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Association between tuberculosis infections and non-pulmonary malignancies: a nationwide population-based study

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Background: In addition to lung cancers, tuberculosis infections have been associated with increased risk of non-pulmonary malignancies in case reports. Our population-based study employed standardized incidence ratios (SIRs) to systemically survey non-pulmonary cancer risks after tuberculosis infections.

Methods: Data of patients who had newly diagnosed tuberculosis, were aged 20 years or older, and had no prior cancer or tuberculosis were sampled from the Taiwan National Health Insurance database between 2000 and 2010. SIRs compared cancer incidence in patients with tuberculosis infections to the general population. SIRs of specific cancers were further analyzed with respect to gender and time after tuberculosis infections.

Results: After a follow-up period of 28 866 person–years, 530 tuberculosis cases developed cancers compared with 256 cases in the general populations (2.07, 95% confidence interval (CI), 1.90–2.26). The SIR of non-pulmonary malignancies was also increased (1.71, 95% CI, 1.54–1.90). For males, SIRs were increased within 1 year after tuberculosis diagnosis for the following cancers: head and neck, esophageal, colorectal, liver, lung, melanomas, and Hodgkin's disease. SIRs were increased for liver, biliary, lung, and bladder cancers beyond the first year after tuberculosis diagnosis. For females, SIRs were increased for leukemia, esophageal, and lung cancers within the first year, and only for leukemia beyond 1 year post diagnosis.

Conclusion: Having found increased risks of several cancers that differ with gender and time after tuberculosis diagnosis, physicians may consider these factors in patients following tuberculosis diagnosis.

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Tuberculosis is an important public health issue with high mortality in low- and middle-income countries. In 2011, 8.7 million new cases were diagnosed and 1.4 million died of tuberculosis worldwide (WHO, 2012). In developed countries, mortality attributable to tuberculosis infections was rare (Sterling *et al*, 2006). However, caseous granulomas, tissue liquefaction, and cavity formation in lungs of infected patients often result in long-term deficits, such as impaired pulmonary function (Maguire *et al*, 2009). In addition, tuberculosis has been associated with subsequent risk of lung cancers (Pasipanodya *et al*, 2007; Engels *et al*, 2009). Although the etiological relationship between the two diseases is unknown, increased risk is consistently shown by population-based studies (Wu *et al*, 2011a; Yu *et al*, 2011), suggesting that physicians should be aware of lung cancers in patients with prior tuberculosis infections.

Chronic infections and inflammation are associated with carcinogenesis (Ohshima and Bartsch, 1994; Pisani *et al*, 1997). Tuberculosis is associated with subsequent malignancies other than lung cancer, such as pyothorax-associated lymphoma (Nakatsuka *et al*, 2002) and hematological malignancies (Vineis *et al*, 2000). Owing to the low incidence of malignancies following tuberculosis, the few previous investigations with small sample sizes did not provide comprehensive information regarding non-pulmonary cancers. Therefore, this nationwide, population-based study was to describe the risk of many types of cancers, especially non-pulmonary malignancies, 1 year following tuberculosis diagnosis.

MATERIALS AND METHODS

Background information of tuberculosis in Taiwan. In Taiwan, the total population is around 23 million. Tuberculosis is an endemic disease. The incidence of tuberculosis was 68 per 100 000 persons and mortality rate was 0.036 per person–year (Liao *et al*, 2012). Taiwan regulations stipulate mandatory registry and treatment of tuberculosis via the Directly Observed Treatment Short Course (DOTS) program, which is monitored by the Center for Disease Control (CDC, Taiwan). DOTS workers and public health nurses follow tuberculosis cases to monitor compliance and side effects, and they report directly to the local health authority. National Health Insurance (NHI) provides coverage for antituberculosis treatment and monitors the cost.

Data sources. The NHI program is a mandatory health insurance program that covers up to 98% of medical care for all Taiwanese residents (Lin *et al*, 2009). Owing to its compulsive characteristics, management by government, and high coverage of whole population, the loss-of-follow-up rate is low. The NHI Research Database (NHIRD) catalogs all computerized claims data for inpatient and outpatient care including demographic data, examinations, drug prescriptions, and diagnosis by the international classification of disease, ninth revision (ICD-9-CM) (Deyo *et al*, 1992). The NHI sample files contain complete data of 1 000 000 randomly sampled beneficiaries from the original NHIRD, representing ~5% of all enrollees in Taiwan. There were no significant differences in age or gender distribution in this sample of 1 000 000 beneficiaries and the original NHIRD.

