RESEARCH ARTICLE

Clinicopathological Characteristics of Iranian Patients with Lung Cancer: a Single Institute Experience

Khosravi Adnan[1], Esfahani-Monfared Zahra[2], Seifi Sharareh[2], Karimi Shirin[3], Emami Habib[4], Khodadad Kian[5]*

Abstract

Background: Lung cancer has long been a leading cause of cancer related death in both women and men worldwide. The focus of this study was to review clinicopathological features of Iranian patients diagnosed with lung cancer. Materials and Methods: Clinicopathological data of 1353 primary lung cancer patients diagnosed during 17 years (1997-2014) in the "National Institute of Tuberculosis and Lung Disease" (NRITLD), Tehran, Iran, were retrospectively reviewed. Results: The median age of patients was 60 (mean: 58.95 years, range: 16-99) and adenocarcinoma was the most prevalent pathology (45.2%). Male/female ratio was 3.22 and 57.2% of patients were smokers (men 70.3%, women 15%). The majority (85.3%) were referred in advanced stages (stage IIIB and IV). Conclusions: Although some of our findings are in concordance with other studies in lung cancer but there are some discrepancies particularly in terms of smoking status and median age of Iranian patients. Further clinical and epidemiological studies are warranted to elucidate etiologic and factors other than smoking contributing to development of lung cancer such as environmental exposures or genetic predisposition.

Keywords: Lung cancer - epidemiology - non-small cell - small cell - clinicopathological characteristics

Asian Pac J Cancer Prev, **17 (8)**, 3817-3822

Introduction

Lung cancer has been leading most cancer related death in both women and men worldwide (Siegel et al., 2015; American Cancer Society. Cancer Facts & Figures., 2015). Five-year survival rate of only 15.9% of patients has been reported (Garcia et al., 2007). It is estimated 158,040 Americans are expected to die from lung cancer in 2015 (American Cancer Society. Cancer Facts & Figures., 2015)

Iran is the second-largest nation in the Middle East (southwest Asia) and the 18th-largest in the world. With 78.4 million inhabitants, Iran is the world's 17th most populous nation. (Encyclopædia Britannica., 2012)

In Iran, lung cancer with an incidence rate of 4.7-9.2 per 100,000 people (Garcia et al., 2007; Mosavi-Jarrahi., 2009), ranks second in men and third in women as the cause of cancer related death but frequency of this malignancy is lower than in Central and Eastern Europe (53.5 per 100,000), Eastern Asia (50.4 per 100,000) (Ferlay et al., 2012) and USA (221,200 new cases in 2015) (Siegel et al., 2015). Incidence of Lung cancer is increasing in Iran (Almasi et al., 2016). Likewise, incidence of cancer differs dramatically between geographic regions that might be due to genetic differences, kind of life-styles, environmental exposures and variety of medical health services such as screening (Lam et al., 2004).

It's shown that changes in prevalence and types of tobacco smoking consumed in the population (Couraud et al., 2012), diet (Ruano-Ravina et al., 2006), alcohol (Freudenheim et al., 2005), physical activity (Higgins et al., 2014), air pollution (Hoek et al., 2014), occupational exposure (Malhotra et al., 2015), in indoor radon environments (Gilliland et al., 2000) and in our country traffic injuries (Hosseini et al., 2009) can affect the pattern of lung cancer in terms of gender ratio, histopathology, incidence and mortality. Periodic and accurate data on the magnitude of these changes are essential for better and timely therapies, early detection and quality of life improvement.

The purpose of this review is to describe the epidemiologic, pathologic and clinical data of lung cancers which developed in a limited number of Iranian patients, referred to our institute.

*[1]Medical Oncology, Tobacco Prevention and Control Research Center, [2]Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, [3]Pathology, Mycobacteriology Research Center, [4]Tobacco Prevention and Control Research Center, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [5]Internal Medicine, Dalhousie University, Cape Breton Cancer Centre, Nova Scotia, Canada *For correspondence: khodadadk@cbdha.nshealth.ca*

Materials and Methods

This retrospective hospital-based study included patients with definite primary lung cancer pathology, diagnostic based on pathology specimens from "National Research Institute of Tuberculosis and Lung Disease" (NRITLD), between August of 1997 and June of 2013. NRITLD is a referral academic hospital, affiliated to Shahid Beheshti University of Medical Sciences, in Tehran, Iran. Metastatic lung neoplasms from the other primary sites were excluded. Information on demographic characteristics, smoking, histological subtype, and stage were obtained by chart reviewing.

