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A STUDY ON RISK FACTORS OF LUNG CANCER AND ITS RELATION WITH PATHOLOGICAL TYPES AND STAGING—A RETROSPECTIVE STUDY IN A TERTIARY CARE HOSPITAL.

Pulmonary Medicine

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ABSTRACT

BACKGROUND & OBJECTIVE: Incidence of lung cancer is increasing globally and most cases are diagnosed in late stages. This study was undertaken to asses various risk factors among the diagnosed cases of lung cancer, find a correlation between various risk factors and specific pathological types of lung cancer and staging of the lung cancer.

METHODS: A retrospective case control study done in IPGMER, Kolkata, India after taking Institutional Ethics Committee approval. 110 lung cancer patients who met inclusion criteria were selected. 110 matched controls were also taken. Patients were evaluated for various risk factors for development of lung cancer. Staging done and specific pathological type ascertained. Normally distributed data compared by "students unpaired t test". Not normally distributed variables were compared by "Mann Whitney U test". Categorical variables were compared by Fischer's Exact Test. p value <0.05 considered statistically significant.

RESULTS: Smoking ($p<0.001$), Environmental tobacco smoke ($p<0.002$) and Biomass fuel exposure ($p<0.001$) were significantly associated with development of lung cancer. Other significant risk factors were arsenic exposure (p 0.002), hypertension (p 0.003) and family history of cancer(p 0.002). No significant association was found with tobacco chewing, alcohol consumption, diegel engine exposure, coal exposure in workplaces, cytotoxic drug intake in early life, past history of tuberculosis and diabetes mellitus with development of lung cancer.

Smoking was associated with squamous cell carcinoma and environmental tobacco smoke with adenocarcinoma. Most cases were diagnosed in stage IV. Females were more diagnosed in late stages compared to males.

CONCLUSION: Patients with lung cancer still present at an advanced stage with less curative scope. Identification and modification of risk factors is the major strategy of our battle against lung cancer.

KEYWORDS

lung cancer, risk factor, staging, pathological type

INTRODUCTION

Lung cancer has been the most common cancer in the world for several decades. The disease remains as the most common cancer in men worldwide (1.2 million, 16.7% of the total).

The American Cancer Society's estimates for lung cancer in the United States for 2017 are:

- About 222,500 new cases of lung cancer (116,990 in men and 105,510 in women)
- About 155,870 deaths from lung cancer (84,590 in men and 71,280 in women)

Each year, more people die of lung cancer than of colon, breast, and prostate cancers combined.

A data[1] from the population based cancer registry of Indian Cancer Society from Maharashtra which covers Mumbai, Pune, Nagpur and Aurangabad showed that among 24,270,077 Indians (in the year 2011) 3170 new cases had lung cancer. By extrapolating this data to the 1.16 billion Indians, it shows that the actual new cases across India were 156,736 new cases, more than double of what is estimated by Globocan.[2]

A risk factor is anything that affects a person's chance of getting a disease such as cancer. Various risk factors are implicated in development of lung cancer like age >40 years and male sex(males have a lifetime risk of 8% of lung cancer development compared to 6% in females). Other risk factors are tobacco smoking(active), environmental tobacco smoking(ETS)exposure, pulmonary diseases like chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, systemic Sclerosis related interstitial lung disease, pneumoconiosis, systemic disease like HIV, air Pollution, environmental exposure of radon, arsenic, nickel, chromium, asbestos; dietary factors like alcohol consumption, less intake of vitamins, fruits, vegetables; hormonal therapy and genetic factors (Familial or Specific genetic abnormality). These risk factors are related to the development of different pathological types of lung cancer and may have a role in the clinical presentation of the disease and staging. It is mostly diagnosed in late stages in developing country like India due various sociodemographic factors[3]. Staging of lung cancer is important in the following perspectives: to aid the clinician in treatment planning, to give some indication of prognosis, to assist in evaluating the results of treatment.

Aims & Objectives

I) Studying the various risk factors among the diagnosed cases of lung cancer in hospitalized patient of SSKM Hospital.
II) Finding a correlation between various risk factors and specific pathological types of lung cancer.
III) Staging of the lung cancer and finding a relation at what stage mostly the lung cancer are diagnosed in a Tertiary Care Hospital with pathological type of lung cancer and risk factors thereby involved.

