Selected biological and behavioural risk factors associated with pulmonary tuberculosis

C. Kolappan, P. G. Gopi, R. Subramani, P. R. Narayanan

Tuberculosis Research Centre, Indian Council of Medical Research, Chennai, India

SUMMARY

OBJECTIVES: To measure the independent association of risk factors age, sex, smoking and alcoholism with pulmonary tuberculosis (TB) in terms of prevalence odds ratio (POR).

METHOD: A community-based cross-sectional survey was conducted from June 2001 to December 2003. A total of 93 945 individuals aged ⩾15 years selected from a random sample of villages in a district from South India were screened for pulmonary TB by chest symptoms and chest X-ray (MMR). Two sputum samples were collected (one spot and one early morning) from patients with chest symptoms and those with abnormal X-rays for examination by microscopy for acid-fast bacilli and by culture for *Mycobacterium tuberculosis*. Bacillary cases are bacteriologically positive cases diagnosed by either spu-

tum smear or culture examination. In addition, data on exposure to tobacco smoking and alcohol consumption were collected from the male population only. All females were considered non-smokers and non-alcoholics.

RESULTS: A total of 429 bacteriologically positive cases were detected during the survey. The adjusted PORs (with 95%CI) for age, sex, smoking and alcoholism were 3.3 (2.7–4.1), 2.5 (1.9–3.3), 2.1 (1.7–2.7) and 1.5 (1.2–2.0), respectively.

CONCLUSION: Risk factors such as age, sex, smoking and alcoholism are independently associated with pulmonary TB. Risk factors age and sex show a stronger association than smoking and alcoholism.

KEY WORDS: pulmonary TB; risk factors; alcoholism; smoking; prevalence odds ratio

LARGE-SCALE community-based tuberculosis (TB) surveys in South India have clearly shown that prevalence and incidence of pulmonary TB is considerably higher among males than females.[1–3] The baseline survey of the Chingleput bacille Calmette-Guérin (BCG) trial conducted earlier in the present study area reported infection rates of 54% and 46% among males and females, respectively.[1] These data suggest that men and women have equal opportunities for getting TB infection in the community. Progression to disease occurs in about 10% of infected individuals during their lifetime, although reactivation of latent infection occurs many years after primary infection.

Many risk factors such as age, sex, malnutrition, diabetes, human immunodeficiency virus (HIV) infection (biological factors), tobacco smoking, alcoholism (behavioural factors), poverty, overcrowding and poor housing (socio-economic factors) are known to be associated with the development of pulmonary TB. Some of these risk factors mostly contribute to risk of infection rather than to progression to disease, while others are mostly responsible for progression from infection to disease.

A series of TB prevalence surveys are being conducted in Tiruvallur District, Tamil Nadu, to assess the

impact of the DOTS strategy on the epidemiology of TB. In these surveys, apart from demographic data, such as age and sex, additional information on tobacco smoking and alcohol consumption are being collected from the male population. The data are analysed to study the association of biological risk factors and behavioural risk factors with pulmonary TB, using the prevalence odds ratio (POR) as effect measure. The findings are presented and discussed in this paper.

METHOD

A community-based cross-sectional survey was conducted from June 2001 to December 2003. A total of 93 945 individuals aged ⩾15 years selected from a random sample of villages in a district in South India were screened for pulmonary TB on the basis of chest symptoms and chest X-ray (mass-miniature radiography). Two samples of sputum were collected (one spot and one early morning) from individuals with chest symptoms and/or abnormal X-rays for examination by microscopy for acid-fast bacilli and by culture for *Mycobacterium tuberculosis*. Bacillary cases are bacteriologically positive cases diagnosed by sputum smear or culture examination.

Correspondence to: P R Narayanan, Tuberculosis Research Centre, Mayor V R Ramanathan Road, Chetput, Chennai 600 031, India. Tel: (+91) 44 2836 2525. Fax: (+91) 44 2836 2528. e-mail: prnarayanan@trcchennai.in

By tradition and native culture, the women in the study area neither smoke nor consume alcohol. The prevalence of tobacco smoking among women in India is very low (0.4%),[4] as is the prevalence of alcoholism among females in South India (<1%).[5] The collection of data on exposure to tobacco smoking and alcohol consumption was therefore restricted to the male population. All females were considered non-smokers and non-alcoholics. All male participants were interviewed at the time of X-ray examination, using a questionnaire to collect information such as exposure to these factors, age at which the behaviour started, duration of the habit, average consumption per day (number of cigarettes/beedies or quantity of alcohol in ml), and entered in a pre-coded format.

