

## RESEARCH ARTICLE

# Incidence and Clinicopathologic Features of Primary Lung Cancer: A North-Eastern Anatolia Region Study in Turkey (2006-2012)

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### Abstract

**Background:** Lung cancer is the most frequent cancer among men and second highest among women overall, including in Turkey. Cigarette smoking is the most important etiologic factor for the development of cancer in both men and women. **Objective:** To determine the lung cancer incidence in Northeastern Anatolia Region of Turkey with a focus on clinical properties, cancer subtypes, the relationships of tumors with cigarette smoking and radiological properties of the lesions. **Materials and Methods:** In a retrospective study design, 566 lung cancer cases diagnosed at the Pathology Department of Ataturk University in Erzurum over the last seven years extending from January 2006 to June 2012 were investigated. The results were compared with statistical analyses. **Results:** The most common histopathological subtype of primary bronchogenic carcinoma in our study was found to be the squamous cell carcinoma, 46.1% (261 out of 566), and the second was small cell lung carcinoma 15.7% (89 out of 566). Based on our data, an overall male predominance was noted with a male/female ratio of 6.1/1. While 296 (52.2%) of the patients were found to be smokers at the time of diagnosis, 125 (22.0%) were nonsmokers and 145 (25.6%) were ex-smokers. Smoking status was found to have a strong correlation with primary lung cancer ( $p < 0.05$ ), and there were significant differences between males and females ( $p < 0.001$ ). **Conclusion:** Although relative prominence of subtypes of lung cancers differ between Turkish and other populations, lung cancer overall remains as an important health problem in Turkey. Our findings stress the critical need for effective cancer prevention programs such as anti-smoking campaigns.

**Keywords:** Lung cancer - histopathology - incidence data - smoking

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### Introduction

Lung cancer is the leading cause of cancer mortality worldwide, and has led to a number of important public health problems. Despite advances in treatment, the 5-year survival rate is only 9-20% (Hsu et al., 2012). Lung cancer is a disease which has increased incidence with age, and is the most common cancer between the ages of 50-70 (95%) (Bozkurt et al., 2004). Today, it is a leading cause in both males and females of all cancer deaths with the ratio of 28% (Atıcı et al., 2012; Günbatar et al., 2012)

Smoking is the most important etiologic factor for the development of lung cancer in both men and women. It was reported in studies which evaluating the relationship between tumor histology and smoking, the most important relationship was detected in small cell lung carcinoma and squamous cell carcinoma. (Arınç et al., 2007). Also

environmental factors (radioisotopes, mustard gas, asbestos, polycyclic aromatic hydrocarbons, nickel, chromium, cadmium, inorganic arsenic, chloromethyl ether, formaldehyde), radioactivity, genetic factors including age and sex and diet may cause lung cancer in non-smokers (Günbatar et al., 2012).

Classically, the pathology of lung cancer can be classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), depending on both the different tumor biology and susceptibility to treatments (Navani et al., 2012). While the majority of patients are seen with locally advanced or metastatic disease, almost 85% of lung cancers can be counted as NSCLC, which is the most common form of lung cancer (De Geer et al., 2013). Non-small cell lung cancer could be divided into several histologic subtypes: mostly lung adenocarcinoma (LADC) or squamous cell carcinoma (SCC) (Tacha et al., 2012). When the histological differences in lung

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cancer are evaluated together with the epidemiological data, interesting results draws the attention. As the ratio of squamous cell carcinoma decreases, the ratio of adenocarcinoma and the bronchoalveolar carcinoma increases, over the years (Yurdakul et al., 2002). Although the adenocarcinoma is considered as the most commonly seen histologic type of lung cancer, indeed the squamous cell carcinoma is the most common histologic type of primary lung cancers in developing countries, as in our country (Travis et al., 2011; Günbatar et al., 2012).

The aim of this study was to determine the lung cancer incidence in North-eastern Anatolia Region of Turkey, its clinical properties, cancer subtypes, the relationships of tumors with cigarette smoking and radiological properties of the tumors.

