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Effect of Smoking Duration and Pack-Year History on Histological Subtypes of Lung Cancer

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Abstract **Original Research Article**

Background: Lung cancer is the leading cause of cancer-related mortality worldwide, with smoking as the principal risk factor. The histological subtypes of lung cancer, including adenocarcinoma, squamous cell carcinoma, and small cell carcinoma, vary according to smoking history and intensity. This study investigates the effect of smoking duration and pack-year history on the histological subtypes of lung cancer in Bangladesh. ***Methods:*** A cross-sectional study was conducted at the National Institute of Diseases of the Chest and Hospital (NIDCH) from July 2007 to June 2008. A total of 98 patients with confirmed primary lung cancer were included, comprising 81 smokers and 17 non-smokers. ***Results:*** Among the 98 patients, 45% had adenocarcinoma, 28.6% squamous cell carcinoma, 16.3% small cell carcinoma, 6.1% large cell carcinoma, and 3.1% other subtypes. Smokers exhibited a higher incidence of squamous cell carcinoma (33.3%) and small cell carcinoma (19.8%), while adenocarcinoma was more common in non-smokers (88.2%). Majority (94.1%) of the patients with lesions in the upper lobe was smokers compared to 56.7% of patients with lesions in the lower lobe ($p < 0.001$) Ratio of upper and lower lobe tumour among smoker was roughly of 4:1. A significant association was found between smoking duration, pack-years, and the occurrence of squamous and small cell carcinoma ($p < 0.001$). ***Conclusion:*** Smoking duration and pack-years have a significant impact on the histological subtypes of lung cancer. Squamous cell carcinoma and small cell carcinoma are more prevalent in smokers, while adenocarcinoma is more common in non-smokers.

Keywords: lung cancer, smoking duration, pack-years, histological subtypes, adenocarcinoma.

INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for a significant percentage of all cancer deaths. It is responsible for approximately 12.8% of new cancer cases annually, with an incidence rate of 37.5 per million among men and 10.8 per million among women [1]. Smoking is the primary risk factor for lung cancer, contributing to nearly 90% of cases in the United States. Other risk factors include occupational exposure, environmental carcinogens, and air pollution, which together account for a smaller percentage of cases [2]. Compared to non-smokers, smokers have a nearly 20-fold increased risk of developing lung cancer [3].

Histologically, lung cancer is classified into four primary subtypes: squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and large cell carcinoma [4]. These subtypes represent 95% of all primary lung cancer cases, with squamous cell carcinoma and small cell carcinoma showing the strongest associations with smoking history [5]. Studies indicate that smoking duration, more than smoking intensity, is most strongly associated with the development of squamous cell carcinoma and small cell carcinoma [6]. In contrast, adenocarcinoma occurs more frequently among individuals with fewer pack-years and among those who have quit smoking, suggesting that different patterns of smoking exposure impact lung cancer histology in distinct ways [7,8].

Over recent decades, the histological distribution of lung cancer has shifted, with adenocarcinoma becoming more common than squamous cell carcinoma. This change may be linked to

modifications in cigarette composition, such as the use of filter tips and altered tobacco blends, which influence inhalation patterns and the type of carcinogens deposited in the lungs [9]. As a result, adenocarcinoma now surpasses squamous cell carcinoma in incidence—a reversal from the 1950s when squamous cell carcinoma was more prevalent. Understanding the connection between smoking patterns and lung cancer subtypes is essential for assessing risk and developing targeted screening measures [10].

In addition to histology, the location of lung tumors shows an association with smoking. Research suggests that smoking-related lung tumors tend to arise more often in the upper lobes, with studies showing an upper-to-lower lobe ratio of approximately 2.5:1 [4]. This phenomenon may be due to variations in lung ventilation and perfusion, with lower ventilation in the upper lobes potentially allowing carcinogens to persist longer. Additionally, differences in lymphatic drainage and blood circulation to the upper lobes may contribute to the predominance of smoking-related tumors in these areas [11]. Such locational patterns could influence cancer management and prognosis, as certain lung cancer subtypes exhibit different survival outcomes based on their location [12].

