RESEARCH COMMUNICATION

Characteristics of Lung Cancer Patients - the Shaukat Khanum Memorial Experience

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Abstract

   <u>Objectives</u>: The aims of this descriptive study were to characterize lung cancer patients by age at diagnosis, smoking status, and histology and, also to explore the histologic sub-type according to cigarette smoking, in a tertiary care setting. <u>Patients and methods</u>: A retrospective review of 830 patients for whom smoking status was available in the records was carried out at a comprehensive cancer care facility, the Shaukat Khanum Memorial Cancer Hospital and Research Center, situated in Lahore, Pakistan. <u>Results</u>: The mean age at presentation of the 830 evaluable cases was 59.8 years (standard deviation 11.8, range 18-90). Stratifying by gender, statistically significant differences were found in the average age at diagnosis between males (60.1 years) and females (57.5 years) and, in the distributions of non-smokers, current smokers, and ex-smokers, but none for histology. <u>Conclusions</u>: Similar to other populations, the age of disease onset amongst females was lower than that seen in males. The proportion of smokers was higher amongst males versus females. The reversal of smoker to non-smoker ratio when stratified by gender, may highlight the importance of exploring alternate pathways implicated in the etiology of lung cancer in our population.

Key Words: Lung cancer - smoking status - histopathological diagnosis - Pakistan

Introduction

Smoking has been established as a leading cause of lung cancer through various studies conducted over the past decades (Fu et al., 2005). However, a common observation tells us that despite claims of tobacco control legislation in the country (http://www.tobacco.org, 2003; http://www.thenetwork.org.pk, 2004), cigarette smoking seems to continue unabated in this part of the world. Not only this, cigarette advertisements have been on the rise in the form of billboards and at main counters in supermarkets, thereby increasing the promotion and sale of cigarettes. It seems as if a few words stating that smoking is not good for health and that, it can cause cancer and heart diseases, are enough to satisfy our policy makers. Further, it has also been seen that smoking is popular not only amongst individuals in the uneducated lower socio-economic class, it is also found in those in the highly educated, middle to upper socio-economic strata. It is a sad state of affairs to see, amongst other people, health professionals as avid smokers close to the "No Smoking" sign(s) on hospital walkways, thereby exposing passersby, including non-smokers, to passive smoke. Overall, the negative impact of tobacco inhalation is also shared by the so called "non-smokers" exposed to the environmental tobacco smoke (ETS).

Background

Statistics for bronchogenic carcinoma

The American Cancer Society (ACS) has projected that during 2006, worldwide, lung cancer will account for about 12 percent of all cancer cases, with approximately 1.7 million new cases of lung carcinoma diagnoses, 92,700 amongst men and 81,770 amongst women (http://www.cancer.org, 2006). It has also been estimated that it will account for about 28 percent of all cancer deaths including 90,330 in men and 72,130 in women; (http://www.cancer.org, 2006). ACS further reports that the one-year survival probability for those with bronchogenic carcinoma is 40 percent only and has not changed over a decade, whereas, the 5-year relative survival rate is a mere 15 percent. In developing countries, a remarkable increase has already been reported in the share of new lung cancer cases from a figure of 31 percent in 1980 to 49.9 percent in 2002 (http://www.cnn.com, 2005).

In a study based on the National Health Survey of Pakistan covering the period from 1990 to 1994, the prevalence of current smoking amongst 13,104 individuals interviewed was found to be 14.2 percent (Nasir et al., 2001). The sample included people in the 8-96 year age range who had smoked at least 100 cigarettes or bidies in their lifetime

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and were still smoking. Nearly 26 percent of the 6,337 male patients and 3.6 percent of the 6,767 females reported being current smokers; the difference was found to be statistically significant (p = 0.001). Also, in another study conducted on medical students in Karachi in which there were 264 responders, 26 percent of the male, and 1.7 percent of the female students were found to be smokers (Omair et al., 2002). These scenarios depict a male inclination for tobacco smoking. Quite ironical is the fact that the likelihood that current tobacco users, regardless of gender, compared to non-tobacco users, will rate their health as fair or poor as opposed to excellent is relatively high (Khabir et al., 2004).

The well established hazards of cigarette smoking are due to its gaseous and particulate compounds composed of nicotine and tar (http://lungcancerfrontiers.org, 2001). These reach the lungs as "mainstream smoke" inhaled during smoking. Smoldering of cigarettes between puffs also produces the "sidestream smoke", which is a source of ETS. The mainstream smoke contains a number of potential carcinogens obtained from nitrosation of nicotine. These include tobacco specific n-nitrosamines (TSNA) that are delivered to the lungs both directly and systemically after being absorbed in the lungs. It has been determined that the risk of lung cancer amongst smokers compared to non-smokers goes up exponentially with the pack-years smoked and, also with the tar and nicotine levels in the cigarette smoked (http://www.medicinenet.com, 2005). It is clear that the intensity of tobacco use is a function of a smoker's nicotine dependence (http://lungcancerfrontiers.org, 2001). It has also been reported that Pakistani cigarettes contain one of the highest tar and nicotine concentrations in the world (Nasir et al., 2001). Further, of significance is the fact that the risk of developing lung cancer decreases each year following smoking cessation and, about fifteen years after cessation of smoking, the risk begins to approach that of a non-smoker (http://www.medicinenet.com, 2005). Despite this plethora of information, it has been projected that by 2020, in developing regions of the world, deaths attributed to smoking will go up to one in three from one in six seen in 1990 (Nasir et al., 2001).

