

Original Research Article

Case-control study to evaluate the role of smoking, alcohol abuse, intravenous drug abuse, tobacco use and biomass fuel exposure as risk factor in pulmonary tuberculosis

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Received: 23 March 2020

Accepted: 20 April 2020

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ABSTRACT

Background: An association between smoking and tuberculosis disease has been shown in various studies, it is less clear to what extent smoking increases the risk of Mycobacterium tuberculosis infection. Therefore the aim of this study is to evaluate the role of smoking, alcohol abuse, intravenous drug abuse, tobacco use and biomass fuel exposure as a risk factor for the development of pulmonary tuberculosis.

Methods: This is a case control study and total 200 subjects will be included with 100 sputum smear positive pulmonary tuberculosis cases and 100 age and sex matched healthy subjects as controls. Data collected from both cases and controls using a proforma by enquiring smoking habits, alcohol abuse, intravenous drug abuse, biomass fuel exposure and documenting chest X-ray features.

Results: The study showed significant association between tuberculosis and smoking as a risk factor with beedi smoking, early age of starting smoking, increased duration and quantity of smoking increases risk for tuberculosis. There was significant association between intravenous drug abuse, biomass fuel exposure and risk of tuberculosis. There was no significant association in the study between alcohol abuse, tobacco chewing and tuberculosis, but heavy drinking and tuberculosis showed significant association. The study also showed significant association of cavitory lesion with smoking.

Conclusions: There is significant association between smoking, intravenous drug abuse, biomass fuel exposure and tuberculosis, since these risk factors impairs host immune defences that allows the development of active tuberculosis.

Keywords: Alcohol abuse, Biomass fuel, Intravenous drug abuse, Pulmonary Tuberculosis, Smoking, Tobacco

INTRODUCTION

Tuberculosis remains a worldwide public health problem despite the fact that the causative organism was discovered more than 100 years ago.¹

Worldwide around 10 million people fall ill with tuberculosis each year. Tuberculosis is one of the top 10 causes of death, and the leading cause from a single infectious agent (mycobacterium tuberculosis), ranking above HIV/AIDS. The disease can affect anyone anywhere, but most people who develop Tb (about 90%)

are adults, the male female ratio is 2:1, and case rates at national level vary from less than 50 to more than 5000 per 1 million population per year. Almost 90% of cases each year are in 30 high TB burden countries. Globally, an estimated 1.7 billion people are infected with mycobacterium tuberculosis and are thus at risk of developing the disease.²

Tuberculosis is an infectious disease caused by Mycobacterium Tuberculosis (MTB), a small aerobic non-motile bacillus. The organism was discovered by Robert Koch on 24th march 1882.³ The disease primarily affects

lungs but can also affect intestine, meninges, bones and joints, lymph nodes, skin and other tissues of the body.

The estimated TB incidence in India is 27 lakh. In 2018, RNTCP was able to achieve a notification of 21.5 Lakh. This is a 16% increase as compared to 2017 and the highest so far. Of the total notification, 25% (5.4 lakh) cases was from the private sector; a 40% increase from last year. Among the notified, treatment was initiated for about 19.1 lakh cases (~90%), across both public and private sectors. The characteristics of the affected population largely remain similar with majority of the affected individuals being in the age group of 15-69 years and 2/3rd being males. HIV co-infection among TB was nearly fifty thousand cases amounting to TB HIV co infection rate of 3.4%.⁴

Tobacco smoking and Tuberculosis are the two major health problems, especially in developing countries. As per estimates, deaths from tobacco consumption will be around 8.4 million in 2020, almost double to that estimated in 1990.⁵

The shift in smoking paradigm from industrialized world to developing world coincides with the increased prevalence of Tuberculosis in these regions. About 17% of smoking population lives in India.^{6,7} At least one-third of the smokers belong to middle age group, and as per surveys, it is in this age group pulmonary tuberculosis is most prevalent. Males are affected two-four times more than females.⁸

It is estimated that, worldwide, 1.3 billion people consume tobacco and that most of them live in underdeveloped or developing countries, where the tuberculosis rates are also higher.⁹ Therefore, the greatest impact of smoking in terms of public health issues related to infection is probably the increase in the risk of tuberculosis. Some systematic reviews and meta-analyses of observational studies have shown an unfavorable association between the global epidemics of tuberculosis and smoking, exposure to tobacco smoke having been associated with tuberculosis infection, active tuberculosis, and tuberculosis-related mortality.^{10,11}

