



ASSOCIATION OF TOBACCO USE AND RISK OF GASTRIC CANCER

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Abstract

In Mizoram, one of the north eastern states of India, a very high age-adjusted incidence of gastric cancer is recorded. A hospital based case-control study was carried out to assess the association of tobacco use and risk of gastric cancer in Mizoram. The risk of gastric cancer elevated among ex-smokers (OR, 2.95; 95% CI, 1.70-5.12) but not among current smokers. Higher risk was seen among *meizial* (a local cigarette) smokers. The increased risk was apparent among subjects who had smoked for 21 years. The increased risk was significant with 3.02-fold increase in risk among the subjects who smoked for 11 pack years. *Tuibur* (tobacco smoke-infused water), used mainly in Mizoram, was seen to be increased the risk of gastric cancer among former users in univariate and multivariate models (OR, 3.47; 95% CI, 1.83-6.54). Betel with tobacco chewer showed significant risk. Tobacco use in any form smoking and smokeless (*tuibur* and chewing) increased the risk of gastric cancer in Mizoram independently after adjusting for confounding variables.

Keywords: Betel Nut, Gastric Cancer, Mizoram, Smoking, *Tuibur*.

Introduction

Stomach cancer is one of the main health issues in Mizoram. Despite the declining incidence and mortality rates, gastric cancer remains the fourth most commonly diagnosed cancer and second most common cause of death from cancer worldwide (1). The considerable geographic variation in incident and mortality rates, as well as the observed decrease in risk among migrants from high-risk to low-risk areas (1, 2) indicate that environmental factors play a critical role in the etiology of gastric cancer. Infection with *Helicobacter pylori* (3-5) and diet (6-8) are among the most widely accepted environmental risk factors, but the etiology of gastric cancer remains to be fully understood. Identifying highly prevalent risk factors may aid in developing prevention strategies to reduce the incidence and mortality of this malignancy.

Mizoram is situated between 92.15' to 93.29'E longitude and 21.58' to 24.35' N latitude and virtually land locked and situated between Myanmar in the east and Bangladesh in the west. The Mizo people have their ancestral origin in China (9). Tobacco smoking rate in Mizoram is very high among adults (10). A peculiar habit of using "*tuibur*" (tobacco smoke-infused water) has also been observed in Mizoram. The habit of chewing *betel quid* is also widespread in Mizoram. Tobacco is often used. Dried tobacco mixed with lime processed with tips of thumb on the palm of other hand into a powder that is place near the gum known locally as "*Khaini*" also chewed in Mizoram. About 67.2 percent of Mizoram's around 11 lakh population uses various types of tobacco products, the total percentage of male tobacco users in Mizoram is 73.6 percent against a national average of 32.1 percent and the percentage of female tobacco users is 16.1 percent during the year 2015. Besides, there are about 62 percent non-smokers in Mizoram were exposed to passive smoking (11).

The use of tobacco is highly associated gastric cancer. The people of Mizoram are culturally and ethnically different from other tribes and other communities in India. Due to peculiar smoking habits and use of other tobacco products and high prevalence of stomach cancer in Mizoram. A matched case control study was conducted at Aizawl Civil Hospital, Aizawl to assess the association of tobacco use and gastric cancer.

Tuibur. A number of smoking and smokeless tobacco products are in use all over the world. But unlike other smokeless tobacco products, unique tobacco smoke-infused water is used in Mizoram and is locally known as *tuibur*. This product is made locally by passing smoke, generated by burning tobacco, through water until the preparation turns cognac in color and has a pungent smell. In vitro studies using the allium root test show the toxic nature of *tuibur* (12).

Indigenous crude devices are used for the production of *tuibur* on small scale. Users take about 5 to 10 ml *tuibur* orally and keep it in the mouth for some time and then spit it out. Most of the users take it several times a day.

Meizial. It is a local cigarette made from *vaihlo* (*Nicotiana glauca*) tobacco. After plucking, the tobacco leaves are thrashed by feet until the leaves become soft and most of the juices flow out. Then they are dried in the sun or sometimes in a warm place like over the fireplace without applying direct heat. Then they are cut into small pieces and rolled directly using a thin paper. The tobacco content of each *meizial* is about 0.8 to 1 g. The length of each *meizial* is 6 to 7 cm (13).



Materials and Methods

A hospital based matched case control study was carried out 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 11 lakh (2011 census). 160 cases were collected from gastric cancer patients admitted in the hospital during March 2015 to March 2016. 320 controls were taken from same hospital, during the same period from an individual who are free from all types of cancer. The controls were individually matched to the cases by gender, ethnicity and age (± 5 years). The ratio of cases and controls was 1:2.