At the Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH & RC) situated in Lahore, Pakistan, an attempt was made to study the characteristics of lung cancer patients through information collected in the hospital-based registry, an integral part of the Hospital Information System (HIS). During the period from December 1994 to October 2005, of the 48,723 patients listed in the System, 4.2 percent were found to be smokers (2,037); nearly 1,896 were recorded as being male smokers in contrast to 141 female smokers. The rest were identified as being non-smokers. The ratio of non-smokers to smokers amongst females was 1000 to 5 whereas amongst males, it was 1000 to 86. Further, primary lung cancer was identified as the fifth commonest malignancy registered at the hospital since December 1994 when the hospital came into existence. One thousand and sixty-seven cases were registered from December 1994 to October 2005.

Patients and Methods

From a total of 1,067 consecutive invasive lung cancer patients registered at the hospital from December 1994 to October 2005, the authors excluded 225 patients (21.1%) on whom information on smoking and/or addiction was missing and 12 (1.1%) cases with history of other types of addiction. Of the remaining 830 patients, 661 (79.6%) were identified as being smokers and 169 (20.4%) as non-smokers. The category "smokers" were further dichotomized into current and past smokers and the category "non-smokers" was inclusive of those who had neither smoked in the past nor were smokers when their history was being recorded. A total of 830 patients on whom smoking status was available in the hospital registry were included in the analysis. Analyses were conducted using the Statistical Package for Social Sciences (SPSS) software, version 10.0. Results were considered significant at an alpha-level of 0.05.

Results

Of the total patients, 88.2% were male (732/830) and 11.8% female (98/830). Of the 661 identified as being smokers, only 23 were females versus 638 males. The proportion of smokers amongst males was substantially high in contrast to that amongst females. The smoker to non-smoker ratio amongst males was 6.8 to 1, whereas, amongst females, it was 0.31 to 1. A statistically significant association between gender and smoking status was found (Chi-square = 216, df = 1, p < 0.001).

The overall mean age at diagnosis was measured to be 59.8 years (range 18-90, standard deviation 11.85, mode 66 years (57 cases, 6.9% patients)). The age distribution was checked for normality by generating a Q-Q plot of the standardized residuals for "age at diagnosis". The sample was considered from a normal distribution as the points clustered around a straight line in the graph. The age at diagnosis was further stratified by gender. Using a one-way analysis of variance to conduct pairwise comparisons for sub-groups within the variable gender, it was demonstrated that females had a lower average age at diagnosis (57.5 years) than males (60.1 years) and that, there was a statistically significant difference between the mean ages reported (F = 4.08, df = 1, p = 0.04).

Invasive lung cancer was further studied according to cigarette smoking habits defined above. Based on these, it was found that amongst males, current smokers accounted for the vast majority of cases (484/830), followed by ex-smokers (154/830) and those who had never smoked (94/830). However, most of the female patients did not give any history of having smoked (75/830) and very few of them admitted to having been either current (16/830) or ex-smokers (7/830). The deviations of the relative frequencies across cells from the expected pattern were significant (Chi-square = 216, df = 2, p < 0.001).

Bronchogenic cancer was also stratified into small cell lung cancer (SCLC) accounting for 178 (21.4%) of the total

Table 1. Detailed Distributions of the Histologic Sub-types of Bronchogenic Carcinoma by Gender

Tumor Subtype	Male No. (%)	Female No. (%)	Total No. (%)
NSCLC	491	70	561
Squamous cell ca	197 (30.2)	10 (11.6)	207 (28.0)
Non-small cell ca	188 (28.8)	28 (32.6)	216 (29.2)
Adenocarcinoma	83 (12.7)	27 (31.4)	110 (14.9)
Large cell ca	23 (3.5)	5 (5.8)	28 (3.8)
SCLC	162	16	178
Small cell ca	160 (24.5)	15 (17.4)	175 (23.7)
Oat cell ca	2 (0.3)	1 (1.2)	03 (0.4)
Total	653 (100)	86 (100)	739 (100)

Table 2. NSCLCs and SCLCs Represented as Fractions of the Total Diagnosed Tumours by Smoking History

