SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2010; 27; 19-26

Is tobacco smoking protective for sarcoidosis? A case-control study from North India

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Abstract. *Background:* While tobacco smoking is commonly believed to be negatively associated with the occurrence of sarcoidosis, the relationship of environmental tobacco smoke (ETS) exposure with sarcoidosis is largely un-explored. We studied the impact of active smoking and ETS exposure on disease severity in newly diagnosed cases of sarcoidosis from India. *Methods:* Data on demographic variables, smoking habits and exposure to environmental tobacco smoke (ETS) among non-smoker sarcoidosis patients was collected prospectively. Presence of smoking and ETS exposure were compared among cases and controls. Among the sarcoidosis patients, clinical manifestations, radiology, spirometry and histopathological grading of lung biopsy were compared between the smokers vs. non-smokers and ETS exposed vs. not-exposed. *Results:* We studied 98 newly diagnosed cases of sarcoidosis and 196 age, sex and religion- matched healthy volunteers. The study group comprised of 62 (63%) men and 36 (37%) women. The prevalence of smoking was similar in cases and controls (12.2% vs. 15.3%, p = 0.48). Among the never smoker patients with sarcoidosis, 20 (23%) reported ETS exposure vis-a-vis 57 (34%) in the matched controls. A conditional logistic regression analyses showed insignificant negative association with active smoking (OR 0.75; 95% CI, 0.35-1.56) or ETS exposure (OR 0.58; 95% CI, 0.32-1.06) after adjusting for age, gender, religion, and education. There were no differences in the clinical manifestations, radiological staging, spirometry and histopathological grading of lung biopsy in any of the group comparisons studied. *Conclusion:* Smoking or ETS exposure may not have significant negative association with sarcoidosis. Also, tobacco smoke might not have any effect on the clinical behavior or disease severity in sarcoidosis. The belief that smoking is protective for sarcoidosis is not substantiated in this study and appears to be misfounded. *(Sarcoidosis Vasc Diffuse Lung Dis 2010; 27: 19-26)*

Key words: Sarcoidosis, smoking, tobacco smoking, ETS exposure, passive smoking, disease severity, histological grading

Received: 20 May 2009
Accepted after Revision: 10 March 2010
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Introduction

Tobacco smoking and exposure to environmental tobacco smoke (ETS) are major health hazards. Smoking is the major causative factor for lung cancer and chronic obstructive airway disease. Cigarette smoking is also related to the development of various interstitial lung diseases such as desquamative interstitial pneumonia, respiratory bronchiolitis associat-

ed interstitial lung disease, pulmonary Langerhan's cell histiocytosis and idiopathic pulmonary fibrosis.(1) However, this major life-threatening risk factor has been reported to be negatively associated in epidemiological studies with some diseases such as extrinsic allergic alveolitis,(2) ulcerative colitis(3) and sarcoidosis (1, 4-11).

In 1961, Comstock et al, in their study of possible risk factors for sarcoidosis, observed that patients with sarcoidosis smoked less than matched controls. This inverse association was however noted only among white subjects (12). Similar findings were subsequently reported in several studies with a reduction in prevalence of smokers among sarcoidosis patients varying between 21 to 79% (1, 6-10, 13, 14), including the recent large multi-centric ACCESS study which demonstrated lesser odds for ever smoking among patients (OR 0.65, CI 0.51-0.82) in a multivariate logistic regression model (11). Some studies have also studied cellular and other immune responses in sarcoidosis, and showed that fewer alveolar macrophages were recovered by lavage from smokers with sarcoidosis than from normal subjects with a similar smoking history. This supports the possibility that smokers, particularly those with a lower accumulation of alveolar macrophages in the lower respiratory tract, may be less prone to develop sarcoidosis (1, 7). This was further supported by Blanchet and coworkers, who demonstrated in animal models and cell lines that concomitant exposure to nicotine with agents known to induce granulomatous inflammation, had a protective effect (15). However, simultaneously studies have reported insignificant association or even increased prevalence of smoking among sarcoidosis patients (2, 4). Exposure to environmental tobacco smoke (ETS) has also been identified as a risk factor for lung cancer and chronic obstructive pulmonary disease among non-smokers and practically known to possess all the adverse health effects of active smoking (16).

Clear data on effects of active smoking and ETS exposure in sarcoidosis, is however lacking from developing countries including India. Herein, we studied the association of active smoking and ETS exposure with pulmonary sarcoidosis, and their effects on the clinical behavior and disease severity.

