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Etiology of lung cancer among the Mizo people

Lalpawimawha[1] and B. Lalruatfela[2]*

[1]*Department of Statistics, Pachhunga University College, Aizawl 796001, India*
[2]*Department of Zoology, Mizoram University, Aizawl 796004, India*

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Abstract

According to the National Cancer Registry Programme, Mizoram has the highest cancer incidence among the states of India. Lung cancer has been found to be very common among the Mizos and its etiology has never been scientifically analyzed in this high cancer incidence population. A hospital based case-control study was conducted during March, 2014 to February, 2016. The study involved 106 histologically confirmed lung cancer patients and 212 matched cancer-free subjects acting as controls, all with the same ethnic background, i.e. Mizo. Among the cases, the risk of lung cancer was significantly elevated among ex-smokers (OR, 4.69; 95% CI, 2.36-9.32), but not among current smokers. Higher risks were seen for *zozial* smokers (OR, 2.51; 95% CI, 1.28-4.92). The increased risk was apparent among subjects who had smoked for $\geq$40 years. Exposure to environmental smoke at home and workplace were significantly associated with an increased risk of lung cancer. Higher risk was also observed for previous diagnosis of asthma (OR, 4.62; 95% CI, 1.75-12.23). Lower consumption of alcohol related with decreased risk of lung cancer (OR, 0.87; 95% CI, 0.37-2.05). Tobacco smoking was found to be the primary factor for developing lung cancer. Certain occupations like the transport industry, farming, carpentry or automobile works were found to increase the risk of lung cancer. Prior affliction with tuberculosis might also have the potential to increase the risk. However, low and moderate consumption of alcohol leads to decrease risk of lung cancer.

Key words: Alcohol, etiology, lung cancer, Mizoram, risk, smoking.

Introduction

Cancer is a major health problem all over the world. Lung cancer has been referred to be the leading cause of death from cancer,[1] and its etiology may be age, genetic, environmental, gender, ethnic, hormonal or viral factors.[2,3] The primary factor attributed for the development of lung cancer is tobacco smoking.[4] This does not come as a surprise given that tobacco has been known to contain varieties of carcinogens.[5]

Corresponding author: Lalruatfela
Phone: : +91-9862292744
E-mail: b.atetea@gmail.com

However, since only a small percentage of smokers developed tobacco related lung cancer, differential susceptibility to carcinogens has been suggested and some studies implicated the elderly and women to be more susceptible than the vernal and men respectively.[6-8] Other environmental factors including exposure to radon, asbestos, solid fuel use, environmental tobacco smoke (ETS), cooking oil fumes, etc., have also been attributed to cause lung cancer.[1,9-11]

The state of Mizoram located in the north eastern part of India, in spite of its small population size, has one of the highest records of different forms of cancer not only in India but the world. Among the different districts in India, the district capital of Mizoram, the Aizawl district has the highest age adjusted rate (AAR) of cancer in both males and females. Stomach, lung and cervix are the three most common cancer organs in Mizoram.[12]

The Mizos are the dominant inhabitants of this state and the rate of cancer incidence among them is rather interesting. Despite this, only a handful of researches on cancer have been conducted in this attention demanding state. The dietary pattern of the Mizos, although not the most unique in the area around is noteworthy when it comes to cancer. Many of the Mizo traditional foods as recorded by Lalthanpuii *et al.* require intense analysis of its chemical constituents.[13] From the available data, limited as they are, the amount of tobacco used by the Mizos seemed to have a great influence on the etiology of cancer of certain sites. Many of the Mizos indulged in smoking local cigarette called "*zozial*" and tobacco brew or tobacco smoke-infused water locally called "*tuibur*". The consumption of betel with or without tobacco is very common and they also largely consumed smoked vegetables and meats.[14,15]

We believe this is the first report on the epidemiological study of lung cancer in this high cancer incidence population of Mizoram.

