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A Clinicopathologic Study of Lung Cancer Cases in Iran

Mostafa Hosseini [1], Seyed Ahmad Seyed Alinaghi [2], Parisa Adimi Naghan [3,4], Shirin Karimi [5,6], Moslem Bahadori [5], Kian Khodadad [4,7], Forozan Mohammadi [5,6,8], Kaveh Keynama [3], Laleh Rahmani [3], Mohammad Reza Masjedi [3,4]

[1] Department of Epidemiology and Biostatistics, School of Public Health, [2] Iranian Research Center for HIV/AIDS (IRCHA), Tehran University of Medical Sciences, [3] Department of Pulmonary Medicine, [4] Chronic Respiratory Disease Research Center, [5] Department of Clinical Anatomical Pathology, [6] Mycobacteriology Research Center, [7] Department of Medical Oncology, [8] Lung Transplantation Research Center, NRITLD, Masih Daneshvari Hospital, Shahid Beheshti University, M.C, TEHRAN-IRAN.

ABSTRACT

Background: *Lung cancer remains the leading cause of cancer-related deaths in the world. In Iran, lung cancer is the fifth leading cancer and its prevalence rate has been increasing steadily. In this study, the clinicopathological aspects of lung cancer are discussed.*

Materials and Methods: *Between October 2002 and November 2005, 242 (178 men, 64 women) patients with histologically confirmed lung cancer were interviewed according to a questionnaire.*

Results: *Women developed the disease at an earlier age than men (55.9±14.2 versus 61.3±12.3 years; p=0.004); 66.5% of lung cancer patients (85.4% of men and 14.1% of women) were smokers (p<0.0001); 76.3% of participants, who had exposure to secondhand smoke, were females. Among the environmental carcinogens, the most exposures were to inorganic dusts (49.8%) and chemical compounds (34.9%).Most male and female patients suffered from adenocarcinoma (28.9%) and non small cell carcinoma (28.5%). The prevalence of adenocarcinoma was higher in the non-smoker group, whereas incidence of squamous cell carcinoma and small cell carcinoma was higher among smokers (p<0.0001). In this study, most patients (74.0%) presented with an advanced-stage tumor (IIIB or IV).*

Conclusion: *Our results suggest that in addition to cigarette smoking, other environmental, occupational and socioeconomic factors may play a role in the development of lung cancer.* ***(Tanaffos 2009; 8(3): 28-36)***

Key words*: Lung cancer, Smoking, Exposure, Histology.*

INTRODUCTION

Lung cancer is the most common fatal malignant disease worldwide, with an estimated 160,390 related deaths in the United States in 2007 (1). Lung cancer is the fifth leading tumor in Iran, and its incidence is very low, but has been increasing steadily in both men and women during the recent years. The low incidence of lung cancer is surprising, since the prevalence of smoking in Iranian males over the age of 15 is 12.9%. Under reporting and difficulty in tissue

Correspondence to: Masjedi MR

Address: NRITLD, Shaheed Bahonar Ave, Darabad, TEHRAN 19569, P.O:19575/154, IRAN

Email address: mrmasjedi@nritld.ac.ir

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diagnosis may explain this low incidence (2- 4).

Despite the improvements in the treatment, the vital prognosis remains poor with an estimated 5-year survival rate of 10-15 % for all stages. Cigarette smoking is the principal cause of lung cancer (5-7). However, additional significant risk factors including passive smoking (8, 9), occupational exposure to carcinogens (10, 11), ambient air pollutants (12, 13), dietary factors (14, 15) and cooking fuels (16, 17) can independently cause lung cancer. The significance of each of these factors varies with gender, country, and region within a given country (18).

Even though the epidemiology of lung cancer has been extensively investigated for over 50 years, there are still active areas of research such as lung cancer and pollutants, some quite relevant to prevention. There has also been a need for further research on the risks of smoking over time, since the cigarette has changed in its design characteristics and yields of nicotine and tar (18).