Material and methods

This was a case-control study in which the subjects were sequentially recruited, with two age, gender and religion-matched controls enrolled for each patient of sarcoidosis studied. For sample size estimation, we assumed probability of exposure (tobacco smoking) in controls as 16% based on our earlier description of smoking habits in this region (17). Accordingly, the minimum sample size necessary to detect a true odds ratio of 0.3 with 80% power at 5% significance, using two matched controls for each patient and assuming a case-control correlation of 0.3, was calculated as 100 patients and 200 controls (18). The study was approved by the Institute Ethics Committee and a written informed consent was taken from all cases and controls.

All consecutive newly diagnosed cases of pulmonary sarcoidosis were included in the study. Diagnosis of sarcoidosis was established on the basis of following criteria: (i) compatible clinical picture, including consistent radiology; ii) presence of non-caseating granuloma in lung biopsy sample; (iii) absence of mycobacterial or fungal infection in BAL fluid cultures; and, (iv) absence of exposure to beryllium. Patients who had received any glucocorticoid treatment in the three months before initial evaluation, or had any concomitant cardiopulmonary disease were excluded. For every case of sarcoidosis two healthy volunteers were studied as controls. The controls were healthy volunteers defined as asymptomatic individuals without any diagnosed illness and were normal on detailed physical examination. The controls were recruited from the healthy attendants accompanying the patients attending the outpatient departments of our institute. Hospital employees and direct family members of the study patients were not recruited as controls. Details of clinical history, physical examination and laboratory findings were recorded for each case. Detailed smoking history and exposure to ETS among non-smokers were recorded according to a pre-designed questionnaire for all the subjects.

Spirometry was performed using a dry rolling seal spirometer (Spiroflow, PK Morgan Ltd, Kent UK) using the standard ATS guidelines. The results were interpreted based on the observed values expressed as the percentage of the predictive obtained from the normal values drawn in our laboratory for the North Indian population (19).

Active smokers were defined as subjects who were currently smoking or stopped less than 12 months prior to study with smoking history of > 1 cigarette/bidi per day for at least one year. *Ex-smokers* were defined as subjects who had successfully stopped smoking and were abstinent for > 12 months prior to study and had consumed > 1 cigarette/bidi per day for at least one year prior to quitting. *Ever smokers* were either of the active or ex-smokers. All other smoking categories not fitting into active or ex smokers were classified as *Never smoker. Passive smokers* were defined as non-smoker subjects who live or spend time during work with a person who smokes > 1 cigarette per day. *ETS exposure index* at home and work was calculated as product of hours exposed to ETS per day *multiplied by* number of smokers from whom exposed *multiplied by* number of years of exposure. *Cumulative ETS exposure* was defined as the sum of ETS exposure index at home and ETS exposure index at work place.

The disease severity at the time of initial evaluation was determined by radiological stage, spirometric values and histological grading. The radiological staging of the disease was made according to Scadding's classification (Stage 0: normal chest radiograph; Stage I: bilateral hilar lymphadenopathy (BHL); Stage II: BHL with pulmonary infiltrates; Stage III: pulmonary infiltrates without BHL; Stage IV: Diffuse fibrosis with upward retraction of hilar areas, honey-combing, bullae formation and pleural involvement) (20). The abnormalities in pulmonary function test were categorized into normal, obstructive and restrictive pattern, and were further classified into mild, moderate or severe based on the percent predicted FEV_1 or FVC respectively (mild: 60-80%; moderate: 40-59%; and, severe <40%) (21).

The histopathological grading was done by the pathologist (KJ), who was blinded to clinical and other details. The histological classification used has been described earlier by us and others and known to correlate with functional status in sarcoidosis (22, 23). It essentially grades three specific pathological changes, namely granuloma density, interstitial pneumonitis and fibrosis into minimal, moderate and severe categories as follows: (A) Granulomas: (i) Minimal – few scattered granulomas; (ii) Moderate – more than few but occupying less than two-thirds of the area; (iii) Severe – more than two-thirds of the area; (B) Interstitial pneumonitis (IP): (i) minimal – less than 1/3 of the area; (ii) moderate – lesions between 1/3 and 2/3 of the area; (iii) severe – more than 2/3 of the area; and, (C) Fibrosis: (i) Absent – no fibrosis; (ii) Focal – focal and scattered; (iii) Diffuse – diffuse and extensive. The overall pathological changes are graded as: (i) mild – no fibrosis with minimal granulomas and IP; (ii) severe – diffuse fibrosis with extensive granulomas and IP; and, (iii) moderate – by exclusion of mild and severe.

