Pulmonary tuberculosis is associated with elevated risk of lung cancer in South Korea : Nationwide retrospective cohort study

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INTRODUCTION

- In South Korea, pulmonary tuberculosis is endemic and shows highest incidence and mortality rate of pulmonary tuberculosis among OECD countries. Lung cancer is also the leading cause of death among cancer patients in South Korea.

- Although epidemiological evidence concerning **the association between pre-existing pulmonary tuberculosis and lung cancer** has accumulated in recent years, **this evidence is conflicting**: the relationship may be over- or underestimated.

OBJECTIVES

- Our study aims to **investigate the association between pulmonary tuberculosis and the risk of lung cancer in the Korean general population**.

  : Using linked data of the Korea National Cancer Incidence Database (KNCIDB) – the Korean National Health and Nutritional Examination Survey (KNHANES) Database - Cause of death data

METHODS

- **Data source**

KNHANES	▫ A nationwide representative cross-sectional survey that has been conducted annually (since 2007~): consisting of health interviews, health examinations, and nutrition surveys ▫ Collected by the Korean Center for Disease Control and Prevention ▫ This study used a pooled dataset from 2008 to 2013
KNCIDB	▫ National cancer incidence data: the completeness was estimated to be 97.5% (in 2014) ▫ Collected by the Korea Central Cancer Registry ▫ This study used incidence data from 1993 to 2014
Cause of Death	▫ National data records complete death statistics ▫ Collected by Statistics Korea ▫ This study used cause of death data from 2008 to 2014

- A retrospective cohort study was conducted by linking two large national databases: the KNHANES database was merged with KNCIDB from the Korea Central Cancer Registry.

- **Case Definition**

  ▫ Old pulmonary tuberculosis (TB)
  - Past medical history of pulmonary tuberculosis diagnosed by doctor [KNHANES]
  - Inactive pulmonary tuberculosis based on chest X-ray [KNHANES]
  ※ Sensitivity Analysis: for each cases of above two definitions for old pulmonary TB

  ▫ Lung cancer
  - Newly diagnosed lung cancer, defined as ICD-10 "C33" and "C34"
  - Excluded people from KNCIDB diagnosed with lung cancer before 2008

- **Follow-up**
  - Using data from Statistics Korea, the participants' status were followed up until December 31, 2014

- **Study participants**

  Assessed for eligibility (n = 49,435)

  Excluded (n=23,828)
  - Participants aged <40 years (n=23,692)
  - Patients diagnosed with lung cancer before participating this study (n=136)

  Eligible participants (n = 25,607)

  Excluded from analysis (n=5,355)
  - No measurement for major covariates (n=1,379)
  - Missing for past history for pulmonary tuberculosis (n=3,965)
  - Patients diagnosed with lung cancer within six months since participating this study (n=11)

  Study participants (n = 20,252)

- **Other variables**
  - Smoking status: never, ex-, current
  - Alcohol intake   - Physical activity
  - Equivalent household income

  $$= \frac{\sqrt{monthly\ household\ income}}{\sqrt{number\ of\ family\ members\ in\ the\ household}}$$

  - Education level   - Body Mass Index

- **Statistical analysis**
  - Analyses were conducted using sampling weights considering the survey design
  - Cumulative incidence risk of lung cancer: incidence cases per 100,000 PYs
    → assessed by an incidence rate ratio, comparing between patients with old pulmonary TB and the control group
  - Independent t-test and the chi-square test, Kaplan-Meier plot and log-rank test
  - Cox proportional hazards models (3 models of different adjusting variables) for the associations between old pulmonary TB and an elevated risk of lung cancer
  - Statistically significant: $P<0.05$ - SAS 9.4 and STATA version 14
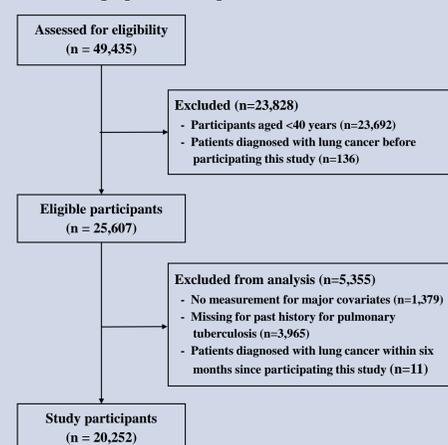
RESULTS

Table 1. Baseline characteristics of patients with old pulmonary tuberculosis   * mean±SD or number(%)

