RESEARCH ARTICLE

Risk Factors for Lung Cancer in the Pakistani Population

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Abstract

Background: Lung cancer is one of the most prevalent malignancies in the world and both incidence and mortality rates are continuing to rise in Pakistan. However, epidemiological studies to identify common lung cancer determinants in the Pakistani population have been limited. Materials and Methods: In this retrospective case-control study, 400 cases and 800 controls were enrolled from different hospitals of all provinces of Pakistan. Information about socio-demographic, occupational, lifestyle and dietary variables was extracted by questionnaire from all subjects. Odd ratios (ORs) and 95% confidence intervals (CIs) were calculated. and dose-response associations were also assessed for suitable factors. Results: Strong associations were observed for smoking (OR=9.4, 95%CI=6.9-12.8), pesticide exposure (OR=5.1, 95%CI=3.1-8.3), exposure to diesel exhaust (OR=3.1, 95%CI=2.1-4.5), red meat consumption (OR=2.9, 95%CI=1.8-4.7) and chicken consumption (OR=2.8, 95%CI=1.7-49). Other associated factors observed were welding fumes (OR=2.5, 95%CI=1.0-6.5), sedentary living (OR=2.0, 95%CI=1.6-2.6), family history (OR=2.0, 95%CI=0.8-4.9), wood dust (OR=1.9, 95%CI=1.2-3.1), tea consumption (OR=1.8, 95%CI=1.2-2.6), coffee consumption (OR=1.8, 95%CI=1.1-2.8), alcoholism (OR=1.7, 95%CI=1.1-2.5) and asbestos exposure(OR=1.5, 95%CI=0.5-4.4). Consumption of vegetables (OR=0.3, 95%CI=0.2-0.4), juices (OR=0.3, 95%CI=0.3-0.4), fruits (OR=0.7, 95%CI=0.5-0.9) and milk (OR=0.6, 95%CI=0.5-0.8) showed reduction in risk of lung cancer. Strongest dose-response relationships were observed for smoking (X^2=333.8, p≤0.0000001), pesticide exposure (X^2=50.9, p≤0.0000001) and exposure to diesel exhaust (X^2=51.8, p≤0.0000001). Conclusions: Smoking, pesticide exposure, diesel exhaust and meat consumption are main lung cancer determinants in Pakistan. Consuming vegetables, fruits, milk and juices can reduce the risk of lung cancer risk, as in other countries.

Keywords: Risk factors - occupational factor - dietary factors - lung cancer - Pakistan

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Introduction

Lung cancer is one of the most prevalent malignancies in the world (Wahab et al., 2007; Tas et al., 2008). Incidence and mortality rates due to lung cancer are continuing to increase in developing countries like Pakistan (Lam, 2005), which is contrary to the situation in many developed countries, where it is showing declining trend (Kwong et al., 2005; Wahab at al., 2007). Genetic, non-genetic determinants and late detection are important reasons for high mortality rates due to lung cancer (Ahmed at al., 2013).

In Pakistan, it is most frequent malignancy in males and incident rate is also increasing in females (Hussain et al., 2009). Lung cancer has been well co-related with smoking but high frequency of lung cancers cases (25%) are non-smokers (Sun et al., 2007). Development of malignancy of lung is a multifactorial interacting process. Many suspect factors including life style, social and also filial factors are contributory causes for development of lung cancer in non-smokers. Humans are exposed to organic and inorganic pollutant through environmental and occupational sources. Epidemiological evidences shows link between exposure to occupational and non-occupational pollutants and risk of cancer (Bruske et al., 2000). The main occupational exposures occur in workers who are engaged in smelting and refining of metals, production of pesticides, pigments, dyes, glass, semiconductors, wood/cotton products and various pharmaceutical substances (Ferreccio et al., 2000). Non-occupational exposures mostly occur due to outdoor air pollution including residence near major industrial emission sources, asbestos, in-door air pollution, arsenic in drinking water, chlorinated by-products in drinking water, dioxins and electromagnetic fields (IARC, 1994; Ferreccio et al., 2000).

Many studies has have shown that environmental and

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genetic factors interactively play their role in development of lung cancer (Bailey, 2004). Lung cancer susceptibility genes have also been identified (Bailey, 2004), making certain individuals more susceptible to lung cancer over exposure to environmental factors than others.

Smoking trend is increasing in Pakistan. Tobacco is being used in the form of high tar cigarettes, hukka, cigar, shisha, biri and pan in Pakistan (Alam, 1998). Growing incidence of lung cancer in non-smokers suggests that population is bare to several types of other environmental risk factors like lifestyle, dietary and occupational exposures. No epidemiological study to evaluate these common risk factors for lung cancer in Pakistani population has been reported. The current study is preliminary effort to evaluate these determinants for lung cancer in this country.

