Letter to the Editor

Risk of Active Pulmonary Tuberculosis among Patients with Coal Workers' Pneumoconiosis: A Case-control Study in China*

JIN Yan[1,2], FAN Jing Guang[3], PANG Jing[4], WEN Ke[1], ZHANG Pei Ying[4], WANG Huan Qiang[1,#], and LI Tao[1,#]

The aim of this study was to estimate the association between occupational, environmental, behavioral risk factors, and active pulmonary tuberculosis (PTB) among coal workers' pneumoconiosis (CWP) patients. A matched case-control study was conducted in 86 CWP patients with active PTB and 86 CWP controls without TB. A standardized questionnaire was used for risk factors assessment. Conditioned logistic regression analysis was used to identify associations between the risk factors and active PTB among CWP patients. The results showed that the stage of CWP, poor workplace ventilation, family history of TB, and exposure to TB were independent risk factors for active PTB in patients with CWP with which recommendations for improving work environments, and for case finding activities in patients with CWP could be made.

Key words: Pulmonary tuberculosis; Coal workers' pneumoconiosis; Risk; Case-control study

Pneumoconiosis is a well-known occupational fibrotic lung disease with no specific treatment currently available. China has one of the highest rates of pneumoconiosis in the world. It accounts for over 85% of all reported occupational diseases in the country. Coal workers' pneumoconiosis (CWP) is believed to be the commonest type, accounting for approximately 60% of the total number of new cases of pneumoconiosis[1]. The association between pneumoconiosis and pulmonary tuberculosis (PTB) has been well established in previous studies. Epidemiological studies and case reports have verified that workers exposed to silica dust have increased morbidity and mortality from PTB[2]. Therefore, the prevention and control of the risk of contracting PTB in patients with CWP, thereby preventing *M. tuberculosis* infection and the development of PTB, is crucial. To further evaluate the occupational, environmental, and behavioral risk factors influencing the development of PTB in patients with CWP, we performed a matched case-control study.

The present matched case-control study was conducted at the Hunan Institute for Tuberculosis Control (HITC) and the Hunan Prevention and Treatment Center for Occupational Diseases (HPTCOD), between April and November, 2017. HITC, an 800-bed specialized TB hospital, and HPTCOD, a 520-bed specialized occupational diseases hospital, are located at Changsha, Hunan Province, China. HITC has more than 1,000 TB hospitalizations and HPTCOD has 2,000 occupational disease hospitalizations each year. The study protocol was approved by the Ethical Clearance Committee of the National Institute of Occupational Health and Poison Control of the Chinese Center for Disease Control and Prevention. All study participants provided written consent.

A sample size of 86 case-control pairs was estimated to be sufficient to detect a significant association between active TB and risk factors among CWP patients. Cases were CWP patients with active PTB (CWP-TB) diagnosed using the 'WS 288-2017'[3] diagnostic criteria for PTB, while controls were CWP patients without TB (CWP only), reconfirmed based on the 'GBZ 70-2015'[4] diagnostic criteria for pneumoconiosis using a good quality chest X-ray. For each case, non-TB CWP patients,

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1. National Institute of Occupational Health and Poison Control, Chinese Center for Disease Control and Prevention, Beijing 100050, China; 2. Department of Infectious Disease, Taizhou Center for Disease Control and Prevention, Taizhou 318000, Zhejiang, China; 3. Research Center for Occupational Safety and Health, State Administration of Work Safety, Beijing 102308, China; 4. Department of Orthopedics and Chinese-Western Medicine, Hunan Institute for Tuberculosis Control, Changsha 410013, Hunan, China

matched in ethnicity, sex and age group, were selected as controls. Cases were recruited from all wards within HITC and controls were selected from HPTCOD. The selection of controls was started after completion of the selection of cases to allow for age, sex, and ethnicity differences (Table S1 available in the www.besjournal.com).

Information on a wide range of host characteristics, and occupational, environmental, and behavioral factors relevant to active TB was collected from the cases and controls. The host information collected included body mass index (BMI), highest educational level, marital status, family size, and place of residence. Occupational factors included the stage of CWP, years of work, dust exposure period, age at which exposure to dust was initiated, and length of dust exposed employment. Environmental and behavioral factors obtained included workplace ventilation, accommodation, smoking, and alcohol consumption, among others.

