

RESEARCH ARTICLE

Epidemiological and Clinicopathological Characteristics of Lung Cancer in a Teaching Hospital in Iran

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Abstract

Background: Lung cancer is one of the most commonly diagnosed cancers and the most frequent cause of cancer-related death worldwide. In Iran, it ranks second and third as the cancer-causing death in men and women, respectively. We carried out this study to find out the demographic, clinical, and histological characteristics and risk factors of lung cancer in a referral tertiary center in Iran. **Materials and Methods:** A retrospective study was conducted on cases of primary lung cancer based on the results of registered cancer reports of cytological and pathological specimens between March 2001 and March 2012. Demographic variables, clinical manifestations, histology and location of tumors were determined based on the data found in the medical records of each patient. Definite or probable etiologic factors were identified. Data analysis was performed with SPSS version 16 and a p-value ≤ 0.05 was considered as significant. **Results:** A total of 203 patients, with a mean age of 65.7 years (SD=11.2), with primary lung cancer were identified, 81.3% being men. Of the total, 110 cases (54.2%) were living in urban areas. In 53.2% of cases, the site of tumor was on the right side and in 72.9% of cases the lesion was centrally located. The histological types of lung cancer were squamous cell carcinoma (SCC) in 107 cases (52.7%), adenocarcinoma (AC) in 30 cases (14.8%), and small cell carcinoma (SC) in 27 cases (13.3%). Significant correlations between the gender and residence, smoking, and the histological type and location (central or peripheral) of tumor were found. The percentage of smokers was 75.2% in men and 15.8% in women. **Conclusions:** Smoking was the most important risk factor and squamous cell carcinoma the most common histological type of lung cancer in our study. Male sex and being a smoker was associated with histological types of SCC while being nonsmoker had relationship with adenocarcinoma.

Keywords: Lung cancer - epidemiology - histological type - risk factor

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Introduction

In 2008, lung cancer was the cause of 13% of all new cases of cancers and 18% of all cancer-related mortality, worldwide (Jemal et al., 2011). Lung cancer is the most commonly diagnosed cancer and the most prevalent cause of cancer-related death throughout the world (Jemal et al., 2011; Kummar et al., 2013). The frequency of lung cancer in Iran is lower than in Europe and the USA (Jemal et al., 2011). On a nationwide scale, lung cancer ranks 7th or 8th in men and beyond 10th in women whereas on a global scale it ranks 1st and 4th in men and women, respectively (Emami et al., 2009; Mousavi et al., 2009). Despite lower frequency of lung cancer in Iran, the patients with this type of cancer have a short-term survival (Zahir and Mirtalebi, 2012) ranking 2nd in men and 3rd in women as the cause of cancer-related death (Mousavi et al., 2009). Tobacco smoking alone is the most important risk factor for lung

cancer as it accounts for more than 70% of pulmonary carcinomas (WHO, 2013). However, the relationship of smoking with different types of histological findings of lung cancer is not the same and while there is a strong correlation between smoking and the incidence of SCC and SC, its association with AC is lower (Rosai, 2009). Differences between men and women in developing this type of cancer is evident while more susceptibility to smoking-related lung cancer in women is still controversial (Matteis et al., 2013). Also, despite low prevalence of cigarette smoking in Chinese women, the incidence of lung cancer among these women is even higher than those in a number of European countries (Jemal et al., 2011). Although the importance of smoking in developing lung cancer is crucial, yet 10-15% of all lung cancers occur in never smoker (Rosai, 2009). In a study of lung cancer in Asian countries, the attribution of never smokers was as high as 30% in whole and 50% in women (Zhou and

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Christiani, 2011). In addition to smoking, there are other factors for which a well-established correlation with lung cancer including the profession-related carcinogens particularly in men is documented (Couraud et al., 2012). Feminine sexuality, histological type of adenocarcinoma (Rosai, 2009; Yang, 2011; Couraud et al., 2012; Matteis et al., 2013), and low age (Zhou and Christiani, 2011) comprise a higher proportion of non-smokers with lung cancer. Furthermore, the incidence of adenocarcinoma in non-smokers is higher in Asian population (Rosai, 2009) particularly in women (Kadara et al., 2012). The histological type of lung cancer which consists of 4 major classes (Petersen, 2011) is of prime importance in determining the type of therapy and prognosis. Changes in the frequency of different histological types and an increase in AC type are reported in several studies (Nakamura and Saji, 2013).

