ORIGINAL ARTICLE

ASSOCIATION OF SMOKING WITH RECURRENCE OF PULMONARY KOCHS; AFTER COMPLETION OF ANTITUBERCULOUS TREATMENT

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Background: Smoking is one of the most important yet modifiable risk factors for incidence, morbidity, recurrence and mortality from Pulmonary Koch's or tuberculosis. This study attempted to demonstrate the association between smoking and recurrence risk of Pulmonary Koch's in Pakistani male population. **Methods:** This case control study was conducted at Federal Government Tuberculosis Hospital, Rawalpindi from 2015 to 2016. It included 332 study participants; 166 recurrent cases of Pulmonary Tuberculosis within two years of completion of Anti-tuberculous therapy (ATT) and 166 non-recurrent controls. Smoking status of all study participants was assessed. **Results:** Amongst 166 cases of recurrence, 75 (63.6%) had continued smoking after ATT compared to 43 (36.4%) controls who continued smoking (*p*-value 0.00, OR=2.35, 95% CI=1.48 to 3.74, NNH=4.75). Highly statistically significant associations of recurrence were observed with smoking>10 years (*p*-value 0.00, OR=3.67, CI=1.55–8.71 NNH=4.75) and if ever smoked in life (*p*-value 0.00, OR=2.05, CI=1.32–3.19, NNH=5.61). Mean duration of smoking in cases (12.37±8.72 years) was statistically different from controls (9.54±7.01 years), with *p*-value of 0.04. **Conclusion:** There is strong association of recurrence of Pulmonary Kochs with continuation of smoking within 2 years of completion of ATT, with ever smoking in life and smoking >10 years in life.

Keywords: Pulmonary; Tuberculosis; Smoking; Cigarette smoking; Recurrence

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INTRODUCTION

"One third of the world's population is infected with tuberculosis (TB)."[1] If left untreated, each sputum positive case is capable of infecting 10–15 people in one year.[2] According to World Health Organization (WHO) global TB report, global incidence of Tuberculosis in 2014 was 9.6 million, which included 5.4 million men, 3.2 million women and 1 million children. Out of those reported TB positive, 480000 people developed multidrug-resistant TB (MDR-TB). The same report cited the prevalence of tuberculosis in Pakistan to be 341 per 100,000 and incidence of 270 per 100,000, thus ranking Pakistan as fifth among the high TB burden countries worldwide.[3] Pakistan is also estimated to have the fourth highest prevalence of MDR-TB globally.[4] Even more concerning however, is the fact that in Pakistan alone, there were a total of 8067 reported cases of TB relapse (7420 pulmonary bacteriologically confirmed, 426 clinically diagnosed pulmonary, 221 extra-pulmonary cases) and 8160 recurrent cases excluding relapse in the year 2014 alone[3]. Global TB recurrence rates range between 4.1 and 8.6%[5–9] with most cases occurring within the first 3 years after primary infection, with the exception of one study conducted in Cape Town South Africa where the TB recurrence rate was 18%[10], even higher than the rate of primary TB.

The geographical heterogeneity in the rates of recurrence is largely explained by the distribution of risk factors for recurrence. The major risk factors studied till date are HIV coinfection[8,9,11], smoking[8,12–18], Intravenous Drug abuse,[9,12], previous history of tuberculosis[8], Diabetes Mellitus[8,19–21], Acid Fast Bacillus (AFB) positivity[11], homelessness[11] and alcohol consumption (at least 50 grams of alcohol)[14]. Keeping in mind that any and all data we have available is just from 205 countries and approximately one million cases go unreported.[5] This is an alarming situation; thus, greater efforts must be made to identify risk factors for recurrence and prevent it from occurring.

International research suggests that recurrence rates of tuberculosis in smokers range from twice to five times as high as those in non smokers.[11,13,16] A prospective cohort study conducted in South Korea by Jee *et al* suggested that current/ex-smoker males are 1.4 times likely to develop TB recurrence than non-smokers with Hazard Ratio 1.4 (95 % CI 1.3–1.5).[14] Another study in Iran by Moosazadeh *et al* found the odds ratio of relapse in smokers to be 1.99 as compared to non-smokers.[8] Given the high prevalence of both smoking and tuberculosis in Pakistan, it is quite concerning that no documented studies at the national level are available to support this.

