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Environmental risk factors for lung cancer in Iran: a case–control study

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Background Lung cancer remains the leading cause of cancer death in the world. In Iran, lung cancer is one of the five leading tumours and its incidence has been increasing steadily in both men and women. There is a paucity of data from Iran on risk factors for lung cancer. We evaluated environmental risk factors for lung cancer in a case–control study in five hospitals of Tehran.

Methods Between October 2002 and October 2005, 242 (178 male, 64 female) patients with histologically confirmed lung cancer and two controls for each patient (242 hospital controls and 242 visiting healthy controls) matched for age, sex and place of residence were interviewed using a structured questionnaire on potential risk factors for lung cancer, including environmental and occupational exposures. Associations between risk factors and lung cancer were assessed using conditional logistic regression.

Results Smokers were 66.5% of all cases (85.4% of men and 14.1% of women) and smoking was the strongest correlate of lung cancer in multivariate analysis [odds ratio (OR) 5.4, 95% confidence interval (CI) 3.2–8.9]. Occupational exposures to inorganic dusts (OR 4.2, 95% CI 2.8–6.7), chemical compounds (OR = 3.4, 95% CI 2.1–5.6) and heavy metals (OR 3.0, 95% CI 1.3–7.0) were also independent risk factors for lung cancer.

Conclusions In our study, smoking was the principal risk factor for lung cancer. However, preventable exposures in the environment, including occupational settings, should not be ignored.

Keywords Lung cancer, risk factors, smoking, environmental exposures, Iran

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Introduction

Lung cancer remains the leading cause of cancer death in the world with an estimated 160 390 deaths in the USA alone in 2007.[1] Almost half of known cases occur in developing countries. Worldwide, the highest incidence rates are reported from North America and Europe. Moderately high rates are also seen in Australia/New Zealand and eastern Asia (primarily China and Japan). To date, the rate of lung cancer has been relatively low in Iran.[2]

In recent years, however, cancer has become the third major cause of mortality in Iran after cardiovascular disease and accidents.[3] Lung cancer is one of the five leading tumours in Iran, and the rate has been increasing steadily in both men and women, similar to trends in Southern and Eastern Europe.[2,3] The trend is likely linked to marked changes in lifestyle and the distribution of risk factors in the population in the last 30 years.[4] In contrast, the USA and many countries in Northern and Western Europe have now passed the peak of the lung cancer epidemic, and incidence rates are now declining.[2] Despite some improvements in treatment, the prognosis for lung cancer remains poor with an estimated 5-year survival rate of 10–15% in all stages together. Primary preventive measures and research on environmental causes of lung cancer, therefore, remain of paramount importance.[5]

Epidemiological studies indicate that most lung cancer can be explained by external environmental or behavioural factors. Of these, cigarette smoking is the main risk factor.[6] Passive smoking, occupational exposure to carcinogens, ambient air pollutants and cooking fuels are other risk factors that may independently cause lung cancer. The significance of each of these factors appears to vary with sex, country and region within a given country.[6–9] Although the epidemiology of lung cancer has been extensively investigated for over 50 years, there are still active areas of research. For example, active investigation continues on the links between lung cancer and diet and pollutants. There will also be continuing need for research to track the risks of smoking over time as the design and yields of tar and nicotine in tobacco products have changed greatly since the 1950s.[6]

There is a particular paucity of data from Iran on the causative risk factors for lung cancer. In the present study, we present the results of the first analytic study on environmental risk factors of lung cancer in Iran.

Materials and methods

Two hundred and forty-two lung cancer cases were consecutively recruited among the patients with histologically and cytologically confirmed primary lung cancer in five university hospitals located in different geographical areas in Tehran, Iran, between October 2002 and October 2005. Patients were from different economical, social and educational status. There were no differences in probability of being taken to hospital as cases between men and women.

