ORIGINAL RESEARCH

DOI: 10.37047/jos.2020-73409

Epidemiology of Lung Cancer in Women: A Hospital-Based Descriptive Study

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The study was presented as an oral presentation at the ICONS 2018 congress in Antalya, 20-23 September 2018.

ABSTRACT Objective: Lung cancer required much greater attention as it is the most common cause of death. According to statistics in 2010, 85% of lung cancer in men and 57% in women are attributed to tobacco smoking. The aim of the study was to describe the clinical and pathologic characteristics of the female patients who visited the Department of Medical Oncology of Acıbadem Maslak Hospital between 2009 and 2017. **Material and Methods:** Clinicopathologic data collected for analyses included age at diagnosis, history of cigarette use, comorbid conditions, family history, tumor-node-metastasis stage, pathologic subtypes of lung carcinoma, and the given therapy. From July 2017 to February 2018, we collected data of 540 female patients with lung cancer at the Department of Medical Oncology of Acıbadem Maslak Hospital. **Results:** Among 540 patients, 185 patients (34.3%) were nonsmokers, 106 (19.6%) were current smokers, and 210 (38.9%) were former smokers. Data on common comorbid conditions such as hypertension, diabetes mellitus, and coronary artery disease were collected, and the conditions were classified according to the smoking status of the patients. Among current and former smokers, 36.7% were diagnosed with hypertension, 18.3% with diabetes mellitus, and 11% with coronary artery diseases. Moreover, 75% of all patients were diagnosed with nonsmall-cell lung cancer (NSCLC), whereas 16% were diagnosed with small-cell lung cancer. Adenocarcinoma is the most common histological type of cancer seen in patients with NSCLC (77%), followed by patients with squamous cell carcinoma (15%). **Conclusion:** Factors other than tobacco use, such as radon exposure, air pollution, radiation exposure, and an unbalanced diet are responsible for the increasing incidence of lung cancer. However, further studies are warranted to investigate the cause of the epidemic differences in women, particularly the gender bias in nonsmoker patients with lung cancer.

Keywords: Lung cancer; epidemiology; nonsmoker women; smoking; cancer

Cancer is a worldwide growing health problem with high mortality and morbidity rates, along with expensive treatment costs. According to the updated GLOBOCAN 2018 data, cancer is the first cause of death worldwide. In 2018, 18.1 million people were diagnosed with cancer, and 9.6 million deaths occurred from cancer.[1]

Lung cancer, which was described as "one of the rarest forms of cancer" in 1912 before the introduction of cigarettes, was the most common diagnosed cancer in 2018 (2.1 million, 11.6% of the total). Lung cancer needs to be considered as it is the most common cause of death (1.8 million, 18.4% of the total).[1] Although several developed nations now have declining rates of lung cancer, the incidence and mortality rates among women have increased in several western countries. Although the incidence of lung cancer decreased among men, an increasing pattern was noted among women, which was associated with increased smoking rates after the second

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Peer review under responsibility of Journal of Oncological Sciences.

Received: 08 Jan 2020 ***Received in revised form:*** 14 Mar 2020 ***Accepted:*** 18 Mar 2020 ***Available online:*** 17 Apr 2020

world war. However, according to the statistics in 2010, 85% of lung cancer in men and 57% in women were attributed to tobacco smoking. This difference suggests other carcinogenic pathways in women, unlike men.[2]

According to the data retrieved from the Turkish Ministry of Health Department of Cancer Control database in 2014, lung cancer is the most common cancer (30.13%), accounting to 52.5% in men and 8.7% in women.[3] Similar to the western countries, the incidence of lung cancer raised insidiously among women in Turkey, although it decreased in men.[3] No study exists on the trend of lung cancer in Turkey since 2014; therefore, the current epidemics cannot be accurately evaluated. Epidemiologic data can be extremely helpful in designing new prevention and treatment strategies for several diseases.[4] Therefore, this study aimed to show the demographic and clinical features of female patients diagnosed with lung cancer and presented to Acıbadem Maslak Hospital between 2009 and 2017.