The NHI Registry for Catastrophic Illness provided comprehensive utilization and enrollment information for all patients with severe diseases under the NHI program. All cancers were included in the category of catastrophic illness. Catastrophic illness certificate exempts the patients from copayment. Bureau of NHI performs strict validations of the cancer diagnoses; at least two independent specialists reviewed the medical records, laboratory, histological, and image studies of each patient who applied for catastrophic illness registration (Hwang *et al*, 2012). The data set used in our study consisted of de-identified secondary data released to the public for research purposes and, therefore, was exempt from full review by our institutional review boards.

Study population. From 1 January 2000 to 31 December 2010, data of adult patients (>20) with newly diagnosed tuberculosis were retrieved from NHI sample files according to ICD-9-CM code 010.x to 018.x. plus prescription of at least two antituberculosis drugs (for example, isoniazid, ethambutol, rifampin, and pyrazinamide) for 2 months. We also extracted their data between 1 March 1995 and 1 January 2000 to exclude patients with history of tuberculosis and/or cancers before their entry into the study.

Statistical analyses. The main outcome was the risk of cancers. The Registry for Catastrophic Illness was used to identify subjects who were diagnosed with cancer. We examined the risk of cancers among the tuberculosis cohort using the standardized incidence ratio (SIR), which is the ratio of observed cancer cases to the expected number of cancer cases. SIR has been used to systematically examine the association between a variety of inflammatory diseases and cancers (Chen *et al*, 2010a; Spanogle *et al*, 2010). The expected number of cancer cases was obtained from Taiwan National Cancer Registry by multiplying the national incidence rate of cancers according to gender, calendar year, and age in different intervals by the corresponding stratum-specific person–time accrued in the cohort. The 95% confidence intervals (CIs) for the SIRs were estimated under the assumption that the observed number of cancers followed a Poisson probability distribution. We determined the SIRs for subgroups according to gender and age, as well as each cancer type. Owing to a potential surveillance bias, subgroup analyses by the length of time since tuberculosis diagnosis were carried out. Extraction and computation of data were performed using the Perl programming language (version 5.12.2 http://www.perl.org/). Microsoft SQL Server 2005 (Microsoft Corp, Redmond, WA, USA) was used for data linkage, processing, and sampling. All statistical analyses were performed using SPSS statistical software version 17.0 for Windows (SPSS Inc, Chicago, IL, USA). Statistical significance was defined as a *P*-value of less than 0.05.

RESULTS

A total of 6699 patients with tuberculosis diagnosis with a median follow-up period of 3.8 years (interquartile range 1.3–6.9) were included (Table 1). The majority (69.1%) was male. The median age of tuberculosis diagnosis was 64 (range 47–76), but was older for males (66, range 50–77) than females (59, range 40–75). Females were distributed more equally in all ages than males.

Risk of all cancers. During a follow-up period of 28 866 person–years, 530 tuberculosis cases developed cancer compared with 256

Table 1. Characteristics of patients with tuberculosis diagnosis

	Total	Male	Female
No. of patients	6699	4630	2069
Person–years at risk	28 866	19 297	9569
Median follow-up, years (interquartile range)	3.8 (1.3–6.9)	3.6 (1.2–6.7)	4.4 (1.4–7.5)
Median age, years (interquartile range)	64.3 (46.7–76.1)	66.3 (49.5–76.6)	59.2 (40.2–74.9)
Age at diagnosis, years			
20–39	1157 (17.3%)	644 (13.9%)	513 (24.8%)
40–59	1744 (26.0%)	1194 (25.8%)	550 (26.6%)
60–79	2739 (40.9%)	2033 (43.9%)	706 (34.1%)
⩾80	1059 (15.8%)	759 (16.4%)	300 (14.5%)

cases in the general population. The overall risk of any cancer in all patients with newly diagnosed tuberculosis was higher than general population (2.07, 95% CI, 1.90–2.26), both for males (2.18, 95% CI, 1.98–2.40) and females (1.67, 95% CI, 1.34–2.05) (Table 2). For males, the elevated cancer risk was lessened with increasing age. SIRs for males in the age ranges of 20–39, 40–59, 60–79, and >80 were 6.32, 2.73, 2.16, and 1.83, respectively. For females, however, only patients aged between 40–59 or 60–79 years carried elevated risk. The period following tuberculosis diagnosis revealed further gender distinctions. For males, the SIR was increased within the first year (4.72, 95% CI, 4.08–5.43) and remained 1.52 thereafter. For females, increased risk of cancer was only elevated during the first year (SIR, 4.08, 95% CI, 2.97–5.48).

