Increased Lung Cancer Risk among Patients with Pulmonary Tuberculosis -A Population Cohort Study

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ABSTRACT

INTRODUCTION: Given one-third of the human population have been infected with tuberculosis, it is important to delineate the relationship between tuberculosis and lung cancer. This study explored whether contracting pulmonary tuberculosis is associated with an increased risk of developing lung cancers. **METHODS:** In a cohort of 716,872 insured subjects, free from cancers, 20 years of age and above, 4480 patients with newly diagnosed tuberculosis were identified from the universal insurance claims in 1998-2000, and tracked until 2007 with the remaining insured without tuberculosis. We compared the incidence of lung cancers between the two cohorts and measured the associated hazard of developing lung cancer. **RESULTS:** The incidence of lung cancers was approximately 11-fold higher in the cohort of tuberculosis patients than non-tuberculosis subjects (26.3 vs. 2.41 per 10,000 person-years). Cox proportional hazard regression analysis showed a hazard ratio of 4.37 (95% confidence interval (CI) 3.56-5.36) for the tuberculosis cohort after adjustment for the sociodemographic variables, or 3.32 (95% CI 2.70-4.09) after further adjustment for chronic obstructive pulmonary disease (COPD), smoking-related cancers (other than lung cancer), etc. The hazard ratio increased to 6.22 with the combined effect with COPD, or to 15.5 with the combined effect with other smoking-related cancers. **CONCLUSIONS:** This study provides a compelling evidence of increased lung cancer risk among individuals with

tuberculosis. The risk may increase further with coexisting COPD or other smoking-related cancers.

KEYWORD: lung cancer, tuberculosis, chronic obstructive pulmonary disease, comorbidity, retrospective cohort study.

Abbreviations

COPD: Chronic obstructive pulmonary disease

CI: Confidence interval

DOH: Department of health

ICD-9-CM: International Codes of Diseases 9th Edition Clinical Modification

NHI: National Health Insurance

HR: Hazard ratio

SCC: Squamous cell carcinoma

DOTS: Directly Observed Therapy Short-course

INTRODUCTION

Lung cancers are among the neoplastic diseases with the worst prognosis. The etiology of the disease has been associated with smoking, occupational exposure to arsenates, nitrosamines, asbestos, and aromatics, and indoor exposures to radon, and to fumes from fires or cooking stoves.[1-4] Outdoor air pollutions also substantially contribute to the burden of lung cancers in urban dwellers. Inflammation processes have long been linked to cancer development.[5,6] Among intrinsic lung diseases with inflammatory components, chronic obstructive pulmonary disease (COPD),[7] asthma,[8] and pulmonary fibrosis[9] have been linked to lung cancers. Tuberculosis with more than 80% of the cases primarily affecting the lungs entails a chronic inflammatory process. Coexistence of tuberculosis and lung cancers is not uncommon clinically.[10,11] However, a clear association of tuberculosis with lung cancers remains to be established.

Several studies have examined the association between tuberculosis and lung cancer using hospital/community-based populations.[12-21] Results of these studies were inconclusive. Two studies were conducted in Montreal, Canada in 2 different periods (1979-1986, and 1996-2001) to evaluate the association between previous lung diseases and lung cancers.[15] For tuberculosis, the evidence is inconsistent between these two studies. Littman *et. al.* tracked a large community population (n = 17,698)

with respiratory diseases for a median follow-up of 9.1 years, and found 1028 cases of lung cancers.[16] Chronic obstructive pulmonary disease, but not tuberculosis, was associated with higher risk of lung cancers in this study. Among non-smoker women in Hong Kong[16] and USA,[17] pre-existing pulmonary tuberculosis, asthma, pneumonia, and chronic bronchitis were more frequently noted in patients with lung cancers than without. However, in these 2 studies only asthma, but not tuberculosis, bore a significant impact. In a hospital based case-control study in Taiwan, Lee *et. al.* found that history of pulmonary tuberculosis was an independent risk factor for lung cancers, outweighing chronic bronchitis.[18]

To characterize the relationship between pulmonary tuberculosis and lung cancers, a cohort study with population-based large representative sample is highly desirable but has rarely been conducted. The only published cohort study on this topic to date was conducted among farmers in a remote countryside in China using retrospective analysis based on self-reported questionnaire data.[22] The risk of lung cancer mortality was 8-fold (25 vs. 3.1 per 1000 person-years) higher for those with tuberculosis than those without in a population of 42,422. However, this study did not include review of medical records making it possible for recall biases.