After obtaining written consent, the participants were interviewed using structured questionnaire approved by Mizoram State Ethical Committee. The questionnaire included age, gender, ethnicity, occupation, income, family history, and details of habits about tobacco use. Subjects who reported that they were regularly smoking/ using *tuibur*/chewing during the index year were defined as current users, those who reported that they had stopped regular using any habits the year before the index year or before were defined as ex-smokers/ex-users/ex-chewers, and people who reported that they never had smoked before or during the index year were defined as never-smokers or never-users or never chewers. The cumulative dose of smoking was expressed as pack-years. One pack-year was regarded as the equivalent of 20 cigarettes smoked per day for 1 year.

Univariate and multivariate logistic regression were used to analyze data. Conditional maximumlikelihood method (14) was used to estimate the variables of regression models due to matched design and significance was taken at $p = 0.05$ (two tailed). Initially, a univariate analysis was done. The crude measure of association between single putative risk factors and stomach cancer was expressed as odds ratio (OR) and its 95% confidence interval (95% CI) was calculated from the SE of the regression coefficient. For controlling confounding variables and other covariables like alcohol drinking, level of education, occupation, income, etc., the data were analyzed by conditional multiple logistic regressions to evaluate the extent to which risk factors are associated independently with stomach cancer in Mizoram. The categories used for each adjusting variable in the logistic regression are frequency per day, age began (years) and duration (years). All calculations were performed with SPSS version 20 and Software R version 2.10.1 program.

Results

The distribution of socio-demographic characteristics and selected risk factors among cases and controls is shown in Table 1. Cases had significantly lower education as compared to controls group, mostly resided in urban area and they are from middle income group. There were no statistical differences between the age of cases and controls, suggesting that age matching was effective. Education level, income level and residence, which were not matching factors in the study, were also included in all the models to control for their confounding effect.

ORs were calculated using non-chewers as reference group to see the association with betel nut consumption (Table 2). In univariate analysis, both current users and ex-users had higher risk (1.37-1.53times) of gastric as compared to non-chewers. But in multivariate analysis, after controlling for other habits, statistically non-significant risks were observed compared with non-chewers. Increased risk of gastric cancer was also observed among the betel nut chewers as the amount of betel nut consumption (OR, 1.41; 95% CI, 0.77-2.60) per day increases in a dose dependent manner. Statistically higher risk were seen for chewers of combined users of betel with tobacco with OR, 1.44 (95% CI, 0.76-2.70) in the multivariate model in comparison to betel with lime. Risk also tend to increase with duration (OR, 1.21; 95% CI, 0.68-2.15) and age started if before 15 years (OR, 1.32; 95% CI, 0.63-2.78).

The risk associated with *tuibur* mainly seen in Mizoram. Non-users were kept as reference group to compute the risk estimates. The OR of former *tuibur* users (OR, 3.16; 95% CI, 1.37-7.26) was higher than current *tuibur* users. Consumption of any amount of *tuibur* per day (OR, 1.74; 95% CI, 0.77-3.95), age began (OR, 4.28; 95% CI, 1.90-11.99) and duration (OR, 2.31; 95% CI, 0.92-5.77) also associated with the increased risk of gastric cancer (Table 3).

Association of different type of smoking habit with gastric cancer has been shown in Table 4. The ORs of ex-smokers (OR, 2.95; 95% CI, 1.70-5.12) was found to be statistically significant compared with current smokers. After controlling the other habits and co-factors in multivariate model, a significant risk had been observed. Indicating independent effect on the development of gastric cancer. Statistically significant higher risks were seen for smokers of *meizial* with OR, 3.47 (95% CI, 1.83-6.54) in the multivariate model in comparison to cigarette smokers and smokers of combined *cigarette* and *meizial*. Overall, the excess risk was limited to smokers of 11 *meizial* per day. Risk also tended to increase with duration and with pack-years, with an OR of ~ 3 among smokers of 21 years and those who smoked 11 pack-years. Increasing trend was



observed as the frequency of smoking per day increased in the multivariate model with the statistically significant trend ($p < 0.001$).