MATERIAL AND METHODS

PATIENTS

From July 2017 to February 2018, we collected data of 540 female patients with lung cancer at the Department of Medical Oncology of Acıbadem Maslak Hospital. Information about the patients who visited the department between 2009 and 2017 was obtained from the hospital information system. This study was approved by the ethical committee. According to the ethical committee, informed consent was not needed as no names or ID numbers of the patients were used. Female patients with pathologically confirmed primary lung cancer were included in the study. Patients with lung metastases secondary to other primary carcinomas were excluded.

CLINICOPATHOLOGIC VARIABLES

Clinicopathologic data collected for analyses included age at diagnosis, history of cigarette and alcohol use, comorbid conditions, pathologic tumor-node-metastasis stage, tumor differentiation, and histologic subtypes of lung carcinoma according to the 2015 World Health Organization Classification of Lung Tumors.

Statistical Methods

An R program was used to analyze the collected data.

RESULTS

DESCRIPTIVE EPIDEMIOLOGY

Smoking and Age

Among 540 patients, 185 patients (34.3%) were nonsmokers, 106 (19.6%) were current smokers, and 210 (38.9%) were former smokers. However, the smoking status of 39 patients (7.2%) was unknown because of missing records. The mean age at diagnosis of all patients according to smoking status is provided in Table 1. No significant difference was observed between the age of smokers and nonsmokers (p=0.4005; 95% CI: -1.25 to 3.12). The mean age at diagnosis of all patients was 60 years. The youngest patient was 24 years old, and the oldest was 89 years old.

According to the records of 316 patients who are current smokers, and the ones who quitted smoking, the number of cigarette package × year is provided in Table 2. However, this information was not available in the health records for 166 patients.

Comorbidities

Information on common comorbid conditions such as hypertension, diabetes mellitus, and coronary artery disease was collected from the patients' medical records, and the conditions were classified according to the smoking status of the patients. Among current (106 patients) and former (210 patients) smokers, 116 (36.7%) were diagnosed with hypertension, 58 (18.3%) with diabetes mellitus, and 35 (11%) with coronary artery diseases. These numbers were lower among nonsmoker patients. Among nonsmokers, 66 patients (35.6%) were diagnosed with hypertension, 26 (14%) with diabetes, and six (3.2%) with coronary artery disease. In addition, among patients with unknown smoking status, hypertension was noted in five patients (12%), diabetes in four (10.2%), and coronary artery disease in three (7%).

Other Primary Malignancies of Patients

According to medical history, 48 (8.9%) patients had other primary cancers, except lung cancer; 44 had malignancy before lung cancer, and four of them de-

TABLE 1: Age distribution according to smoking status.

Smoking status	Mean age (years)	Minimum age (years)	Maximum age (years)
Current Smoker	60	40	86
Non-smoker	61	24	87
Former Smoker	61	25	89
All patients	60	24	89

veloped another malignancy afterward. After developing lung cancers, rectum, Merkel cell, uterus, and esophagus cancers were noted. Whereas, breast, bladder, gynecological, and head, and neck cancers developed before lung cancer. As expected, breast cancer is the most common, with the highest incidence rate (24.9%) among women in Turkey.[3]

TABLE 2: Smoking frequency as Package × Year.

Package × Year	
Minimum	2
Mean	37.8
Maximum	100

HISTOPATHOLOGY

The main histopathologic subtypes in this study were nonsmall-cell lung cancer (NSCLC), small-cell lung cancer (SCLC), carcinoid tumors, neuroendocrine tumors, mesothelioma, and mixed tumors that comprise both SCLC and NSCLC.

Table 3 shows the percentages of the main histological types of lung cancer according to the smoking status. In addition, 75% of all patients are diagnosed with NSCLC, and 16% with SCLC. The other rarely seen histologic subtypes are shown in Table 3.