Given the huge burden of disease, TB killing almost 40,000 people each day globally[3], a lukewarm

response to smoking generally and in Tuberculosis patients particularly, is no longer acceptable. Quitting smoking rapidly brings down the escalated risk. According to a study by Wen[22], smoking cessation brings down the TB mortality by almost two-thirds, compared to those who continue to smoke. The purpose of this study is to assess the magnitude of this problem in Pakistani Population and its findings can substantiate the importance of awareness of patients undergoing Anti-tuberculous therapy regarding prospects of recurrence associated with continuation of smoking. It may contribute in bringing the attention of all stake holders be it patients themselves, their attendants, health care providers, public health consultants or policy makers regarding prevention of recurrence through smoking cessation leading to decreased morbidity and burden of disease.

The objective of our study was to determine association between smoking and recurrence of pulmonary tuberculosis or Koch's, within 2 years after completion of Anti-tuberculous treatment (ATT) regime, in patients presenting to TB Hospital Rawalpindi. The single sided, alternate Hypothesis (H_A) of study was that the odds of recurrence of Pulmonary Tuberculosis in smokers are more than the odds of recurrence in non-smokers. (or $H_A =$ OR>1)

MATERIAL AND METHODS

This **c**ase control analytic study was conducted at Federal Government Tuberculosis Hospital, Rawalpindi from November 2015 to August 2016 after ethical approval of Institutional Research Forum of Rawalpindi Medical College and Allied Hospitals and also permission from the administration of Federal Government Tuberculosis Hospital, Rawalpindi. Our study included 332 study participants where 166 were cases of recurrent cases of Pulmonary Tuberculosis within two years of completion of Anti-tuberculous therapy and 166 patients were controls who did not develop Pulmonary tuberculosis within 2 years of completion of Anti-tuberculous therapy. Complete Anti-tuberculous treatment was considered as treatment with all four first line Anti-tuberculous drugs (Isoniazid, Rifampin, Pyrazinamide and Ethambutol) and Vitamin B6. All 4 drugs in the first 2 months (intensive phase of treatment) followed by just Isoniazid and Rifampin in the continuation phase. Continuation phase was considered to have started once the patients became smear negative. Duration of therapy and add on treatments were according to the Pakistan National TB guidelines.

Recurrence of tuberculosis was defined as reappearance of symptoms in a patient who was smear negative at or one month prior to the completion of treatment (WHO and IUALTD criteria)[14] and included re-infection and relapse too. Only those patients, with first time recurrence of pulmonary tuberculosis, within two years of completion of treatment were included in cases. Recurrence was confirmed if AFB smear test was found to be positive.

Using the WHO sample size calculator, minimally required sample size was calculated to be 166 cases and 166 controls, at 5% level of significance, keeping power of test 80%, anticipated odds ratio 1.99[8] where anticipated probability of smoking given recurrence was 0.292 and anticipated probability of smoking given no recurrence was 0.172. So, a total of 332 participants were included with equal proportion of cases and controls (case: control =1:1).

Since gender was a potential confounder and considering the fact that majority of smokers in Pakistan are males, sample was restricted to males only. Moreover, only sputum AFB smear positive (sputum smear 2+ to 3+) patients with primary pulmonary tuberculosis (before initiation of treatment) were included and all above age of 10 years. In order to control for potential confounders, patients with any potential risk factors for TB incidence or recurrence were excluded from the study including known cases of Human Immunodeficiency Virus infection, Diabetes mellitus, Hypertension, known immune-compromised, intravenous drug abuser or involved in any form of addiction other than smoking. Also excluded were patients with extra pulmonary tuberculosis, those previously not treated under TB DOTS program, having primary treatment failure or if were non-compliant or discontinued their Anti-tuberculous therapy.