There are only a limited number of published studies associated with lung cancer reported from Iran. Since investigating the demographic, clinical, and histological characteristics and risk factors is the first yet essential step in achieving a clear and accurate picture of a cancer therefore, the present study attempted to perform an 11-year study based on hospital records to evaluate the cases of primary lung cancers at a referral hospital for respiratory diseases in one of the provinces of Iran. Obviously, this could lead to better recognition of this cancer and a pace towards the early detection, timely treatment, and prevention of the disease.

Materials and Methods

This retrospective study included all cases of primary lung cancer based on the results of registered cancer reports on cytological and pathological specimens at Bou-Ali Sina Hospital in Qazvin (Iran) during March 2001 to March 2012. Cases suspected but not confirmed of having malignancy, secondary malignancies and those with unidentified primary or secondary causes were excluded from the study. Variables including age, gender, residential location (urban/rural), use of tobacco, substance abuse, being a hospitalized or non-hospitalized patient, and the history of tuberculosis were determined according to patient's medical records. There are 4 major types of primary lung cancer including squamous cell carcinoma (SCC), small cell carcinoma (SC), adenocarcinoma (AC), and large cell carcinoma (LCC). In fact, LCC is, by definition, a poorly differentiated malignant squamous or glandular tumor (Rosai, 2009) and since the differentiation of these poorly differentiated types in small size biopsy is impossible therefore, in these cases it is necessary to use a more general term i.e. non-small cell lung cancer (NSCLC) (Petersen, 2011). As the samples of this study were all biopsy specimens, the cases of poorly differentiated non-small cell found in this study were classified in a group marked as undifferentiated carcinoma. Primary malignancies were classified into 5 types including AC, SC, SCC, undifferentiated carcinoma, and the last one as "other types" that is every type of cancer other than above.

Regarding the location of tumor, we considered

different types of classifications. A) The orientation of tumor as right, left, and bilateral or unknown. B) Tumor location as central or peripheral based on the method of obtaining specimen (bronchoscopy with biopsy or bronchoalveolar lavage (BAL) as central versus pleural needle biopsy or cytology exam of pleural fluid marked as peripheral). C) The exact place of central tumor included the main, superior, middle, and inferior lobe bronchi, lingula and multifocal or unidentified.

Based on clinical manifestations, the patients were classified into two groups: (a) those with non-advanced and general manifestations including cough, dyspnea, chest pain, hemoptysis and fever and (b) those with advanced manifestations such as hoarseness and the existence of metastatic lesions in the brain and adrenal gland, as well as the presence of superior vena cava syndrome (SVCS).

Definite or possible etiologic agents were determined through inspecting the patients' medical records. If there was a history of working in mines or industrial factories with profession-related carcinogens, this was also taken into consideration. In addition, a history of long-term home-made bread baking was regarded as a possible cancer-related risk factor and documented. Data were analyzed through descriptive and analytical statistics including frequency distribution, chi square test, and t-test. A p-value ≤ 0.05 was considered as significant.

Results

A total of 203 cases of lung cancer as primary tumor were included of which 165 (81.3%) were men and 38 (18.7%) women. The age of patients ranged between 19-81 years and the mean age was 65.7 years (SD=11.2) on the whole [62.7 years (SD=15) for women and 66.4 years (SD=9.8) for men] with no significant difference in mean age between them ($p=0.171$) however, women group included all individuals under 30. Of 203 patients, 155 (76.4%) cases were hospitalized and 48 (23.6%) outpatients. Of total patients, 110 (54.2%) cases were living in urban areas and 93 (45.8%) in rural. Cigarette smoking was found in 130 (64%) of cases while 45 (22.2%) were non-smokers and in 28 (13.8%) cases the status was unclear. The percentage of smokers was 75.2% in male patients and 15.8%, in female patients and there was a significant relationship between smoking and gender ($p<0.001$). History of substance abuse (mostly opiates) were positive in 35 (17.2%) of subjects, negative in 126 (62.1) cases, and unknown in 42 (20.7%) patients. The history of profession-related lung cancer was available for 27 (13.3%) patients among those 3 cases (men) with history of working in mines and 5 cases (men) with history of working in industrial-chemical factories (occupation-related cancer in 4.8% of male patients). A history of home-made bread baking was found for 18 female and 1 male villagers (47.4% of female patients).