BMI was calculated as the ratio between body weight in kilograms and squared body height in meters (kg/m^2). Stages of CWP were confirmed based on the 'GBZ 70-2015' diagnostic criteria for pneumoconiosis by performing a good quality chest X-ray. Smoking index was defined as the product of the number of cigarettes smoked per day and years of smoking. Smoking frequently was defined as a person who smoked more than one cigarette per day for more than 6 months, whereas, smoking occasionally was defined as a person who smoked cigarettes more than four times every week but less than once per day. Drinking frequently was defined as a person who consumed alcohol more than one day a week, whereas occasional drinking was defined as a person who consumed alcohol less than one day a week. Frequent intake of fruit was defined as a person who ate fruit no less than two days a week, occasional intake of fruit as a person who ate fruit less than two days a week but no less than one day a month, and never eating fruit as a person who ate fruit less than one day a month. Doing physical exercise frequently was defined as a person who exercised for 30 or more minutes no less than three days a week, doing occasional physical exercise as a person who exercised for 30 or more minutes less than three days a week but no less than one day a month, and never doing physical exercise as a person exercised for 30 or more minutes less than one day a month. Each study participant was interviewed in person with a standardized questionnaire.

The questionnaire data was entered into the Epi Data v3.1 program (Epi Data Association, Odense, Denmark) and was analyzed using Epi-Info version 7.2.2.2 (CDC, Atlanta, GA, USA). Analysis was done using the index case and control pairs to assess the effect of risk factors. Odds ratios (*OR*s) and their 95% confidence intervals (*CI*s) were estimated using conditional logistic regression, with active TB as the outcome. Univariable analyses were performed to examine the effect of each variable of interest on the risk of active TB. A multivariable model was then constructed, including variables that showed a significant statistical effect by univariable analyses ($P < 0.05$). Finally, a combined host, occupational, environmental, and behavioral multivariable model was constructed. The adjusted *OR*s and their 95% *CI*s were calculated.

For the study, 86 cases (CWP-TB) and matched controls (CWP only) were recruited from the HITC and HPTCOD. They were all males of Han ethnicity. Of the 86 cases, 44 (51.2%) were diagnosed by clinical examination, chest radiographs, and their responses to treatment, whereas 42 (48.9%) showed a positive smear or culture for PTB. The mean age in the CWP-TB and CWP only groups was 57.3 ± 8.9, and 56.2 ± 9.2 years, respectively, while the mean BMI was 21.7 ± 2.6, and 22.4 ± 3.0, respectively. There was no significant difference between the CWP-TB and CWP only groups in terms of age ($P = 0.410$), BMI ($P = 0.076$), highest education level ($P = 0.635$), and marital status ($P = 0.755$), Implying no significant association. Only one participant had been vaccinated with the bacillus Calmette-Guerin (BCG) vaccine, therefore this study did not analyze its protective effect. Furthermore, all participates tested negative for HIV.

Table 1 shows the assessment of host characteristics, occupational, environmental, and behavioral risk factors for active PTB disease among CWP patients. Using univariate analysis, the occupational risk factors identified for active PTB were the stage of CWP, the age at which exposure to dust was initiated, and the length of dust exposed employment. Using the subgroup stage I CWP as a comparison, the *OR* was elevated for stage II (*OR*: 8.19; 95% *CI*: 2.36-28.38), and stage III (*OR*: 2.21; 95% *CI*: 0.69-7.10). Using the subgroup age at first dust exposure (< 18 years) as a comparison, the *OR* was elevated for the 18-29 years age group (*OR*: 1.91; 95% *CI*: 0.71-5.13), and the ≥ 30 years age group (*OR*: 3.99; 95% *CI*: 1.25-12.80). There was no significant association with the dust exposure period. The

environmental risk factor for active PTB was workplace ventilation. Using the subgroup good workplace ventilation as a comparison, the *OR*s were elevated for moderate workplace ventilation (*OR*: 16.28; 95% *CI:* 2.16-122.56), and poor workplace ventilation (*OR*: 62.18; 95% *CI*: 7.34-526.67). There was no significant association with accommodation and living space per person. The behavioral risk factors for active PTB were family history of TB and history of exposure to TB. The *OR*s were elevated for subjects with a family history of TB (*OR*: 4.00; 95% *CI*: 1.13-14.17), and with exposure to patients with active TB (*OR*: 11.50; 95% *CI*: 2.71-48.77). Of the 25 patients who had been exposed to patients with active TB, 16 (64%) patients had been exposed to a family member or friend infected with active TB, and nine (36%) patients had been exposed to co-workers infected with active TB (unpublished data). There was no significant association with smoking or drinking status, intake of fruit, physical exercise, or duration of sleep.