Histological classification was done according to WHO in 1981 (The World Health Organization histological typing of lung tumours., 1982). There are four major types of primary lung cancer: squamous cell carcinoma (SCC), adenocarcinoma, large cell carcinoma and small cell carcinoma (SCLC). The term" undifferentiated non small cell lung cancer" was used if histologic subtype differentiation was impossible. Performance status (PS) and stages were defined according to Eastern Cooperative Oncology Group performance status (Oken et al., 1982) (ECOG) and "American Joint Committee on Cancer" (AJCC, 6th edition) (Greene et al., 1982), respectively. For patients with SCLC pathology the other staging system was applied as follow: limited disease is defined as disease confined to the ipsilateral hemithorax and within a single radiotherapy port (corresponding in part to TNM stages I through IIIB) and extensive disease is defined as evident metastatic disease outside the ipsilateral hemithorax. (Goldstraw et al., 2007).

Never smoker defined to person who has smoked less than 100 cigarettes in his/her lifetime (Wender et al., 2013) and passive smoking has not been assessed in this study. For testing the differences in categorical variables, the Chi-Square test or Fisher's exact test was used. For all statistical tests, the 5% level was used as cutoff for statistical significance. All analysis was performed using SPSS version 16.

Results

A total of 1353 patients were included that 1033 (76.3%) were male and 320 (23.7%) were female (Male/ Female ratio was 3.22). The median age of patients was 60 years (range 16-99 years). The main patients characteristic are summarized in Table 1.

Non-small cell lung cancer (NSCLC) accounted to 83.07%, while small cell lung carcinoma (SCLC) accounted 16.93% of cases. Histological distribution is shown in Figure 1. Adenocarcinoma was the most prevalent pathology in both sexes (Table 1). Interestingly, after Adenocarcinoma, SCC was second frequent pathology in men while SCLC had this rating in women. Approximately, two-third of patients (67.3%) presented with metastatic disease at time of diagnosis. Sites of distant metastasis were: contralateral lung 34.9% (n=472), bone 11.1% (n=150), liver 7.8% (n=105), brain 5.2%9 (n=70),

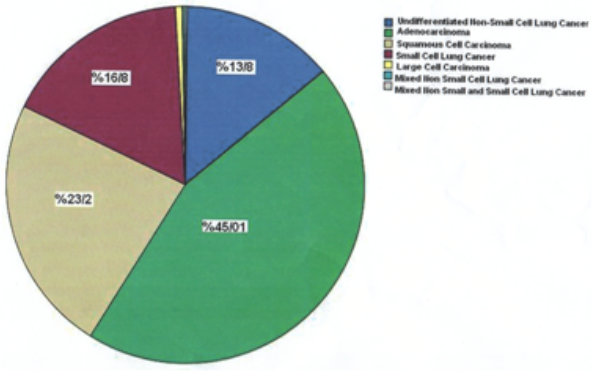

Figure 1. Histopathology Subtypes (n=1353)