Characteristics	Old TB patients[†] (N=2,640)		Control (N=17,612)		p-value[‡]
	Mean	(SE)	Mean	(SE)	
Follow-up years(year)	3.85	(0.05)	4.00	(0.04)	<0.001
Age(year)	62.92	(0.30)	57.77	(0.14)	<0.001
BMI(kg/m²)	22.89	(0.07)	24.15	(0.03)	<0.001
	No	**(%)**	**No**	**(%)**	
Sex					
Men	1,519	(59.73)	7,193	(46.70)	<0.001
Women	1,121	(40.27)	10,419	(53.30)	
Smoking status					
Never smoker	1,274	(45.79)	11,045	(57.70)	<0.001
Ex-smoker	814	(29.90)	3,410	(20.12)	
Current smoker	552	(24.32)	3,157	(22.17)	
Education					
Middle school or lower	1,534	(52.69)	9,173	(45.62)	<0.001
High school	672	(28.91)	5,117	(32.91)	
College or higher	434	(18.40)	3,322	(21.47)	
Income level					
1st quartile(highest)	510	(22.65)	4,666	(28.54)	<0.001
2nd quartile	641	(26.47)	4,501	(28.07)	
3rd quartile	688	(26.22)	4,342	(24.87)	
4rd quartile(lowest)	801	(24.66)	4,103	(18.52)	
Moderate or vigorous physical activity					
No	2,150	(80.33)	13,796	(78.34)	0.059
Yes	490	(19.67)	3,816	(21.66)	

TB, Tuberculosis; BMI, Body mass index; SE, standard error
† Old pulmonary TB included both a past medical history of pulmonary TB or non-active pulmonary TB based on chest X-ray.
‡ Independent t-test and Chi-square test were used to test the difference in continuous variables and categorical variables, respectively.

Table 2. Lung cancer risk of patients with old pulmonary tuberculosis by characteristics

Characteristics	Old TB patients[†]			Control			IRR (95% CI)
	No. of lung ca. cases	(%)	Incidence rates per 100,000 PYs	No. of lung ca. cases	(%)	Incidence rates per 100,000 PYs	
Total	27	1.0	177.6	38	0.2	31.2	5.66 (3.17-10.12)
Sex							
Men	23	85.19	247.8	27	71.1	46.5	5.28 (2.65-10.50)
Women	4	14.81	71.5	11	28.9	17.8	4.06 (1.19-13.89)
Age group							
<60	3	11.11	42.3	9	23.68	17.9	2.19 (0.53-9.12)
≥60	24	88.89	341.7	29	76.32	63.0	5.51 (3.03-10.01)
Smoking status							
Never smoker	6	22.22	84.6	12	31.58	17.8	4.82 (1.60-14.56)
Ex-smoker	10	37.04	197.8	12	31.58	54.1	3.56 (1.13-11.16)
Current smoker	11	40.74	321.7	14	36.84	45.5	7.10 (2.94-17.13)

TB, Tuberculosis; BMI, Body mass index; CI, Confidence interval; IRR, Incidence rate ratio
† Old pulmonary TB included both a past medical history of pulmonary TB or non-active pulmonary TB based on chest X-ray.

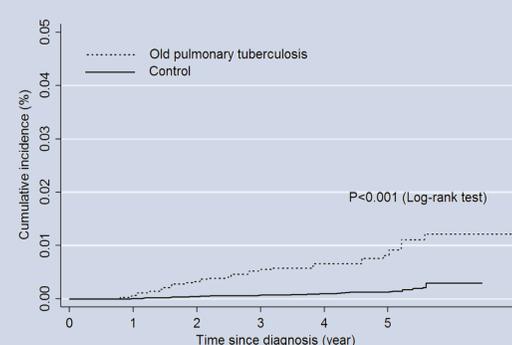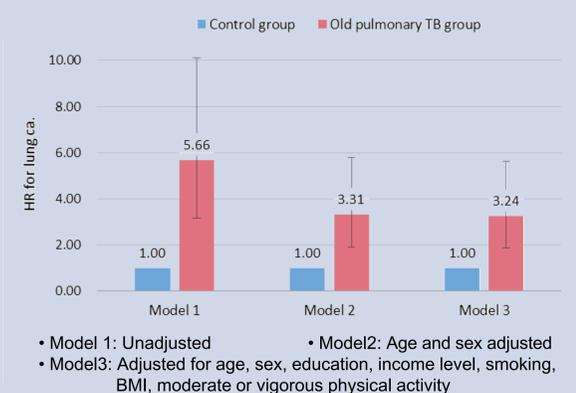**Figure 1. Comparison of incidence rate of lung cancer between patients with old pulmonary TB and control group**

P<0.001 (Log-rank test)

····· Old pulmonary tuberculosis
——— Control

Figure 2. Increased hazards of lung cancer for patients with old pulmonary tuberculosis

■ Control group ■ Old pulmonary TB group

Model 1: 1.00 / 5.66   Model 2: 1.00 / 3.31   Model 3: 1.00 / 3.24

- Model 1: Unadjusted   • Model2: Age and sex adjusted
- Model3: Adjusted for age, sex, education, income level, smoking, BMI, moderate or vigorous physical activity

CONCLUSIONS

- The incidence density and hazard ratio of lung cancer in patients with old pulmonary TB was much higher than those among people without pulmonary TB.

- This study implies that pulmonary tuberculosis could be an independent risk factor for lung cancer in the general Korean population.

- It suggest that the prevention and management of pulmonary tuberculosis is also important for the future prevention of lung cancer. Further efforts are necessary to prevent and screen lung cancer in patients with pulmonary tuberculosis in South Korea.

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