Risk of non-pulmonary cancers. Although the association between lung cancer and tuberculosis has been well documented, we sought to understand the relationship between tuberculosis and non-pulmonary cancers, and examine their impact on elevated SIRs. With cases of lung cancer excluded, 371 cases developed non-pulmonary cancers compared with 217 in controls (Table 3). The increased risk was both observed in males (1.81, 95% CI, 1.61–2.03) and females (1.36, 95% CI, 1.05–1.73). A trend of increasing risk of non-pulmonary cancers with younger age was observed in males. The risk of cancer was elevated for males during the first year following tuberculosis diagnosis and beyond. In contrast, females only had increased risk of non-pulmonary cancer during the first year after tuberculosis diagnosis.

Risk of specific cancers. To further identify increased risks of specific cancers after tuberculosis infection, the SIRs of several cancers were calculated (Table 4). In all patients with newly diagnosed tuberculosis, the SIRs of many cancers were significantly increased, including cancers of the head and neck, digestive tract, lung, skin, bladder, and hematological malignancies. Analysis by

Table 2. Standardized incidence ratios (SIRs) of all cancers according to age at cancer diagnosis, gender and follow-up period after tuberculosis diagnosis

	Total		Male		Female	
Characteristics	**Observed**	**SIR (95% CI)**	**Observed**	**SIR (95% CI)**	**Observed**	**SIR (95% CI)**
All cancers	530	2.07 (1.90–2.26)	439	2.18 (1.98–2.40)	91	1.67 (1.34–2.05)
Age, years[a]						
20–39	17	3.87 (2.25–6.20)	13	6.32 (3.37–10.81)	4	1.71 (0.47–4.38)
40–59	92	2.50 (2.01–3.06)	68	2.73 (2.12–3.47)	24	2.01 (1.29–2.99)
60–79	304	2.05 (1.83–2.30)	261	2.16 (1.90–2.43)	43	1.59 (1.15–2.15)
⩾ 80	117	1.76 (1.46–2.11)	97	1.83 (1.48–2.23)	20	1.51 (0.92–2.33)
Follow-up period, years						
<1	240	4.59 (4.03–5.21)	196	4.72 (4.08–5.43)	44	4.08 (2.97–5.48)
1–5	197	1.44 (1.25–1.66)	165	1.52 (1.30–1.78)	32	1.12 (0.77–1.58)
> 5	93	1.40 (1.13–1.71)	78	1.52 (1.20–1.90)	15	0.99 (0.55–1.63)
Follow-up ⩾1 year	290	1.43 (1.27–1.60)	243	1.52 (1.34–1.73)	47	1.07 (0.79–1.43)

Abbreviation: CI = confidence interval.
[a]The age when the cancer was diagnosed.

Table 3. Standardized incidence ratios (SIRs) of non-pulmonary cancers according to age at cancer diagnosis, gender, and follow-up period after tuberculosis diagnosis

	Total		Male		Female	
Characteristics	**Observed**	**SIR (95% CI)**	**Observed**	**SIR (95% CI)**	**Observed**	**SIR (95% CI)**
Non-pulmonary cancers	371	1.71 (1.54–1.90)	305	1.81 (1.61–2.03)	66	1.36 (1.05–1.73)
Age, years[a]						
20–39	14	3.28 (1.79–5.51)	11	5.54 (2.77–9.91)	3	1.32 (0.27–3.84)
40–59	70	2.06 (1.61–2.61)	56	2.46 (1.86–3.20)	14	1.26 (0.69–2.11)
60–79	199	1.60 (1.39–1.84)	167	1.66 (1.42–1.93)	32	1.35 (0.92–1.91)
⩾80	88	1.62 (1.30–1.99)	71	1.65 (1.29–2.08)	17	1.50 (0.87–2.40)
Follow-up period, years						
<1	134	3.03 (2.54–3.59)	111	3.20 (2.64–3.86)	23	2.41 (1.53–3.61)
1–5	155	1.34 (1.13–1.56)	126	1.39 (1.16–1.66)	29	1.14 (0.76–1.64)
>5	82	1.45 (1.15–1.80)	68	1.58 (1.23–2.00)	14	1.04 (0.57–1.74)
Follow-up ⩾1 year	237	1.37 (1.20–1.56)	194	1.45 (1.25–1.67)	43	1.11 (0.80–1.49)