Considering the paucity of data from Iran on lung cancer, we described the results of a case study on lung cancer undertaken in Iran.

MATERIALS AND METHODS

Our understudy patients were cases with histologically and cytologically confirmed diagnosis of primary lung cancer in 5 educational hospitals between October 2003 and December 2005. The inclusion criteria were: 1- the diagnosis of lung cancer was histologically and cytologically confirmed; 2- the diagnosis was made less than 3 months before the interview; 3- patients' health condition would allow them to have a 1.5-hour interview; 4- there was no suspicion of pulmonary metastases from a different primary tumor.

A total of 242 eligible lung cancer cases entered the study between October 2003 and December 2005. A reference pathologist reviewed patients' records. This study was approved by the International Agency for Research on Cancer (IARC), Ethics Review Committee (ERC) and the ethics committee of the national research institute of tuberculosis and lung diseases (NRITLD).

After obtaining an informed consent, subjects were interviewed by trained interviewers. A detailed standardized questionnaire developed by IARC, was used to determine basic demographic characteristics in addition to details on history of active smoking, exposure to environmental tobacco smoke (ETS), family history of lung cancer, exposure to known and suspected occupational carcinogens, domestic exposure to traditional heating or cooking fuels and type and staging of lung cancer. To avoid misclassification by different pathologists, histopathological diagnosis made by the reference pathologist was used.

In some cases, it was difficult for the pathologist to obtain an adequate biopsy material for examination due to the tumor location that was difficult to reach with the biopsy forceps like tumors that grew mainly inside the bronchial wall with minimal invasion to the mucosal surface, or practical difficulties encountered during the bronchoscopy procedure when the patient was weak or troubled by dyspnea.

In 12 cases, classification to small or non small cell was not possible and 69 cases were identified as non small cell carcinomas, but we could not classify these cases into adenocarcinoma, squamous cell carcinoma or other types of non small cell carcinoma.

Subjects were defined as smokers if they had a history of regular smoking (at least one cigarette per day, 4 cigarillos/week, 3 cigars, or 3 pipes/week) for at least 6 months. For cigarette smokers pack/year was calculated as a cumulative dose indicator categorized into five groups (0-9, 10- 19, 20-29, 30-39, ≥40 pack/year). We collected information on exposure to

ETS from several sources: parents, spouses, other cohabitants at the same house during adulthood, workplace, and vehicles.

Data were also collected on lifetime occupational exposure history. All subjects were asked in detail about working conditions and exposure to known and suspected occupational lung carcinogens (19).

Information on history of lung cancer among first degree relatives (parents and siblings) was collected, including age at the time of diagnosis, and their relation to our patient. Subjects were considered as having positive history of lung cancer in the family if at least one relative with cancer was reported.

The tumor histology was classified according to the WHO guideline (20). The category "other" includes "large cell carcinomas," mixed types, and cases with no possible classification.

Four pulmonologist and radiologists performed clinical staging of lung cancer according to the TNM classification by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre Le Cancer (UICC) (21).

Statistical analyses were performed using STATA software (version 8.0; Stata Corporation). Descriptive statistics were performed to characterize the study population. In order to study the association between variables chi-squared test was used. A p-value <0.05 was considered significant.

RESULTS

During a 3-year-period (2002-2005), 242 consecutive patients with histologically proven lung cancer were recruited for this study. Table 1 presents the characteristics of the study patients. 73.6% of the cases were males. The mean age of patients was 59.9±13.0 years. Women developed the disease at an earlier age compared to men (55.9±14.2 versus 61.3±12.3 years; p=0.004). The majority of patients (90.1%) were married and were illiterate or had an educational level of ≤5 years. 45.5% and 34.3% of cases were Persian and Azari, respectively. Only 11.6% of cases had family history of lung cancer. Father or brother of 61% of the cases with family history of lung cancer, had lung cancer.

