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History of lung disease and risk of lung cancer in a population with high household fuel combustion exposures in rural China

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Abstract

History of chronic lung diseases and household coal use for heating and cooking are established risk factors of lung cancer; however, few studies have been able to explore these risk factors simultaneously. Xuanwei, China, has some of the highest rates of lung cancer in China and most residents experience substantial in-home coal smoke exposures. Using a population-based case-control study of 498 lung cancer cases and 498 age-matched controls, we evaluated the risk of lung cancer in relation to coal smoke exposure and history of chronic lung diseases, including chronic obstructive pulmonary disease (COPD), asthma, tuberculosis (TB), chronic bronchitis, and emphysema. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by conditional logistic regression adjusting for potential confounders. We observed an increased risk of lung cancer with history of any chronic lung disease among males (OR=14.2; 95%CI =4.3 to 46.9), females (OR=2.6; 95%CI =1.1 to 6.3), smokers (OR=12.7; 95%CI =3.5 to 45.8), and nonsmokers (OR=2.6; 95%CI =1.1 to 6.4). Specifically, TB (OR=83.7; 95%CI =11.0 to 634.7), COPD (OR=3.2; 95%CI =1.7 to 6.0), and emphysema and chronic bronchitis (OR=3.3; 95%CI =1.7 to 6.4) were associated with increased risks. These findings suggest that history of chronic lung diseases may also increase risk of lung cancer in populations with indoor coal smoke exposures.

Keywords

Chronic lung disease; lung cancer; never smoking; Xuanwei; China

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Conflicts of Interest None declared.

Introduction

Lung cancer is estimated to account for 1.4 million incident cancer cases per year and has been the most common cancer in the world for over two decades[1]. Lung cancer mortality accounts for 1.2 million cancer deaths per year, accounting for more deaths than any other cancer worldwide[1]. Since the seminal report by Doll and Hill in 1950, tobacco smoking has been recognized as an important risk factor for lung cancer[2]. It has been estimated that 85% of lung cancer in men and 47% of lung cancer in women is attributable to tobacco smoking[1]. A recent systematic review of the risk of lung cancer associated with history of lung diseases found elevated risks associated with chronic obstructive pulmonary disease (COPD), chronic bronchitis, and tuberculosis (TB)[3]. Further analyses found pneumonia and TB to be associated with lung cancer among never smokers[3].

Household solid fuel use for heating and cooking, particularly coal, is also an established environmental risk factor for lung cancer[4, 5]. This is an especially prominent risk factor throughout China[6, 7]. A retrospective cohort study of Xuanwei, China, residents, who used either bituminous (“smoky”) or anthracite (“smokeless”) coal for their household cooking and heating needs, provided some of the strongest epidemiological evidence linking lung cancer and household coal burning among both women and men[8, 9]. COPD was also positively and significantly associated with lung cancer risk in a cohort study in Xuanwei[10]. A previous case-control study in Xuanwei with limited sample size also found that coal use is associated with chronic bronchitis risk[11]. To follow-up on these previous findings, we evaluated the effects of COPD and additional nonmalignant respiratory diseases on lung cancer development in a larger population-based case-control study consisting of 498 cases and 498 controls conducted in Xuanwei.

Methods

This population-based case-control study of lung cancer in Xuanwei, China has been previously described[12]. Briefly, cases comprised all newly diagnosed lung cancer cases from November 1985 through February 1990 in four hospitals. Eligible participants included farmers 18-85 years of age, who resided in Xuanwei for more than one year prior to diagnosis. Eligible participants were restricted to farmers, as more than 90% of the total population in Xuanwei is farmers[13]. A total of 500 eligible lung cancer cases were enrolled. After exclusion of 2 cases with incorrect addresses, 498 cases were eligible for analysis. Cases were diagnosed based on sputum cytology, or pathological findings from needle biopsy, bronchofiberoscopy, or surgery (39%), or based on chest X-ray and clinical history (61%), which common in this region[8].