From the recorded data of Federal Government Tuberculosis Hospital, patients who had completed Anti-tuberculous therapy, exactly two years prior to collection of data, were sorted out. The patients fulfilling the selection criteria were approached and included after informed consents, followed by confirmation of presence or absence of recurrence. For cases, recurrence was confirmed through presence of positive AFB smear test in records however patients with negative AFB smear tests were included as controls. In controls absence of following; any positive sign or symptom of Pulmonary Kochs, raised ESR and positive smear in period after completion of treatment and at time of enrolment was also ensured. Matching was attempted to find a control matched with a case based on the fact that both completed Anti-tuberculous therapy within same month of year.

Smoking status of all study participants was assessed not only through interview of patients

themselves but it was also reconfirmed by the attendants of each participant. Smokers in our study population were defined as the people using tobacco in any form (cigarette, snuff, sheesha, pipe or cigar). Cigarette smokers for this study population were defined as patients who smoked on an average, at least 1 pack (20 cigarettes) per week (or about three per day). Similarly, for participants using remaining forms like huqqa, snuff, sheesha, pipe or cigar or, average intake of each item at least 20 times a week (or about three per day) was included in smoking. As regards the smoking status of cases, it was made sure to confirm information about their smoking status between the period of completion of Anti-tuberculous therapy and incidence of recurrence, to confirm the fact that the exposure should have preceded the outcome. Information regarding smoking status before or till completion of Anti-tuberculous treatment and details of abstinence, if any were also noted. In cases, current smoking status after recurrence or any abstinence after recurrence was also assessed.

Data was entered and analysed using the Statistical Package for Social Sciences (SPSS-22). To compare the proportions of smoking attributes in both study groups, Pearson's Chi-squared test was applied at 5% level of significance. *p*-value of <0.05 was considered statistically significant. The odds ratios and adjusted odd's ratios were also calculated along with 95% confidence interval. To have an estimate of detrimental effect of smoking attributes, Number Needed to Harm (NNH)=1/ attributable risk was also calculated along with 95% confidence interval. Med calc 3000 was used for calculation of these epidemiological measures.

RESULTS

A total of 332 patients were included in this study and all were currently residents of Rawalpindi and Islamabad cities. The mean age of all 332 study participants was 34.91±15.12 years, multiple modes existed (lowest being 18 years) and median of 32 years. The youngest participant was 12 years old while the eldest was 82 years old. The mean age of cases was 36.64±14.86 years and controls had a mean age of 33.17±15.20 years, the difference being statistically significant (*p*-value=0.03). Age was also categorized as up to 30 years and above 30 years and cases and controls were still not homogenous, with cases having majority 98 (59.0%) above 30 years of age and controls had most participants 94 (56.6%) up to 30 years (*p*-value of 0.00).

The type of smoking was also assessed in the study participants, cigarette being the commonest form in 118 (84.9%) of the smokers amongst all participants. The distribution of type of smoking was homogenous in both cases and controls (*p*-value 0.48), where 69(83.1%) of cases and 49 (87.5%) of controls were cigarette smokers, as compared to all other forms of smoking, comparison being displayed in figure-1.

Amongst all 332 study participants, 118 (36.5%) participants were smokers who continued to smoke even after diagnosis of Pulmonary Koch's and not only even during their Anti-tuberculous therapy but also after completion of therapy. Those participants who used to smoke previously but had quit it once they were diagnosed to have pulmonary Koch's and have abstained smoking over last three years were 25 (7.5%). Those who never were smokers according to our operational definition, were 189 (56.9%) and were labelled as 'never smokers' while those who ever started smoking in life and irrespective of the fact whether they quit it later or continued were 143 (43.1%) and all were collectively labelled as 'ever smokers' in results.

The 143 participants who 'ever smoked' were inquired about the duration in years, for which they had smoked and 88 (26.7%) of them had smoked ≤10 years while 55 (16.6%) were those who had been smoking more than 10 years. Overall the mean duration of smoking in 'ever smokers' was 11.24±8 years; the shortest period of smoking was only 2 years while longest period was of 40 years. The mean duration of smoking in cases with recurrence was 12.37±8.72 years, comparative to 9.54±7.01 years of controls, the difference being statistically significant with a p-value of 0.04. The comparison is also displayed as a box plot in figure-2.