Materials & Methods

1. **Study setting**- West Bengal and its neighbourhood.
2. **Time line-**One and half year from September 2015 to March 2017.
3. **Definition of the problem**- Lung cancer is the leading cancer in the world and various risk factors are related to the development of different pathological types.
4. **Inclusion criteria -** 1)Cases--Patients(>18years) diagnosed to have any type of lung cancer by standard methods like Bronchoscopic biopsy, CT or USG guided biopsy, FNAC/biopsy of lymph node and admitted in the Department of Pulmonary Medicine of SSKM hospital. 2) Control - Patients >18 years not having lung cancer either by symptoms or imaging and admitted with disease other than lung cancer in the department of

Pulmonary Medicine of SSKM Hospital.

5. **Definition of population**- Patients admitted in the Indoor Department of Respiratory Medicine IPGME&R.

Exclusion criteria-

a) Patient with primary pleural malignancy like mesothelioma.
b) Patient with metastatic lung cancer with the primary being any other than the lung.

6. **Sample size**-110 cases and 110 controls.
7. **Informed consent** is taken from both cases and controls.
8. History taking about presence of various risk factors.
9. Thorough clinical examination to be done.
10. Investigation by which lung cancer is diagnosed to be ascertained by Bronchoscopic biopsy, Bronchial brush, Lavage fluid study, CT/USG guided FNAC. CT guided trucut biopsy, pleural fluid for cell block, pleural biopsy, bronchial brush, lymph node FNAC/biopsy.
11. **Experiment design**- Retrospective case control study in a hospital based population.

SCHEDULE OF DATA COLLECTION: Selected Patients were subjected to detailed history taking and clinical examination. They were investigated as necessary for within the selected study duration and subsequently data was subjected to appropriate statistical analysis.

STATISTICAL ANALYSIS: Data was first collected on Excel sheet ,the statistical software used Statistica version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001] , GraphPad Prism version 5 [San Diego, California: GraphPad Software Inc., 2007]. Numerical variables normally distributed by Kolmogorov-Smirnov goodness-of-fit test other than Duration Symptoms in months, SizeFamily, Duration of smoking in years and Duration Fuel Exposure in years. Normally distributed variables are compared among cases and controls by "students unpaired t test". Not normally distributed variables are compared by "Mann Whitney U test". Categorical variables are compared by Fischer's Exact Test.

Results & Analysis

In our study there are 110 cases, who were admitted in IPGME&R Chest indoor, and diagnosed with lung cancer and similar number of age and sex matched controls not having lung cancer also admitted in the Chest indoor of IPGME&R during the same time period.
There are 71 males and 39 females in cases.

Table 1: Age Distribution of Males and Females among cases (N = 110):

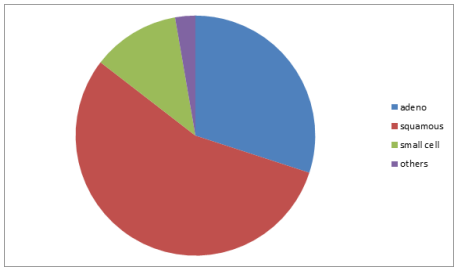
	30-50year	51-70 years	71-90 years	>90years	Total
Females	**10**	**23**	**5**	**1**	**39**
Males	**14**	**47**	**10**	**0**	**71**
Total	**24**	**70**	**15**	**1**	**110**

From the above tables it is clear that in female 58.97% of females are in age group 50-70 years group and 66.19% male are in 50-70 years group.

Pathological type of cancer

Among the cases majority was Squamous cell carcinoma (55.45%) and next in line was Adenocarcinoma (30.09%).

Figure 1: Pathological types of lung cancer



So in this study there has been found a higher prevalence of squamous cell carcinoma (55%) compared to other pathological types.

Prevalence of adenocarcinoma in females is 48.71% and in males 22.53%; that of squamous cell carcinoma in males 63.38% and females 43.58%.

Smoking distribution:

Among the cases, 67(60.91%) were smoker and 43(39.09%) non smokers. Among females only 3(7.6%) were smoker and rest non smoker. Among males 64 were smokers out of 71 (90%).

There are 60.91% smokers in the cases and 11.82% smokers in controls**. Fisher's exact test 2-tailed *p* value < 0.001.** There is significant difference in exposure to smoking and development of lung cancer among cases and controls groups (p< .001).

So smoking can be considered as significant risk factor for development of lung cancer and duration and amount of cigarette affect the development of lung cancer.

Passive smoking :

In our study there were 10(9.09%) patient exposed to passive smoking (all females) in cases and no patient in the control.

Passive smoking is the inhalation of smoke, called **second-hand smoke** (**SHS**), or **environmental tobacco smoke** (**ETS**), by persons other than the intended "active" smoker. It occurs when tobacco smoke permeates any environment, causing its inhalation by people within that environment [51].

Analysis has showed that passive smoking or second hand smoke is significantly associated with development of lung cancer among the cases (p < .002).