The results, according to the smoking status, were as expected. It is known that SCLC is almost always seen in smokers.[5] As shown in Table 3, 4% of nonsmokers and 24% of smokers were diagnosed with SCLC. NSCLC is dominant in both smokers and nonsmokers; it is more prevalent in nonsmokers than patients with smoking history (88% and 67%, respectively).

The three main subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, and their prevalence according to the smoking status is shown in Table 4. Adenocarcinoma is the most common cancer (77%), followed by squamous cell carcinoma (15%) in all patients. Moreover, it was most frequent among female smokers and never smokers.

Molecular Pathology and Targeted Therapy

Cancer results from mutations in the cellular genome. Therefore, along with the histopathology, it is crucial to find the genomic abnormalities to understand cancer better and ascertain more effective treatment for every patient. The targeted therapies

TABLE 3: Main subtypes of lung cancer.

Main Subtypes	Patients with a smoking history (n=316), %	Patients without a smoking history (n=185), %	Unknown smoking status (n=39), %	All Patients (n=540), %
NSCLC	67	88	69	75
SCLC	24	4	12	16
Mixed type	0.7	0	0	0.37
Neuroendocrine	1.3	2	0	1.18
Mesothelioma	0	1	4	0.5
Not known	7	4	15	7

NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer.

TABLE 4: NSCLC subtypes.

NSCLC Subtypes	Patients with smoking history (n= 213), %	Patients without smoking history (n=163), %	Unknown smoking status (n=27), %	All Patients with NSCLC (n=403), %
Adenocarcinoma	69	87	81	77
Squamous cell	20	7	19	15
Large cell	2	1	0	7
Adenosquamous	1	0.5	0	3
Not known	8	4.5	0	25

against endothelial growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) have changed the clinical prognosis of patients over the past years.[6]

As we considered data from 2009 to 2017, the genetic tests were not common in the hospital setting in these years; however, lately, it is used for the patients diagnosed with NSCLC. The reported molecular alterations in each NSCLC subtype are given in Table 5. As shown in Table 5, the listed alterations were mainly found in adenocarcinoma, as most of them are specific to adenocarcinoma, such as ALK and ROS.[6] EGFR mutations are almost always seen in adenocarcinoma, as these are the most frequently detected mutation before ALK translocation.

The used targeted therapies are summarized in Table 6. Other treatment modalities other than targeted therapy are listed in Table 7.

Stage

Although in 7% of the cases, the disease stage could not be found in the records, most of the patients were in stage IV during the diagnosis. Table 8 shows the stages of our patients in more detail.

DISCUSSION

The epidemiologic study by Jemal A et al. found that the incidence rate of lung cancer is significantly higher in Hispanics and non-Hispanic white women who were born in the 1960s. Furthermore, they indicated that smoking behavior does not explain this finding, and still, the average number of cigarettes smoked per day by women was lesser than that by men. The hypothesis that women are more susceptible to smoking was studied; however, no convincing results have been found in the literature. The risk of developing lung cancer after smoking cessation differs according to subtypes in both men and women, and the risk reduction of adenocarcinoma, which is the main histological subtype in women patients, was 8% and that of small cell lung cancer was 17%.[7]

The World Health Organization estimates that 25% of lung cancer worldwide occurs in never smokers, named as "lung cancer in never smokers" (LCINS). However, this rate is considerably different between women and men. For instance, a study of Bas-Rhin Cancer Registry in France found that the prevalence of LCINS was 1.4% and 28.9% among men and women, respectively. Furthermore, KBP-

TABLE 5: Molecular pathology.

	Adenocarcinoma (n)	Squamous (n)	Adenosquamous (n)	Large Cell (n)	Total (n)
EGFR	50	1	1	-	52
ALK	20	-	-	-	20
KRAS	1	-	-	-	1
NRAS	1	-	-	-	1
ROS	1	-	-	-	1
Nothing found	56	8	1	1	66

EGFR: Endothelial receptor growth factor; ALK: Anaplastic lymphoma kinase.