Abbreviation: CI = confidence interval.
[a]The age when the cancer was diagnosed.

Table 4. Standardized incidence ratios (SIRs) for specific cancer types among patients with tuberculosis diagnosis

	Total		Male		Female	
Site of cancers	**Observed**	**SIR (95% CI)**	**Observed**	**SIR (95% CI)**	**Observed**	**SIR (95% CI)**
All cancers	530	2.07 (1.90–2.26)	439	2.18 (1.98–2.40)	91	1.67 (1.34–2.05)
Head and neck	41	2.02 (1.45–2.74)	37	1.96 (1.38–2.70)	4	2.77 (0.75–7.08)
Digestive	183	1.70 (1.46–1.96)	156	1.78 (1.51–2.09)	27	1.34 (0.88–1.95)
Esophagus	20	3.36 (2.05–5.19)	17	3.00 (1.74–4.80)	3	11.07 (2.28–32.37)
Stomach	22	1.35 (0.85–2.04)	18	1.33 (0.79–2.10)	4	1.47 (0.40–3.76)
Colon and rectum	57	1.40 (1.06–1.82)	44	1.39 (1.01–1.87)	13	1.43 (0.76–2.45)
Anus	0	0.00 (0.00–14.12)	0	0.00 (0.00–20.47)	0	0.00 (0.00–45.53)
Liver	66	1.84 (1.42–2.34)	61	2.03 (1.55–2.61)	5	0.85 (0.28–1.99)
Biliary tract	11	3.14 (1.57–5.62)	9	3.55 (1.62–6.75)	2	2.07 (0.25–7.47)
Pancreas	7	1.38 (0.55–2.84)	7	1.80 (0.72–3.71)	0	0.00 (0.00–3.08)
Lung	159	4.09 (3.48–4.78)	134	4.09 (3.42–4.84)	25	4.13 (2.67–6.10)
Bone and soft tissue	1	0.53 (0.01–2.93)	1	0.67 (0.02–3.71)	0	0.00 (0.00–9.24)
Skin cancer	12	2.08 (1.07–3.63)	11	2.62 (1.31–4.69)	1	0.63 (0.02–3.53)
Melanoma	4	4.76 (1.30–12.19)	4	6.38 (1.74–16.35)	0	0.00 (0.00–17.27)
Non-melanoma	8	1.62 (0.70–3.19)	7	1.96 (0.79–4.04)	1	0.73 (0.02–4.08)
Breast	9	0.93 (0.43–1.77)	0	0.00 (0.00–15.93)	9	0.95 (0.44–1.81)
Genitourinary	72	1.51 (1.18–1.90)	62	1.61 (1.23–2.06)	10	1.10 (0.53–2.02)
Cervix	3	0.95 (0.20–2.79)	0	—	3	0.95 (0.20–2.79)
Uterus	3	2.17 (0.45–6.35)	0	—	3	2.17 (0.45–6.35)
Ovary	1	0.79 (0.02–4.38)	0	—	1	0.79 (0.02–4.38)
Prostate	32	1.34 (0.91–1.89)	32	1.34 (0.91–1.89)	0	–
Bladder	22	1.95 (1.22–2.96)	21	2.15 (1.33–3.28)	1	0.67 (0.02–3.74)
Kidney	11	1.66 (0.83–2.97)	9	1.86 (0.85–3.54)	2	1.12 (0.14–4.03)
CNS	4	1.77 (0.48–4.53)	3	1.73 (0.36–5.06)	1	1.89 (0.05–10.51)
Thyroid	2	0.81 (0.10–2.92)	0	0.00 (0.00–3.80)	2	1.33 (0.16–4.81)
Hematologic malignancies	26	2.30 (1.51–3.38)	18	2.02 (1.20–3.20)	8	3.34 (1.44–6.59)
Non-Hodgkin's lymphoma	11	1.95 (0.97–3.49)	9	2.05 (0.94–3.89)	2	1.61 (0.19–5.80)
Hodgkin's disease	2	9.94 (1.20–35.91)	2	12.83 (1.55–46.35)	0	0.00 (0.00–81.48)
Multiple myeloma	4	2.43 (0.66–6.21)	3	2.28 (0.47–6.65)	1	3.03 (0.08–16.86)
Leukemia	9	2.37 (1.08–4.50)	4	1.32 (0.36–3.38)	5	6.49 (2.11–15.15)

