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ORIGINAL ARTICLE

Association between cigarette smoking and pulmonary tuberculosis in men: A case-control study in Mazandaran, Iran

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ABSTRACT

Background: The annual risk of tuberculosis (TB) in Iran is about 0.5% with annual incidence rate of 23/100000 (16322 cases). Different factors have been postulated as TB predisposing factors. Several studies have linked smoking with pulmonary tuberculosis as the TB incidence in their adult men was 2.4 times higher than women. In Iran, however, this ratio is equal and somewhere the ratio in women is greater. We decided to carry out a case control study in order to evaluate the effect of cigarette smoking on pulmonary TB.

Patients and methods: A case-control study was achieved in health care centers of Mazandaran province (affiliated to Mazandaran University of Medical Sciences). Participants were men aged 15 years and older who were enrolled in health care centers with the diagnosis of active pulmonary tuberculosis. One hundred men (aged 15-85 years) with bacteriological TB (smear or culture positive) were selected as cases and 300 age-matched men without TB were selected randomly as controls. Information on smoking status, quality of tobacco smoked and duration of cigarette smoking and also the age at which smoking was first commenced were collected by a questionnaire.

Results: Smokers were 2.1 times more likely to develop pulmonary TB (OR=2.10, 95% confidence interval (CI):1.33-2.33, p<0.04). The age adjusted odds ratio was 1.804 (95%CI:1.66-2.5, p<0.05). Quantity of cigarette smoking and duration of smoking had positive association with pulmonary TB. The ORs for mild (1-10 cigarette/day), moderate (11-20/day) and heavy (>20/day) smoking were 1.68, 2.46, and 2.56, respectively (p<0.05). The ORs for duration of smoking with <10 years, 11-20 years and >20 years of smoking were 0.91, 2.48, and 2.9, respectively (p< 0.001).

Conclusion: We conclude that smoking may increase the risk of pulmonary TB in men. Further studies should be conducted to investigate this association and to establish whether smoking reduction strategies contribute to tuberculosis control.

Keywords: *Pulmonary tuberculosis, Cigarette smoking, Predisposing factor.*
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INTRODUCTION

Worldwide, approximately 1.3 billion people currently smoke cigarettes or other products (almost one billion men, 250 million women) (1). With the decline in tobacco use in many industrialized countries, the geography of smoking continues to shift from the developed to the developing world, which harbors the majority of cases of TB (2). As a result, the growing number of person who smokes will have contact with tuberculosis. The annual tobacco-attributable mortality was about 1.7 million in 1985, 3.0

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million in 1990 and has been projected to rise to 8.4 million by 2020 (2).

In 1992, when it was estimated that approximately a third of the world's population (1.7 billion people) was latently infected with *Mycobacterium tuberculosis*, the World Health Organization (WHO) declared tuberculosis a 'global emergency (3). The emergence of HIV related tuberculosis and multidrug-resistant tuberculosis have brought into focus the importance of socio-economic conditions, including poverty, crowding, homelessness, malnutrition, immigration and alcohol abuse. Although it is a major health hazard, smoking has unfortunately received social acceptance worldwide. This harmful socio-economic factor is less thought as a contributor to the morbidity and mortality of tuberculosis, and this prompted us to review its influence or association with tuberculosis, a disease that is pandemic.

The likelihood of active disease developing varies with the intensity and duration of exposure to infection sources. Besides these two important factors, there are some other risk factors including: malnutrition, alcoholism, socioeconomic level, underlying disease such as renal failure, AIDS, which all favor progression of infection with tuberculosis to active disease (4). Both tuberculosis and tobacco represent a substantial hazard to worldwide wellbeing.

In our country we have governmental organization as well as several non-governmental organizations taking care of tuberculosis control, meanwhile, different governmental organizations as well as several non-governmental organizations are active in controlling and reducing smoking hazard. The emphasis has been on independent effects on health and on independent strategies to control. However, there are few studies that indicated tobacco could be a risk factor for tuberculosis and its subsequent death especially in young people with a dose-response relationship with the number of cigarettes consumed daily (5-10).

