A Case-Control Study of Alcohol Consumption and Esophageal Cancer in the Northeast State of Mizoram, India

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Abstract: *Summary*: Esophageal cancer is one of the main health issues in Mizoram. The risk factors of the disease are related to consumption of alcohol. There have not been any epidemiological studies on this subject in the state. The aim of the study is to assess the relationship between esophageal cancer and consumption of alcohol.

Materials and Methods: A hospital based matched case-control study was conducted comprising of 138 cases with histologically confirmed diagnosis of esophageal cancer and 276 controls that were cancer and esophageal cancer disease free. Cases and controls matched by gender and age (± 5 years). Ratio of cases and controls were 1:2. A questionnaire was used to collect information on possible risk factors of esophageal cancer. The odds ratios (OR) and 95% confidence intervals (CI) for gastric cancer were calculated by a conditional logistic regression.

Results: Cases had significantly lower education level. Most of the cases are from middle income class. After adjustment for consumption of betel quid, tobacco, smoking, body mass index (BMI), family history of cancer, education level and income level, higher risk of esophageal cancer was found for those who have the habit of consuming alcohol in the morning. After controlling for consumption of betel quid, tobacco, smoking, body mass index (BMI), family history of cancer, education level, income level, dietary habits, physical activity, consumption of Zu(locally brewed alcohol) and both Zu(locally brewed alcohol) and commercial alcohol(rum, whisky, vodka and beer, etc) are also associated with higher risk of esophageal cancer (O.R = 9.820, 95% CI = 2.029-47.523).

Keywords: Alcohol consumption, betel quid consumption, tobacco consumption, smoking, esophageal cancer, Mizoram.

INTRODUCTION

Esophageal cancer is the eighth most common form of cancer in the world with 456,000 new cases in 2012 alone [1]. National cancer registry program report of India during 2009-2011 reported the highest incidence of esophageal cancer in the East Khasi Hills District of Meghalaya (Age Adjusted Rate (AAR) 71.4 among males and 30.2 among females) followed by Aizawl District in Mizoram (AAR 42.0 among males and 7.0 among females) and Kamrup Urban District of Assam (AAR 27.0 among males and 18.3 among females) in North East India [2]. There is a wide geographical disparity in the incidence of esophageal cancer [3]. This variation may be attributed to diverse ethnicity, environmental factors and dietary habits in North East India [4]. Environmental and dietary factors like smoking and smokeless tobacco consumption, betel quid chewing, alcohol intake, poor nutrition, etc., are associated with Esophageal Squamous Cell Carcinoma (ESCC) in the high risk region of North East India [5, 6].

Mizoram is one of the eight sister states of northeast India and lies between 21°56'N latitude, and 92°16'E and 93°26'E longitude. The state has an area of 21,081 sq km, and shares an international boundary with Bangladesh in the west and Myanmar in the east and south. It also shares interstate boundary with Tripura in the northwest, Assam in the north and Manipur in the northeast [7]. Majority of the native people in habiting Mizoram were previously called “Lushai” and now “Mizo” and they are known to have a unique tradition and ethnicity when compared with other states of India. The major tribes of Mizo are Lusei, Ralte, Hmar, Pawi, Paite and other groups [8]. Hence, they also possess different traditional techniques of processing foods [9]. Consumption of Zu, traditional rice beer, was a common phenomenon in Mizo society [10]. In Mizo culture, Zu was made from husked rice through a process of distillation. The brewing of Zu for commercial purposes, in the Mizo society in the past has not been documented.

The MLTP (Mizoram Liquor Total Prohibition) Act, 1995 was enacted by the Mizoram government to ban the importing, transport, brewing, possession, sale and consumption of liquor in the year 1995. Numerous measures have been undertaken by the State Government and the state officials to implement the Act. However, the MLTP had its own lapses and the illicit liquor trade and brewing continued within Mizoram [11]. The measures taken by Mizoram government to implement the MLTP Act have failed. Due to Mizoram Liquor Total Prohibition Act, 1995, alcohol like rum, wine, whisky, vodka, etc., were not easily available. Most of the people consumed Zu which could be easily