Table 1. General characteristics of lung cancer patients.

Characteristics		
Age		(Mean ± SD)
	Male	61.3±12.3 yr
	Female	55.9±14.2 yr
	Total	59.9±13.0 yr
Sex		N(%)
	Male	178 (73.6%)
	Female	64 (26.4%)
Religion		
	Muslim	238 (98.4%)
	Christian	4 (1.6%)
Ethnicity		
	Persian	109 (45.5%)
	Azari	83 (34.3%)
	Kurd	10 (4.2%)
	Lur	8 (3.3%)
	Arab	0 (0%)
	Turkmen	0 (0%)
	Baloch	2 (0.8%)
	Other	30 (12.4%)
Marital status		
	Married	218 (90.1%)
	Unmarried	24 (9.9%)
	Single	8 (3.3%)
	Widowed	16 (6.6%)
	Divorced	0 (0%)
Education		
	Nil	99 (40.9%)
	<5 years	27 (11.2%)
	5-8 years	63 (26.0%)
	8-12 years	46 (19.0%)
	>12 years	7 (2.9%)
Family history of lung cancer		
	No	214 (88.4%)
	Yes	28 (11.6%)

66.5 percent of cases were smokers. Amongst the male cases, 85.4% were smokers, whereas only 14.1% of females had a history of smoking (p<0.0001). Most smokers (85.5%) had a cumulative lifetime cigarette consumption of greater than 20 packs/year (Table 2). The majority of cases were heavy smokers (consumed ≥40 packs/year; p<0.0001), and were males. Thirty-eight (15.7%) cases were passive smokers. 76.3% (29 out of 38) of those exposed to secondhand smoke were females. The number (%) of fathers, mothers, brothers, sisters and daughters with lung cancer was 9 (32%), 5 (18%), 8 (28%), 5 (18%) and 1 (4%), respectively.

Table 2. Smoking status, passive smoking sources, use of opium and lifetime cumulative tobacco consumption (pack/year) among smokers.

Characteristics	Males N (%)	Females N (%)	Total N (%)
Smoking category			
Non-smoker	17 (9.5%)	26 (40.6%)	43 (17.8%)
Passive smoker	9 (5.1%)	29 (45.3%)	38 (15.7%)
Smoker	152 (85.4%)	9 (14.1%)	161(66.5%)
Pack/year			
0-9	6 (4.4%)	2 (22.2%)	8 (5.5%)
10-19	12 (8.8%)	1 (11.1%)	13 (9.0%)
20-29	16 (11.8%)	4 (44.4%)	20 (13.8%)
30-39	28 (20.6%)	1 (11.1%)	29 (20.0%)
≥ 40	74 (54.4%)	1 (11.1%)	75 (51.7%)
Passive smoking sources			
Spouse	0 (0.0%)	21 (55.3%)	21 (55.3%)
Father	5 (13.2%)	7 (18.4%)	12 (31.6%)
Mother	2 (5.3%)	4 (10.5%)	6 (15.8%)
Brother	2 (5.3%)	3 (7.9%)	5 (13.2%)
Sister	0 (0.0%)	1 (2.6%)	1 (2.6%)
Work place	3 (7.9%)	1 (2.6%)	4 (10.5%)
Public settings	9 (23.7%)	29 (73.6%)	38 (0.0%)
Use of oral opium			
No	142 (79.8%)	63 (98.4%)	205 (84.7%)
Yes	36 (20.2%)	1 (1.6%)	37 (15.3%)

Thirty-seven cases (15.3%) were oral opium users. Also, 42.2% of smoker patients were illiterate and only 3.7% had university education (p<0.0001).

Table 3 presents characteristics of occupational exposure to potential carcinogens in patients. Among the carcinogens, most exposures were to inorganic dusts (49.8%) and chemical compounds (34.9%). Wood and kerosene were the most common (80.4%) fuels used for cooking and heating in their houses.