Table 2 shows the results of a multivariable model assessing the occupational, environmental, and behavioral risk factors that were significant in their respective individual analyses. The adjusted *OR*s of the risk factors for active PTB were calculated. Stage II of CWP (adjusted *OR*: 19.64; 95% *CI*: 1.02-378.13), moderate (adjusted *OR*: 12.88; 95% *CI*: 1.24-132.21) and poor workplace ventilation (adjusted *OR*: 45.08; 95% *CI*: 3.42-594.40), family history of TB (adjusted *OR*: 15.44; 95% *CI*: 1.03-233.98), and exposure to TB (adjusted *OR*: 14.94; 95% *CI*: 1.28-174.17) remained independent risk factors for active PTB. The age at initial exposure to dust, and the length of dust exposed employment lost significance in this combined model.

Table 1. Univariate Analysis of the Association of Risk Factors with TB-CWP and CWP Only Cases

Factors	Total No. of Pairs	TB-CWP Patients *n* (%)	CWP Only Patients *n* (%)	*OR* (95% *CI*)	*P*
Socio-demographic characteristics					
BMI (kg/m^2) *	83				
< 18.5 or ≥ 25		19 (23)	24 (29)	1	
18.5-24.9		64 (77)	62 (71)	1.33 (0.68-2.60)	0.400
Highest education level	86				
Primary school or lower		56 (65)	53 (62)	1	
Middle school		30 (35)	33 (38)	0.87 (0.48-1.58)	0.648
Marital status	86				
Married		80 (93)	81 (94)	1	
Divorced or Widowed		6 (7)	5 (6)	1.20 (0.37-3.93)	0.764
Family size	86				
< 4		39 (45)	31 (36)	1	
≥ 4		47 (55)	55 (64)	0.69 (0.38-1.26)	0.230
Place of residence	86				
City		8 (9.3)	4 (4.7)	1	
Countryside		78 (90.7)	82 (95.3)	0.43 (0.11-1.66)	0.220
Family history of TB	86				
No		73 (84.9)	82 (95.3)	1	
Yes		13 (15.1)	4 (4.7)	4.00 (1.13-14.17)	0.016
Exposure history to TB	86				
No		63 (73.3)	84 (97.7)	1	
Yes		23 (26.7)	2 (2.3)	11.50 (2.71-48.77)	< 0.001
Occupational factors					
Stages of CWP*	77				
I		5 (6.5)	17 (22.1)	1	
II		46 (59.7)	19 (24.7)	8.19 (2.36-28.38)	
III		26 (33.8)	41 (53.2)	2.21 (0.69-7.10)	< 0.001
Dust exposure period	86				
Before 1980		25 (29.0)	22 (25.6)	1	
1980-1990		33 (38.4)	36 (41.9)	0.60 (0.19-1.92)	
After 1990		28 (32.6)	28 (32.5)	0.66 (0.20-2.15)	0.682