Cases were eligible if the following conditions were met: (i) the diagnosis of lung cancer was histologically and cytologically confirmed; (ii) they were well enough to undergo an interview of 1.5 h duration; and (iii) there was no suspicion of pulmonary metastases from a different primary tumour. One trained pathologist determined the tumour histology according to World Health Organization (WHO) guidelines[10] as adenocarcinoma, squamous cell carcinoma, small cell carcinoma, other non-small cell carcinoma, and others that included a few large cell carcinomas, mixed types, and when no classification was possible. Four pulmonologists and radiologists performed clinical staging according to the characteristics of primary tumor (T), regional lymph node involvement (N), and metastasis (M) (TNM) classification of the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre Le Cancer (UICC).[11] A total of 265 eligible lung cancer cases were identified. Of these, 11 patients had died or were discharged by the time the interviewers visited the wards, five were too ill to participate, and seven declined to be interviewed (91.3% participation rate).

For each lung cancer case, two controls were drawn matched on sex, age (± 3 years) and place of residence, one in-house patient and one healthy visitor. The first control group comprised patients treated at the hospitals, excluding those with neoplasms and respiratory diseases. The second control group comprised healthy persons visiting patients other than the cases, other cancer patients or the in-patient controls. Overall, 47 potential controls declined to be interviewed (91.1% participation rate). The study was approved by Ethics Review Committee (ERC) of the National Research Institute of Tuberculosis and Lung Disease (NRITLD).

After informed consent, interviews were conducted for all participants by physicians who were specifically trained for this study at the NRITLD. A detailed structured questionnaire was used to determine basic demographic characteristics, active smoking history, exposure to passive smoking, family history of lung cancer, exposure to known and suspected occupational lung carcinogens, and domestic exposure to traditional heating or cooking substances. Participants were defined as smokers if they had ever smoked regularly (at least one cigarette per day for 6 months). Pack-years were calculated as a cumulative dose categorized into three levels (1–19, 20–39 and $\geqslant 40$ pack-years). We assessed exposure to passive smoking from several sources, including parents, siblings, spouses, co-workers, and from persons in public settings. Participants were also asked detailed questions about workplace conditions and specific exposures to known and suspected occupational

lung carcinogens.[12] History of lung cancer among parents and siblings was gathered, including age at disease diagnosis and relation to the subject. These data could not be validated by death certificate, and information on the smoking habits of relatives was not obtained. Participants were classified as having a family history if at least one first degree relative (father, mother, brother, daughter or son) had lung cancer.

Data were entered in Epi-Info (6.04) and analysed using STATA (8.0). After preliminary description of the data, bivariate conditional logistic regression analyses assessed associations between lung cancer and risk factors. Potentially important risk factors at a $P \leqslant 0.10$ were considered in multivariate conditional logistic regression analysis and retained as independent predictors at a $P < 0.05$. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated in bivariate and multivariate models.

Results

During the 3-year study period, 242 consecutive patients with histologically proven lung cancer and their two controls (242 hospital controls and 242 healthy visiting controls) matched for age, sex and place of residence were enrolled (Table 1). As fixed by matching, the average age of lung cancer cases (59.9 ± 13.0 years) was similar to hospital controls (59.5 ± 12.7) and healthy visiting controls (59.2 ± 12.9). Most cases and controls (73.6%) were men, although women developed disease at an earlier age (55.9 ± 14.2 vs 61.3 ± 12.3 years, $P = 0.004$). Cases were more likely to be unmarried (i.e. divorced, widowed or single) (OR 2.0, 95% CI 1.1–3.8, $P = 0.03$). In bivariate analysis, lower education was associated with lung cancer (OR 2.3, 95% CI 1.6–3.2, $P < 0.001$), with 52.1% of cases having <5 years of schooling. In this study, 11.6% of the cases had a family history of lung cancer, with a significant inverse association (OR 0.5, 95% CI 0.3–0.8, $P = 0.005$). The proportion of fathers, mothers, brothers, sisters and daughters who had lung cancer were 32, 18, 28, 18 and 4%, respectively.