Table 3. Occupational exposure to potential carcinogens in lung cancer patients.

Carcinogen	N (%)
Asbestos	1 (0.4%)
Heavy metals	19 (7.9%)
Coal tar	6 (2.5%)
Soot	7 (1.5%)
Engine exhaust	24 (10.0%)
Paints	14 (5.8%)
Inorganic dusts	120 (49.8%)
Wood dust	8 (3.3%)
Cotton dust	17 (7.1%)
Silica	8 (3.3%)
Chemical weapon exposure	7 (2.9%)
Chemical compounds	84 (34.9%)
Wood and/or kerosene	148 (80.4%)

Table 4 shows the distribution of the histological types of lung cancer in patients. Histopathologically, 70 (28.9%) cases were adenocarcinomas, 69 (28.5%) cases were non small cell carcinomas, 46 (19.0%) cases were squamous cell carcinomas, 45 (18.6%) cases were small cell carcinomas, and 12 (5.0%) cases were classified as other histologies.

Most of the male and female patients suffered from adenocarcinoma (28.9%) and non small cell carcinoma (28.5%), respectively. The tumor type distribution of squamous cell carcinoma, small cell carcinoma and adenocarcinoma of the lung between genders was significantly different (P=0.001). For example, the ratio of small cell carcinoma was higher in males compared to females (20.8% versus 12.5%).

Table 4. Distribution of lung cancer based on histopathology, gender and smoking status

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

[a] AD: Adenocarcinoma, [b] Other NSCL: Non small cell lung carcinoma, these cases were identified as NSCL, but it was impossible to classify these cases into subtypes of NSCL, [c] SQ: Squamous cell carcinoma, [d] SC: Small cell carcinoma, [e] Others: Large cell carcinoma, mixed types, and no classification possible.

The distribution of cell types was significantly different between non-smokers and smokers ($p<0.0001$). While the incidence of adenocarcinoma was higher in the non-smoker group, the incidence of squamous cell carcinoma and small cell carcinoma was higher in the smoker group.

There was a suggestion on increasing ratio of squamous and small cell carcinoma in association with increasing lifetime cumulative tobacco consumption (pack/year) (P=0.20).

Furthermore, data regarding the clinical stage of cancer was 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 cancers.

DISCUSSION

In our study, women were younger than men. Most previous studies have reported that women develop lung cancer at a younger age. They are more likely to be life time non-smokers and smoker women smoke fewer cigarettes per day and for a shorter period of time. These factors suggest that women are more susceptible to carcinogenic compounds of cigarette smoke and noxious environmental conditions due to genetic background and hormonal factors (22-24). Overall, the incidence of lung cancer is higher among males than females. Sex ratios differ between the countries. Among the European countries, the lowest male/female ratio is in Denmark (1.7) and the highest is in Spain (13.4) (25, 26).

We also did not find any significant association between smoking and level of education in smoker patients (P=0.75). It indicated that, there was no significant difference in smoking rate between highly educated and low educated patients. This finding could be explained by the educational level of Iranian smokers. In some studies, prevalence of smoking among high school and university students (16.3%-29%) was higher than general population (13.1%) and the smoking rate increased in those with higher levels of education (4, 27). In developed countries such as the US and Australia, increased school-based efforts to prevent tobacco use, and increased exposure of youth to the media campaigns on smoking prevention contributed to the decline in cigarette use among students (28, 29).

Extensive prospective epidemiologic data clearly establish cigarette smoking as the major cause of lung cancer (30, 31). Tobacco smoke is a complex mixture of over 4000 different chemicals, of which over 40 compounds have been evaluated by the

IARC in animals and are considered as carcinogens (21). It is estimated that about 90% of annual lung cancer-related deaths in males and 75%–80% of such deaths in females in the United States and Europe are caused by smoking (18, 32, 33). A lower percentage of smokers among female lung cancer patients was reported from Hong Kong (56%) and China (35%) compared to 70–90% in Europe and America (18, 34). We found that 66.5% of the cases were smokers, only 14.1% of females were smokers; whereas 85.4% of male patients had a history of smoking. Smoking prevalence among U.S. adults was 29.3% in males and 18.0% in females (32). In a study on general population in Iran in 2001, the prevalence of smoking in women aged over 16 years (3.6%) was significantly lower than men (26%) (35).

