Original Article

Active tuberculosis risk associated with malignancies: an 18-year retrospective cohort study in Korea

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Background: Active tuberculosis (TB) develops in approximately 10% of people with a latent tuberculosis infection (LTBI). TB guidelines recommend that LTBI screening and treatments target high-risk patients. Malignancies are not universally considered a high-risk factor for active TB. This study aimed to determine the degrees to which active TB risk was associated with various cancers in a Korean population.

Methods: This study involved patients aged ≥20 years who were diagnosed with cancer at Ulsan University Hospital (UUH) from January 2000 to December 2014 and individuals who visited UUH for health screening and were age- and sex-matched randomly with cases in a 1:2 ratio. Using retrospective cohort study, the development of bacteriologically confirmed TB (BCTB) within 3 years after enrollment was investigated. The relative risks of BCTB were estimated using incidence rate ratios (IRRs) and a Poisson regression analysis.

Results: During the study period, 380 of 34,783 cancer patients and 79 of 69,566 control subjects developed BCTB, yielding respective incidence rates of 535 and 37/100,000 person-years, respectively. In all cancer cases, the IRR of BCTB was 14.30, and especially high rates were associated with the following cancers: esophageal cancer (74.72), multiple myeloma (70.76), lung cancer (50.35), pancreatic cancer (46.04), leukemia (40.45), head and neck cancer (24.60), and lymphoma (22.67).

Conclusions: The incidence of active TB was higher in cancer patients than in control subjects. In particular, lung cancer, esophageal cancer, pancreatic cancer, hematologic malignancy and head and neck cancer were identified as high-risk factors for active TB, as indicated by IRRs of 20-75. These findings suggest that patients with high-risk cancers should be targeted for LTBI screening and treatment.

Keywords: Tuberculosis (TB); latent tuberculosis infection (LTBI); *Mycobacterium tuberculosis*; tuberculosis screening; cancer; malignancy

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Introduction

Tuberculosis (TB), remains a significant public health problem worldwide. Latent TB infection (LTBI) describes the condition wherein an individual is infected with *Mycobacterium tuberculosis* but not currently manifesting active disease (1). For a person with documented LTBI, the estimated lifetime risk of developing active TB is 10%, although preventive treatment can avert this risk and confer an estimated protective effect of 60–90% (2,3). To reduce both the incidence of active TB and the associated screening costs, LTBI screening and treatment are applied selectively to those with high risk of developing active TB. However, target populations for screening vary among countries and guidelines (1,4-7).

Patients with cancer may exhibit deficiencies in cell-mediated immunity as either a direct effect or an indirect effect related to chemotherapy (8,9). Accordingly, many patients with LTBI and cancer develop active TB (10,11). However, the 2015 World Health Organization (WHO) guidelines do not recommend LTBI screening and treatment for patients with cancer, and the current Korean guidelines recommend targeting only patients with hematologic or head and neck cancers (7). Nonetheless, the WHO guidelines also emphasize the importance of further research on the benefits and harms of LTBI screening and treatment in this patient population (12).

Objectively quantifying the magnitude of active TB risk faced by patients with various malignancies remains challenging. Although a single-center study reported an increased incidence of TB in patients with cancer (9), no studies have investigated the risks associated with various malignancies in a geographical region. A recent meta-analysis by Cheng reported an increased risk of TB development in patients with solid cancers, particularly hematologic, head and neck, and lung cancers [incidence rate ratio (IRR) =12]. Accordingly, those patients faced a higher risk of developing active TB and would benefit from LTBI screening and treatment (13). Dobler *et al.* further performed a meta-analysis estimating the incidence of TB relative to a reference group after adjusting for age, and found that the IRR of TB associated with cancer was 2.61; those authors concluded that LTBI screening in patients with cancer may be unnecessary except for patients with hematologic malignancies and children with cancer (14).

The accuracy and reliability of TB diagnoses are often questionable, as many clinical diagnoses of TB are not confirmed using microbiological evidence such as cultures or polymerase chain reaction (PCR). Given the lack of studies investigating associations of active TB with multiple types of malignancies in a single population, as well as the conflicting results of previous studies, additional research is needed to better define high-risk patients and determine the optimal management of LTBI in patients with various malignancies. In this study, we aimed to evaluate the degree of risk of active TB, including bacteriologically confirmed TB (BCTB) and clinically diagnosed TB (CDTB), in patients with various cancers in Korea.