A highly statistically significant difference of smoking exposure after completion of ATT (*p*-value 0.00) was observed in cases of recurrence and the controls, as displayed in table-1 along with associations of other attributes of smoking status. Out of the 166 patients who developed recurrence of Tuberculosis within two years after completion of therapy, 75 (63.6%) were current smokers smoking at least 1 pack per week (3 or more cigarettes per day). While only 43 (36.4%) participants in the control group were current smokers. The odds of TB recurrence within 2 years of ATT completion, in smokers continued after therapy are 2.31 times the odds of recurrence amongst those who did not smoke after ATT. Number needed to harm was 4.75, therefore on an average, 5 patients need to be exposed to smoking even after ATT, to cause recurrence in an average of one patient who would not otherwise have developed recurrence.

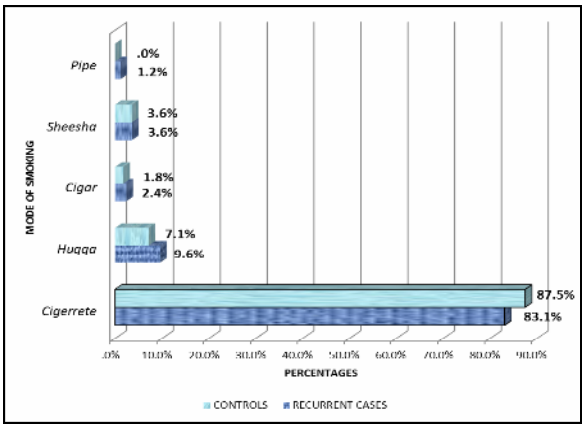

Figure-1: A bar chart displaying the comparison of distribution of modes of smoking in cases (n=166) and controls (n=166).

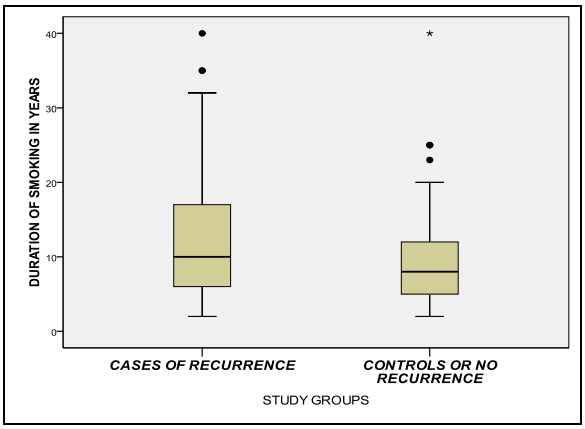

Figure-2: A box plot exhibiting comparison of duration of smoking (in years) amongst cases (n=86) and controls (n=57)

Table-1: Comparison of various attributes of smoking amongst cases and controls

Smoking status	Cases with Recurrence F (%)	Controls with no recurrence F (%)	*p*-value (χ-value)	OR (95%CI)	aOR (% diff)	NNH {95%CI}
Smokers after ATT	75 (63.6%)	43 (36.4%)	0.00* (13.46)	2.35 (1.48–3.74)	2.18 (7.23%)	4.75 {9.97 (Harm) to 3.12 (Harm)}
Nonsmokers after ATT	91 (42.5%)	123 (57.5%)				
Cigarette smokers	69 (83.1%)	49 (87.5%)	0.48 (0.49)	0.70 (0.26–1.87)	0.73 (4.28%)	12.20 (Benefit) {6.880 (Harm) to ∞ to 3.234 (Benefit)}
Other types of smokers	14 (16.9%)	7 (12.5%)				
Smokers for >10 years	37 (49.3%)	9 (20.9%)	0.00* (9.26)	3.67 (1.55–8.71)	1.65 54.76%)	3.61{9.464 (Harm) to 2.235 (Harm)}
Smokers for ≤10 years	38 (52.8%)	34 (79.1%)				
Ever smoked	86 (51.8%)	57 (39.9%)	0.00* (10.33)	2.05 (1.32 to 3.19)	1.86 (9.26%)	5.61 {14.04(Harm) to 3.50 (Harm)}
Never smoked	80 (48.2%)	109 (65.7%)				
Ex-smokers (Smoked till diagnosis of TB then had quit before ATT)	11 (12.1%)	14 (11.4%)	0.87 (0.02)	1.07 (0.46 to 2.48)	0.99 (7.07%)	59.81 {4.48(Harm) to ∞ to 5.27 (Benefit)}
Never smoked	80 (87.9%)	109 (86.6%)				

f=exact frequency, %=percentages within cases and percentages within controls, p-value=probability value, χ-value=Chi statistic, OR=Odds Ratio, CI=Confidence interval, aOR=Adjusted Odds Ratio for categories of age up to 30 years and >30 years.