Table 1. Patients characteristic at time of diagnosis

	All (*n*=1353)	Male (*n*=1033)	Female (*n*=320)	*P* value
Mean age at diagnosis ± SD *Median* *Range*	58.95 ± 11.74 60 16-99	59.93 ± 11.35 60 21-99	55.78 ± 12.40 57 16-90	0.001*
Histology				
Adenocarcinoma	609 (45.01%)	393 (38.04%)	216 (67.5%)	
SCC [a]	315 (23.28%)	286 (27.68%)	29 (9.06%)	
NSCLC [b]	187(13.82%)	155 (15%)	32 (10%)	
Mixed NSCLC+SCLC [c]	2 (0.14%)	2 (0.19%)	0 (0.0)	
Mixed NSCLC [d]	3 (0.22%)	1 (0.09%)	2 (0.62%)	
LCC [d]	8 (0.59%)	8 (0.77%)	0 (0.0)	0.0001*
SCLC [c]	229 (16.85%)	188 (18.1%)	41 (12.5%)	
Total	1353 (100%)	1033(100)	320(100)	
Disease Stage in NSCLC [e]				
NA	8(0.71%)	7(0.82%)	1(0.71%)	
IA	8(0.71%)	4(0.47%)	4(1.4%)	0.002*
IB	18(1.6%)	17(2.01%)	1(0.35%)	
IIA	12(1.06%)	8(0.94%)	4(1.4%)	
IIB	28(2.49%)	19(2.45%)	9(3.2%)	
IIIA	101(8.98%)	82(9.7%)	19(6.78%)	
IIIB	166(14.76%)	143(16.8%)	23(8.21%)	
IV	783(69.6%)	565(66.8%)	218(77.85)	
Total	1124(100)	845(100)	279(100)	
Disease Stage in SCLC				
Limited stage	101 (43.85%)	77 (40.95%)	24 (58.6%)	0.056
Extensive stage	128 (56.1%)	111 (59.05%)	17 (41.4%)	
Total	229(100)	188(100%)	41(100)	
Performance Status [f]				
0	44 (3.25%)	31 (3%)	13 (4.06%)	
1	403 (29.7%)	309 (29.91%)	94 (29.3%)	
2	861 (63.6%)	655 (63.4%)	206 (64.35%)	
3	44 (3.25%)	37 (3.58%)	7 (2.18%)	0.612
4	1 (0.07%)	1 (0.09%)	0	
Total	1353(100)	1033(100)	320(100%)	
Smoking status *Smoker* *Non smoker*	 775 (57.2 %) 551 (40.7 %)	 727 (70.3%) 292 (28.2%)	 48 (15%) 259 (80.9%)	
Missing data	27(1.99%)	14(1.3%)	13(4.06%)	P=0.0001*

Abbreviations: *a SCC: Squamous cell carcinoma, b NSCLC: Non small cell lung cancer, c SCLC: Small cell lung cancer, d LCC: Large cell carcinoma e according to AJCC, 6th edition, f according to ECOG .*

*significant *P value*

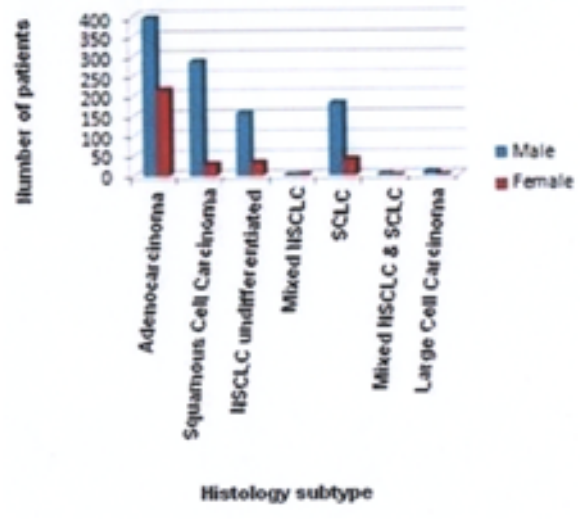

Figure 2. Distribution According to Gender and Histological Subtypes

lymphadenopathy 3.6 % (n=48), adrenal 2.8% (n=38) and other sites 2.8% (n=38). Majority of the patients had PS two (63.6%). Significant differences between male and female were seen in terms of age, histology and NSCLC stage at the time of diagnosis (P=0.001, 0.0001 and 0.002, respectively). About 58% of patients were smoker. Also, men had significantly higher incidence of smoking compared to women (P=0.0001).

Discussion

This study provides an overview of demographic and clinico-histopathological features of a number of Iranian patients with lung cancer. To the best of our knowledge, no single- institute study has been done yet with this number of patients with lung cancer in Iran. According to this study, median age of patients was 60 years (men: 58.95), and adenocarcinoma was the most prevalent pathology. The male/female ratio was 3.22 and 57.2% of patients (70.3% and 15%, in men and women, respectively) had a history of smoking. In this population of patients their majority (85.30%) were referred in advanced stages.