Microscopic type / Cigarette smoker	NSCLC Count (%)	SCLC Count (%)	Total Count (%)
Yes	445 (60.2)	153 (20.7)	598 (80.9)
No	116 (15.7)	25 (3.4)	141 (19.1)
Total	562 (75.9)	178 (24.1)	739 (100)

cases and non-small cell lung cancer (NSCLC) comprising 562 (67.6%) of the 830 cases. When gender was cross-tabulated with NSCLC and SCLC in 739 cases, (excluding other cancers including those which were unspecified (81/830), carcinoid tumor (6/830), and sarcoma (4/830)), no substantial association was found between the two (p > 0.05). Further the two main types (NSCLC and SCLC) were stratified into sub-types as shown in Table 1. Squamous cell carcinoma was established as the commonest type of NSCLC (207/561) and small cell cancer (175/178) as that of SCLC. The ratio of smokers to non-smokers for the two main microscopic types was computed and for SCLC, it was determined to be 6.12 to 1, whereas, for NSCLC, it was 3.87 to 1. Finally, data were further explored to see if the distributions of the two main types differed by smoking status (Chi-square = 3.85, df = 1, p = 0.05). A summary of the results as counts and proportions is given in Table 2.

Discussion

In our review, fewer women were identified with lung cancer diagnoses than were men. This may be due to the fact that, whereas, smoking is an established cause of the disease, the overall ratio of non-smokers to smokers amongst women was high as compared to that in men. The mean age at onset in patients with bronchogenic carcinoma was found to be almost the same as determined by Radzikowska et al (2002). The striking result was an early age at diagnosis in females compared to males. However, many studies have reported that women receive diagnoses at a younger median age than do men (Fu et al., 2005). Also, in a 1995 to 1998 population-based study conducted on 20,561 cases in Poland, Radzikowska et al documented that women reported with lung cancer at a younger average age (60.02 years) than did

men (62.18 years) and that, the difference was statistically significant (p < 0.001). The same study also reported that women were more frequently non-smokers than were men (18.8% versus 2.4%; p < 0.001). These patterns are consistent with what was seen in our study although ours was an institutional study, implicating a non-representative subset of the population. Further, it has been questioned if the ages of the females have been underreported in our study. An answer to this question has yet to be sought and it may be difficult, though not impossible, to do so methodologically, as research is generally considered to be a low priority area in our society. Moreover, a concern that has been posed is if non-smokers were exposed to carcinogens in the form of environmental tobacco smoke, thus triggering carcinogenesis in this particular category. The likelihood of this is high as studies conducted by the International Agency for Research on Cancer have proven that non-smokers are exposed to the same carcinogens as are active smokers and, even typical levels of passive exposure have been shown to cause lung cancer amongst never smokers (http://www.emaxhealth.com, 2004). Not only this, many substances, including asbestos, have been incriminated as occupational causes of lung cancer (http://lungcancerfrontiers.org, 2001).

Also, in a multicentric case-control study conducted in Eastern/Central Europe and United Kingdom, an interesting finding has been that, compared to those not using solid fuel for heating or cooking, the risk of lung cancer in those using it for cooking only was 1.37, for cooking/heating was 1.24 and, for heating only, it was 1.08 (Lissowska et al., 2005). In our culture, it may be a fruitful area for prospective studies on lung cancer, to evaluate exposure to solid fuel, which is still being used in many rural areas. Further our study found that the predominant histologic sub-type(s) was squamous cell carcinoma in males and, non-small cell carcinoma and adenocarcinoma in females. It has been reported that there appears to be a difference in the relative distribution of histologic features between men and women not explained entirely by differences in smoking pattern and that, women smokers are more likely to develop adenocarinoma of the lung with estrogens playing a causative role in this phenomenon (Baldini EH et al., 1997).

The World Health Organization (2005) has published that in patients with bronchogenic carcinoma, the proportion of smokers and/or bidi users amongst females is far less (5%) than that amongst males (66%) (http://www.who.int, 2005). Bidi is a small, brown, hand-rolled cigarette that is made in India and other Southeast Asian countries, and consists of tobacco that is wrapped in a tendu leaf. Accordingly, what needs to be probed is whether non-smokers were exposed to carcinogens in the form of ETS, if there have been genetic alternations associated with the disease in this cohort, or were there co-morbid conditions in these patients influencing pathogenesis. Interestingly, the genetic aberrations associated with p53 tumor suppressor genes have been seen not only amongst smokers, they have also been reported in non-smokers.

Our review failed to capture any substantial association between histology with smoking. However, in the sub-type SCLC, the ratio of smokers to non-smokers was relatively high in comparison to that seen in NSCLC (Table 2). This may be attributed to the fact that SCLC is strongly related to cigarette smoking (http://www.medicinenet.com, 2005).

The present study has several limitations including the lack of data on pack-years of smoking history. As with other retrospective studies, many issues, as mentioned in the paragraphs above, remain unsolved. The need at this hour is to conduct a population-based study in this part of the country so as to consider the potential confounding effects of, and effect modification by, selected factors including age at diagnosis, gender, pack-years smoked, histology, and stage of the stage. These activities must run concomitantly with high priority measures for controlling and reducing tobacco promotion and smoking in our population.

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