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Risk of Lung Cancer and Risk Factors of Lung Cancer in People Infected with Tuberculosis

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This study investigated lung cancer risk in people infected with tuberculosis (TB) compared to the general population and evaluated factors associated with lung cancer in TB-infected individuals. Mandatory reported TB infection case data in Gyeonggi Province, South Korea (2010 to 2016) were obtained and linked with medical usage and health screening data from the National Health Information Database. Lung cancer incidence in patients with TB was compared to that in the general population using standardized incidence ratio (SIR), adjusted for age and sex. Lung cancer risk factors in patients with TB were studied using the Cox proportional hazards model. By April 2022, 1.26% (n = 444) of 35,140 patients developed lung cancer after TB diagnosis. Compared to the incidence in the general population, increased lung cancer risk in people with TB was observed (SIR: 2.04, 95% CI: 1.85-2.23). Multivariate analysis showed increased lung cancer in TB-infected individuals, associated with being male (hazard ratio [HR]: 2.24, 95% CI: 1.65-3.04), 1-year increase of age (HR: 1.09, 95% CI: 1.08-1.10), ever smoking (HR: 1.42, 95% CI: 1.02-1.97), and amount of daily smoking with one pack or more (HR: 2.17, 95% CI: 1.63-2.89). Increased lung cancer risk was noted in patients with TB compared to the general population, and sex, age, and smoking were factors associated with lung cancer in patients with TB.

Key Words Tuberculosis, Lung neoplasms, Risk factors, Smoking

INTRODUCTION

According to the World Health Organization Global Tuberculosis (TB) Report, which has been published annually since 1997, approximately 10 million people were estimated to develop TB annually and 1.5 million people died from TB in 2020, making TB the most common cause of death from a single infection. Despite the decreasing trend of deaths due to TB between 2005 and 2019, an increasing number of cases in 2020 and 2021 confirms that TB is a major health burden worldwide [1]. South Korea showed the highest TB incidence and second highest TB mortality rate among the Organization for Economic Cooperation and Development member countries despite the continuous decrement of TB since 2011 [2]. In 2019, the number of TB cases in Korea was 23,821 (46.4 per 100,000 people) and the number of deaths due to TB was 1,610 [3].

Patients with TB showed more than 3-times higher long-term mortality than the general population, which could be attributed to decreased lung function and lung damage [4]. After TB treatment, the possibility of colonization of residual cavity lesions by *Aspergillus* spp. and other fungi remains, which can cause life-threatening massive hemoptysis [5]. Chronic inflammation of TB itself can promote tumor growth and carcinogenesis [6]; thus, the hypothesis of increased risk of lung cancer associated with TB has been suggested. A recent meta-analysis including 29 cohort studies and 44 case-control studies identified an increased lung cancer risk in people with TB infection, especially within the first 2 years after TB diagnosis [7]. However, it is challenging to ascertain causal association because of the possibility of the presence of lung cancer at the time of TB diagnosis, followed by possible reverse causation [7,8]. Another meta-analysis showed an increased risk of TB in people with previously diagnosed cancer, especially those with hematologic, head and neck, and lung cancers [8]. In addition, even cohort studies includ-

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ed in the meta-analysis might have a selection bias because not all TB cases could be included [7,8].

Therefore, this study investigated the association between TB and lung cancer risk based on linkage data from region-wide reported TB cases and nationwide health coverage data in Korea.

MATERIALS AND METHODS

Study settings and data sources

In South Korea, several infectious diseases have been designated as national notifiable infectious diseases. Medical providers report identified cases to regional health centers, and the data are reviewed by local health authorities and transferred to the Korea Disease Control and Prevention Agency following the Infectious Disease Control and Prevention Act [9]. TB is one of the diseases included in the mandatory surveillance system, which requires compulsory reporting of all infectious diseases within 24 hours to a regional health center [9]. To identify all reported TB cases from the mandatory surveillance system in a certain region, we applied data from the Gyeonggi Infectious Disease Control Center (GIDCC) from 2010 to 2016. Gyeonggi-do is located in the central western part of the Korean Peninsula with 13.93 million residents (27.0% of the total Korean population) in a 10,195 km^2 area (10.1% of Korea's national territory) as at 2021.