Among cases, 85.4% of men and 14.1% of women (overall 66.5%) were smokers compared with 52.2 and 7.1% of controls, respectively (Table 2). Most male smoking lung cancer patients (72.9%) had cigarette consumption >20 pack-years. The OR for cumulative lifetime consumption of cigarettes among smokers showed a steep gradient, especially for men. Also, 76.3% of lung cancer patients who had exposure to passive smoke were females. Among cases, 15.3% were oral opium users, whereas only 9.1% of hospital controls and 5.8% of healthy visitor controls had a history of opium use (overall 7.4%). The OR for opium use and lung cancer was 2.2 (95% CI 1.4–3.6, $P = 0.001$).

Associations of lung cancer with occupational and environmental exposures are shown in Table 3. In bivariate analysis, exposure to inorganic dusts ($P < 0.001$), chemical compounds (including detergents, cleaners, disinfectants and bleaching agents) ($P < 0.001$) and heavy metals ($P = 0.003$) were significantly associated with lung cancer. In addition, among non-smoking lung cancer patients, exposure to inorganic dusts ($P = 0.01$) and chemical compounds ($P = 0.01$) remained risk factors. Wood and kerosene, the most common fuels used for cooking and heating, were not associated with lung cancer (OR 1.43, 95% CI 0.86–2.35; $P = 0.16$). In multivariate analysis, cigarette smoking (OR 5.4, 95% CI 3.2–8.9), exposure to inorganic dusts (OR 4.2, 95% CI 2.8–6.7), chemical compounds (OR 3.4, 95% CI 2.1–5.6), heavy metals (OR 3.0, 95% CI 1.3–7.0) and family history of lung cancer (OR 0.58, 95% CI 0.34–0.99) remained as significant independent risk factors.

The distribution of the cases of lung cancer by histological type, sex and smoking status is shown in Table 4. According to histology, 70 (28.9%) cases were adenocarcinomas, 46 (19.0%) were squamous cell carcinomas, 69 (28.5%) were non-small cell carcinomas, 45 (18.6%) were small cell carcinomas and 12 (5.0%) were classified as other. Squamous cell carcinoma, small cell carcinoma and adenocarcinoma tumour types differed significantly between genders ($P = 0.001$). For example, the proportion of small cell carcinoma was higher in the males than females (20.8 vs 12.5%, respectively). The distribution of cell types also significantly differed between non-smokers and smokers ($P < 0.0001$), with the proportion of adenocarcinoma higher in non-smokers and the proportions of squamous cell and small cell carcinoma higher in smokers. There was some suggestion of increasing proportion of squamous and small cell carcinoma with increasing cumulative lifetime smoking ($P = 0.20$). Data regarding clinical stage were available for 196 patients (81%). There were 1 (0.5%) stage IA, 7 (3.6%) stage IB, 2 (1.0%) stage IIA, 14 (7.1%) stage IIB, 27 (13.8%) stage IIIA, 50 (25.5%) stage IIIB and 95 (48.5%) stage IV (data not shown).

Discussion

Our data from the first analytic study on the causes of lung cancer in Iran confirms the primary risk factor of smoking, but also detected other potential environmental causes, including heavy metals, inorganic dusts and chemical compounds. Overall, one-third of lung cancer cases were non-smokers. We also note that only one in seven female cancer patients have a history of smoking, further highlighting the importance of eliminating other environmental exposures in the primary prevention of lung cancer, particularly among women.

Worldwide, the incidence of lung cancer is higher among men than women, in a ratio that differs widely between countries. In European countries, the lowest male:female ratio is in Denmark (1.7),

Table 1 General characteristics of lung cancer cases and their age- and sex-matched controls, Iran, 2002–05