Materials and Methods

The study was a hospital based matched case-control study carried out at Aizawl Civil Hospital and Mizoram State Cancer Institute in Mizoram, India. The hospitals served as a tertiary health care facility and are accessible to patients from all socioeconomic categories. The study included 106 histologically confirmed lung cancer patients diagnosed during March, 2015 to February, 2016. Controls were individually matched to case by gender and age (±5 years) and the ratio of cases and controls was 1:2. In total, we had 212 controls that were cancer free during the investigation. All the cases and controls have the same ethnicity, i.e. Mizo.

A questionnaire was developed and approved by Mizoram State Ethical Committee to study the risk factors of lung cancer, and was translated in the mother tongue of the volunteers. It included questions on smoking habit, exposure to ETS, occupation, cooking practices and workplace exposure. In addition, the questionnaire included detailed questions on demographic characteristics and life time residence.

All the volunteers were asked to fill the consent form and questionnaire by themselves. If there were any reason not to do so, like dire general status, poor vision, pathology of upper extremities or personal wish for assistance of filling out the questionnaire, they were interviewed by trained interviewers.

To minimize errors in quantitative data due to incorrect recall, we used a structured questionnaire in order to collect categorized information. A smoker was defined as someone who had smoked one or more *zozial* (local cigarette) or cigarette or both *zozial* and cigarette per day for at least one year. Smoking during the index year were defined as current smokers; those who reported that they had stopped regular use of smoke the year before the index year or before were defined as ex-smokers, and people who reported that they had never smoked before or during the index year were defined as never-smokers. To assess passive smoking, each individual were asked about lifetime exposure to ETS generated by family member(s) and co-workers. Anyone who lived or worked with smokers and was exposed to tobacco smoke was

considered to be passive smoker. Cumulative tobacco exposure was estimated in pack-years, where a pack is 20 cigarette equivalents. Cooking fuels were categorized as gas, electric stove, wood or charcoal. Workplace exposures to potential lung carcinogens including petrol/diesel exhaust, paints and/or solvent, welding equipment, pesticides, wood dust were dichotomized as exposed or unexposed.

A conditional logistic regression was used to calculate odd ratios (OR), and corresponding 95% confidence interval (CI) for lung cancer in relation to exposure of interest. Test for trend were computed by fitting conditional logistic model to ordinal values representing levels of exposure. The χ^2 test was utilized to calculate the difference between the proportions. The level of significance was set at 5%. All the calculations were performed with software R version 2.10.1 and SPSS version 20 software program.

RESULTS

The distribution of socio-demographic variables of cases and controls are shown in Table 1. The mean age of the cases and controls was 62.51 and 62.24 years respectively. Cases had significantly lower education level and mostly resided in rural area. There was a statistical difference among income group, occupation and

Table 1. Distribution of cases and controls according to socio-demographic factors.

Variable	Category	Cases		Controls		p-value
		n	%	n	%	
Age	≤49	12	11.32	26	12.26	matched
	50-59	23	21.70	45	21.23	
	60-69	41	38.68	83	39.15	
	≥70	30	28.30	58	27.36	
	Mean± SD	62.51-11.20		62.24-11.37		
Sex	Male	62	58.49	131	61.79	matched
	Female	44	41.51	81	38.21	
Residence	Rural	50	47.17	160	75.47	<0.000001
	Urban	56	52.83	52	24.53	
Education level	Illiterate	10	9.43	5	2.36	<0.00001
	Secondary	56	52.83	56	26.42	
	Higher Secondary	32	30.19	55	25.94	
	UG & above	8	7.55	96	45.28	
Income level	Low income	36	33.96	44	20.75	<0.001
	Middle income	60	56.60	113	53.30	
	High income	10	9.43	55	25.94	
Occupation	Office workers	13	12.26	35	16.51	<0.00003
	Farmers	50	47.17	47	22.17	
	Business	19	17.92	67	31.60	
	Others	24	22.64	63	29.72	
Marital status	Married	101	95.28	153	72.17	<0.00001
	Unmarried	5	4.72	59	27.83	

Table 2. Odds ratios (OR) and 95% confidence interval (CI) for lung cancer in relation to smoking habits and environmental tobacco smoke.

