases/ controls	Univariate ^a		Multivariate ^b	
		OR	95% CI	OR	95% CI
Education*					
College and above	42/106	1.0	Ref	1.0	Ref
Illiterate	165/195	2.17	1.30–8.22	1.85	1.00–7.54
Up to class XII	122/364	1.47	1.00–5.32	1.18	0.80–5.21
Income (Rs. /month)**					
Low (<Rs. 500)	48/70	1.0	Ref	1.0	Ref
Middle (Rs. 500–2500)	123/288	0.84	0.1–6.3	0.75	0.05–6.21
High (>Rs.2500)	158/307	0.64	0.06–4.10	0.27	0.007–4.200
Occupation**					
Office worker	65/178	1.0	Ref	1.0	Ref
Skilled worker	26/38	2.0	1.3–9.2	1.2	0.35–7.10
Unskilled worker	49/34	4.2	2.6–17.4	2.7	1.3–9.5
Cultivator	95/200	1.4	0.7–9.1	1.2	0.04–6.20
Others	94/208	1.2	0.03–6.20	1.0	0.53–7.30

OR, odds ratio; CI, confidence interval

* $P < 0.001$ (for trend)

** $P > 0.05$ (for trend)

^aUnivariate odds ratio estimated by conditional logistic regression analysis

^bAdjusted odds ratios (adjusted for tobacco use, alcohol drinking habits, and dietary habits) obtained by conditional multiple logistic regression analysis using the maximum likelihood approach

Table 2. Tobacco smoking and alcohol as risk factors of stomach cancer

Habits	Cases/ controls	Univariate ^a		Multivariate ^b	
		OR	95% CI	Adjusted OR	95% CI
Smoking status					
Nonsmokers	85/389	1.0	Ref.	1.0	Ref.
Ex-smokers	75/104	3.1	1.6–11.3	1.8	0.4–7.7
Current smokers	169/157	4.6	2.7–14.7	2.3	1.4–8.4
Smoking types					
Nonsmokers	85/389	1.0	Ref.	1.0	Ref.
Cigarette	13/39	1.8	0.8–7.2	1.2	0.5–14.2
Meiziol	167/170	4.0	1.7–10.4	2.2	1.3–9.3
Cigarette + meiziol	64/50	5.9	2.5–12.1	3.1	2.0–11.1
Drinking status					
Nondrinkers	131/450	1.0	Ref.	1.0	Ref.
Ex-drinkers	69/46	2.4	1.5–9.3	1.6	1.1–3.6
Current drinkers	40/40	3.8	1.8–9.7	2.1	1.5–4.7
Drinking types					
Nondrinkers	131/450	1.0	Ref.	1.0	Ref.
Branded alcohol	9/13	1.9	0.4–9.3	1.2	0.4–7.1
Rakzu	79/65	3.4	1.1–14.3	2.1	1.4–10.2
Branded + local liquor	21/10	4.7	2.4–20.2	2.8	1.7–11.4

^aUnivariate odds ratio estimated by conditional logistic regression analysis

^bAdjusted odds ratios (adjusted for chewing, level of education, and dietary habits) obtained by matched conditional multiple logistic regression analysis using maximum likelihood approach

Table 3. Risk factors according to consumption of dietary habits

Food habits	Cases/ controls	Univariate ^a		Multivariate ^b	
		OR	95% CI	OR	95% CI
Smoked dried fish					
Never	60/228	1.0	Ref.	1.0	Ref.
Occasionally	43/89	1.7	0.07–6.30	1.1	0.05–4.20
Once a week	87/207	2.2	1.0–8.3	1.7	0.01–7.10
Twice or more a week	139/141	3.6	1.5–10.6	2.4	1.1–9.2
Smoked dried meat					
Never	77/285	1.0	Ref.	1.0	Ref.
Occasionally	33/86	2.3	1.0–5.2	1.5	0.03–8.40
Once a week	86/165	2.9	1.6–8.3	1.8	0.24–8.20
Twice or more a week	133/101	3.7	1.8–10.2	2.6	1.2–7.3
Smoked dried salted fish					
Never	58/244	1.0	Ref.	1.0	Ref.
Occasionally	16/68	1.8	0.2–6.1	1.4	0.04–9.30
Once a week	107/193	2.9	1.04–8.12	1.9	1.1–7.5
Twice or more a week	148/160	3.8	1.81–7.31	2.8	1.8–8.4
Smoked dried salted meat					
Never	43/197	1.0	Ref.	1.0	Ref.
Occasionally	38/91	2.7	1.3–6.6	1.6	0.04–9.20
Once a week	113/191	3.3	1.7–9.2	2.1	1.2–8.4
Twice or more a week	135/186	3.8	2.6–17.2	2.8	1.7–8.8
Soda (alkali)					
Never	89/290	1.0	Ref.	1.0	Ref.
Occasionally	55/93	1.9	0.04–5.20	1.1	0.01–8.30
Once a week	61/184	2.7	1.2–8.5	1.9	1.0–7.4
Twice or more a week	124/98	3.8	1.8–9.4	2.9	1.2–6.5
Sa-um					
Never	84/296	1.0	Ref.	1.0	Ref.
Occasional	37/86	1.8	0.03–6.20	1.2	0.02–5.20
Once a week	87/123	2.5	1.0–8.4	1.9	1.0–9.1
Twice or more a week	121/160	3.8	1.7–9.2	3.4	1.7–10.3
Bekang					
Never	83/301	1.0	Ref.	1.0	Ref.
Occasional	38/67	1.2	0–8.3	0.6	0.02–6.66
Once a week	89/137	1.7	0.1–7.3	1.2	0.2–9.3
Twice or more a week	119/160	1.9	0.6–9.2	1.6	1.0–7.2

