ORIGINAL ARTICLE

Trends in Development of Various Types of Lung Cancer after Cessation of Smoking

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ABSTRACT

Aim: This research aims at categorizing the different types of lung cancer in patient population unique to Pakistan and providing an insight in the occurrence of various histological subtypes relative to the patient's smoking status.
Study design: Cross-sectional study.
Study setting and duration: February to June 2015 at four major hospitals of Lahore
Methods: All diagnosed cases of lung cancer presenting between January 2013 to December 2014 were considered eligible for the study. A questionnaire regarding smoking status, particulars of the disease and risk factors was filled either by accessing patient records or contacting the patient/next of kin. Statistical analyses were performed using IBM's SPSS, version 24.0.
Results: 229 patients were considered eligible for the study. The study population consisted of 84.3% males and 15.7% females. Univariate analyses showed that the non-smokers were more likely to have adenocarcinoma (63.6%) vs. 28.8% for ever-smokers. Small cell lung cancer and squamous cell carcinoma were more common among smokers (18.4% and 39.3%) vs. 6.1% and 27.3% for non-smokers respectively. Among ex-smokers histopathologies observed were 23.7% adenocarcinoma, 7.9% small cell lung cancer(SCLC), 47.4% squamous cell carcinoma(SCC) and 21.1% cases of non-specified non-small cell lung cancer(NSCLC). As the time period since quitting increased, in case of ex-smokers in our study population, the number of cases who presented with both non-small cell lung cancers and small cell lung cancer continue to increase reaching peak level at five years followed by a sharp decline.
Conclusion: The histopathology of lung cancer varied with smoking status. Adenocarcinoma was a predominant finding in non-smokers while SCLC and SCC showed a stronger association with ever-smokers, showing a continuous rise with increasing pack years. In our study, we conclude that risk of lung cancer continues to rise till five years after cessation of smoking and it may be protective of lung cancer after 10 years of quitting.
Key words: Lung neoplasms, histopathology, smoking, small cell lung cancer, non-small cell lung cancer, ex-smokers

INTRODUCTION

Lung cancer is the third most common cancer worldwide and has a high mortality rate with one in five cases resulting in death.[1]Figures are even higher for developing countries such as Pakistan where the incidence is 4.6% and more than 6,000 estimated deaths occurred in the year 2012[1]. According to a 2014 report, it is the sixth most commonly reported malignancy in males in Punjab (6.1% of total cancer cases)[2] and ranks ninth among both genders combined (3.4%)[2].

Up to 25% of the total lung cancer cases globally are not linked to tobacco use. [3] It is stressed that lung cancer in smokers and never-smokers are separate clinical entities with uniqueness in their tumorigenesis, histopathology and response to targeted chemotherapy. [3]Besides this, the residual effects of smoking on lung cancer risk remains quite notable in former smokers and a significant proportion of lung cancer is now diagnosed in this group.[4] Extensive work has been done on the subject throughout the world but data unique to Pakistan is sparse, especially with regards to ex-smokers. Some studies have managed to establish risk factors[5] but they have failed to capture any significant association between histology of cancer and smoking status[6]. Besides, there is ethnic disparity associated with differences in smoking prevalence, environmental exposures, genetic and gender predisposition which is unique to this region.

This research aims at categorizing the different types of lung cancer in patient population unique to Pakistan and providing an insight in the occurrence of various histological subtypes relative to the patient's smoking status. This can serve as baseline data

which will further help to customize cancer treatment and prevention in a better way.

METHODS

This is a cross-sectional study conducted between February 2015 to June 2015 at four major hospitals of Lahore; namely Mayo Hospital, Jinnah Hospital, Gulab Devi Chest Hospital and INMOL Cancer Hospital. Records of lung cancer cases presenting to the above mentioned hospital settings between January 2013 and December 2014 were retrieved. Data was collected by accessing patient records and any ambiguities were clarified by contacting the patient or next of kin. Exclusion criteria consisted of patients with incomplete data regarding smoking history, histopathology or contact information.