Table 1: Distribution of cases and controls according to selected socio-demographic and risk factors

Variable	Category	Cases		Controls		p-value
		n	%	n	%	
Age	44	45	28.13	89	27.81	matched
	45-54	32	20.00	63	19.69	
	55-64	45	28.13	86	26.88	
	65	38	23.75	82	25.63	
Gender	Male	106	66.25	211	65.94	matched
	Female	54	33.75	109	34.06	
Residence	Rural	55	34.38	58	18.13	<0.0001
	Urban	105	65.63	262	81.88	
Education level	Illiterate	3	1.88	9	2.81	<0.000
	Primary School	23	14.38	6	1.88	
	Middle School	30	18.75	18	5.63	
	High School	47	29.38	32	10.00	
	Higher Secondary	20	12.50	32	10.00	
	UG and above	37	23.13	223	69.69	
Income level	Low	27	16.88	77	24.06	<0.000
	Middle	118	73.75	170	53.13	
	High	15	9.38	73	22.81	

Table 2: Chewing of betel nut and risk of gastric cancer

Habits	Category	Cases	Controls	Univariate*,OR(95% CI)	Multivariate ,adjusted OR(95% CI)
Chewing status	Non-chewers	52	131	1(reference)	1(reference)
	Current chewers	60	110	1.37(0.87-2.15)	1.02(0.58-1.79)
	Ex-chewers	48	79	1.53(0.94-2.47)	1.06(0.58-1.92)
Ingredients	Non-chewers	52	131	1(reference)	1(reference)
	Betel quid with lime	43	125	0.86(0.54-1.39)	0.71(0.40-1.27)
	Betel quid without lime	49	52	2.37(1.43-3.93)	1.44(0.76-2.70)
	Betel quid with tobacco	16	12	3.35(1.48-7.58)	2.55(0.96-6.72)
Frequency/d	Non-chewers	52	131	1(reference)	1(reference)
	5	24	95	0.65(0.37-1.12)	0.64(0.33-1.24)
	6-10	31	37	2.14(1.20-3.80)	1.37(0.68-2.74)
	11	52	55	2.46(1.50-4.04)	1.41(0.77-2.60)
$P_{trend} < 0.05$					
Age began (years)	Non-chewers	52	131	1(reference)	1(reference)
	15	28	33	2.09(1.15-3.79)	1.32(0.63-2.78)



	16 - 20	52	68	1.89(1.17-3.06)	1.50(0.82-2.75)
	21	28	88	0.79(0.46-1.35)	0.62(0.33-1.17)
P _{trend} <0.034					
Duration (years)	Non-chewers	52	131	1(reference)	1(reference)
	10	24	70	0.86(0.49-1.15)	0.97(0.49-1.92)
	11 - 20	20	41	1.22(0.65-2.29)	0.81(0.38-1.73)
	21	64	78	2.06(1.30-3.27)	1.21(0.68-2.15)
P _{trend} <0.090					

*Matched (cases and controls were matched for age and gender) univariate OR estimated by conditional logistic regression analysis

Adjusted ORs (adjusted for alcohol drinking, smoking, using of tuibur, residence, education level, income level) obtained by matched conditional multiple logistic regression analysis using maximum likelihood approach.

Table 3: Tuibur (tobacco smoke-infused water) and risk of gastric cancer

Habits	Category	Cases	Controls	Univariate*,OR(95% CI)	Multivariate ,adjusted OR(95% CI)
Tuibur status	Non-users	123	286	1(reference)	1(reference)
	Current users	14	20	1.62(0.79-3.32)	1.44(0.60-3.44)
	Former users	23	14	3.90(1.90-7.67)	3.16(1.37-7.26)
Frequency/d	Non-users	123	286	1(reference)	1(reference)
	5	19	14	3.15(1.53-6.49)	2.78(1.17-6.63)
	6	18	20	2.09(1.07-4.09)	1.74(0.77-3.95)
P _{trend} <0.0001					
Age began (years)	Non-users	123	286	1(reference)	1(reference)
	16	21	11	4.43(2.07-9.48)	4.28(1.90-11.99)
	17	16	23	1.61(0.82-3.16)	1.16(0.51-2.65)
P _{trend} < 0.0001					
Duration (years)	Non-users	123	286	1(reference)	1(reference)
	14	14	15	2.17(1.01-4.63)	2.15(0.99-4.66)
	15	23	19	2.81(1.47-5.35)	2.31(0.92-5.77)
P _{trend} < 0.0001					

*Matched (cases and controls were matched for age and gender) univariate OR estimated by conditional logistic regression analysis

Adjusted ORs (adjusted for alcohol drinking, smoking, chewing, residence, education level, income level) obtained by matched conditional multiple logistic regression analysis using maximum likelihood approach.

