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Association of tobacco use, betel consumption and gastric cancer in Mizoram

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Abstract

Cancer is a disease that affects the livelihood of humankind for ages. Dietary habit and lifestyle have been attributed to the development of many forms of cancer including gastric cancer. The state of Mizoram located in the northeastern India has been recorded to be a cancer prone area. Most Mizo people indulge in the use of smoke and smokeless tobacco and betel chewing. A study in this high cancer incidence zone is necessary to determine the actual cause of the disease. In this study, we evaluate the influence of tobacco use and betel consumption on gastric cancer. We conclude that individuals with a family history of cancer who consumed betel, smoke and smokeless tobacco have a higher risk of gastric cancer. We also found an association between increased risk of gastric cancer and consumption of betel or *sahdah* alone and betel with *sahdah*.

Key words: Betel; gastric cancer; Mizoram; multiple logistic regression; tobacco.

Introduction

Cancer has always been a major health problem all over the world. In 2012, an estimated 14.1 million cases of cancer were diagnosed.[1] Gastric cancer is known to be the fourth most common form of cancer and second leading cause of death from cancer worldwide.[2] Among male, gastric cancer have been found to be highest in the population of Changle in China whereas among female, it is highest in the population of Yamagata in Japan.[3] The etiology of gastric cancer is not singly but multi-factorial.[4] Many studies have implicated *Helicobacter pylori* and Epstein-Barr virus infection, alcohol, tobacco and diet as co-factors for its development. Diet low in vegetable and fruits and high in salt, high temperature cooked meat and preserved foods have been known to increase the risk of gastric cancer,[5-9] however other studies have the opposite conclusion.[10,11] Underweight or low

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body mass index (BMI) has also been attributed to be associated with increased risk of gastric cancer.[12]

In India gastric cancer is most prevalent in the state of Mizoram. An age-adjusted rate of 42.9 and 20.5 per 10^5 population have been computed for male and female respectively.[13,14] The dietary pattern and lifestyle of the people of Mizoram are rather different than that of other parts of the country. Some of the indigenous food of the Mizo contain smoked and fermented meats and vegetables, and the use of alkali in the form of soda for the preparation of local food called "Bai" is fairly common.[15] Smoke and smokeless tobacco have also been used by many of the Mizo. Phukan *et al.* in 2005 had shown that the use of tobacco in smoke and smokeless form had increased the risk of gastric cancer in Mizoram.[3] In this study, the association of tobacco use and betel (areca nut + betel leaf) consumption as causative factors for gastric cancer among the ethnic group of the Mizo has been analyzed. The Mizo generally smoked cigarette (company packed) and *zozial* (local cigarette), and also use smokeless tobacco like *tuibur* (tobacco brew) and *sahdah* (ground/shredded tobacco) viz,. khaini, raja, etc.

Materials and Methods

A case-control study has been carried out at Civil hospital, Aizawl, Mizoram, Mizoram State Cancer Institute and other private hospitals as well as at private houses of patients or relatives within Aizawl, Lunglei and Kolasib, Mizoram. The study included a case group of 41 individuals suffering from gastric cancer diagnosed and pathologically confirmed during 15th October, 2014-20th March, 2015. The control group consisted of 120 individuals who, at the time of the interview, did not suffer from any form of cancer. The controls were individually matched to the cases by gender and age (±5 years). The ratio of cases and controls was 1:3.

After obtaining written consent, the participants were interviewed using structured questionnaire approved by Mizoram State Ethical Committee. The questionnaire includes the dietary habit, lifestyle and family history of cancer of the participants. In cases where the patients were unable to comply, the relatives were allowed to give consent and information on behalf of the patients. Cancer patients were asked to advert about their diet and lifestyle habits before the disease was diagnosed.

Chi square (χ^2) –test and multiple logistic regression (enter and stepwise method) were employed to calculate the differences between proportions. The level of significance was set at 5%, and odds ratio (OR) and corresponding 95% confidence interval (CI) for gastric cancer in relation to exposures of interest were calculated. All calculations were performed with Software R version 2.10.1 program.