Materials and Methods

In this case-control study, 400 cases (histologically confirmed lung cancer patients) from all over the Pakistan were enrolled from various public and private sector hospitals and health centers during 2010 to 2013. Subjects were briefed about the study and their written consent was taken on consent form. Agreed subjects were interviewed and data was recorded in the pre-designed questionnaire. The questionnaire body was composed of questions regarding age, sex, education, occupational exposure, tobacco smoking/chewing habits, alcoholism, physical activity, geographical location, family history, chronic respiratory diseases and dietary habits. Total 800 Hospital controls were also enrolled in the study after their written consent. Controls were free of all types of cancers and any chronic respiratory ailments. Odds ratio, its 95% confidence interval, X^2 value and p values were calculated by using EpiTools Epidemiological Calculator (Sergeant 2014). Doze response analysis was performed for suitable risk factors to find out chi-square value for linear tren d and p value for one degree of freedom by using

Results and Discussion

Socio-demographic features of the participants (Table 1)

Out of 400 cases, 282 were male and 118 were female. Among controls 589 were male and 211 were female. Study participants were belonging to all five provinces of Pakistan and Azad Jammu and Kashmir (AJK). Maximum numbers of cases were collected from Sindh (132) and then Punjab (119), KPK (71), Balochistan (55) and AJK (22). It was our effort to collect controls from all these provinces and AJK with similar proportion to cases. Religious affiliations of the cases were very much comparable to their proportion in the population. Majority of the cases and controls were literate, but overall controls were having more literacy rate (81.25) than cases (76.25). High frequency of lung cancer cases (89.50%) was belonging to the age group of 50-70 years. 9.25% of the cases were belonging to age group of >70 years and only 1.25% of the cases were less than 50 years of age. Most of the participants both in cases and controls were married (almost 98%). Similar pattern of gender, race and education differences among cases and controls in this region has been observed in Nepal (Hashibe et al., 2010) and in Kerala, India (Bhaskarapillai et al., 2012).

Majority of the variables studied were showing

Table 1. Socio-Demographic Features of the Subjects

Variables		Total No. %	Cases No. %	Controls No. %
Age	<40	2 (00.16)	2 (00.50)	0 (00.00)
	40-50	7 (00.58)	3 (00.75)	4 (00.50)
	50-60	642 (53.50)	211 (52.75)	431 (58.88)
	60-70	411 (34.25)	147 (36.75)	264 (33.00)
	>70	138 (11.50)	37 (09.25)	101 (12.62)
Gender	Males	871 (72.58)	282 (70.50)	589 (73.63)
	Females	329 (27.42)	118 (29.50)	211 (26.37)
Marital status	Single	20 (01.67)	8 (02.00)	12 (01.50)
	Married	1180 (98.33)	392 (98.00)	788 (98.50)
Province	Punjab	390 (32.50)	119 (29.75)	271 (33.88)
	Sindh	434 (36.17)	132 (33.0)	302 (37.75)
	KPK	174 (14.50)	71 (17.75)	103 (12.88)
	Balochistan	135 (11.25)	55 (13.75)	80 (10.00)
	AJK	67 (05.58)	23 (05.75)	44 (05.50)
Religion	Muslim	1141 (95.09)	382 (95.5)	759 (94.87)
	Christian	40 (03.33)	11 (02.75)	29 (03.63)
	Others	19 (01.58)	7 (01.75)	12 (01.50)
Literacy	literate	955 (79.58)	305 (76.25)	650 (81.25)
	Illiterate	245 (20.42)	95 (23.75)	150 (18.75)