To identify lung cancer occurrence after TB diagnosis, the National Health Information Database (NHID) of the National Health Insurance Service (NHIS) was linked to reported TB cases using resident registration numbers from January 1, 2002, to April 30, 2022. The NHIS is a universal and compulsory health insurance system for all residents of Korea and offers benefits for disease/injury diagnosis, treatment, rehabilitation, birth, death, and health promotion, including general health screening and cancer screening. Thus, the NHID has nationwide records of healthcare utilization, prescriptions, and screening results [10]. This study was approved by the Institutional Review Board of Hanyang University (No. HYUIRB-202206-003-1). Informed consent was waived because the database was constructed after anonymization of individual identities.

Definition of lung cancer development

The NHIS provides a cost-sharing system for co-payment of medical expenditures for diseases with high medical costs, such as cancer, rare diseases, and incurable diseases [11]. Special codes are given to the beneficiaries of the cost-sharing system. Lung cancer development was identified using a combination of International Classification of Diseases, 10th revision codes for lung cancer (C33 and C34) and catastrophic illness codes (V193, V194, and V027) from the healthcare utilization database.

Risk factors

Sociodemographic variables in the NHID, including age, sex, and income, were considered. Income level was divided into medicaid, lower 50% of premium, and higher 50% of premium.

During general health screening, a self-reported questionnaire including health behaviors, past medical history, and family history was administered to all participants. Smoking status was categorized as "never smokers" or "ever smokers" (past or current smoking) based on participants' response to the question, "Have you ever smoked 100 cigarettes or more in the course of your lifetime?". Daily smoking amount was classified as < one pack/day and ≥ one pack/day. Based on participant responses to whether or not they consumed alcohol once or more per week, we considered them as current alcohol drinkers or non-drinkers, respectively. Participants' moderate or vigorous physical activity once or more per week as well as for ever diagnosis of hypertension, diabetes, stroke, heart disease, and dyslipidemia by a physician were asked. Body mass index (BMI), which was calculated using participant height and weight and measured by trained staff during the health screening, was classified < 23 kg/m^2 or ≥ 23 kg/m^2.

Compliance with TB treatment was defined as a prescription history of TB treatment medication for more than 120 days [12]. In the case of a single drug, prescription of two or more drugs together for more than 120 days was defined as compliance of treatment. The list of TB treatment drugs is as follows: (1) combination drugs: rifampicin and isoniazid (380200ATB), rifampicin, pyrazinamide, ethambutol, and isoniazid (519500ATB); (2) single drugs: isoniazid (178101ATB), rifampicin (223901ACH, 223902ACH, 223902ATB, 223903ATB, 223904ATB), rifabutin (364401ACH), ethambutol (155602ATB, 155605ATB), and pyrazinamide (221201ATB, 221202ATB).

Study participants

According to the GIDCC, the reported number of TB patients in Gyeonggi-do between 2010 and 2016 was 120,802. Of these, 107,118 patients were linked to the NHIS according to their resident registration number. To investigate the association between risk factors and lung cancer in patients with TB, those patients who had received health screening at least one year in advance of lung cancer development and had information on self-reported questionnaires at health screening were included. Thus, 68,045 individuals who had not received health screening at least 1 year before lung cancer development were excluded. To define lung cancer occurrence after TB diagnosis, those who developed lung cancer before the date of TB diagnosis were excluded (n = 3,405). In addition, to avoid the possibility of reverse causation by including lung cancer prevalent cases at TB diagnosis, those patients whose date of lung cancer diagnosis was within 365 days from TB diagnosis were excluded (n = 604), leaving 35,140

patients with TB in the analysis.

Statistical analysis

The baseline characteristics of patients with TB included in the analysis were presented as numbers and percentages according to lung cancer development. The incidence of lung cancer according to baseline characteristics was presented as the incidence rate per 100,000 person-years. The fol-

Table 1. Baseline characteristics of patients with tuberculosis in Gyeonggi Province, South Korea