It has been noted that in some countries the differences in TB disease rates by sex begin to be seen in age cohorts when young men start smoking (11). A recent article presents evidence for the hypothesis that the differences in TB rates among men and women are influenced by the sex differences in tobacco use, in terms of prevalence of use, shorter duration of use or lower frequency of use (12).

Although smoking is a man habit in Iran (13), there isn't any sex difference among TB cases and the prevalence of pulmonary TB is usually equal in both sexes (13). However, there are some important differences, (especially in sex distribution) (13) between epidemiology of tuberculosis in Iran and other countries (3-6,14-16). In fact, the main hypothesis of those studies was the 2-4 folds of TB prevalence among men group.

The present study was designed to evaluate the effect of cigarette smoking on pulmonary tuberculosis in a group of Iranian men in Mazandaran in order to address a question that how could tobacco be a risk factor for pulmonary tuberculosis while women smoke significantly less than men while disease rate is equal in both sexes.

PATIENTS and METHODS

The cross sectional study was carried out from December 2004 to December 2006 in two cities of Mazandaran province, northern Iran. Each year, 100 to 120 new cases of pulmonary TB with equal sex distribution are enrolled in this region. Since the prevalence of tobacco smoking is much less among Iranian females (22.2% in men versus 2.1% in women) (12), females were excluded. Therefore, men aged 15 years and older with the diagnosis of active TB were included to minimize the confounding effect of other risk factors. Subjects with clinical symptoms suggestive of tuberculosis

were further investigated to confirm the diagnosis and begin the treatment.

A current diagnosis of pulmonary tuberculosis was verified on a recent chest radiography interpreted by a radiologist as well as two positive sputum smears for acid-fast bacilli and/or one positive sputum culture for *Mycobacterium tuberculosis* interpreted by the reference laboratory of Mazandaran province.

Written informed consent was obtained from all cases and controls.

For each case, 3 aged-matched (±3 years) healthy men were randomly selected as control. Control subjects were examined by an infectious disease specialist and chest radiography was ordered to rule out pulmonary diseases. In order to overcome confounding factors, we selected the control group from the same socioeconomic and geographical area.

Immunosuppressed patients (those who received ≥10mg/d prednisone for more than 2 weeks, or other immunosuppressive drugs), and those receiving treatment for tuberculosis were excluded from the study. Those with human immunodeficiency virus infection were also excluded if the T helper lymphocytes CD4 positive count was less than 350/mm.

Tobacco smoke exposure was measured according to one or more of the following: type of exposure (active and/or passive), current and past exposure, duration and frequency of exposure and age at initial exposure. Self- or family-reported exposure was considered an acceptable measure (9). Smoking habit was categorized; mild with 1–10, moderate 11–20, and heavy >20 cigarettes smoking per day.

The interview was carried out by two experienced health workers from the Unit of the Tuberculosis Control Centre in Mazandaran University of Medical Sciences. Interviewers were blinded to the disease status.

Initial data collected at baseline and included demographic information, age, living area, educational level, job, insurance status, disease related data, cigarette smoking status, alcohol consumption state, hookah smoking, working in asbestos factory or living near it, and working in a coal factory.

Data were analyzed using SPSS (version 12.0, SPSS Inc, Chicago, USA). The significance of proportional differences between nominal variables was determined using the chi-square test or Fisher's exact test, and differences between continuous variables were determined using student t-test. A two-tailed $p<0.05$ was used to define statistical significance. Odds ratios were estimated as the measure of effect. The age distribution of cases and controls was found to be significantly different so the crude odds ratio was adjusted for age by the Mantel-Hanszel technique. The dose-response relationship was studied by the test for linear trend using Epi Info 6 software.

RESULTS

Totally, 43% were smokers and 57% were nonsmokers. The mean age at which smoking was first commenced was 26 years while mean duration of cigarette smoking was 19.8±13.0 years. Smokers used 15±9 cigarettes per day, however, hookah was used 2±1 times per day by 25% of subjects. Meanwhile, 25% were passive smokers at least during the recent year.

Mean age of subjects was 46±7 (17-85) years. Family history of pulmonary TB was reported by 9% of subjects.