Characteristics	Cases	Hospital controls	Healthy controls
N	242	242	242
Age (mean ± SD), years			
Male	61.3 ± 12.3	61.0 ± 12.0	60.5 ± 12.2
Female	55.9 ± 14.2	55.3 ± 13.8	55.6 ± 14.4
Total	59.9 ± 13.0	59.5 ± 12.7	59.2 ± 12.9
Sex (%)			
Male	178 (73.6)	178 (73.6)	178 (73.6)
Female	64 (26.4)	64 (26.4)	64 (26.4)
Religion (%)			
Muslim	238 (98.4)	238 (98.4)	238 (98.4)
Christian	4 (1.6)	4 (1.6)	4 (1.6)
Ethnicity (%)			
Persian	109 (45.5)	119 (49.2)	137 (56.6)
Azeri	83 (34.3)	78 (32.2)	51 (21.1)
Kurd	10 (4.2)	8 (3.3)	13 (5.4)
Lur	8 (3.3)	11 (4.5)	13 (5.4)
Arab	0 (0)	5 (2.1)	5 (2.1)
Turkmen	0 (0)	2 (0.8)	3 (1.2)
Baloch	2 (0.8)	2 (0.8)	0 (0)
Other	30 (12.4)	17 (7.0)	20 (8.2)
Marital status (%)			
Married	218 (90.1)	227 (93.8)	229 (94.6)
Unmarried	24 (9.9)	15 (6.25)	13 (5.4)
Single	8 (3.3)	5 (2.1)	7 (2.9)
Widowed	16 (6.6)	6 (2.5)	6 (2.5)
Divorced	0 (0)	5 (1.6)	0 (0)
Education (%)			
⩾5 years	116 (47.9)	146 (60.4)	168 (69.5)
Nil and <5 years	126 (52.1)	96 (39.6)	74 (30.5)
Family history of lung cancer (%)			
No	214 (88.4)	202 (83.5)	184 (76.0)
Yes	28 (11.6)	40 (16.5)	58 (24.0)

the highest in Spain (13.4). The sex ratio in the USA is 1.7.[13] In our study, the ratio is 2.8, due to the lower prevalence of smoking among women in Iran. In a survey of the general population of Iran in 2001, the prevalence of smoking for men was nearly 7-fold higher than for women aged over 16 years, 26 vs 4%, respectively.[14] This pattern of high male: female sex ratio in smoking prevalence in Iran is similar to that of USA and other developed countries 40 years ago.[15–17] These findings suggest that even if tobacco smoking appears to be the main cause of lung cancer, other risks may be specific to Iranian patients, particularly in women. Similar to other studies, our study found women developed lung cancer at a younger age than men, were more likely to be non-smokers, and, when they were smokers, consumed fewer cigarettes per day and smoked for a shorter period of time.[13] Lower percentages of smokers among female lung cancer patients were also reported from Hong Kong (56%) and China (35%), compared with 70–90% in Europe and America.[6,18]

An estimated one-quarter of lung cancer cases among never smokers are attributed to exposure to passive smoking. However, this attributable fraction depends on the prevalence and history of passive smoking in the population.[19] In a case series conducted in Olmsted County, Minnesota, for example, 57% of never smoking female lung cancer cases

Table 2 Smoking status, cumulative lifetime consumption of cigarettes (pack-years), passive smoking sources and use of opium among lung cancer patients and controls, Iran, 2002–05

Characteristics	Males			Females		
	Cases (%)	Controls (%)	OR (95% CI)	Cases (%)	Controls (%)	OR (95% CI)
Smoking category						
Non-smoker	17 (9.5)	127 (35.7)	1[a]	26 (40.6)	68 (53.1)	1[a]
Passive smoker	9 (5.1)	43 (12.1)	1.5 (0.6–3.6)	29 (45.3)	51 (39.8)	1.5 (0.8–3.0)
Smoker	152 (85.4)	186 (52.2)	6.0 (3.4–10.6)	9 (14.1)	9 (7.1)	3.1 (1.0–9.6)
Pack-year[b]						
1–19	18 (11.1)	70 (21.2)	1.8 (0.8–3.9)	3 (4.7)	8 (6.3)	1.1 (0.2–5.2)
20–39	44 (27.2)	53 (16.1)	8.5 (3.8–19.1)	5 (7.8)	0 (0.0)	28.4 (1.5–532)
40+	74 (45.7)	37 (11.2)	25 (10.6–59)	1 (1.6)	0 (0.0)	7.8 (0.4–146)
Passive smoking sources						
Spouse	0 (0.0)	4 (7.7)		21 (56.8)	28 (45.9)	
Parents or siblings	9 (75.0)	34 (65.4)		15 (40.5)	30 (49.2)	
Workplace	3 (25.0)	13 (25.0)		1 (2.7)	0 (0.0)	
Public settings	0 (0.0)	1 (1.9)		0 (0.0)	3 (4.9)	
Use of opium						
No	142 (79.8)	322 (90.4)	1[a]	63 (98.4)	126 (98.4)	1[a]
Yes	36 (20.2)	34 (9.6)	2.3 (1.4–3.7)	1 (1.6)	2 (1.6)	1 (0.1–11.0)

[a]Reference category.
[b]For this analysis the reference group was non-smokers.