In Bangladesh, lung cancer remains a significant health concern, yet there is limited local data on how smoking influences lung cancer type and tumor location. Given the shift toward adenocarcinoma and the influence of smoking history on lung cancer histology, this study aims to investigate the effect of smoking duration and pack-year history on lung cancer subtypes among patients with confirmed diagnoses. Understanding these associations could provide valuable insights for developing targeted screening measures and tailored therapeutic approaches. This research seeks to address current knowledge gaps, offering a foundation for improved lung cancer management in Bangladesh that considers local smoking patterns and histological trends.

METHODOLOGY & MATERIALS

In this cross-sectional study, conducted from July 2007 to June 2008 at the National Institute of Diseases of Chest and Hospital (NIDCH), Dhaka, 98 patients diagnosed with primary lung cancer participated. Patients were selected consecutively based on predefined inclusion and exclusion criteria. Both smokers and non-smokers with primary lung cancer presenting with a solitary lung lesion were included, while cases with metastatic cancer, bilateral or multi-lobe involvement, and contraindications to fiberoptic bronchoscopy (FOB) were excluded. Informed consent was obtained from all participants, and ethical considerations were adhered to, ensuring minimal invasiveness and immediate management of any complications. Detailed smoking histories, including duration, pack-years (calculated as packs smoked per day multiplied by years smoked), and other relevant factors, were collected through face-to-face interviews. Clinical data, such as age of smoking initiation, time since smoking cessation, and type of cigarettes used, were also recorded. Routine investigations included chest X-rays, complete blood counts, sputum analysis, ECG, spirometry, and coagulation tests. For tumor localization and histological analysis, flexible FOB with biopsy, brushing, and bronchoalveolar lavage (BAL) were performed for central lesions, while CT-guided fine-needle aspiration cytology (FNAC) was utilized for peripheral lesions or cases where bronchoscopy was inconclusive. Tumors were categorized as upper or lower lobe based on CT and FOB findings. Histological and cytological diagnoses were confirmed through analysis at NIDCH's Department of Pathology. Data were analyzed using SPSS 10.0, with statistical tests such as Student's t-test or chi-square applied to assess relationships between smoking variables and lung cancer subtypes. A p-value of less than 0.05 was deemed statistically significant.

RESULTS

Table I: Distribution of Patients by Smoking Habit (n = 98)

Smoking Habit	Frequency	Percentage (%)
Present smokers	41	41.8
Past smokers	40	40.8
Non-smokers	17	17.2
Total	98	100

Table I shows the majority of the patients had a history of smoking, with 41.8% being current smokers and 40.8% being former smokers. Only 17.2% of the patients were non-smokers.

Table II: Comparison of Smoking Habit between Sex (n = 98)

Smoking Habit	Male (n = 87)	Female (n = 11)	p-value
Smokers	79 (90.8%)	2 (18.2%)	<0.001
Non-smokers	8 (9.2%)	9 (81.8%)	

Figures in the parentheses denote corresponding %.
*Data were analysed by using Chi-square (x^2) Test with Yate's correction.

Table II shows a significant difference in smoking habits between males and females. A significantly higher proportion of males were smokers (90.8%) compared to females (18.2%), as indicated by the p-value of <0.001. Conversely, a significantly higher proportion of females were non-smokers (81.8%) compared to males (9.2%).