The ethics committee of the Tuberculosis Research Centre approved this study and informed consent was obtained from all the participants in the study.

Data analysis

Data on the prevalence of exposure and disease for the present study were obtained by comparing disease occurrence between exposed and non-exposed groups. Persons aged ≥45 years were considered an exposed group and compared with persons aged 15–44 years (non-exposed group). Males were considered an exposed group and females a non-exposed group.

The POR was used as the effect measure. The POR was calculated by measuring the ratio of the prevalence odds of the exposed and non-exposed groups for each risk factor. The crude POR was obtained by univariate analysis and the adjusted POR for pulmonary TB was obtained by the multivariate logistic regression analysis of the risk factors, i.e., age, sex, smoking and alcoholism, using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA).

The attributable proportions for all four risk factors were estimated as follows:

$$\text{Attributable proportion} = \frac{P(\text{POR} - 1)}{P(\text{POR} - 1) + 1}$$

where *P* is the prevalence of exposure and POR is the adjusted prevalence odds ratio.

RESULTS

Table 1 shows the age and sex distribution of the study population. Of the total population of 93 945 subjects, 45.5% were male and 54.5% were female. About 70% of the study sample belonged to the younger age group 15–44 years.

Table 2 shows the prevalence of disease for all the strata for the risk factors studied. The prevalence rates for the younger and older age groups were 2.5 and 9.3 per 1000 population, respectively. Males had higher prevalence (7.8/1000) than females (1.9/1000), and the highest prevalence (17.3/1000) was observed among smokers who were also alcoholics.

Table 1 Age and sex distribution of the study population

Age group, years	Males n (%)	Females n (%)	Total n (%)
15–44	29 863 (31.8)	35 452 (37.7)	65 315 (69.5)
≥45	12 873 (13.7)	15 757 (16.8)	28 630 (30.5)
Total	42 736 (45.5)	51 209 (54.5)	93 945 (100)

Table 2 Prevalence of disease by risk factor

Risk factors	Cases n	Population n	Prevalence/1000 (95%CI)
Age, years			
15–44	162	65 315	2.5 (2.1–2.9)
≥45	267	28 630	9.3 (8.3–10.5)
Sex			
Male	332	42 736	7.8 (7.0–8.6)
Female	97	51 209	1.9 (1.6–2.3)
Smoking and alcoholism			
Non-smoker, non-alcoholic	209	77 050	2.7 (2.3–3.1)
Smoker	81	6 885	11.8 (9.5–14.6)
Alcoholic	21	3 187	6.6 (4.3–10.1)
Smoker, alcoholic	118	6 823	17.3 (14.5–20.7)

CI = confidence interval.

Table 3 shows the crude and adjusted POR for the following risk factors: age, sex, smoking and alcoholism. Persons aged ≥45 years had a 3.3 times higher risk than persons aged 15–44 years. Males had a 2.5 times higher risk than females. Smokers had a 2.1 times higher risk than non-smokers. Alcoholics had a 1.5 times higher risk than non-alcoholics.

Table 4 shows the attributable proportions for the risk factors. Among the total prevalent cases, 41%

Table 3 Crude and adjusted PORs (95%CI) of pulmonary TB for selected risk factors

Risk factors	TB cases	Non cases	Crude POR	Adjusted POR (95%CI)
Age, years				
15–44	162	65 153	1.0	1.0
≥45	267	28 363	3.8	3.3 (2.7–4.1)
Sex				
Female	97	51 112	1.0	1.0
Male	332	42 404	4.1	2.5 (1.9–3.3)
Smoking				
Non-smoker	230	80 007	1.0	1.0
Smoker	199	13 509	5.1	2.1 (1.7–2.7)
Alcoholism				
Non-alcoholic	290	83 645	1.0	1.0
Alcoholic	139	9 871	4.0	1.5 (1.2–2.0)

POR = prevalence odds ratio; CI = confidence interval; TB = tuberculosis.

