ORIGINAL ARITICLE

Association between pulmonary tuberculosis and smoking: a case control study

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Abstract

Background: India has very high rates of tuberculosis and smoked tobacco use among adults. Efforts to control both tobacco use and tuberculosis in India need to be addressed. Our objective is to examine the role of smoking as a risk factor for the development of pulmonary tuberculosis. **Methods:** A total of 613 TB patients frequency matched with 1226 controls were interviewed by using a structured questionnaire. The associations between cigarette smoking and risk of TB were estimated by computing odds ratios (ORs) and 95% confidence intervals (95% CIs) from logistic regression model. Patients' smoking behavior and patterns of smoking cessation were followed after TB diagnosis. **Results:** The proportion of cigarette smoking was 54.6% in TB cases, which was significantly higher than that in controls (45.1%) with adjusted OR of 1.93(95% CI: 1.51–2.48) **Conclusion:** Cigarette smoking was associated with lifetime TB infection and the association was most evident among the heaviest smokers (> 1 pack per day, > 30 pack years). Interventions of smoking cessation are recommended to be included in the current TB control practice.

Key Words

Diagnosis; India; Smoking; Tobacco; Tuberculosis

Introduction

Tuberculosis (TB) is one of the leading causes of death in the world and remains a major public health burden in many developing countries (1). From worldwide epidemic of TB in 2006, around 9.2 million new cases and 1.7 million deaths were expected every year, of which 0.7 million cases and 0.2 million deaths were in HIV-positive people (2).

As a risk factor of TB, tobacco smoking has increased substantially over the past three decades, especially in developing countries (3, 4). Globally, TB and smoking are simultaneously increasing, both of which could damage the lungs, and interact at an immunologic and cellular level (5). Studies investigating the association between smoking and TB have been published since 1918 (6).Both passive and active exposures to tobacco smoke have been shown to be associated with TB infection and the transition from being infected to developing TB disease.

Moreover, cigarette smoking is also associated with the prognosis of TB.

During the past six decades, population-based evidence has accumulated that attributes a major TB burden to smoked tobacco (7-10). Specifically, early evidence linking smoked tobacco to TB came from samples of high risk adults (i.e. health care workers, migrants, patients, elderly, prisoners) (11-13). Recently, in a 2008 case control study of 1.1 million households in India, Jha et al. found that the TB death rate was 1.7 times higher in smokers as compared to non-smokers (14). In 2009, Jee et al. reported a significant 60% increase in risk of death among 1,294,504 South Korean adults (15), and a similar association with incident TB in men (15). In the Taiwan National Health Interview Survey (n=17,699, e" 12 y and older), Lin et al (10) found a significant two-fold increase in risk of incident, active TB among current smokers (10).

Aims and Objectives

In this study our specific aims are as follows: 1) To examine the relation between manufactured cigarette smoking and TB 2) To examine whether the intensity of cigarette smoking (pack-years, number of cigarettes smoked) among daily smokers further increased the likelihood of developing TB.

Methods

This study was carried out in the Department of Pulmonary Medicine of the Bundelkhand Government Medical College, Sagar. A total of 613 patients (men 458, women 155) and 1226 healthy controls (men 916, women 310) subjects were recruited from January 2011 to August 2012.

Sputum smear–positive pulmonary tuberculosis patients were taken as cases. Controls were taken from among the healthy bystanders of that patient. They were matched for age (5 years), sex and place. To exclude any respiratory disease, all controls were subjected to clinical evaluation, chest radiograph and sputum examination. All subjects with co-morbid 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 was taken from all subjects. Approval for this study was also obtained from the review board of our institution. Ethics has been respected throughout the whole study period.

A predesigned questionnaire enquiring about smoking history, household smoke exposure, environmental smoke exposure, tobacco chewing, alcoholism, housing characteristics and score on the modified Kuppuswamy socioeconomic status scale was used as instrument for data collection. This modified Kuppuswamy socioeconomic status classification contemplates five social classes: Upper (I), upper middle (II), lower middle (III), upper lower (IV) and lower (V). Details of smoking were noted carefully with regard to type, current smoking status, age of starting smoking, duration of smoking and quantity of smoking. For cigarette smoking status, a person who smoked at least once a day and lasted for more than 6 months in his or her lifetime was regarded as a smoker. Ex-smoker (former smoker) was defined as a smoker who had stopped smoking for at least 3 months. For alcohol drinking, it was defined as those who reported drinking alcohol more than 3 times per week.