Variable	Total	Lung cancer development		*P*-value
		Yes	No	
Patients	35,140 (100.00)	444 (1.26)	34,696 (98.74)	
Sex				< 0.001
Male	20,359 (57.94)	359 (80.86)	20,000 (57.64)	
Female	14,781 (42.06)	85 (19.14)	14,696 (42.36)	
Age at tuberculosis diagnosis (yr)				< 0.001
< 40	9,856 (28.05)	3 (0.68)	9,853 (28.40)	
40-59	13,474 (38.34)	107 (24.10)	13,367 (38.52)	
≥ 60	11,810 (33.61)	334 (75.22)	11,476 (33.08)	
Income group				0.528
Medicaid	1,299 (3.70)	20 (4.50)	1,279 (3.69)	
Lower 50%	14,419 (41.03)	189 (42.57)	14,230 (41.01)	
Upper 50%	18,532 (52.74)	227 (51.13)	18,305 (52.76)	
Missing	890 (2.53)	8 (1.80)	882 (2.54)	
Smoking history				< 0.001
Never smokers	19,222 (54.70)	148 (33.33)	19,074 (54.97)	
Ever smokers	15,918 (45.30)	296 (66.67)	15,622 (45.03)	
Smoking per day in ever smokers				< 0.001
< 1 pack/day	6,549 (41.14)	67 (22.63)	5,688 (36.41)	
≥ 1 pack/day	6,877 (43.20)	163 (55.07)	6,372 (40.79)	
Missing	2,492 (15.66)	66 (22.30)	3,562 (22.80)	
Alcohol consumption once or more per week				0.015
No	16,014 (45.57)	177 (39.86)	15,837 (45.65)	
Yes	19,126 (54.43)	267 (60.14)	18,859 (54.35)	
Moderate or vigorous physical activity once or more per week				< 0.001
No	6,657 (18.94)	52 (11.71)	6,605 (19.04)	
Yes	28,483 (81.06)	392 (88.29)	28,091 (80.96)	
Body mass index				0.968
< 23 kg/m^2	21,221 (60.39)	266 (59.91)	20,955 (60.40)	
≥ 23 kg/m^2	12,942 (36.83)	165 (37.16)	12,777 (36.82)	
Missing	977 (2.78)	13 (2.93)	964 (2.78)	
Diabetes				0.001
No	31,403 (82.73)	376 (84.68)	31,027 (89.43)	
Yes	3,737 (10.63)	68 (15.32)	3,669 (10.57)	
Hypertension				< 0.001
No	29,072 (82.73)	325 (73.20)	28,747 (82.85)	
Yes	6,068 (17.27)	119 (26.80)	5,949 (17.15)	
Stroke				0.293
No	34,635 (98.56)	435 (97.97)	34,200 (98.57)	
Yes	505 (1.44)	9 (2.03)	496 (1.43)	
Heart disease				0.058
No	34,155 (97.20)	425 (95.72)	33,730 (97.22)	
Yes	985 (2.80)	19 (4.28)	966 (2.78)	
Dyslipidemia				0.385
No	34,116 (97.09)	428 (96.40)	33,688 (97.09)	
Yes	1,024 (2.91)	16 (3.60)	1,008 (2.91)	
Compliance with treatment				0.236
Yes	26,182 (74.51)	320 (27.93)	25,862 (25.46)	
No	8,958 (25.49)	124 (72.07)	8,834 (74.54)	

Values are presented as number (%).

low-up time was estimated from the date of TB diagnosis to the date of cancer diagnosis, the date of death, or April 30, 2022, whichever came first. The diagnosis date of TB in the mandatory surveillance system was used as the date of TB diagnosis.

Incidence rate of lung cancer in patients with TB was compared with that of the general population in Gyeonggi-do between 2010 and 2016 obtained from the Korea Central Cancer Registry using the standardized incidence ratio (SIR), adjusted for sex and age. Cox proportional hazards model was used to analyze the relationship between each risk factor and lung cancer risk, adjusted for other variables. The variables included in the Cox proportional hazards model were sex, age at TB diagnosis, income, smoking status, amount of smoking per day, alcohol consumption, moderate or vigorous physical activity, BMI, past history of diabetes, hypertension, stroke, heart disease, and/or dyslipidemia, and compliance with TB treatment. Statistical analyses were performed using the SAS statistical software ver. 9.4 (SAS Institute).

RESULTS

The baseline characteristics of patients with TB included in the study are summarized in Table 1 by lung cancer development. From 2010 to 2016, 35,140 people infected with TB in Gyeonggi-do, including 20,359 (57.94%) male and 14,781 (42.06%) female, were included. The proportion of males, older age group at TB diagnosis (≥ 60 years), ever smokers, smoking ≥ one pack/day, alcohol consumption once or more per week, past history diabetes, and past history of hypertension were significantly higher in TB patients with lung cancer development than in those without lung cancer ($P < 0.05$).