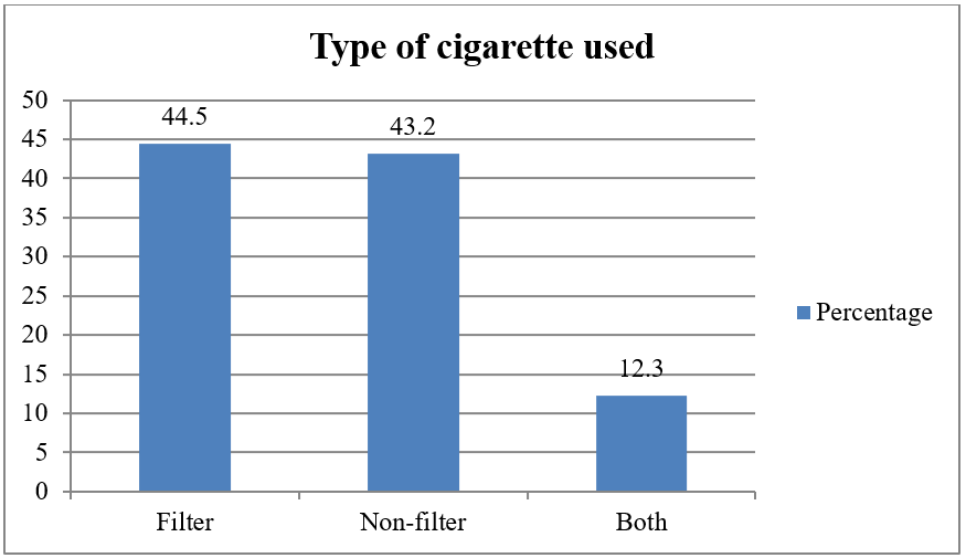

Figure 1: Distribution of patients by type of cigarettes used (n = 81)

Figure 1 shows the distribution of patients based on their use of filters. Majority 44.5% of the patients used filters, 43.2% used non-filter cigarettes, and 12.3% used both filter and non-filter cigarettes.

Table III: Association between Histologic Cell Type and Smoking Habit

Histologic Cell Type	Smoker (n = 81)	Non-smoker (n = 17)	p-value
Adenocarcinoma	30 (37.0%)	15 (88.2%)	0.001
Squamous cell carcinoma	27 (33.3%)	1 (5.9%)	
Large cell carcinoma	5 (6.2%)	1 (5.9%)	
Small cell carcinoma	16 (19.8%)	0 (0.0%)	
Other	3 (3.7%)	0 (0.0%)	

Table III shows a significant association between histologic cell type and smoking habit. In the smoker group, 37% had adenocarcinoma, 33.3% squamous cell carcinoma, 6.2% large cell carcinoma, 19.8% small cell carcinoma and 3.7% others. In the non-smokers majority (88.2%) adenocarcinoma followed by 5.9% squamous cell and another 5.9% large cell carcinoma. No other cell type was found among non-smokers. Chi-square (x^2) test revealed that the incidence of squamous cell carcinoma was significantly higher among smokers than that among non-smokers (p = 0.001).

Table IV: Association between Smoking-Related Variables and Cancer Cell Type

Smoking-Related Variables	SCC & SCLC (n = 44)	Adenocarcinoma & Others (n = 54)	p-value
Age at starting smoking (yrs)	22.1 ± 3.9	26.0 ± 3.7	<0.001
Duration of smoking (yrs)	34.5 ± 8.9	18.5 ± 8.5	<0.001
Pack-years of smoking	48.1 ± 12.5	12.8 ± 11.0	<0.001
Time since quitting smoking (yrs)	4.1 ± 5.4	17.2 ± 9.9	<0.001

Table IV compares smoking-related variables between the major cell types: squamous cell & small cell carcinoma (SCC & SCLC) versus adenocarcinoma & others. The SCC & SCLC group began smoking at a significantly younger age (22.1 ± 3.9 years) compared to the adenocarcinoma group (26 ± 3.7 years, p < 0.001) and had a much longer smoking duration (34.5 ± 8.9 years vs. 18.5 ± 8.5 years, p < 0.001). Pack-years of smoking were also substantially higher in the SCC & SCLC group (48.1 ± 12.5) than in the adenocarcinoma group (12.8 ± 11, p < 0.001). Additionally, there was a significantly longer lag time between quitting smoking and the development of adenocarcinoma compared to SCC & SCLC (p < 0.001).

Table V: Association between Smoking Habit and Pulmonary Lobe Affected

Smoking Habit	Upper Lobe (n = 68)	Lower Lobe (n = 30)	p-value
Smoker	64 (94.1)	17 (56.7)	<0.001
Non-smoker	4 (5.9)	13 (43.3)	

Figures in the parentheses denote corresponding percentage.
Chi-square (x^2) Test was employed to analyze the data.

Table V shows that the majority (94.1%) of the patients with lesions in the upper lobe was smokers compared to 56.7% of patients with lesions in the lower lobe ($p < 0.001$) Ratio of upper and lower lobe tumour among smoker was roughly of 4:1. Smoking tends to be significantly associated with malignancy in the upper lobe of the lungs ($p < 0.001$).