Since the study groups were heterogeneous based on age and variables of status of smoking mentioned in table-1 also had statistically significant differences of age, hence each association was also observed for each stratum, i.e., patients less than 30 years and those above 30 years. Adjusted odds ratios were calculated along with percent difference of adjusted odds ratios from crude odds ratios. Percent Difference of Adjusted Odds Ratios of age exceeded 10% only in case of association of recurrence with smoking more than 10 years; hence age was found to be strong confounder only for this relationship. Since age above 30 years contribute to development of recurrence too, however removing the contribution of age shows that smoking more than 10 years increased the odds of occurrence of recurrence, only 1.65 times and not 3.67 times.

The mean duration of recurrence after completion of treatment in months was calculated for all 166 patients of recurrence 13.09±4.86 months, median 13 months and mode 12. Almost half of patients developed recurrence within 13 months of completion of treatment, while remaining developed recurrence in second year after completion of treatment.

DISCUSSION

One third of the world's population is infected with *Mycobacterium tuberculosis*; among them nine million develop active tuberculosis every year and two million die annually.[23]

It is a well-known fact that smoking predisposes patients to progression of latent to active pulmonary tuberculosis by impairing movement of cilia and inhibiting production of TNF-alpha by pulmonary macrophages.[24–26] It shall also be emphasized that smoking also increases recurrence of and mortality from tuberculosis.

Eighty percent of the tuberculosis cases are saturated in just 22 countries, which, not surprisingly are the very same countries where there is the highest prevalence of tobacco smoking. The results of our

study displayed that odds of TB recurrence in current smokers at least within 2 years of completion of therapy are 2.31 times the odds of recurrence within same period in non-smokers. These results are largely in agreement with other international studies. Our results compare well with those of studies in South Korea[14], Iran[8] and Taiwan[11] which suggested that smoking increases the risk of recurrence by 1.44,1.99 and 2 times respectively. It is however a little lower than the odds ratio obtained by studies conducted in India (3.1)[17] and Bydgoszcz (5%).[13]

We found the odds of ex-smokers developing recurrence after complete ATT to be 1.06 times that of never smokers; however, this result was not statistically significant.

This is in contrast to a study in Hong Kong by Leung *et al* (2014)[18] who demonstrated a downward but definitive trend in relapse risk from current smokers to ex to never smokers. The discrepancy might be attributable to the fact that the sample size of ex-smokers was small. It may also be due to the short duration of our study.

One alarming aspect evident from our findings was that 36.5% of our participants had continued to smoke even after diagnosis of Pulmonary Kochs and not only even during their Anti-tuberculous therapy but also after completion of therapy. Amongst 332 cases of pulmonary kochs selected from a single health care facility at one period of time, this proportion might only be the tip of ice berg. Only 7.5% stated that they had discontinued smoking once they were diagnosed and still are abstained. There was not even a single patient who declared that he had initiated smoking again after quitting. Similar concern was highlighted by Wang J who followed up Chinese TB patients and observed that 54.9% smokers stopped smoking after being diagnosed with TB, but still more than 18% relapsed during the follow-up period[27]. An Indonesian study also demonstrated this where more than 1/3rd of patients admitted smoking relapse within 6 months after ATT. It also observed the grievous fact that almost 30% were never asked about their smoking behaviour or advised about quitting. Of relapsed smokers, 60% received only general health messages and not TB-specific smoking messages.[28]

This reflects the dire need of continuous, effective and assertive health education of patients once diagnosed with Pulmonary Kochs to abstain from smoking, and incessant monitoring and assurance that they do not relapse smoking after it.

