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Risk of mycobacterial disease among cancer patients: A population-based cohort study in a TB endemic area

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ABSTRACT

Objectives: Tuberculosis (TB) and nontuberculous mycobacteria (NTM) disease have similar symptoms, which makes them difficult to distinguish clinically and leads to the danger of NTM disease being neglected. The aim of this study was to assess the risk of developing mycobacterial disease among cancer patients.

Methods: We conducted a retrospective cohort study using a population-based database. The multivariable Cox proportional hazards model was adjusted to identify independent factors contributing to the development of mycobacterial disease in the cancer cohort.

Results: The results showed that the increased risk of developing TB and NTM disease was 1.84-fold and 4.43-fold, respectively, in cancer patients compared with the general population. Advanced age (≥65years) and being male were risk factors for developing TB disease. There was a 4.09-fold significantly increased risk of TB disease within six months of a cancer diagnosis. Hematological cancer patients were most likely to develop mycobacterial disease. Younger hematological cancer patients (< 45years) had a higher risk of NTM disease development.

Conclusion: There is an increasing risk of mycobacterial disease in cancer patients. We suggest that the possibility of mycobacterial disease in cancer patients should be assessed during the period of cancer therapy, particularly in those who have risk factors.

1. Introduction

Tuberculosis (TB) and nontuberculous mycobacteria (NTM) are the major clinical spectrum of mycobacterial disease. Although significant progress has been made toward the elimination of TB, it remains a leading cause of morbidity and mortality worldwide [1]. NTM are ubiquitous environmental microorganisms that cause chronic pulmonary and extrapulmonary infection [2]. Public health administration in most countries does not require that NTM disease cases are reported [2], however, NTM diseases are recently being diagnosed with increasing frequency worldwide [3], including in Taiwan [4]. A laboratory-based study indicated a trend toward a decrease in TB cases but a significant increase in NTM cases in Taiwan between 2000 and 2012 [4]. Because TB and NTM disease have similar symptoms and pulmonary radiographic findings, these infections are difficult to distinguish clinically [2] and this leads to the danger of NTM disease being neglected [3]. Several NTM strains are resistant to many antibiotics, making treatment difficult [5,6]. Increasing evidence suggests that an elevated risk of mycobacterial disease is most likely to be associated with the global trend in advanced aging, immunosuppressive medication use, and the elevated prevalence of immune-modulating comorbidities [7–9].

Cancer is a major cause of disease worldwide. There were an estimated 14.1 million new onset cancer cases in the world in 2012 [10].

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Cancer patients have higher risks of infectious morbidity and mortality, which may be due to disease-related immune dysfunction, the immunosuppressive effects of receiving chemotherapy or following long-term vascular catheter placement [11]. The prevalence of mycobacterial disease in the general Asian population is higher than that in the United States (US) and Europe [1,7], however, very few population-based studies have investigated the epidemiology of mycobacterial disease among Asian patients with cancer. Here, we utilized more than 20 million enrollees of a population-based database to conduct a retrospective cohort study to investigate the association between cancer and mycobacterial disease.

2. Methods

2.1. Data source

The National Health Insurance Research Database (NHIRD) consists of detailed health-care information representing more than 99% of Taiwan's total population and includes inpatient and ambulatory care claims from 1996 to 2014 [12]. The Longitudinal Health Insurance Database (LHID) contains all the original claim data of 1,000,000 individuals randomly sampled from the registry for beneficiaries of the NHIRD, which was released by the National Health Research Institutes (NHRI). The NHRI confirmed that the random samples were representative of the general population in Taiwan. The data from the NHIRD was de-identified forms of secondary information in an anonymous format released to the public for research purposes. This study was conducted in compliance with the Declaration of Helsinki, has been approved by the Institutional Review Board of Taichung Veterans General Hospital (CE13152B-3) and waived the requirement of patient informed consent. The methods were carried out in accordance with the approved guidelines.

2.2. Definitions

Patients with different diseases in this study were primarily classified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. There is a registry system for catastrophic illnesses in the NHIRD, and cancer is included in this database. The diagnosis of cancer was made according to the ICD-9-CM codes 140–208 and the NHIRD's Registry of Catastrophic Illness Patient Database (RCIPD).