Table 2. Association Measurement of Risk Factors

Factors: Exposed		Cases (400)	Controls (800)	OR*	95%CI	p value**
Tobacco smoking:	Yes	337	290	9.4	6.9-12.8	<0.0001
	No	63	510			
Tobacco chewing:	Yes	70	124	1.2	0.8-1.6	0.3750
	No	330	676			
Sedentary living:	Yes	186	242	2	1.6-2.6	<0.0001
	No	214	558			
Chlorinated water:	Yes	210	382	1.2	1.0-1.5	0.1208
	No	190	418			
Meat (Red) consumption:						
	Yes	378	684	2.9	1.8-4.7	<0.0001
	No	22	116			
Chicken consumption:	Yes	384	715	2.8	1.7-4.9	<0.0001
	No	16	85			
Alcohol consumption:	Yes	50	62	1.7	1.1-2.5	0.0077
	No	350	738			
Vegetable consumption:	Yes	302	728	0.3	0.2-0.4	<0.0001
	No	98	72			
Fruit consumption:	Yes	296	642	0.7	0.5-0.9	0.0135
	No	104	158			
Juices consumption:	Yes	226	638	0.3	0.3-0.4	<0.0001
	No	174	162			
Tea consumption:	Yes	362	674	1.8	1.2-2.6	0.0003
	No	38	126			
Coffee consumption:	Yes	36	42	1.8	1.1-2.8	0.0013
	No	364	758			
Milk consumption:	Yes	246	586	0.6	0.5-0.8	<0.0001
	No	154	214			
Pesticide exposure:	Yes	54	24	5.1	3.1-8.3	<0.0001
	No	346	776			
Wood dust worker:	Yes	32	35	1.9	1.2-3.1	0.0099
	No	368	765			
Welding fumes:	Yes	10	8	2.5	1.0-6.5	0.0439
	No	390	792			
Asbestos/silicon:	Yes	6	8	1.5	0.5-4.4	0.4470
	No	394	792			
Diesel exhaust at work place:						
	Yes	64	47	3.1	2.1-4.5	<0.0001
	No	336	753			
Family history:	Yes	10	10	2	0.8-4.9	0.1108
	No	390	790			

*Reference value for OR is=1; **chi-square test

positive association with lung cancer with varying degree of strength (Table 2). However some variables have shown preventive association and some others have shown very weak or no association.

Causative factors

Tobacco smoking has shown most strong association with lung cancer (OR=9.4, p≤0.0001) in Pakistani population, which means that smokers in Pakistan are almost 9-10 times at higher risk lung cancer. This outcome is analogous to the previous results of global and regional research on lung cancer (IARC, 1994; Stellman et al., 2001; Hussain et al., 2009; Ganesh et al., 2011., Matteis, 2013). But the current value of OR is among the highest values observed in any segment of population in Asia. High values of association with smoking is depicting factual picture of increasing lung cancer in Pakistan, where high percentage of population is smokers and smoking habit is on the rise (Alam, 1998). It is worth mentioning that Pakistani cigarettes have high tar contents than other countries in the world (Alam, 1998).

Other variable which have shown strong association with lung cancer was pesticide exposure (OR=5.0, p≤0.0001). Status of pesticide exposure as causative factor is not easy to conclude from the past studies (Pesatori et al., 1994; Menvielle et al., 2003; Michael et al., 2004; Michael et al., 2013). In the studies carried out on Caucasian and Asian populations, some of the results presented no association while others have shown positive association. Current high value for this variable strengthens the results which have documented this factor as causative one. Being an agricultural country 40% of rural population is directly related with agriculture profession in Pakistan. Pesticide use without protective measures is common practice. Similarly individuals involved in manufacturing and packing are 5 times at higher risk to get lung cancer.

Exposure to diesel exhaust has also shown a three times higher risk of lung cancer than unexposed (OR=3.1, p≤0.0001). Several studies have found that long-term, heavy exposure to diesel exhaust can cause lung cancer in lab animals (Mauderly et al., 1987) and it has also been documented as an established human carcinogen (IARC, 2012). Though many studies have found a modest link between diesel exhaust exposure and lung cancer, some have reported no link between them (Garshick et al., 1987; Steenland et al., 1990; 1998; Attfield et al., 2012). The current study has shown a solid link between lung cancer and exposure to diesel exhaust at work place in Pakistani population.

Red meat consumers are three times at higher risk of lung cancer (OR=2.9, p≤0.0001). Some of previous studies have also reported this a causative variable (Alavanja et al., 2001; Lam et al., 2009; Yang et al., 2012; Gnagnarella et al., 2013), but OR values was much lower as compared to present study. Per capita Red meat consumption in Pakistan is higher than its neighboring countries like India and Afghanistan. Similarly significant association of chicken consumption with lung cancer has been observed (OR=2.8, p≤0.0001). Although some of the earlier studies had reported this variable as preventive factor for lung cancer (Lim et al., 2011), currently it is reported as causative factor in Asian populations.

Other associated factors observed were welding fumes (OR=2.5, 95%CI=1.0-6.5), sedentary living (OR=2.0, 95%CI=1.6-2.6), family history (OR=2.0, 95%CI=0.8-4.9), wood dust (OR=1.9, 95%CI=1.2-3.1), tea consumption (OR=1.8, 95%CI=1.2-2.6), coffee consumption (OR=1.8, 95%CI=1.1-2.8), alcoholism (OR=1.7, 95%CI=1.1-2.5) and asbestos (OR=1.5, 95%CI=0.5-4.4). Exposure to welding fumes at work place (Mannetje et al., 2012), cooking fumes (Yin et al., 2013), sedentary living (Yang et al., 2003), family history (Cote et al., 2012), exposure to wood dust (Bhatti et al., 2011), alcoholism (Bagnardi et al., 2010) and asbestos exposure (Markowitz et al., 2013) has also been reported in Caucasian, American, African and Asian populations as positive risk factors of lung cancer. But high OR value of 2.5 in Pakistani population for welding fumes in present study is higher than any other parts of the world.