Table 4 Attributable proportions for the risk factors

Risk factors	Prevalence of exposure	Adjusted POR	Attributable proportions, %
Age ≥45 years	0.30	3.3	41
Male sex	0.46	2.5	41
Smoking	0.15	2.1	14
Alcoholism	0.11	1.5	5

POR = prevalence odds ratio.

can be attributed to ageing, 41% to male sex, 14% to smoking and 5% to alcoholism.

DISCUSSION

TB infection in the general population in this study area was 50%:[1] 80% of males aged $\geqslant$25 years and 70% of females aged $\geqslant$35 years were infected.[1] Only about 10% of infected individuals progress to disease in their lifetime.

The lower prevalence rate among the younger age group indicates that HIV prevalence is too low to influence TB occurrence in this vulnerable younger age group. Females have significantly lower prevalence than males. This difference cannot be attributed to gender bias because the coverage for screening examinations in this active case detection survey was uniformly high for both males and females. Smoking and alcoholism seem to interact to give a higher prevalence than the prevalence for either smoking or alcohol independently among males.

As the POR estimates the incidence rate ratio with fewer assumptions than the prevalence ratio, POR is preferred as the measure of association between risk factors and pulmonary TB.[6]

Persons aged $\geqslant$45 years had an adjusted POR of 4, signifying a strong association of ageing with TB. All the earlier surveys from this study area have consistently reported higher prevalence rates among older age groups.[1–3] Yu et al. reported a relative risk of 2.7 for persons aged $\geqslant$50 years as compared to persons aged $\leqslant$30 years.[7] Ageing is a major risk factor for any disease. The effects of ageing have been attributed to a decline in numerous macrophage functions which figure prominently in host defence in pulmonary TB.[8]

According to the present study, males have an adjusted POR of 2.6 as compared to females. Yu et al. reported a relative risk of 1.9 for males.[7] Buskin et al. also reported a relative risk of 1.9 for males.[9] Gustafson et al. reported an odds ratio (OR) of 2.6 for males.[10]

The immune response is different in the two sexes, indicating sexual dimorphism. Evidence suggests that at physiological levels, oestrogen is beneficial to the immune system,[11] whereas the male sex hormone, testosterone, is immunosuppressive.[12] This sexual dimorphism in immune response may explain the higher risk among males of developing TB.

According to the present study, smokers have a 2.1 times higher risk of developing TB than non-smokers after controlling for the effects of other factors. Yu et al. reported a relative risk of 3.6 for heavy smokers.[7] Buskin et al. also reported a relative risk of 2.6 for smokers of $\geqslant$20 years' duration than non-smokers.[9] Kolappan et al. reported an OR of 2.2 for smokers.[13] Tocque et al. reported that individuals who had smoked for at least 30 years had an OR of 2.3.[14] Tekkel et al. reported an OR of 4.6 for current smokers.[15] Leung et al. reported ORs of 2.4 and 2.2 for smokers aged 16–

64 years and $\geqslant$65 years, respectively.[16] Alcaide et al. reported that active smokers, passive smokers and active plus passive smokers had ORs of 3.6, 2.7 and 5.7, respectively.[17]

Recent work on the physiological effects of nicotine, the major toxic compound in tobacco smoke, showed that nicotine turns off the production of tumour necrosis factor-alpha by lung macrophages, thereby rendering smokers more susceptible to the progression of latent infection to active disease.[18]

Our study shows that alcoholics have a 1.5 times higher risk of developing TB than non-alcoholics, after controlling for the effects of age, sex and smoking on alcoholism. Alcohol has a significant inhibitory effect on cell-mediated immunity.[19] Buskin et al. reported a relative risk of 2.0 for heavy alcohol consumers.[9]

TB control programmes worldwide attempt to control TB essentially by trying to cure patients using short-course chemotherapy to reduce the caseload in the community (prevalence), which in turn should lead to a reduction in the occurrence of new infections in the community. This reduction in disease prevalence is achieved more by reduction in the duration of disease than by the reduction in incidence. The endogenous reactivation of latent infection following deficiency in the host immunity contributes more to the incidence of pulmonary TB than exogenous reinfection.[20] The current incidence is due to the progression of infection acquired in the past, which is not influenced by short-course chemotherapy among prevalent cases.