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procured from local alcohol sellers. Zu was considered an important commodity with a market, value and was seen as profitable to the common person. The commercialization of Zu is also related to the socio economic factors such as poverty and unemployment [12]. The volume of Zu trade and consumption has increased exponentially over the past decades. Alcoholism, crime and domestic violence became more evident [13] due to illicit trade and consumption of Zu. Many people lost their life due to consumption of bad quality of Zu. Mizoram's Legislative Assembly passed a new law to legalize the sale and consumption of alcohol with stringent restrictions after a five-hour debate involving two-thirds of all members to end 18 years of prohibition in the state. It was called Mizoram Liquor Prohibition and Control Bill 2014, or MLPC Bill. MLPC Act replaced the Mizoram Liquor Total Prohibition Act of 1995 and allows the consumption, sale, retail, manufacture, storage and transport of various kinds of alcohol including country-made ones.

In spite of good advancements for diagnosis and treatment, cancer is still a big threat to our society [14]. This is the second most common disease after cardiovascular disorders for maximum deaths in the world [15]. It accounts for about 23% and 7% deaths in USA and India, respectively. The prevalence of cancer in India is estimated to be around 2.5 million, with about 8,00,000 new cases and 5,50,000 deaths per annum[16]. During last one decade, about 70% cancer cases have been diagnosed and treated with survival of a few patients [17]. It is believed that in the near future the number of cancer patients will increase in the developing and under developed countries, which may rise up to 70% ; a serious issue for all of us.

The biological mechanisms that mediate alcohol-related cancer are not fully understood [18]. Alcoholic beverages can contain at least 15 carcinogenic compounds, including acetaldehyde, acryl amide, aflatoxins, arsenic, benzene, cadmium, ethanol, ethyl carbamate, formaldehyde, and lead. Ethanol is the most important carcinogen in alcoholic beverages [19], and the rate of ethanol metabolism is genetically determined [20].

The first and most toxic product of alcohol metabolism is acetaldehyde. Ingested ethanol is oxidized by the enzymes alcohol dehydrogenase, cytochrome, and catalase to form acetaldehyde [21]. Acetaldehyde also occurs naturally in alcoholic beverages. This metabolite is carcinogenic and genotoxic when in contact with the mucosa of the upper aero digestive tract (pharynx, oral cavity, esophagus, larynx), where high concentrations of acetaldehyde induce mucosal hyper proliferation [21]. Even low doses of alcohol in direct contact with these areas can increase the risk for cancer. Several different causative pathways are implicated in alcohol-related cancer [18].

Esophageal cancer is emerging as a common cancer in India [22]. Squamous cell carcinoma of the esophagus is the third leading cancer in men and fourth leading cancer in women in India [23-25], Esophageal cancer is the third leading cancer in Mizoram, during the last five years 503 new cases was diagnosed out of which 427 are male and 76 are female [26].

MATERIALS AND METHODS

A hospital based case-control study has been carried out at Civil Hospital, Aizawl. It is the leading hospital for the treatment of cancer in Mizoram. The study included 138 patients aged 30 – 86 years who had histologically confirmed diagnosis of esophageal cancer, admitted in that hospital during March, 2015 to February, 2016. Controls are taken from those who have visited the Civil Hospital during the same period. Controls were individually matched to case-patients by gender and age (±5 years). Ratio of cases and controls was 1:2. There were a total of 276 controls that were cancer and esophageal diseases free.

A structured questionnaire was developed that included questions on dietary habits, tobacco consumption, residence, income, education, occupation, marital status, drinking status, age when started, dosage, duration, time of drinking, types of alcohol (i.e. Zu and commercial alcohol like rum, whisky, vodka and beer, etc) consumed and family history of cancer.

All the subjects were asked to fill the questionnaire by themselves. In case of inability to do so for various reasons, such as, bad general status, poor vision, pathology of upper extremities or personal wish for assistance of filling out a questionnaire, they were interviewed by an interviewer. One interviewer was engaged who was not aware of the study hypothesis.