Data analysis: Data were managed with EpiData 3.1 (Denmark) and analyzed by STATA 10.0 (College station, TX, USA). Differences in the distribution of demographic characteristics (gender, age, education and marital status) and selected variables (alcohol drinking

history) between cases and controls were tested by using the Student *t*-test (for continuous variables) or ÷2-test (for categorical variables). The associations between cigarette smoking and risk of TB were estimated by computing odds ratios (ORs) and their 95% confidence intervals (CIs) using logistic regression model. Crude odds ratios and corresponding adjusted odds ratios by controlling age, gender and alcohol drinking history for cigarette smoking history, age of starting smoking, smoking years and cumulative pack-years were calculated respectively. To evaluate the effects of cigarette smoking on TB risk according to selected variables (gender, age, education and alcohol drinking), stratified analysis was also performed.

Result

Cigarette smoking and risk of TB: A total of 613 patients (men 458, women 155) and 1226 healthy controls (men 916, women 310) were included in the analysis. The average age (mean ± SD) was 56.0 ± 16.5 years among cases and 56.0 ± 16.4 years among controls, respectively. As a result of frequency-matching, there were no significant differences in the distribution of gender and age between cases and controls (Table 1). The proportion of smokers was 54.6% in TB cases, which was significantly higher than that in controls (45.1%) with the crude OR of 1.47 (95% CI: 1.21–1.78). After adjusting for gender, age and alcohol drinking history, the OR was 1.93 (95% CI: 1.51–2.48). For former and current smokers, the adjusted ORs were 1.95 (95% CI: 1.32–2.87) and 1.93 (95% CI: 1.49–2.49), respectively. Both of the cumulative smoking years and amount of cigarette consumption were associated with a significantly increased risk of TB. Compared with nonsmokers, the ORs were 1.73(95% CI: 1.30–2.31) and 2.18(95% CI: 1.63–2.91) for those with cumulative pack-year less than 29 and over 29, respectively. Individuals who started smoking earlier than 25-year-old had higher risk than those who started smoking later, with the ORs of 2.09(95% CI: 1.59–2.75) and 1.72(95% CI: 1.28–2.33), respectively (Table 2). To evaluate the effects of cigarette smoking on TB risk according to selected variables, we further performed stratified analyses. As shown in (Table 3) the increased risk of TB associated with smoking was more evident among the older adults (age e• 56 years) (OR: 2.56, 95% CI: 1.84–3.56), less educated individuals (< 6 years) (OR: 2.23, 95% CI: 1.56–3.17) and people with alcohol drinking history (OR: 2.45, 95% CI: 1.48–4.06).

Discussion

Apart from HIV/AIDS, tobacco smoking is the only major cause of death that is increasing rapidly (16). It is estimated that smoking will cause about 10 million adult deaths from all causes in 2030 and most of the increased tobacco-related deaths will take place in Asia, Africa and South America (16). India has the largest production and consumption of tobacco worldwide. Long-term inhalation of tobacco smoke alters a wide range of immunological functions, resulting in significantly increased risk of heart disease, lung cancer, microbial infections and delayed recovery from these diseases (17). Though the underlying biological mechanism is unclear, strong associations between tobacco smoking and TB have been proved in several areas (18). Results from our study also corroborated these former reports. Furthermore, a dose-response relationship between cigarette smoking and TB was also demonstrated in the present study: with the increase of daily cigarettes consumption and duration of smoking, the risk for TB also increased accordingly.

Our findings is in agreement with the previous Indian studies (14) as well as from South Korea

(15), Taiwan (10), Thailand (9), and Malaysia (19) that identify smoked tobacco as a major contributor to the TB burden in Asia. Taken together with meta-analyses from small samples from 19 nations (11,13), and recent global estimates from mathematical modeling (8), these data support that the global reduction of tuberculosis infection is heavily dependent on successful tobacco control being achieved in Asia.(20)

Pathophysiology of smoking intensity and tuberculosis infection: Our findings identify a more than 3-fold increase in odds of TB among adults who were smoking one pack a day or more or those who had smoked greater than 30 pack-years (Figure 1), (Figure 2) These data on heavy smokers are concordant with much of what is known of the mechanism of increased susceptibility to TB infection in smokers.(9,21) Such smoking-induced mechanisms include: 1) an impairment of mucociliary function (22,23) 2) lower airway epithelial damage and inflammation (22,24) 3) a constriction of the alveolar air sac (22,24) 4) an increase in the number of circulating alveolar macrophages (the cells targeted by tuberculosis).(20,26) 5) A collapse of the bronchioles.(7,27-29) Beyond physical changes, the immune suppression from heavy smoking could also contribute to TB infection of the lung. (20, 29)

Cigarette smoking as a component of a Bio-behavioral framework linking TB infection with respiratory disease risk factors in rural adults of India: The association between TB and smoking among the primarily rural adults of India that we studied, needs to be considered in the context of the many other environmental factors in this region that can contribute to TB infection. Specifically, much of the smoking-related lung damage described above that potentially increases risk of TB infection, can also be caused by the high rates of exposure to Second hand smoke indoor cooking fires, crop-burning, and occupational dust and dirt that is highly prevalent in the region.