Abbreviations: CI = confidence interval; CNS = central nervous system.

gender revealed that males had elevated risk for most of these cancers. Females, on the other hand, had elevated risks only for leukemia, esophageal, and lung cancers.

Risk of specific cancers in different follow-up periods. As the time after tuberculosis diagnosis had great impact on the SIR of lung cancers and non-pulmonary cancers (Tables 2 and 3), we further analyzed the SIRs of specific cancers with regard to the time between tuberculosis and cancer diagnoses (Table 5). For males, most of the cancers (except cancers of the biliary tract and bladder) developed within the first year of tuberculosis diagnosis. The risks of liver, biliary tract, and lung cancers were elevated during 1–5 years after tuberculosis diagnosis, but the risk of bladder cancer did not emerge until 5 years post-tuberculosis diagnosis. Females showed increased risk for esophageal cancer, lung cancer, and leukemia during the first year, but only a risk for leukemia persists beyond 5 years post diagnosis.

DISCUSSION

Several population-based and clinical studies have shown chronic infections and inflammations, such as hepatitis virus, Epstein–Barr virus, and autoimmune diseases, are correlated with cancers (Wei and Sham, 2005; Chen *et al*, 2010b; Wu *et al*, 2011a; Yu *et al*, 2011; Forner *et al*, 2012; Weng *et al*, 2012). Elevated risk for lung cancer has been repeatedly documented in patients with tuberculosis infections (Engels, 2008; Wu *et al*, 2011a; Yu *et al*, 2011). Although pilot studies implicated the association of tuberculosis with other cancers (Vineis *et al*, 2000; Falagas *et al*, 2010), systematic investigations have been sparse, given the relatively low incidence of cancers following tuberculosis infections. Our population-based study including 6699 tuberculosis patients with a follow-up of 28 866 person–years revealed elevated risk for several non-pulmonary malignancies after tuberculosis infections. Our study further characterized the incidence of specific cancer types and their correlation with gender and time after tuberculosis diagnosis. This study suggested that in addition to lung cancers, physicians should consider the increased risk of several solid and hematological malignancies, and how the risk varies by gender and time after tuberculosis diagnosis.

It is possible that the elevated SIRs observed within the first year were due to surveillance bias (Spanogle *et al*, 2010). In Taiwan, however, surveillance bias for cancer alone may not significantly skew the overall cancer incidence over a long study period because of the accessibility to medical service, high coverage of NHI (>98% of the population), and ongoing follow-up of the entire population by this database. Therefore, the surveillance bias for

Table 5. Standardized incidence ratios (SIRs) for specific cancer types stratified by time after tuberculosis diagnosis among male and female patients

	<1 Year		1–5 Years		>5 Years	
Site of cancers	Observed	SIR (95% CI)	Observed	SIR (95% CI)	Observed	SIR (95% CI)
Male						
Head and neck	14	3.74 (2.05–6.28)	15	1.48 (0.83–2.44)	8	1.61 (0.69–3.17)
Esophagus	8	6.96 (3.01–13.72)	6	1.96 (0.72–4.26)	3	2.05 (0.42–6.00)
Colon and rectum	14	2.18 (1.19–3.65)	18	1.06 (0.63–1.68)	12	1.46 (0.75–2.55)
Liver	17	2.72 (1.59–4.36)	31	1.90 (1.29–2.70)	13	1.73 (0.92–2.96)
Biliary tract	2	3.77 (0.46–13.62)	5	3.66 (1.19–8.54)	2	3.15 (0.38–11.37)
Lung	85	12.39 (9.90–15.33)	39	2.21 (1.57–3.02)	10	1.21 (0.58–2.23)
Melanoma	2	15.39 (1.86–55.59)	2	5.86 (0.71–21.16)	0	0.00 (0.00–23.77)
Bladder	3	1.47 (0.30–4.30)	9	1.71 (0.78–3.24)	9	3.64 (1.67–6.92)
Hodgkin's disease	2	58.21 (7.05–210.27)	0	0.00 (0.00–44.57)	0	0.00 (0.00–95.18)
Female						
Esophagus	3	52.11 (10.75–152.28)	0	0.00 (0.00–25.96)	0	0.00 (0.00–51.79)
Lung	21	17.24 (10.67–26.36)	3	0.95 (0.20–2.77)	1	0.60 (0.02–3.34)
Leukemia	2	13.14 (1.59–47.45)	1	2.46 (0.06–13.72)	2	9.45 (1.14–34.12)