Smoker's lung - pathology and pathophysiology

Smoking impairs the host immune defences right from the beginning. Smoking impairs the clearance of secretions present on tracheobronchial mucosa. This is the first line of defence which aids in clearance of inhaled particles. Thus, by impairing the clearance, it allows the tubercle bacilli to escape the defence and propels it to reach alveoli.¹² Pulmonary alveolar macrophages constitute early defence mechanism against the tubercle bacilli. Studies have shown that smoking alters the function of these macrophages and thus impairing their ability to clear the bacilli from airways. The macrophages from smokers were bigger in size, had abnormal surface morphology which led to impaired antigen presenting function.¹³ The

alveolar macrophages of smokers had reduced phagocytic activity and low levels of pro-inflammatory cytokines.¹⁴

The role that cigarette smoke plays in the pathogenesis of tuberculosis is related to ciliary dysfunction, to a reduced immune response, and to defects in the immune response of macrophages, with or without a decrease in the CD4 count, increasing susceptibility to infection with *Mycobacterium tuberculosis*.⁹ The alveolar macrophage binds to the bacillus through complement receptors 1, 3, and 4. Activated lymphocytes release cytokines while recruiting macrophages, fibroblasts, and other lymphocytes. The major cytokine involved in granuloma formation is TNF- α , which is released by macrophages immediately after exposure to *M. tuberculosis* antigens. The TNF- α activates macrophages and dendritic cells. In smokers, nicotine, acting through the $\alpha 7$ nicotinic receptor, reduces the production of TNF- α by macrophages, thereby preventing its protective action and favouring the development of tuberculosis.^{15,16}

Secretion of IL-12 by macrophages induces the production of IFN- γ in natural killer cells. This immune response aspect, known as the Th1 response, aims to destroy *M. tuberculosis* by forming a fibrous granuloma. Cigarette smoke selectively promotes low production of interleukin-12 and TNF- α , impeding granuloma formation, which would contain the infection at this stage in immunocompetent individuals, smoking therefore creating conditions that allow the development of active tuberculosis.^{15,16}

There is evidence of imbalance between oxidant and anti-oxidant levels in smokers. This imbalance leads to increased oxidative stress on lung tissues primarily by oxidants contained in cigarette smoke and the decreased anti-oxidant mechanism of aging macrophages.¹⁷

Recently, a novel mechanism suggesting the role of nicotinic cholinergic receptors on macrophages has been proposed. Nicotine in cigarette smoke acts on these receptors and decrease the production of tumour necrosis factor, thus impairing the killing ability of macrophages.¹⁸

This study will be carried out to affirm the strength of association between smoking and pulmonary tuberculosis.

METHODS

This study was carried out in the Department of Pulmonary Medicine of Government Medical College, Amritsar over a period of 2 years from November 2017 to November 2019. This is a case control study and total 200 subjects will be included with 100 sputum smear positive pulmonary tuberculosis cases and 100 age and sex matched healthy subjects as controls.

This study will be conducted after approval from the institutional ethics committee and informed written consent of each patient.

Inclusion criteria

- Patients consenting for the study.
- Adult patients aged 12 years and above.
- Sputum smear-positive pulmonary tuberculosis patients.
- For each case, one control will be taken from among the healthy bystanders of patients.
- They were matched for age and sex.

Exclusion criteria

- Patients not consenting for the study.
- All subjects with comorbid conditions such as diabetes mellitus, human immunodeficiency virus infection and malignancy; and those on any immunosuppressive drugs were also excluded from the study.

Informed consent will be taken from all subjects. Approval for this study will also be obtained from the review board of our institution. A pre-structured proforma will be filled in those cases which are included in the study. The following details will be recorded:

- **Personal Data:** Age, sex, occupation, address (including phone number) will be noted down. A detailed occupational history will be sought, inquiring about the age at start of the occupation, exact nature of work, hours of work, nature of any protective devices used etc.
- **Symptoms:** Chief complaints will be noted and a detailed account of each will be obtained. The complaints specifically sought for include: fever, cough, expectoration, hemoptysis, chest pain, breathlessness, loss of weight, loss of appetite etc.
- **Past History:** Any significant past medical history will be noted.
- **Personal History:** Whether the person is or was a smoker. 'Smoker' is defined as a person who had smoked more than 100 cigarettes/bidis during his/her lifetime. 'Non-smoker' is defined as a person with exposure less than that stated above.

In case of yes answer, whether he is smoking bidis, cigarettes or any other forms of tobacco smoke; the number smoked per day, current smoking status, age of starting smoking, duration of smoking and quantity of smoking, any other addiction tobacco chewing, alcoholism. In case of non-smokers, any history of smoking among other family members or friends will be noted.

Household smoke exposure, environmental smoke exposure if any will also be noted.

- **Physical Examination:** A complete clinical examination will be performed in all cases including

general examination, examination of respiratory system in detail and other systems.