Control subjects were matched with case subjects on age and sex. Control subjects were selected from the general population of Xuanwei[12]. Controls were only eligible if they were farmers. Briefly, a three-stage, randomized recruitment strategy for control selection was used that first randomly selected a commune, then a large farming group, and then a small farming group within that commune. From this small farming group, a control subject was matched to each case by randomly selecting an individual matched with the case based on age at interview (± 2 years) and sex. The participation rate was 100% for cases and 97% for controls. This study was approved by the Institutional Review Board of the Chinese Academy of Preventive Medicine, and was conducted according to the recommendations of the World Medical Association Declaration of Helsinki for human study subject protection. Informed consent was obtained from all study subjects.

The distribution of subject characteristics were compared between cases and controls using chi-squared tests, or Fisher’s exact test when expected cell counts were less than 5. History

of chronic lung diseases, including COPD, chronic bronchitis, asthma, TB, and emphysema, was obtained by a questionnaire-based interview. The subject was asked if they had ever been diagnosed by a doctor of the pulmonary diseases of interest. Risk of lung cancer was estimated by odds ratios (ORs) and 95% confidence intervals (95% CIs) using conditional logistic regression. The risk of lung cancer associated with history of lung diseases was first analyzed by combining all diseases listed above. Further analyses of the association were conducted separately for each disease. Gender-specific analyses were also conducted. All analyses were adjusted, when appropriate, for gender, subtype of fuel used for household heating and cooking (coal; wood; none), educational status (literate, illiterate), lung cancer in first-degree relatives (yes, no), cumulative lifetime hours spent indoors at home (< 300,000, >300,000 hours), passive smoke exposure history (yes, no), and tobacco use [never users, sole users of other forms of tobacco or cigarettes smoked with a water pipe, 20 pack-years of cigarettes smoked without a water pipe, >20 pack-years of cigarettes smoked without a water pipe].

Results

Cases tended to be more often Han Chinese ($p=0.004$), literate ($p=0.026$), and smokers ($p<0.001$) than controls (Table 1). Further, cases had a greater frequency of history of lung cancer among first degree relatives ($p<0.001$).

History of chronic lung diseases was associated with lung cancer among all subjects (OR=4.9; 95% CI=2.6 to 9.2) (Table 2). This association remained when stratifying by gender [(males: OR=14.2; 95% CI=4.3 to 46.9)/(females: OR=2.6; 95% CI=1.1 to 6.3)]. The association between lung cancer and history of chronic lung diseases was also observed among smokers (OR=12.7; 95% CI=3.5 to 45.8) and nonsmokers (OR=2.6; 95% CI=1.1 to 6.4).

Evaluating history of each chronic disease independently found that lung cancer risk was associated with history of TB (OR=83.7; 95% CI=11.0 to 634.7), COPD (OR=3.2; 95% CI=1.7 to 6.0), and emphysema or chronic bronchitis (OR=3.3; 95% CI=1.7 to 6.4) (Table 3). Lung cancer was not associated with asthma in this population.

When stratified by gender, these associations seen with TB (OR=infinite; 95% CI=not applicable; all males with TB were cases ($n = 17$)), COPD (OR=6.2; 95% CI=2.0 to 18.9), and emphysema or chronic bronchitis (OR=6.2; 95% CI=2.0 to 19.0) were observed among males. The associations among females were suggestive of an association for COPD (OR=2.0; 95% CI=0.8 to 5.0) and emphysema or chronic bronchitis (OR=2.0; 95% CI=0.8 to 5.1). There were too few females with TB (7 female cases and 2 female controls had TB) to evaluate the association between TB and lung cancer risk.

Discussion

We evaluated the risk of lung cancer associated with chronic lung disease history in a population with unique environmental exposures to indoor air pollution attributed to household coal use. Increased risk of lung cancer was associated with history of any chronic lung disease among both genders, and smokers and nonsmokers alike. Our findings support the weight of evidence that history of TB, COPD, emphysema and chronic bronchitis increase risk of lung cancer[3]. We extend this literature by finding that these associations are also evident in populations with substantial coal smoke exposures.

