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Correlation Between Smoking History and Histological Subtypes of Primary Lung Cancer: A Single-Center Experience

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ABSTRACT
Background: Lung cancer remains a major global health burden with tobacco smoking being the predominant etiological factor. The histopathological distribution of lung carcinoma varies significantly between smokers and non-smokers. This study aimed to evaluate the correlation between smoking history and histological subtypes of primary lung carcinoma in an Indian population. **Methods:** This cross-sectional observational study included 110 histopathologically confirmed cases of primary lung carcinoma diagnosed at a tertiary care center over a period of two years. Demographic data, smoking history, and histopathological findings were analyzed. Statistical analysis was performed using Chi-square test and Fisher's exact test. **Results:** The mean age was 58.4±11.2 years with a male-to-female ratio of 4.5:1. Among 110 patients, 74 (67.3%) were smokers and 36 (32.7%) were non-smokers. Squamous cell carcinoma (38.2%) was the most common histological subtype, followed by adenocarcinoma (32.7%), small cell carcinoma (16.4%), and large cell carcinoma (5.5%). Squamous cell carcinoma showed a strong association with smoking ($p<0.001$), while adenocarcinoma was more prevalent in non-smokers ($p<0.01$). **Conclusion:** Squamous cell carcinoma remains the predominant histological subtype in Indian smokers, while adenocarcinoma is increasingly common among non-smokers, particularly in females. These findings emphasize the need for targeted screening and preventive strategies based on smoking status.

1. INTRODUCTION:
Lung cancer represents a formidable global health challenge, ranking as the most frequently diagnosed malignancy and the leading cause of cancer-related mortality worldwide. According to GLOBOCAN 2022 estimates, approximately 2.48 million new cases and 1.8 million deaths from lung cancer occurred globally, accounting for 12.4% of all cancer diagnoses and 18.7% of cancer-related deaths [1,2]. In India, lung cancer constitutes approximately 5.9% of all cancers and 8.1% of cancer-related deaths, reflecting a significant public health burden[3].

Tobacco smoking remains the most important etiological factor for lung cancer development, being implicated in approximately 80-90% of all lung cancer cases[4]. The carcinogenic effect of cigarette smoke involves exposure to over 60 identified carcinogens that induce genetic mutations through multiple signaling pathways[5]. However, the epidemiological profile of lung cancer is evolving, with an increasing proportion of cases occurring in never-smokers, particularly among women and Asian populations [6,7].

The World Health Organization (WHO) 2021 classification categorizes lung tumors based on morphological features, with non-small cell lung carcinoma (NSCLC) comprising approximately 85% of cases and small cell lung carcinoma (SCLC) accounting for the remaining 15%[8,9]. Among NSCLC, adenocarcinoma and squamous

cell carcinoma are the most prevalent subtypes. Historically, squamous cell carcinoma was the predominant histological type; however, global trends demonstrate a shift toward adenocarcinoma as the most common subtype, particularly in developed countries [10].

The relationship between smoking and specific histological subtypes is well-established. Squamous cell carcinoma and small cell carcinoma demonstrate the strongest association with cigarette smoking, whereas adenocarcinoma occurs more frequently in never-smokers and is associated with distinct molecular profiles, including EGFR mutations [11,12]. In Asian populations, EGFR mutations are detected in approximately 40-60% of adenocarcinomas, with higher prevalence in female never-smokers [13].

Indian epidemiological data on lung cancer histopathology and its correlation with smoking patterns remain limited, with regional variations in reported findings. Some studies from different parts of India have reported squamous cell carcinoma as the predominant subtype, while others have documented a rising trend of adenocarcinoma [14,15]. Understanding the local patterns of lung cancer histopathology in relation to smoking status is crucial for developing targeted screening programs, treatment strategies, and public health interventions.

This study was undertaken to evaluate the histopathological spectrum of primary lung carcinoma and its correlation with smoking history in patients presenting to a tertiary care center in India. The objectives were to determine the distribution of various histological subtypes, analyze the demographic profile of lung cancer patients, and assess the association between smoking status and specific histopathological types.