- **Investigations:** Investigations will be done to arrive at a diagnosis and detect any associated condition or comorbidities. These includes routine blood examination - Hemoglobin, Total counts, Differential counts, Erythrocyte sedimentation rate, Fasting blood sugar, Urine routine, renal function tests, liver function tests, ECG, HIV, HBsAg (Hepacard).
- Chest X-Ray.
- Sputum examination for AFB-2 samples (1-spot sample and 1-early morning sample) carried out by Ziehl-Neelsen staining technique
- CT- Scan of thorax wherever needed
- Tuberculin test.
- The data will be documented, tabulated and analyzed by calculating odds ratio and using Chi-square test wherever applicable.

RESULTS

The majority of smokers belonged to the labourer (66.67%) and driving (18.18%) profession among the cases. The majority of smokers among controls belonged to labourers (58.82%) and driving (23.32%) professions (Figure 1).

The unadjusted odds ratio comes out to be 2.40 (confidence interval 95%; 1.23-4.69 with a significance level $p=0.0100$). Thus there is significant association between tuberculosis and smoking as a risk factor (Figure 2).

The odds ratio for tuberculosis in smokers who doesn't drink was calculated to be 14.77 (confidence interval 95%: 3.32-65.68 with significance level $p=0.0004$). Thus there is significant association between tuberculosis in smokers who doesn't drink compared to non-smokers and non-drinkers (Figure 3).

The odds ratio of tuberculosis for beedi smokers found to be 3.51 times (confidence interval 95%: 1.31-9.4 with a significance level $p=0.0125$) compared to non-smokers. The odds of tuberculosis in cigarette smoker is 1.23 times (confidence interval 95%: 0.49-3.15 with significance level $p=0.6531$) compared to non-smokers. The odds ratio of beedi smokers for tuberculosis in comparison with non-smokers showed significant association found between beedi smoking and tuberculosis (Figure 4).

Among cases 18 (54.55%) started smoking at an adolescent age and the odds ratio for tuberculosis was found to be 3.19 (confidence interval 95%: 1.26-8.08 with a significance level $p=0.0147$) and for those who started ≥ 20 years it was found to be 1.86 (confidence interval 95%: 0.78-4.4 with significance level $p=0.1591$). Thus there is significant association between an early age of starting smoking (adolescent age group) and tuberculosis (Figure 5).

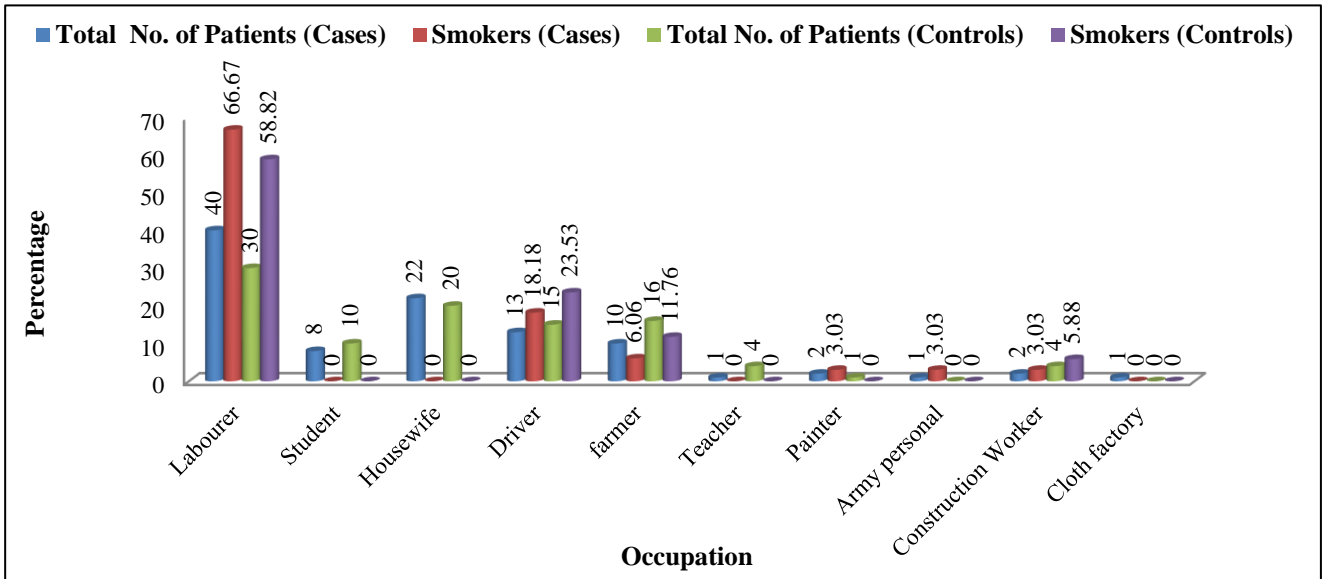


Figure 1: Occupation of cases and controls and smoking habit among them.