The total follow-up time for 35,140 individuals with TB was 281,284.47 person-years with a range of 1.0-12.3 person-years. The average follow-up time was 8.01 person-years. During follow-up, 444 lung cancer cases were identified with an incidence rate per 100,000 person-years of 157.85 (95% CI = 134.18-184.48, Table 2). As the age at TB diagnosis increased, the incidence rate of lung cancer per 100,000 person-years increased from 3.39 in people aged < 40 years to 96.58 in those aged 40-59 years and 407.69 in people aged 60 years or older. Lung cancer incidence in TB patients was higher in ever-smokers (233.05 per 100,000) than in never-smokers (95.93 per 100,000), and people who smoked ≥ 1 pack/day (311.98 per 100,000) showed higher lung cancer incidence compared with people who smoked < 1 pack/day (79.46 per 100,000). The SIR of lung cancer in TB patients was 2.04 (95% CI = 1.85-2.23), suggesting a higher incidence rate of lung cancer in patients with TB compared to the general population (Table 3).

The factors associated with lung cancer risk in patients with TB are presented in Table 4. The risk of lung cancer was higher in males than that in females, with a hazard ratio (HR) of 2.24 (95% CI = 1.65-3.04). Additionally, increased age at TB diagnosis was associated with increased lung cancer risk (HR 1.09, 95% CI = 1.08-1.10 per 1-year increment). Ever-smokers compared with never-smokers (HR 1.42, 95% CI = 1.02-1.97) and higher amounts of smoking (HR 2.17, 95% CI = 1.63-2.89 in TB patients smoking ≥ 1 pack/day compared with those smoking < 1 pack/day) were associated with increased lung cancer risk in TB patients.

Smoking was significantly associated with lung cancer risk across different socioeconomic status (SES) groups, but the association varied by SES level. Specifically, the lower SES group showed a slightly weaker association (HR 0.92, 95% CI = 0.58-1.47) compared with the higher SES group (HR 0.71, 95% CI = 0.45-1.13). Other factors, such as alcohol consumption, physical activity, body mass index, diabetes, hypertension, stroke, heart disease, and dyslipidemia, did not show statistically significant associations with lung cancer risk in TB patients.

DISCUSSION

This study identified an increased risk of lung cancer development in people with TB infection based on reported TB cases compared to the general population in one Korean province. Male sex, increased age at diagnosis of TB, ever smoking, and increased amount of smoking were associated with an increased risk of lung cancer in patients with TB.

The mechanism of the increased risk of lung cancer after TB was suggested to be chronic TB infection followed by lung scarring, chronic inflammatory responses, and lung metaplasia [6,13,14]. Previous meta-analyses showed increased risk of lung cancer in TB patients with HR and OR between 1.5 and 2, after adjusting for age and smoking [7,15,16], which were slightly lower than the result of this study showing a SIR of 1.96 (95% CI = 1.75-2.12). However, the confounding effects of passive smoking [17], environmental pollution, and lower socioeconomic status, which are associated with both TB and lung cancer [18,19] should be considered. When we compared the incidence of lung cancer in TB patients with that in the general population in Gyeonggi-do, we could not adjust for smoking, passive smoking, or socioeconomic status. However, we adjusted for sex and age because of available information on these variables from cancer registry data. The higher SIR in this study may be due to the lack of control of other confounders. A study that linked a nationwide representative survey and the cancer registry in Korea identified that previous TB infections increased lung cancer risk 3.24-fold [20]. However, the age of the study population was higher than that in our study, and the lag period was not considered [20].

Other issues related to increased risk of lung cancer in TB patients include surveillance bias due to more frequent follow-up medical imaging of TB patients than the general population and possible inclusion of prevalent lung cancers in TB diagnosis [7]. Despite the increased repeated follow-up of

Table 2. Lung cancer incidence per 100,000 person-years in patients with tuberculosis according to characteristics