Table 3 Risk factors for lung cancer, Iran, 2002–05

Carcinogen	Cases *N* (%)	Controls *N* (%)	OR[a] (95% CI)	P^a	OR[b] (95% CI)	P^b
Asbestos	1 (0.4)	0 (0.0)	6.0 (0.2–148.3)	0.33		
Heavy metals	19 (7.9)	13 (2.7)	2.9 (1.4–5.9)	0.003	3.0 (1.3–7.0)	0.012
Coal tar	6 (2.5)	4 (0.8)	3.0 (0.8–10.6)	0.09		
Soot	7 (1.5)	7 (2.9)	2.0 (0.7–5.7)	0.19		
Engine exhaust	24 (10.0)	64 (13.3)	0.7 (0.4–1.2)	0.21		
Paints	14 (5.8)	20 (4.2)	1.4 (0.7–2.9)	0.31		
Inorganic dusts	120 (49.8)	98 (20.3)	4.2 (2.9–6.1)	<0.0001	4.2 (2.8–6.7)	0.0001
Wood dust	8 (3.3)	13 (2.7)	1.2 (0.5–3.1)	0.64		
Cotton dust	17 (7.1)	19 (3.9)	1.8 (0.9–3.5)	0.09		
Silica	8 (3.3)	8 (1.7)	2.1 (0.8–5.9)	0.15		
Chemical weapon exposure	7 (2.9)	0 (0.0)	30.9 (1.8–542)	<0.0001		
Chemical compositions	84 (34.9)	84 (34.9)	4.3 (2.8–6.6)	<0.0001	3.4 (2.1–5.6)	0.0001
Exposure to inorganic dust in non-smoker[c]	35 (43.1)	35 (43.1)	4.9 (1.4–17.4)	0.01		
Exposure to chemical compositions in non-smoker[c]	29 (35.8)	29 (35.8)	5.1 (1.4–18.5)	0.01		
Wood and/or kerosene	148 (80.4)	243 (71.9)	1.43 (0.86–2.35)	0.16		
Family history of lung cancer	28 (11.6)	98 (20.2)	0.5 (0.3–0.8)	0.005	0.58 (0.34–0.99)	0.046
Smoking	161 (66.5)	195 (40.3)	4.7 (3.0–7.2)	<0.0001	5.4 (3.2–8.9)	0.0001
Opium	37 (15.3)	26 (7.4)	2.2 (1.4–3.6)	0.001		

[a]ORs and *P*-values were derived from bivariate conditional logistic regression model.
[b]ORs and *P*-values were derived from multivariate conditional logistic regression model.
[c]ORs and *P*-values were derived using conditional logistic regression model in non-smokers.

Table 4 Distribution of lung cancers by histological type, sex and smoking status, Iran, 2002–05

Characteristics		AD (%)	SQ (%)	Other NSCL (%)	SC (%)	Others (%)	*P*
Sex							
Male		40 (22.5)	41 (23.0)	50 (28.1)	37 (20.8)	10 (5.6)	0.001
Female		30 (46.9)	5 (7.8)	19 (29.7)	8 (12.5)	2 (3.1)	
Smoking							
Smoker		29 (18.0)	41 (25.5)	43 (26.7)	40 (24.8)	8 (5.0)	<0.0001
Passive-smoker		22 (57.9)	0 (0.0)	12 (31.6)	3 (7.9)	1 (2.6)	
Non-smoker		19 (44.2)	5 (11.6)	14 (32.6)	2 (4.6)	3 (7.0)	
Total	242 (100%)	70 (28.9)	46 (19.0)	69 (28.5)	45 (18.6)	12 (5.0)	

AD = adenocarcinoma; SQ = squamous cell carcinoma; Other NSCL = non-small cell lung carcinoma, these cases identified as NSCL, but it was impossible to classify these cases to subtypes of NSCL; SC= small cell carcinoma; Others, large cell carcinoma, mixed types and no classification possible.

reported environmental tobacco smoke exposure.[13,20] This is similar to the 52.7% in our study. However, in the current study, passive smoke was not correlated significantly with an elevated risk of lung cancer.