The most common complaint regarding the presentation of the disease was due to pulmonary or systemic symptoms present in 185 (91.1%) cases. These symptoms were cough (76.5%), dyspnea (59.4%), weight loss (51.9%), hemoptysis (33.5%), fever (8.64%), and chest pain

(2.16%). In other patients (18/8.9%), there were more severe symptoms indicative of regional and distant spread of tumor including hoarseness (4 cases), brain metastasis (6 cases), adrenal gland metastasis (3 cases), superior vena cava syndrome (SVCS) (2 cases), dysphagia (1 case), cervical lymphadenopathy (1 case), and bone lesions (1 case). Meanwhile, except these 18 patients, 4 other patients had died shortly after hospitalization; therefore, 10.8% of total or 14.2% of hospitalized patients were admitted while having advanced signs of the disease or died several days after hospitalization. Laboratory report on confirmed pulmonary tuberculosis was present for 3 hospitalized patients (2% of inpatients).

Anatomically, in 108 (53.2%) cases the tumor location was on the right side, 73 (36%) cases on the left side, and in 22 (10.8%) cases unclear or bilateral. Also, in 148 (72.9%) cases the lesion was centrally located. In central tumors, 56 (37.8%) cases were in the superior lobe bronchus, 38 (25.7%) cases in the main bronchus, 27 (18.2%) cases in the inferior lobe bronchus, 12 (8.1%) cases in the middle lobe bronchus, 3 (2%) cases in the lingula lobe, and 12

Table 1. Distribution of Variables among Different Histologic Types of Tumors

	Histological type				
	SCC (%)	SC (%)	AC (%)	Undifferentiated (%)	Other (%)
Gender					
Male	96(58.2)	22(13.3)	19(11.5)	9(5.5)	19(11.5)
Female	11(28.9)	5(13.2)	11(28.9%)	4(10.5)	7(18.4)
p-value	0.008				
Smoking					
Yes	73.80	70.40	36.70	46.20	57.70
No	8.40	18.50	56.70	34.60	38.50
p-value	<0.001				
Place of residence					
Urban	60.00	14.50	10.00	5.50	10.00
Rural	44.10	11.80	20.40	7.50	16.10
p-value	0.084				
High risk professions					
Yes	29.60	3.70	37	14.80	14.80
No	56.20	14.80	11.40	5.10	12.50
p-value	0.001				

*SCC: Squamous cell carcinoma; SC: Small cell carcinoma; AC: Acenocarcinoma; Undifferentiated: Undifferentiated Carcinoma; Other types: other types cancer

Table 2. Distribution of Variables among Different Locations of Tumors

		Location		p-value
		Central	Peripheral	
Histological type	SCC	88.90%	11.10%	<0.001
	SC	88.80%	11.20%	
	AC	33.30%	66.70%	
	Undifferentiated	61.50%	38.50%	
	Other types	42.30%	57.70%	
Gender	Male	77%	23%	0.009
	Female	55.30%	44.70%	
Smoking	Yes	77.70%	22.30%	<0.001
	No	44.40%	55.60%	
Place of residence	Urban	76.40%	23.60%	0.268
	Rural	68.80%	31.20%	

*SCC: Squamous cell carcinoma; SC: Small cell carcinoma; AC: Acenocarcinoma; Undifferentiated: Undifferentiated Carcinoma; Other types: other types cancer.

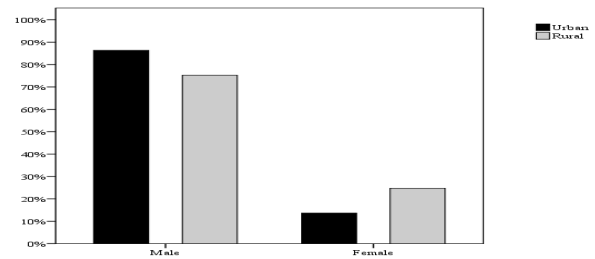


Figure 1. Urban and Rural Residential Location of Male and Female Patients

(8.1%) cases with multi-focal or unidentified nature.