Methods

Case cohort and control cohorts (control cohort 1 and control cohort 2)

This study was approved by the Institutional Review Board of Ulsan University Hospital (no. UUH 2018-04-006). We retrospectively established case and control cohorts (control cohort 1 and control cohort 2) to estimate the relative risk of developing active TB. Patients aged ≥20 years who were newly diagnosed with malignancies at Ulsan University Hospital (UUH) between January 2000 and December 2014 were collected as case cohort. Diagnoses of malignancy were based on International Classification of Diseases, Tenth Revision (ICD-10) codes (C000–C999). The malignancies and ICD-10 codes included in this study are listed in *Table S1*. In patients with multiple or duplicate cancers, the first registered cancer was selected for analysis. Patients who developed active TB within 2 years before a cancer diagnosis were excluded. Patients in whom active TB and cancer were diagnosed simultaneously were also excluded to avoid ascertainment bias. The development of active TB for 3 years after a cancer diagnosis was investigated in the case cohort (9).

Individuals who had no history of cancer, visited UUH for health screening during the case cohort enrollment period, and were followed for more than 3 years after health screening were enrolled randomly via a 1:2 sex- and age-matching strategy as the control cohort 1. Those who developed active TB within 2 years before enrollment were excluded. Those with active TB as determined by chest radiography or chest computed tomography (CT) at the time of enrollment were also excluded to avoid ascertainment bias. The development of active TB for 3 years after enrollment was also investigated in the control cohort 1.

The incidence of newly developed TB was expressed

in terms of 100,000 person-years (py) to account for differences in the follow-up periods between the case cohort and control 1 cohort. Clinical data of the case cohort and control cohort1 were extracted using the Ulsan University Hospital Information of Clinical Ecosystem, a clinical data warehouse.

We additionally set the total population of Ulsan province (Korea) as the control cohort 2 and surveyed the annual population of Ulsan from 2000–2017 and the number of TB patients per year for the period from the Korean Statistical Information Service (http://kosis.kr) to determine the incidence of TB.

Definition of active tuberculosis

Active TB was defined as follows: (I) the isolation of *M. tuberculosis* using any mycobacterial culture method; or (II) the isolation of *M. tuberculosis* using any molecular methods; or (III) a diagnosis of TB by a physician (ICD-10 codes A15–A19) AND prescription of medication for TB, such as isoniazid, rifampin (rifampicin), rifabutin, ethambutol, pyrazinamide, cycloserine, prothionamide, streptomycin, kanamycin, or amikacin. Patients who met criterion (I) or (II) were classified further as BCTB, while those who met criterion (III) were classified as CDTB. "All TB" included both BCTB and CDTB cases (15).

Statistical analysis

The IRR was used to estimate the risk of developing TB according in all malignancies and each type of malignancy were estimated using a Poisson regression analysis. The IRR was calculated by dividing the incidence rate (IR) of TB in the cancer cohort by that in the control cohorts; this was performed separately for each control cohort. All cancer patients were analyzed by age group, and additionally analyzed by cancer type in five most common malignancies of developing TB. All statistical analyses were performed using Stata SE software, version 12 (Stata Corporation, College Station, TX, USA) and R package, version 3.5.1 (R Project for Statistical Computing, Vienna, Austria).

Results

Incidence rate of tuberculosis in the case cohort

A total of 34,783 patients with cancer were enrolled, with a male proportion of 50.2% and median age of 58 years (interquartile range, 68–48). The numbers of cases of each type of cancer are shown in *Table S2*. During the study period, 496 of 34,783 cancer patients developed TB and the incidence rates of BCTB and all TB were 535 and 699/100,000 py, respectively. The incidence rates of TB according to the type of cancer are shown in *Table 1*.

Incidence rate of tuberculosis in the control cohorts 1 and 2

As the cohort 1, 69,566 age- and sex-matched subjects were registered. The incidence rates of all TB and BCTB in the control cohort 1 were 65 and 37/100,000 py, respectively.

In the control cohort 2, the TB incidence rate was calculated from 2000 to 2017 using the annual changes in population and the number of TB patients per year. The estimated annual average population size was 1,151,402 persons, and the average annual number of TB cases was 829. The calculated TB incidence rate in the control cohort 2 was 72/100,000 year; BCTB cases were not identified separately. The TB incidence rates in the control cohorts 1 and 2 are shown in *Table 2*.