Variable	Category	Cases	Controls	Univariate*,OR(95% CI)	Multivariate[ł], adjusted OR (95% CI)
Smoking status	Non smokers	11	108	1(reference)	1(reference)
	Ex-smokers	57	33	6.31(3.70-10.74)	4.69(2.36-9.32)
	Current smokers	38	71	1.11(0.68-1.80)	0.63(0.32-1.24)
Types of smoking	Non smokers	11	108	1(reference)	1(reference)
	Meizial	45	45	2.73(1.64(4.54)	2.51(1.28-4.92)
	Cigarette	18	25	1.53(0.79-2.95)	0.72(0.29-1.81)
	Meizial+Cigarette	32	34	2.26(1.30-3.93)	2.24(1.05-4.77)
Frequency (pieces/day)	Non smokers	11	108	1(reference)	1(reference)
	≤10	33	46	1.63(0.96-2.75)	1.17(0.57-2.37)
	11-15	24	44	1.12(0.63-1.96)	0.76(0.37-1.55)
	≥16	38	14	7.90(4.03-15.47)	6.21(2.54-15.16)
P_{trend}<0.007					
Age began (years)	Non smokers	11	108	1(reference)	1(reference)
	≤15	55	33	5.85(3.43-9.95)	2.50(1.25-4.96)
	16-20	27	36	1.67(0.94-2.94)	1.32(1.06-5.08)
	≥21	13	35	0.71(0.35-1.40)	0.51(0.21-1.26)
P_{trend}<006					
Duration (years)	Non smokers	11	108	1(reference)	1(reference)
	≤29	17	53	0.57(0.31-1.04)	0.51(0.24-1.10)
	30-39	24	15	3.84(1.91-7.69)	2.35(1.01-5.53)
	≥40	54	36	5.07(3.01-8.56)	3.32(1.61-6.49)
P_{trend}<0.010					
Pack years of smoking	Non smokers	11	108	1(reference)	1(reference)
	≤19	22	55	0.74(0.42-1.31)	0.69(0.33-1.43)
	20-29	48	38	3.78(2.25-6.36)	2.03(1.03-4.01)
	≥30	25	11	5.64(2.65-11.99)	3.91(1.52-10.08)
P_{trend}<0.013					
ETS exposure at home	No	11	129	1(reference)	1(reference)
	Childhood	24	24	2.29(1.23-4.27)	2.10(0.98-4.51)
	Adult	17	30	1.15(0.61-2.21)	1.11(0.58-2.14)
	Adult+child	54	29	6.55(3.79-11.31)	6.51(3.38-12.53)

ETS exposure at work(years)	No	8	125	1(reference)	1(reference)
	≤9	32	31	2.52(1.43-4.43)	2.35(1.18-4.67)
	≥10	66	56	4.59(2.79-7.55)	4.38(2.41-7.94)

*Matched (cases and controls were matched for age and sex) univariate estimate by conditional logistic regression analysis.
[ł]AdjustedORs(adjusted for previous medical history, workplace exposure, alcohol consumption, residence ,education level, income level, occupation and marital status) obtained by matched conditional multiple logistic regression analysis using maximum likelihood approach.

Table 3. Odds ratios (OR) and 95% confidence interval (CI) for lung cancer in relation to previous medical history.

Variable	Category	Cases	Controls	Univariate*,OR(95% CI)	Multivariate[ł], adjusted OR (95% CI)
Previous medical history	No	47	162	1(reference)	1(reference)
	Bronchitis	6	10	1.21(0.42-3.42)	1.09(0.27-4.36)
	TB	21	15	3.24(1.59-6.59)	2.11(0.91-4.87)
	Asthma	20	10	4.69(2.11-10.45)	4.62(1.75-12.23)
	Other illness	12	15	1.67(0.75-3.72)	1.64(0.61-4.39)

*Matched (cases and controls were matched for age and sex) univariate estimate by conditional logistic regression analysis.
[ł]Adjusted ORs (adjusted for smoking habits, workplace exposure, alcohol consumption, residence, education level, income level, occupation and marital status) obtained by matched conditional multiple logistic regression analysis using maximum likelihood approach.

