BMJ Open

Risk of active tuberculosis in migrants diagnosed with cancer in British Columbia, Canada

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-037827
Article Type:	Original research
Date Submitted by the Author:	24-Feb-2020
Complete List of Authors:	Kumar, Divjot; The University of British Columbia Faculty of Medicine, Respiratory Medicine Ronald, Lisa; BC Centre for Disease Control Romanowski, Kamila; The University of British Columbia Department of Medicine, Respiratory Medicine; BC Centre for Disease Control Rose, Caren; BC Centre for Disease Control Shulha, Hennady; BC Centre for Disease Control Cook, Victoria; The University of British Columbia Faculty of Medicine, Respiratory Medicine; BC Centre for Disease Control Johnston, James; The University of British Columbia Faculty of Medicine, Respiratory Medicine; BC Centre for Disease Control,
Keywords:	Tuberculosis < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Respiratory tract tumours < ONCOLOGY, PREVENTIVE MEDICINE, ONCOLOGY, EPIDEMIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Risk of active tuberculosis in migrants diagnosed with cancer in British Columbia, Canada

Divjot S. Kumar[1], B.Sc., MD, Lisa A. Ronald[2], PhD, Kamila Romanowski[1,2], MSc, Caren Rose[2], PhD, Hennady P. Shulha[2], PhD ,Victoria J. Cook[1,2], MD, FRCPC, James C. Johnston[1,2], MD, MPH, FRCPC

[1]Division of Respiratory Medicine, Faculty of Medicine, University of British Columbia, Vancouver, Canada, [2]British Columbia Centre for Disease Control, Vancouver, British Columbia, Canada

Corresponding Author information:
James Johnston, MD, MPH, FRCPC
British Columbia Centre of Disease Control
655 W 12th Avenue Vancouver, BC, V5Z 4R4
James.Johnston@bccdc.ca

The authors have no conflicts of interest to declare.

Current main text word count: **3,456**
Current abstract word count: **268**

ABSTRACT

Objectives: To describe the association between types of cancer and active TB risk in migrants. Additionally, in order to better inform Latent TB infection (LTBI) screening protocols, we assessed proportion of active TB cases potentially preventable through LTBI screening and treatment in migrants with cancer.

Design: Population based, retrospective cohort study

Setting: British Columbia (BC), Canada

Participants: 1,000,764 individuals who immigrated to Canada from 1985 to 2012 and established residency in BC at any point up to 2015.

Primary and secondary outcome measures: Using linked health administrative databases and disease registries, data on demographics, comorbidities, cancer type, TB exposure and active TB diagnosis were extracted. Primary outcomes included: time to first active TB diagnoses, and risks of active TB following cancer diagnoses which were estimated using Cox extended hazard regression models. Potentially preventable TB was defined as active TB diagnosed greater than 6 months post cancer diagnoses.

Results: Active TB risk was increased in migrants with cancer [(HR (95% CI))= 2.5 (2.0, 3.1)], after adjustment for age, sex, TB incidence in country of origin, immigration classification, contact status, and comorbidities. Highest risk was observed with lung cancer [HR=11.2 (7.4, 16.9)] and sarcoma [HR=8.1 (3.3, 19.5)], followed by leukemia [HR=5.6 (3.1, 10.2)], lymphoma [HR=4.9 (2.7, 8.7)], and gastrointestinal cancers [HR=2.7 (1.7, 4.4)]. The majority (65.9%) of active TB cases were diagnosed greater than 6 months post cancer diagnosis.

Limitations: We were unable to assess variables such as smoking, alcohol use, and chemotherapy.

Conclusion: Specific cancers increase active TB risk to varying degrees in the migrant population of BC, with approximately two-thirds of active TB cases identified as potentially preventable.

Strengths and Limitations of study:

- Our study included a large cohort with >1 million people over 19 year period
- First study to assess risk of active TB amongst different malignancies in an immigrant population, and include other common malignancies such as prostate, breast, and gastrointestinal cancers.
- Risk of active TB amongst different malignancies were adjusted for other commonly recognized TB risk factors
- Unable to account for impact of smoking, alcohol use, and chemotherapy
- Unable to account for TB contact outside of British Columbia.

Original study protocol: Refer to Ronald et al. 2016 (1)

External funding: This work was supported by the Michael Smith Foundation for Health Research and the Canadian Institutes for Health Research [Grant: 377364].
Keywords: Tuberculosis, Cancer, Malignancy, Prevention, Immigrant

INTRODUCTION

Tuberculosis (TB) remains the top single infectious disease cause of death worldwide, with an estimated 10 million cases and 1.3 million deaths in 2017 (2). Recognizing this, the World Health Organization (WHO) created the EndTB Strategy with a vision of global TB elimination (2,3). A core part of the EndTB strategy is identification and treatment of latent tuberculosis infection (LTBI) in regions with low TB incidence (3–6). In many low incidence regions, such as Canada, efforts to meet EndTB elimination goals have been hindered by high TB rates in specific populations (6–8). People that migrate to Canada, in particular, experience rates of TB over 20 times greater than the Canadian-born non-Indigenous population (3,9). There are also clear links between certain comorbidities and TB risk (10). New strategies to identify and treat people at highest risk for TB are required to accelerate TB elimination in Canada.