A meta-analysis carried out by the US Environmental Protection Agency concluded that ETS exposure is associated with an increased risk of lung cancer in nonsmoking adults (36). In a case series conducted in Minnesota, 57% of never smoking female lung cancer cases reported a history of ETS exposure (37). This compares with the 52.7% rate in our study.

A reported family history of lung cancer increases the risk of lung cancer significantly in men and women (38, 39). Since only a small proportion of smokers develop lung cancer, genetic susceptibility might be important, although recall bias could also contribute to this finding (40, 41).

Lung cancer has been observed to be associated with many occupational exposures to tar, soot and asbestos (42, 43) and the concentration of metals including arsenic, nickel and chromium (44). In developed countries these hazards have largely been controlled (18). For some other occupational agents, the evidence has been less clear. A weak association between exposure to diesel exhaust and development of lung cancer has been found (45). Exposure to heavy metals (nickel and chromium), was mostly seen in metal casting industries and related activities. Exposure to inorganic dusts was also seen in building laborers. Chemical compounds include detergents, cleansers, and disinfectant agents. Bleaching agents are widely used in homes, schools, hospitals, swimming pools and drinking water supplies. Therefore, many people may be at risk of exposure to these agents. The number of patients occupationally exposed to agents such as silicosis and asbestos was too small.

The most common histological type of lung cancer has changed over time from squamous cell carcinoma to adenocarcinoma. A recent growing trend towards adenocarcinoma has been documented in many regions around the world (46, 47). Risk factors for lung cancer may vary with the histological type in addition to alternative patterns of diagnosis and classification of lung cancers (18).

There are gender differences in the distribution of lung cancer according to the histopathological type (18). In general, adenocarcinoma tends to be the major histological type seen in women (48). In men, squamous cell carcinoma is still the most common cell type in some geographic locations such as Canada, Australia, and Scandinavia, but trends indicate that the overall percentage of this cell type has fallen over time to 40% or less (48).

We found that squamous cell carcinoma (23.0%) was the predominant type of lung cancer among men, and 22.5% of them had adenocarcinoma. The major histopathological type in females was adenocarcinoma (46.9%). The heterogeneity of risk factors in both sexes could partly explain the gender differences in the distribution of the histopathological type (49).

Cigarette smoking was found to be strongly associated with squamous cell and small cell carcinomas, but less strongly with adenocarcinoma (49).

Most lung carcinomas are diagnosed at an advanced stage (IIIB or IV) (50). In this study, most patients (74.0%) presented with advanced stage carcinomas.

Wood and other solid fuels are used for cooking and heating in developing countries. Exposure to biomass smoke has been associated with lung cancer and other respiratory diseases such as chronic bronchitis, emphysema, and asthma (51). In our study, wood and kerosene were the commonest fuels used for cooking and heating.
Limitations of this study included as follows:

First, there was no control group to evaluate the risk factors. Second, the recall bias for the data on exposure and family history may have influenced the results.

In summary, our results suggest that in addition to cigarette smoking, other environmental, occupational and socioeconomic factors may be important in the development of lung cancer. Efforts are needed in Iran to reduce smoking rates especially among men. Measures that could be taken to reduce tobacco use include imposition of additional taxation on tobacco products, banning smoking in all work and public places, and holding intensive community and school-based educational programs.