Biomass fuel exposure:

In our study there were 30.91 % patient exposed to biomass fuel exposure in the cases and 9.09% in controls. In Indian population a vast majority of population, particularly females use coal. cow dung, wood as the main medium for cooking. In our study population 31 out of 39 females in the cases having lung cancer had biomass fuel exposure in form of wood, coal, cowdung. So in females with lung cancer there is significant exposure to biomass fuel and the exposure is statistically significant in the case and control groups (p < .0001).

Among other risk factors arsenic exposure (p 0.002), hypertension (p 0.003) and family history of cancer(p 0.002) were significantly associated with development of lung cancer. No significant association was found with tobacco chewing, alcohol consumption, diegel engine exposure, coal exposure in workplaces, cytotoxic drug intake in early life, past history of tuberculosis and diabetes mellitus with development of lung cancer.

Figure 2: Different risk factors found in our study with Odds ratio

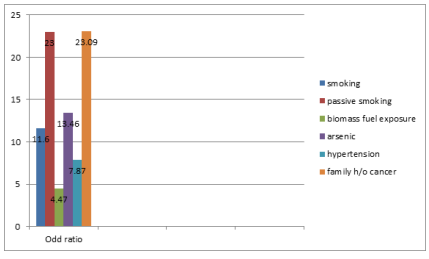


Table 2: Significant risk factors with p value

Risk Factors	% percentage	P value
Smoking	60.91%	.001
Passive smoking	9.09%	.002
Biomass fuel exposure	30.91%	.001
Arsenic	5.45%	.002
Hypertension	12.73%	.003
Family history of cancer	9.09%	.002

Figure 3: Anatomical Staging of the lung cancer

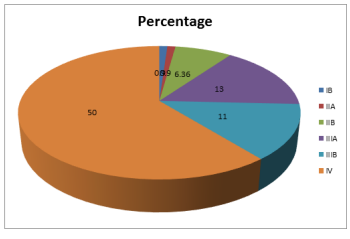


Table 3: Stage of diagnosis and sex distribution

STAGE	MALE	FEMALE
IIIA	10	5
IIIB	9	4
IV	31	23

So among the males there 43% cases and among females 58% are diagnosed at stage IV of their disease.

Table 4: Stage of diagnosis and pathological type of lung cancer

Stage	Squamous cell cancer	Adeno carcinoma
IIIA	13	3
IIIB	8	4
IV	29	25

47% in the squamous cell group are diagnosed at stage IV and 75% in the adenocarcinoma group are diagnosed at stage IV.

Relationship of risk factors with pathological type:
There were 67 smokers among the cases among which 45 are smokers had squamous cell carcinoma (n=61) and 13 smokers had adenocarcinoma(n=33).

(Fischer's exact test p <.002)
So smoking is significantly associated with increased risk of Squamous cell carcinoma.

There were 10 persons having exposure to passive smoking. Among them 6 developed adenocarcinoma group and 4 developed squamous cell carcinoma.

(Fischers exact test p <.062)
So passive smoking significantly increases the risk of adenocarcinoma in non-smoker females.

There are 34 patient exposed to biomass fuel in the cases among them 17 in the adenocarcinoma group and 15 in the squamous cell carcinoma group.

(Fischers exact test p <.062)
So biomass fuel exposure is significantly associated with adenocarcinoma.

No significant relation with a pathological type of cancer development has been found with arsenic exposure, hypertension and family history of lung cancer.

DISCUSSION

In our study males have increased prevalence of lung cancer compared to females.

The mean age of the cases were around 59.88+- SD10.895 and that of controls was 58.54+- SD10.154.

63.63% of the patient are in age group 51-70 years, which means elderly in age group 50-70 are most likely to develop lung cancer.
Among the cases diagnosed with lung cancer, the prevalence of different pathological types of lung cancer are squamous cell carcinoma 61 cases(55%) followed by Adenocarcinoma 34 cases (30%) and small cell carcinoma (n=13)(11.82%).

So in our study squamous cell carcinoma is the prevalent pathological type of cancer.

A study[4] done by Jindal and Behera with 1000 cases of lung cancer, according to that report the male were most common affected, mean age of affection was around 54years, and the predominant cell type pattern was squamous cell though there is increasing incidence of adenocarcinoma and small cell carcinoma.

Studies done in USA about the epidemiology of lung cancer[5] showed that prevalence of adenocarcinoma is 38.5% followed by squamous cell 20%. Another study[6] done in India done at Tata Memorial Hospital showed higher prevalence of adenocarcinoma (43.8%), followed by squamous cell (26.2%). But other studies done in India like that done in AIIMS[7] showed that squamous cell carcinoma (30%) is the most common histological type followed by, followed closely by adenocarcinoma (28.3%).