The association between cancer and TB risk is increasingly recognized in peer-reviewed literature and national TB guidelines. At present, Canadian and American guidelines recognize hematologic and head/neck malignancies as risk factors for TB (10,11), and a recent systematic review and meta-analysis conducted by Cheng *et. al* identified up to a nine-fold increased risk of TB amongst patients with hematologic, head and neck, and lung cancers (12). In migrant populations, the risk of active TB associated with different malignancies has not been well studied and may represent an additive risk. Furthermore, literature is sparse on TB risk in people with many common malignancies such as gastrointestinal, breast, prostate and gynecologic cancers.

In this study, we used linked health administrative data on migrants to the province of British Columbia (BC), Canada to describe the relationship between cancer and active TB. Specifically, we aimed to describe the association between different histologic subtypes of cancer and active TB risk, and to assess the proportion of immigrants with cancer in whom active TB was potentially preventable through LTBI screening and treatment.

METHODOLOGY

Study Setting and Data Sources

This study is part of a larger project (1) that describes TB epidemiology in people that migrate to BC, a Canadian province with a population of 5.0 million people and TB incidence of 4.7 per 100,000 persons (13,14). In 2016, approximately 22% of the population of BC, and 85% of people diagnosed with active TB, were born outside of Canada (15).

Descriptions of the databases and methods to identify the cohort have been described in detail in previous publications (1). Briefly, data were extracted from several linked health administrative databases, including a national immigration database, a provincial health insurance registry, hospitalization, physician billing, outpatient pharmacy, vital statistics, HIV, and End-Stage Renal Disease (ESRD) registries (16–28). Extracted data were provided as de-identifiable datasets linked using unique scrambled identification numbers. Full details on this linkage are described in a protocol publication (1).

TB diagnosis and treatment data were obtained from the BC Provincial TB Registry, housed at the BC Centre for Disease Control (BCCDC). The BCCDC is responsible for treatment of all people with active TB and LTBI in the province, and maintains a provincial TB registry that includes data on all people with a history of TB contact, LTBI and active TB diagnosis, and treatment (26). Data on cancer diagnosis were obtained from the BC Cancer Agency (BCCA) registry. The BCCA is a government organization that provides comprehensive cancer care to the people of BC in partnership with regional health authorities. The BCCA registry houses data on all primary cancers diagnosed in BC, with diagnoses confirmed based on pathology, cytology, lab results, cancer centre admissions, and death certificates (27).

Study population and follow-up

Our source population included all foreign-born individuals that obtained permanent residency in Canada between January 1, 1985 and December 31, 2012 and established residency in BC at any point until December 31, 2015. BC residents were identified when they registered in the provincial Medical Services Plan (MSP), a universal health insurance program administered by the BC government. Depending on a household's income, MSP coverage may be free, or may require monthly premiums. Thus, we believe that MSP coverage may be a surrogate marker of residency status in BC (29,30). Individuals who did not acquire an MSP number (e.g. temporary visitors, students, short-term workers or undocumented residents of BC) were not included in the cohort.

We limited the cohort to 1996 onward when community pharmacy data became available. Furthermore, we limited the analysis cohort to individuals aged ≥15 years as there were few cancer cases at younger ages. Calculation of follow-up time began for all individuals at their index event, which was identified as occurring at 90 days before first MSP registration date or at an individual's first health service record in BC, whichever date was earliest. The 90 day window was selected to account for the mandatory 90-day waiting period required for starting MSP after arrival in BC. The follow-up period ended at first active TB diagnosis, end of MSP coverage, death or end of study period (December 31st, 2015), whichever date was earliest.

Definitions of outcome and risk factor variables

The primary outcome measured was time to first active TB diagnosis. TB diagnosis was identified based on BCCDC TB Registry data, and included all TB sites (i.e., pulmonary and extra-pulmonary TB) that were either microbiologically or clinically confirmed. TB diagnosis was established in the BCCDC registry based on the Canadian TB Reporting System Guidelines (31).

The exposure of interest was incident cancer diagnosis occurring after study entry. Specific cancers were identified based on the site of primary malignancy, as reported in the BCCA Registry. Specific cancers identified for this analysis included: lung; breast; gastrointestinal (GI); hematologic cancers (lymphoma and leukemia); head and neck (HN); genitourinary (GU); gynecologic (GYN); prostate; sarcoma; skin (including melanoma and other skin cancers); neural; and other/unknown cancers.