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REFERENCES

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. ***CA Cancer J Clin*** 2007; 57 (1): 43-66.
2. Babaei M, Mousavi S, Malek M, Tosi G, Masoumeh Z, Danaei N, Gafar G. Cancer occurrence in Semnan Province, Iran: results of a population-based cancer registry. ***Asian Pac J Cancer Prev*** 2005; 6 (2): 159- 64.
3. Ferlay J, Bray F, Pisani P, Parkin DM (2004). GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide Version 2.0. IARC Cancer Base No.5. Lyon, IARC Press.
4. Mohammad K, Noorbala AA, Majdzadeh SR, Karimloo M. Trend of smoking prevalence in Iran from 1991 to 1999 based on two national health survey. ***Hakim Research Journal*** 2000; 3 (4): 290-7.
5. Lam WK, White NW, Chan-Yeung MM. Lung cancer epidemiology and risk factors in Asia and Africa. ***Int J Tuberc Lung Dis*** 2004; 8 (9): 1045- 57.
6. Lubin JH, Caporaso N, Wichmann HE, Schaffrath-Rosario A, Alavanja MC. Cigarette smoking and lung cancer: modeling effect modification of total exposure and intensity. ***Epidemiology*** 2007; 18 (5): 639- 48.
7. Lubin JH, Caporaso N, Hatsukami DK, Joseph AM, Hecht SS. The association of a tobacco-specific biomarker and cigarette consumption and its dependence on host characteristics. ***Cancer Epidemiol Biomarkers Prev*** 2007; 16 (9): 1852- 7.
8. Centers for Disease Control and Prevention (CDC). Reduced secondhand smoke exposure after implementation of a comprehensive statewide smoking ban--New York, June 26, 2003-June 30, 2004. ***MMWR Morb Mortal Wkly Rep*** 2007; 56 (28): 705- 8.
9. Stayner L, Bena J, Sasco AJ, Smith R, Steenland K, Kreuzer M, Straif K. Lung cancer risk and workplace exposure to environmental tobacco smoke. ***Am J Public Health*** 2007; 97 (3): 545- 51.
10. Bilello KS, Murin S, Matthay RA. Epidemiology, etiology, and prevention of lung cancer. ***Clin Chest Med*** 2002; 23 (1): 1- 25.
11. Jöckel KH, Ahrens W, Wichmann HE, Becher H, Bolm-Audorff U, Jahn I, et al. Occupational and environmental hazards associated with lung cancer. ***Int J Epidemiol*** 1992; 21 (2): 202- 13.
12. Liu CC, Tsai SS, Chiu HF, Wu TN, Yang CY. Ambient exposure to criteria air pollutants and female lung cancer in Taiwan. ***Inhal Toxicol*** 2008; 20 (3): 311- 7.
13. Lewtas J. Air pollution combustion emissions: characterization of causative agents and mechanisms

associated with cancer, reproductive, and cardiovascular effects. ***Mutat Res*** 2007; 636 (1-3): 95- 133.