Results

The distribution of socio-demographic variables and selected risk factors among the cases and controls is shown in Table 1. The level of education of the cases is significantly lower, mostly residing in villages and their occupation is generally non-governmental (private occupation).

Though the consumption of betel is not found to be significant, it has been calculated to offer a chance of increasing gastric cancer (Table 2). There is a statistically significant relationship between gastric cancer and combined consumption of betel with *sahdah* (Table 3). The dose of *tuibur* use has also been found to have a higher chance to increase the risk of gastric cancer eventhough it is not statistically significant (Table 4). The consumption and duration of alcohol drinking are also pondarable to initiate gastric cancer and are calculated to be statistically significant. Though the years in which the individual has stopped using alcohol (year since stopped) is not significant, it still provide a chance to increase the risk of gastric cancer (Table 6). The combined use of smoking, betel, *tuibur* and *sahdah* and its frequency have higher significant influenced to increase the risk of gastric cancer (Table 7). Family history of cancer

Table 1. Distribution of cases and controls by selected socio-demographic factors.

Variable	Category	Case	Control	Total	χ^2
Gender	Male	20	63	83	0.169
	Female	21	57	78	0.681(match)
Age	≤ 45	13	26	39	1.678
	≥ 46	28	94	122	0.195(match)
Residence	Urban	16	71	87	4.992
	Rural	25	49	74	< 0.025
Education	≤ HSLC	24	45	69	5.522
	>HSLC	17	75	92	< 0.019
Occupation	Govt	26	50	76	5.800
	Private	15	70	85	< 0.016

Table 2. Odds ratio and 95% confidence interval (CI) for gastric cancer in relation to betel consumption.

Variable	Category	Cases		Controls		OR (95 % CI) P for trend
		n	%	n	%	
Betel	yes	22	53.66	81	67.5	5.315 (0.997 -28.338) 0.050
	no	19	46.34	39	32.5	
Dose (piece per month)	≤500	15	36.59	42	35.0	0.706 (0.263 - 1.894) 0.490
	>500	26	63.41	78	65.0	
Frequency (per day)	≤10	8	19.51	33	27.5	1.151 (0.420 -3.157) .784
	>10	33	80.49	87	72.5	
Duration of chewing (year)	≤15	18	43.90	70	58.3	0.809 (0.231 - 2.835) 0.741
	>15	23	56.10	50	41.7	
Year since stopped (year)	≤10	12	29.27	48	40.0	0.913 (0.386 -2.159) 0.836
	>10	29	70.73	72	60.0	

Table 3. Odds ratio and 95% confidence interval (CI) for gastric cancer in relation to betel with *sahdah* consumption

Variable	Category	Cases		Controls		OR (95% CI) P for trend
		n	%	n	%	
Betel with *sahdah*	yes	18	43.90	73	60.83	13.793 **(2.952 - 64.448)** **< 0.001**
	no	23	56.10	47	39.17	
Dose (times per month)	≤100	10	24.39	50	41.67	3.231 **(0.899 -11.615)** .072
	>100	31	75.61	70	58.33	
Frequency (times per day)	≤10	12	29.27	36	30.00	0.407 **(0.110 -1.505)** 0.178
	>10	29	70.73	84	70.00	
Duration (year)	≤15	10	24.39	45	37.50	1.510 **(0.431 - 5.294)** 0.519
	>15	31	75.61	75	62.50	
Year since stopped (year)	≤10	11	26.83	37	30.83	2.176 **(0.585 - 8.100)** 0.246
	>10	30	73.17	83	69.17	

Table 4. Odds ratio and 95% confidence interval (CI) for gastric cancer in relation to the use of *tuibur* (tobacco brew)