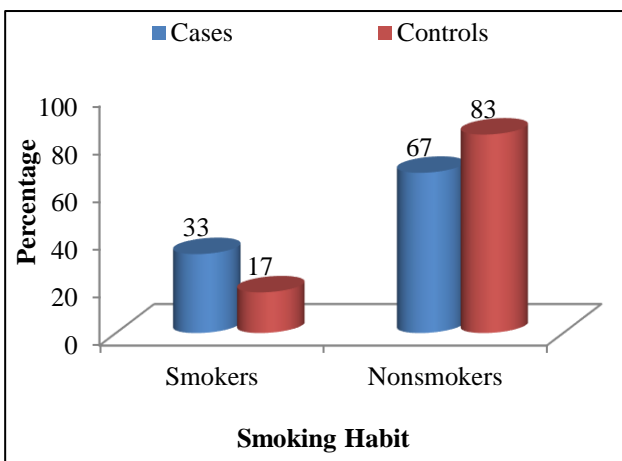


Figure 2: Smoking habit among cases and controls.

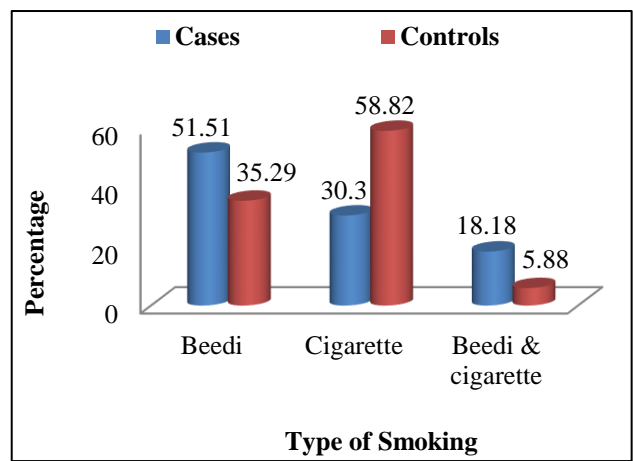


Figure 4: Type of smoking among cases and controls.

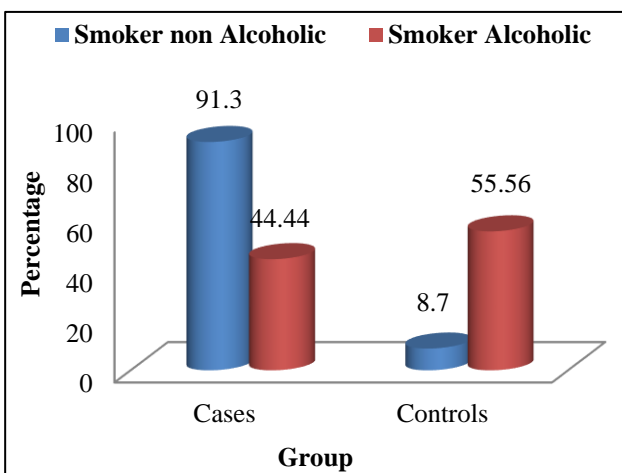


Figure 3: Cases and controls with only smoking habit and with smoking and alcohol abuse.

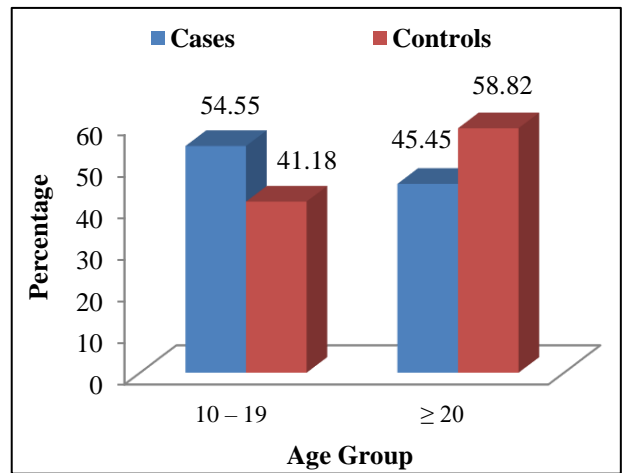


Figure 5: Age of starting smoking among cases and controls.