A recent systematic review of 41 studies was performed to determine whether pre-existing tuberculosis increased the risk of developing lung cancers. Association of

tuberculosis with lung adenocarcinoma group was noted particularly in non-westernized countries.[23] The impact of tuberculosis on lung cancers varied among different ethnic groups and in different regions. The inconclusive results led the authors of this systematic review to call for more cohort studies with larger sample sizes to confirm the association between tuberculosis and lung cancers.

To gain better knowledge on tuberculosis in relation to lung cancers, we conducted a population-based cohort study using patient care data compiled into a large cohort of 1 million patients under the universal National Health Insurance (NHI) program in Taiwan with a follow-up period of 7 to 9 years.

METHODS AND MATERIALS

Study Design and Sample

The NHI in Taiwan has registered all medical claims since 1996 with insured identification numbers scrambled for protecting patients' privacy. Sets of information available for this study include gender, birthdates, disease codes, health care rendered, medications prescribed, admissions, discharges, medical institutions and physicians providing the services and others. In this longitudinal cohort study in a randomly selected population of 1 million insured subjects, we identified all patients aged 20 years and above with a new diagnosis of tuberculosis in 1998-2000 as the exposed

cohort and all people without tuberculosis history as the non-exposed cohort also identified in 1998-2000. We also excluded patients with any cancer diagnosis to make sure participants were cancer-free at the start of both cohorts. Overall, 716,872 insured adult population were eligible for the prospective analysis. This follow-up design would last until the date of censored or the end of 2007 for a period of 7 to 9 years to explore whether individuals with tuberculosis were associated with increased risk of developing lung cancers.

Criteria and Definition

The International Codes of Diseases 9th Edition Clinical Modification (ICD-9-CM) was used to identify the individual health status. The exposure group consisted of patients with diagnosis of tuberculosis (ICD-9-CM of 011 and A-code of A020), and the non-exposure group consisted of all insured without tuberculosis. Both groups were treated as fixed cohorts. Even if a person develops tuberculosis 2001 or later, the person remains classified as no tuberculosis by the end of 2007. We then identified new lung cancer cases (ICD-9-CM of 162 and A-code of A101) from outpatient and inpatient medical records. To ensure the accuracy of reimbursement claims, the NHI system required experts review conducted for every 50-100 claims. The institutions with false diagnosis are subject to penalties.[24]

In addition to tuberculosis, COPD, characterized by chronic airway

inflammatory process, has been linked to lung cancers.[7,25] Metabolic syndromes have also been linked to several types of cancers.[26,27] Diabetes was found to be associated with breast cancer.[28] However, its relationship with lung cancers remains controversial. Two articles addressed its "protective" effect[29,30] and another was negative.[31] Impaired glucose intolerance, elevated blood pressure, and dyslipidemia comprise the major components of metabolic syndromes, which were therefore included in the comorbidity analysis.

Data analysis

We first compared the distribution of sociodemographic factors between the cohorts with and without tuberculosis. The proportions of comorbidities were also compared between the 2 cohorts. The incidence rates of lung cancers were calculated in the follow-up period until the end of 2007 adjusted by the sociodemographic factors and comorbidities. The duration of observation for each person was calculated until lung cancer diagnosed or censored for death, migration or discontinued enrolment in the insurance system.

Crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for factors associated with lung cancer risk were calculated using both the univariate and multivariate Cox proportional hazard analyses with the variables categorized. Two multivariate Cox proportional hazard models were used. The model 1 adjusted for age,

sex, and occupation. Model 2 further adjusted for diabetes, hypertension, dyslipidemia, and COPD. We also included in the Model 2 the smoking-related cancers other than lung cancer (ICD-9-CM of 140-150, 157, 160–161, 189, and A08, A090, A096, A100, A109 and A123). We further applied a multivariate Cox proportional hazard model to investigate the combined effect of tuberculosis and COPD or other smoking-related cancers on lung cancer risk. The Kaplan-Meier model was used to compare the probabilities of being free from lung cancer between the 2 cohorts. SAS software version 9.1 (SAS Institute Inc., Carey, NC) was used for data analyses with two-sided probability values less than 0.05 considered statistically significant.

RESULTS

The eligible study subjects included 4480 persons in the tuberculosis cohort and 712,392 persons in the non-tuberculosis cohort (Table 1). Compared with individuals without tuberculosis, those with tuberculosis were dominated by males (57.9 vs. 49.2, $p < 0.0001$), the elderly with age of 60 or greater (52.4% vs. 19.0%, $p <0.0001$) and blue collars (18.5% vs. 13.9%, $p <0.0001$). Table 2 shows that the tuberculosis patients were more prevalent than the non-tuberculosis group with hypertension, dyslipidemia, diabetes mellitus and COPD ($p <0.0001$ for all the listed parameters). Patients who had other smoking-related cancers were more prevalent in the

tuberculosis cohort than in the non-tuberculosis cohort ($p = 0.008$).

The follow-up results showed that tuberculosis patients were 10.9 times more likely than non-tuberculosis patients to develop lung cancer (26.3 vs. 2.41 per 10,000 person-years) (Table 3). A separate analysis calling deaths as failures showed that the mortality was also much higher in the tuberculosis patients than in the non-tuberculosis patients (51.1 vs. 8.2 per 10,000 person-years, data not shown). The Kaplan-Meier analysis showed that the tuberculosis patients had less subjects remained in the study than non-tuberculosis patients during a follow-up period of 7-9 years (97.2% vs. 99.8%, Log-rank $p < 0.0001$) (Figure 1).

In Table 4, the univariate Cox proportional regression model shows that, in addition to tuberculosis, age, sex, occupation, hypertension, dyslipidemia, diabetes and COPD were also significant factors relevant to the development of lung cancers. After controlling for these variables, the tuberculosis patients had a HR of 4.37 (95% CI 3.56-5.36) for lung cancers (model 1). When all comorbidities were included in model 2 multivariate analyses, the HR decreased to 3.32 (95% CI 2.70-4.09). COPD and other smoking-related cancers remained as significant independent comorbidities associated with lung cancer development. This model also shows that the risk of lung cancers increased as age advanced, was higher in men than in women, and higher in blue collar populations. Further analysis showed that tuberculosis and COPD had a combined

effect on the risk of lung cancers with an HR of 6.22 (95% CI = 4.87-7.94) (data not shown). The HR increased to 15.5 (95% CI = 2.17-110) with the combined effect with other smoking-related cancers.

DISCUSSION

Previous studies on association between tuberculosis and lung cancer using hospital/community-based populations gave conflicting conclusions.[12-22] The recent meta-analysis of 41 studies has concluded that tuberculosis link to lung cancers varied among different ethnic groups and in different regions.[23] The inconclusive results raise the need for cohort studies with larger sample sizes to confirm the association between tuberculosis and lung cancers. However, a large cohort study conducted in a remote country side in China, based on self-reported questionnaire data, was without valid confirmation of diagnosis for both tuberculosis and lung cancer.[22]

The present cohort study explored the longitudinal association between tuberculosis and lung cancer risk using a nationwide population-based sample of patients and complete ascertainment of care that are verified with stringent national health insurance claim procedures. Our analyses revealed that the incidence of lung cancer is much greater in tuberculosis patients than in the general population, with an adjusted hazard ratio of 3.32 during a follow-up of 7-9 years. It is also not surprise to

observe a much higher mortality in the tuberculosis cohort.

