



Received on 12 October, 2018; received in revised form, 26 November, 2018; accepted, 29 November, 2018; published 01 December, 2018

RELATIONSHIP BETWEEN SMOKING AND HISTOLOGY OF LUNG CANCER IN MALAPPURAM DISTRICT OF KERALA, SOUTH INDIA

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Keywords:

Lung cancer, Smoking, Histology, Adenocarcinoma, Squamous cell carcinoma

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ABSTRACT: Background: Lung Cancer is the commonly diagnosed neoplasm in males in India. The main histological types of lung cancer are squamous cell carcinoma, adenocarcinoma, small cell carcinoma and large cell carcinoma. However, histological types may vary with the changes in geographical region, smoking status and other social factors. This study aimed to find out the relationship of smoking and histological types of lung cancer. **Methods:** We performed a prospective observational analysis of 238 histopathologically proven cases of lung cancer in Malappuram district of Kerala during the period of 2017 and 2018. **Results:** A total of 238 patients involved, 82.77% were males and the male to female ratio was 4.8:1. Of the 238 patients, 166 patients (69.75%) had history of smoking in their life time and 72 patients (30.25%) were non-smokers. In males, majority of patients were smokers (83.25%) and in female patients, 39 (95.12%) were non-smokers. Among Smokers, squamous cell carcinoma (63.25%) is the most common histological type followed by adenocarcinoma (22.89%). In case of non-smokers, the status is entirely different and here adenocarcinoma is the most common type and which constitute 66.67% and the presence of squamous cell carcinoma in non-smokers is very less and only 15.27%. **Conclusion:** In male smokers, squamous cell carcinoma is still the most frequent histological type of lung carcinoma in our study area. In case of females and non-smokers adenocarcinoma is the predominant histological type.

INTRODUCTION: Lung cancer is the most common malignant neoplasm worldwide, accounting for greater mortality than due to any other cancer¹.

In the mid-1900s lung carcinoma was an uncommon disease. Now, it is in relevant proportions and is presently the prominent cause of cancer related deaths in the western countries^{1,2}.

Thus, it is viewed as a dreadful disease with a poor response to chemotherapeutic regimens³. In 2012, nearly 1.8 million new cases of lung cancer were reported, which represented about 12.9% of the total cancer incidence globally⁴. The GLOBOCAN 2018 estimated that in both genders combined, lung malignancy is the most diagnosed (11.6% of the

	<p>QUICK RESPONSE CODE</p>
	<p>DOI: 10.13040/IJPSR.0975-8232.9(12).5490-95</p>
<p>Article can be accessed online on: www.ijpsr.com</p>	
<p>DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(12).5490-95</p>	

aggregate cases) and the prominent reason of cancer deaths (18.4% of the total deaths due to cancer). Death rates due to lung cancer is more prominent among males, followed by prostate and colorectal cancer (in terms of incidence) and liver and gastric cancer (in terms of mortality)⁵. The death statistics due to lung neoplasms is expected to raise to ten million deaths per year by 2030⁶.

Compared to western population, epidemiological study reveals increased incidence of lung tumour in Indian population⁷. India has a high mortality of lung cancer, and the incidence for both genders has increased over the past 3 decades^{3, 8, 9}. Of the 11.3% of new lung cancer cases reported in India, the incidence is more frequent in men and this represents up to 13.7% of the total cancer deaths¹⁰. In Kerala, in 2013, according to hospital based cancer registries (HBCRs) of Trivandrum RCC reported that lung cancer (15%) was the most common cancer among males¹¹. The main trigger for developing lung cancer is use of tobacco. It is often regarded solely as smokers' disease. However, high rates of lung cancer are also prevalent among non-smoking women and 10-25% of cases are observed in non-smokers. Multiple risk factors such as occupational, environmental, genetic, dietary factors, etc. are involved in the pathogenesis of lung cancer in non-smokers¹²⁻¹⁴.