All TB and NTM cases were determined by using (1) ICD-9-CM codes, (2) laboratory mycobacterium examination codes, and (3) anti-mycobacterial therapy receipts [12]. All three items above must be met. The definition of TB was the same as in previously published literature [13] and the detail is provided in the supplementary information. The NTM disease definition was based on the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) guidelines [5], which include clinical, radiographic, and microbiologic criteria. All items must be met for NTM lung disease diagnosis [5]. A detailed definition of NTM disease is provided in the supplementary information. If a patient had both TB and NTM disease simultaneously, we defined the patient as a TB case only. The first diagnosis of TB or NTM disease was also required to be after the cancer identification index date. The study end point was defined as the onset of new mycobacterial disease or death during the 12-year follow-up period (2001–2012).

We chose several comorbidities to study in order to understand the association between comorbidities and mycobacterial disease [9,14]. The definitions of each comorbidity were based on the ICD-9-CM codes, including cardiovascular diseases (ICD-9-CM codes 390–438), chronic kidney disease (CKD, ICD-9-CM code 585), diabetes mellitus (DM, ICD-9-CM code 250), and hypertension (ICD-9-CM code 401.9).

2.3. Study design

We conducted a retrospective cohort study of patients ≥18 years old who were newly diagnosed with cancer from January 1, 2001, to December 31, 2010, in the NHIRD Longitudinal Health Insurance Database (LHID). We excluded patients who had received a TB or NTM diagnosis before cancer diagnosis, as well as those who died within 180 days of cancer diagnosis. An age- and sex-matched non-cancer control group (age ≥18 years) was selected and excluded individuals with missing information regarding age or gender, those with a history of cancer, TB or NTM diagnosis, and those who died within 180 days of the index date. The cancer diagnosis date was in the index date for cancer cases and their matched controls. Newly diagnosed cancer cases and non-cancer controls were matched by age and sex using a ratio of 1:2. Cancer patients and comparison cohort members were followed for incident TB/NTM occurrence from the cancer diagnosis/index date until the date of death, or December 31, 2012, whichever came first.

2.4. Statistical analysis

The ICD-9-CM codes for TB were 010–018. Among TB cases, ICD-9-CM codes 010–012 and 018 are used for pulmonary TB and codes 013–017 are used for extrapulmonary TB. The ICD-9-CM codes of NTM disease were 031.0, 031.1, 031.2, 031.8, and 031.9. Among the NTM diseases, ICD-9-CM code 031.0 is for pulmonary NTM disease, and the others are for extra pulmonary NTM disease [13]. Data is presented as means ± standard deviations (SD) for continuous variables and as proportions for categorical variables. The differences between continuous values were analyzed using the independent *t*-test for continuous variables and the chi-square test for categorical variables. The incidences of newly diagnosed mycobacterial disease in malignancy patients and the control group were calculated. The multivariable Cox proportional hazards model was adjusted for age, sex, and comorbidity to identify independent factors contributing to the development of mycobacterial disease in the malignancy-to-control cohort. The 95% confidence interval (CI) for each variable was also determined. Cumulative incidence and Cox regression were used to calculate the hazard ratios (HRs) of TB or NTM after cancer diagnosis/index date in total follow-up period, or different time-period (including < 6 months, 6 months^{-1} year, and > 1 year) respectively.

All analyses were conducted using SAS statistical software version 9.3 (SAS Institute, Inc., Cary, NC, USA). A *P*-value of < 0.05 was considered to indicate statistical significance.

3. Results

3.1. Characteristics of study cohort

In the LHID, a total of 27,680 cases were newly diagnosed with cancer from 2001 to 2010 (Fig. 1). We excluded patients who had received a TB or NTM diagnosis before cancer diagnosis, as well as those who died within 180 days of cancer diagnosis (7,224 cases). Newly diagnosed cancer cases (20,456 cases) and non-cancer controls (40,912 cases) were matched by age and sex using a ratio of 1:2 (Fig. 1). Approximately 40.0% of the cancer patients were older than 65 years, and there were no significant differences in sex (Table 1). Cancer patients had a significantly higher prevalence of cardiovascular disease, chronic kidney disease, diabetes mellitus and hypertension than the non-cancer controls ($P < 0.001$).