Results from the present study are consistent with the report by Gao and Blot *et. al.* that lung cancers were more frequently found in recent survivors of tuberculosis infection.[32] The risk is higher for men than for women and much higher for the elderly. The data also shows tuberculosis is an independent predictor of lung cancer risk, stronger than COPD. The changing incidence shows a trend of lung cancer shifting from developed to less-developed countries,[33,34] where tuberculosis poses a major health risk. Our findings point to a potential health burden of lung cancer risk in developing countries. In these countries, the populations are also aging with tuberculosis more prevalent in men. These features together with results presented here heighten the need for the developing countries to contain tuberculosis.

Smoking and air pollutions are the two major risk factors causing airway diseases by repeatedly irritating respiratory epithelium, resulting in a chronic inflammatory condition. The link of chronic inflammation to the lung cancer development has been demonstrated in animal models.[35,36] COPD is a known risk for lung cancer. Cohort studies have shown the association of COPD with lung cancers.[37] It has been reported that smokers with COPD had increased risk of developing lung cancers by 1.3 to 4.5 folds in comparison with smokers without COPD.[37-39] Our analysis shows a similar trend for COPD to increase the risk of lung cancers with a

hazard ratio of 2.30 (Table 4). The combined effect of tuberculosis and COPD increased the hazard ratio of lung cancer risk from 3.32 to 6.22, a risk measure comparable to smoking, the major etiologic factor of lung cancer.[40,41]

This causal association between chronic inflammatory conditions and lung cancers has been observed not only clinically but also in a mice model. Using mutated K-ras restricted to Clara cells of the conducting airway, Moghaddam *et. al*. reported that a chronic inflammatory airway, mimicking COPD condition, promoted cancer progression.[35] The infected sites of tuberculosis are under a chronic inflammatory condition with inflammatory cells and mediators that may facilitate carcinogenesis.

The longitudinal survey applied in the present study is a better approach in establishing a link of tuberculosis to lung cancers. It avoids the selection and recall biases in previous cross-sectional and case-control studies.[12-14,17,21] The population-based insurance data allow this study to avoid recall biases inherent to a previous self-reported questionnaire study, which has been the only cohort study on association of tuberculosis to lung cancers published to date.[22] The larger representative sample sizes collected in the present study provide a more reliable statistical power for assessing the increase in lung cancer risk in patients with tuberculosis as compared to a control cohort without tuberculosis.

Using a nationwide insurance database for an epidemiology study, the accuracy

of clinical coding could be questioned. Tuberculosis is one of the communicable diseases under intense national surveillance in Taiwan. Reporting patients with tuberculosis is mandatory and is enforced by the Department of Health (DOH) in Taiwan. Cases reported to the Center for Disease Control, DOH, were under the WHO recommended Directly Observed Therapy Short-course (DOTS) Care.

The diagnosis of cancers, including lung cancer, entitles the patients to qualify for special healthcare privileges in the class of "major critical diseases" in Taiwan's NHI system. Once a patient is claimed to have this disease entity; co-payments for healthcare are waived. This health benefit program has been under stringent NHI auditing to avoid abuse or frauds. Thus, results derived from the NHI database for the diagnosis of tuberculosis and lung cancer are reliable.

In this study, none of the three metabolic syndrome related comorbidities was significantly associated with the lung cancer risk in the multivariate analysis. There is a significant collinearity among the components of the metabolic syndrome, supporting the validity of the data retrieved from the NHI cohorts. The findings that metabolic syndrome related comorbidities did not bear any weight on lung cancer development in these cohorts support the contention that a close association of tuberculosis with lung cancer is not a chance observation.