Among the 34 cases of adenocarcinoma , 15 in males and 19 in females.

Among 61 cases of squamous cell carcinoma, there are 45 cases in males and 16 cases in females.

So there is higher prevalence of squamous cell carcinoma in males and adenocarcinoma in females.

Risk Factors:
SMOKING:
The first risk factors studied in our study is SMOKING with number of cigarettes/bidis smoked per day and years of smoking. The number of pack years and smoking index was also calculated.

Among the cases there were 67(60.91%) smoker and 43(39.09%) non smokers. Among females only 3(7.6%) were smoker, rest non-smoker. Among males 64 were smokers out of 71 cases (90%). Smoking habits predominate in males with lung cancer compared to females in our country.

There is significant difference in cigarettes smoked per day among cases and controls. The mean cigarette smoked per day in the cases is 19.64± SD12.698 and in controls is 8.5± SD7.998. There is also difference in Smoking index and Pack year among cases and controls. The mean pack years of smoking among the cases are **33.97±SD23.184** and controls(n=110) were 12.5+_12.187. In cases(n=110) the smoking index was **654.4±SD480.52** and in controls are 250±SD242.74.

Thus Smoking was found to be associated with increased risk of lung cancer (**Fisher's exact test 2-tailed *p* value < 0.001).** The odds ratio for smoking and lung cancer in our study was found to be **11.626 (confidence interval 5.807 to 23.278).**

Among 67 smokers with lung cancer 45 are smokers have squamous cell carcinoma (n=61) and 13 smokers have adenocarcinoma (n=33). By applying fischers exact test (p <.002) it was found that there is significant relation with smoking and squamous cell carcinoma development.

A case control study done in Scotland[8] showed smoking of 15-24 cigarette per day is associated with risk of squamous cell and small cell carcinoma.

PASSIVE SMOKING AND BIOMASS FUEL EXPOSURE:
Passive smoking was also studied as potential risk factor for lung cancer. Our study also showed that there is significant relation between lung cancer development and passive smoking(**Fisher's exact test 2-tailed *p* value 0.002).**

By fischers exact test (p <.062) it was found that there were significant relation with adenocarcinoma in females with passive smoking.

Among the 34 patient 31 were females i,e about 79% of females with lung cancer in our study had biomass fuel exposure. So there is significant risk of development of lung cancer with biomass fuel exposure among females(**Fisher's exact test 2-tailed *p* value < 0.001** Odd ratio was 4.474 confidence interval 2.080 to 9.621).

In our study it was found that there are 34 patient exposed to biomass fuel in the cases among them 17 had adenocarcinoma group and 15 had squamous cell carcinoma group. By Fischers Exact test (p <.062) it was found in our study that there significant relation with adenocarcinoma and biomass fuel exposure.

A case-control study[9] of adenocarcinoma of the lung and exposure to environmental tobacco smoke (ETS) was studied in 7 countries showed weak dose response relation of adenocarcinoma with environmental tobacco smoke.

Another case control study[10] done in PGI Chandigarh about risk of lung cancer in women showed biomass fuel exposure had ODD ratio of 3.59 for development of lung cancer in women.

So like past studies, our present study also show a significant relation

of passive smoking and biomass fuel exposure to development of lung cancer both being associated with increased risk of development of adenocarcinoma in females, this is more relevant in Indian context where a vast majority of women use biomass fuel for cooking and are vulnerable to develop lung cancer.

ALCOHOL INTAKE:

In an unmatched hospital-based case-control study[11] conducted at Tata Memorial Hospital alcohol consumption (OR=1.8) was found as risk factor for lung cancer. But no significant relation has been arrived at between alcohol exposure and lung cancer in our study.(Fisher's exact test 2-tailed *p* value 0.437).

ARSENIC EXPOSURE:

Arsenic exposure was also significantly associated with lung cancer (**Fisher's exact test 2-tailed *p* value 0.029**) with an Odd s ratio of 13.746 (CI 1.7643 to 247.24).

A case control study[12] done in Chile by Ferrecio et al, with total of 151 lung cancer cases and 419 controls (167 with cancer and 242 without cancer),showed a clear dose-response relationship between mean Arsenic exposure levels, with an OR (95% CI) of: 1, 1.7 (0.5-5.1), 3.9 (1.2-13.4), 5.5 (2.2-13.5), and 9.0 (3.6-22) for strata one to five respectively.