Age is the determining factor for cancer risk. Some investigators believe that incidence of lung cancer is relatively low before the age of 50 years and begins to increase rapidly afterward (Wender et al.,2013; Radzikowska et al., 2002). The average age of most populations in developed nations is increasing, and cancer is a disease of the elderly (Dela Cruz et al., 2011). The mean age at diagnosis of our study was 58.95 years which is almost similar to other studies from Iran (Mehrabani et al., 2008; Sadraei et al., 2013; Tarrahi et al., 2009) and our neighbor country ,Turkey (60 yrs)(Gonlugur et al., 2008) and India(56 yrs) (Noronha et al., 2012) while the mean age for diagnosis is higher in other regional Arab countries such as Saudi Arabia, Kuwait and UAE (66 yrs) (AL-Hashimi et al., 2014)and even other developed countries such as Canada (75 yrs) (Navaneelan et al., 2011), USA (74 yrs) (Surveillance Epidemiology and End Results., 2012), Japan (66.3 yrs) (Osawa et al., 2012)and Australia (71 yrs)(Australian Institute of Health and Welfare & Australasian Association of Cancer Registries., 2011).

The best possible explanation for discrepancy of age at diagnosis is some differences in racial/ethnic characteristics which may be attributed to a complex interaction between genetic and lifestyle factors.(Hamid et al., 2015) Another reason can be related to higher mortality rate due to cardiovascular events among young smokers in Iran. Therefore, with improvement of cardiovascular care in smokers much more patients do survive longer to develop lung cancer and this may lead to increase in the incidence and median age of patients diagnosed with lung cancer in developing countries such as Iran.

In our study, most women patients were younger at diagnosis than their male counterpart as in most, but not all, prior studies that have demonstrated that women are diagnosed at an earlier age than men.(Thomas et al., 2005; Radzikowska et al., 2002; Perrot et al., 2000; Baldini et al., 1997; Minami et al., 2000) Despite of women are more likely to be lifetime non-smokers, consumed fewer cigarettes per day and smoked for a short period of time, they are younger than men at time of lung cancer diagnosis in most population. (Wender et al., 2013, Fontham et al., 1994; Wang et al., 1996) It has been suggested that genetic background of women make them more susceptible to carcinogenic effect of cigarette smoke and environmental adverse conditions .(Koo et al., 1990)

Male/female ratio differs widely between countries. We observed that this ratio was 3.22 which is almost similar to the ratio of other studies from Iran (2.79-5.09) (Hajmanoochehri et al., 2014), Kuwait and Japan. (Ei-Basmy., 2013, Kanematsu et al., 2010) Higher ratios has been reported in some countries such as Spain (8.1) (Santos-Martines et al., 2005) and India (4.1) (Dey et al., 2012). This discrepancy may be due to differences in smoking status, DNA capacity repair (Chang et al., 2009), histological subtypes and alcohol consumption. Also, the differences in incidence patterns of lung cancer between men and women may be due to historical differences in smoking; the peak of cigarette smoking is about 20 years later in women than in men. (Siegel et al., 2013)

According to studies 80-91% of all lung cancers in men and 45-69% in women are attributable to cigarette smoking. (Sasco et al., 2004; Salim et al., 2011) Although, active smoking is the most important contributor to the lung cancer burden(Thompson et al., 2012) but it has been estimated that approximately 25% of lung cancer patients are never-smokers worldwide.(Wender et al., 2013) Lung cancer patients who are never-smokers are predominantly women with adenocarcinoma histology and with younger age at onset. (Ou et al., 2009) Different studies in Iran showed the overall prevalence of daily smoking is 23.9%-26% and 1.7%-3.6% in men and women, respectively. (Ahmadi et al., 2001, Yunesian et al., 2008) This may be due to the social stigma of smoking for women in Iranian culture. In current study, from 307 female with available smoking history only 48 (15%) were smoker and this finding proved that there are interactions between environmental, genetic factors and lung cancer.(Lam., 2005) One study found that variations at three locations in the genome—two on chromosome 6 and one on

chromosome 10 - are in association with lung cancer in Asian women who have never-smoked. (Lan et al., 2012) Furthermore, Asian women may be more susceptible to the effects of environmental tobacco smoke. (Lan et al., 2012; Koo et al., 1990) In addition, the activation of some genes (such as gastrin-releasing peptide receptor: GRPR) has been associated with bronchial cells proliferation. (Shriver et al., 2000) GRPR gene was expressed more frequently in non-smoker women than in men, and activation of this gene was done earlier in smoker women. One study showed ER gene polymorphisms are related to lung adenocarcinoma in never smoker (Chen et al., 2015) woman that can be considered in future studies. Likewise, a genetic component to the pathogenesis of lung cancer may be involved that it relates to host susceptibility to lung cancer, with or without smoking.