MATERIALS AND METHODS:

Study Design and Setting

This was a cross-sectional observational study conducted at the Department of Pathology in collaboration with the Department of Pulmonary Medicine at a tertiary care teaching hospital in India. The study was carried out over a period of two years (January 2022 to December 2023). Institutional Ethics Committee approval was obtained prior to commencement of the study (IEC/2022/XXX).

Sample Size

The sample size was calculated using the formula for estimating proportions: $n = Z^2pq/d^2$, where Z = 1.96 (for 95% confidence interval), p = 0.35 (expected proportion of adenocarcinoma based on previous studies), q = 1-p = 0.65, and d = 0.10 (acceptable margin of error). The calculated minimum sample size was 88, which was rounded up to 110 to account for potential data incompleteness [16].

Inclusion and Exclusion Criteria

Inclusion criteria comprised: (1) patients aged 18 years or above, (2) histopathologically confirmed diagnosis of primary lung carcinoma on tissue biopsy, bronchoscopic biopsy, or surgical resection specimen, and (3) availability of complete clinical and smoking history data. Exclusion criteria included: (1) metastatic carcinomas to the lung from other primary sites, (2) cases diagnosed solely on cytology without histopathological confirmation, (3) malignant pleural effusion of unknown primary, and (4) rare tumors such as sarcomatoid carcinomas and carcinoid tumors [17].

Data Collection

Demographic data including age, gender, and clinical presentation were recorded. Detailed smoking history was obtained, including type of smoking (cigarette, bidi, hookah), duration of smoking, and number of cigarettes/bidis smoked per day. Smoking index (SI) was calculated as: number of cigarettes/bidis smoked per day × duration of smoking in years. Patients were categorized as never-smokers (<100 lifetime cigarettes), former smokers (quit smoking >1 year prior to diagnosis), or current smokers. For analysis purposes, former and current smokers were grouped together as 'smokers' [18].

Histopathological Examination

Tissue specimens were fixed in 10% neutral buffered formalin and processed routinely. Sections of 4-5 µm thickness were stained with hematoxylin and eosin (H&E). Histopathological typing was performed according to the WHO 2021 classification of thoracic tumors [8]. Immunohistochemistry (IHC) was performed in cases requiring differentiation between adenocarcinoma and squamous cell carcinoma, using a panel including TTF-1, Napsin A, p40, and CK5/6 [19]. TTF-1 and Napsin A positivity favored adenocarcinoma, while p40 and CK5/6 positivity indicated squamous differentiation.

Statistical Analysis

Data were entered in Microsoft Excel and analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY). Categorical variables were expressed as frequencies and percentages, while continuous variables were expressed as mean ± standard deviation. Chi-square test was used to assess the association between categorical variables. Fisher's exact test was applied when expected cell

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frequencies were less than 5. A p-value of <0.05 was considered statistically significant [20].

RESULTS:

Demographic Profile

A total of 110 patients with histopathologically confirmed primary lung carcinoma were included in this study. The mean age of the study population was 58.4±11.2 years, ranging from 32 to 82 years. The majority of patients (45.5%) were in the 51-60 years age group, followed by 61-70 years (29.1%) and 41-50 years (14.5%). There were 90 males (81.8%) and 20 females (18.2%), with a male-to-female ratio of 4.5:1. The demographic characteristics are summarized in Table 1.

Table 1: Demographic Profile of Study Population (n=110)

Characteristic	Number (n)	Percentage (%)
Age Groups (years)		
≤40	8	7.3
41-50	16	14.5
51-60	50	45.5
61-70	32	29.1
>70	4	3.6
Gender		
Male	90	81.8
Female	20	18.2
Smoking Status		
Smokers	74	67.3
Non-smokers	36	32.7