Abbreviations: SIR = standardized incidence ratio; CI = confidence interval.

cancers may shorten the time of cancer diagnosis (increased SIRs within the first year), but may not be the main reason behind the observed increase of cancer incidence over the study period, especially beyond 1 year. As the compromised immunity in cancer patients may render cancer patients susceptible to new tuberculosis infections or reactivations (Wu *et al*, 2011b), another explanation is reverse causality; tuberculosis was diagnosed before cancers that actually predated the tuberculosis infections, leading to the increased SIRs within the first year.

The association of tuberculosis infections and cancers with higher SIRs 1 year after tuberculosis infections was less arguable. Previous population-based studies concluded that tuberculosis increased the risk of lung cancers because the incidence-rate ratio of lung cancers elevated 1 year after tuberculosis diagnosis (1.76, 95% CI 1.33–2.32 during 1–5 years after tuberculosis infections) (Wu *et al*, 2011a). The elevated SIRs of lung cancers 1 year after tuberculosis diagnosis in males in our study were consistent with this. Interestingly, our study also found other non-pulmonary malignancies with higher SIRs 1 year after tuberculosis diagnosis, namely, liver, biliary tract, and bladder cancers in males, and leukemia in females. However, whereas tuberculosis may contribute to increased risk of these cancers, the observed associations may also be due to shared risks. Tobacco smoking has been associated with malignancies (liver, biliary tract, and bladder cancers, and leukemia) as well as tuberculosis (Sasco *et al*, 2004; Yagyu *et al*, 2008; Lawn and Zumla, 2011). Impaired cellular immunity may contribute to both malignancies and tuberculosis infections (Wu *et al*, 2011b). The human susceptibility to tuberculosis has been also associated with the polymorphism of several innate immunity and inflammatory response genes (Azad *et al*, 2012) such as toll-like receptors, IL-1beta, and tumor necrosis factors, and inducible nitric oxide that have been associated with cancer susceptibility (Kamangar *et al*, 2006; Sawa *et al*, 2008; Kutikhin, 2011; Qidwai and Khan, 2011). Although the association of several non-pulmonary malignancies and tuberculosis infections was observed in our study, this relationship and mechanisms will require substantial and in-depth future studies.

The strengths of the current study include taking advantage of large longitudinal national databases and usage of well-documented methodology to compare the correlation of tuberculosis and cancers (Chen *et al*, 2011; Hwang *et al*, 2012; Wang *et al*, 2012). The limitations of this study include the difficulty to adjust confounding factors from smoking. However, the exact prevalence of smoking in patients with tuberculosis is not known in Taiwan and the effect of smoking on the development of each specific cancer differed. Avoidance of the confounding effect from smoking can only be accomplished by conducting a large prospective cohort study in patients with tuberculosis infections. Another limitation is the relatively small number of enrollees compared with >10 000 new tuberculosis cases per year in Taiwan. The NHI policy prohibits release of >10% of total data in the NHIRD. We were unable to access the data of all of the tuberculosis patients. However, the NHI sample files have been validated and applied for many population-based studies about risks of many cancers (Chen *et al*, 2010b, 2011). As for rare cancers, the cohort of this study may not be able to detect elevated risks.

In conclusion, our study revealed increased risk for several non-pulmonary malignancies after tuberculosis infections. The risk for specific cancers differed with gender and time after tuberculosis diagnosis. Physicians may consider the risk for these solid and hematological malignancies in relation to gender and time after tuberculosis diagnosis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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