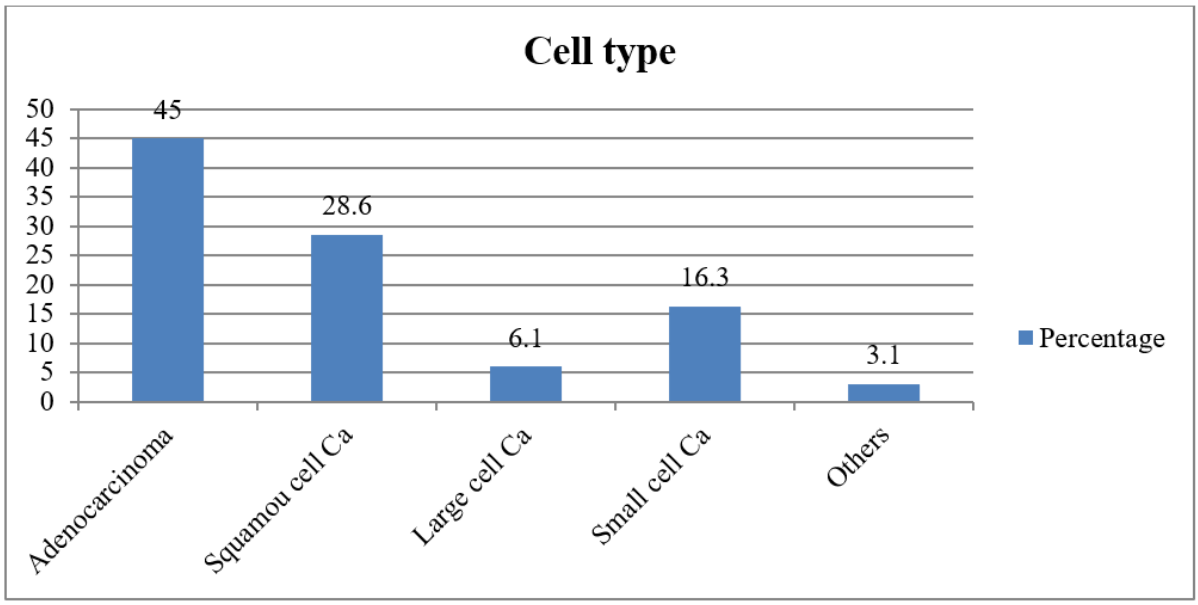

Figure 2: Distribution of patients by type of cell (n = 98)

Figure 2 shows the histologie and/or cytologic cell type of the lesions. Forty five percent of patients exhibited adenocarcinoma, 28.6% squamous cell carcinoma (SCC), 6.1% large cell carcinoma (LCC), 16.3% small cell carcinoma (SCLC) and 3.1% other cytologic cell type.

DISCUSSION

Lung cancer remains the leading cause of cancer-related mortality worldwide, with smoking identified as the primary etiological factor [13]. Studies have shown that both smoking duration and cumulative exposure, often expressed in pack-years, are significant predictors of lung cancer risk and histological subtype distribution. This study investigates these associations, with a specific focus on the role of smoking habits in the development of specific histological types of lung cancer.

This cross-sectional study, conducted at the National Institute of Diseases of Chest & Hospital (NIDCH), analyzed 98 patients with confirmed primary lung cancer. After excluding benign cases, inflammatory conditions, and non-localized lung lesions, 98 cases were finalized for analysis. Of these, 81 were smokers and 17 were non-smokers, enabling a comparative analysis of lung cancer subtype distribution in relation to smoking history.

The study sample had a significant male predominance, with an 8:1 male-to-female ratio, consistent with Hussain and Qayyum [14,15]. This trend likely reflects the higher prevalence of smoking among males in Bangladesh and perhaps societal factors limiting healthcare-seeking behavior among females. Smoking was notably more common among males, with a statistically significant difference ($p < 0.001$), further highlighting the correlation between smoking habits and lung cancer incidence.