Also noteworthy are pathogen transmission pathways present in the rural lifestyle such as crowding in household environments and health and hygiene practices

It should be noticed that behavior of tobacco use is very difficult to change, even with medicinal aids for cessation. Only a small proportion of smokers stop smoking successfully on their own. Thus smoking cessation support should be incorporated with TB control programs. As attitudes and knowledge can change, change of smoking behaviors needs to be reinforced regularly. Repeated brief cessation advice has been shown to be a feasible and inexpensive addition to routine TB case management. Thus, offering advice to TB patients when they seek healthcare can influence unhealthy behaviors. The central strategy recommended by WHO for controlling TB is DOTS. However, smoking cessation has not been involved in the DOTS framework in India. TB patients lack access to smoking intervention services and social supports, resulting in lower cessation and higher relapse rate. It is essential to revise current TB treatment guidelines and provide regular medical advice on smoking behaviors involved in standard practice of DOTS and other TB control programs. However, additional research is needed in the form of pilot study to determine the feasibility of this intervention, random controlled study to test methods in various settings, and evaluation study to determine effects after widespread application of such practices.

One intriguing finding from the present study was that the higher risk of smoking relapse occurred in the period of 6–9 months and 12–15 months after diagnosis. It might be related with the traditional anti-tuberculosis

treatment period and patient's recovery from disease. Thus interventions on smoking cessation should be focused on such special risk periods.

There are several potential limitations of this study. Firstly, our findings are based on the results of observational investigations. Though we have performed multivariate regression model and stratified analyses to control the potential confounders, other factors including economic status, intensive contact with TB patients, nutrition intake, as well as exposure to other's smoke may also confound the association between smoking and TB. Secondly, we enrolled TB patients with phone number and interviewed those who were successfully contacted through telephone. Selection bias should not be neglected. Thirdly, recall bias would also influence the results. Compared with healthy controls, TB patients could attribute disease to smoking and aggrandized it, resulting in the overestimate of smoking effects. Fourthly, a major limitation of this study was that smoking status was based on the patient's self-report rather than the detection results of nicotine levels. On one hand, some patients may decline to admit to smoking, especially if a connection between the disease and smoking has been accepted by people in the community, which will underestimate the relation between cigarette smoking and TB. On the other hand, TB patients would be more likely to falsely admit to quitting smoking for fear of disappointing the interviewers, resulting in the overestimate of smoking cessation proportion among TB patients.

Conclusion

Cigarette smoking is associated with TB in the India. Interventions of smoking cessation among patients were insufficient in rural areas of India. Physicians and DOTS providers should be actively involved in smoking cessation activities. Regular and repeated medical advices on smoking behaviors are recommended to be included in DOTS practice.

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Tables

TABLE 1 BASIC CHARACTERISTICS OF CASES AND CONTROLS

Variables	Case (n = 613) n (%)	Control (n = 1226) n (%)	P Value
Gender			
Men	458(74.7)	916(74.7)	1.000†

Women	155(25.3)	310(25.3)	
Age (years)			
Mean ± SD	56.0 ± 16.5	56.0 ± 16.4	0.963‡
< 56	270(44.0)	545(44.5)	0.868†
≥ 56	343(56.0)	681(55.5)	
Education(years)			
< 6	309(50.4)	675(55.1)	0.060†
≥ 6	304(49.6)	551(44.9)	
Marital status			
Single	32(5.2)	54(4.4)	0.175†
Married	537(87.6)	1054(86.0)	
Divorced/widowed	44(7.2)	118(9.6)	
Alcohol drinking			
Never	450(73.4)	839(68.4)	0.028†
Ever	163(26.6)	387(31.6)	
Sputum smear test*			
Negative	274(45.1)		
Positive	334(54.9)		

†: Chi-square test; ‡: Student *t*-test; *Five patients without sputum smear test results