Incidence rate ratio of tuberculosis in the case cohort compared to the control cohort 1 and 2

In the entire case cohort, the overall IRR for the development of all TB compared to the control cohort 1 was 10.68 [95% confidence interval (CI), 8.83–12.99], while the IRR for BCTB was 14.30 (95% CI, 11.91–17.18). Among all patients with cancer, the overall IRR for the development of all TB was 9.71 (95% CI, 8.99–10.48), compared to control cohort 2. The IRRs for each type of cancer relative to the control cohorts 1 and 2 are shown in *Table 3*, *Figures 1* and *2*. Regardless of the type of control cohort, common cancers of developing all TB and BCTB include esophageal cancer, lung cancer, pancreatic cancer, head and neck cancer and hematologic malignancies. All cancer patients were analyzed by age group, and additionally analyzed by cancer type in five most common malignancies of developing TB, esophageal cancer, lung cancer, pancreatic cancer, head and neck cancer, and hematologic malignancies. The risk of developing TB increased with old age. The IRRs in overall patients and in each cancer types are shown in *Table 4*.

Discussion

This case-control cohort study revealed that patients with cancer at our institution faced a significantly increased risk

Table 1 TB incidence rates in cancer patients stratified by cancer type

Type of cancer	Cancer patients, N (%)	Cancer patients with TB			IR of TB in cancer patients/100,000 person-year		
		BCTB	CDTB	All TB	BCTB	CDTB	All TB
Malignant brain tumor (including eye, spinal cord)	474 (1.36)	3	0	3	436	–	436
Head and neck cancer[a]	994 (2.86)	18	4	22	921	202	1,126
Lung cancer	3,454 (9.93)	78	38	116	1,886	907	2,804
Esophageal cancer	446 (1.28)	16	3	19	2,798	520	3,323
Stomach cancer	6,120 (17.59)	75	18	93	575	137	713
Colorectal cancer	4,145 (11.92)	37	17	54	407	186	594
Hepatobiliary/pancreatic cancer							
Hepatocellular carcinoma	3,496 (10.05)	25	11	36	468	205	674
Biliary tract cancer	1,073 (3.08)	6	1	7	397	66	463
Pancreatic cancer	907 (2.61)	13	1	14	1,724	131	1,857
Hematologic cancer							
Lymphoma	756 (2.17)	14	1	15	849	60	909
Leukemia	576 (1.66)	14	1	15	1,515	107	1,623
Multiple myeloma	208 (0.60)	10	0	10	2,649	–	2,649
Thyroid cancer	4,824 (13.87)	19	6	25	145	46	191
Breast cancer	3,216 (9.25)	12	8	20	144	96	240
Uterine and ovary cancer							
Cervical cancer	1,031 (2.96)	10	1	11	415	41	457
Uterine cancer	302 (0.87)	2	0	2	278	–	278
Ovary cancer	527 (1.52)	6	1	7	533	88	622
Urological cancer							
Kidney cancer	603 (1.73)	8	1	9	516	64	580
Ureter and bladder cancer	838 (2.41)	4	4	8	215	215	430
Prostate cancer	793 (2.28)	10	0	10	551	-	551
Total	34,783 (100.0)	380	116	496	535	163	699

[a], malignancy above chest except brain, eye, and thyroid. BCTB, bacteriologically confirmed tuberculosis; CDTB, clinically diagnosed tuberculosis; IR, incidence rate; IRR, incidence rate ratio; TB, tuberculosis.

Table 2 Tuberculosis statistics in the control cohort 1 [1:2 matched (age/sex) health screening subjects] and control cohort 2 (total population of Ulsan province)

Parameters	Control 1 (N=69,566)			Control 2 (N=1,151,402[a])
	BCTB	CDTB	All TB	
Number	79	59	138	829[a]
Duration	210,972.772 person-year	210,996.493 person-year	210,875.326 person-year	18 years
Incidence rate	37/100,000 person-year	28/100,000 person-year	65/100,000 person-year	72/100,000 year

[a], annual average. BCTB, bacteriologically confirmed tuberculosis; CDTB, clinically diagnosed tuberculosis.