### Materials and Methods

To complete the incidence study reported in our region on 2005 this study included 566 lung cancer cases diagnosed at the Pathology Department of Ataturk University in Erzurum over last seven years extending from January 2006 to June 2012. This study is a retrospective analysis basing on the pathology reports and accesible patient files. Those cases are investigated according to their age, sex, hometown, smoking status, the radiographic findings, location of the lesion and histopathological diagnosis. The definition of non-smoker/never-smoker, ex smoker and smoker is designed as: never smoker/non smoker; as a person who had never smoked or had smoked <20 cigarettes in his or her lifetime, ex smoker; those who stopped smoking for more than ten years, and smoker; those who have smoked ever in their life more than just occasional smoking (Bryant et al., 2007).

The radiographic findings were obtained from visual imaging methods such as lung X-rays, thorax CT. Lesion location, which can be accompanied by chest computed tomography findings as “central”, “intermediate” and “peripheral” settlements, respectively.

The tumors were classified according to 2004 World Health Organization (WHO) criteria for tumors of the lung. Conventional and immunohistochemical stained preparations existing in our archive examined by two pathologists as well independent of each other and histopathologic diagnosis and the distribution of the subgroup was revised. SPSS 20.0 was used for statistical calculations. Pearson’s chi-square, Kruskal Vallis, T test was used to compare categorical variables. P values <0.05 were accepted as statistically significant.

### Results

A total of 566 patients were included in this study in which patients were diagnosed at the Pathology Department of Ataturk University in Erzurum, between 31 June 2012 and 1 January 2006. While the 487 of the patients (86.0%) were male, the 79 (13.9%) were female. There was an overall male predominance with male/female ratio of 6.16/1. Female patients are presented with significantly younger age ( $59.1 \pm 14.9$  years), ranging from

38 to 89, when compared with the male patients ( $64.1 \pm 11.9$  years), ranging from 31-85 ( $p < 0.001$ ) (Table 1, Figure 1).

Relationship between the tumor and smoking status of the patients was analyzed. At the time of diagnosis, a total of 296 (52.2%) patients were smokers, 125 (22.0%) were nonsmokers and 145 (25.6%) were ex-smoker. There was a strong correlation between smoking status and primary lung cancer ( $p < 0.05$ ). 55.2% (269/487) of male patients with lung cancer were smokers and 25.2% (123/487) of them were ex smoker. Only 34.1% (27/79) of the female patients were smokers ( $p < 0.01$ ). In our study, the female patients with lung cancer were more commonly nonsmokers or ex smoker (Table 2). The most common histopathological subtypes of primary bronchogenic carcinoma in our study population were SCC 46.1% (261 out of 566) and then small cell carcinoma with the ratio of 15.7% (89 out of 566). 66 patients (11.7%) were diagnosed with adenocarcinoma and 82 patients (14.4%)