Secondhand smoking or passive smoking can contribute to an increased risk for lung cancer but there is controversy.(Peres., 2013) Other forms of tobacco use, such as pipe smoking, water-pipe smoking (which be used frequently in Iran and eastern Mediterranean region) and inhaling smoke from opium are less studied than cigarette smoking.

Over the last several decades, adenocarcinoma becoming more prevalent than squamous cell carcinoma (Houston et al.,2014) which has been hypothesized to be due to changes in cigarette composition and the way smokers smoked (inhaling smoke more vigorously in to the peripheral lung where adenocarcinoma is found). (Burns et al., 2011) Improvement in detecting of peripheral pulmonary lesions (Mirtcheva et al., 2002) and altering WHO classification together with an improved staining of mucin-producing cells resulted in a shift of cases from large cell carcinoma to adenocarcinoma64 should be considered. Additional explanations for the prevalence of Adenocarcinoma could include the impact of the atmospheric air pollution, particularly oxides of nitrogen which had been suggested to increase Adenocarcinoma. (Lortet-Tieulenta et al., 2014) In current study adenocarcinoma was the most frequent pathology which is similar to findings reported by other studies (Thompson et al., 2012; Nakamura et al., 2013) .

In our study, most of patients had advanced stages which is in concordance with international reports.(Howlader et al., 2011)

This retrospective study has a few limitations as well. First, smoking data can be inaccurate, particularly when collected retrospectively. Moreover, unfortunately, we could not separately and/or directly evaluate the exposure effect of other contributing factors such as passive smoking, air pollution, silica or asbestos exposure. Also, Lung cancer in never-smokers is still heterogeneous biologically. The differences between rural and urban population was not recorded, too. Some investigators demonstrated increased risk for lung cancer specifically for persons with a family history of early-onset lung cancer (<60 years of age). (Matakidou et al., 2005) In this study the family history of patients was not assessed since the data in the patients charts were considered not accurate. The role of infection as a causative factor in lung cancer remains debatable. Some investigators believed oncogenic viruses such as human papillomavirus (HPV serotypes 16 and 18) (Rezazadeh et al., 2009), Epstein-Barr virus (especially in Asian population) (Castro et al., 2001), human cytomegalovirus, simian virus 40, and measles virus (Giuliani et al., 2007) associated as a cause of lung cancer. Association of pulmonary tuberculosis, which is not an uncommon infection in Iran, with lung cancer, has been reported. (Yu et al., 2011)Further studies should be considered to determine association of infections and lung cancer in different geographical regions.

Besides, this study was performed on all patients who were referred to the tertiary centre of NRTLD from across Iran but may not really reflects the exact clinicopathologic and demographic characteristics of all Iranian patients with lung cancer.

In conclusion, It seems that lung cancer pattern and etiology in Asia and developing countries may be different from developed countries. This study highlighted clinicopathologic features of Iranian patients with lung cancer. Our findings were mostly in concordance with the studies reported from the most of regional or developing countries. Interestingly, this study revealed lower median age at the time of diagnosis and lower incidence of smoking compare to other studies. This might be due to other intervening factors or etiologies such as genetic predisposition, endemic infectious diseases, and environmental exposures.

To elucidate the role of smoking and other possible etiologies in development of lung cancer in developing countries, a comprehensive and precise national cancer registry along with a systematic regional and international collaboration are warranted.

Acknowledgements

We thank all the participating investigators and clinical staff.

References

Ahmadi J, Khalili H, Jooybar R, et al (2001). Prevalence of cigarette smoking in Iran. *Psychol Rep*, **89**, 339-41.