Variable	Lung cancer	Person-years	Incidence rate (95% CI)[a]
Total	444 (100.00)	281,284.47	157.85 (134.18-184.48)
Sex			
Male	359 (80.86)	159,971.26	224.42 (196.01-255.78)
Female	85 (19.14)	121,313.22	70.07 (54.63-88.52)
Age at tuberculosis diagnosis (yr)			
< 40	3 (0.68)	88,575.01	3.39 (0.79-9.34)
40-59	107 (24.10)	110,785.18	96.58 (78.29-117.87)
≥ 60	334 (75.22)	81,924.28	407.69 (369.07-449.25)
Income group			
Medicaid	20 (4.50)	9,698.32	206.22 (179.03-236.37)
Lower 50%	189 (42.57)	116,647.05	162.03 (138.04-188.99)
Upper 50%	227 (51.13)	147,568.16	153.83 (130.48-180.15)
Missing	8 (1.80)	7,370.95	108.53 (89.08-130.98)
Smoking history			
Never smokers	148 (33.33)	154,274.48	95.93 (77.70-117.16)
Ever smokers	296 (66.67)	127,009.99	233.05 (204.09-264.97)
Smoking per day in ever smokers			
< 1 pack/day	37 (12.50)	46,564.31	79.46 (62.95-98.97)
≥ 1 pack/day	163 (55.07)	52,247.71	311.98 (278.31-348.59)
Missing	96 (32.43)	28,197.97	340.45 (305.24-378.60)
Alcohol consumption once or more per week			
No	177 (39.86)	126,670.08	139.73 (117.53-164.92)
Yes	267 (60.14)	154,614.40	172.69 (147.89-200.45)
Moderate or vigorous physical activity once or more per week			
No	52 (11.71)	53,410.47	97.36 (78.98-118.73)
Yes	392 (88.29)	227,874.00	172.02 (147.28-199.74)
Body mass index			
< 23 kg/m^2	266 (59.91)	170,449.60	156.06 (132.53-182.55)
≥ 23 kg/m^2	165 (37.16)	103,123.38	160.00 (136.17-186.81)
Missing	13 (2.93)	7,711.49	168.58 (144.09-196.04)
Diabetes			
No	376 (84.68)	253,868.55	148.11 (125.22-173.97)
Yes	68 (15.32)	27,415.92	248.03 (218.12-280.90)
Hypertension			
No	325 (73.20)	236,934.06	137.17 (115.18-162.14)
Yes	119 (26.80)	44,350.41	268.32 (237.17-302.42)
Stroke			
No	425 (95.72)	277,722.11	153.03 (129.75-179.29)
Yes	19 (4.28)	3,562.37	533.35 (489.04-580.60)
Heart disease			
No	435 (97.97)	274,280.63	158.60 (134.87-185.29)
Yes	9 (2.03)	7,003.84	128.50 (107.24-152.74)
Dyslipidemia			
No	428 (96.40)	273,471.32	156.51 (132.95-183.04)
Yes	16 (3.60)	7,813.15	204.78 (177.69-234.83)
Compliance with treatment			
Yes	320 (72.07)	209,914.80	152.44 (129.20-178.65)
No	124 (27.93)	71,369.68	173.74 (148.87-201.59)

Values are presented as number only or number (%). [a]per 100,000 person-years.

Table 3. SIR and expected lung cancer cases with 95% CI

Variable	Lung cancer	Expected lung cancer cases	SIR (95% CI)
Total	444	217.45	2.04 (1.85-2.23)

Values are presented as number only. SIR, standardized incidence ratio.

chest radiography in TB patients [21], possibly leading to surveillance bias, studies have shown that chest radiography did not increase diagnostic accuracy of lung cancer both in the general population and in TB patients [22]. In Korea, national health screening, including chest radiography, is offered to all people aged 40 years or older, and the participation rate is

Table 4. Factors associated with lung cancer risk in patients with tuberculosis

Variable	Hazard ratio (95% CI)	*P*-value
Sex		
Male	2.24 (1.65-3.04)	< 0.001
Female	1 (ref)	
Age at tuberculosis diagnosis (yr)		
One-year increment	1.09 (1.08-1.10)	< 0.001
Income group		
Medicaid	1 (ref)	
Lower 50%	0.92 (0.58-1.47)	0.739
Upper 50%	0.71 (0.45-1.13)	0.148
Smoking history		
Never smokers	1 (ref)	
Ever smokers	1.42 (1.02-1.97)	0.035
Smoking per day in ever smokers		
< 1 pack/day	1 (ref)	
≥ 1 pack/day	2.17 (1.63-2.89)	< 0.001
Alcohol consumption once or more per week		
No	1 (ref)	
Yes	1.06 (0.85-1.32)	0.595
Moderate or vigorous physical activity once or more per week		
No	0.78 (0.58-1.05)	0.098
Yes	1 (ref)	
Body mass index		
< 23 kg/m^2	1 (ref)	
≥ 23 kg/m^2	0.92 (0.76-1.12)	0.414
Diabetes		
No	1 (ref)	
Yes	0.94 (0.72-1.23)	0.647
Hypertension		
No	1 (ref)	
Yes	0.92 (0.73-1.15)	0.441
Stroke		
No	1 (ref)	
Yes	0.81 (0.51-1.29)	0.365
Heart disease		
No	1 (ref)	
Yes	0.91 (0.47-1.76)	0.774
Dyslipidemia		
No	1 (ref)	
Yes	0.98 (0.59-1.63)	0.941
Compliance with treatment		
Yes	1 (ref)	
No	0.92 (0.74-1.13)	0.411

ref, reference.