3.2. Increased risk of TB and NTM disease in cancer patients

Of 20,456 cancer patients, 316 (1.54%) were newly diagnosed with TB after they had been diagnosed with cancer during the 12-year follow-up period (2001–2012) (Fig. 1). The median follow-up of TB among cancer patients and comparisons was 4.40 and 6.68 years ($P <$

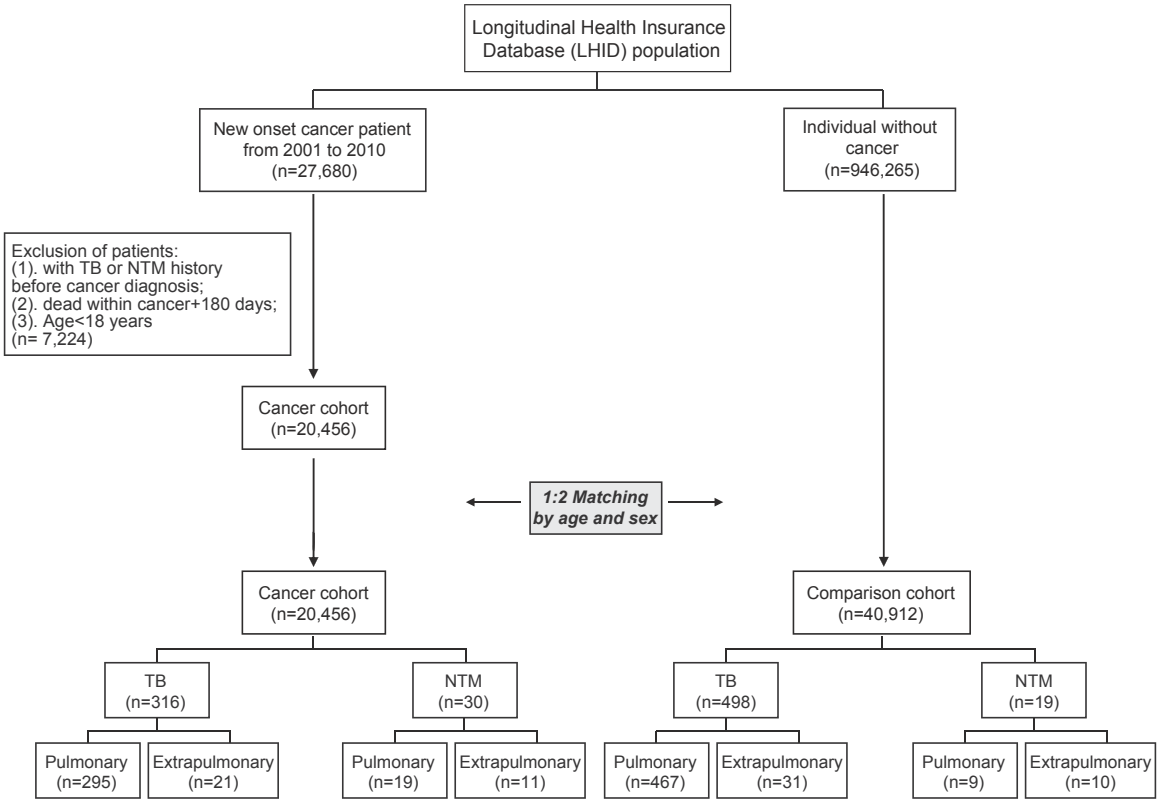

Fig. 1. Flow chart of case selection in this study. The selection of cancer patients and age- and sex-matched non-cancer comparison control subjects from the Longitudinal Health Insurance Database (LHID). TB, tuberculosis; NTM, nontuberculous mycobacteria.

Table 1
Baseline characteristics (N = 61,368).

Variables	Cancer (n = 20,456)		Non-cancer (n = 40,912)		*P* value
	n	%	n	%	
Age at entry, years	59.6	14.8	59.5	14.9	0.49
18–44	3307	16.1	6614	16.1	
45–64	8977	43.9	17954	43.9	
≧65	8172	40.0	16344	40.0	
Gender					> 0.99
Female	9824	48.0	19648	48.0	
Male	10632	52.0	21264	52.0	
Comorbidity					
Cardiovascular disease	4773	23.3	9044	22.1	0.0006
Chronic kidney disease	761	3.72	879	2.15	< 0.0001
Diabetes mellitus	4672	22.8	7722	18.9	< 0.0001
Hypertension	9409	46.0	17374	42.5	< 0.0001

0.0001), respectively. The incidence rate of TB was higher in cancer patients compared to non-cancer controls (31.1 vs. 17.5 per 10,000 person-years; Table 2). After multivariable analysis, there was a 1.84-fold increased risk of developing TB in cancer patients compared with that in the non-cancer controls (95% CI 1.59–2.12, $P <$ 0.0001). Pulmonary is the common invasive site of TB disease among cancer patients (n = 295, 93.4%).

