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Original Research Article.

A Study of the Clinical, Pathological and Radiological Profile of Lung Cancer in Non-Smokers

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ABSTRACT

Aim and Objective: To study the clinical, pathological and radiological profile of lung cancer in non-smokers in a tertiary care center.

Methods: 53 non-smokers diagnosed with lung cancer attending the Department of Respiratory Medicine, King George's Medical College from September 2015 to August 2017 were enrolled. Record of all diagnostic investigations and procedures performed namely transthoracic fine needle aspiration cytology (FNAC) and biopsy, bronchoscopy, thoracoscopy, closed pleural biopsy, lymph-node FNAC and biopsy, routine blood and sputum examinations and a detailed history were obtained. Data was analysed retrospectively.

Results: The mean age of presentation was 53.8±11.6 years. Majority were females (60.4%). Most common presenting symptom was cough (84.9%). Mean duration of symptoms was 6.9 months. Pallor was the most common clinical examination finding (41.5%). Mass with effusion was the most common radiological lesion (45.3%). 22.6% masses were centrally located. Transthoracic biopsy could diagnose 32 (60.4%) cases. Adenocarcinoma was the most common type in both males (76.2%) and females (78.1%). Epidermal growth factor receptor (EGFR) mutation was positive in 46.3% of adenocarcinoma. Exon 19 deletion was the more common mutation.

Conclusion: Lung cancer among never smokers is a distinct class with risk factors and genetic features discrete from those associated with tobacco smoke. Indoor air pollutants as well as ETS are definitely implicated risk factors. Targetable mutations are commoner in non-smokers and hence mutation testing should always be done in such patients. It is important to conduct studies about the diverse characteristics of this entity to consolidate our knowledge of this growing group of cancer.

Keywords: Non-Smoker, Lung Cancer, Adenocarcinoma, Profile, EGFR.

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INTRODUCTION

Lung cancer is not only the most commonly diagnosed cancer worldwide but also the leading cancer killer, accounting for 18.4% of all cancer related deaths.[1] The most commonly implicated risk factor for lung cancer is tobacco smoking. But the incidence of lung cancer continues to rise despite more number of people quitting to smoke as a result of awareness. This has interested researchers to explore other risk factors for this dreaded type of cancer. Recent studies have found that approximately 25% of all lung cancers are not attributable to tobacco.[2] Some of the established risk factors for lung cancer besides tobacco smoking

are environmental tobacco smoke, asbestos, chromium, arsenic, cadmium, silica, nickel and polycyclic aromatic hydrocarbons.[2,3]

Over the past 20 years many driver mutations for lung cancer have been identified. Activating mutations in the Epidermal growth Factor receptor (EGFR) gene and Anaplastic lymphoma kinase (ALK) rearrangement are the most common and widely studied of such molecular targets for therapy. Other potential driver mutations are in the KRAS, BRAF, HER2 genes and fusions in the RET and ROS oncogenes.

Such molecular abnormalities which are effective targets for Tyrosine kinase inhibitor(TKI) based therapies are more frequent in never smokers and Asians.[2,4] TKI based treatments have nearly doubled the median survival of patients who harbor these mutations.

Lung cancer in non-smokers can thus be considered a distinct group with different clinicopathological characteristics and geographical differences. A never smoker is defined as an individual who has smoked less than 100 cigarettes in a lifetime. There is limited Indian data on lung cancer in non-smokers. The present study hence explores the various aspects of this entity in India.

AIMS AND OBJECTIVES

To study the clinical, radiological and pathological profile of lung cancer in non-smokers in a tertiary care center in North India.

MATERIALS AND METHODS

Study Design: Cross sectional observation study.

Study Setting: Department of Respiratory Medicine, King George's Medical University, Lucknow.

Patients who were non-smokers and diagnosed with lung cancer attending the Department of Respiratory Medicine, King George's Medical College from September 2015 to August 2017 were enrolled in the study. Record of all diagnostic investigations and procedures performed namely CECT thorax, transthoracic fine needle aspiration cytology (FNAC) and biopsy, bronchoscopy, thoracoscopy, closed pleural biopsy, lymph node FNAC and biopsy, routine blood and sputum examinations and a detailed history of present and past illness were obtained from the patients. EGFR mutation and ALK rearrangement testing was done in patients with adenocarcinoma histology. 53 patients were enrolled and data was analysed retrospectively at the end of the 2 year study period.

Table 1. Age-wise distribution of patients.