Tumor localization, assessed through chest CT and fiber-optic bronchoscopy, revealed a predominance of upper lobe tumors among smokers, with nearly 94% of upper lobe tumors occurring in this group ($p < 0.001$). This finding aligns with prior studies that suggest a higher ventilation-perfusion ratio in the upper lobes, leading to prolonged exposure to inhaled carcinogens in smokers [16]. In contrast, non-smokers more frequently presented with lower lobe tumors. The observed tendency of carcinogens to settle in the upper lobes may contribute to this distribution, with upper lobe tumors being four times more prevalent among smokers

compared to non-smokers. This distribution was similar to findings from other studies, such as Jamnik, Uehara, and Silva, who observed a statistically significant predominance of upper lobe tumors among smokers (69.6%) compared to non-smokers (54.2%) [13].

Among the 98 patients, adenocarcinoma was the most common subtype, observed in 45% of cases, followed by squamous cell carcinoma (28.6%), small cell carcinoma (16.3%), and large cell carcinoma (6.1%). These findings align with those of Strauss, but differ from Hussain, who reported a higher prevalence of squamous cell carcinoma than adenocarcinoma in Bangladesh [14,17]. However, an increasing trend in adenocarcinoma prevalence, particularly among smokers, has been noted in recent years.

Within the smoker subgroup, adenocarcinoma accounted for 37% of cases, followed by squamous cell carcinoma (33.3%) and small cell carcinoma (19.8%). This pattern contrasts with previous findings from Hussain's study, which indicated a higher prevalence of squamous cell carcinoma and small cell carcinoma among smokers [14]. The shift toward adenocarcinoma in smokers may be attributable to changes in cigarette composition, specifically the adoption of filtered, low-tar cigarettes. These design changes, intended to reduce harm, encourage deeper inhalation and may lead to a greater accumulation of carcinogens in the peripheral lung tissue, the primary site for adenocarcinoma development [18].

The relationship between smoking duration, cumulative exposure (pack-years), and histological subtype was examined. The data demonstrated that longer smoking duration and higher pack-year history were more strongly associated with squamous cell carcinoma and small cell carcinoma than with adenocarcinoma. In particular, the mean duration of smoking and the mean pack-year history were significantly higher in patients with squamous and small cell carcinomas, supporting previous research findings by Lee *et al.*, that linked higher smoking intensity with these histological types [11]. Notably, the squamous cell and small cell carcinoma group had a lower average age at smoking initiation and a higher pack-year history, reinforcing the association of smoking intensity with these histological types.

Additionally, patients who had quit smoking exhibited a higher prevalence of adenocarcinoma, which may reflect a delayed response to cessation among this subtype compared to squamous cell and small cell carcinomas. This aligns with Khuder *et al.*, who found that cessation of smoking showed the greatest reduction in risk for squamous and small cell carcinoma, with adenocarcinoma displaying the least reduction [19].

The study further examined the effect of cigarette type on lung cancer histology, observing a higher prevalence of adenocarcinoma among filter cigarette users compared to non-filter cigarette users. Conversely, squamous cell and small cell carcinomas were more common among those who smoked non-filter cigarettes. This difference was statistically significant, aligning with previous studies that associate filtered cigarettes with a shift toward peripheral adenocarcinoma, possibly due to the inhalation depth promoted by filtered cigarettes [9].

The study noted a gender-based difference in lung cancer histology, with males showing a higher prevalence of squamous cell and small cell carcinoma, while adenocarcinoma was more common among females. This finding may be attributable to non-smoking-related factors such as genetic predispositions, hormonal influences, or environmental exposures, as suggested in prior research.

Limitations of the study

This study's single-center design may limit the generalizability of findings to broader populations. Additionally, the relatively small sample size could affect the statistical power and precision of subtype-specific analyses.

CONCLUSION

The findings indicate that upper lobe tumors are more common among smokers, with a significant association between smoking intensity (duration and pack-years) and the histological types most closely linked to tobacco exposure, namely squamous cell and small cell carcinoma. Adenocarcinoma emerged as the most prevalent subtype among both smokers and non-smokers, underscoring a shifting trend toward adenocarcinoma, possibly due to changes in cigarette design and smoking patterns. The study confirms that smoking duration, pack-years, and cigarette type are influential in determining lung cancer histology, which has important implications for tailoring prevention and intervention strategies in lung cancer patients.

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Ethical approval: The study was approved by the Institutional Ethics Committee.

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