Approximately 0.08% (49 cases) of the population in this study developed new-onset NTM disease during the 12-year follow-up period (Fig. 1). The median follow-up of NTM disease among cancer patients and comparisons was 4.44 and 6.72 years ($P <$ 0.0001), respectively. Among the 20,456 cancer patients, 30 (0.15%) had a newly diagnosed NTM disease after they were diagnosed with cancer (Fig. 1). The major invasive site of cancer patients with NTM disease is pulmonary infection (n = 19, 63.3%, Fig. 1). The incidence rate of NTM disease was significantly higher in cancer patients than in the controls (2.93 vs. 0.66 per 10,000 person-years, Table 2). After the multivariable analysis, there was a 4.43-fold elevated risk of developing NTM disease in cancer patients compared to non-cancer controls (95% CI 2.48–7.92, $P <$ 0.0001). Kaplan-Meier analysis also showed that the cumulative incidence of TB and NTM disease was higher in cancer patients than in non-cancer subjects ($P <$ 0.0001, Fig. 2).

3.3. The temporal relationship between occurrence of TB/NTM disease and cancer diagnosis

We analyzed the temporal relationship between mycobacterial disease occurrence and cancer. The results showed a 4.09-fold significantly increased risk of TB disease within the 6 months after cancer diagnosis in patients compared to those without cancer (95% CI 2.68–6.24, $P <$ 0.0001, Table 2). The crude incidence rate of TB disease declined following cancer disease duration (< 6 months: 64.8 per 10,000 person-year; 6 months–1 year: 40.5 per 10,000 person-year; > 1 year: 25.8 per 10,000 person-year), but it still remained higher than that of the general population after one year. There was a significantly elevated risk of NTM disease until after cancer diagnosis of more than 1 year (aHR = 4.09, 95% CI 2.22–7.54, $P <$ 0.0001, Table 2).

3.4. Risk factors for developing mycobacterial disease in cancer cohort

As illustrated in Supplementary Table 1, advanced age (≥65 years, aHR = 3.40, 95% CI 2.15–5.38, $P <$ 0.0001) and male gender (aHR = 2.61, 95% CI 2.03–3.37, $P <$ 0.0001) were risk factors for the development of TB diseases in cancer patients, however there was no significant difference in age or sex for NTM disease development risk in cancer patients.

Table 2
The risk of TB and NTM in different cancer disease duration (n = 61,368).

	Cancer cohort			Comparison cohort			Adjusted HR†	*P* value
Time	Event	PYs	IR*	Event	PYs	IR*	(95% CI)	
TB								
All patients	316	101642	31.1	498	285455	17.5	1.84(1.59–2.12)	< 0.0001
< 6 month	66	10187	64.8	32	20446	15.7	4.09(2.68–6.24)	< 0.0001
6 months-1 year	38	9383	40.5	35	20323	17.2	2.31(1.45–3.66)	0.0004
> 1 year	212	82071	25.8	431	244685	17.6	1.57(1.33–1.85)	< 0.0001
NTM								
All patients	30	102282	2.93	19	286966	0.66	4.43(2.48–7.72)	< 0.0001
< 6 month	3	10206	2.94	0	20453	0	–	–
6 months-1 year	2	9416	2.12	1	20347	0.49	4.01(0.36–44.3)	0.26
> 1 year	5	82660	3.02	8	246166	0.73	4.09(2.22–7.54)	< 0.0001

TB, tuberculosis; NTM, nontuberculous mycobacteria; PYs, person-years.
* IR, incidence rate, per 10,000 person-years.
† Adjusted for age, sex, cardiovascular disease, chronic kidney disease, diabetes mellitus, and hypertension.