Subjects who reported that they were regular drinkers during the index year are defined as 'current drinkers', while a 'former drinker' was defined as having stopped drinking the year before index year, former

drinkers are those who have given up alcohol drinking when the cancer was diagnosed or before cancer was diagnosed and never drinker was defined as a person who never drinks any type of alcohol. Time of drinking was assessed as morning, evening, night and any time. And types of alcohol was differentiated as Zu and commercial alcohol and the consumption of alcohol was assessed by the frequency of consumption in a week; family history was categorized into two: those having family history of cancer was 'yes' and 'no' for those free from all types of cancer; physical activity at leisure time was estimated by the answers (yes and no) to a question "Do you perform exercise?"; subjects according to body mass index (BMI; calculated as weight (kg)/height^2(m)) at 20 years of age were divided into two groups, ≤ 24.99 kg/m^2 and ≥ 25 kg/m^2. Residence was categorized into rural and urban only. Education level was grouped as up to secondary, secondary and under graduate and above. Income was assessed by low income, middle income and high income groups. Occupation was categorized as office worker, farmer, business and others (driver, student, etc). Diet was assessed according to consumption frequency (almost never, 1–3 times per week, ≥ 4 times per week, 0-6 times per week, daily and ≥ 1 times in a month) of different food items. Cigarette smoking was measured in pack-years (number of cigarettes smoked per day/20 × smoking time (in years)). Consumption of betel quid also categorized as 'yes' for betel quid chewers and 'no' for 'never chewers'. Tobacco consumption was divided into 'yes' for tobacco users and 'no' for 'never users'. Marital status was assessed by married or unmarried.

A conditional logistic regression was employed to assess the association of risk factors and esophageal cancer and was expressed as the odds ratios (OR), and corresponding 95% confidence interval (CI) for esophageal cancer in relation to exposures of interest. Tests for trend were calculated by fitting conditional logistic regression model to ordinal values representing levels of exposure. All reported trend test significance levels (p-values) were two-sided [27]. The Chi square was utilized to calculate the difference between proportions. The level of significance was set at 5%. The calculations were performed with SPSS version 20 and R version 3.1.2 software.

RESULTS

The distribution of socio-demographic variables and selected risk factors among cases and controls is shown in Table **1**. The mean age of the cases and controls was 53.74 and 53.20 years, respectively. There were no statistically significant differences between the age of cases and controls, suggesting that age matched was effective. Of the cases 65.94% were male and majority (40.58%) of the esophageal cancer patients were in the age group of 45 to 54 years at the time of diagnosis of esophageal cancer. Cases had significantly lower education level. Most of the cases are in middle income level. There were more controls without history of family cancer as compared to cases. Therefore, education level, income level and history of family cancer were included into logistic regression model like betel quid consumption, tobacco consumption, smoking, physical activity and BMI at 20 years of age as variables to adjust for.

The study also examined the relationship between risks of esophageal cancer and drinking status, types of alcohol consumed, dosage, age started and duration.

ORs were calculated using non-drinkers as reference group to see the association with alcohol consumption. The risk of esophageal cancer was associated with drinking status, types of alcohol consumed, time of drinking, age started, dosage and duration in univariate logistic regression model. After controlling for consumption of betel quid, tobacco, smoking, BMI, family history of cancer, higher risk of developing esophageal cancer was observed among former drinkers, those who are used to drinking in the morning, consumption of both Zu and commercial alcohol, amount of alcohol consumed increased, age started if before 20 years and longer durations. Although the trend test was not statistically significant, an elevated risk was observed as the amount of alcohol consumed per week and duration in years increased and decreased risk was observed for the increased of age of start. Significant dose-response effects were observed as the intensity of alcohol consumed per day and duration in years increases and decreasing trend was observed for the increase increase of age at which alcohol consumption was started with the statistically significant trend ($P < 0.044$) after further control for education level and income level.

Inasmuch as the risk of esophageal cancer is related to many factors. Finally, multivariate conditional logistic regression model was used that included risk factors like drinking status, time of drinking, types of alcohol, dosage, age when started and duration and other variables such as consumption of vegetables,

Table 1: Distribution of Cases and Controls According to Social-Demographic and Risk Factors