The histological types of tumors were SCC (107/52.7%), AC (30/14.8%), SC (27/13.3%), undifferentiated carcinoma (13/6.4%), and other types (26/12.8%). A significant relationship was found between the histological type of tumor and gender ($p=0.008$). SCC type was the most common type in men while in women the malignancies were due to both SCC and AC types which occurred at a similar proportion (Table 1). Also, there was a significant relationship between the histological type of tumor and smoking ($p<0.001$) in which the highest rate of smoking was found in SCC and SC (70.4%) while the lowest rate was observed for AC (Table 1). No significant relationship between the histological type of tumor and age was established ($p=0.412$). Table 2 shows the distribution of variables among central and peripheral tumors.

No association between smoking and the place of residence (urban/rural) was found ($p=0.189$). Furthermore, there was a significant relationship between the place of residence and gender ($p=0.049$); 60.5% of women were from rural regions and proportion of women in rural areas was greater than urban (24.7% vs 13.6%) (Figure 1). Statistically, no significant association between the place of residence and the histological type of tumor, location of tumor (central vs peripheral), orientation of tumor, and mean age was shown ($p>0.05$).

Finally, there was a significant relationship between high risk professions and the histological type of tumor ($p<0.001$) (Table 2). Among these 27 cases, 19 subjects were non-smokers, 6 were smokers, and 2 with unknown history of smoking.

Discussion

The present study is an investigation on lung cancer in a tertiary and referral hospital in Qazvin, a central province of Iran. The mean age of our patients was 65.7 years (SD=11.2) years which was close to other studies previously reported from Iran (Ehteshamifar et al., 2001; Hosseini et al., 2009; Tarrahi et al., 2009; Zahir and Mirtalebi, 2012; Ghobadi et al., 2013). This finding was also similar to those found in several studies carried out in other countries (Santos-Martinez et al., 2005; Missaoui et al., 2011; Demirci et al., 2013; El-Basmy, 2013). Clinically, similar to other studies, the majority of patients seeking medical advice complained of cough, dyspnea, chest pain, and hemoptysis (Ehteshamifar et al., 2001; Ghobadi et al., 2013; Mandal et al., 2013). Also at least 14.2% of hospitalized patients were admitted while

having advanced signs including metastases. Metastases were reported in 32.5% of lung cancer patients in a study from India (Mandal et al., 2013). Comparable to previous studies, the involvement of lung was higher in the right side with the lesions mostly within the superior lobes rather than in other areas (Missaoui et al., 2011; Sahin and Yildiz, 2011; El-Basmy, 2013; Ghobadi et al., 2013; Mandal et al., 2013).

In the present study, the male/female (M/F) ratio was 4.34. In similar studies reported from Iran, the M/F ratio varied between 2.79 and 5.09 (Ehteshamifar et al., 2001; Hosseini et al., 2009; Tarrahi et al., 2009; Najafi et al., 2010; Zahir and Mirtalebi, 2012; Ghobadi et al., 2013). Lower M/F ratios have been reported in the studies from Southern Asian and Middle Eastern countries [1.1 in India (Mandal et al., 2013) and 3.01 in Kuwait (El-Basmy, 2013)]. Concerning the prevalence of smoking in Qazvin, no comprehensive study was available however, the results of a meta-analytic review, including a national study, showed the prevalence rate of smoking among Iranian men is 2-20 times (4-5 times on average) higher than in women (Meysamie et al., 2012).

Considering the importance of smoking in the development of lung cancer, the M/F ratio found in this study is not beyond our expectation although the percentage of smoker female patients in our study was relatively low. The rate of smoking in the present study was 64%, a figure close to the result of most studies carried out in Iran (Ehteshamifar et al., 2001; Hosseini et al., 2009; Tarrahi et al., 2009; Zahir and Mirtalebi, 2012) although lower than the finding of a single study conducted in one of the provinces of Iran in which the frequency of smoker patients was reported 90.8% (Ghobadi et al., 2013). The contribution of smoker women in our study was 15.8%. This contribution was 13-14% (Ehteshamifar et al., 2001; Hosseini et al., 2009) or 38.7% (Tarrahi et al., 2009) in other Iranian studies. Meanwhile, the proportion of female smokers in some reports from other countries was much higher than what we found, including 34.1% in Turkey (Demirci et al., 2013), 38% in Spain (Santos-Martinez et al., 2005), and 68% in India (Mandal et al., 2013). A probable reason for this could be a lower rate of smoking in Iranian women than those countries.