Variable	Category	Cases		Controls		OR (95% CI) P for trend
		n	%	n	%	
Betel with *sahdah*	yes	17	41.46	58	48.33	2.777 **(0.662 - 11.644)** 0.163
	no	24	58.54	62	51.67	
Dose (times per month)	≤1000	7	17.07	22	18.33	1.466 **(0.498 - 4.309)** 0.487
	>1000	34	82.93	98	81.67	
Frequency (times per day)	≤10	13	31.71	41	34.17	0.725 **(0.225 - 2.332)** 0.590
	>10	28	68.29	79	65.83	
Duration (year)	≤15	10	24.39	39	32.50	1.309 **(0.450 -3.810)** 0.621
	>15	31	75.61	81	67.50	
Year since stopped (year)	≤10	4	9.76	29	24.17	1.073 **(0.385 -2.988)** 0.893
	>10	37	90.24	91	75.83	

Table 5. Odds ratio and 95% confidence interval (CI) for gastric cancer in relation to smoking habit

Variable	Category	Cases		Controls		OR (95% CI) P for trend
		n	%	n	%	
Betel with *sahdah*	Smoker	20	48.78	79	65.8	1.194 **(0.235 - 6.074)** 0.831
	Non-smoker	21	51.22	41	34.2	
Dose (times per month)	≤1000	15	36.59	70	58.3	.419 **(0.075 - 2.348)** 0.323
	>1000	26	63.41	50	41.7	
Frequency (times per day)	≤10	10	24.39	56	46.7	7.385 **(0.542 -100.571)** 0.133
	>10	31	75.61	64	53.3	
Duration (year)	≤15	11	26.83	59	49.2	10.974 **(0.921 - 130.787)** 0.058
	>15	30	73.17	61	50.8	
Year since stopped (year)	≤10	9	21.95	55	45.8	0.599 **(0.067 -5.384)** 0.648
	>10	32	78.05	65	54.2	

Table 6. Odds ratio and 95% confidence interval (CI) for gastric cancer in relation to alcohol drinking habit

Variable	Category	Cases		Controls		OR (95% CI) P for trend
		n	%	n	%	
Betel with *sahdah*	yes	19	46.34	42	35.0	0.109 **(0.014-0.825)** < 0.032
	no	22	53.66	78	65.0	
Dose (times per month)	≤20	10	24.39	26	21.7	1.407 **(0.405-4.894)** 0.591
	>20	31	75.61	94	78.3	
Frequency (times per day)	≤0.5	16	39.02	31	25.8	1.397 **(0.319-6.110)** 0.657
	>0.5	25	60.98	89	74.2	
Duration (year)	≤15	10	24.39	28	23.3	1.200 **(0.273-5.283)** < 0.002
	>15	31	75.61	92	76.7	
Year since stopped (year)	≤10	9	21.95	33	27.5	11.607 **(2.401-56.120)** 0.055
	>10	32	78.05	87	72.5	

Table 7. Odds ratio and 95% confidence interval (CI) for gastric cancer in relation to combine use of *tuibur*, betel, *sahdah* and smoking

Variable	Category	Cases		Controls		OR (95% CI) P for trend
		n	%	n	%	
Betel with *sahdah*	yes	16	39.02	53	44.17	0.068 **(0.008 – 0.609)** < 0.016
	no	25	60.98	67	55.83	
Dose (times per month)	≤100	9	21.95	29	24.17	1.975 **(0. 368 – 10.611)** 0.427
	>100	32	78.05	91	75.83	
Frequency (times per day)	≤5	10	24.39	48	40.00	18.872 **(4.998 – 71. 257)** < 0.000
	>5	31	75.61	72	60.00	
Duration (year)	≤10	7	17.07	43	35.83	1.689 **(0.046 – 1.492)** 0.625
	>10	34	82.93	77	64.17	
Year since stopped (year)	≤5	13	31.71	44	36.67	1.401 **(0.120 – 16.421)** 0.778
	>5	28	68.29	76	63.33	

Table 8. Odds ratio and 95% confidence interval (CI) for gastric cancer in relation to BMI and family history of cancer

Variable	Category	Cases		Controls		OR (95% CI) P for trend
		n	%	n	%	
BMI	≤18	16	39.02	43	35.83	0.627 **(0.265 – 1.487)** .771
	>18	25	60.98	77	64.17	
Family history of cancer	Yes	17	41.46	56	46.67	28.238 **(10.704– 74.492) <0.000**
	No	24	58.54	64	53.33	