Moreover, association of increased age with recurrence was also noticed in our study and this might have been resulted from the fact that increasing age also is related to increase in duration of smoking period. Even though the median age of cases with recurrence was also observed to be higher than non-recurrent cases by Millet J-P *et al* but that association was not statistically significant like ours[9]. Further exploration of role of age in recurrence is recommended, in our population through future research.

Our study is one of the pioneer study to provide evidence of association of smoking with recurrence in Pakistani population but still it had the limitation that due to retrospective nature of the study, we weren't able to differentiate reinfection from relapse cases, neither were we able to categorize recurrent cases as MDR, XDR or sensitive. However, we successfully attempted to control confounding through restriction as well as stratified analysis later. Another fact is that due to paucity of data available, we weren't able to include controls in the study who presented for treatment before 2014 and we are afraid that some of the people in control group, if followed for 2–3 more years, may develop recurrence.

Since patients themselves are aware of the serious risks attributed to smoking in deteriorating their health and exacerbating their disease, there is an intentional trend of concealment of their smoking status from their health care providers. Hence to overcome any information bias or recall bias, the smoking status of each patient was reconfirmed by attendants too.

A prospective study, i.e., cohort would have been an ideal study design to provide evidence and magnitude of risk of recurrence of Pulmonary Kochs in patients after completion of ATT, of tuberculosis, but it implicated a serious ethical concern. It would have involved following up an exposed group of patients who would continue smoking even after ATT, till incidence of recurrence, compared with a control unexposed group. But would that be ethical to continue to observe patients infusing smoke, when it already is a proven hazard to their lives, just for the sake of research while not educating them and not restraining them from smoking instead? The alternate option would have been retrospective cohort, but in our setup the scarcity of surveillance and keeping updated records of patients, especially relevant to the risk factors and exposures, made it impossible.

Pakistan along with China, India, Bangladesh and Indonesia shoulders more than half of the total TB burden of the world. There is no denying that cigarette smoking influences each and every step in the spectrum of disease of TB. It increases the risk of being infected with *Mycobacterium tuberculosis*, conversion into active infection, accelerates progression of disease, delays AFB seroconversion even when treatment is begun and accounts for majority of cases of treatment failure. Smoking increases the rate of recurrence of

TB even after successful treatment and increases mortality from TB. Although ours was a small study, larger studies need to be conducted at a national level to assess risk and account for hidden confounders if any. Special emphasis and attention should be paid in conducting intervention studies targeted at identifying the most effective and efficient way of self-restraining from smoking and minimizing the relapse of smoking in patients of tuberculosis.

In perspective of our findings we strongly recommend that smoking cessation should be made an integral part of the TB DOTS program. The government should start educational campaigns to warn people against this possible risk, encourage and facilitate them to quit smoking. People should be facilitated at all levels for smoking cessation including provision of nicotine gums, nicotine patches and drugs such as Buprenorphine and Varenicycline that reduce craving at subsidized rates. People should be made aware of the increased risk of second hand smoke with TB recurrence especially in children so that they may encourage their friends at work places and public places to abstain from smoking. Free educational and treatment camps should be set up in areas far away from hospitals. Adequate follow up should be made for all the TB patients who were enlisted in the TB Control program database and were smokers, as the relapse rates for smoking are quite high even in those who quit smoking. A separate database for surveillance should be established for reporting and monitoring of all TB recurrent cases to assess all risk factors in further detail. Smoking should strictly be banned in all public places and fine should be introduced for offenders.

CONCLUSION

Our study concluded that there is strong association of recurrence of Pulmonary Kochs with continuation of smoking within 2 years of completion of ATT. Recurrence is also statistically associated with smoking >10 years in life, status of being ever smoker in life and age. No statistical association was observed between type of smoking, or quitting smoking before completion of ATT with recurrence.

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AUTHORS' CONTRIBUTION

DA: Conceptualized the research question and did all the literature search, contributed in synopsis development and data collection. MMK: Did the literature search and contributed to synopsis development and discussion formulation. FA: Formulated the research methodology and synopsis, developed data sheet, did analysis and formulated results. SA & QUA: Contributed in data collection and data entry in SPSS.

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