14. Shen M, Chapman RS, He X, Liu LZ, Lai H, Chen W, Lan Q. Dietary factors, food contamination and lung cancer risk in Xuanwei, China. ***Lung Cancer*** 2008; 61 (3): 275- 82.
15. Byers T. Nutrition and lung cancer: lessons from the differing effects of foods and supplements. ***Am J Respir Crit Care Med*** 2008; 177 (5): 470- 1.
16. Lissowska J, Bardin-Mikolajczak A, Fletcher T, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Fabianova E, et al. Lung cancer and indoor pollution from heating and cooking with solid fuels: the IARC international multicentre case-control study in Eastern/Central Europe and the United Kingdom. ***Am J Epidemiol*** 2005; 162 (4): 326- 33.
17. Ramanakumar AV, Parent ME, Siemiatycki J. Risk of lung cancer from residential heating and cooking fuels in Montreal, Canada. ***Am J Epidemiol*** 2007; 165 (6): 634- 42.
18. Alberg A, Yung R, Samet J. Epidemiology of Lung Cancer. In: Mason R, Murray J, Broaddus V, Nadel J, editors: Mason: Murray & Nadel's Textbook of Respiratory Medicine, 4th Ed. New York (NY): Saunders, An Imprint of Elsevier;2005:1328-48.
19. Ahrens W, Merletti F. A standard tool for the analysis of occupational lung cancer in epidemiologic studies. ***Int J Occup Environ Health*** 1998; 4 (4): 236- 40.
20. Travis W, Colby T, Corrin B, Shimosato Y, Brambilla E. Histological typing of lung and pleural tumours. 3rd ed. Springer, Berlin; 1999.
21. International Agency for Research on Cancer. Tobacco smoking. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol 38. Lyons, France: IARC, 1986.
22. Koo LC, Ho JH. Worldwide epidemiological patterns of lung cancer in nonsmokers. ***Int J Epidemiol*** 1990; 19 Suppl 1: S14- 23.
23. Fontham ET, Correa P, Reynolds P, Wu-Williams A, Buffler PA, Greenberg RS, et al. Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. ***JAMA*** 1994; 271 (22): 1752- 9. Erratum in: ***JAMA*** 1994; 272 (20): 1578.
24. Gonlugur U, Gonlugur TE, Kaptanoglu M, Nadir A, Cinar Z. The changing epidemiological trends for carcinoma of the lung in Turkey. ***Saudi Med J*** 2008; 29 (5): 749- 53.
25. Bener A, Ayub H, Kakil R, Ibrahim W. Patterns of cancer incidence among the population of Qatar: a worldwide comparative study. ***Asian Pac J Cancer Prev*** 2008; 9 (1): 19- 24.
26. Chen K, Wang PP, Sun B, Li Q, Perruccio A, Power D, Wang C, et al. Twenty-year secular changes in sex specific lung cancer incidence rates in an urban Chinese population. ***Lung Cancer*** 2006; 51 (1): 13- 9.
27. Ollakavari SH. Study of evaluation of outbreak of cigarette smoking and age distribution of first smoking experience among high school and pre-university students. ***Med East J Fam Med*** 2006; 4 (2): 16- 20.
28. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the future: national results on adolescent drug use-overview of key findings. Bethesda, Maryland. National Institute on Drug Abuse, 2004; NIH publication no. 04-5506.
29. Substance Abuse and Mental Health Services Administration. Overview of findings from the 2002 National Survey on Drug Use and Health. Rockville, Maryland: U.S. Department of Health and Human Services, 2003; DHHS publication no. (SMA) 03-3774.
30. Wu-Williams AH, Samet JM: Lung cancer and cigarette smoking. In: Samet JM, ed. Lung Biology in Health and Disease. Vol 74: Epidemiology of Lung Cancer, chap 4, New York: Marcel Dekker; 1994:71-108.
31. Wynder EL, Covey LS. Epidemiologic patterns in lung cancer by histologic type. ***Eur J Cancer Clin Oncol*** 1987; 23 (10): 1491- 6.
32. Dubey S, Powell CA. Update in lung cancer 2007. ***Am J Respir Crit Care Med*** 2008; 177 (9): 941- 6.
33. Shopland DR. Tobacco use and its contribution to early cancer mortality with a special emphasis on cigarette smoking. ***Environ Health Perspect*** 1995; 103 Suppl 8: 131-42.
34. Ko YC, Lee CH, Chen MJ, Huang CC, Chang WY, Lin HJ, et al. Risk factors for primary lung cancer among non-

smoking women in Taiwan. ***Int J Epidemiol*** 1997; 26 (1): 24- 31.