Table 4. Odds ratios (OR) and 95% confidence interval (CI) for lung cancer in relation to workplace exposure.

Variable	Category	Cases	Controls	Univariate*,OR(95% CI)	Multivariate[ł], adjusted OR (95% CI)
Diesel smoke	No	95	196	1(reference)	1(reference)
	Yes	11	16	1.45(0.63-3.32)	0.94(0.29-3.06)
Solvent,paint or thinner	No	96	202	1(reference)	1(reference)
	Yes	10	10	2.33(0.92-5.85)	1.30(0.40-4.22)
Welding	No	14	10	1(reference)	1(reference)
	Yes	92	202	3.38(1.43-7.96)	3.16(0.97-10.33)
Pesticides	No	12	16	1(reference)	1(reference)
	Yes	94	196	1.45(0.64-3.27)	1.03(0.35-2.96)
Wood dust	No	12	18	1(reference)	1(reference)
	Yes	94	194	1.39(0.63-3.08)	1.41(0.49-4.05)

*Matched (cases and controls were matched for age and sex) univariate estimate by conditional logistic regression analysis.
[ł]Adjusted ORs (adjusted for smoking habits, workplace exposure, alcohol consumption, residence, education level, income level, occupation and marital status) obtained by matched conditional multiple logistic regression analysis using maximum likelihood approach.

marital status. Therefore, education level, residence, income, occupation and marital status were included into logistic regression model as variables to adjust for.

The ORs were calculated using non-smokers as reference group to see the association of smoking (Table 2). The ORs of ex-smokers (OR, 4.69; 95% CI, 2.36-9.32) was found to be statistically significant compared with current smokers after controlling other habits and co-factors in a multivariate model and a significant risk had been observed, indicating independent effect on the development of lung cancer. Statistically significant higher risks were observed for *zozial* (local cigarette) smokers (OR, 2.51; 95% CI, 1.28-4.92) in the multivariate model in comparison to cigarette and both *zozial* and cigarette smokers. Overall, the excess risk was limited to smokers of >16 *zozial* per day. Increased risk was also observed when age began of smoking decreased. Risk also tended to increase with duration and pack years, with an OR of ~3 among smokers of ≥40 years and those who smoked ≥30 pack-years. Exposure to ETS (at home and at work for more than 10 years) showed significant increase in risk for lung cancer (adjusted OR, 6.5; 95% CI, 3.38-12.53 and OR, 4.38; 95% CI, 2.41-7.94).

The risk of lung cancer and previous medical history is shown in Table 3. A significant higher risk of lung cancer was observed among patients with previous diagnosis of asthma after adjusting for cooking fuels, smoking habits, workplace exposure, alcohol consumption, residence, educational level, income level, occupation and marital status in the multivariate model (OR, 4.62; 95% CI, 1.75-12.23). The association of lung cancer and various workplace exposures is show in Table 4. After controlling for cooking fuels, smoking habits, previous medical history, alcohol consumption, residence, educational level, income level, occupation and marital status, a higher risk of lung cancer was seen among workshop welders (OR, 3.16; 95% CI, 0.97-10.33) in the multivariate model.

The relationship between lung cancer and alcohol consumption is given in Table 5. Interestingly a decreased risk of lung cancer was seen among alcohol drinkers. But, significant dose-response effects were observed as the intensity of alcohol consumed per week (OR, 1.01; 95% CI, 0.41-2.46) and duration in years increases (OR, 1.16; 95% CI, 0.41-3.30) and decreasing trend was observed for the increase in age started in the multivariate model with a statistically significant trend (P<0.026) indicating independent effect of the habit.