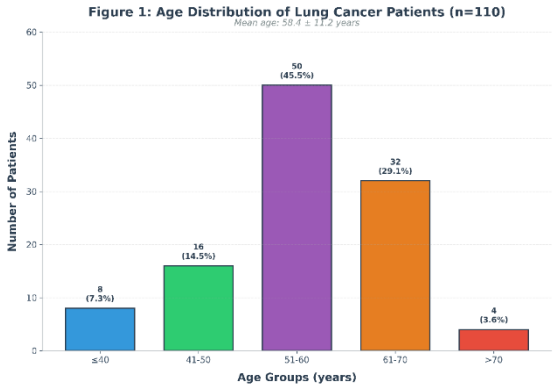

Fig 1: Bar chart showing age distribution of lung cancer patients

Smoking Patterns

Among the 110 patients, 74 (67.3%) were smokers and 36 (32.7%) were non-smokers. Of the 74 smokers, 52 (70.3%) were current smokers and 22 (29.7%) were former smokers. Bidi smoking was the most common form (56.8%), followed by cigarette smoking (35.1%), and mixed pattern (8.1%). The mean smoking index was 412.5±186.3. Among smokers, 78.4% (n=58) had a smoking index >300. Among male patients, 82.2% were smokers, whereas only 10% of female patients reported a history of smoking (Table 2).

Table 2: Smoking Characteristics of Study Population

Parameter	Number (n=74)	Percentage (%)
Type of Smoking		
Bidi	42	56.8
Cigarette	26	35.1
Mixed (Bidi + Cigarette)	6	8.1
Smoking Index		
≤300	16	21.6
301-600	38	51.4
>600	20	27.0

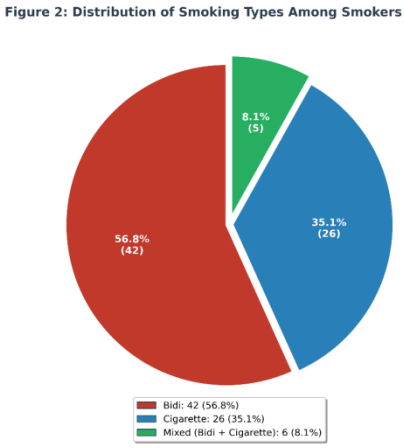

Fig 2: Pie chart showing distribution of smoking types

Histopathological Distribution

The histopathological distribution of lung carcinoma is presented in Table 3. Non-small cell lung carcinoma (NSCLC) constituted 83.6% (n=92) of all cases, while small cell lung carcinoma (SCLC) comprised 16.4% (n=18). Among NSCLC, squamous cell carcinoma was the most common subtype (42 cases, 38.2%), followed by adenocarcinoma (36 cases, 32.7%), NSCLC-NOS (8 cases, 7.3%), and large cell carcinoma (6 cases, 5.5%).

Table 3: Histopathological Distribution of Lung Carcinoma (n=110)

Histological Type	Number (n)	Percentage (%)
Non-Small Cell Lung Carcinoma	**92**	**83.6**
Squamous Cell Carcinoma	42	38.2
Adenocarcinoma	36	32.7
Large Cell Carcinoma	6	5.5
NSCLC-NOS	8	7.3
Small Cell Lung Carcinoma	**18**	**16.4**
Total	**110**	**100**

NSCLC-NOS: Non-Small Cell Lung Carcinoma - Not Otherwise Specified

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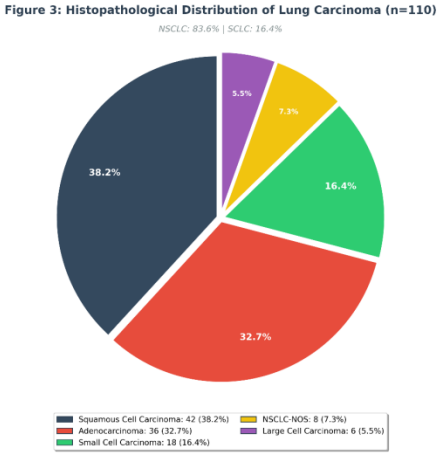

Fig 3: Pie chart showing distribution of histological subtypes

Correlation of Histological Subtypes with Smoking Status

A statistically significant correlation was observed between histological subtypes and smoking status ($p<0.001$). Among squamous cell carcinoma cases, 85.7% (36/42) were smokers, demonstrating the strongest association with tobacco use. In contrast, adenocarcinoma showed a higher prevalence among non-smokers, with 52.8% (19/36) of adenocarcinoma patients being never-smokers. Small cell carcinoma showed a strong smoking association, with 88.9% (16/18) cases occurring in smokers. The correlation is detailed in Table 4.