Variable	Category	Cases	%	Controls	%	p-value
Age group	≤44	19	13.77	38	13.77	Matched
	45-54	56	40.58	120	43.48	
	55-64	37	26.81	73	26.45	
	≥65	26	18.84	45	16.30	
	Mean±SD	53.74±10.33		53.20±10.48		
Gender	Male	91	65.94	183	66.30	Matched
	Female	47	34.06	93	33.70	
Residence	Rural	33	23.91	45	16.30	0.062
	Urban	105	76.09	231	83.70	
Education level	Up to secondary	41	29.71	34	12.32	<0.001
	Higher secondary	41	29.71	62	22.46	
	UG and Above	56	40.58	180	65.22	
Income level	<8000	29	21.01	103	37.32	<0.001
	8000-30000	91	65.94	112	40.58	
	>30000	18	13.04	61	22.10	
Occupation	Office worker	44	31.88	104	37.68	0.563
	Farmer	36	26.09	72	26.09	
	Business	21	15.22	41	14.86	
	Other	37	26.81	59	21.38	
Marital status	Married	82	59.42	172	62.32	0.321
	Unmarried	56	40.58	104	37.68	
Family history of cancer	Yes	80	57.97	121	43.84	<0.005
	No	58	42.03	155	56.16	

smoked vegetables, pickled vegetables, fresh meat, smoked meat, dried meat, pickled meat, tinned meat, fruits, fermented soybean, fermented pork, chilies, spices that were associated with the disease as well as betel quid, tobacco, smoking, BMI and history of cancer, education level and income level and physical activity. A significant increase in the risk was observed among former drinkers of alcohol and those who are used to drinking in the morning as well as those who start drinking before 20 years of age, consumption of both Zu and commercial alcohol, amount of alcohol consumed per day increased and longer duration of regular drinking. The ORs and the dose-response relationships remained significant in multivariate model (Table **2**).

DISCUSSION

Before Mizoram Liquor Prohibition and Control Act, 2014 was introduced; consumption of Zu (local alcohol) was very popular in Mizoram. In the present study, our results confirmed that alcohol drinking is a strong risk factor for esophageal cancer in Mizoram. There is sufficient evidence that moderate and heavy alcohol drinking were associated with higher risk of the esophageal cancer. These results are consistent with most of the epidemiological studies carried out in Western countries and some areas of Asia [28-35].

A beneficial effect has been found in some studies particularly 10 years after giving up drinking [34, 36] although some studies have shown a rapid decline in risk after cessation of drinking [28, 37, 38]. On the contrary, the study showed a statistically significant increased risk among former drinkers. Other studies also found that either there is a non-beneficial effect [32] or a higher risk among former drinkers [38, 39].

An attempt was made to explore the effects of different types of alcohol since the consumption of Zu is quite common and thus, it may have a great interest for public health. The study revealed that consumption

Table 2: Alcohol Consumption and Risk of Esophageal Cancer

Variable	Category	Cases		Controls		OR[1] (95% CI)	OR[2] (95% CI)	OR[3] (95% CI)
		n	%	n	%			
Drinking status	Non-drinkers	68	49.28	193	69.93	1(reference)	1(reference)	1(Reference)
	Current drinkers	18	13.04	40	14.49	0.79 (0.39-1.58)	0.88 (0.43-1.81)	0.28 (0.07-1.07)
	Former drinkers	52	37.68	43	15.58	1.79 (1.01-3.18)	1.60 (0.86-2.94)	2.46 (0.93-6.49)
Time of drinking	Non-drinkers	68	49.28	193	69.93	1(reference)	1(reference)	1(reference)
	At morning	18	13.04	8	2.90	3.80 (1.50-9.61)	2.99 (1.14-7.85)	4.77 (1.11-20.50)
	At evening	5	3.62	15	5.43	0.45 (0.14-1.38)	0.50 (0.16-1.58)	0.82 (0.11-5.77)
	At night	20	14.49	33	11.96	1.027 (0.513-2.055)	1.080 (0.513-2.272)	0.831 (0.264-2.620)
	Any time	27	19.57	27	9.78	1.32 (0.66-2.67)	1.27 (0.60-2.66)	1.09 (0.32-3.73)
Types of alcohol	Non-drinkers	68	49.28	193	69.93	1(reference)	1(reference)	1(reference)
	Local alcohol	32	23.19	28	10.14	1.91 (0.98-3.75)	1.66 (0.82-3.39)	1.34 (0.45-3.99)
	Commercial alcohol	17	12.32	43	15.58	0.64 (0.31-1.30)	0.75 (0.36-1.57)	0.66 (0.19-2.28)
	Local+ Commercial alcohol	21	15.22	12	4.35	2.61 (1.11-6.12)	2.18 (0.88-5.36)	9.82 (2.02-47.52)
Dosage cup/week	Non-drinkers	68	49.28	193	69.93	1(reference)	1(reference)	1(reference)
	0 - 4	24	17.39	45	16.30	0.89 (0.47-1.70)	0.83 (0.43-1.62)	0.69 (0.23-2.06)
	5 - 9	27	19.57	26	9.42	1.59 (0.80-3.16)	1.85 (0.88-3.86)	3.99 (1.16-13.77)
	≥ 10	19	13.77	12	4.35	2.39 (1.01-5.62)	2.043 (0.79-5.25)	1.200 (0.30-4.73)
Ptrend						**0.272**	**<0.030**	**<0.0001**
Age when started	Non-drinkers	68	49.28	193	69.93	1(reference)	1(reference)	1(reference)
	≤ 20 year	36	26.09	34	12.32	1.78 (0.96-3.32)	1.76 (0.90-3.44)	1.63 (0.57-4.63)
	≥ 21year	34	24.64	49	17.75	1.01 (0.55-1.84)	0.97 (0.51-1.82)	1.13 (0.41-3.16)
Ptrend						**0.322**	**<0.044**	**<0.0001**
Duration	Non-drinkers	68	49.28	193	69.93	1(reference)	1(reference)	1(reference)
	≤ 16 year	22	15.94	50	18.12	0.73 (0.38-1.40)	0.77 (0.39-1.52)	0.82 (0.26-2.56)
	≥ 17 year	48	34.78	33	11.96	2.22 (1.20-4.09)	2.04 (1.06-3.91)	1.83 (0.68-4.92)
Ptrend						**0.284**	**<0.025**	**<0.0001**