DISCUSSION

In this study, as expected, we found that tobacco smoking is the primary factor for the development of lung cancer. However, smoking of the local cigarette *zozial* seemed to have a more profound contribution on the risk than smoking branded cigarette alone or in combination with *zozial*. It would be very interesting to direct future research to determine the chemical constituents of *zozial*. The contribution of tobacco smoking does not come as a surprise given that tobacco is a well known carcinogen and many smoking and smokeless tobaccos have been known to cause many forms of cancer. In fact, many studies suggested tobacco smoking as the primary cause of lung cancer.[5,9] Other studies have shown that the duration and quantity of cigarettes smoked seemed to have a positive relationship with lung carcinogenesis. The risk of lung cancer for smokers has been shown to increase as the number of cigarettes smoked increased.[16-18] These findings are in agreement to ours where we suggested that the duration and number of pack years seemed to have a direct correlation to the risk of lung cancer. The age at which a person started smoking has also been found to be inversely correlated with the risk. Similar to our findings, Hegmann *et al.* also showed that men who began to smoke before the age of 20 had a higher risk of developing lung cancer than men who started smoking at the age of 20 or older.[19]

Even though the use of tobacco has been characterized as the primary cause of lung cancer, many non-smokers have also developed the

Table 5. Odds ratios (OR) and 95% confidence interval (CI) for lung cancer in relation to alcohol consumption.

Variable	Category	Cases	Controls	Univariate*,OR(95% CI)	Multivariate[ł], adjusted OR (95% CI)
Alcohol Drinking status	Non drinkers	73	146	1(reference)	1(reference)
	Past drinkers	33	66	0.97(0.59-1.61)	0.94(0.46-1.92)
Dosage (cup/week)	Non drinkers	73	146	1(reference)	1(reference)
	≤5	18	39	0.91(0.49-1.71)	0.87(0.37-2.05)
	≥6	15	27	1.06(0.53-2.12)	1.01(0.41-2.46)
P_{trend}<0.022					
Age began (years)	Non drinkers	73	146	1(reference)	1(reference)
	≤17	21	40	1.03(0.57-1.85)	0.89(0.40-1.95)
	≥18	12	26	0.91(0.44-1.89)	0.82(0.32-2.08)
P_{trend}<0.026					
Duration (years)	Non drinkers	73	146	1(reference)	1(reference)
	≤20	10	17	0.79(0.37-1.66)	0.43(0.15-1.21)
	21-30	11	26	1.04(0.50-2.20)	0.97(0.37-2.55)
	≥31	12	23	1.19(0.52-2.70)	1.16(0.41-3.30)
P_{trend}<0.0001					

*Matched (cases and controls were matched for age and sex) univariate estimate by conditional logistic regression analysis.
[ł]Adjusted ORs (adjusted for smoking habits, previous medical history, workplace exposure, residence, education level, income level, occupation and marital status) obtained by matched conditional multiple logistic regression analysis using maximum likelihood approach.

disease suggesting the involvement of other environmental carcinogens in the course of lung carcinogenesis.[20] The other risk factors for lung cancer include exposure to ETS, radon, asbestos, traffic gas combustion, indoor air pollution like cooking-oil fumes and coal burning, family history of cancer, dietary factors, etc.[2, 9, 10]

Exposure to ETS, or otherwise called passive smoking is an established risk factor of lung cancer among non-smoking individuals.[21] Non-smoking wives of heavy smokers, or non-smokers living with smokers were found to have higher risk of developing lung cancer when compared with a completely unexposed group.[22,23] Exposure to ETS not only at home but also at the workplace has been found to be positively associated with lung cancer risk. Exposure to ETS has also been associated with bronchitis, pneumonia, reduced pulmonary function and acute respiratory disease in children.[11,21] Pfeifer showed that benzopyrene, a constituent of tobacco smoke, has the ability to cause mutations in the tumor suppressor p53 gene.[24] These studies might explain our findings that showed that exposure to ETS at home and at work for more than 10 years showed an increase lung cancer risk. Contrastingly, it has also been proposed that ETS may not have any significant association with lung cancer or any other form of pulmonary diseases.[25]