Table 3: Tobacco smoking and risk of gastric cancer

Habits	Category	Cases	Controls	Univariate*,OR(95% CI)	Multivariate ,adjusted OR(95% CI)
Smoking Status	Non-smokers	63	201	1(reference)	1(reference)
	Current smokers	29	65	1.42(0.84-2.39)	0.93(0.49-1.77)
	Ex-smokers	68	54	4.01(2.54-6.33)	2.95(1.70-5.12)
Types of	Non-smokers	63	201	1(reference)	1(reference)



smoking	Zozial	62	29	6.78(4.01-11.46)	3.47(1.83-6.54)
	Cigrattee	25	67	1.18(0.69-2.03)	1.13(0.45-2.81)
	Zozial+Cigrattee	10	23	1.38(0.62-3.05)	1.25(0.67-2.33)
Frequency/d	Non-smokers	63	201	1(reference)	1(reference)
	5	14	46	0.97(0.50-1.88)	0.75(0.35-1.61)
	6 - 10	26	42	1.97(1.12-3.47)	1.79(0.92-3.50)
	11	57	31	5.86(3.48-9.87)	3.57(1.90-6..73)
P _{trend} <0.001					
Age began (years)	Non-smokers	63	201	1(reference)	1(reference)
	15	28	20	4.46(2.35-8.46)	3.01(1.38-6.57)
	16 - 20	55	62	2.83(1.78-4.48)	2.08(1.18-3.66)
	21	14	37	1.20(0.61-2.37)	0.91(0.41-1.98)
P _{trend} <0.0004					
Duration (years)	Non-smokers	63	201	1(reference)	1(reference)
	10	24	41	1.86(1.04-3.32)	1.54(0.98-3.88)
	11 - 20	11	35	1.01(0.48-2.09)	0.57(0.24-1.36)
	21	62	43	4.60(2.84-7.44)	3.04(1.69-5.49)
P _{trend} <0.001					
Pack years of smoking	Non-smokers	63	201	1(reference)	1(reference)
	5	15	52	0.92(0.48-1.74)	0.74(0.35-1.55)
	6 - 11	34	39	2.78(1.62-4.77)	2.64(1.39-5.01)
	11	48	28	5.46(3.17-9.43)	3.02(1.56-5.86)
P _{trend} <0.005					

*Matched (cases and controls were matched for age and gender) univariate OR estimated by conditional logistic regression analysis

Adjusted ORs (adjusted for alcohol drinking, using of *tuibur*, chewing, residence, education level, income level) obtained by matched conditional multiple logistic regression analysis using maximum likelihood approach.

Discussion

Tobacco smoking and use of *smokeless tobacco*, chewing of *tobacco* and *tuibur*, are common in both the sexes in Mizoram. We found tobacco smoking to be a significant risk factor. Relatively high prevalence of *tobacco smoking* in Mizoram (10) may have contributed to the high rates of stomach cancer.

An increased risk of stomach cancer among smokers has been observed in numerous case-control and cohort studies (15-21) and is consistent with our study too. However, studies from Europe have reported no association between stomach cancer and smoking (22-28). Smoking as a variable risk factor for stomach cancer has also been reported from India (29,30). In our study, ex-smokers appeared to have an elevated risk for gastric cancer. However most of the studies have found that increased risk of gastric cancer associated with current smokers (15, 17, 18, 21, 31). Furthermore, we are also reporting smoking of crude tobacco, *meizial* (local cigarette) in this study, and its association with higher risk. Our study has shown significant dose response relationship with the quantity of smoked like other studies (15, 24, 32-36). Tobacco smoke contains a variety of carcinogen including N-nitroso compounds and nitrogen oxides that may promote endogenous formation of N-nitroso compounds (37), which have been linked to gastric carcinogenesis (38). IARC has revealed that smoking is causally associated with cancer of the stomach (39). A potential causal role of tobacco in causation of pre-cancerous lesions, in a high-risk area of China, where smoking was found to nearly double the risk of transition to gastric dysplasia (40). Another study



(41) carried out in the United States revealed that current smokers had 2.3 times increased risk of dying from stomach cancer compared with non-smokers.

The Third National Cancer Survey of the United States (42) and studies elsewhere reported a non-significant risk of stomach cancer with smokeless tobacco use (36, 43, 44). Our study revealed significant elevated risk among the *tuibur* users than the nonusers, which supported the findings of toxicity of *tuibur*(12).

The study also revealed no significant association between betel quid chewers and stomach cancer like other study (30), a risk (OR, 2.55) had been observed in persons who consumed *betel quid* along with tobacco and those who were early chewers. However, there are sufficient evidence of *betel quid* with tobacco is carcinogenic to humans in sites other than stomach like oropharynx, hypopharynx, larynx, and esophagus, but betel quid without tobacco is not classifiable as to its carcinogenicity to humans (45).

Conclusion

In conclusion, consumption of betel nut, tuibur and tobacco smoking displayed the associations with increased gastric cancer risk in this study. Further understanding of the role of these factors in gastric cancer etiology may ultimately lead to improve gastric cancer prevention strategies for Mizo people.

Ethical Clearance: This study was approved by Mizoram Ethics Committee. Conflict of Interest: None declared.

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