For the effective control of adult pulmonary TB in a community, disease incidence has to be reduced by arresting the progression from infection to disease. This can be achieved by strengthening specific immunity against TB by effective vaccine. Global research in TB control should focus on developing an effective vaccine against *M. tuberculosis*. Smokers and alcoholics should also be counselled effectively to wean them away from these unhealthy behaviours and minimise the risk of progression to disease.

A limitation of the present study is that it assessed only selected risk factors. The confounding effects of the remaining potential confounders were not controlled when assessing the effects of the selected risk factors. This might have resulted in an overestimation or underestimation of their true effects.

CONCLUSION

Risk factors such as age, male sex, smoking and alcoholism are all independently associated with pulmonary TB. These factors may play a role in the progression of TB infection to disease. Risk factors age and sex have stronger associations than smoking and alcoholism. Effective TB control can be achieved only when this progression from infection to disease is arrested. The DOTS strategy mainly controls the spread of the

infection and duration of disease, but it does not affect the current rate of incidence. Future research should focus on arresting the progress of infection to disease through appropriate interventions such as effective vaccine and counselling of smokers and alcoholics to wean them away from these dangerous habits.

References

1 Tuberculosis Research Centre. Tuberculosis prevention trial. Indian J Med Res 1980; 12 (Suppl): 1–74.
2 Tuberculosis Research Centre. Trends in the prevalence and incidence of tuberculosis in South India. Int J Tuberc Lung Dis 2001; 5: 142–157.
3 Gopi P G, Subramani R, Radhakrishna S, et al. A baseline survey of the prevalence of tuberculosis in a community in South India at the commencement of a DOTS programme. Int J Tuberc Lung Dis 2003; 7: 1154–1162.
4 Prakash G. Survey of socio-demographic characteristics of tobacco use among 99 598 individuals in Bombay, India using hand-held computers. Tob Control 1996; 5: 14–20.
5 http://web.archive.org/web/20041215113058/www.medivision india.com/addiction/introduction.phtml.
6 Pearce N. Effect measures in prevalence studies. Environ Health Perspect 2004; 112: 1047–1050.
7 Yu G-P, Hsieh C-C, Peng J. Risk factors associated with the prevalence of pulmonary tuberculosis among sanitary workers in Shanghai. Tubercle 1988; 69: 105–112.
8 Meyer K C. Aging. Proc Am Thorac Soc 2005; 2: 433–439.
9 Buskin S E, Gale J L, Weiss N S, et al. Tuberculosis risk factors in adults in King County, Washington, 1988 through 1990. Am J Public Health 1994; 84: 1750–1756.
10 Gustafson P, Gomes V F, Vieria C S, et al. Tuberculosis in Bissau: incidence and risk factors in an urban community in sub-Saharan Africa. Int J Epidemiol 2004; 33: 163–172.
11 Markovic L. Interaction involving the thymus and the hypothalamus-pituitary axis, immunomodulation by hormones. Srp Arh Celok Lek 2004; 132: 187–193. [Abstract—article in Serbian]
12 Cutolo M, Sulli A, Capellino S, et al. Sex hormones influence on the immune system: basic and clinical aspects in autoimmunity. Lupus 2004; 13: 635–638.
13 Kolappan C, Gopi P G. Tobacco smoking and pulmonary tuberculosis. Thorax 2002; 57: 964–966.
14 Tocque K, Bellis M A, Beeching N J, et al. A case control study of life style risk factors associated with tuberculosis in Liverpool, North West England. Eur Respir J 2001; 18: 959–964.
15 Tekkel M, Rahu M, Loit H M, et al. Risk factors for pulmonary tuberculosis in Estonia. Int J Tuberc Lung Dis 2002; 6: 887–894.
16 Leung C C, Yew W W, Chan C K, et al. Smoking and tuberculosis in Hong Kong. Int J Tuberc Lung Dis 2003; 7: 980–986.
17 Acaide J, Alter M N, Plans P, et al. Cigarette smoking as a risk factor for tuberculosis in young adults: a case control study. Tubercle and Lung Dis 1996; 77: 112–116.
18 Sopori M L, Kozak W, Savage S M, et al. Nicotine-induced modulation of T-cell function. Implications for inflammation and infection. Adv Exp Med Bio 1998; 437: 279–289.
19 Jacobson J M. Alcoholism and tuberculosis. Alcohol Health Res 1992; 16: 39–45.
20 Narayanan S. Molecular epidemiology of tuberculosis. Indian J Med Res 2004; 120: 233–247.