For all parameters, $P < 0.001$ (for trend)

^aUnivariate odds ratio estimated by conditional logistic regression analysis

^bAdjusted odds ratios (adjusted for level of education, tobacco use, alcohol drinking, and each dietary variable for another) obtained by conditional multiple logistic regression analysis using the maximum likelihood approach

A multivariate model of the risk was constructed to see the effects of dietary variables on stomach cancer after controlling for education (Table 1), tobacco use in any form (smoking versus smokeless), alcohol drinking (Table 2), and each dietary variable for another, as they are not correlated (Tables 3, 4).

Consumption of smoked salted fish (OR 2.5, 95%CI 1.8–8.4) and smoked salted meat (OR 2.8, 95%CI 1.7–8.8) for the highest quartile of twice or more a week showed significant high risk for stomach cancer in a dose-dependent manner (Table 3).

Consumption of food items peculiar to Mizoram, such as sa-um (OR 3.4, 95%CI 1.7 to 10.3) and the use of soda (alkali, used as a food additive) (OR 2.9, 95%CI 1.2 to 6.5) were found to be significantly associated

with stomach cancer. The risk for both habits remains high even after adjusting for other variables.

Consumption of green leafy vegetables and fruits emerged as a nonsignificant protective factor for stomach cancer (Table 4); even the occasional users experienced some benefit. Consumption of fresh meat and fish were also found to be protective (chicken: OR 0.17, 95%CI 0.04 to 6.40; beef: OR 0.23, 95%CI 0.04 to 6.10; fish: OR 0.97, 95%CI 0.02 to 4.10) among occasional users compared to those with frequent consumption.

The spot urease test was positive in 46.8% of the stomach cancer patients. Although the rate of infection was high among the stomach cancer patients, the IgG, IgM, and IgA antibody levels against *H. pylori* were not

Table 4. Risk factors according to consumption of vegetables, fruits, and animal proteins

Food habits	Cases/ controls	Univariate ^a		Multivariate ^b	
		OR	95% CI	OR	95% CI
Leafy vegetables*					
Never	30/36	1.0	Ref.	1.0	Ref.
Occasionally	46/87	1.4	0.03–4.30	0.8	0.07–8.20
Once a week	114/254	0.7	0.08–4.80	0.5	0.01–5.60
Twice or more a week	139/288	0.6	0.1–5.3	0.2	0.09–3.10
Fruits**					
Never	66/84	1.0			
Occasionally	263/581	0.84	0.06–5.10	0.41	0.03–6.2
Fresh chicken meat					
Never	96/156	1.0	Ref.	1.0	Ref.
Occasional	48/94	0.47	0.05–7.30	0.17	0.04–6.40
Once a week	107/196	0.84	0.03–5.10	0.62	0.02–6.10
Twice or more a week	78/219	1.25	0–6.2	0.87	0.06–4.70
Fresh beef meat**					
Never	42/78	1.0	Ref.	1.0	Ref.
Occasional	67/112	0.52	0.02–4.21	0.23	0.04–6.10
Once a week	197/372	0.68	0.08–6.11	0.46	0.06–5.30
Twice or more a week	23/103	1.12	0.09–5.29	0.89	0.03–9.40
Fresh pork meat***					
Never	29/114	1.0	Ref.	1.0	Ref.
Occasional	47/116	1.23	0.21–8.25	1.07	0.06–6.27
Once a week	96/160	1.84	0.85–7.37	1.26	0.02–9.11
Twice or more a week	157/275	2.04	1.21–10.30	1.98	0.01–6.42
Fresh fish*					
Never	90/150	1.0	Ref.	1.0	Ref.
Occasional	56/118	1.31	0.04–7.30	0.97	0–4.1
Once a week	104/214	0.93	0.08–6.40	0.64	0.11–8.30
Twice or more a week	79/183	0.62	0.04–8.10	0.18	0.02–5.30

* $P > 0.05$ (for trend)** $P < 0.01$ (for trend)*** $P < 0.001$ (for trend)^a Univariate odds ratio estimated by conditional logistic regression analysis^b Adjusted odds ratios (adjusted for level of education, tobacco use, alcohol drinking, and each dietary variable for another) obtained by conditional multiple logistic regression analysis using the maximum likelihood approach**Table 5.** *Helicobacter pylori* infection and stomach cancer in Mizoram