Continued

Factors	Total No. of Pairs	TB-CWP Patients *n* (%)	CWP Only Patients *n* (%)	*OR* (95% *CI*)	*P*
Age at first dust exposure	86				
< 18		11 (12.8)	19 (22.1)	1	
18-29		49 (57.0)	52 (60.5)	1.91 (0.71-5.13)	
≥ 30		26 (30.2)	15 (17.4)	3.99 (1.25-12.80)	0.041
Duration of dust exposure (years)	86				
< 20		45 (52.9)	59 (68.6)	1	
≥ 20		40 (47.1)	27 (31.4)	2.08 (1.07-4.02)	0.025
Environmental factors					
Workplace ventilation	86				
Good		2 (2.3)	26 (30.2)	1	
Moderate		43 (50.0)	47 (54.7)	16.28 (2.16-122.56)	
Poor		41 (47.7)	13 (15.1)	62.18 (7.34-526.67)	< 0.001
Accommodation	86				
House		18 (20.9)	12 (14.0)	1	
Bungalow		68 (79.1)	74 (86.0)	0.57 (0.24-1.36)	0.198
Living space of per person*	75				
< 20		27 (36.0)	33 (44.0)	1	
20-40		39 (52.0)	29 (38.7)	1.69 (0.81-3.52)	
≥ 40		9 (12.0)	13 (17.3)	0.85 (0.30-2.37)	0.233
Behavioral factors					
Smoking	86				
Never		14 (16.3)	18 (20.9)	1	
Occasionally		2 (2.3)	6 (7.0)	0.46 (0.08-2.55)	
Frequently		70 (81.4)	62 (72.1)	1.55 (0.67-3.56)	0.204
Age when started smoking*	49				
< 18		13 (26.5)	15 (30.6)	1	
≥ 18		36 (73.5)	34 (69.4)	1.22 (0.51-2.95)	0.655
Smoking years*	52				
< 30		23 (44.2)	22 (42.3)	1	
≥ 30		29 (55.8)	30 (57.7)	0.90 (0.37-2.22)	0.819
Smoking index*	52				
< 400		14 (26.9)	9 (17.3)	1	
400-800		25 (48.1)	27 (51.9)	0.65 (0.25-1.69)	
≥ 800		13 (25.0)	16 (30.8)	0.56 (0.19-1.66)	0.528
Drinking	86				
Never		26 (30.2)	28 (32.6)	1	
Occasionally		15 (17.4)	22 (25.6)	0.75 (0.33-1.73)	
Frequently		45 (52.4)	36 (41.8)	1.55 (0.71-3.42)	0.230
Intake of fruits	86				
Never		30 (34.9)	30 (34.9)	1	
Occasionally		45 (52.3)	48 (55.8)	0.92 (0.48-1.78)	
Frequently		11 (12.8)	8 (9.3)	1.32 (0.50-3.49)	0.766
Physical exercise	86				
Never		59 (68.6)	54 (62.8)	1	
Occasionally		8 (9.3)	14 (16.3)	0.45 (0.15-1.32)	
Frequently		19 (22.1)	18 (20.9)	0.96 (0.44-2.09)	0.314
Average duration of sleep (hours)	86				
< 6		26 (30.2)	34 (39.5)	1	
6-8		26 (30.2)	21 (24.5)	1.56 (0.72-3.39)	
≥ 8		34 (39.6)	31 (36.0)	1.36 (0.66-2.79)	0.459

Note. *Sum not always equal to the total because of missing data.

The present study is one of the first to assess occupational, environmental, and behavioral risk factors of active PTB disease in patients with CWP. In this matched case-control study, we adjusted for several confounders like sex, age, and ethnicity, and identified key risk factors. The stage of CWP, poor workplace ventilation, family history of TB, and exposure to TB were significant risk factors for active PTB disease in patients with CWP.

The finding that the stage of CWP was an important risk factor for PTB disease is consistent with previous studies[5]. However, we found that only stage II of CWP was a significant risk factor, whereas stage III was not. This finding is different from previous cross-sectional studies in which the prevalence of TB was shown to increase significantly with progressive stages of CWP[5]. This may be explained, firstly, by the fact that the sample size of this case-control study was insufficient. Secondly, in this study, the clinical stages of cases were diagnosed by experts from the HITC but the clinical stages of controls were assessed by experts from the HPTCOD based on the 'GBZ 70-2015' diagnostic criteria for pneumoconiosis, consequently, bias might have been introduced. Thirdly, workers diagnosed as stage III might have been prevented from undertaking underground mining or tunneling work, and might have instead been given underground auxiliary work or surface work due to poor health. Therefore, the risk of infection and development of TB in stage III might be underestimated.

In our study, poor workplace ventilation conditions were associated with active PTB disease among CWP patients, in agreement with previous studies[6]. It is, therefore, recommended that measures to improve dust control in workplaces are implemented to reduce exposure to dust. Interestingly, the duration of dust exposure was associated with active PTB disease among CWP patients in the univariate analysis, however, multivariate logistic regression analysis indicated that it may not have had an independent effect on active PTB. Further studies should be carried out to verify this result.