Lung cancer mainly originates from the basal epithelial cells and is mainly classified into two types, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Among these NSCLC is more common and which accounts for around 85% of lung cancer cases¹⁵. The main histological types of lung cancer are adenocarcinoma, squamous cell carcinoma, large cell carcinoma and small cell carcinoma¹⁶. All the diverse histological types are somehow associated to tobacco smoking. However, the intensity of association differs with the type of lung cancer. Several reports have suggested the strength of association between smoking and adenocarcinoma is much lesser than that between smoking and squamous cell carcinoma or small cell carcinoma¹⁷. In the recent decades, the percentage of squamous cell carcinomas (which was predominant) has decreased and the trend shows an increase of adenocarcinoma in both genders¹⁶. This histological shift could be correlated to the

variation in the smoking habits of the population as well as in the composition and design of cigarettes being marketed¹⁸. The main aim of this study is to find out the relation between smoking status and histological type of lung cancer in Malappuram district of Kerala. This type of study has not been conducted in this district till now to the best of our knowledge.

MATERIALS AND METHODS: This is a prospective, observational, cross sectional study conducted in patients those who registered in various palliative care clinics in Malappuram district, Kerala, India for a period of one year (2017 - 2018). These various palliative care clinics in the district together formed a district umbrella organisation called Malappuram Initiative in Palliative Care (MIP) in the year 2000, the objectives being to improve the quality of care, share good and bad experiences and provide training to professionals and volunteers. While access to palliative care is calculated to be less than 3% nationally, it is more than 85% in Malappuram district. The institutional ethics committee permission was obtained for carrying out this study from Malappuram Initiative in Palliative care (MIP) (112/MIP/MPM/2017).

Inclusion Criteria:

- Both genders.
- All confirmed cases of lung cancer patients registered at palliative clinic during the study period.
- Physically well enough to participate.

Exclusion Criteria:

- Those who registered but not alive.
- Patients with any other cancer.
- The cases having doubts about primary origin.
- Patients whose biopsy report not available.
- Patients who is not willing to participate.

A well designed patient data collection form was developed and used for the study. The data collection form was developed by consulting physician of palliative clinics, staff of pharmacy practice department. The following information like patient demographic details like age, gender, marital status, religion, education is included.

Details of few life style characteristics such as smoking, alcohol, chewing habits and information of passive smoking & family history of cancer were also included in data collection form. Drug and disease details like stage, histology type, co-morbidities are also included in the data collection form. Each eligible case was contacted, informed consent was obtained, and a personal interview was completed either at the clinic or at the home of the patient. Information on specifics of the diseases such as (stage, histology) were abstracted from the patient's case sheets at the clinic.

In this study, smoking status was categorized as smokers or non-smokers. A non-smoker was coded as a patient who smoked less than 100 cigarettes during life time; and a patient who smoked more than 100 cigarettes was called as a smoker¹⁹. The cases were categorized based on the histology into different types using WHO classification of lung tumours²⁰.

RESULTS: A total of 238 lung cancer patients were included in this study, among which 197 were males (82.77%). The male female ratio was found to be 4.8:1. The mean age of the study subjects was 63.16 years. For male patients, the mean age was 64.04 years and for female patients, it's found to be 58.7 years. Only 12 (05.04%) cases were below the age of 40 years, 26.47% patients in the 41-60 and maximum patients were present in the 61-80 age group (65.13%). The youngest patient was aged 24 years and the oldest was aged 80 years **Table 1**.

TABLE 1: DEMOGRAPHIC PROFILE OF STUDY GROUP (N = 238)

Variable	No. of patients	Percentage
Gender		
Male	197	82.77
Female	41	17.23
Age		
≤40	12	05.04
41-60	63	26.47
61-80	155	65.13
>80	08	03.36

Of the 238 patients, 166 patients (69.75%) had history of smoking in their life time and 72 patients (30.25%) were non-smokers. In males, majority of patients were smokers (83.25%) and in female patients, 39 (95.12%) were non-smokers. Men had significantly higher incidence of smoking compared to women and the male female ratio in

case of smoking was 82:1. The smoker: non-smoker ratio in this study was found to be 2.3:1 **Table 2**.

TABLE 2: SMOKING STATUS OF THE STUDY GROUP (N = 238)

Variable	Male	Female	M:F ratio
Smoker	164	02	82:1
Non-smoker	33	39	0.84:1

Small cell lung cancer (SCLC) was diagnosed in 10.08% of patients, while 89.92% of the patients presented with non-small cell lung cancer (NSCLC). The most common histological presentation among non-small cell lung cancer was found to be Squamous cell carcinoma in 116 patients (48.74%) followed by adenocarcinoma in 86 patients (36.13%), undifferentiated group present in 09 patients (03.78%) and large cell carcinoma found only in 03 patients (01.26%) **Table 3**.