Table 9. Odds ratio and 95% confidence interval for gastric cancer by Stepwise method

Steps	**Variable**	**SE**	**P for trend**	**OR**	**95% CI**
1	Betel with *sahdah*	0.430	0.000	26.333	11.327 – 61.220
	Constant	0.299	0.000	0.250	-
2	Betel with *sahdah*	0.778	0.000	65.249	14.203 – 299.751
	Family history of cancer	0.823	0.000	68.506	13.652 – 343.774
	Constant	0.726	0.000	0.032	-

also has also been found to play a crucial role to increase the risk of gastric cancer and has been calculated to be statistically significant at 95% confidence interval (Table 8).

Further, multiple logistic regression analysis of risk of gastric cancer by step wise method (forward wald) to identify the most significant variables having significant influence and are indispensible to the study of the risk of gastric cancer established that only two variables, that is, family history of cancer and consumption of betel with *sahdah* have been computed to have significant impact on the risk of developing gastric cancer (Table 9). Here, alcohol drinking, duration of alcohol drinking and combined use of smoking, betel, *tuibur* and *sahdah* are excluded.

Discussion

Tobacco has been known to cause cancer in many parts of the body.[16-18] Studies have shown that persons smoking a pack of cigarette per day showed 50% increased in colon cancer than non -smokers and those who discontinued smoking remained at increased risk even if they stopped very early. The amount smoked may have been a more important factor than the number of years smoked. The interaction of tobacco with alcohol has also been found to be a powerful carcinogen.[19, 20] Tobacco smoking, alcohol consumption and betel quid chewing have been observed to significantly increased the risk of lung cancer.[21, 22] Lung, laryngeal and pharyngeal cancers have highest relative risk for current smokers than former smokers.[23] Smokeless tobacco has also been attributed to the increased risk of many tobacco related cancers.[24] Some studies have established a protective effect for terminated smoking.[25] Among tobacco users, many genes have been observed to show differences in their expression pattern. Some genes are up regulated while others are down regulated.[26] Methylation of RAR-B gene has been found to be positively associated with the use of tobacco in non-small cell lung cancer.[27]

Areca nut is a confirmed group I carcinogen. A study on animal model has shown that areca nut can induce stomach cancer. Initial exposure to areca nut up regulated the expression of p53, bax, securin, p38, MKP-1 phosphatase and p65 while other cell cycle check point proteins were down regulated. The presence of lime in betel quid consumption has been featured in promoting cell proliferation and hence developed cancer earlier.[28, 29] The consumption of betel with or without tobacco has been known to elevate the risk of developing oral cancer.[30] Chiang *et al.,* (2008) has found that betel chewing has posed a much higher risk of oral cancer than alcohol drinking and cigarette smoking.[31]

Our study has shown similar results to the work done by Phukan *et al.*.[3] We have observed a higher risk of gastric cancer for people with a family history of cancer. Although the consumption of betel alone does not have a significant relationship with gastric cancer, we have found a significant association between increased risk of gastric cancer and combined consumption of betel with *sahdah*. Drinking of alcohol has also been calculated to be statistically significant. Though our statistics have shown that the dose and duration of *tuibur* usage as not significant, it clearly has a positive impact on an increased risk of gastric cancer. The combined use and frequency of smoking, betel, *sahdah* and *tuibur* have been shown to have a higher significant relationship to the increase risk of gastric cancer. Even though most studies stated tobacco, areca nut and alcohol as carcinogenic, to draw conclusion on their involvement in gastric carcinogenesis may be very bias as many factors may be responsible for the induction of gastric cancer. A drawback in our study is that the cases and controls were not interviewed under the same condition. Many of the controls were interviewed at the hospitals while the controls are mainly interviewed at their residences. A detail analysis on the genomic differences between the Mizo ethnic group and other ethnic groups to determine the exact cause of the highly elevated cases of the different forms of cancer in this particular ethnicity, which maybe a result of inbreeding, would be an interesting line of investigation.

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