Age	Male	Female	No. of patients (N=53)
≥30	2	0	2 (3.8%)
31-40	2	3	5 (9.4%)
41-50	4	8	12 (22.6%)
51-60	7	14	21 (39.6%)
>60	6	7	13 (24.5%)

Table 2. Distribution according to symptoms

Symptoms	No. of Patients	Percentage of Total (%)
Cough	45	84.90%
Sputum	8	15.09%
Chest pain	34	64.15%
Hemoptysis	5	9.43%
Dyspnoea	41	77.35%
Hoarseness of voice	3	5.66%
Fever	11	20.75%
Loss of appetite	35	66.03%
Pedal edema	5	9.43%
Neck and face swelling	2	3.77%
Weight loss	38	71.69%

Table 3. Distribution according to duration of symptoms

Duration of symptoms	No. of patients (N=53)
<1 month	0
1-<3 Months	2 (3.8%)
3-<6 months	18 (33.9%)
6-12 Months	33 (62.3%)
>12 months	0
Total	53

Table 4. Distribution according to radiological lesion.

Radiological lesion	No. of patients (N=53)
Mass	22 (41.5%)
Mass with effusion	24 (45.3%)
Effusion*	6 (11.3%)
Collapse with effusion	1 (1.9%)
Total	53

*No mass could be localized: Tx lesion

Table 5. Table showing yield of various procedures (multiple procedures were done in some patients)

	Transthoracic Biopsy	Endobronchial Biopsy	Closed pleural Biopsy	Thoracoscopic Biopsy	Non biopsy procedure*
Adenocarcinoma (n=41)	24	5	8	2	2
SCC£ (n=8)	5	2	1	0	0
SCLCμ (n=2)	1	1	0	0	0
Adenosquamous (n=0)	0	0	0	0	0
NSCLC(NOS)@ (n=2)	2	0	0	0	0
Total	32	8	9	2	2

*non-biopsy procedures include FNAC of peripheral lymph node or metastatic lesions.

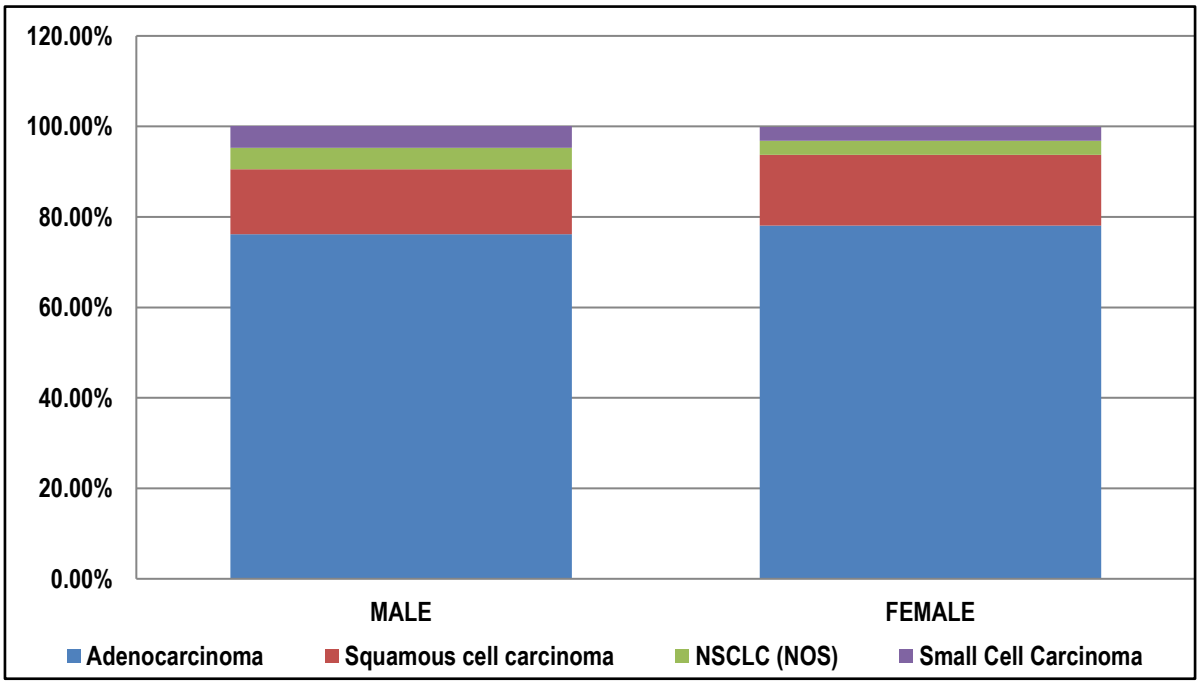
£ Squamous cell carcinoma, μ Small cell lung cancer, @ Non small cell lung cancer, not otherwise specified.