Almasi Z, Salehiniya H, Amoori N, et al (2016). Epidemiology characteristics and trends of lung cancer incidence in Iran. *Asian Pac J Cancer Prev*, **17**, 557-62.

AL-Hashimi MMY, Wang XJ (2014). Trend analysis of lung cancer incidence rates in ninawa province, iraq, from 2000 to 2010 - decrease and recent stability. *Asian Pac J Cancer Prev*, **15**, 385-90.

American Cancer Society. Cancer Facts & Figures 2015(2015). Atlanta: American Cancer Society; 2015.

Australian Institute of Health and Welfare and Cancer Australia. (2011). Lung cancer in Australia: an overview. Cancer series no. 64. Cat. no. CAN 58. Canberra: AIHW.

Baldini E, Strauss, GM (1997). Women and lung cancer: waiting to exhale. *Chest*, **112**, 229-34.

Burns D.M, Anderson C.M, Gray N (2011). Do changes in cigarette design influence the rise in adenocarcinoma of the lung? *Cancer Causes Control*, **22**, 13-22.

Castro CY, Ostrowski ML, Barrios R, et al (2001). Relationship between Epstein-Barr virus and lymphoepithelioma-like carcinoma of the lung a clinicopathologic study of 6 cases and review of the literature. *Hum Pathol*, **32**, 863-72.

Chang JS, Wrensch MR, Hansen HM, et al (2009). Base excision repair genes and risk of lung cancer among San Francisco Bay Area Latinos and African-Americans. *Carcinogenesis*, **30**,78-87.

Chen K-Y, Hsiao C-F, Chang G-C, et al (2015). Estrogen receptor gene polymorphisms and lung adenocarcinoma risk in never-smoking women. *J Thorac Oncol*, **10**, 1413-20.

Couraud S, Zalcman G, Milleron B, et al (2012). Lung cancer in never smokers - A review. *Eur J Cancer*, **48**, 1299-311.

Dela Cruz CS, Tanoue LT, Matthay RA (2011). Lung cancer: epidemiology, etiology, and prevention. *Clin Chest Med*, **32**, 605-44.

Dey A, Biswas D, Saha SK, et al (2012). Comparison study of clinicoradiological profile of primary lung cancer cases: An Eastern India experience. *Indian J Cancer,* **49**, 89-95.

Ei-Basmy A (2013). Profile of lung cancer in Kuwait. *Asian Pac J Canccer Prev*, **14**, 6181-4.

Ferlay J, Soerjomataram I, Dikshit R, et al (2012). Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*, **136**, 359-86.

Freudenheim JL, Rits J, Smith-Worner S (2005). Alcohol consumption and risk of lung cancer: a pooled analysis of cohort studies. *Am J Clin Nutr*, **82**, 657-67.

Fontham ET, Correa P, Reynolds P, et al (1994). Environmental tobacco smoke and lung cancer in non-smoking women. A multicenter study. *JAMA*, **271**, 1752-9.

Garcia M, Jemal A, Ward EM, et al (2007). Global cancer facts & figures 2007.Atlanta, GA: American Cancer Society 2007.

Gilliland FD, Hunt WC, Archer VE, et al (2000). Radon progeny exposure and lung cancer risk among non-smoking uranium miners. *Health Phys*, **79**, 365-72.

Goldstraw P, Crowley J, Chansky K, et al (2007). The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groups in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol*, **2**, 706-14.

Gonlugur U, Gonlugur TE, Kaptanoglu M, et al (2008). The changing epidemiological trends for carcinoma of the lung in Turkey. *Saudi Med J*, **29**, 749-53.

Greene FL, Page DL, Fleming ID, et al (2002). AJCC Cancer Staging Manual 6th ed. Chicago: Springer-Verlag.

Hajmanoochehri F, Mohammadi N, Zohal MA, et al (2014). Epidemiology and clinicopathological characteristics of lung cancer in a teaching hospital in Iran. *Asian Pac J Canccer Prev*, **15**, 2495-500.

Hamid MS, Shameem R, Gafoor K, et al (2015). Non-small-cell lung cancer clinicopathologic features and survival outcomes in asian pacific islanders residing in the United States: A SEER Analysis. *J Cancer Epidemiol*, **2015**, 269304??