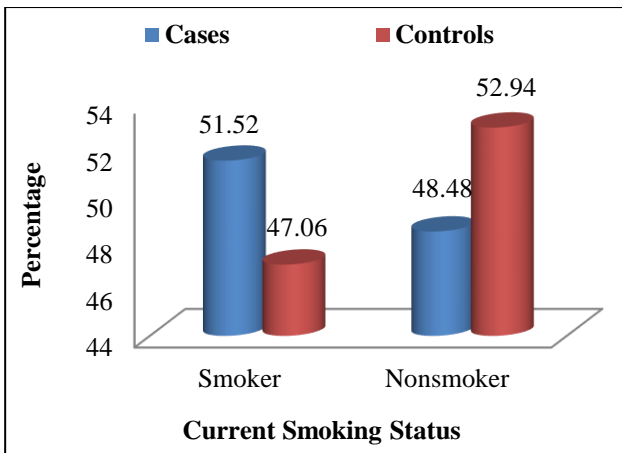


Figure 6: Current smoking status among cases and controls.

The odds ratio of current smokers is 2.63 (confidence interval 95%: 1.07-6.47 with a significance level $p=0.0350$), there is significant association between current smoking and tuberculosis with odds ratio 2.63 times compared to non-smokers (Figure 6).

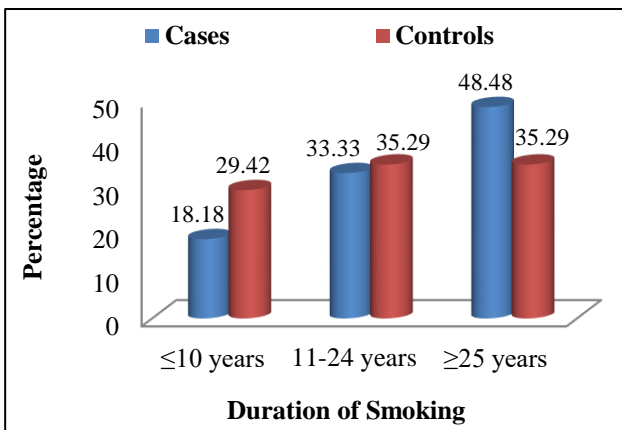


Figure 7: Duration of smoking among cases and controls.

The odds ratio among smokers of duration ≤ 10 years is 1.48 (confidence interval 95%: 0.43 to 5.08 with a significance level $p=0.5274$), 11-24 years is 2.21 (confidence interval 95%; 0.79-6.46 with a significance level $p=0.1241$) and among smokers with duration of smoking ≥ 25 yrs the odds ratio for tuberculosis is 3.22 (confidence interval 95%: 1.09– 9.48 with significance level $p=0.0339$). Thus there is significant association of odds ratio for tuberculosis in those who had duration of smoking for ≥ 25 years (Figure 7).

The odds ratio for cases with ≤ 5 and 6-10 pack years is 2.06 (confidence interval 95%: 0.47-8.95 with a significance level $p=0.3328$) and the odds ratio among cases who smoked 11-25 pack years is 2.12 (confidence interval:0.79-5.69 with a significance level $p=0.1344$) and with cases who smoked more than 25 pack years were

having odds for tuberculosis was found to be 3.40 (confidence interval 95%: 1.03-11.18 with significance level $p=0.0433$). There is significant association in cases who smoked more than 25 pack years the odds for tuberculosis was found to be 3.40 times more compared to non-smokers (Figure 8).

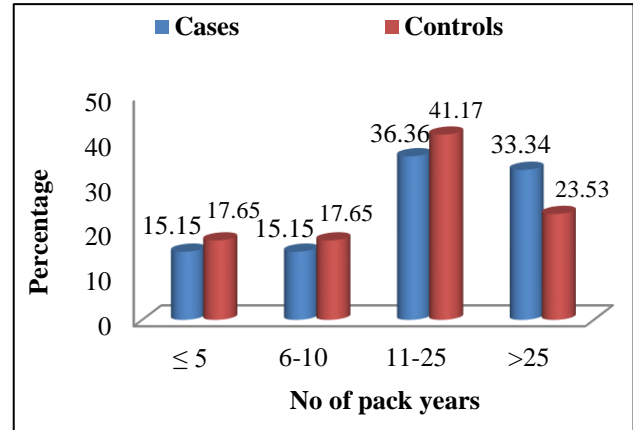


Figure 8: Quantity of smoking among case and controls.