The survey form consisted of preliminary biodata (name, sex, age, occupation, contact information),details pertaining to smoking (smoking status, product used and pack years) and information regarding histopathology, symptoms and their duration, site, stage, metastasis, treatment given, fuel used, history of prior lung disease, family history, co-morbidity and co-malignancy.

Smoking status was divided into two broad categories, ever-smokers and non-smokers. Ever-smoker was defined as a person who smoked 100 or more cigarettes (or the equivalent amount of tobacco) in his/her lifetime. The magnitude of tobacco exposure was quantified in pack-years. Ever-smokers were subdivided into current and ex-smokers.with ex-smokers having given up at least 8 months before the time of presentation. Non-smokers were further divided into never-smokers and passive smokers. Passive smoker was described as someone who didn't smoke but was exposed to secondhand smoke by live-in family members (workplace smoking was not accounted for).

The histopathological sub-types, determined by biopsies, were classified as small cell lung cancer (SCLC) or non-small cell (NSCLC), with NSCLC comprising of adenocarcinoma and squamous cells carcinoma (SCC). The synopsis was presented to KEMU's institutional review board and was approved in February, 2015.

Statistical analysis: Quantitative variables were presented as mean ± Standard Deviation. Qualitative variables were calculated as frequency and percentages. Comparison across groups, on the basis of smoking status and histopathology, was done using chi-square test and fisher's exact test for 2x2 contingency tables. IBM's Statistical Package for the Social Sciences, version 24.0, was used for statistical analysis. All hypothesis tests were two-tailed, and the level of significance was set at 5%.

RESULTS

Six hundred and nineteen lung cancer patients were diagnosed in the four hospitals mentioned, in the years 2013 and 2014. Out of those, 229 fulfilled the criteria to be included in the analysis, 193 (84.3%) males and 36 (15.7%) females. Mean age at diagnosis was 59.7 (± 11.2) years. Only 26 patients were alive at the time of this study.

A wide variety of symptoms were noted; most common being cough, dyspnea, chest pain, hemoptysis, weight loss, either alone or in various combinations. Mean duration of the symptoms was 7.1 (±11.6) months. However, a majority of the patients (71.2%) presented within 1-6 months. 119(52%) patients had documented regional or distant metastasis at the time of diagnosis. The most common distant site being bone (40.3%) followed by brain (10.9%) and the most common combination involved these two as well.

Around two-thirds of the cases were ever-smokers (71.2%). Gender distribution among smoking status showed a male preponderance in both groups, distinctly so in ever-smokers (97% of ever-smokers and 53% of non-smokers were males). Among smokers mean pack years were 33.9 (± 21.9).

For ex-smokers (n=38), the length of smoking cessation to cancer diagnosis was <1 year for 7.9%, 1-5 years for 63.2%, 6-10 years for 18.4% and >10 years for 10.5%.

Histopathology was compared across smoking status, increasing pack years in smokers and cessation time in ex-smokers. In smokers, SCLC and SCC showed a rise with increasing pack years while the opposite trend was observed with adenocarcinoma.

Among ex-smokers when the histopathologies were compared across time since quitting, all three showed a rising trend for upto 5 years. After that the graph for adeno reached a plateau. While SCC and SCLC kept on decreasing, with SCLC showing a sharp decline and not appearing beyond 6 or more years of cessation time.