Our findings also provide further insight into multifactorial lung cancer etiology in Xuanwei, and perhaps elsewhere. Previous studies in Xuanwei have shown that household coal exposures are independently associated with lung cancer risk[8, 9] and with COPD

risk[10]. Here we report that COPD is associated with lung cancer risk, furthering the previous observations and supporting the hypothesis that COPD is not only an independent risk factor for lung cancer, but also that COPD may mediate the coal exposure and lung cancer relationship by serving as an intermediary in the causal pathway. A study carried out in Northeast China also supports this hypothesis[14]. Galeone *et al* found that history of COPD was associated with about a 4-fold increased risk of lung cancer in Harbin[14]. While they did not stratify their results by gender, they were able to stratify by high and low indoor air pollution levels. Compared with participants with no history of COPD and reporting low indoor air pollution exposures, the OR was similarly elevated for subjects with COPD and reporting either low or moderate/high indoor air pollution exposures. Those subjects without COPD and reporting moderate/high exposures had lower risks. The combination of Galeone *et al*'s results and ours thus suggests an interaction between fuel use and chronic lung disease in promoting lung cancer risk. Further research is needed on this important topic.

A recent systematic review of case-control and cohort studies concluded that increased lung cancer risk is associated with pre-existing TB[15]. While pre-existing tuberculosis is associated with lung cancer risk, the magnitude we observed for this association may be higher than most reports in the literature. This phenomenon is most likely due to the statistical instability from there only being two controls with tuberculosis in our study population. Of note, our observed confidence interval does overlap with some previously published studies[16, 17]. Our findings, as well as those from the study in Harbin[14], suggest that TB is associated with lung cancer in populations with household exposures to solid fuel smoke. Lending strength to our findings is the strong biological plausibility that patients with TB are at an increased risk of lung cancer, as evident in Xuanwei[18], presumably through the sustained inflammation experienced by the patient during TB infection and treatment[19].

Similarly, lung cancer and chronic lung diseases could well be etiologically related through inflammatory mechanisms. As a first line of defense against inhalation exposures, the respiratory tract utilizes, among other things, cytokines (i.e. TNF-alpha, and IL-1) in response to site-specific inflammation[20]. Repetitive exposures to inflammatory exposures, such as coal combustion by-products from solid fuel use, can lead to chronic airway inflammation, a characteristic of COPD and other respiratory diseases. In support of this mechanism by which inflammatory pathways are involved in lung cancer development in populations with chronic coal smoke exposures through secreting growth stimulatory cytokines and chemokines, genetic variation in immunoregulatory genes have been previously associated with lung cancer risk in Xuanwei with some of effects being potentially modified by cumulative smoky coal use[21].

Tobacco smoking is also a known risk factor for malignant[22] and non-malignant respiratory diseases[23]. The higher risks of chronic respiratory diseases that we observed in our smokers compared to our nonsmokers, support the hypothesis that tobacco smoke may play an etiologic role between lung cancer and chronic lung diseases in our population. Although we were able to adjust for smoking in our analyses and stratify by smoking status, additional research is needed in a larger study population, to determine if tobacco smoke influences the association between lung cancer risk and history of chronic diseases as either an independent risk factor or an effect modifier.

In summary, our population-based case-control has found that history of TB, COPD, emphysema and chronic bronchitis, but not asthma, may increase risk of lung cancer in populations with unique environmental coal smoke exposures. A major strength of our study is the large sample size available for analysis, along with detailed information on confounders, such as smoking, familial lung cancer, and household fuel use. Our ability to

control for smoking and other confounders, and this population-based case-control study's very high participation rates, adds confidence in our observations. A limitation of our study is that we were not able to confirm diagnoses of the chronic diseases through medical records. Review of the patients' medical records is also of importance for future studies as it is sometimes difficult to differentiate between a lung cancer diagnosis and a chronic respiratory disease diagnosis as they can share similar symptoms. Further, we were did not have ample power to evaluate the impact coal exposure levels had on our observed associations. We are currently carrying out a case-control study of lung cancer among never smoking females in this region that will allow for the integration of additional exposure data for dose-response analyses.