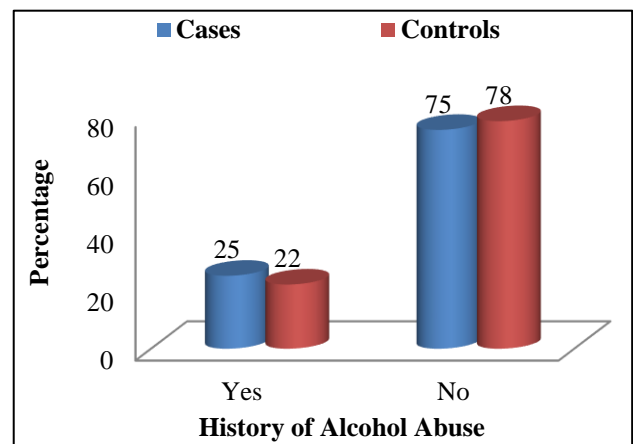


Figure 9: Alcohol abuse among cases and controls.

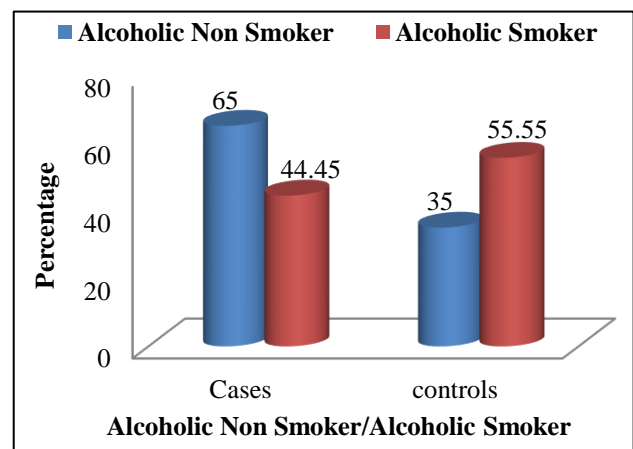


Figure 10: Alcoholic non-smoker among cases and controls.

The unadjusted odds ratio among cases who are alcohol abusers is 1.18 (confidence interval 95%: 0.61-2.27 with significance level $p=0.6170$). Significant association could not be established in the study between alcohol abuse and tuberculosis since p value >0.05 (Figure 9).

The odds ratio for tuberculosis in alcoholic non-smokers comes out to be 1.94 (confidence interval 95%: 0.73-5.10 with a significance level $p=0.1844$). Significant association can't be established for tuberculosis odds in alcoholic non-smokers since p value >0.05 (Figure 10).

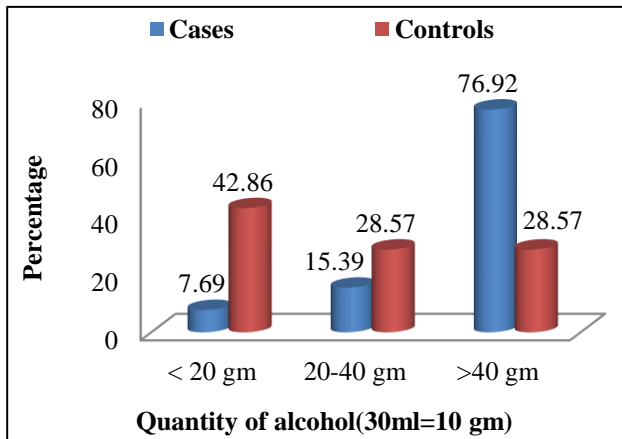


Figure 11: Quantity of alcohol consumption in alcoholic non-smokers.

The odds ratio of these subjects for tuberculosis was calculated to be 5.20 (confidence interval 95% =1.10-24.52 with significance level $p=0.0372$). Thus there is significant association between heavy drinking (>40 gm alcohol) and tuberculosis (Figure 11).

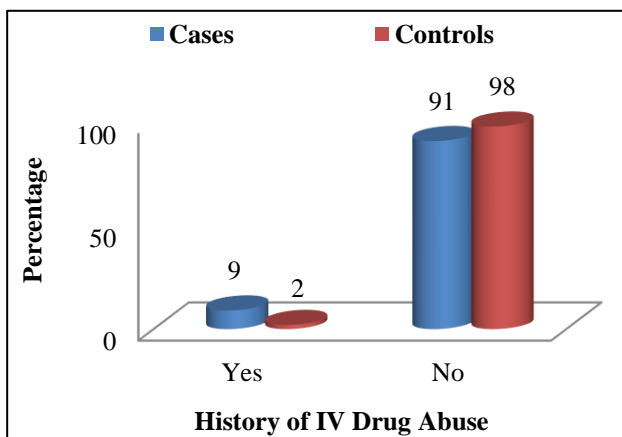


Figure 12: Intravenous drug abuse among cases and controls.