There are potential limitations in the present study. First, the major concern in

this study is that the smoking data of the study cohorts were available only for the smoking cessation history. Some studies have addressed the positive association between smoking and tuberculosis.[40,42] The estimate of smoking is an important issue in the risk measurement of lung cancers.[40] The prevalence of smoking in Taiwan has been in the range of 50–60% in men and 3-4% in women.[43,44] We used COPD and other smoking-related cancer to substitute smoking as one of covariates in the adjustment measures. The present study showed patients with other smoking-related cancers were more prevalent in tuberculosis cohort. A case-control study has indicated that 40% of patients with tuberculosis in Taiwan were smokers.[45] A lower smoking rate in tuberculosis patients reflects greater efforts for this group to quit smoking. Thus, the confounding impact of smoking on the risk of lung cancer may be lower in the tuberculosis group. A higher risk of lung cancer in men than in women may reflect the smoking impact. Smoking has been associated with metabolic syndrome.[46] The negative associations between metabolic syndromes related comorbidities and lung cancer risk may also alleviate the potential bias that is not adjusted without smoking data.

Second, even if tuberculosis is associated with lung cancers, more questions could be raised. Does tuberculosis affects some types of lung cancer but not others? Clinically, squamous cell carcinoma (SCC) was found in over 50% of cases with

coexistence of tuberculosis and lung cancers.[11] SCC of lung was also found in mice subjected to chronic infection of mycobacterial tuberculosis.[36] A recent meta-analysis of epidemiological data, however, revealed the association was only significant with adenocarcinoma, but not SCC.[23] Without information on lung cancer types, whether tuberculosis is preferentially associated with select types of lung cancer cannot be addressed based on results derived from the present study. Finally, there is a remote possibility that a small number of tuberculosis patients may have the disease before being selected into the cohorts because of receiving no medical care until 1998-2000. It is likely, however, the bias will affect both groups with and without lung cancer. Further more, 1,584 lung cancer patients in the non-tuberculosis cohort had received 2,480 person-times of X-ray examinations, while there were 1,973 person-times for the 100 patients in the tuberculosis cohort necessary for the treatment progress. It is possible the x-ray examinations increased the risk of lung cancer as well.

In conclusion, this nationwide population-based cohort study provides evidence supporting the contention that patients with pulmonary tuberculosis carried higher risk of developing lung cancers. COPD and smoking enhanced the risk of lung cancer further in patients with tuberculosis.

CONFLICT OF INTEREST DISCLOSURES

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Table 1. Comparison in sociodemographic factors between cohorts with and without tuberculosis.

Factors	Tuberculosis				Total		p-value
	No		Yes				
	N =712,392		N = 4,480		N =716,872		
Sex	n	(%)	n	(%)	n	(%)	<0.0001
Female	361,749	(50.8)	1,887	(42.1)	363,636	(50.7)	
Male	350,643	(49.2)	2,593	(57.9)	353,236	(49.3)	
Age, years							<0.0001
20-39	297,705	(41.8)	678	(15.1)	298,383	(41.6)	
40-59	279,312	(39.2)	1,453	(32.4)	280,765	(39.2)	
60-79	111,010	(15.6)	1,601	(35.7)	112,611	(15.7)	
≥80	24,365	(3.4)	748	(16.7)	25,113	(3.5)	
Occupation							<0.0001
Public*	380,233	(53.4)	2,053	(45.8)	382,286	(53.3)	
Labor	99,028	(13.9)	830	(18.5)	998,585	(13.9)	
Business	173,473	(24.4)	986	(22.0)	174,459	(24.3)	
Low income†	3,029	(0.4)	31	(0.7)	3,060	(0.4)	
Others	56,629	(8.0)	580	(13.0)	57,209	(8.0)	

*Government, education and military

Table 2. Comparison in comorbidity between cohorts with and without tuberculosis.