Of 100 cases, 57 were smokers, while of 300 controls, 116 were revealed to have smoking habit (estimated odds ratio (unadjusted) 2.10, 95% confidence interval (CI):1.33-2.33, $p<0.04$). Adjusted OR for some of the studied parameters are shown in table 1.

The mean of pack/year in case and control group was 11.6 and 5.6, respectively (OR=1.03, 95%CI: 1.01-1.04). Study population were assigned in 5 different subgroups on the basis of

their age, then age-adjusted odds ratio was calculated (OR=1.804, 95%CI: 1.66-2.5, p<0.05) (table 2).

Table 1. Adjusted odd's ratio (OR) and 95% confidence interval (CI) for the influence of presumed risk factors on pulmonary tuberculosis

	Adjusted OR	95%CI
Smoking(pack/year)	1.84	1.15 - 2.95
Living area (Urban or Rural)	0.91	0.52 - 1.56
Positive family history of TB	2.89	1.38 - 6.03
Hookah smoking	0.72	0.42 - 1.21
Living near asbestos factory	0.64	0.22 - 1.81

Table 2. Age adjusted crude odd's ratio*

Age group (year)		Case group	Control group	Odd's ratio
15-24	S†	2	12	0.44
	NS‡	9	24	
25-34	S	8	26	0.80
	NS	10	26	
35-44	S	14	26	2.42
	NS	8	36	
45-54	S	13	22	3.05
	NS	6	31	
≥55	S	20	30	4.47
	NS	10	67	

*Age adjusted crude odd's ratio:1.80 (95%CI:1.66-2.50, p<0.0001), mantel hanzsel estimate

† Smokers, ‡ Non-smokers

Table 3 represents the dose-response relationship between smoking and tuberculosis. Smokers were categorized as mild, moderate and heavy smokers on the basis of mean number of cigarette smoked per day. Odd's ratio was calculated for each group. The association was statistically significant (p<0.001).

To estimate the cumulative effect of smoking on the occurrence of pulmonary tuberculosis, smokers were classified on the basis of smoking duration into following three groups: <10 years, 11-20 years, and >20 years and the following odd's ratios were calculated 0.91, 2.48, and 2.90, respectively (p<0.001) (table 4).

Table 3. Dose-response relationship*

Smokers	Case group	Control group	Odd's ratio
Mild (1-10/day)	22	56	1.68
Moderate(11-20/day)	23	40	2.46
Heavy (>20/day)	12	20	2.56
Non-smokers	43	184	

* p<0.05

Table 4. Cumulative effect of smoking on occurrence of pulmonary tuberculosis*

Smoking duration (yrs)	Case group	Control group	Odd's ratio
<10	7	43	0.91
11-20	18	31	2.48
>20	32	42	2.42
Non-smokers	43	184	

* p<0.001

The age at which smoking was commenced, educational level, living area (urban or rural), house class, hookah smoking and its frequency, alcohol consumption, living near or work in asbestos factory, and passive smoking failed to show statistically significant association (table 1).

Positive family history of TB was noted in 17% of cases and 6% of controls (OR=2.89, 95%CI: 1.38-6.03, p<0.002) (table 1).

DISCUSSION

Although smoking is a man habit in Iran, almost always the prevalence of pulmonary TB is equal in both sexes (13). Several studies, beginning in 1956, have linked smoking with tuberculosis (reviewed by Maurya et al (14). However, in more recent studies, the possible confounding of socioeconomic factors with both smoking and tuberculosis has only occasionally been examined (15,16). Yu et al used binomial regression to propose that heavy smoking was associated with pulmonary

tuberculosis, although both were associated with male sex and increasing age (8). Although recent studies revealed that cigarette smoking could be a reasonable risk factor for pulmonary tuberculosis, most of them mentioned higher tuberculosis prevalence in men when compared with women (3-6).

Since cigarette smoking is more or less a man habit in most of the studied regions it could be a reasonable factor to justify this difference. Nevertheless, none of these studies accounted for socioeconomic status and its possible confounding effect on smoking and tuberculosis. On the other hand, there are some differences, especially in sex distribution, between the epidemiology of tuberculosis in Iran and other societies (3-6,13,15-16).