There are number of studies that supported the construct that prior affliction with any form of pulmonary diseases like asthma, chronic bronchitis, pneumonia, and tuberculosis might

be a predisposition to lung cancer; however, a more conclusive confirmation is required.[26,27] Among smokers, infection with *Chlamydophilia pneumonia* and chronic bronchitis has been found to been an independent risk factor for the etiology of lung cancer.[28] However, it has also been argued that the possible association between cancer and other pulmonary diseases might perhaps be a sheer coincidence without any significant correlation; merely metastatic tumor and other diseases developing subsequently or at the same time.[29] In this study, we found a positive association of lung cancer and prior affliction with asthma but not with other pulmonary diseases under consideration.

Certain occupations have been suggested to be linked with lung cancer.[30] Occupations involving frequent exposure to pesticides and diesel engine exhaust were known to pose higher lung cancer risk.[31,32] In the present study, however, even though our evaluation involved such professions, a positive association with lung cancer has been found among workshop welders. Depending on the materials and process employed, welding fumes have been known to contain oxides of metals as Chromium, Nickel, Iron, Manganese, Zinc, Aluminum, Cadmium, Copper, Lead, Fluoride, Silicon, Barium, Magnesium, Calcium and Tin.[33] The International Agency for Research on Cancer has concluded welding fumes as possibly carcinogenic to human. Chromium and Nickel present in stainless steel welding fumes have been shown to increase the level of DNA damage[35] and a case-control study has referred both stainless and mild steel welding to equally contribute to the risk of lung cancer.[36]

Our analysis on the relationship between lung cancer and alcohol consumption showed that an increase in alcohol consumption and duration presented a significant increase in lung cancer risk. This risk, however, decreased as the age at which a person started drinking increased. Interestingly, our data have also showed that light or moderate drinkers (≤5 cups/week) have a lower lung cancer risk than the non-drinking reference group. We would not be surprised to see an insignificant association between moderate alcohol consumption and lung cancer risk, but the protective effect of moderate drinking as in this result, we must admit, is totally unexpected. Other cohort and hospital based case-control studies found that only very high consumption of alcohol had an association with lung cancer.[37-39] However, other studies did not agree the involvement of alcohol in the etiology of lung cancer.[19,24]

In this epidemiological study, tobacco smoking was found to be the primary cause of lung cancer. A more detail analysis showed that smoking *zozial* had a more profound contribution on lung cancer risk than smoking branded cigarettes alone or in combination with *zozial*. Increased smoking duration and pack years also have a direct correlation to lung cancer. The age at which a person started smoking was found to be inversely correlated to the risk. Exposure to ETS at home or at work for more than 10 years showed an increased in lung cancer risk. A positive association was also observed for lung cancer and prior affliction with asthma. Among the occupations studied, only workshop welders were found to have a higher probability of developing lung cancer. Increased alcohol consumption and duration showed an increased risk of lung cancer. However, this risk was found to decrease as the age at which a person started alcohol consumption increased. Fascinatingly, moderate consumption of alcohol was found to have a protective effect on lung cancer.

A possible drawback of this study is that the cases and controls were not interacted under the same condition. Many of the cases, if not all, were interviewed at the inward patient departments of the hospitals, while controls were interviewed either at the outward patient departments or at their homes. To determine the familial inheritance of any form of cancer in this high cancer incidence population would be most interesting. But we found the probability of obtaining false positive result to be enormous because a non-official source reported that most of the Mizos have either a first or second degree relationship with probands (cancer patients). This

report, nonetheless, must be validated. However, if such is the circumstance, we strongly suggest the scientific community to further investigate this population.

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