OR[1] Adjusted for betel quid consumption, tobacco consumption, smoking, BMI at 20 years of age and family history of cancer;
OR[2] further adjustment for education level and income level;
OR[3] further adjustment for dietary habits (vegetables, smoked vegetables, pickled vegetables, fresh meat, smoked meat, dried meat, pickled meat, tinned meat, fruits, fermented soya bean, fermented pork, chilies, spices) and physical activity except for each independent variable.

of Zu and both Zu and commercial alcohol was highly related with increased risk of esophageal cancer. It was found that in practically all the studies the risks are greatest for drinkers of commercial or hard liquors which is consistent with evidence that the concentration of ethanol plays an important role in alcohol related tumors of the upper aero-digestive tract [40-42].

An increased risk among those who got into the habit of regular drinking from a younger age, longer duration of regular drinking, and increasing amount of alcohol consumed daily and over lifetime was observed. These results are consistent with the epidemiological studies carried out in Shanghai among 18,244 middle-aged and older men [43].

The case-control study conducted in northern Italy reported that the Esophageal Squamous Cell Carcinoma (ESCC) risk was unaffected by duration of alcohol drinking [32]. However, the present study found a significant association between duration of alcohol drinking and esophageal cancer risk. This study has shown significant dose response relationship with the quantity of alcohol consumed. The other data also indicated that amount of alcohol consumed per day was significantly associated with elevated risk of this malignancy [40, 43]. When daily ethanol consumption exceeded 53.3 g, the risk of developing ESCC within the next 20 years was increased. The exact mechanism by which ethanol causes esophageal cancer has not been elucidated, although several possible pathways have been proposed. Although ethanol itself is not carcinogenic, its major intermediary metabolite, acetaldehyde, is a known carcinogen in animals; alcohol may act as a solvent that enhances the penetration of carcinogens from other environmental sources; the regular intake of alcohol may reduce the intake and bioavailability of certain nutrients that have chemo-preventive properties; and alcohol may directly irritate the esophageal epithelium, creating the potential for ESCC pathogenesis [43].

CONCLUSION

In conclusion, this case-control study shows that the risk of esophagus cancer is strongly associated with alcohol past drinkers, consumption of Zu and both Zu and commercial alcohol, regular drinking from a younger age, longer duration of regular drinking, and increasing amounts of alcohol consumed daily and over lifetime and those who are used to drink alcohol at any time of the day. Higher risk was also observed among those who use to drink in the morning.

CONFLICT OF INTEREST

None declared.

ETHICAL PERMISSIONS

This study was approved by Mizoram Ethics Committee.

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