The odd's ratio (2.10) and the age adjusted odds ratio (1.80) obtained in our setting were statistically significant. Although, male and female prevalence of pulmonary tuberculosis is more or less the same in Iran (13), this study showed the significant effect of cigarette smoking on pulmonary TB. This association could be realistic or may be caused by chance or bias. It has already been shown that the probability of obtaining this odd's ratio by chance is very low ($p<0.001$).

Since all studied cases were positive bacillary pulmonary TB subjects, selection bias could be ruled out. Similarly, controls were selected randomly from healthy subjects residing in cases' neighborhood to eliminate as much as confounding factors. Therefore, the observer's bias is the only possible pitfall, however, since interviewers were unaware to the study hypothesis their confounding effect could be ignorable.

The estimated OR in patients younger than 35 years old was less than 1 (table 1). As a point of statistical view, it could be interpreted as the protective effect of smoking in patients aged less than 35, however, it could not be true and we think this effect is secondary to the low number of cases in this age group. We need to conduct further studies with larger sample size to address this controversy.

Prior investigators have mostly measured active smoking of cigarettes. There are few available studies looking at the impact of exposure to passive smoking. Investigating the effects of passive smoking is fraught with difficulty in clearly identifying non-exposed individuals. Present study failed to show significant relation between passive smoking and pulmonary TB. Altet et al defined a high risk of disease progression to active disease in children who encounter with passive smoking in their houses (17). Absence of this association in our study could be in part explained by underreporting of passive smoking and also ignorance of such an important factor.

In addition to the number of cigarette smoked per day (dose-response relation), duration of smoking had strong influence on active disease, however, the age at which smoking was first commenced was not significantly associated with pulmonary TB (OR=0.98, 95%CI:0.96-1).

Prospective evaluation of 42655 individuals registered with the Elderly Health Service in Hong Kong noted that pulmonary tuberculosis was more common in current smokers than in ex-smokers, and both were more common than in never smokers (18). There was also a dose-response relationship in current smokers for the development of pulmonary tuberculosis. This cohort involved elderly person in the community, and the majority of TB cases could arise from reactivation rather than secondary to smoking effect on TB reactivation.

Kolappan and Gopi proved this effect in their study (19). The positive dose-response relationship is one of the most important criteria for a causal association. With increase of cigarette use especially greater than 20 cigarettes per day, risk of active disease grows up. Alcaide et al conducted a case-control design and multiple logistic regression model for analysis of variables of interest, reported an odds ratio of 3.8 (95%CI:1.5-9.8) for active

smokers (11). They also found a dose-response relationship between the number of cigarettes smoked daily and active pulmonary tuberculosis.

During a survey among hospital employee in Shanghai, effect of smoking specially in heavy smokers on progression of pulmonary tuberculosis was proved (RR=2.17)(8). Seden Boon et al observed a positive relationship between pulmonary TB and pack-years, while smoking more than 15 pack-years having the highest risk (adjusted OR=1.90, 95%CI:1.28-2.81) (20).

Adelstein and Rimingston studied volunteers in a radiographic survey of the association between smoking and pulmonary tuberculosis (7). They reported disease rates of 0.42/1000 for male non-smokers and 2.09/1000 for current male smokers with a rate ratio of 1:5.

Existence of another case of tuberculosis among family members showed significant relation with pulmonary tuberculosis (OR=3.2). It could be the effect of exposure to common risk factors. However, there was no significant association between the educational level, job, living area, house owning condition, hookah smoking and living around or working in an asbestos factory and pulmonary tuberculosis.

In conclusion, the results of this study showed that smokers have greater risks for TB disease in men. There is a strong need to carry out similar studies in Iranian women with a special attention to the effect of passive exposure to cigarette smoking. Meanwhile, cohort studies are to be conducted in order to identifying transition from infection to disease in relation to active and passive exposure in both sex group and to establish whether smoking reduction strategies contribute to tuberculosis control. Then there is a clear case for closer partnering among organizations, health service providers and policy makers in addressing tuberculosis and tobacco.

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