Table 6: Distribution of patients according to diagnosis

Diagnosis	Male (no. and %)	Female (no. and %)	Total
Adenocarcinoma	16(76.2)	25(78.1)	41(77.4)
SCC*	3(14.3)	5(15.6)	8(15.1)
NSCLC (NOS)£	1(4.8)	1(3.1)	2(3.8)
SCLC+	1(4.8)	1(3.1)	2
Adenosquamous	0(0)	0(0)	0
Total	21	32	53

*Squamous cell carcinoma, £Non-small cell carcinoma, not otherwise specified, +Small cell lung carcinoma

Figure 1. Graphical representation of sex-wise distribution of diagnosis



RESULTS

Data of 53 nonsmoker patients with lung cancer was analysed. 32 (60.4%) patients were females and 21 (39.6%) were males giving a male: female ratio of 0.6:1. The mean age of presentation was 53.8±11.6 years. The age wise distribution of patients is given in Table 1. Maximum patients (39.6%) presented in the age group of 51-60 years.

Table 2 shows the distribution of patients according to presenting symptoms. Cough was the most common presenting complaint and was seen in 84.9% of the patients. Dyspnoea (77.35%), chest pain (64.15%), loss of appetite and subsequent weight loss were other common complaints.

Pallor was the most common general examination finding, seen in 22 (41.5%) patients. Clubbing was seen in 14 (26.4%), peripheral lymphadenopathy in 7 (13.2%) patients and Superior vena cava obstruction in 1(1.9%) patient.

All the patients presented in Stage III and IV. Majority had Eastern co-operative Oncology group (ECOG) score 3.

Table 3 shows the distribution of patients according to duration of symptoms. Mean duration was 6.9 months. Majority (62.3%) presented in between 6-12 months.

Occupational exposure to tar and soot or metal fumes was recorded in 5 patients. The average duration of exposure was 26 years. Environmental Tobacco Smoke (ETS) exposure was elicited in 15 (28.3%) and prolonged exposure to indoor air pollutants from biomass fuels was elicited in 25 (47.2%) patients. The average duration of exposure was 18.56 years.

History of prior treatment for tuberculosis was present in 22 (41.5%) patients. But the history could not be validated with microbiological or radiological proof for all the patients.

On radiological evaluation, the most common finding was a mass lesion associated with a malignant/paramalignant effusion, seen in 24 (45.3%) patients. Other findings are as shown in Table 4.

Tumour was centrally located in 12 (22.6%) patients while it was peripheral in 35 (66%). No mass lesion could be detected in 6 (11.3%) patients.

Table 5 shows the diagnostic yield of various procedures. Maximum diagnosis was reached through transthoracic procedures (32, 60.4%).

The most common histological diagnosis was adenocarcinoma (41, 77.4%), followed by squamous cell carcinoma (8, 15.1%), small cell carcinoma (2, 3.8%) and Non-Small cell carcinoma (NSCLC) not otherwise specified (2, 3.8%).

The sex-wise distribution of the histologic diagnosis is shown Table 6 and graphically represented in Figure 1. Adenocarcinoma was the most common type in both males (76.2%) and females (78.1%). The distribution of other types of malignancy was also more or less similar in both the sexes.

Of all adenocarcinomas, EGFR mutation was positive in 19 (46.3%) of the 41 patients tested. In the 5 patients in whom specific mutation testing for Exon 19 deletion-E746-A750 or Exon 21 L858R mutation was done, all 5 patients (100%) had Exon 19 deletion-E746-A750. ALK mutation was negative in all the 41 patients.

DISCUSSION

Our study found greater number of females than males (60.4% compared to 39.6%). Couraud et al[5] in their study of 384 European patients who had never smoked found 83% females with female-male ratio of 4.9. There are not enough studies to support or refute the notion that females are more prone to lung cancer in the absence of smoking.[6] Most studies though have shown that lung cancer incidence in women smokers are more compared to males.[7]

The mean age of presentation in our study was 53.8±11.6 years. Never smokers with lung cancer usually present late due to absence of a definite risk factor.[8] In a study by Cufari[8] et al. the mean age of presentation in never smokers was found to be 60 years. Other studies conducted across various geographical regions have shown increasing incidence with age.[9,10]

Lung cancer usually presents insidiously as symptoms are non-specific and vague. The most common symptoms usually reported are cough and dyspnoea. In our study the most common presenting complaint was cough, reported by 84.9% patients. In a population based case control study by Hamilton[11] et al. cough was seen in 60-70% patients. In their study they found hemoptysis, dyspnoea and abnormal spirometry to be independently associated with cancer after excluding other variables. Pallor was the most common general examination finding in our study, seen in 22 (41.5%) patients. In the study by Hamilton[11] et al., clubbing was the only examination finding to be associated with malignancy in multivariate analysis.

Mean duration of symptoms was 6.9 months. In a systematic review by Birring[12] et al., the median interval between symptoms to visit to physician for lung cancer patients was found to be 7 months. Jenson[13] et al. also reviewed 16 studies and found the delay in presentation to vary from 7 days to 6 months.