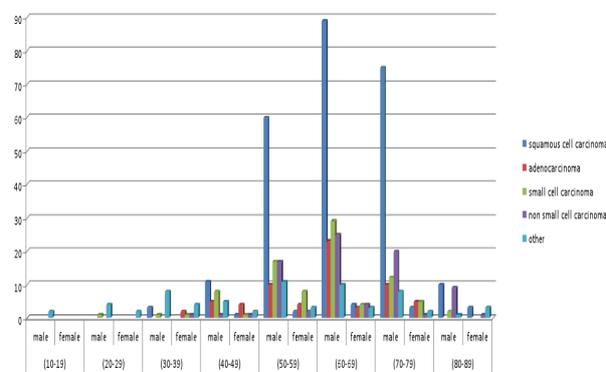


Figure 1. Distribution of Histological Types, Age and Sex

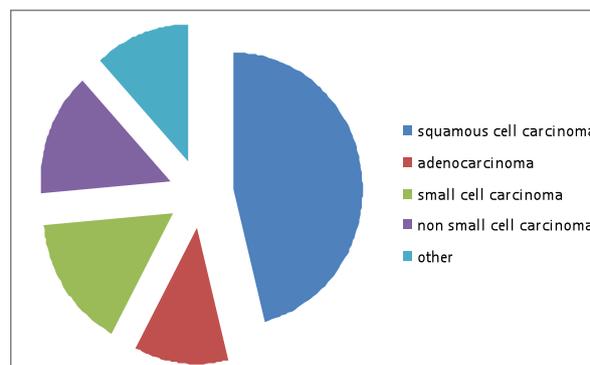


Figure 2. The Distrubition of Histological Subtypes of Lung Cancer

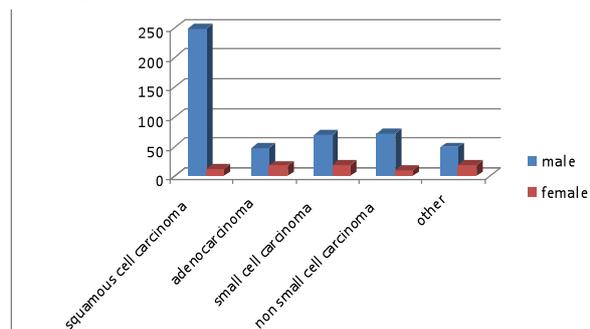


Figure 3. Distribution of Sex and Subtypes of Lung Cancer

were diagnosed with non-small cell lung carcinoma, but the diagnosis was not differentiated as either SCC or adenocarcinoma (Figure 2). The number of nonsmall cell bronchogenic carcinoma diagnosis declined in recent years. And also there were 13 benign lung tumors in our study population. The most common type of lung tumor in male was squamous cell carcinoma with the 248 cases out of 487 (50.9%). Adenocarcinoma was diagnosed in 48 patients (9.8%), small cell carcinoma in 70 (14.3%), and nonsmall cell lung carcinoma, not differentiated in 72 (14.7%). Among the female patients; small cell carcinoma was the most common malignant tumor with a total of 19 cases (24.0%) and the second most common one is adenocarcinoma with a total of 18 cases (22.7%). 13 (16.4%) of the female with lung tumors was squamous cell carcinoma and 10 (12.6%) of them was nonsmall cell lung carcinoma, which is not differentiated ( $p<0.01$ )

**Table 1. Reported Cancer Among First-Degree Relatives of Patients With Lung Cancer by Histologic Type of Tumor and Age at Diagnosis**

	(10-19)	(20-29)	(30-39)	(40-49)	(50-59)	(60-69)	(70-79)	(80-89)
Squamous Cell Carcinoma								
	3	12	62	93	78	13		
Adenocarcinoma								
	2	9	14	26	15			
Small Cell Carcinoma								
	1	2	9	25	33	17	2	
Non Small Cell Carcinoma								
	1	2	19	29	21	10		
Other								
	2	6	12	7	14	13	10	4

**Table 2. Relative Risk of Lung Cancer and Major Subtypes by Smoking Status**

	Non Smoker		Ex Smoker		Smoker	
	Male	Female	Male	Female	Male	Female
Squamous Cell Carcinoma	40	5	64	2	144	6
Adenocarcinoma	10	11	12	2	26	5
Small Cell Carcinoma	7	5	12	6	51	8
Non Small Cell Carcinoma	22	3	23	4	27	3
Other	16	6	12	8	21	5

**Table 3. Comparison of Subtypes of Lung Cancer with Patients Hometown Status**

	Urban		Rural	
	Male	Female	Male	Female
Squamous Cell Carcinoma	126	5	122	8
Adenocarcinoma	24	11	24	7
Small Cell Carcinoma	25	9	45	10
Non Small Cell Carcinoma	29	5	43	5
Other	26	7	23	12

**Table 4. Characteristics of Patients With Lung Cancer in the Study Population**

	(10-19)		(20-29)		(30-39)		(40-49)		(50-59)		(60-69)		(70-79)		(80-89)	
	Male	Female														
Squamous Cell Carcinoma					3	11	1	60	2	89	4	75	3	10	3	
Adenocarcinoma					2	5	4	10	4	23	3	10	5			
Small Cell Carcinoma			1		1	8	1	17	8	29	4	12	5	2		
Non Small Cell Carcinoma					1	1	1	17	2	25	4	20	1	9	1	
Other	2		4	2	8	4	5	2	11	3	10	3	8	2	1	3

(Figure 3, Table 3). When the relationship between sex and tumor type was considered, it was determined that the rates of tumor types among male and female patients were different. Squamous cell lung cancer was the most frequent tumor type among male patients; in addition small cell carcinoma and adenocarcinoma was significantly higher among female patients ( $p<0.01$ ). When the relationship between smoking status and tumor type was evaluated, among patients with squamous cell carcinoma, the ratio of smokers or ex-smokers was 82.7% and nonsmokers was 17.2%. At the time of diagnosis, 86.5% were smokers or ex smokers and only 13.5% were nonsmokers in patients with small cell carcinoma. Among patients with adenocarcinoma, 68.2% were smokers or ex-smokers and 31.8% were nonsmokers (Table 2).