Table 4: Correlation Between Histological Subtypes and Smoking Status

Histological Type	Smokers n(%)	Non-smokers n(%)	p-value
Squamous Cell Carcinoma (n=42)	36 (85.7)	6 (14.3)	<0.001*
Adenocarcinoma (n=36)	17 (47.2)	19 (52.8)	<0.01*
Small Cell Carcinoma (n=18)	16 (88.9)	2 (11.1)	<0.05*
Large Cell Carcinoma (n=6)	4 (66.7)	2 (33.3)	0.68
NSCLC-NOS (n=8)	1 (12.5)	7 (87.5)	<0.01*

Statistically significant (p<0.05)

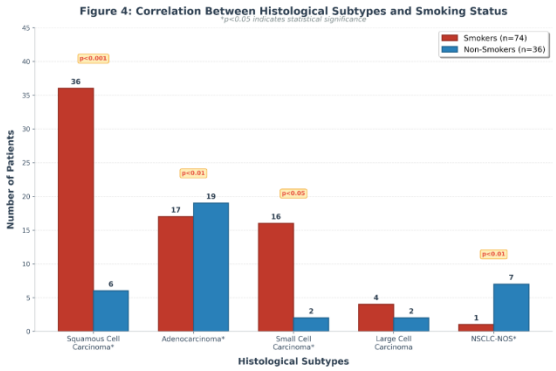

Fig 4: Clustered bar chart comparing histological subtypes between smokers and non-smokers

Gender-wise Distribution of Histological Subtypes

Gender-wise analysis revealed significant differences in histological distribution. In males, squamous cell carcinoma was the most common subtype (43.3%), followed by adenocarcinoma (26.7%) and small cell carcinoma (17.8%). In females, adenocarcinoma predominated (65%), followed by squamous cell carcinoma (15%) and small cell carcinoma (10%). This gender difference was statistically significant ($p<0.01$). The detailed distribution is presented in Table 5.

Table 5: Gender-wise Distribution of Histological Subtypes

Histological Type	Male n(%)	Female n(%)	p-value
Squamous Cell Carcinoma	39 (43.3)	3 (15.0)	<0.01*
Adenocarcinoma	24 (26.7)	13 (65.0)	<0.001*
Small Cell Carcinoma	16 (17.8)	2 (10.0)	0.52
Large Cell Carcinoma	5 (5.6)	1 (5.0)	1.0
NSCLC-NOS	6 (6.7)	1 (5.0)	1.0
Total	**90 (100)**	**20 (100)**	-

Statistically significant (p<0.05)

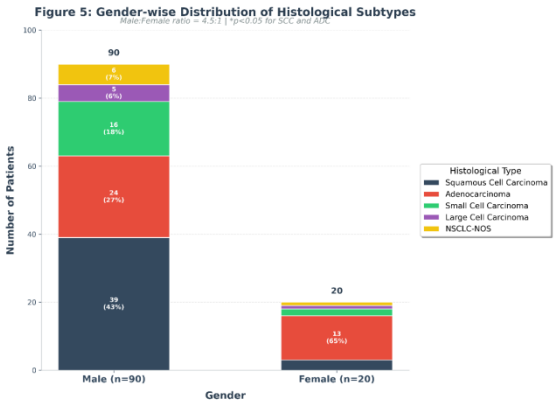

Fig 5: Stacked bar chart showing gender-wise distribution of histological subtypes

DISCUSSION:

This study provides valuable insights into the histopathological spectrum of primary lung carcinoma and its correlation with smoking history in an Indian population. Our findings demonstrate that squamous cell carcinoma remains the most prevalent histological subtype (38.2%), consistent with several previous Indian studies [14,15,21]. However, adenocarcinoma closely follows at 32.7%, reflecting the global trend of increasing adenocarcinoma incidence.