Environmental tobacco smoke (ETS) which includes a mixture of >4000 substances is an established risk factor for lung cancer especially among non-smokers[14]. About 16-24% lung cancer cases are attributable to ETS.[2] In our study 28.3% cases had exposure to ETS for a mean period of 18.56 years. 47.2% of our patients had exposure to biomass fuel and other indoor air pollutants. Occupational exposure to tar and soot and metal fumes was recorded in 5 patients. Increased risk of lung cancer among women and men employed in high risk occupations has been documented in a large case-control study conducted across Europe among never smokers by Zeka[15] et al. Such hazardous occupations include working in industries with exposure to nonferrous metal dust and fumes, crystalline silica, and organic solvents.

History of taking treatment for tuberculosis was present in 22 (41.5%) patients. But the history could not be validated with microbiological or radiological proof for all the patients. It could very well have been the wrong diagnosis of cancer for TB leading to antitubercular treatment. Nevertheless, studies have shown that TB is significantly associated with lung cancer.[16]

The general concept is that adenocarcinomas are usually peripheral in location and squamous cell carcinomas are usually central. Our study found only 19.5% of adenocarcinomas to be central. Moon[17] et al. found 13.3% central adenocarcinomas in their study.

Squamous cell carcinoma (SCC) is usually central and found to be peripheral in only 15-30% cases. In a study by Krimsky[18] et al. conducted in the US on patients with primary squamous cell lung carcinoma, 62% tumours were found to be peripheral and only 38% were centrally located. Similar studies in other areas including Asia found more than 50% SCC to be peripheral.[19,20]

This findings were independent of smoking in all the studies. This concept of changing anatomic location of SCC towards periphery needs to be further investigated. In a review on transthoracic procedures for lung cancer diagnosis by DiBardeno[21] et al., CT and USG-guided transthoracic biopsy showed a yield of 92.1% and 88.7% respectively. Maximum diagnosis was reached through transthoracic procedures 60.4% cases in our study.

Adenocarcinoma was seen in 77.4% in our study. Among non-smokers, most common diagnosis is adenocarcinoma in both males and females.[22] In a Polish study[23] of 20,567 cases of lung cancer, squamous cell carcinoma was the most common among male non-smokers unlike our study. However, the study found that females were more likely to have adenocarcinoma irrespective of smoking status. In the present world, adenocarcinoma is the most common type among smokers as well as non-smokers.[24] In our study, adenocarcinoma was the most common type in both males (76.2%) and females (78.1%). The distribution of other types of malignancy was also more or less similar in both the sexes. Small cell lung carcinoma (SCLC) is very rare in non-smokers.[25] Our study found small cell lung carcinoma in only 3.8%. With increasing cessation of smoking, SCC and SCLC are decreasing in incidence while that of adenocarcinoma is increasing worldwide. This trend in the world is paralleled in India.[26]

It is estimated that the frequency of targetable mutations in never smokers is more than 50%.[27] Driver mutations were seen in 73% nonsmoker patients with NSCLC in the review by Planchard[2] et al. with EGFR (51%), ALK(8%), KRAS(6%), BRAF(3%) and HER2(3%). There was no significant sex difference. In the largest East Asian study among non-smokers with NSCLC by Kim[28] et al., EGFR mutation was reported in 48%. Our study showed a comparable finding of 46.3% patients with positive EGFR mutation. Exon 19 deletions are the most common specific mutation in never smokers with NSCLC. Su[29] et al demonstrated it in 73.1% of non-smokers with NSCLC. In our study, all 5 patients tested for specific mutations were found to have exon 19 deletion (E746-A750). In a study by Gazdar[30] et al., exon 19 and 21 (L858R) mutations were found to be equally prevalent with 44% and 41% respectively. Among other mutations, EGFR (exon 19 del and exon 21 L858R) mutation are the most common and patients who harbor these mutations are most responsive to TKI.[30]

LIMITATIONS

Specific occupational carcinogens could not be named from history alone. Most females and males in India are concomittently exposed to ETS as well as indoor pollutants from burning of biomass fuel due to the traditional way of cooking. Moreover there were no controls to help conclude the definite carcinogenic risks of the same. Specific mutation testing was done only for the most common EGFR (exon 19 and 21) and ALK mutations because of technical and financial constraints at our center.

CONCLUSIONS

Lung cancer among never smokers is a distinct class in itself with risk factors and genetic features discrete from those cases associated with tobacco smoke. Indoor air pollutants as well as ETS are definitely implicated risk factors. Adenocarcinomas with targetable mutations are commoner in non-smokers and hence mutation testing should always be done in such patients. It is important to conduct studies in all regions of the world about the diverse characteristics of this entity to consolidate our knowledge of this growing group of cancer.

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