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Table 1

Characteristics of lung cancer patients and population controls in Xuanwei, China.

	Cases (n = 498)		Controls (n = 498)		
	N	%	N	%	p-value*
Ethnicity					
Han	490	98	474	95	0.004
Other	8	2	24	5	
Education status					
Illiterate	330	66	363	73	0.026
Literate	167	34	135	27	
Gender					
Male	260	52	260	52	1.00
Female	238	48	238	48	
History of lung cancer in first-degree relatives					
No	460	92	495	99	<0.001
Yes	38	8	3	1	
History of cooking					
No	167	34	170	34	0.82
Yes	330	66	326	65	
Passive smoke exposure**					
No	29	5	45	9	0.053
Yes	469	94	453	91	
Smoking status (males only)					
Never smoker	26	10	34	13	<0.001
Other tobacco***	112	43	123	47	
20 pack-years cigarettes	64	25	81	31	
>20 pack-years cigarettes	55	21	21	8	

* chi-squared test, or Fisher's exact test when expected cell counts <5, comparing cases and controls;

** Smoking by any family member who lived with subject;

*** Sole users of other forms of tobacco (e.g. tobacco leaves) or cigarettes smoked with a water pipe.

Table 2

Risk of lung cancer associated with history of chronic lung diseases among males, females, smokers, and nonsmokers in Xuanwei, China*

		History of Chronic Lung Disease			
		Yes (n)	No (n)	OR	CI
All Subjects					
	cases	105	393	4.9	2.6-9.2
	controls	37	461	reference (OR = 1.0)	
Males					
	cases	63	197	14.2	4.3-46.9
	controls	11	249	reference (OR = 1.0)	
Females					
	cases	42	196	2.6	1.1-6.3
	controls	26	212	reference (OR = 1.0)	
Smokers					
	cases	58	173	12.7	3.5-45.8
	controls	10	216	reference (OR = 1.0)	
Nonsmokers					
	cases	47	217	2.6	1.1-6.4
	controls	27	243	reference (OR = 1.0)	

* Odds ratios (ORs) and 95% confidence intervals (CIs) estimated by conditional logistic regression and adjusted for fuel type used for household heating and cooking, educational status, lung cancer in first-degree relatives, cumulative lifetime hours spent at home, ever worked as a coal miner, tobacco use (coded as never users; sole users of other types of tobacco or cigarettes smoked with a water pipe, <= 20 pack-years of cigarettes smoked without a water pipe; >20 pack-years of cigarettes smoked without a water pipe, passive smoke exposure history (yes/no), and gender (when applicable)

Table 3Risk of lung cancer associated with history of specific chronic lung diseases in Xuanwei, China^{*}

Lung Disease	All Subjects			
	cases (n)	controls (n)	OR	CI
Tuberculosis				
No	474	496	reference (OR = 1.0)	
Yes	24	2	83.7	11.0-634.7
COPD				
No	411	463	reference (OR = 1.0)	
Yes	87	35	3.2	1.7-6.0
Emphysema or Chronic Bronchitis				
No	419	467	reference (OR = 1.0)	
Yes	79	31	3.3	1.7-6.4
Asthma				
No	484	492	reference (OR = 1.0)	
Yes	14	6	1.9	0.4-8.4

* Odds ratios (ORs) and 95% confidence intervals (CIs) estimated by conditional logistic regression and adjusted for fuel type used for household heating and cooking, educational status, lung cancer in first-degree relatives, cumulative lifetime hours spent at home, ever worked as a coal miner, tobacco use (coded as never users; sole users of other types of tobacco or cigarettes smoked with a water pipe, ≤ 20 pack-years of cigarettes smoked without a water pipe; >20 pack-years of cigarettes smoked without a water pipe, passive smoke exposure history (yes/no), and gender