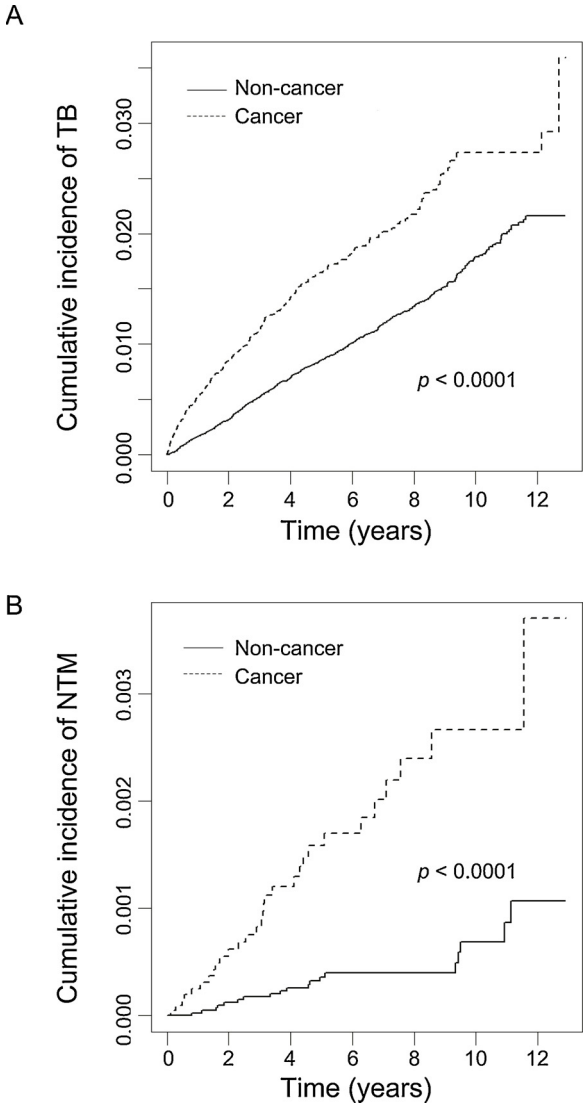

Fig. 2. Cumulative incidence of (A) tuberculosis (TB) and (B) nontuberculous mycobacteria (NTM) disease in cancer patients and non-cancer comparison subjects.

3.5. Varying degrees of mycobacterial disease risk among patients with different cancer types

We further analyzed the risk of mycobacterial disease in patients with different cancer types (Table 3). The results showed a significantly increased risk of mycobacterial disease in patients with hematological cancer (aHR = 3.93, 95% CI 2.59–5.98, $P <$ 0.0001 for TB; aHR = 30.4, 95% CI 13.1–70.5, $P <$ 0.0001 for NTM) compared to solid cancer (aHR = 1.76, 95% CI 1.52–2.04, $P <$ 0.0001 for TB; aHR = 3.38, 95% CI 1.82–6.29, $P =$ 0.0001 for NTM) or non-cancer patients. The risk of mycobacterial disease in all age- and gender-stratified hematological cancer patients was higher than that in those with solid cancer or non-cancer (Table 4). Additionally, younger hematological cancer patients had a higher incidence rate for NTM disease (< 45 years vs. ≥ 65 years: 41.1 vs. 8.92 per 10,000 person-years).

The risk of mycobacterial disease in patients with different solid cancer types is summarized in Table 3. The predominant solid cancer type for TB disease development was lung cancer (aHR = 3.63, 95% CI 2.52–5.24, $P <$ 0.0001), followed by head and neck cancer (aHR = 3.19, 95% CI 2.39–4.26, $P <$ 0.0001), and then stomach cancer (aHR = 2.30, 95% CI 1.50–3.53, $P =$ 0.0001). The predominant solid cancer type for NTM disease development was lung cancer (aHR = 20.30, 95% CI 7.42–55.30, $P <$ 0.0001), followed by stomach cancer (aHR = 7.63, 95% CI 1.77–33.00, $P =$ 0.007), and then head and neck cancer (aHR = 5.62, 95% CI 1.86–17.10, $P =$ 0.002).

4. Discussion

Of the more than 20 million enrollees in Taiwan's NHIRD, the risk of developing TB was 1.84-fold in cancer patients compared to the control cohort. The TB incidence (43.9 cases per 100,000 population in 2016) and the mortality rate (2.3 cases per 100,000 population in 2016) in Taiwan were higher than those in other Asian countries (e.g. Japan, Korea) or in western countries [15]. Even though the incidence rate of TB in the general population declined over time [15], our data showed that the incidence rate of TB in cancer patients was still higher than that in the non-cancer controls (31.1 vs. 17.5 per 10,000 person-years). Our results showed that cancer is a risk factor for developing TB, which was consistent with other recent population-based studies in Korea and Europe [16,17]. Our data also demonstrated that advanced age (≥ 65 years, aHR = 3.40, $P <$ 0.0001) and being male (aHR = 2.61, $P <$ 0.0001) were risk factors for developing TB diseases in Taiwan, which was consistent with local government surveillance data [15].