The mean age of 58.4 years in our study aligns with the reported median age of lung cancer diagnosis in India, typically occurring in the sixth decade of life [22]. The male predominance (M:F ratio 4.5:1) observed in our study is consistent with other Indian studies reporting ratios ranging from 3.5:1 to 4.7:1 [15,21,23]. This high male-to-female ratio can be

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attributed to the significantly higher prevalence of smoking among Indian males compared to females. The proportion of smokers in our study (67.3%) is comparable to findings from other Indian studies, which have reported smoking prevalence ranging from 60% to 78% among lung cancer patients [14,15,24]. Bidi smoking emerged as the most common form of tobacco use (56.8%), reflecting the socioeconomic profile of our patient population. This finding has important public health implications, as bidi smoking is often perceived as less harmful despite delivering higher concentrations of tar and carcinogens compared to manufactured cigarettes [25].

The strong association between squamous cell carcinoma and smoking (85.7% of SCC cases were smokers) corroborates established evidence linking cigarette smoke carcinogens to squamous metaplasia and subsequent malignant transformation in bronchial epithelium [5,11]. The predominant central location of squamous cell carcinoma in major bronchi explains its strong association with inhaled tobacco smoke carcinogens, which directly contact and damage the bronchial epithelium [26].

Notably, adenocarcinoma showed a higher prevalence among non-smokers (52.8%), particularly in females (65% of female cases). This finding is consistent with global observations of adenocarcinoma as a distinct disease entity in never-smokers, characterized by different molecular pathways and higher rates of actionable driver mutations such as EGFR mutations [12,13]. Studies have reported EGFR mutation rates of 40-60% in Asian never-smoker adenocarcinoma patients, significantly higher than in smokers [13,27]. This has important therapeutic implications, as EGFR-mutant tumors demonstrate remarkable responses to tyrosine kinase inhibitors.

Small cell lung carcinoma demonstrated the strongest smoking association (88.9% in smokers) in our study, consistent with its well-established pathogenic link to tobacco carcinogens [11]. The aggressive biological behavior and neuroendocrine differentiation of SCLC make it a distinct clinical entity with limited therapeutic options compared to NSCLC.

The gender-based differences observed in histological subtypes have significant clinical implications. The predominance of adenocarcinoma in females (65%) compared to squamous cell carcinoma in males (43.3%) reflects both the lower smoking rates in Indian women and the increasing recognition of non-smoking-related lung cancer in Asian females [6,7]. Environmental factors such as indoor air pollution from biomass fuel combustion, secondhand smoke exposure, and genetic susceptibility may contribute to adenocarcinoma development in never-smoking women [28].

Comparing our findings with recent Indian studies, Banerjee et al. reported adenocarcinoma and squamous cell carcinoma at equal prevalence (36.4% each) in Eastern India, while Rawat et al. found squamous cell carcinoma (49.6%) predominating in Central India [15,21]. These regional variations may reflect differences in smoking patterns, environmental exposures, and access to advanced diagnostic modalities including immunohistochemistry. The reduction in NSCLC-NOS category (7.3% in our study) compared to older studies reflects improved diagnostic accuracy through routine use of immunohistochemical markers [19].

Our study has certain limitations. The single-center design may limit generalizability to the broader Indian population. Additionally, molecular testing for driver mutations was not routinely performed, which would have provided additional insights into the biological differences between smoking-related and non-smoking-related lung cancers. Future multicentric studies with comprehensive molecular profiling are warranted to better characterize the evolving landscape of lung cancer in India.

The findings of this study have important implications for lung cancer prevention and screening strategies. The persistent strong association between squamous cell carcinoma and smoking underscores the critical need for tobacco control measures. Simultaneously, the increasing recognition of adenocarcinoma in never-smokers, particularly women, calls for attention to non-smoking risk factors and consideration of screening strategies for high-risk non-smoking populations [29,30].

CONCLUSION:

This study demonstrates that squamous cell carcinoma remains the most common histological subtype of lung cancer in the Indian population, with a strong association with tobacco smoking. Adenocarcinoma shows increasing prevalence, particularly among non-smokers and females, reflecting global epidemiological trends. The differential distribution of histological subtypes based on smoking status and gender has important implications for targeted screening programs, molecular testing strategies, and personalized treatment approaches. Continued efforts in tobacco control, along with attention to non-smoking risk factors, are essential for reducing the burden of lung cancer in India.

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