Higgins K.A, Park D, Lee G.Y, et al (2014). Exercise-induced lung cancer regression: Mechanistic findings from a mouse model. *Cancer*, **120**, 3302-10.

Hoek G, Raaschou-Nielsen O (2014). Impact of fine particles in ambient air on lung cancer. *Chin J Cancer*, **33**, 197-203.

Hosseini M, Naghan PA, Karimi S, et al (2009). Environmental risk factors for lung cancer in Iran: a case-control study. *Int J Epidemiol*, **38**, 989-96.

Houston KA, Henley SJ, Li J, et al (2014). Patterns in lung cancer incidence rates and trends by histologic type in the United States, 2004-2009. *Lung Cancer*, **86**, 22-8.

Howlader N, Noone AM, Krapcho M, et al (eds) (2014). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014

Iran. Encyclopædia Britannica. Encyclopædia Britannica (2012). Retrieved 8 August 2012.

Kanematsu T, Hanibuchi M, Tomimoto H, et al (2010) . Epidemiological and clinical features of lung cancer patients from 1999 to 2009 in Tokushima Prefecture of Japan. *J Med Investigation*, **57**, 327-33.

Koo LC, Ho JH-C (1990). World wide epidemiological patterns of lung cancer in non-smokers. *Int J Epidemiol*, **19**, 14-2.

Lam WK (2005). Lung cancer in Asian women-the environment and genes. *Respirol*, **4**, 408-17.

Lam W. K, White N. W, Chan-Yeung M. M(2004). Lung cancer epidemiology and risk factors in Asia and Africa. *int j tuberc lung*, **8**, 1045-57.

Lan Q, Hsiung CA, Matsuo K, et al (2012). Genome-wide association analysis identifies new lung cancer susceptibility loci in never-smoking women in Asia. *Nat Genet*, **44**, 1330-5.

Lortet-Tieulenta J, Soerjomataram I, Ferlaya J, et al (2014). International trends in lung cancer incidence by histological subtype: Adenocarcinoma stabilizing in men but still increasing in women. *Lung Cancer*, **84**, 13-22.

Malhotra J, Sartori S, Brennan P, et al (2015). Effect of occupational exposures on lung cancer susceptibility: a study of gene-environment interaction analysis. *Cancer Epidemiol Biomarkers Prev*, **24**, 570-9.

Matakidou A, Eisen T, HoulstonBritish RS (2005). Systematic review of the relationship between family history and lung cancer risk. *J Cancer*, **93**, 825-33.

Mehrabani D, Tabei SZ, Heydari ST, et al (2008) . Cancer occurrence in Fars Province, Southern Iran. *Iranian Red Crescent Med J*, **10**, 314-22.

Minami, H, Yoshimura, M, Tsubota, N, et al (2000). Lung cancer in women: sex-associated differences in survival of patients undergoing resection for lung cancer. *Chest*, **118**, 1603-9.

Mirtcheva RM, Vazquez M, Yankelevitz DF, et al (2002). Bronchioloalveolar carcinoma and adenocarcinoma with bronchioloalveolar features presenting as ground-glass opacities on CT. *Clin Imaging*, **26**, 95-100.

Mosavi-Jarrahi A, Gouya MM, Ramazani R, et al (2009). Cancer incidence and mortality in Iran. *Ann Oncol*, **20**, 556-63.

Nakamura H, Saji H (2013). A worldwide trend of increasing primary adenocarcinoma of the lung. *Surg Today*. [Epub ahead of print]

Navaneelan T, Janz T (2011). Cancer in canada: focus on lung, colorectal, breast and prostate. *Statistics Canada Catalogue* no. 82-624 - X

Noronha V, Dikshit R, Raut N, et al (2012). Epidemiology of lung cancer in India: Focus on the differences between non-smokers and smokers: A single-center experience. *Indian J Cancer*, **49**, 74-81.

Oken MM, Creech RH, Tormey DC, et al (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*, **5**, 649-55.

Osawa K, Nakarai C, Uchino K, et al (2012). XRCC3 Gene polymorphism is associated with survival in japanese lung cancer patients. *Int J Mol Sci*, **13**, 16658-67.