NTM are ubiquitous environmental microorganisms. A study in the US reported that the incidence of NTM disease was increasing among patients without HIV infection and with various immunosuppressive conditions, including malignancy [18]. Our results indicated that the

Table 3
The risk of TB and NTM in different cancer type and comparison cohort (n = 61,368).

Cancer type	TB					NTM				
	Event	PYs	IR*	Adjusted HR† (95% CI)	*P* value	Event	PYs	IR*	Adjusted HR† (95% CI)	*P* value
None	498	285455	17.5	1.0 (reference)	–	19	286966	0.66	1.0 (reference)	–
Solid tumor	293	97483	30.1	1.76(1.52–2.04)	< 0.0001	22	98101	2.24	3.38(1.82–6.29)	0.0001
Lung	31	3819	81.2	3.63(2.52–5.24)	< 0.0001	5	3871	12.9	20.3(7.42–55.3)	< 0.0001
Head and neck	53	11454	46.3	3.19(2.39–4.26)	< 0.0001	4	11546	3.46	5.62(1.86–17.1)	0.002
Stomach	22	3840	57.3	2.30(1.50–3.53)	0.0001	2	3874	5.16	7.63(1.77–33.0)	0.007
Liver	22	7276	30.2	1.44(0.94–2.21)	0.10	2	7322	2.73	3.81(0.87–16.6)	0.08
Colorectal	40	15506	25.8	1.16(0.84–1.60)	0.36	4	15583	2.57	3.72(1.26–11.0)	0.02
Uterine	9	9758	9.22	1.26(0.64–2.46)	0.51	0	9780	0	–	–
Breast	18	18675	9.64	1.59(0.96–2.64)	0.07	2	18745	1.07	2.68(0.54–13.3)	0.23
Prostate	26	5743	45.3	1.06(0.71–1.58)	0.79	1	5785	1.73	1.22(0.15–9.81)	0.85
Others	72	21411	33.6	1.91(1.49–2.45)	< 0.0001	2	21593	0.93	1.31(0.30–5.69)	0.71
Hematological cancer	23	4159	55.3	3.93(2.59–5.98)	< 0.0001	8	4181	19.1	30.4(13.1–70.5)	< 0.0001

TB, tuberculosis; NTM, nontuberculous mycobacteria; PYs, person-years.
* IR, incidence rate, per 10,000 person-years.
† Adjusted for age, sex, cardiovascular disease, chronic kidney disease, diabetes mellitus, and hypertension.

incidence rate of NTM disease was significantly higher in cancer patients than in the controls (2.93 vs. 0.66 per 10,000 person-years). Cancer patients may be examined for NTM more often than the normal population, which would result in surveillance bias. Additional in-depth studies are needed to confirm our conclusions. On the other hand, the risk in cancer patients with NTM disease was higher compared to that in patients with TB (4.43 vs. 1.84). In Taiwan, TB should be reported to the public health administration, and control measures should be conducted immediately, however, NTM disease cases do not have to be reported, and very few hospitals can fully identify NTM [4,6]. Furthermore, NTM disease is present with various levels of disease severity, resulting in missed diagnoses in mild and asymptomatic infection. It is therefore easy to ignore and underestimate the consequences of NTM disease. Our findings in this study might reflect an increased incidence of NTM disease in Taiwan, but awareness of NTM disease is not enough.

Most of the cancer patients (93.35%) and non-cancer controls (93.78%) with TB in our study had pulmonary invasion. For NTM disease, more than half (63.33%) of the cancer patients had pulmonary invasion; the remainder were skin/soft tissue or disseminated NTM infection (36.67%). The ratio of pulmonary invasion in cancer patients (63.33%) was higher than in non-cancer controls (47.37%). In the past few years, the incidence of NTM-associated pulmonary diseases and hospitalization has increased in Europe and the US [19,20]. Previous studies have indicated that the most distinct syndrome of cancer patients with NTM infection was pulmonary disease [21–23]. Several factors affected the variation of symptoms, including age of onset, underlying cancer type, and NTM species of infection [24,25].