Table 3 TB incidence rate ratios (IRRs) in cancer patients stratified by cancer types, compared to the control cohort 1 (age-/sex-matched health screening subjects, 1:2 ratio) and control cohort 2 (Ulsan population)

Type of cancer	Cancer-specific IRR (95% CI) using control cohort 1			Cancer-specific IRR (95% CI) relative to the control cohort 2
	BCTB	CDTB	All TB	All TB
Malignant brain tumor (including eye, spinal cord)	11.64 (4.70–28.84)	–	6.66 (2.48–17.90)	6.05 (2.24–16.33)
Head and neck cancer[a]	24.60 (17.43–34.72)	7.23 (3.05–17.17)	17.21 (12.40–23.88)	15.64 (11.45–21.35)
Lung cancer	50.35 (42.22–60.06)	32.45 (25.10–41.96)	42.85 (37.06–49.54)	38.95 (34.84–43.54)
Esophageal cancer	74.72 (56.94–98.06)	18.63 (8.12–42.75)	50.77 (38.77–66.49)	46.15 (35.58–59.85)
Stomach cancer	15.35 (12.12–19.42)	4.90 (3.04–7.89)	10.89 (8.83–13.43)	9.90 (8.37–11.70)
Colorectal cancer	10.87 (7.96–14.83)	6.65 (4.17–10.60)	9.07 (7.00–11.75)	8.25 (6.59–10.33)
Hepatobiliary/pancreatic cancer				
Hepatocellular carcinoma	12.49 (8.81–17.71)	7.34 (4.24–12.70)	10.29 (7.66–13.83)	9.36 (7.15–12.24)
Biliary tract cancer	10.60 (5.45–20.60)	2.36 (0.35–16.03)	7.08 (3.69–13.56)	6.43 (3.38–12.25)
Pancreatic cancer	46.04 (32.82–64.59)	4.70 (0.78–28.23)	28.37 (19.84–40.58)	25.79 (18.18–36.58)
Hematologic cancer				
Lymphoma	22.67 (15.35–33.47)	2.16 (0.31–14.84)	13.90 (9.27–20.84)	12.63 (8.53–18.71)
Leukemia	40.45 (28.82–56.77)	3.84 (0.61–24.06)	24.80 (17.33–35.47)	22.54 (15.91–31.93)
Multiple myeloma	70.76 (50.47–99.20)	–	40.49 (27.61–59.37)	36.80 (25.18–53.77)
Thyroid cancer	3.87 (2.43–6.16)	1.63 (0.71–3.75)	2.92 (1.94–4.38)	2.65 (1.82–3.87)
Breast cancer	3.85 (2.19–6.76)	3.43 (1.71–6.86)	3.67 (2.37–5.68)	3.33 (2.20–5.05)
Uterine and ovary cancer				
Cervical cancer	11.09 (6.57–18.69)	1.47 (0.21–10.50)	6.98 (4.12–11.82)	6.34 (3.79–10.62)
Uterine cancer	7.44 (2.26–24.51)	–	4.25 (1.18 –15.32)	3.87 (1.07–13.99)
Ovary cancer	14.25 (7.60–26.70)	3.16 (0.49–20.51)	9.51 (5.12–17.68)	8.64 (4.67–15.99)
Urological cancer				
Kidney cancer	13.78 (7.92–23.98)	2.29 (0.34–15.66)	8.87 (5.08–15.48)	8.06 (4.66–13.96)
Ureter and bladder cancer	5.75 (2.37–13.95)	7.68 (3.26–18.09)	6.58 (3.55–12.19)	5.98 (3.25–11.00)
Prostate cancer	14.73 (8.98–24.15)	–	8.43 (4.94–14.38)	7.66 (4.53–12.95)
Total	14.30 (11.91–17.18)	5.82 (4.41–7.67)	10.68 (8.83–12.99)	9.71 (8.99–10.48)

[a], malignancy above the chest, except brain, eye, and thyroid. BCTB, bacteriologically confirmed tuberculosis; CDTB, clinically diagnosed tuberculosis; CI, confidence interval; IRR, incidence rate ratio; TB, tuberculosis.