35. Ahmadi J, Khalili H, Jooybar R, Namazi N, Mohammadagaei P. Prevalence of cigarette smoking in Iran. ***Psychol Rep*** 2001; 89 (2): 339- 41.
36. Taylor R, Gumming R, Woodward A, Black M. Passive smoking and lung cancer: a cumulative meta-analysis. ***Australian and New Zealand Journal of Public Health*** 2007; 25 (3): 203- 11.
37. de Andrade M, Ebbert JO, Wampfler JA, Miller DL, Marks RS, Croghan GA, et al. Environmental tobacco smoke exposure in women with lung cancer. ***Lung Cancer*** 2004; 43 (2): 127- 34.
38. Wu AH, Fontham ET, Reynolds P, Greenberg RS, Buffler P, Liff J, Boyd P, et al. Family history of cancer and risk of lung cancer among lifetime nonsmoking women in the United States. ***Am J Epidemiol*** 1996; 143 (6): 535- 42.
39. Wu AH, Fontham ET, Reynolds P, Greenberg RS, Buffler P, Liff J, et al. Family history of cancer and risk of lung cancer among lifetime nonsmoking women in the United States. ***Am J Epidemiol*** 1996; 143 (6): 535- 42.
40. Bartsch H, Nair U, Risch A, Rojas M, Wikman H, Alexandrov K. Genetic polymorphism of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers. ***Cancer Epidemiol Biomarkers Prev*** 2000; 9 (1): 3- 28.
41. Bouchardy C, Benhamou S, Jourenkova N, Dayer P, Hirvonen A. Metabolic genetic polymorphisms and susceptibility to lung cancer. ***Lung Cancer*** 2001; 32 (2): 109- 12.
42. Doll R, Fisher RE, Gammon EJ, Gunn W, Hughes GO, Typer FH, Wilson W. Mortality of gasworkers with special reference to cancers of the lung and bladder, chronic bronchtis, and pneumoconiosis. ***Br J Ind Med*** 1965; 22:1- 12.
43. Lloyd JW. Long-term mortality study of steelworkers. V. Respiratory cancer in coke plant workers. ***J Occup Med*** 1971; 13 (2): 53- 68.
44. Alberg AJ, Yung R, Strickland PT, et al: Respiratory cancer and exposure to arsenic, chromium, nickel, and polycyclic aromatic hydrocarbons. ***Clin Occup Environ Med*** 2002; 2: 779- 801.
45. Cohen AJ, Higgins MWP: Health effects of diesel exhaust: Epidemiology. Health Effects Institute, Diesel Working Group: Diesel Exhaust: A Critical Analysis of Emissions, Exposure, and Health Effects. A Special Report of the Institute's Diesel Working Group, Cambridge, Mass: Health Effects Institute; 1995:251-92.
46. Wingo PA, Ries LA, Giovino GA, Miller DS, Rosenberg HM, Shopland DR, et al. Annual report to the nation on the status of cancer, 1973-1996, with a special section on lung cancer and tobacco smoking. ***J Natl Cancer Inst*** 1999; 91 (8): 675- 90.
47. Charloux A, Quoix E, Wolkove N, Small D, Pauli G, Kreisman H. The increasing incidence of lung adenocarcinoma: reality or artefact? A review of the epidemiology of lung adenocarcinoma. ***Int J Epidemiol*** 1997; 26 (1): 14- 23.
48. Janssen-Heijnen ML, Coebergh JW. Trends in incidence and prognosis of the histological subtypes of lung cancer in North America, Australia, New Zealand and Europe. ***Lung Cancer*** 2001; 31 (2-3): 123- 37.
49. Le CH, Ko YC, Cheng LS, Lin YC, Lin HJ, Huang MS, et al. The heterogeneity in risk factors of lung cancer and the difference of histologic distribution between genders in Taiwan. ***Cancer Causes Control*** 2001; 12 (4): 289- 300.
50. Beadsmoore CJ, Screaton NJ. Classification, staging and prognosis of lung cancer. ***Eur J Radiol*** 2003; 45 (1): 8- 17.
51. Chen BH, Hong CJ, Pandey MR, Smith KR. Indoor air pollution in developing countries. ***World Health Stat Q*** 1990; 43 (3): 127- 38.