Majority of the patients in this study population are from rural area (52.80%). The ratio of primary lung cancer in the male and female among urban versus rural population ( $p=0.688$ ) was not significantly different. When compared to urban (77.0%), smoking habit (smokers and ex smokers) is higher among rural population (78.6%), but this difference was not significant ( $p=0.239$ ). The age of patients from rural area was higher ( $63.96\pm 12.136$  years) as compared to urban population ( $62.83\pm 13.640$  years), but the difference was not significant ( $p=0.309$ ). SCC (131/267, 49.1% versus 130/299, 43.5%) and small cell carcinoma (34/267, 12.7% versus 55/299, 18.4%) are the two most common variety of primary bronchogenic carcinoma in both urban and rural population but the difference is not significant ( $p=0.254$ ) (Table 4). The relationship between the tumor location and tumor type was also evaluated in this study. The data presents that majority of the tumor is centrally located in the squamous cell carcinoma cases (184/261, 70.49%) and in the small cell carcinoma cases (75/89, 84.2%) but is located peripheral in adenocarcinoma cases (45/66, 68.18%) ( $p<0.01$ ).

## Discussion

One of the leading cause of cancer-related death worldwide is lung cancer with 1.18 million deaths of the world total (Kanematsu et al., 2010). Recent studies about epidemiology of lung cancer have showed that disease continues to be diagnosed considerably more in men than women (Araz et al., 2010; Kanematsu et al., 2010; Dey et al., 2012). When the minor variations excluded, lung cancer is the most frequent cancer among men and the second most common cancer among women in the World, including Turkey (Araz et al., 2010). The data about the incidence of lung cancer in men and women is conflicting in Turkey. According to the data from Izmir Cancer

Control Center; lung cancer is the most frequent cancer and the rate of lung cancer among all cancer types was 38.6% in men, in 1993-1994. However, among women, this rate is 5.2% women and is the seventh most frequent cancer. Data obtained from Ministry of Health showed that lung cancer incidence in Turkey is 11.5/100,000 in 1997 (Akcığer, 2006). The percentage of men with lung tumors in our study was 86.0% whereas the percentage of women with lung tumor was 14.0%, and the mean age of patients at the time of diagnosis was 63±12.77 years old. We found the male/female ratio as 6.1/1. The male/female ratio in India has been found as 4.1/1, which is lower than the results in our study (Dey et al., 2012). In Japan the ratio is 2.8/1 (Kanematsu et al., 2010). In a study in 2010, 255 patients diagnosed with lung cancer in 2005, 220 of whom (86.3%) were male and 35 were female (13.7%) are evaluated in Erzurum (Araz et al., 2010). The ratio in our region was 6/1 in 2005. The results are similar in our region in 2012 and 2005. The ratio in Holland (13.7%) is higher than in our region (Parkin et al., 1992). In Spain the ratio is also higher than our region (8/1) (Santos-Martines et al., 2005).

The frequency of different histological types of lung cancer has changed over the last two decades in the USA and Europe, so that squamous cell carcinoma has become less common and adenocarcinoma has become more frequent (Travis et al., 1995). Changes in diagnostic techniques or classification were mentioned to be responsible for a major part of adenocarcinoma increase in some reports (Charloux et al., 1997; Thun et al., 1997). The reason of this may be introduction of advanced technology such as a fiber optic bronchoscopy, which allows the access to distal areas to the lung (Salim et al., 2011). According to our results; squamous cell carcinoma is still the most common diagnosis, followed closely by small cell carcinoma. Squamous cell carcinoma, with a total of 248 cases (50.9%), was the most common type of lung tumor in male while the adenocarcinoma was diagnosed in 48 patients (9.8%), small cell carcinoma in 70 (14.3%), and nonsmall cell lung carcinoma, not differentiated in 72 (14.8%). Among female, small cell carcinoma was the most common malignant tumor with a total of 19 cases (24.7%) and the second most common one is adenocarcinoma with a total of 18 cases (23.4%) 13 of the (16.9%) female with lung tumors had squamous cell carcinoma and 10 (13.0%) of them had nonsmall cell lung carcinoma, not differentiated ( $p<0.01$ ). The results were similar for male but not for female in central Tunisia. In Central Tunisia, squamous cell carcinoma was the most common histological type in male while adenocarcinoma was predominant among female (Missaouil et al., 2011). Because of the recent successful developments on the treatments of the lung carcinomas, it is essential to diagnose the type of NSCLC although diagnosis for primary lung carcinoma as either NSCLC or SCLC was sufficient previously (Turner et al., 2012). In our study the data showed that the number of diagnosis as non-small cell bronchogenic carcinoma which is not differentiated as either SCC or adenocarcinoma per year was decreasing in recent years.