TABLE 2 ASSOCIATION BETWEEN TUBERCULOSIS AND CIGARETTE SMOKING

Variables	Case (n = 613) n (%)	Control (n = 1226) n (%)	cOR (95% CI)†	aOR (95% CI)‡
Cigarette smoking				
Never	278(45.4)	673(54.9)	Ref.	Ref.
Ever	335(54.6)	553(45.1)	1.47(1.21–1.78)	1.93(1.51–2.48)
Former	58(9.5)	93(7.6)	1.51(1.06–2.16)	1.95(1.32–2.87)
Current	277(45.2)	460(37.5)	1.46(1.19–1.79)	1.93(1.49–2.49)
Age of starting smoking (years)				
Never	278(45.4)	673(54.9)	Ref.	Ref.
< 25	209(34.1)	325(26.5)	1.56(1.25–1.95)	2.09(1.59–2.75)
≥ 25	126(20.5)	228(18.6)	1.34(1.03–1.73)	1.72(1.28–2.33)
Smoking years				
Never	278(45.4)	673(54.9)	Ref.	Ref.
< 30	135(22.0)	256(20.9)	1.28(0.99–1.64)	1.62(1.19–2.19)
≥ 30	200(32.6)	297(24.2)	1.63(1.30–2.05)	2.23(1.68–2.97)
Cigarettes per day				
Never	278(45.4)	673(54.9)	Ref.	Ref.
< 19	107(17.5)	204(16.6)	1.27(0.97–1.67)	1.67(1.22–2.29)
≥ 19	228(37.2)	349(28.5)	1.58(1.27–1.97)	2.08(1.59–2.72)
Cumulative pack-years				
Never	278(45.4)	673(54.9)	Ref.	Ref.
< 29	164(26.8)	299(24.4)	1.33(1.05–1.68)	1.73(1.30–2.31)
≥ 29	171(27.9)	254(20.7)	1.63(1.28–2.07)	2.18(1.63–2.91)

†cOR: crude odds ratio; ‡aOR: adjusted odds ratio, adjusting for age, gender and alcohol drinking history

TABLE 3 STRATIFIED ANALYSIS ON THE ASSOCIATION BETWEEN CIGARETTE SMOKING AND TUBERCULOSIS BY SELECTED FACTORS

Stratified variables	Smoking	Case (n = 613) n (%)	Control (n = 1226) n (%)	aOR (95% CI)†
Gender				
Men	Never	125(27.3)	366(40.0)	Ref.

	Ever	333(72.7)	550(60.0)	1.93(1.50–2.48)
Women	Never	153(98.7)	307(99.0)	Ref.
	Ever	2(1.3)	3(1.0)	2.06(0.30–14.28)
Age (years)				
< 56	Never	148(54.8)	310(56.9)	Ref.
	Ever	122(45.2)	235(43.1)	1.28(0.87–1.89)
≥ 56	Never	130(37.9)	363(53.3)	Ref.
	Ever	213(62.1)	318(46.7)	2.56(1.84–3.56)
Education (years)				
< 6	Never	142(46.0)	385(57.0)	Ref.
	Ever	167(54.0)	290(43.0)	2.23(1.56–3.17)
≥ 6	Never	136(44.7)	288(52.3)	Ref.
	Ever	168(55.3)	263(47.7)	1.68(1.18–2.38)
Alcohol drinking				
Never	Never	255(56.7)	560(66.7)	Ref.
	Ever	195(43.3)	279(33.3)	1.78(1.33–2.38)
Ever	Never	23(14.1)	113(29.2)	Ref.
	Ever	140(85.9)	274(70.8)	2.45(1.48–4.06)

†aOR: adjusted odds ratio, adjusting for age, gender and alcohol drinking history where appropriate

Figures

FIGURE - 1 AGE-ADJUSTED ODDS RATIOS FOR TUBERCULOSIS ARE PRESENTED FOR CATEGORIES OF NUMBER OF CIGARETTES SMOKED

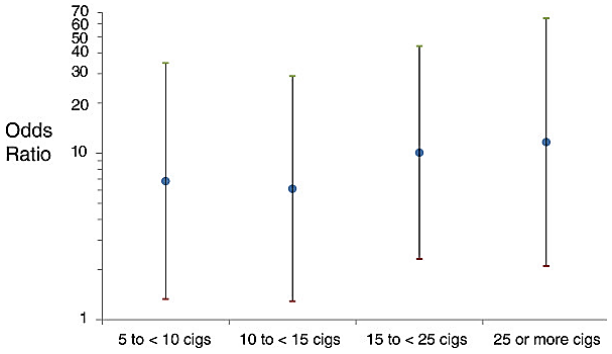

FIGURE - 2 FITTED ODDS RATIOS OF TB DERIVED FROM AGE-ADJUSTED LOGISTIC REGRESSION MODEL WITH A LOG TRANSFORMED VARIABLE FOR PACK YEARS AMONG DAILY SMOKERS