RÉSUMÉ

OBJECTIFS : Mesurer l'association indépendante de facteurs de risque tels que l'âge, le sexe, le tabagisme et l'alcoolisme avec la tuberculose (TB) pulmonaire en termes d'odds ratios de prévalence (POR).

MÉTHODE : Enquête transversale basée sur la collectivité de juin 2001 à décembre 2003. Au total, 93 945 individus âgés de ⩾15 ans ont été sélectionnés à partir d'un échantillon aléatoire de villages dans un district d'Inde du sud et ont fait l'objet d'un dépistage pour la TB pulmonaire sur base des symptômes thoraciques et des clichés thoraciques (MMR). Deux échantillons de crachats ont été recueillis (un échantillon sur place et le deuxième le lendemain matin) chez les sujets ayant des symptômes thoraciques et des anomalies des clichés thoraciques en vue d'un examen microscopique à la recherche de bacilles acido-résistants et d'une culture pour *Mycobacterium tuberculosis*. Les cas bacillaires sont des cas dont l'examen bactériologique est positif, soit par examen des frottis soit à la culture des échantillons de crachats. De plus, on a recueilli les données sur l'exposition à la fumée de tabac et sur la consommation d'alcool uniquement dans la population de sexe masculin. Toutes les femmes ont été considérées comme non-fumeuses et non-alcooliques.

RÉSULTATS : L'enquête a détecté au total 429 cas à examen bactériologique positif. Les odds ratios ajustés de prévalence et les IC95% pour les facteurs de risque ont été de 3,3 (2,7–4,1) pour l'âge, 2,5 (1,9–3,3) pour le sexe, 2,1 (1,7–2,7) pour le tabagisme et 1,5 (1,2–2,0) pour l'alcoolisme.

CONCLUSION : Il existe une association indépendante des facteurs de risque, âge, sexe, tabagisme et alcoolisme avec la TB pulmonaire. L'association est plus forte pour l'âge et le sexe que pour le tabagisme et l'alcoolisme.

RESUMEN

OBJETIVOS : Evaluar los factores de riesgo edad, sexo, tabaquismo y alcoholismo asociados en forma independiente con la tuberculosis (TB) pulmonar en términos de razón de posibilidades de la prevalencia.

MÉTODO : Se llevó a cabo un estudio transversal de base comunitaria entre junio de 2001 y diciembre de 2003. Se practicó una detección sistemática de la TB pulmonar, mediante la presencia de síntomas respiratorios y una fotofluorografia, a un total de 93 945 individuos de edad ⩾15 años, escogidos de una muestra aleatoria de aldeas en un distrito del sur de la India. En las personas con síntomas respiratorios y radiografías anormales, se recogieron dos muestras de esputo (una instantánea y otra matinal) para examen microscópico en busca de bacilos acidorresistentes y cultivo de *Mycobacterium tuberculosis*. Los casos bacilíferos son casos con confirmación bacteriológica, diagnosticados por la baciloscopia o el cultivo del esputo. Se recogieron además datos sobre el tabaquismo y el consumo de alcohol de la población masculina exclusivamente. Se consideró que todas las mujeres no eran fumadoras ni consumían alcohol.

RESULTADOS : En el estudio, se detectaron 429 casos con examen bacteriológico positivo. La razón de posibilidades ajustada de la prevalencia para los factores de riesgo fue 3,3 para la edad (IC95% 2,7–4,1) ; 2,5 para el sexo (IC95% 1,9–3,3) ; 2,1 para el tabaquismo (IC95% 1,7–2,7) ; y 1,5 para el alcoholismo (IC95% 1,2–2,0).

CONCLUSIÓN : Los factores de riesgo edad, sexo, tabaquismo y alcoholismo se asociaron en forma independiente con la presencia de TB pulmonar. La edad y el sexo presentaron una mayor correlación con la TB que el tabaquismo y el alcoholismo.