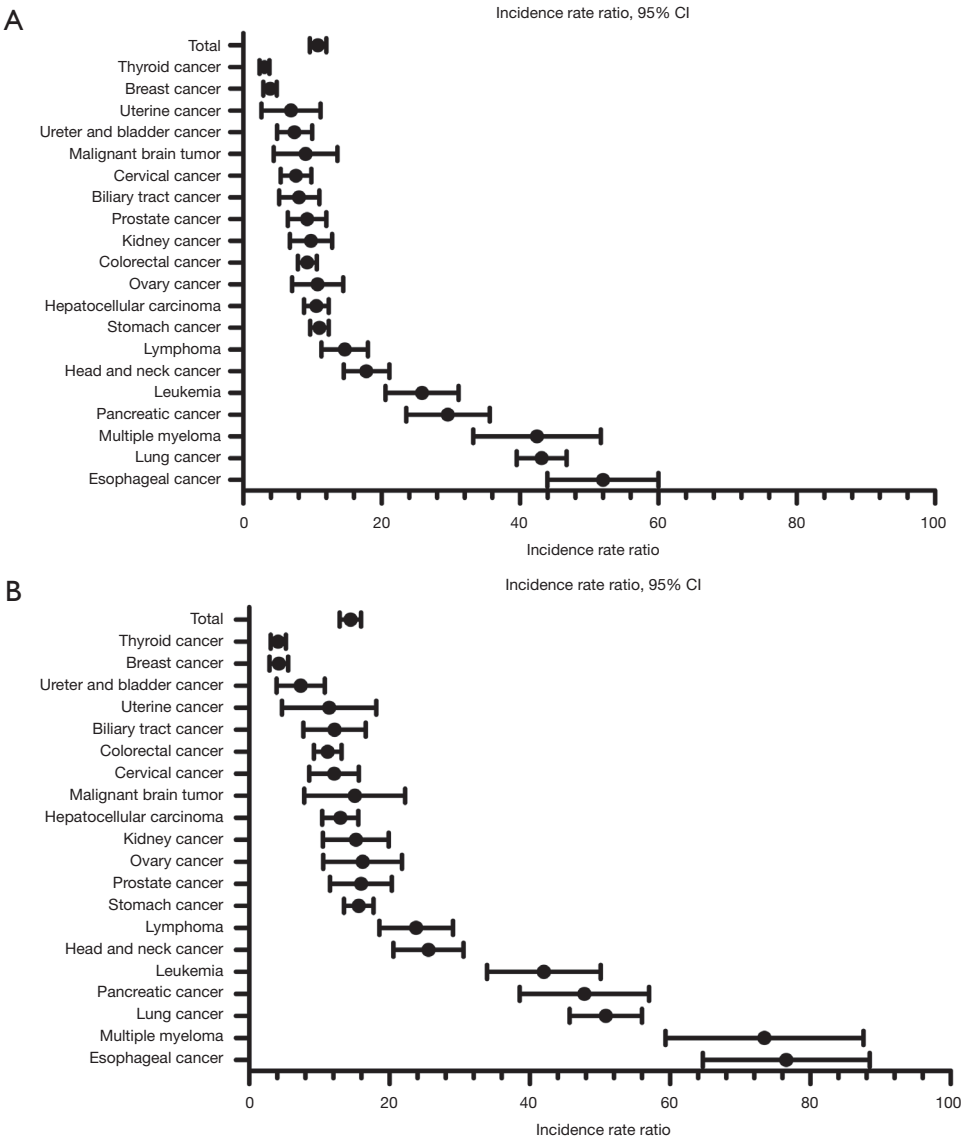

Figure 1 (A) Incidence rate ratios (IRRs) for all tuberculosis (TB) in cancer patients stratified by cancer types, compared to the control 1 cohort (health screening subjects); (B) IRRs for bacteriologically confirmed tuberculosis (BCTB) in cancer patients stratified by cancer types, compared to control 1 cohort (health screening subjects).

of developing TB relative to people who participated in a health screening program at the same institution or to the general population of Ulsan province. Moreover, IRRs were ≥20-fold for the development of BCTB among patients with esophageal cancer, multiple myeloma, lung cancer, pancreatic cancer, leukemia, head and neck cancer, and lymphoma.