Statistical analysis: Data was analyzed using the statistical package SPSS for MS-Windows (version 10, SPSS Inc., Chicago, IL). Prevalence of smoking or ETS exposure and their impact on sarcoidosis was compared between cases and controls. Patients of sarcoidosis were compared with regards to the clinical behavior and severity of the disease between a) ever-smokers vs. never-smokers and b) never-smokers exposed to ETS vs. not exposed to ETS. Data are presented in a descriptive fashion. Differences between categorical and continuous variables were compared using chi-square test and Mann-Whitney U test respectively. A conditional logistic regression analysis was performed using age, sex and religion matched controls for odds of having sarcoidosis in active smokers, passive smokers, and persons never exposed to tobacco smoke.

Results

We initially enrolled 100 cases and 200 age, gender and religion matched controls, however histopathological grading of two cases could not be done due to some technical limitations and finally we included 98 cases and 196 controls. The mean (SD) age of cases and controls was 42.6 (10.2) and 42.9 (10.5) years respectively. Nearly two-thirds of the study population was men (Table 1). Sarcoidosis patients were more educated as compared to controls, mean (SD) years of formal education being 13.4 (5.1) and 11.6 (5.5) respectively (p=0.02).

Twelve (12.2.%) out of 98 patients reported current or ever-smoking compared to 15.3% smokers among controls, this difference was not significant (p=0.48). Similarly there was no significant difference in the prevalence of current-smoking or exposure to the ETS among non-smokers in the two groups (Table 1). All the ever-smokers among sar-

Table 1. Prevalence of active smoking or environmental tobacco smoke (ETS) exposure among sarcoidosis patients and healthy controls

	Sarcoidosis (n=98)	Control (n=196)	p value
Demographic characteristics			
Age (years), mean (SD)	42.6 (10.2)	42.9 (10.5)	0.81
Male sex, n (%)	62 (64.6%)	124 (64.6%)	1.0
Education, mean (SD)	13.4 (5.1)	11.6 (5.5)	0.02
Religion, n (%)			0.99
Hindu	64 (65.3%)	130 (66.3%)	
Muslim	1 (1%)	2 (1%)	
Sikh	33 (33.7%)	64 (32.7%)	
Active Smoking			
History of ever-smoking, n (%)	12 (12.2)	30 (15.3)	0.48
Male sex among ever-smokers, n (%)	12 (100%)	29 (96.7)	0.71
Current smoking, n (%)	6 (6.1)	19 (9.7)	0.3
Frequency of cigarettes per day, mean (SD)	4.83 (3.97)	8.27 (8.14)	0.17
Passive Smoking			
ETS exposure, n/N (%)	20/86 (23)	57/166(34)	0.11
Male sex among ETS exposed, n (%)	11 (55%)	36 (63.1%)	0.53
ETS exposure index (in nonsmokers only), mean (95% confidence intervals), person hour years	535.3 (177.4-893.1)	715.8 (484.3-947.4)	0.41

coidosis patients were men (p=0.02) and were likely to be younger (mean age 31 years, p<0.0001) compared to the non-smokers (irrespective of ETS exposure). There was no difference in the clinical behavior of disease with respect to symptoms, signs, extra pulmonary manifestations and endobronchial abnormalities among the patients with history of smoking or ETS exposure compared to non-smoker, non-ETS exposed patients (Table 2).

There were no significant differences among the three groups in any of the severity indices studied. Most patients had a normal spirometry or restrictive defect on spirometry. On radiological staging, 41% smokers had a stage 2 disease compared to 35% in other two groups however the difference was insignificant (Table 3). Histopathological grading of severity showed an insignificant trend towards a lesser proportion of patients having a severe overall pathology among smokers compared to non-smoker, non-ETS exposed patients, however the difference was not significant.

There were no evident 'protective' effects of ETS exposure seen (Figure 1). Conditional logistic regression model using age, sex and religion-matched control performed to detect odds of having sarcoidosis among various group of patients did not show any significant results (Table 4).