Abuse of opiates was found in 17.2% of our patients. The prevalence of opiate abuse among Iranian lung cancer patients was investigated in two separate studies which produced different results [(13.2% (Ehteshamifar et al., 2001) and 34.7% (Ghobadi et al., 2013)]. The higher rate of smoking (90%) in the study with higher rate of opiate abuse (Ghobadi et al., 2013) could be a reason for observed differences between these studies and also could propose a possible relationship between smoking and opiate abuse in developing lung cancer.

Histologically SCC ranked first, accounting for 52.7% of cases. As the majority of our patients were men with 72.9% of cases with central lesions, this histological majority was not beyond our expectation and in agreement with several reports from Iran (Ehteshamifar et al., 2001; Tarrahi et al., 2009; Najafi et al., 2010; Zahir and Mirtalebi, 2012) and also with some from other areas (Santos-Martinez et al., 2005; Rabahi et al., 2012; Mandal et

al., 2013). Two other histological types of lung cancer (SC and AC), with a tiny difference, ranked second and third which were similar to findings reported by others, nationally and globally (Ehteshamifar et al., 2001; Tarrahi et al., 2009; Najafi et al., 2010; Rabahi et al., 2012; Zahir and Mirtalebi, 2012; Demirci et al., 2013; Mandal et al., 2013). In some other countries, AC type of cancer was reported to be the most common histological type of lung malignancy (Rosai, 2009; Thompson et al., 2012; Nakamura and Saji, 2013) but this trend toward AC was not occurred in our study because of low percentage of female patients and probably no significant change in smoking habits in our patients.

According to the histological distribution of lung cancer based on gender, the findings of this study was comparable to a study reported from Turkey (Demirci et al., 2013) in which SCC comprised the majority of tumors (50.9%) in men. In a study reported from the southern part of Iran, SCC was the most frequent histological type of cancer in men (41.4%) followed by AC and SC, although the difference was negligible (Tarrahi et al., 2009). However, a report from Spain indicated that although SCC in men was at the top of the list (36.2%) but the AC contribution was also high (26.6%) (Santos-Martinez et al., 2005). In a study from India, SCC and AC constituted 58.1% and 25.1% of lung cancer in men (Mandal et al., 2013).

In the current study, the incidence of SCC and AC in women was similar and found to be the most common forms of lung cancer. The most common types of lung cancer, reported in a study from the southern regions of Iran, were SCC (35.1%), SC (26.3%), and AC (12.2%) whereas in Turkey the figures were 16.4%, 24%, and 22% for SCC, SC, and AC, respectively. In a study in India in which 68% of females were smokers, rates for SCC, SC and AC were 41.8%, 37.2% and 17.5%, respectively (Mandal et al., 2013). Smoking is the most common risk factor of lung cancer and associated with these 3 types of malignancies however, this association is higher with SCC and SC than AC. On the other hand, AC in women, regardless of smoking, is higher than men as reported in a study from Spain in which AC in women ranked first with an incidence rate of 56.2% (Santos-Martinez et al., 2005). Therefore, given the low percentage of smoker female patients in our study, it was expected AC to have a higher contribution than SCC which failed to achieve. The reason for this could be due to passive smoking in women which was impossible to investigate because of the retrospective nature of the present study. Furthermore, the air pollution present in the closed environments, which will be discussed later, may have produced a condition similar to that of smoking in women, leading to increased number of SCC cases in our study.

The proportion of patients who lived in urban to rural regions, similar to the reports from both Iran (Ghobadi et al., 2013) and Turkey (Demirci et al., 2013), was almost similar however, a significant association between gender and residential location was found, showing a higher participation (24.7% vs 13.6%) for women among patients living in villages ($p=0.049$). A relationship between gender and residential location was not dealt with or remained

uninvestigated in the studies mentioned earlier (Demirci et al., 2013; Ghobadi et al., 2013). As there was no significant correlation between smoking and residential location ($p=0.189$) and that the majority of female patients were non-smokers, it seems that there was probably other predisposing factor except smoking to have increased the contribution of female patients staying in rural regions. As mentioned earlier, out of 38 female patients, 23 were from rural regions and 18 of them with a history of long-term bread baking; giving the idea that there is possibly a direct correlation between a history of long-term home-made bread baking and the incidence of lung cancer. The results of previous studies could describe the nature of such association. In a study reported from Iran, it was shown that a substantial proportion of women living in rural areas located in one of the provinces of Iran suffered chronic respiratory diseases and this occurred while the frequency of tobacco use among these women was reported around 1%. It was described that bread baking and the use of solid fuel were among the risk factors causing an increase in the number of people with this disease (Golshan et al., 2002). In villages, wood is routinely used for bread baking and other sources of solid fuel (including dung) for heating. Long exposure to the fumes of these types of fuel causes people to face chronic diseases such as asthma and bronchitis. Several studies have shown the relationship between the use of different types of solid fuel and the diseases such as asthma, chronic obstructive pulmonary disease (COPD), and chronic bronchitis (Agrawal, 2012; Kodgule and Salvi, 2012; Kurmi et al., 2012) and even pulmonary tuberculosis and lung cancer (Kodgule and Salvi, 2012; Kurmi et al., 2012).