Status of tea and coffee consumption as a risk factor of lung cancer is not clear. In many parts of the world tea and coffee consumption has been reported as causative factors (Baker et al., 2005; Tang et al., 2010), some others have reported them as preventive factors (Wu et al., 2006; Tand et al., 2009) and still some of the reports has shown no link between coffee and tea consumption with lung cancer (Baker et al., 2005). Current study has documented it as an important risk factor in Pakistani population, where per capita tea consumption is 1kg/year, which is among the highest values of the world.

In the present study, tobacco chewing in the form of Pan/Biri (OR=1.2, 95%CI=0.8-1.6, p=0.3750) and drinking chlorinated water (OR=1.2, 95%CI=1.0-1.5, p=0.1208) has shown weak or no association with lung cancer in Pakistani population.

Preventive factors

Use of vegetable (OR=0.3, 95%CI=0.2-0.4), juices (OR=0.3, 95%CI=0.3-0.4), fruits (OR=0.7, 95%CI=0.5-0.9) and milk (OR=0.6, 95%CI=0.5-0.8) has shown reduction in risk of lung cancer in Pakistani population. These results for vegetables and juices as preventive factors are in line with finding of many regional and global research (Wright et al., 2003; Mannisto et al., 2004) . Status of milk consumption as a preventive factor for lung cancer is debatable. Some earlier epidemiological studies have documented it as a causative factor and some other studies have recognized it as a preventive factor (Axelsson et al., 2002; Ahn et al., 2007; Davoodi et al., 2013). Current study strengthens the role of this suspect determinant as a preventive variable.

Dose-response relationships

Strong dose-response relationship has been observed for smoking (X^2=333.8, p≤0.0000001), pesticide exposure (X^2=50.9, p≤0.0000001) and exposure to diesel exhaust (X^2=51.8, p≤0.0000001) in Pakistani population (Table 3). Strongly positive dose-response relationship has been observed for smoking with multifold increase in lung cancer risk with increase in exposure period. Current findings are analogous to the results reported from Indian population (Ganesh et al., 2011). In the present study, odds

Table 3. Exposure-Response Association Chi-Square for Linear Trend

Factor	Period of exposure (years)	Cases n=400	Controls n=800	OR	Chi-square*	p value
Smoking						
0	No	63	510	1	333.8	<0.0000001
1	41647	29	70	3.4		
2	41898	71	112	5.1		
3	17-24	99	66	12.1		
4	>24	138	42	26.6		
Pesticides						
0	No	346	776	1	50.9	<0.0000001
1	41647	9	8	2.5		
2	41898	11	6	4.1		
3	17-24	15	6	5.6		
4	>24	19	4	10.7		
Diesel exhaust at work place						
0	No	336	753	1	51.8	<0.0000001
1	41647	4	18	0.5		
2	41898	14	13	2.4		
3	17-24	22	12	4.1		
4	>24	24	4	13.5		

*Extended Mantel-Haenszel chi square for linear trend

ratio for 1-8 year smoking period was observed to be 3.4, which increased to 5.1 and 12.1 when exposure period was doubled and tripled up to 16 and 24 years respectively. For the exposure history of more than 24 years, OR was recorded as 26.6. OR for pesticide exposure was recorded as 2.5, 4.1 and 5.6 for exposure periods of up to 8, 16 and 24 years respectively. Then for exposure history of more than 24 years, OR has increased to 10.7. Similarly increase in lung cancer risk with increase in exposure period has been observed for diesel exhaust. Risk increased from 0.5 to 13.5 times for diesel exhaust when exposure period increased from up to 8 years to more than 24 years with linear trend for intervening doses. Uniquely, risk of lung cancer has increases dramatically in Pakistani population for smoking, pesticides and diesel exhaust when exposure period increased from 24 years.

In conclusion, tobacco smoking, pesticide exposure, exposure to diesel exhaust, red meat and chicken consumption are leading lung cancer determinants in the Pakistani population. Other important variables were welding fumes, sedentary living, family history, wood dust, tea/coffee consumption, alcoholism and asbestos exposure. Lung cancer risk increases considerably as the period of exposure to certain variables like smoking, pesticide exposure, and diesel exhaust increases. Use of vegetable, juices, fruits and milk are preventive factors in Pakistani population. Healthy life style, active living with no smoking and alcoholism, using safety measures against pollutants at work place and consuming vegetables, fruits, milk and juices can reduce the risk of lung cancer risks in Pakistani population.

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