Table 2. Multivariate Analysis of the Association of Factors with TB-CWP and CWP Only

Factors	Total No. of Pairs	TB-CWP Patients *n* (%)	CWP Only Patients *n* (%)	a*OR* (95% *CI*)	*P*
Stages of CWP*	77				
I		5 (6.5)	17 (22.1)	1	
II		46 (59.7)	19 (24.7)	19.64 (1.02-378.13)	0.048
III		26 (33.8)	41 (53.2)	5.38 (0.32-90.10)	0.242
Age at first dust exposure	86				
< 18		11 (12.8)	19 (22.1)	1	
18-29		49 (57.0)	52 (60.5)	5.85 (0.60-57.31)	0.129
≥ 30		26 (30.2)	15 (17.4)	9.22 (0.73-116.72)	0.086
Duration of dust Exposure (years)	86				
< 20		45 (52.9)	59 (68.6)	1	
≥ 20		40 (47.1)	27 (31.4)	1.23 (0.28-5.35)	0.783
Workplace ventilation	86				
Good		2 (2.3)	26 (30.2)	1	
Moderate		43 (50.0)	47 (54.7)	12.88 (1.24-133.21)	0.032
Poor		41 (47.7)	13 (15.1)	45.08 (3.42-594.40)	0.004
Family history of TB	86				
No		73 (84.9)	82 (95.3)	1	
Yes		13 (15.1)	4 (4.7)	15.55 (1.03-233.98)	0.047
Exposure history to TB	86				
No		63 (73.3)	84 (97.7)	1	
Yes		23 (26.7)	2 (2.3)	14.94 (1.28-174.17)	0.031

Note. *Sum does not always equal the total because of missing data.

This study confirmed that family history of TB is an important risk factor for active PTB disease among CWP patients, in agreement with previous studies on the general population[7]. This study also demonstrated that history of exposure to a known active PTB case is an important risk factor, consistent with previous findings[8]. Therefore, the management goal is to detect cases of active PTB early among CWP patients by establishing surveillance programs, particularly by monitoring those with family history of TB and those exposed to known active PTB cases. Early identification and treatment of active PTB among CWP patients not only limits the disease in that individual, but also assists in controlling its spread to co-workers and the community.

Our results did not confirm an association between smoking and active PTB among CWP patients. This may be because subjects generally cut down or quit smoking when diagnosed with CWP. However, as many previous studies showed that smoking is significantly associated with TB, and that there is a strong dose-response relationship between smoking and TB in various populations[9], it is necessary to implement smoking cessation programs among CWP patients.

Alcohol use has also been recognized as a risk factor for the development of active TB disease. A systematic review identified that there is a three-fold increased risk of active TB associated with the consumption of more than 40 g of alcohol per day, and/or having an alcohol use disorder[10]. However, our study did not confirm this association probably because we chose the frequency of drinking as an analysis variable which did not reflect the quantitative drinking status. Therefore, we were unable to verify the relationship between drinking and active PTB among CWP patients.

Our study has several potential limitations. Firstly, the sample size was limited. Secondly, the selection of participants based on hospitalized cases at two hospitals may have introduced Berkson's bias. Thirdly, the majority of participants over 60 years of age had retired; so, it was difficult to verify their potential occupational factors, which might have led to possible recall bias. Despite these limitations, the present study provides valuable insight into the influence of multiple factors on the development of active PTB among CWP patients.

This study verified that the stage of CWP, poor workplace ventilation, family history of TB, and history of exposure to TB were independent risk factors for active PTB in patients with CWP. We, therefore, recommend specific screening of individuals at high risk of developing active PTB among CWP cases. We also recommend improvements in the control of TB, implementation of measures to limit exposure to coal dust in work environments, and case-finding activities among patients with CWP.

#Correspondence should be addressed to Dr. LI Tao, Professor, Tel: 86-10-83132513, E-mail: litao@chinacdc.cn and Dr. WANG Huan Qiang, PhD, Professor, Tel: 86-10-83132825, E-mail: huan8885@126.com

Biographical note of the first author: JIN Yan, female, born in 1977, PhD candidate, majoring in infectious diseases control and prevention.

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Table S1. Characteristics of Patients with TB-CWP and CWP Only

Characteristics	TB-CWP Patients (*n* = 86)	CWP Only Patients (*n* = 86)	*P*
Age (mean ± SD)	57.3 ± 8.9	56.2 ± 9.2	0.410
BMI (kg/m^2) (mean ± SD)	21.7 ± 2.6	22.4 ± 3.0	0.076
Highest education level			
Primary school or lower	56	53	0.635
Middle school	30	33	
Marital status			
Married	80	81	0.755
Divorced or widowed	6	5	