Biomass energy is extensively used for heating purposes in rural houses while these residential places lack proper smoke/heat exhaust ventilation system. This type of solid fuel (biomass) is the major origin of air pollutants in such closed environments of rural properties (Balmes, 2010). Women and children in these environments are at higher risk because of increased exposure to air pollutants (Kodgule and Salvi, 2012; Kurmi et al., 2012; Reid et al., 2012). Also, the female villagers engaged in baking home-made bread, experience consecutive hours of working by the side of traditional ovens and long-term exposure to fumes and therefore with a higher risk for air pollutant-associated diseases. In 2010, the International Agency for Research on Cancer (IARC) declared that the pollution produced by biomass utilization is considered as a possible carcinogen for human (Reid et al., 2012). In a study reported in China in 2008, an association between the indoor air pollution (IAP) due to solid fuel and chronic respiratory disease and lung cancer was confirmed (Galeone et al., 2008). Also, the association between more efficient ventilation of residential building and reduced risk of respiratory diseases has been investigated in a study (Kurmi et al., 2010). In a study carried out in the province of Ardebil (northern Iran), it was shown that 11.3% of patients with lung cancer had a history of bread baking (Ghobadi et al., 2013) however there was no further details on the percentage of lung cancer among rural women. Considering the lower number of women among patients, a trend similar to the present study, and that the

people in charge of baking bread in villages are mostly women, probably the history of bread baking in women was higher than 11.3%. In another study reported from Iran (Karimzadeh et al., 2011), it was revealed that there is a correlation between the consumption of home-made bread baked in traditional oven and lung cancer, raising the idea that even the consumers of such breads are at risk of developing lung cancer.

In the current study, tobacco use was the most important risk factor for lung cancer, however, a history of home-made bread baking in 47.4% of women and a history of working in mines and industrial-chemical factories in 8 men (4.8%) were available. Regarding the retrospective nature of the present study and the possibility of failure in recording all cases of occupation-related lung cancer, the role of occupational risk factors associated with cancer should be higher than that found in this study. The contribution of lung cancer due to occupation-related carcinogens was estimated around 1.5% for women and 12% for men, a study in which a history of baking home-made bread was not considered as an occupation-related risk factor of lung cancer (Mosavi-Jarrahi et al., 2009).

Prior to diagnosis of malignancy, pulmonary tuberculosis was detected in 2% of our hospitalized patients based on direct examination of sputum smear prepared from pulmonary secretions. Culture-proven pulmonary tuberculosis was found in 6.8% of patients with lung cancer in Iran (Asnaashari et al., 2013). Positive history of tuberculosis was reported in 16.3% of patients in a study from India (Mandal et al., 2013). Differences in diagnosis methods (direct smear versus culture) and in prevalence rates of tuberculosis in different population are potential causes of different rates while lack of enough investigations for diagnosis of tuberculosis in patients of our study could be another reason.

Limitations-This was a retrospective study based on hospital medical records. Since there was no consistent pattern to be followed in registering such information, we were forced to use the term "unknown" to investigate some variables, particularly when information on some variables were inadequate. Additionally, there was no possibility for dealing with more details such as duration and degree of tobacco use in smoker patients or investigating passive smoking due to absence of comprehensive information.

In conclusion, there was a significant association between gender and residential location, smoking, and the location of tumor (central or peripheral). The location of 77% of tumors in men and 55.3% in women was in the central area. SCC was the major (58.2%) histological type of tumors in men while SCC and AC were found at nearly similar proportion in women. The percentage of male smokers was 75.2% and that of female smokers 15.8%. A long-term history of home-made bread baking was observed in 47.4% of female patients and a history of occupation-related cancer in 4.8% of male patients. It seems that home-made bread baking to be a possible risk factor of lung cancer.

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