Our results showed a 4.09-fold significantly increased risk of TB disease within six months of cancer diagnosis. Even though the crude incidence rate of TB disease gradually declined after one year, there remained a higher risk of TB in cancer patients than in the general population (aHR = 1.57, 95% CI 1.33–1.85, $P < 0.0001$). We speculate that it may be the early treatments of cancer, such as surgery and chemotherapy, that impair immunity leading to increased TB infection or reactivation. Recently, Simonsen et al. also showed that TB risk was highly elevated within the first year of cancer diagnosis (aHR = 4.14, 95% CI 2.88–5.96) [17]. They also demonstrated that the increased risk of TB in cancer patients was associated with receiving cytostatics and/or radiotherapy treatment [17], however, our results did not find any significant association between increased TB risk and anti-cancer treatment (Supplementary Table 2). This may be because most anticancer medications in Taiwan are self-paid during the period of this study (2001–2012); and so information about real drug use was not provided in the NHIRD. On the other hand, there was a significantly elevated risk of NTM disease until more than one year after cancer diagnosis (aHR = 4.09, 95% CI 2.22–7.54). We thought this may be

Table 4
Multivariable analysis for risk for TB and NTM among cancer patients with different cancer type (n = 61,368).

Demographic factor	Cancer type	N	TB				NTM			
			Events	IR*	aHR† (95% CI)	*P* value	Events	IR*	aHR† (95% CI)	*P* value
< 45 years	None	6614	20	3.88	1.0 (reference)	–	1	0.19	1.0 (reference)	–
	Solid tumor	3058	19	10.1	2.43(1.29–4.59)	0.006	3	1.59	8.71(0.90–84.0)	0.06
	Hematological	249	5	34.1	8.05(3.00–21.6)	< 0.0001	6	41.1	225(27.0–1878)	< 0.0001
45-64 years	None	17954	102	7.87	1.0 (reference)	–	5	0.38	1.0 (reference)	–
	Solid tumor	8653	88	19.4	2.44(1.82–3.25)	< 0.0001	9	1.98	5.03(1.66–15.2)	0.004
	Hematological	324	9	57.1	6.43(3.25–12.7)	< 0.0001	1	6.25	14.8(1.72–128)	0.01
≥ 65 years	None	16344	376	36.1	1.0 (reference)	–	13	1.24	1.0 (reference)	–
	Solid tumor	7869	186	55.9	1.52(1.28–1.82)	< 0.0001	10	2.97	2.33(1.01–5.35)	0.04
	Hematological	303	9	80.7	2.29(1.18–4.45)	0.01	1	8.92	7.49(0.97–57.5)	0.05
Female	None	19648	127	9.06	1.0 (reference)	–	7	0.5	1.0 (reference)	–
	Solid tumor	9418	75	14.4	1.67(1.25–2.22)	0.0005	8	1.52	2.97(1.07–8.23)	0.04
	Hematological	406	8	40.2	5.58(2.73–11.4)	< 0.0001	6	30.24	58.1(19.1–176)	< 0.0001
Male	None	21264	371	25.5	1.0 (reference)	–	12	0.82	1.0 (reference)	–
	Solid tumor	10162	218	48.2	1.80(1.52–2.13)	< 0.0001	14	3.07	3.79(1.74–8.28)	0.0008
	Hematological	470	15	69.1	3.39(2.02–5.69)	< 0.0001	2	9.1	13.0(2.87–58.9)	0.0009

TB, tuberculosis; NTM, nontuberculous mycobacteria; PYs, person-years.
* IR, incidence rate, per 10,000 person-years.
† Adjusted for age, sex, cardiovascular disease, chronic kidney disease, diabetes mellitus, and hypertension.

associated with mild and asymptomatic characteristics in the early phase of NTM infection, which resulted in ignored or missed diagnoses. A deeper study is required to confirm our hypothesis.