In contrast to previous studies, our study included almost all types of cancer commonly encountered in clinical practice, and our control cohort 1 included only subjects for whom detailed medical records were available for more than 3 years from the time of health screening. We further determined the TB incidence rate based on the total population of Ulsan province as the control cohort 2, as the control cohort 1 may not have been representative of the general population. Similar incidence rates of all TB were observed in the control cohorts 1 and 2, indicating that control 1 adequately represented the general population. Our findings, derived from a large sample extracted from a single regional population cohort to reduce heterogeneity,

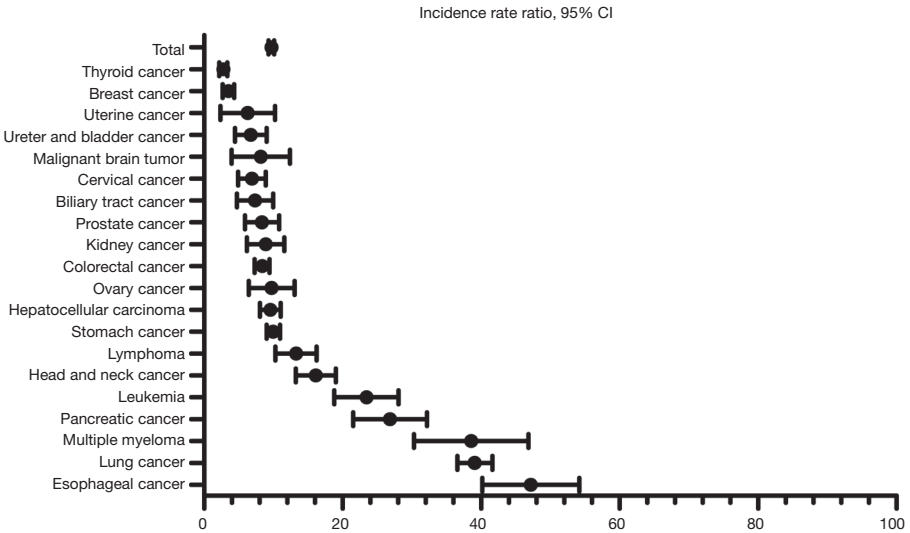

Figure 2 Incidence rate ratios (IRR) for all tuberculosis (TB) in cancer patients stratified by cancer types, compared to the control 2 cohort (population of Ulsan province).

provide a valuable and objective analysis of TB in patients with various malignancies. The IRRs of each malignancy were based on this single population cohort and are therefore more reliable than those obtained in previous meta-analyses involving various populations (13,14). We also included only BCTB cases in some analyses to avoid diagnostic uncertainty (14).

We observed an approximately 10-fold increase in the risk of developing TB among patients with cancer when compared with health screening participants and the general population of Ulsan. The IRRs of patients with cancer in our study were comparable to the estimated risks associated with the indications for current LTBI screening and treatment, such as AIDS (16), recent TB infection within 2 years (17), end-stage renal disease (18,19), organ transplantation (20), and TNF-alpha inhibitor use (21).

Notably, we observed the highest relative risk of TB development among patients with esophageal cancer. This was consistent with a previous report by Wu *et al.*, wherein the risk of TB was highest in patients with esophageal cancer but similar to the risks associated with hematologic malignancies and lung cancer (22). The increased risk of TB development in these patients may be confounded by the associations of heavy smoking and excessive alcohol use, which are also independent risk factors for active TB (23,24). Despite these possible confounding factors, however, the relative risk of BCTB was significantly higher in patients with esophageal cancer than in the control group in our study.

In our study, patients with lung cancer also had a high IRR for TB and BCTB development, which was again consistent with a previous report (22). As the Korean guidelines for initial evaluation include pulmonary TB as a possible differential diagnosis of lung cancer, it may be difficult to obtain an accurate diagnosis of TB in patients with lung cancer. Therefore, a previous analysis by Seo *et al.* (25) excluded patients with lung cancer. Other studies have reported an increased risk of lung cancer in patients with a history of pulmonary TB (26,27), thus obscuring the causal relationship between these diseases. Again, smoking may be a confounding factor for TB development in patients with lung cancer.

Hematologic malignancies are associated with an increased risk of developing active TB. In this study, although all patients with hematologic malignancies faced an increased risk, the risk of developing TB was particularly high among those with multiple myeloma, consistent with a previously reported incidence from a study in Taiwan (28). Compared to other hematologic malignancies, patients with multiple myeloma tend to be older and are more likely to develop chronic kidney disease and receive long-term steroid therapy and chemotherapy, which may account for the increased risk of TB (28). Therefore, previous recommendations regarding LTBI screening for patients with hematologic malignancies, especially multiple myeloma, should be upheld.