The average age of the patients who were diagnosed

with lung cancer was 63.45±12.541 years, the average age of male patients was 64.18±11.974 years, and the average age of female patients was 59.13±14.957 years. The average age of lung cancer patients obtained by the previous study in our region (±SD) was 63±1 (Araz et al., 2010). According to the study in Ankara in 2004; the mean age was 58.7±10.7 (Alpar et al., 2004). In our study, the average age was higher than the ages in previous studies but it is consistent with the peak in lung cancer in the 60-70 age group in the literature (Bozkurt et al., 2004). When the relationship between the type of tumor and age was analyzed, the data showed that the younger patient, the more frequently small cell cancer was detected (61.5±11.2 years) and as age increases, more SCC cases were detected (66.2±11.1 years) ( $p=0.010$ ).

Cigarette smoking causes approximately 85-90% of bronchogenic carcinoma. Smokers have 20-fold increased risk of lung cancer when compared to never-smokers (Dey et al., 2012). Smoking induces all major histological types of lung cancer, the strongest associations are found with squamous cell and small cell carcinoma while the ratio for adenocarcinoma are four- to five fold, which is lower than for other histological types (Thun et al., 1997). Lung cancer incidence has stabilized or even exhibited a slow decrease among men in western countries during the last few decades (Cox and Yesner, 1979; Simonato et al., 2001). This observation based on effective cancer prevention programs; especially campaigns against smoking launched in the second half of the 20<sup>th</sup> century (Simonato et al., 2001). Cigarette sales increased only in the regions of The Middle East and Asia during this period. This trend reflected the high male smoking prevalence in the Arab world and the uptake of smoking by a growing number of women (WHO, 1997). The prevalence of cigarette smoking in Turkey is 63% for male and 24% for female. When the cigarette consumption in Turkey is considered, we can easily say that lung cancer is an important health problem for our country (İtil et al., 2000).

When we consider the relationship between sex and smoking habit, we found that men in our series were mostly smokers or ex-smokers and that the most common histological type of lung cancer among them was squamous cell carcinoma. Among women the most common histologic subtype of lung cancer was small cell carcinoma and the second one was adenocarcinoma. Squamous cell lung cancer cases and small cell carcinoma cases were significantly higher among smokers when the relationship between smoking and lung cancer analyzed ( $p<0.01$ ). Adenocarcinoma was also higher among the smoker or ex smoker group with the percentage of 68.2% but 31.8% of adenocarcinoma cases were non smokers. Female sex was significantly associated with a greater probability of developing small cell carcinoma and adenocarcinoma according to our results.

In our study population majority of the patients were from rural area (52.8%). The difference in the male female ratio of primary lung cancer among urban versus rural population was not significant ( $p=0.668$ ). Similar results are reported in Eastern India in 2012 (Dey et al., 2012)

Although central location is more often seen in squamous cell carcinoma and small cell carcinoma,

peripheral location is seen in adenocarcinoma more frequently (Arınç et al., 2007). Our results were consistent with the literature.

As a result the change in the histological types of lung cancer over time may be due to changes in smoking habits or may be related to exposure to environmental carcinogens or may be due to changes in histopathological diagnosis criteria. Therefore, in terms of diagnosis and treatment determining the distribution of histological types of lung cancers have a particular importance. Presence of each country's statistical information reflecting its own profile is also important.

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