more than 70%. In addition, lung cancer screening using low-dose chest computed tomography is offered to high-risk populations (past or current smokers with ≥ 30 pack-years) [23]. Therefore, surveillance bias did not significantly affect the results in the Korean population. To avoid possible inclusion of prevalent lung cancers in TB diagnosis, this study excluded lung cancer diagnosed within one year of TB diagnosis. A meta-analysis showed a higher occurrence of lung cancer within the second year of TB diagnosis, compared with later years of TB diagnosis, and after excluding the first 2 years of lung cancer incident cases, the strength of the association was decreased [7]. We confirmed that there was no significant difference in the incidence of lung cancer when comparing the period of at least 1 year and within 3 years after TB diagnosis with that after 3 years.

In this study, smoking experience and increased amount of smoking were significantly associated with increased lung cancer risk among patients with TB. Smoking and increased smoking are established risk factors for lung cancer [24] as confirmed in the present study. A study conducted in Korea showed an association between old TB and increased lung cancer risk, irrespective of smoking status (never, past, and current smokers) [20], suggesting an independent role for smoking and TB in lung cancer risk. Meta-analysis studies have shown that the lung cancer risk in TB patients without smoking experience, including Asian never-smoking females, was comparable to the overall risk [15,16]. Based on previous meta-analyses and the results of this study, increased lung cancer risk in TB patients independent of tobacco smoking could be supported. Smoking and increased smoking are associated with an increased risk of TB [25] and negative treatment results [26], thus increasing the inflammatory response followed by tumor growth and carcinogenesis [6].

An interesting finding of this study was that there was no significant association between alcohol consumption and lung cancer risk in patients with TB. Studies have shown an inverse association between alcohol consumption and lung cancer risk in never smokers [27] and the results of this study might support this association. Other significantly-associated factors, including sex and age, are well-established in the general population [28]. Based on the present findings, it could be identified that TB infection increased lung cancer risk compared with the general population and increased factors associated with lung cancer among TB patients may be comparable with known risk factors of lung cancer in the general population. This suggests the independent role of TB and known risk factors on lung cancer development.

Chronic inflammation from TB is a well-established factor that can promote lung carcinogenesis over time. TB infection can lead to persistent inflammation in lung tissues, resulting in repeated cycles of injury and repair. This process includes the release of inflammatory cytokines such as TNF-α, interleukin (IL)-1, and IL-6, which can promote cellular changes conducive to cancer, such as increased cell proliferation, fibrosis, and mutagenesis. Studies have demonstrated that TB-related inflammation and fibrosis can significantly increase the risk of lung cancer, and this elevated risk can persist for years after the initial TB infection [14]. Moreover, our subgroup analysis showed that the lower SES group exhibited a stronger association between smoking and lung cancer risk compared to the higher SES group. Based on these findings, we emphasize the increased vulnerability of the lower SES and the importance of targeted smoking cessation and prevention programs in this population to mitigate lung cancer risk.

This study has several limitations. First, as patients with latent TB show no symptoms, they could not be identified. Thus, although we first included all TB cases within one province in Korea, people with latent TB may not have been included in this study. If latent TB cases were categorized into the non-TB group, the observed association between TB and lung cancer risk is likely to be underestimated. Second, TB patients who had received a medical examination at least one year in advance of lung cancer infection could be included. This resulted in the exclusion of approximately 56% of the participants from the study population. This exclusion was necessary to reduce potential bias, as individuals without recent health screening data were associated with lower socioeconomic status [29]. Thus, participants in this study might have had a higher socioeconomic status than TB patients without screening experience. However, we identified that even TB patients with higher socioeconomic status had an increased risk of lung cancer, possibly excluding the confounding effect of socioeconomic status [19]. Third, despite the different strengths of associations between histological types of lung cancer and TB [24,30], we could not assess the histologic association herein due to unavailable information of cancer types in the NHID. Despite these limitations, this study is the first study that attempts to include all TB cases in a province of Korea with a relatively large number of TB cases and incidence of lung cancer cases.

In conclusion, this study confirmed an increased risk of lung cancer in people with TB compared to that in the general population. The factors associated with lung cancer in patients with TB were sex, age, smoking status, and the amount of smoking, suggesting an independent role of TB and known risk factors in the pathogenesis of lung cancer.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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