The unadjusted odds ratio for tuberculosis in IV drug abusers were found to be 4.84 (confidence interval 95%: 1.01-23.02 with a significance level p value 0.0472). There is significant association between intravenous drug abuse and risk of tuberculosis in cases compared to controls (Figure 12).

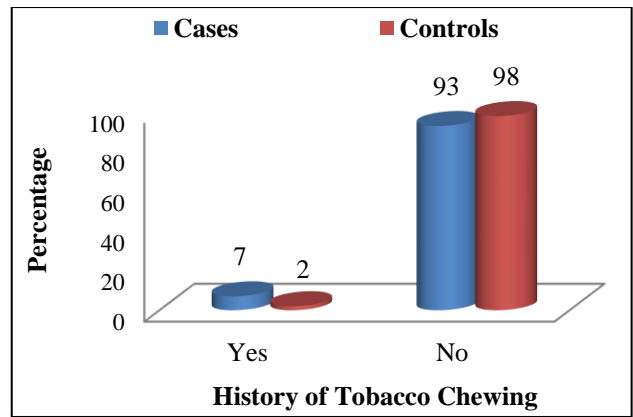


Figure 13: Tobacco chewing among cases and controls.

The unadjusted odds ratio for tuberculosis in tobacco chewers was calculated to be 3.68 times (confidence interval 95%: 0.74-18.21, with a significance level $p=0.1092$) more compared to non tobacco chewers. Significant association could not be established in the study between tobacco chewing and risk for tuberculosis as per odds ratio calculation since p value >0.05 (Figure 13).

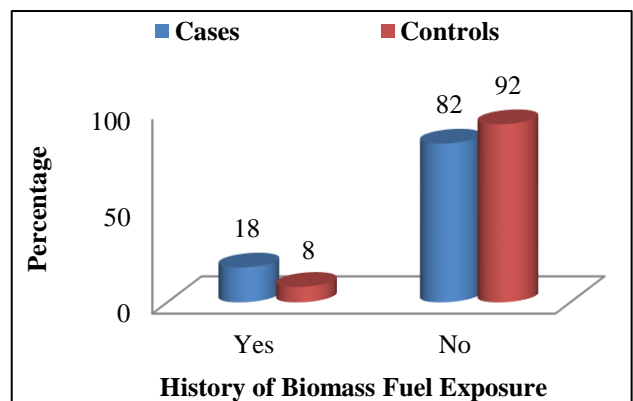


Figure 14: Household smoke exposure.

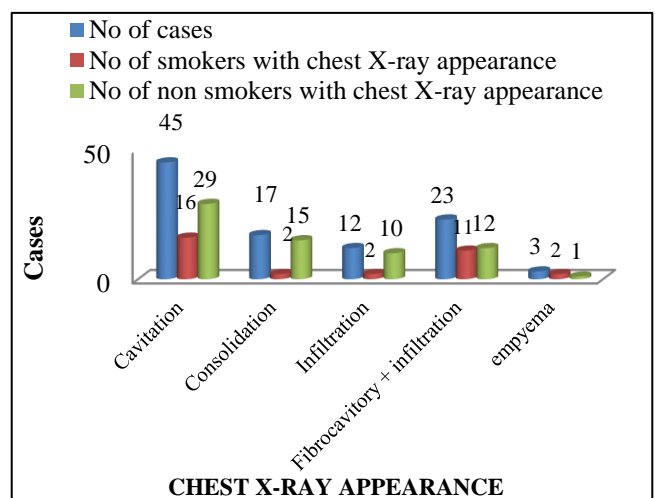


Figure 15: Chest x-ray appearance in cases.

The unadjusted odds ratio for tuberculosis in cases with history of biomass fuel exposure was found to be 2.52 (confidence interval 95%: 1.04-6.11 with a significance level $p=0.0402$) compared to subjects without history of biomass fuel exposure. This shows significant association between biomass fuel exposure and tuberculosis (Figure 14).

Among cases, smokers with tuberculosis showed cavitory lesions with odds ratio 3.21 (confidence interval 95%: 1.57-6.55 with a significance level $p=0.0013$) (Figure 15).

DISCUSSION

A total of 200 subjects were included in the study out of which 100 of them were sputum smear positive cases and 100 of them were healthy controls and the cases and controls were matched for both age and sex.

- There was an overall male preponderance in the study of the 200 subjects included in the study 142 (71%) were males and 58 (29%) were females. Of the 100 cases 71 were males and 29 were females and of the 100 controls 71 were males and 29 were females.
- The majority of smokers belonged to the labourer (66.67%) and driving (18.18%) profession among the cases and in controls too majority of smokers belonged to labourers (58.82%) and driving (23.32%) profession.
- The odds ratio for tuberculosis in smokers comes out to be 2.40 (confidence interval 95%; 1.23-4.69 with significance level $p=0.0100$) times than non-smokers according to the study. There is significant association between tuberculosis and smoking as a risk factor.