Antibody	Cases/controls	Univariate ^a		Multivariate ^b	
		OR	95% CI	OR	95% CI
IgG					
Negative	156/306				
Positive	96/234	0.80	0.36–1.82	0.66	0.29–1.32
Total	252/540				
IgA					
Negative	12/48				
Positive	132/324	1.63	0.28–3.1	1.15	0.12–2.0
Total	144/372				
IgM					
Negative	66/102				
Positive	42/66	0.98	0.25–2.3	0.41	0.17–1.50
Total	108/168				

Ig, immunoglobulin

^a Univariate odds ratio estimated by conditional logistic regression analysis^b Adjusted odds ratios (adjusted for level of education, level of income, occupation, chewing habits, tobacco use, alcohol drinking, and dietary variable for each other) obtained by conditional multiple logistic regression analysis using the maximum likelihood approach

significantly different between cases and controls (Table 5). Analysis of the interaction reveals a significant interaction of *H. pylori* infection with smoked salted meat (OR 1.9; $P < 0.046$) and sa-um (OR 2.1; $P < 0.02$).

Discussion

Stomach cancer in Mizoram has been shown to have a positive association with consumption of smoked, dried, and salted fish and meat. Smoke-drying and preservation leads to formation of *N*-nitroso compounds. Nitrite reacts with amines and amides found in meats and other proteins to form *N*-nitroso compounds, which are animal carcinogens and possible human carcinogens.¹⁸ Furthermore, although salt is not a carcinogen, it is thought to increase the risk of gastric cancer through direct damage to the gastric mucosa, which results in gastritis, increased DNA synthesis, and cell proliferation.⁷ This indirectly contributes to the development of chronic atrophic gastritis, leading to the development of stomach cancer.⁶ Because of the presence of both salt and nitrite in processed fish and meats, its role in the development of stomach cancer cannot be ignored, as was found in the present study. Studies in the past have also shown positive associations of high intake of processed meats as a group or for individual cured meats.^{8,13–15,19–21}

Frequent consumption of sa-um was found to be associated with the risk of developing stomach cancer. This is a food material uniquely consumed in Mizoram. Dietary intakes of total or saturated fat have been shown to be associated with stomach cancer.^{22–24} Boiled pork fat, in addition to being a rich source of saturated fat, may form carcinogenic compounds during long storage, as in other stored meats.

Use of soda was shown to be a risk factor in this study. Indigenous people of the northeastern region of India use soda (alkali) or other alkaline preparations frequently as food additives. Kalakhar (an alkaline preparation), consumed in Assam, was implicated as a risk factor for esophageal cancer.²⁵ Perhaps the high alkaline nature of soda plays a role in inflicting injury and subsequent changes in the gastric mucosa.

Frequent intake of fresh meat (chicken, beef) was found to be protective, which is consistent with the results of a study⁷ conducted elsewhere. There was also an elevated risk with consumption of pork found in another study.²⁶ The protective effect of fruits and green leafy vegetables was also found in other studies.^{27–29} However, the protective effects of fresh meat and vegetables are still inconsistent.^{19,30–32} Micronutrients such as vitamin C in the vegetables has been regarded as a protective factor^{12,33} that acts as an antioxidant and inhibits the formation of intragastric nitrosamines.^{25,34}

Carotenoids, folate, vitamin E, and selenium present in vegetables and fruits have anticarcinogenic properties as well.

Fruits are mostly seasonal and relatively costly in this region, except bananas and papayas, so few people eat fruits daily. Therefore, when the items were analyzed, a variety of fruits were not considered.

The association of *H. pylori* with stomach cancer is variable. Studies conducted in Thailand³⁵ showed no association, whereas studies from Hawaii among Japanese Americans³⁶ showed a strong association. The present study failed to incriminate *H. pylori* infection as an independent risk factor as in the Chinese study.³⁷ The incidence of *H. pylori* infection is high (75.4%) in this population, which might have masked an independent association. Multiple regression analysis with backward elimination of the present data set showed significant associations ($P < 0.046$ and $P < 0.02$) when *H. pylori* infection interacted with consumption of smoked dried meat (OR 1.9) or sa-um (OR 2.1). Therefore, *H. pylori* infection might act as a co-carcinogen or promoter of stomach cancer risk in association with other factors in Mizoram.

This study highlighted the risk of consuming a unique food (sa-um), prevalent only in izoram, for stomach cancer. This study also provided evidence that the people who consume smoked and salted food items are at a higher risk of developing stomach cancer perhaps due to ingestion of greater amounts of nitrates and nitrites along with the food. Although a unique food in Mizoram (i.e., sa-um) proved to be an associated risk factor, its carcinogenicity has yet to be proved in the laboratory.

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