Discussion

Sarcoidosis is a multisystem disorder of unknown cause (s) (24). In the past it was considered that sarcoidosis is rare in India, as much because of the lack of awareness and diagnostic facilities as also the presence of other, more commonly recognized granulomatous diseases (tuberculosis, leprosy, fungal infection) that obscure sarcoidosis recognition (25). But it is now recognized more frequently all over the country and in fact, we diagnose 8-10 new cases of sarcoidosis in our clinics every month (26). Despite the advances in the modern medicine, the cause/risk factors for sarcoidosis remain unknown, even though the causal link to tuberculosis is often discussed (27). It is generally believed that tobacco smoking is in some way protective for sarcoidosis since sarcoidosis is seen less frequently in smokers. We in this study could not demonstrate any 'protective effect' of tobacco smoking (active or passive) in sarcoidosis.

Although tobacco smoking, both active and passive, is a major risk factor for obstructive lung diseases, its role in interstitial lung diseases particularly sarcoidosis is less clearly defined. Similar findings were subsequently reported in several studies with a reduction in prevalence of smokers among sarcoidosis patients varying between 21 to 79% (1, 5-7, 9-

Table 2. Clinical behavior of disease with respect to symptoms, signs, extra pulmonary manifestations and endobronchial abnormalities among the patients of sarcoidosis with history of smoking or ETS exposure compared to non-smoker, non-ETS exposed patients

Variables	Non-smoker (n=86)		Smoker (n=12)	p value
	Non-ETS exposed (n=66)	ETS exposed (n=20)		
Age (years), mean (SD)	44.92 (9.99)	41.65 (9.42)	31.67 (3.70)	0.0001
Male sex	39 (59.1%)	11 (55.0%)	12 (100.0%)	0.02
Education, mean (SD)	13.14 (5.59)	14.00 (4.36)	14.17(3.27)	0.7
Symptoms				
Symptomatic patients	64 (97.0%)	20 (100.0%)	12 (100.0%)	0.61
Duration, mean (SD)	6.78 (8.50)	6.38 (7.09)	3.17 (2.40)	0.58
Cough	36 (54.5%)	13 (65.0%)	6 (50.0%)	0.64
Dyspnea	37 (56.1%)	13 (65.0%)	6 (50.0%)	0.68
Extrapulmonary symptoms	40 (60.6%)	12 (60%)	11 (91.7%)	0.11
Anorexia	13 (19.7%)	4 (20%)	1 (8.3%)	0.58
Weight loss	16 (24.24%)	5 (25%)	2 (16.7%)	0.77
Arthralgia	10 (15.1%)	5 (25%)	0	0.16
Fever	12 (18.18%)	3 (15%)	1 (8.3%)	0.64
Dry eyes	1 (1.5%)	0	0	0.79
Red eye	2 (3%)	1 (5%)	0	0.73
Skin rash	1 (1.5%)	1 (5%)	0	0.54
Signs				
Normal chest	60 (90.9%)	16 (80%)	9 (75%)	0.2
Crackles	9 (13.6%)	2 (10%)	0	0.73
Wheeze	1 (1.5%)	0	1 (8.3%)	0.27
Uveitis	4 (6.1%)	2 (10%)	0	0.52
Erythema nodosum	6 (9.1%)	2 (10%)	1 (8.3%)	0.97
Hepatomegaly	6 (9.1%)	3 (15%)	5 (41.7%)	0.07
Splenomegaly	1 (1.5%)	2 (10%)	0	0.15
Facial nerve palsy	2 (3%)	1 (5%)	0	0.73
Parotidomegaly	4 (6.1%)	1 (5%)	0	0.68
Abnormal findings on fiberoptic bronchoscopy	12 (18.2%)	5 (25%)	4 (33.3%)	0.74

All results are expressed as number (percentage) unless otherwise stated

11). However simultaneously studies have reported insignificant association (4) or even increased prevalence of smoking among sarcoidosis patients (2, 8). The observed differences could be due to genuine differences in the populations where these studies were carried out, as was pointed out originally by Comstock who could demonstrate the protective effect only among whites (12). Many of the studies that reported a protective effect had a very high prevalence of smoking among controls, up to 75% among men (6), whereas the population prevalence of smoking in our population is quite low and we had calculated the sample size taking the population prevalence that has been earlier reported by us (17). Demirkok et al have also observed that the effects of nonsmoking could be more pronounced in females than in males (28). Since none of the women in this study group were smokers, we cannot comment on this observation, however no such effect was demonstrable in non-smoking women who were exposed to ETS. Although the reported odds for smokers among sarcoidosis patients in literature have varied between 0.2 to 0.8 as cited above and we had taken odds of 0.3 in our sample size calculations, the recent ACCESS study had shown OR of 0.6, and going by which our study might have been underpowered.