Ou SH, Ziogas A, Zell JA-J (2009). Asian ethnicity is a favorable prognostic factor for overall survival in non-small cell lung cancer (NSCLC) and is independent of smoking status. *Thorac Oncol*, **4**, 1083-93.

Peres J (2013). No clear link between passive smoking and lung cancer. *J Natl Cancer Inst*, **105**, 1844-6.

Perrot M, Licker M, Spiliopoulous A, et al (2000). Sex differences in presentation, management and prognosis of patients with non-small cell lung carcinoma. *J Thorac Cardiovasc Surg*, **119**, 21-6.

Radzikowska E, Głaz P, Roszkowski K (2002). Lung cancer in women: age, smoking, histology, performance status, stage, initial treatment and survival. Population-based study of 20

561 cases. *Ann Oncol*, **13**, 1087-93.
Rezazadeh A, Laber DA, Ghim SJ, et al (2009). The role of human papilloma virus in lung cancer: a review of the evidence. *Am J Med Sci*, **338**, 64-7.
Ruano-Ravina A, Figueiras A, Feire-Garbal-M, et al (2006). Antioxidant vitamins and risk of lung cancer. *Curr Pharm Des*, **12**, 599-613.
Sadraei NH, Taghi Riahi (2013) . Idiopathic pulmonary fibrosis in a referral center in Iran: Are patients developing the disease at a younger age? *Arch Iranian Med*, **16**, 177-81.
Salim E.I, Jazieh A.R, Moore M.A (2011). Lung cancer incidence in the Arab League countries: risk factors and control. *Asian Pac J Cancer Prev*, **12**, 17-34.
Santos-Martines MJ, Curull V, Blanco ML, et al (2005). Lung cancer at a university hospital: epidemiological and histological characteristics of a recent and a historical series. *Arch Bronconeumo*, **l41**, 307-12.
Sasco A.J, Secretan M.B, Straif K (2004). Tobacco smoking and cancer: a brief review of recent epidemiological evidence. *Lung Cancer*, **45**, 3-9.
Shriver SP, Bourdeau HA, Gubish CT, et al (2000). Sex-specific expression of gastrin realizing peptide receptor: relationship to smoking history and risk of cancer. *J Natl Cancer Inst*, **92**, 24-33.
Siegel RL, Naishadham D, Jemal A (2013). Cancer statistics, 2013. *CA Cancer*, **63**, 11-30.
Siegel RL, Miller KD, Jemal A (2015). Cancer statistics, 2015. *CA Cancer J*, **65**, 5-29.
Surveillance Epidemiology and End Results (2012). SEER stat fact sheets: lung and bronchus. National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/statfacts/html/lungb.html. Accessed March 22, 2012.
Tarrahi MJ, Mehrabani D, Khademolhosseini F, et al (2009). Lung cancer occurrence in Southern Iran. *J Res Med Sci*, **14**, 139-40.
The World Health Organization histological typing of lung tumours. Second edition (1982). *Am J Clin Pathol*, **77**, 123-36.
Thomas L, Doyle LA, Edelman MJ (2005). Lung cancer in women: emerging differences in epidemiology, biology, and therapy. *Chest*, **128**, 370-81.
Thompson CA, Waldhur T, Schernhammer ES, et al (2012). Smoking and lung cancer: current trends in Austria. *M.Wien Klin Wochenschr*, **124**, 493-9.
Wang T, Zhou B, Shi J (1996). Lung cancer in non-smoking Chinese women: a case-control study. *Lung Cancer*, **14**, 93-5.
Wender R, Fontham ET, Barrera E, et al (2013). American cancer society lung cancer screening guidelines. *Ca Cancer J Clin*, **63**, 106-17.
Yu YH, Liao CC, Hsu WH, et al (2011). Increased lung cancer risk among patients with pulmonary tuberculosis: a population cohort study. *J Thorac Oncol*, **6**, 32-7.
Yunesian M, Homayoun-Vash J, Asghari F, et al (2008). Smoking-related respiratory symptoms in Tehran: a cross-sectional study. *Arch Iran Med*, **11**, 507-14.