Table 4 TB incidence rate ration (IRRs) in cancer patients by age, compared to the control cohort 1 [age-/sex-matched health screening subjects, 1:2 ratio]

Age-group (years)	Case cohort (/100,000 py)	Control cohort (1/100,000 py)	IRR	Cancer type (/100,000 py, by each cancer type)						IRR by each cancer type					
				Esophageal cancer	Lung cancer	Pancreatic cancer	Head and neck cancer	Hematologic malignancies		Esophageal cancer	Lung cancer	Pancreatic cancer	Head and neck cancer	Hematologic malignancies	
<40	366.34	75.52	4.85	0.00	7502.16	0.00	428.34	774.61		0.00	99.34	0.00	5.67	10.26	
40–49	351.29	58.59	6.00	0.00	2,749.60	0.00	323.28	1048.35		0.00	46.93	0.00	5.52	17.89	
50–59	494.14	57.40	8.61	3,072.58	1,312.00	2,859.40	1273.42	928.42		53.52	22.86	49.81	22.18	16.17	
≥60	1166.08	117.99	9.88	3,854.39	3,247.24	1,957.24	1509.46	2,297.33		32.67	27.52	16.59	12.79	19.47	
Total	698.94	65.44	10.68	3,322.57	2,804.13	1,856.79	1126.05	1,341.71		50.77	42.85	28.37	17.21	20.50	

py, person-years.

Previously, Seo *et al.* reported that pancreatic cancer was associated with the highest risk of TB among all solid organ cancers except lung cancer (25). In our study, pancreatic cancer was associated with the fourth highest risk of BCTB development among the investigated cancers. Most patients with pancreatic cancer are diagnosed at an advanced stage of disease, and the associated malnutrition, and deteriorated general condition might be associated with a higher risk of TB development. Moreover, patients with advanced pancreatic cancer have a markedly reduced life expectancy, which is also associated with an increased IRR for active TB. Still, pancreatic cancer has a much higher IRR for TB bile duct or liver cancer, although both latter cancers are also largely diagnosed at an advanced stage and are associated with a short life expectancy. Accordingly, currently unknown and potentially independent mechanisms may contribute to the development of TB in patients with pancreatic cancer, such as tumor-associated inflammation, the decreased production of immune-related proteins due to decreased fat absorption, and cancer-induced diabetes. Further research is needed to clarify this mechanism.

A diagnosis of active TB affects the treatment administered to a cancer patient. For example, chemotherapy or surgery may be delayed due to a TB diagnosis or associated medication therapy. In a study by Ahn *et al.*, the identification of TB infection interrupted the administration of bortezomib in patients with multiple myeloma, which significantly affected patient outcomes (29). LTBI screening at the time of a diagnosis of a high TB risk cancer may enable the prevention of active TB during cancer treatment and enable the appropriate administration of chemotherapy.

Developments in chemotherapeutic drugs and treatment modalities for cancer patients have led to increases in life expectancies. It is increasingly important to identify patients at a high risk of developing active TB and provide appropriate treatment. As noted previously, cancer patients with decreased cellular immunity face an increased risk of active TB (30) and remain in a prolonged state of immunocompromise. Therefore, LTBI screening and treatment is needed to prevent opportunistic infection and should be performed at the time of cancer diagnosis, as LTBI screening is performed at the time of HIV diagnosis in developing countries.

This study had several limitations. First, it was performed retrospectively at a single center, and therefore the results may not reflect the general population in Korea. Further, risk of active tuberculosis in cancer patients depends to great extent on tuberculosis epidemiological situation in

certain geographic region. Therefore, the results of this study should be carefully generalized in countries with low TB incidence. Second, the possibility of sampling bias in the diagnosis of active TB could not be excluded. Patients with malignancy usually received more medical attention in terms of frequent physical examination, or medical procedure such as laboratory or radiologic tests. The third shortcoming was that we could not identify comorbidities such as diabetes, malnutrition, HIV infection, renal insufficiency and immunosuppressant therapies that might have affected the development of TB. These potential predisposing factors were not extracted because the data of comorbidities were not accurately collected from big data. Other factors such as the disease stage at cancer diagnosis, chemotherapy, surgery, and radiotherapy, were not included in the analysis. Lastly, our study does not justify unconditional LTBI testing for cancers with high TB incidence. If there are a previous history of tuberculosis treatment and a radiologically stable scar lesion, LTBI testing is not necessary. In addition, if there is currently evidence of active tuberculosis, tuberculosis treatment may be performed without the LTBI test. The indications for LTBI and preventive anti-tuberculous therapy in cancer patients should be much better defined by future studies.