Table 1- Epidemiology

			Count	Percentage
Gender	Male		193	84.3%
	Female		36	15.7%
Alive/ Deceased	Alive		203	88.6%
	Deceased		26	11.4%
Smoking Status	Ever-Smokers (163/229) (71.2%)	Smoker(cigarettes)	105	45.9%
		Smoker(Cigarette + Huqqa)	17	7.4%
		Smoker(Huqqa)	3	1.3%
		Ex-smoker	38	16.6%
	Never-Smokers (66/229) (28.8%)	Never-smoker	59	25.8%
		Passive Smoker	7	3.1%
Histopathology	SCLC (34/229) (14.8%)	SCLC	34	14.8%
	NSCLC (195/229) (85.2%)	NSCLC (Non-specified)	24	10.5%
		Adenocarcinoma	89	38.9%
		SCC	82	35.8%
Stage	Locally Advanced (Stages I,II,III)		71	31%
	Metastatic (Stage IV)		158	69%

Fig. 1: Association of histopathology with smoking status.

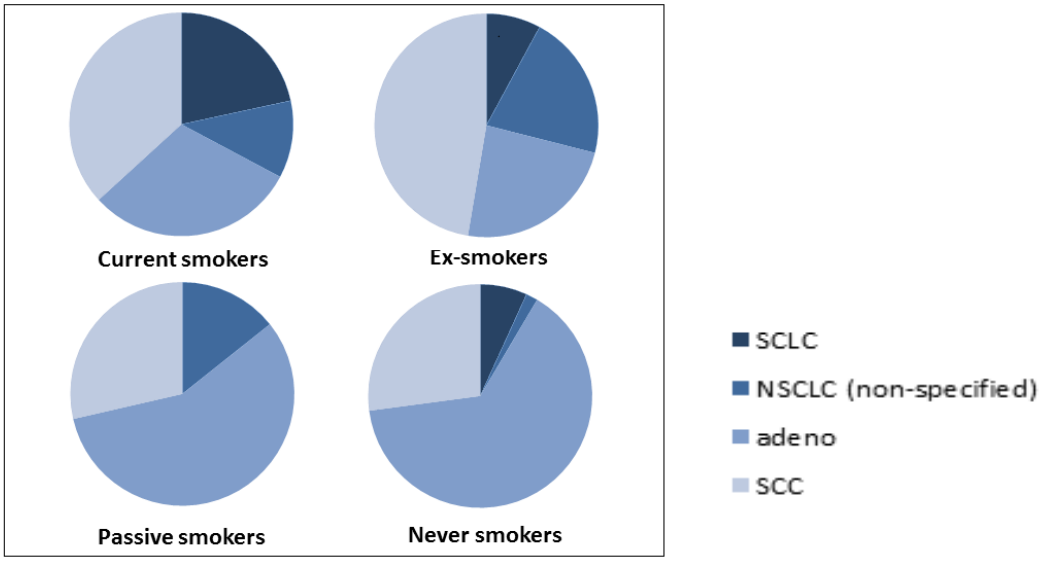
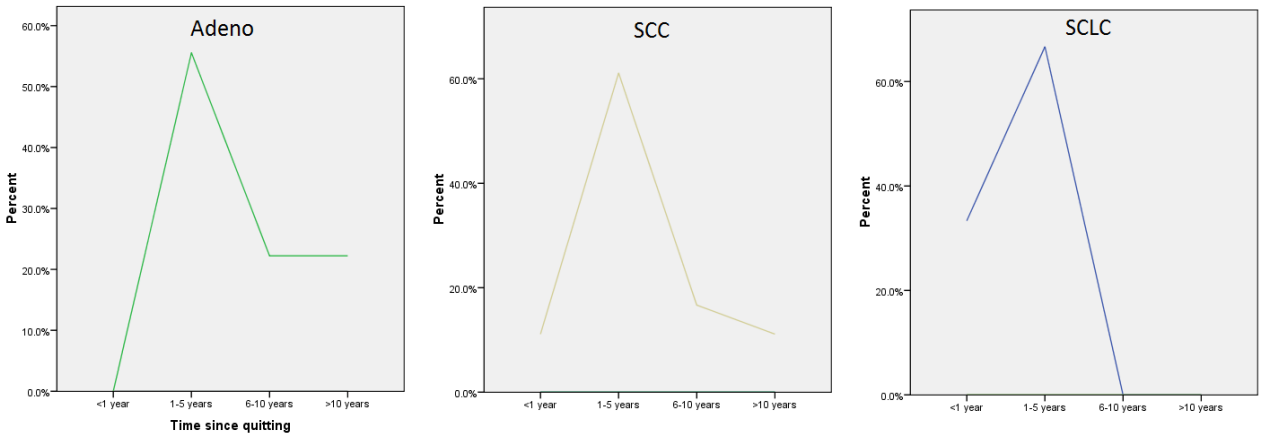