DIESEL ENGINE AND COAL EXPOSURE

A study[13] conducted in China by H. Dean Hosgood et al showed potential risk of coal exposure with lung cancer. However in our study no significant relation was arrived at between diesel (**Fisher's exact test 2-tailed *p* value 0.247**) and coal exposure (Fisher's exact test 2-tailed *p* value 0.389) and lung cancer.

FAMILY HISTORY OF CANCER:

Among the cases there were history of cancer in first degree relative and death due to cancer in the first degree relatives 10 person. So there is significant relation with family history of cancer in first degree relatives and lung cancer with odd ratio of 23.090 (95% CI 1.335 to 399.400) . A study[14] was conducted in Texas university about lung cancer in smokers family history of any cancer with onset before age 50 in at least 1 first degree relative was a significant risk predictor (OR 1.70, 95% CI 1.10–2.64) in that study.

METABOLIC RISK FACTOR:

A study[15] was conducted in Finland to assess the effect of blood pressure and its possible interaction with smoking on lung cancer incidence in hypertensive patients, it showed that both systolic and diastolic blood pressures were significant predictors of lung cancer, with a 10% increase in risk per 10-mmHg increment in blood pressure. In smokers, the age-adjusted hazard ratio associated with a 10-mmHg increment in diastolic blood pressure was 1.17 (95% confidence interval: 1.05, 1.29), and in non smokers it was 0.98 (95% confidence interval: 0.80, 1.16). For systolic blood pressure, these hazard ratios were 1.11 (95% confidence interval: 1.05, 1.17) for smokers and 1.04 (95% confidence interval: 0.95, 1.14) for non smokers.

Our present study also shows significant relationship of lung cancer and hypertension but it needs to be studied further, with larger sample size as smoking may be common confounding factor both for lung cancer and hypertension.

Staging and relation with pathological types:

In our present study it is found that most patient are diagnosed in stage IV of their disease (50%) followed by diagnosis in stage IIIA (13.8%) stage IIIB (11%).

Earlier studies[16] also say that majority of lung cancers (>80%) are diagnosed at an advanced stage, i.e. Stage IIIB and IV, by when they are beyond the scope of curative resection. Pleural metastasis is the commonest site of metastasis (29.09%) found in this study followed by cervical lymph node metastasis(16%),opposite lung invasion(10%) and liver metastasis(7.27%).

43% of males and 58% females are diagnosed in stage IV of the disease. This suggests that though males are more commonly affected by lung cancer, females may have worse prognosis. In a study done in Singapore showed Asian women who never smoke are being diagnosed with late stage lung cancer and the number of new cases seen at the National Cancer Centre Singapore is increasing.

47% in the squamous cell group and 75% in the adenocarcinoma group are diagnosed in stage IV of their disease. Greater preponderance of adenocarcinoma in stage IV may be partly due to higher incidence of malignant pleural effusion (29%) requiring hospitalisation. This is also due to increased pleural metastasis in adenocacinoma causing malignant pleural effusion. Also adenocarcinomas have female preponderance.

In our study the clinical performance status of the patient were also studied. Majority of the patient were in stage II (40%) and stage III(38.18%).

Among 55 patient in stage IV, 52% are in ECOG II score and 29% in ECOG scale III.

Thus lung cancer cases on initial presentation have both advanced anatomical staging and poor performance status.

Our study had some limitations like this was a single centre based study so the results cannot be applied to the whole population. Sample size was small. Study is biased as done only with the indoor or admitted patients with lung cancer. Immunohistochemistry /molecular analysis of biopsy samples could not be done.

CONCLUSION

Despite many advances in diagnostic tools, cases with lung cancer still present at an advanced stage with less curative scope. So identification and modification of risk factors is the major strategy of our battle against lung cancer. The present study reiterates that modifiable risk factors chiefly smoking is the major risk factors for lung cancer in our country. So implementation of lifestyle modification like smoking cessation can play a major role in controlling lung cancer. Government across countries should enforce strict regulation against the use of the tobacco to halt the growing epidemic.

Non-smoking females are also at high risk of lung cancer and advanced disease due to exposure to passive smoke in their homes and also from the use of biomass fuel for cooking. Women should be provided with cleaner fuels like LPG and stopped from using biomass fuels.

Significant genetic influence in development of lung cancer is also evident from our study. Whether hypertension is a real risk factor for development of lung cancer or smoking is the common confounding factor needs to be evaluated further.

Many risk factors like Asbestos exposure, COPD, Interstial Lung disease and prior history of tuberculosis need to be evaluated in a larger study.

Newer risk factors like Pesticide Exposure Radioactive mining are emerging and needs to be studied in future in larger perspective of prevention of lung cancer .

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