TABLE 6: Molecular therapy.

Molecular agent	Number of patients
EGFR (Erlotinib, Afatinib, Gefitinib)	57
ROS, ALK (Alectinib, Crizotinib, Ceritinib, Lorlatinib)	14
Not given	304

TABLE 7: Treatment modalities.

Treatment	Number of patients
Surgery	109
Radiotherapy	282
Chemotherapy	384
Immunotherapy	18

2000 study revealed a similar rate in men and women (2.5% and 32.3%, respectively).[8] These studies indicate that women are more affected by carcinogens other than smoking.

In this study, we reported the epidemiological and clinical properties of 540 female patients diagnosed with lung cancer. Several studies that have examined the histological subtypes of lung cancer have shown that the incidence of adenocarcinoma is rising in both sexes and surpasses the rate of squamous cell carcinoma. Moreover, these studies indicate that adenocarcinoma is the main histological subtype in female never smokers.[8] Our findings showed 87% of never smokers were diagnosed with adenocarcinoma, thus supporting the results of previous studies (Table 3).

Our study had several limitations, and the first one was its retrospective design. Information with respect to smoking status, package × year, histopathology, treatment modalities, and survival information was lacking. Moreover, several new mutations have been reported in recent years associated with lung cancer, which were not documented in our study. Therefore, no molecular alterations were found in 47% of the examined tissues in this study. We found that 34.3% of the patients were nonsmokers, and adenocarcinoma was found to be the main histologic subtype. Another limitation of this study was that the risk factors other than smoking were not studied. This point is almost always missing in the health records of hospitals. However, in Turkey, where women were often exposed to passive smoking or cooking oil fume, it can be a crucial issue while investigating the occurrence of lung cancer in the nonsmoker women population.[9]

We studied the comorbidities of the patients and found that it differs from the general population. The most common comorbidity was hypertension, followed by diabetes mellitus and thyroid disorders in this study. Contrary to this, chronic obstructive pulmonary disease (COPD) was found to be the most common comorbidity.[10] However, COPD was the third common comorbidity in our study population. As smoking is not very common among women, this difference can be understood.

To conclude, we can say that lung cancer is one of the most common malignant tumors with high mortality and morbidity. In the report of GLOBOCAN 2018, the rising incidence of lung cancer in women was emphasized, and it was said that precautions should be taken against it, including the smoking behavior of women. We know that factors other than tobacco use such as radon exposure, indoor and outdoor air pollution, relative harmful occupational exposure, hereditary susceptibility, radiation exposure, and an unbalanced diet are re-

TABLE 8: Stage of lung cancer at diagnosis.

Stage	Current smokers	Former smokers	Never smokers	Unknown status	All patients
1	14	31	20	1	66
2	10	30	25	0	65
3	15	36	26	0	77
4	53	108	107	28	296
Unknown	14	5	7	10	36

sponsible for the increasing incidence of lung cancer.[11] However, the cause of the epidemic differences in women, particularly the gender bias in nonsmoker patients with lung cancer, has not yet been clearly identified. Further studies need to investigate the factors contributing to these gender differences.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Özlem Er, Didem Saka;* ***Design:*** *Özlem Er;* ***Control/Supervision:*** *Özlem Er;* ***Data Collection and/or Processing:*** *Didem Saka, Elif Özuğuz;* ***Analysis and/or Interpretation:*** *Özlem Er, Didem Saka;* ***Literature Review:*** *Elif Özuğuz, Didem Saka;* ***Writing the Article:*** *Didem Saka, Elif Özuğuz, Özlem Er;* ***Critical Review:*** *Özlem Er;* ***References and Fundings:*** *Özlem Er;* ***Materials:*** *Özlem Er.*

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