Our study discovered several unexpected findings. First, a substantial proportion of cases (13.6%) reported concomitant consumption of cigarettes and opium. Our analysis showed that the 5.4 OR for lung cancer for smokers increased to 8.1 ($P < 0.0001$) among those who were also opium addicted. However, the finding merits confirmation in a specifically designed study.

After adjusting for the effect of other factors, no significant association was found between lung cancer and education status. We also did not find any significant association between smoking and education level in lung cancer patients ($P = 0.43$). These findings could be explained by education patterns of smoking among Iranian people. In some studies, smoking rate increased with increasing in years of education.[21,22] We also found a significantly lower family history of lung cancer among cases. Nonetheless, family history has been shown to be only a weak risk factor for lung cancer and is also very rare in Iran overall.[2]

Our most novel findings are the strong associations we found between lung cancer and occupational and environmental exposures in Iran apart from smoking. Lung cancer has been associated with workplace exposures such as tar and soot,[23,24] a number of metals including arsenic, chromium and nickel,[25] and weakly associated with diesel exhaust.[26] In our study, a significantly increased risk of lung cancer was found among patients exposed to inorganic dusts, heavy metals and chemical compounds. Unfortunately, we could not separately evaluate the effect of each substance. We did not have direct measures of exposure in the workplace or home. Moreover, the number of participants with occupational exposure to some agents, such as silica and asbestos, was too small for analysis to be meaningful. We acknowledge that the assessment of exposure is difficult, usually retrospective, and therefore susceptible to recall or information bias and misclassification.[27] Findings are, therefore, suggestive and also merit confirmation in specifically designed studies. Fortunately, we did not find an association between lung cancer and the fuels most commonly used for cooking and heating in Iran and most developing countries.[28]

Our study also had the opportunity to use the case series to describe the types of lung cancers found in Iran and their stages at diagnosis. Historically, the most common histological types of lung cancer diagnosed appears to have shifted over time, from squamous cell carcinoma to adenocarcinoma.[29,30] Risk factors for lung cancer may vary with histological type and with changes in patterns of diagnosis and classification.[6,30] We also confirm gender differences in the distribution of lung cancer by histological type, even after controlling for smoking.[6] Worldwide, adenocarcinoma tends to be the most common cell type seen in women. In men, squamous cell carcinoma is still the most common in some geographic such as Canada, Australia and Scandinavia.[31] In our study, we found that squamous cell carcinoma and non-small cell carcinoma were the predominant types of lung cancer among men. Adenocarcinoma was the major histological type in women. Of note, cigarette smoking was found to be strongly associated with squamous cell and small cell carcinoma, but less strongly with adenocarcinoma.[32,33] The heterogeneity of risk factors in both sexes may explain part of the gender difference in the distribution of histological type.[32] We also discovered that most lung carcinomas in Iran were diagnosed at an advanced stage, with nearly three-quarters of our patients presenting at stage IIIB or IV.

In conclusion, this study shows that preventable behavioural and environmental factors are responsible for most lung cancer in Iran. While smoking was the single strongest risk factor in the causation of lung cancer, we also detected other potential occupational exposures in the aetiology of lung cancer. In addition to smoking cessation, public health measures are

needed to eliminate or mitigate such exposures among Iranian women and men.

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Conflict of interest: None declared.

KEY MESSAGE

- Smoking is confirmed as the principal risk factor for lung cancer in Iranian men and women; however, other potentially preventable risk factors related to occupational exposures were also implicated.

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