TABLE 3: HISTOLOGICAL TYPES OF LUNG CANCER (N = 238)

Histology	No. of patients	Percentage
Squamous cell carcinoma	116	48.74
Adenocarcinoma	86	36.13
Small cell carcinoma	24	10.08
Large cell carcinoma	03	01.26
Undifferentiated	09	03.78

In case of males, squamous cell carcinoma was the predominant histologic type of lung cancer (55.84%) followed by adenocarcinoma (29.95%) and small cell carcinoma (10.15%); but in case of females, Adenocarcinoma is the most prevalent histologic type and which accounts for 65.85% and squamous cell carcinoma present only 14.63% **Table 4**.

TABLE 4: HISTOLOGY TYPE ACCORDING TO SEX

Histology	Male (n=197)	Female (n=41)
Squamous cell carcinoma	110 (55.84%)	06 (14.63%)
Adenocarcinoma	59 (29.95%)	27 (65.85%)
Small cell carcinoma	20 (10.15%)	04 (09.76%)
Large cell carcinoma	02 (01.01%)	01 (02.43%)
Undifferentiated	06 (03.04%)	03 (07.31%)

Among smokers, squamous cell carcinoma (63.25%) is the most common histological type followed by adenocarcinoma (22.89%). In case of non-smokers, the status is entirely different and here adenocarcinoma is the most common type and which constitute 66.67% and the presence of squamous cell carcinoma in non-smokers is very less and only 15.27% **Table 5**.

The presence of squamous cell carcinoma was more common in age group of 61-80 (72.14%) followed by the group 41-60 (18.96%).

Adenocarcinoma was also more common in the age group of 61-80 (55.81%) followed by 41-60 age group (33.72%) **Table 6.**

TABLE 5: HISTOLOGY TYPE ACCORDING TO SMOKING STATUS

Histology	Smokers (n = 166)	Non-smokers (n = 72)
Squamous cell carcinoma	105 (63.25%)	11 (15.27%)
Adenocarcinoma	38 (22.89%)	48 (66.67%)
Small cell carcinoma	18 (10.84%)	06 (08.33%)
Large cell carcinoma	00 (00%)	03 (04.16%)
Undifferentiated	05 (03.01%)	04 (05.55%)

TABLE 6: AGE DISTRIBUTION OF PATIENTS BASED ON HISTOLOGY

Age	Squamous cell carcinoma (n = 116)	Adenocarcinoma (n = 86)	Small cell carcinoma (n = 24)	Large cell carcinoma (n = 03)	Undifferentiated (n = 09)
≤40	06 (05.17%)	05 (05.81%)	01 (04.17%)	00 (00%)	00 (00%)
41-60	22 (18.96%)	29 (33.72%)	06 (25.00%)	01 (33.33%)	04 (44.44%)
61-80	84 (72.41%)	48 (55.81%)	17 (70.83%)	02 (66.67%)	04 (44.44%)
>80	04 (03.44%)	04 (04.65%)	00 (00%)	00 (00%)	01 (11.11%)

DISCUSSION: In the present study, a male to female ratio of 4.8:1 was observed and another study from RCC Trivandrum, Kerala was also found the similar male to female ratio of 4.7:1¹¹. The sex ratio reported in several Indian studies ranged from 4.5:1 to 8.2:1^{21, 22}. In another Indian study, a male: female ratio of 2.7:1 was reported and in a US based study, the male: female ratio was 5:1^{23, 24}. In the present study, the sex ratio demonstrates a clear male predominance. The mean age of patients with lung carcinoma has remained consistent over the years²³. In the present study, the mean age at diagnosis is 63.16 years which is almost similar to other studies from India, Iran and Turkey^{25, 26}. While the mean age for diagnosis is higher in other Gulf countries, Canada and USA^{27, 28}. This study reveals that the age group, in which lung cancer was most commonly affected, was in the sixth and seventh decades of life. The increasing number of incidence in older age group, particularly in the sixth and seventh decades of life shows that lung cancer is an old age disease¹⁶.