Not only we failed to demonstrate any significant protection in occurrence of sarcoidosis, we also could not find any differences in the clinical or histopathological severity of disease among sarcoidosis patients who were smokers or were exposed to ETS compared to the non-smoker-non-ETS exposed patients. The clinical severity of disease is poorly defined in sarcoidosis. The general estimates of clinical severity are radiological stage, spirometry, extra-pulmonary manifestations and severe organ dysfunctions (29). None of the parameters that we studied had shown any significant difference in this

Table 3. Spirometry and radiological staging among the patients of sarcoidosis with history of smoking or ETS exposure compared to non-smoker, non-ETS exposed patients

Variables	Non-smoker (n=86)		Smoker (n=12)	p value
	Non-ETS exposed (n=66)	ETS exposed (n=20)		
FVC %, mean (SD)	85.31 (19.24)	92.09 (15.65)	96.42 (10.91)	0.11
FEV1 %, mean (SD)	87.08 (21.56)	92.88 (18.32)	94.82 (11.22)	0.36
FEV1/FVC, mean (SD)	79.74 (7.44)	78.40 (10.63)	80.82 (2.96)	0.26
Normal	47 (71.2%)	14 (70.0%)	11 (91.7%)	0.11
Restrictive defect	14 (21.2%)	2 (10.0%)	1 (8.3%)	0.52
Obstructive defect	5 (7.6%)	4 (20.0%)	0	0.13
Chest radiograph staging				
Stage 1	38 (57.6%)	13 (65.0%)	6 (50.0%)	0.7
Stage 2	23 (34.8%)	7 (35.0%)	5 (41.7%)	0.9
Stage 3	5 (7.6%)	0	1(8.3%)	0.44
CT findings				
CT chest study	50 (75.8%)	15 (75%)	10 (83.3%)	0.84
Hilar lymph nodes	43 (86%)	15 (100%)	6 (60%)	0.36
Mediastinal lymph nodes	39 (78%)	14 (93.3%)	7 (70%)	0.66
Perilymphatic nodules	28 (56%)	4 (26.7%)	4 (10%)	0.03
Pleural effusion	3 (6%)	0	1 (10%)	0.49