In this study, the predominant cancer type developing mycobacterial disease was hematologic malignancy (aHR = 3.93 for TB; aHR = 30.4 for NTM), followed by lung cancer (aHR = 3.63 for TB; aHR = 20.3 for NTM). Recently, another nationwide population-based study in Korea also found that the highest incidence rate of TB among cancer cohorts was in patients with hematologic malignancy [16]. Our results also showed that there was a significantly increased risk of NTM disease in young hematological cancer patients (< 45 years, aHR = 225, 95% CI: 27.0–1878.0). A hospital-based study in the US also observed similar results [21]. Previous studies suggested that increased mycobacterial disease in patients with hematologic malignancy may be associated with catheter placement and bloodstream and disseminated infections [21,25]. Hematopoietic stem cell transplants (HSCTs) are commonly used to treat a number of hematologic malignancies, which are usually associated with catheter and bloodstream NTM infections [26]. Moreover, a study demonstrated that combination therapies caused more deeply immunosuppression in cancer patients [27], however, there was no statistically significant difference in NTM diseases in cancer patients receiving different therapies in our study. The decrease in statistical power might be associated with small NTM case numbers in this study.

Among patients with solid tumors, our results showed that the predominant cancer type for developing mycobacterial disease was lung cancer (aHR = 3.63 for TB; aHR = 20.3 for NTM). Lung cancer patients have an increased risk of developing mycobacterial infection probably because of localized airway destruction or damage [25]. Lung cancer–related risk factors, including smoking and alcohol consumption, may also be the cause of the mycobacterial disease [9,28,29]. Underlying cellular immunity impairment and immunosuppression from anti-tumor chemotherapy also contribute to the increased risk of infection [24,30].

This study has several limitations. First, the NHIRD only contains medical claims data without available laboratory data. NTM species distribution and antimicrobial resistance information were therefore lacking. In accordance with our previous results and other hospital-based laboratory data, the predominant species causing NTM disease in Taiwan was *Mycobacterium intracellulare* [4,6]. Most NTM isolates were resistant to most of the antibiotics that are currently available, which was consistent with a previous study in another local medical center [31]. Second, most anticancer medications were not paid for in Taiwan's NHI during the period of study. Whether the subjects took these medications on a self-paid basis is not noted in the database, and therefore our study could not provide information about the real association with anti-cancer medication and risk of mycobacterial disease. Additional detailed analysis may be necessary in the future. The small number of NTM events is another limitation of the study. This may be because NTN is a non-mandatory reported disease and few hospitals can fully identify it [4]. The severity of NTM disease also varies, resulting in missed diagnoses for patients with mild and asymptomatic infection. Finally, the NHIRD does not contain detailed information on the lifestyle factors (e.g. smoking, alcohol, BMI) or individual health status (e.g. malnutrition, BMI) that are associated with mycobacterial disease and cancer [9]. The major strength of this study is that we used a nationwide database with medical care records that is minimally affected by selection and recall biases. The large sample size of the NHIRD (over 20 million enrollees, including patients and the general population) and a long-term follow-up period (2001–2012) of records enhanced the statistical power and accuracy of this study.

5. Conclusions

Accumulating evidence indicates an increased risk of TB reactivation among immunocompromised people or patients receiving immunosuppressive medications [7–9]. A recent systematic review and meta-analysis study suggested that people living in the US with hematologic, head and neck, and lung cancers would benefit from targeted latent tuberculosis infection (LTBI) screening and therapy [32]. The guidelines of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC) also suggested that patients with specific malignancies (e.g. hematologic malignancy, head and neck cancer, and lung cancer) may consider screening and treatment for LTBI [33]. We believe that this study provides useful information that can help increase a physician's awareness in assessing the potential of mycobacterial disease in cancer patients. It may be beneficial to perform latent tuberculosis screening and therapy before cancer therapy, particularly in those with risk factors.

Author contribution statement

T-LL conceived of the study, generated the original hypothesis, designed the study, analyzed data, and drafted and revised the manuscript. Y-MC and C-HL designed the study, analyzed data, and drafted and revised the manuscript. H－HC, W－CC, D-YC and C-CL conceived of the study, analyzed data, and drafted the manuscript.

Authors contributions statement

1) conceived and designed the experiments; (T-LL, Y-MC, C-HL)
2) performed the experiments; (T-LL, H－HC, W－CC, D-YC, C-CL)
3) analyzed and interpreted the data; (T-LL, Y-MC, C-HL)
4) contributed reagents, materials, analysis tools or data; (C-HL, C-CL)
5) wrote the paper* (T-LL, Y-MC, C-HL, H－HC, W－CC, D-YC, C-HL)

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Competing financial interests statement

The authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.01.010.

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