Fig. 2: Association of histopathology with time since quitting.



DISCUSSION

The differences in lung cancer among ever-smokers and non-smokers are primarily in distribution of histology, as supported by our data. The results showed a predominance of adenocarcinoma among never-smokers, consistent with various studies over time. [7, 8, 9, 10] Various genetic alterations have been reported tolead to the development of adenocarcinoma in non-smokers. Generally, KRAS mutations areassociated with tobacco consumption, while EGFR mutations are linked to non-smokers[3, 8, 11].

Gender differences have also been demonstrated, with females tending to have adenocarcinomas more commonly than parallel male subjects[7,10,12,13]. In our study however, both male and female non-smokers had equal proportions of adenocarcinoma. Data on female smokers however was limited due to just four patients in this category, probably related to less frequent smoking in females of this region[14,15].

As lung cancer is customarilyregarded a disease of smokers, never-smoker patients may either present late or experiencelate diagnosis on the part of physicians and might present with more advanced stage disease than smokers.[8] In our study, most patients presented at stage IV independent of their smoking status. Non-smokers, however, had a greater mean duration of symptoms as compared to ever-smokers.

Our study was consistent with literature review that SCLC and SCC are strongly linked to smoking[10,16,17,18]. With increasing tobacco exposure, as measured by pack years, there was a pronounced shift towards higher proportion of SCLC and SCC relative to adenocarcinoma[19].

Among non-smokers, passive smokers showed a higher proportion of SCC and lower proportion of adenocarcinoma as compared to never smokers [20]. This might be due to the fact that passive smokers do inhale the tobacco smoke, though in lesser amount than smokers themselves. So, lung cancer may follow, in some part, the same pathogenesis as smokers.

It has been postulated that lung cancer in ex-smokers more closely resembles the tumors from non-smokers than the tumors from current smokers. Our study showed a decline in SCLC and SCC with increasing cessation period, in contrast to the rising proportion of adenocarcinoma, In fact, SCLC did not appear in patients who had quit smoking for six years or more[21] All three diagnosed histopathologies showed a sharp peak upto 5 years of cessation time. This is in accordance with studies citing the "quitting ill effect" or the excessive lung cancer risk experienced by former smokers 5 years directly following smoking cessation[4].

Only 119 cases had documented metastasis. A variety of combinations were observed involving bone, brain, contralateral lung, adrenal glands and lymph nodes. NSCLC was found confined to lymph nodes and greater proportion of NSCLC metastasized only to contralateral lung. This is compatible with the fact that SCLC is more aggressive and spreads to distant sites more often. However NSCLC, when compared with SCLC, showed a greater percentage of metastasis to more than one site and was also seen at unconventional sites such as kidney, salivary glands and pericardial fluid.

CONCLUSION

The histopathology of lung cancer varied with smoking status. Adenocarcinoma was a predominant finding in non-smokers while SCLC and SCC showed a stronger association with ever-smokers, showing a continuous rise with increasing pack years. For ex-smokers all three diagnosed histopathologies showed a sharp peak upto 5 years of cessation time. Beyond which falling trends were observed for both SCLC and SCC. Hence, with increasing cessation time the histopathology of lung cancer approaches more closely to that of non-smokers. Other variables did not vary significantly among ever and non-smokers. However ours was a small study with limited patient population and further research is needed on country-wide level on this subject.

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