Comorbidities	Tuberculosis						
	No		Yes		Total		
	N=712,392		N=4,480		N=716,872		p-value
Hypertension							<0.0001
No	572,900	(80.4)	2,657	(59.3)	575,557	(80.3)	
Yes	139,492	(19.6)	1,823	(40.7)	141,315	(19.7)	
Hyperlipidemia							<0.0001
No	657,385	(92.3)	38,32	(85.5)	661,217	(92.2)	
Yes	55,007	(7.7)	648	(14.5)	55,655	(7.8)	
Diabetes							<0.0001
No	650,162	(91.3)	3,654	(81.6)	653,816	(91.2)	
Yes	62,230	(8.7)	826	(18.4)	63,056	(8.8)	
COPD[†]							<0.0001
No	638,130	(89.6)	2,505	(55.9)	640,635	(89.4)	
Yes	74,242	(10.4)	1,975	(44.1)	76,237	(10.6)	
Smoking-related cancer							0.008
No	709,926	(99.6)	4,454	(99.4)	714,380	(99.6)	
Yes	2,466	(0.4)	26	(0.6)	2,492	(0.4)	

[*] Missing value: 11 in urbanization.

[†] Chronic obstructive pulmonary disease.

[‡] ICD-9-CM and A-codes for hypertension were 401, 402, 403, 404, A260, A269; for hyperlipidemia 272.0, 272.1, 272.2, 272.3, 272.4, A189; for diabetes 250, A181; for COPD 491, 492, 496, A323.01, A323.03, A325; and for Smoking-related cancer 140-150, 157, 160–161, 189, A08, A090, A096, A100, A109, A123.

Table 3. Incidence of lung cancer between cohorts with and without tuberculosis

Tuberculosis	Population	Person-years	Cancer, n	Incidence rate*
No	712,392	6,571,088	1,584	2.41
Yes	4,480	37,951	100	26.3

* per 10,000 person-years

Table 4. Crude and adjusted hazard ratios and 95% confidence intervals of lung cancer and associated factors

	Univariate		Multivariate model 1		Multivariate model 2	
Factors	**HR**	**(95% CI)**	**HR**	**(95% CI)**	**HR**	**(95% CI)**
Age, years						
20-39	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
40-59	13.0	(9.02-18.8)	12.9	(8.94-18.6)	12.0	(8.31-17.3)
60-79	73.4	(51.3-105)	69.1	(48.2-98.8)	52.2	(36.2-75.3)
≥80	168	(117-242)	143	(99.2-207)	92.8	(63.5-136)
Sex						
Female	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Male	1.77	(1.60-1.95)	1.74	(1.57-1.92)	1.68	(1.52-1.86)
Occupation						
Public*	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Labor	2.62	(2.33-2.96)	1.21	(1.07-1.37)	1.14	(1.01-1.30)
Business	1.08	(0.95-1.23)	1.03	(0.90-1.17)	1.01	(0.88-1.15)
Low income	2.08	(13.15-3.78)	1.43	(0.79-2.61)	1.30	(0.71-2.36)
Others	2.26	(1.95-2.63)	1.17	(0.995-1.37)	1.09	(0.93-1.28)
Tuberculosis						
No	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Yes	11.9	(9.73-14.6)	4.37	(3.56-5.36)	3.32	(2.70-4.09)
Hypertension						
No	1.00	(Reference)			1.00	(Reference)
Yes	5.31	(4.82-5.84)			1.11	(0.99-1.24)
Hyperlipidemia						
No	1.00	(Reference)			1.00	(Reference)
Yes	2.45	(2.17-2.80)			1.05	(0.92-1.20)
Diabetes						
No	1.00	(Reference)			1.00	(Reference)
Yes	3.31	(2.96-3.71)			1.07	(0.95-1.20)
COPD†						
No	1.00	(Reference)			1.00	(Reference)
Yes	6.15	(5.59-6.78)			2.30	(2.07-2.55)
Smoking-related cancer						
No	1.00	(Reference)			1.00	(Reference)
Yes	4.67	(3.17-6.88)			2.06	(1.40-3.03)

*Government, education and military; † Chronic obstructive pulmonary disease.

Figure 1. Kaplan-Meier curves for probabilities of study subjects remained in the study cohorts with and without tuberculosis