All results are expressed as number (percentage) unless otherwise stated

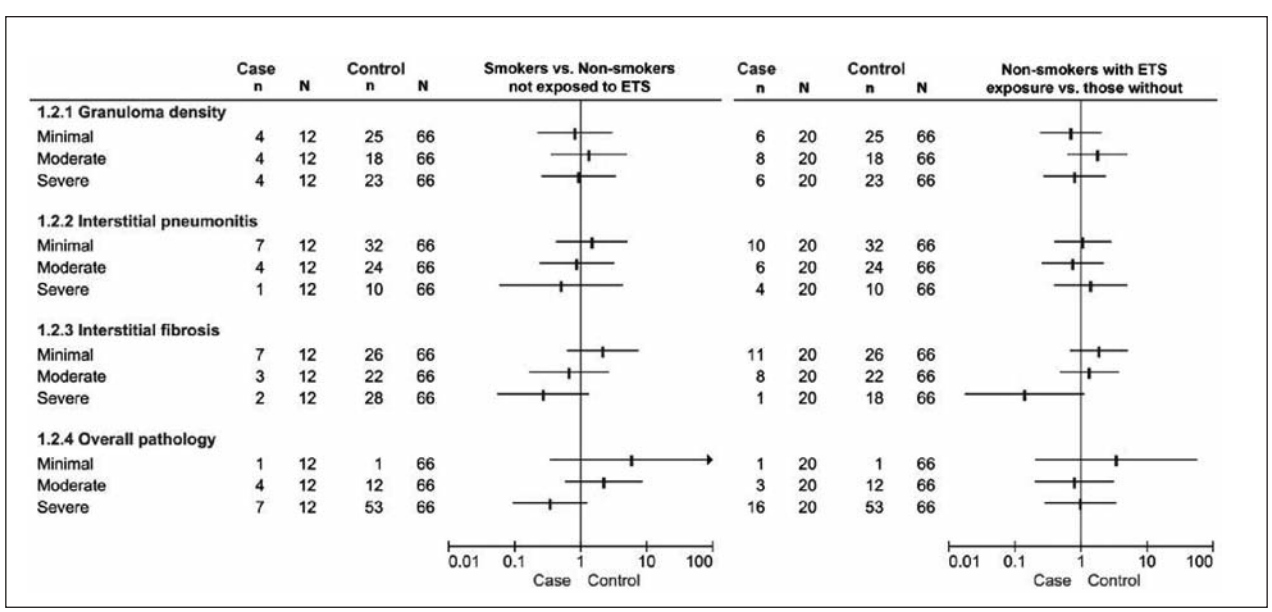

Fig. 1. Comparison of histological grading among the patients of sarcoidosis with history of ever-smoking or ETS exposure compared to non-smoker, non-ETS exposed patients (The units represent the odds ratio and the horizontal lines the 95% confidence intervals)

study. Similar observations have also been reported earlier. Some studies, which reported a reduced prevalence of smoking among sarcoidosis patients failed to show any effect on the extent, course and outcome of the disease (7, 9). If at all, there are reports to suggest that patients with sarcoidosis who smoke are functionally worse than their non-smoking counterparts, having a higher degree of obstruc-

Table 4. Conditional logistic regression model using age, sex and religion matched controls for odds of having sarcoidosis in active smokers, passive smokers, and persons never exposed to tobacco smoke

Model	Sarcoidosis N; n (%) positive	Controls N; n (%) positive	Adjusted odds ratio (95% confidence intervals)	P value
Ever smokers vs. Non-smokers	98; 12 (12.2)	198; 30 (15.3)	0.75 (0.35-1.56)	0.45
Ever smokers vs. Non-smokers without ETS exposure	78; 12 (15.4)	139; 30 (21.6)	0.73 (0.49-1.1)	0.73
ETS vs. never ETS in non-smokers	86; 20 (23.3)	166; 57 (34.3)	0.58 (0.32-1.06)	0.08

tive ventilatory defects and higher values of residual volume (RV) and total lung capacity (TLC) (9, 30). Cigarette smoking is also associated with a significant increase in the serum angiotensin converting enzyme activity (SACE) and pulmonary gallium-67 uptake (7). It is possible that these differences could have been obscured by a small number of smokers/ETS exposed patients in this study, coupled with the fact that all our patients were newly diagnosed and relatively young patients and thus may not have had time to develop progression of disease or to develop any impact of smoking on disease course.

We also studied the histopathological severity based on a previously described grading system. Histopathological scoring and grading systems have been used as marker of disease severity and have been shown to correlate well with lung functions and oxygen uptake (22, 23, 31). Several mechanisms have been proposed for the possible 'protective' effects of tobacco smoking in sarcoidosis (7, 15, 32-35). Recently some investigators in an experimental mouse cell line model, using the antigens to induce granulomatous inflammation, have demonstrated that simultaneous nicotine exposure reduces the bronchoalveolar lavage cellular response, including the total lavage white blood cell and lymphocyte cell count, and the extent of lung inflammation on biopsy (15). Whatever these proposed mechanism may be, results of our study show that they fail to translate into any significant differences in the histopathological severity as measured by granuloma density, interstitial pneumonitis or extent of fibrosis.

To the best of our knowledge the effects of ETS exposure on sarcoidosis have not been reported so far. We could not detect any effects of ETS exposure on sarcoidosis. ETS exposure has been variously described as passive smoking, 'second-line smoke' or involuntary smoking. In the past little attention, beyond its nuisance effect, was paid to the consequences of passive smoking. Exhaustive report on health consequences of involuntary smoking by US Surgeon General highlights the increased risks of several diseases similar to those seen among smokers in persons exposed to ETS at home or at work place (16). In a developing country like India, environmental conditions like overcrowding make the health effects of ETS more pronounced and many adverse health effects of ETS exposure have been reported (36). In general odds/relative risks for all the deleterious effects of ETS exposure are lower than those with active smoking. As a corollary any protective effect of ETS in sarcoidosis would also be lesser, which our study might not be powered to detect.

Conclusions

To conclude, the result of this study suggests that smoking or ETS exposure may not have significant negative association with sarcoidosis. Also, tobacco smoke might not have any effect on the clinical behavior or disease severity in sarcoidosis. The belief that smoking is protective for sarcoidosis is not substantiated in this study and could be misfounded.

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