Similar results of significant association between smoking and tuberculosis were also found by a study from India by Kolappan et al, and found smoking to have an adjusted odds ratio for smear or culture positive TB of 2.24 (95%CI=1.27-3.94) with a dose effect for both quantity and duration of smoking, adjusted for age.¹⁹

- The odds ratio for tuberculosis in smokers who doesn't drink was calculated to be 14.77 (confidence interval 95%: 3.32-65.68 with significance level $p=0.0004$). Thus there is significant association between tuberculosis in smokers who doesn't drink compared to non-smokers and non-drinkers.
- The odds ratio for tuberculosis for beedi smokers found to be 3.51 (confidence interval 95%: 1.31-9.4 with significance level $p=0.0125$) times compared to non-smokers. This shows significant association between beedi smoking and tuberculosis.
- The odds ratio for tuberculosis was found to be 3.19 (confidence interval 95%: 1.26-8.08 with significance level $p=0.0147$) among cases who started smoking at an adolescent age group. There is significant association between early age of starting smoking at an adolescent age and risk of tuberculosis.

- With cases who smoked more than 25 pack years were having an odds ratio for tuberculosis found to be 3.40 (confidence interval 95%: 1.03-11.18 with significance level $p=0.0433$). There is significant association in cases who smoked more than 25 pack years the odds for tuberculosis was found to be 3.40 times more compared to non-smokers.

The den Boon et al, cross-sectional study in South Africa, found an association between pack years and infection among adults in a high risk area. The OR for infection among smokers of >15 pack years was 1.90 (95%CI=1.28-2.81).²⁰

- The odds ratio of current smokers for tuberculosis is 2.63 (confidence interval 95%: 1.07- 6.47 with a significance level $p=0.0350$). There is significant association between current smoking and tuberculosis with odds ratio 2.63 times compared to non-smokers.
- Among smokers with duration of smoking ≥ 25 years the odds ratio for tuberculosis is 3.22 (confidence interval 95%: 1.09-9.48 with significance level $p=0.0339$), thus there is significant association of odds ratio and relative risk for tuberculosis in those who has a duration of smoking ≥ 25 years.
- Significant association could not be established in the study between alcohol abuse and tuberculosis since p value >0.05 .
- Significant association could not be established between tuberculosis odds in alcoholic non-smokers since p value >0.05 .
- In heavy drinkers of >40gm of alcohol at a time the odds ratio of these subjects for tuberculosis was calculated to be 5.20 (confidence interval 95%=1.10-24.52 with significance level $p=0.0372$). Thus there is significant association between heavy drinking (>40gm alcohol) and tuberculosis.
- The unadjusted odds ratio for tuberculosis in cases with history of biomass fuel exposure was found to be 2.52 (confidence interval 95%: 1.04-6.11 with a significance level $p=0.0402$) times compared to subjects without history of biomass fuel exposure. The study shows significant association between biomass fuel exposure and risk of tuberculosis.

The results were in congruence with the following study by Perez Padilla et al's case-control study²¹ was undertaken primarily to measure the effect of biomass fuels on TB disease risk in Mexico. Only 10% of the study sample smoked, but a modest effect was nevertheless found for smoking (ever smoking OR 1.5, 95%CI=1.0-2.3). The authors note: "Tobacco smoke, which resembles biomass smoke in several aspects can reduce several defence mechanisms that may be important against TB."

- Significant association could not be established in the study between tobacco chewing and risk for tuberculosis as per odds ratio calculation since p value >0.05 .

- Smokers with tuberculosis showed cavitory lesions with odds ratio 3.21 (confidence interval 95%: 1.57-6.55 with a significance level $p=0.0013$).

The study showed significant association between tuberculosis and smoking as a risk factor. It also reveals significant association between beedi smoking, early age of starting smoking, duration of smoking, quantity of smoking and tuberculosis. It also showed significant association between intravenous drug abuse, biomass fuel exposure and risk of tuberculosis. Significant association could not be established in the study between alcohol abuse, tobacco chewing and tuberculosis as per odds ratio calculation since p value >0.05 , but there is a significant association between heavy drinking and tuberculosis. The study also showed significant association of cavitory lesions with smoking.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Mathew L, Pandhi N, Kajal NC, Gunet. Case-control study to evaluate the role of smoking, alcohol abuse, intravenous drug abuse, tobacco use and biomass fuel exposure as risk factor in pulmonary tuberculosis. *Int J Adv Med* 2020;7:940-7.