In conclusion, the incidence of active TB was higher in cancer patients than in health screening recipients or the general population of Ulsan province. Patients with lung cancer, esophageal cancer, pancreatic cancer, hematologic malignancy, and head and neck cancer faced a particularly high risk of developing TB. Therefore, we recommend targeted LTBI screening and treatment strategies for patients with these high-risk cancers.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd.2020.02.50). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Review Board of UUH (approval no. 2018-04-006) and was performed in accordance with the ethical standards of the institutional research committee and the latest Declaration of Helsinki. Informed consent was waived for its nature of retrospective analysis.

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Supplementary

Table S1 Malignancies according to ICD-10 codes

Type of cancer	ICD-10 codes
Malignant brain tumor (including eye, spinal cord)	C69–C72
Head and neck cancer[a]	C00–C14, C30–C32, C76
Lung cancer	C33–C34
Esophageal cancer	C15
Stomach cancer	C16
Colorectal cancer	C18–C20
Hepatobiliary/pancreatic cancer	
Hepatocellular carcinoma	C22
Biliary tract cancer	C23–C24
Pancreatic cancer	C25
Thyroid cancer	C73
Breast cancer	C50
Uterine and ovary cancer	
Cervical cancer	C53
Uterine cancer	C54–C55
Ovary cancer	C56
Urological cancer	
Kidney cancer	C53
Ureter and Bladder cancer	C54–C55
Prostate cancer	C56
Hematologic cancer	
Lymphoma	C81–C88
Leukemia	C91–C95
Multiple myeloma	C90

[a], malignancy above the chest, except brain, eye, and thyroid.

Table S2 Case group: annual number of cancer patients stratified by cancer type

Type of cancer	Total	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Malignant brain tumor (including eye, spinal cord)	474	29	20	19	27	36	29	31	34	40	30	34	29	33	47	36
Head and neck cancer[a]	994	60	71	35	60	69	77	83	81	47	53	61	57	68	82	90
Lung cancer	3,454	130	154	209	210	207	242	223	236	253	246	239	215	266	315	309
Esophageal cancer	446	13	24	33	38	39	28	19	34	33	29	29	28	26	37	36
Stomach cancer	6,120	236	252	302	381	363	425	406	459	509	467	457	440	438	482	503
Colorectal cancer	4,145	116	152	151	230	200	206	261	271	308	356	325	349	386	439	395
Hepatobiliary/pancreatic cancer																
Hepatocellular carcinoma	3,496	214	199	219	224	193	215	203	250	267	220	221	239	257	285	290
Biliary tract cancer	1,073	40	47	51	62	55	61	72	66	90	80	69	92	94	121	73
Pancreatic cancer	907	32	39	43	57	50	49	51	60	76	64	74	64	73	83	92
Hematologic cancer																
Lymphoma	756	20	17	19	34	55	35	46	40	50	64	60	66	76	95	79
Leukemia	576	17	23	19	28	31	42	52	31	41	59	50	49	33	39	62
Multiple myeloma	208	5	3	11	13	16	9	5	14	10	15	14	21	21	24	27
Thyroid cancer	4,824	38	45	77	137	173	167	236	302	345	403	501	515	563	699	623
Breast cancer	3,216	80	94	130	156	153	177	174	227	211	229	260	289	315	322	399
Uterine and ovary cancer																
Cervical cancer	1,031	83	107	66	52	57	62	79	64	60	73	68	66	58	70	66
Uterine cancer	302	8	3	6	9	11	14	15	29	17	28	24	25	37	41	35
Ovary cancer	527	26	24	30	30	26	40	32	38	35	39	44	30	34	50	49
Urological cancer																
Kidney cancer	603	27	8	27	17	56	46	47	33	33	43	51	45	54	65	51
Ureter and Bladder cancer	838	35	45	49	53	57	63	45	50	43	69	57	62	58	78	74
Prostate cancer	793	23	21	26	44	43	42	41	60	61	66	47	60	87	79	93
Total	34,783	1,232	1,348	1,522	1,862	1,890	2,029	2,121	2,379	2,529	2,633	2,685	2,741	2,977	3,453	3,382

[a], malignancy above the chest, except brain, eye, and thyroid.