The current study reveals that around 83.25% of the male patients were habited to smoking; while the trend is very less among females. Majority of female patients (95.12%) were non-smokers. This clearly notes that the elevation in the rate of lung carcinoma in males could be related to the increasing consumption of tobacco in any form. In Kerala, the frequency of tobacco habits among females is very low compared to male¹⁶. The increasing percentage of smoking in males is in

consistent with the reports from various parts of India and also from other developing nations^{22, 29}. Hence, the significance of tobacco cessation programmes, together with mass education and awareness plans among adolescents needs to be strongly implemented. The present study shows a smoker: non-smoker ratio of 2.3:1 in patients with lung carcinoma, similar to other studies which reported a ratio of 2:1 and 2.4:1^{30, 31}.

The pattern of lung cancer has shown a drastic change in the western region³². In the initial decades, smoking was the root cause of lung cancer as an epidemic worldwide. Squamous cell carcinoma was the most frequent lung cancer, which was followed by small cell carcinoma³³. In the late seventies, the prevalence of adenocarcinoma was observed as an evidence of shift^{34, 35}. Nowadays, in western countries, lung cancer is being increasingly detected in women and adenocarcinoma has surpassed squamous cell carcinoma as the most common histological type³². This difference in histopathology may be due to the fact that smoking is less prevalent among women in India especially in Kerala as opposed to the west, where it is rising²². The hypothesis, concerning the histopathological changes, have emphasised the probable role of changes in the features of cigarettes and the resulting changes in the proportion of carcinogens inhaled³⁵. Additional explanations for the prevalence of adenocarcinoma could include the impact of the atmospheric air pollution, particularly oxides of nitrogen which had

been suggested to increase adenocarcinoma³⁶. There are studies which reported adenocarcinoma was the most frequent histological type of lung malignancy^{25, 37}. A study conducted at RCC Trivandrum, Kerala found that adenocarcinoma (28.5%) was the most common histology type followed by Squamous cell carcinoma (12.9%)¹¹. However, the pattern seen at our study district was different and squamous cell carcinoma (48.74%) was still the most frequent, followed by adenocarcinoma (36.13%). This is in consistence with similar reports from other part of India^{22, 38, 39}. In the present study adenocarcinoma is the most common histological type in females (65.85%) but in male's squamous cell carcinoma is the predominant type.

It was initially presumed that squamous cell carcinoma of the lung was due to smoking rather than adenocarcinoma. The shift and drastic increase in the frequency of adenocarcinoma was thought to be primarily attributed to the altered smoking pattern⁴⁰. Previous reports suggested the increased rate of adenocarcinoma was limited to smokers^{41, 42}. However, current studies suggest that the correlation between smoking and squamous cell carcinoma or small cell carcinoma is stronger than that between smoking and adenocarcinoma¹⁷.

In the current study squamous cell carcinoma (63.25%) is the most predominant histological type in smokers, which shows a similar pattern as in other reports^{21, 43}. It was also observed with a higher incidence of adenocarcinoma among non-smokers (66.67%) in comparison to smokers (22.89%), which is also supported by other studies^{44, 45}.

CONCLUSION: Lung cancer is one of the major cancer affecting males in India. The incidence rate is highly increased in the South Indian State, Kerala. This community based study also found that lung cancer is an old age disease and smoking as the principle etiological factor in the development of lung carcinoma among men in Malappuram district of Kerala. This mainly reveals the importance of tobacco cessation programmes in the community as well as education and awareness programme among teenagers should be strongly executed. In male smokers, squamous cell carcinoma is still remains the most common

histological type of lung cancer in our study area. In case of females and non-smokers adenocarcinoma is the predominant histological type.

ACKNOWLEDGEMENT: We acknowledge Malappuram Initiative in Palliative care (MIP) for giving all facilities to complete our work and also those patients who participated in this study.

CONFLICT OF INTEREST: Nil

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How to cite this article:

Muhās C, Kumar PRAV, Seenivasan P and Raja D: Relationship between smoking and histology of lung cancer in Malappuram district of Kerala, South India. *Int J Pharm Sci & Res* 2018; 9(12): 5490-95. doi: 10.13040/IJPSR.0975-8232.9(12).5490-95.

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