TB incidence rate per 100,000 person-years (PYs) was calculated in people with and without a diagnosis of cancer. We identified the cancer risk start date as 90 days before the recorded cancer diagnosis date, and the cancer risk end date occurring 5 years after cancer diagnosis, at which time patients who were alive and without TB contributed time to the non-cancer group. If there were multiple overlapping cancer episodes of the same type, we tied these together and counted them as one episode only, with the first cancer diagnosis date identified as the start date of the episode. We also limited our analysis to incident cancers occurring after study entry (i.e. 2,014 people with prevalent cancers at the index date were excluded from analyses).

Other risk variables included sex, age at follow-up (10-year age categories), time since arrival in BC (0-5 years and >5 years), immigration classification (refugee, family or economic), high-risk medical co-morbidities, and TB incidence in country of origin (8). For the TB incidence in country of origin, we used country-level WHO TB incidence data at year of arrival to Canada from 1990-2012 (32). For years prior to 1990, we applied 1990 TB incidence rates.

For medical co-morbidities, we established diagnosis dates of the following conditions: HIV, dialysis dependent end stage kidney disease (ESKD), diabetes, and medical immune-suppression (including use of TNF-alpha inhibitors, high-dose steroids, high-risk DMARDS, or receipt of solid organ or bone marrow transplantation). We also identified if an individual was a known contact of a person diagnosed with active TB in BC. Disease registries were used as the gold standard for disease diagnoses, supplemented with data

from health administrative databases using validated algorithms (1). Detailed definitions and exposure risk periods for each comorbidity have been described previously (1,33).

Statistical analysis

Analyses were conducted in R (version 3.6.0; The R Project for Statistical Computing) and SAS/STAT (V.9.4, SAS Institute, Cary, USA). This study received ethical approval from the University of BC Clinical Ethics Review Board (H16 -00625).

We produced descriptive statistics for our study cohort at the time of cohort entry, defined by index date. Rates of active TB and median years from cancer diagnosis to active TB were calculated for each cancer subtype. Cancer diagnoses may occur with or after a diagnosis of active TB, and therefore, to understand the potential impact of LTBI screening and prevention amongst people with cancer, we plotted the time of active TB diagnoses against the time of cancer diagnoses for each cancer type. The proportion of active TB cases that were potentially preventable was then calculated as those occurring more than 6 months after cancer diagnosis. This time point was set to capture preventable TB cases amenable to LTBI testing and treatment at cancer diagnosis.

We used extended Cox regression to model the risk of active TB. We ran separate models based on site of primary malignancy. For sex-predominant cancers, we restricted models by sex (i.e. breast and gynecologic cancer models were restricted to females; the prostate cancer model was restricted to males). We included all identified risk variables in multivariable models, determined *a priori* based on clinical relevance. Schoenfeld residuals were used to test extended Cox model parameters.

Model assumptions were tested through sensitivity analyses, including testing different age at risk for cancer thresholds and the time window for the cancer at-risk period. As an additional sensitivity analysis, we assessed for impact of LTBI screening within our cohort. We also examined whether radiotherapy during cancer treatment increased the risk of active TB, as this has previously been suspected to be a risk factor for active TB (34,35). Results of sensitivity analyses are reported in the Appendix. Incomplete data was identified as "missing data" in results.

Patient and Public Involvement:

Patients or public were not involved in the methodology, conduct, analyses, or reporting of this research.

RESULTS

Population characteristics:

Our study population included 1,000,764 individuals aged ≥15 years, with a mean of 13.4 person-years of total follow-up time per individual. Population characteristics are outlined in Table 1. Median age was 32.3 years, 48.5% were male, and 58.0% migrated from countries with TB incidence >100 per 100,000 persons. A small proportion of individuals (0.6%) were contacts of people diagnosed with active TB at any time in BC.

Table 1: Cohort characteristics at entry and co-morbidities over study follow-up (N=1,000,764)

Cohort Characteristics	Without Cancer [n (%)]	Cancer ǂ [n (%)]	Total [n (%)]
Age group (years)			
15-24	311,087 (31.1%)	1,747 (0.2%)	312,834 (31.3%)
25-34	255,477 (25.5%)	4,431 (0.4%)	259,908 (26.0%)
35-44	214,955 (21.5%)	6,997 (0.7%)	221,952 (22.2%)
45-54	101,959 (10.2%)	5,402 (0.5%)	107,361 (10.7%)
55-64	50,987 (5.1%)	5,235 (0.5%)	56,222 (5.6%)
65-74	27,322 (2.7%)	4,148 (0.4%)	31,470 (3.1%)
75-84	8,051 (0.8%)	1,336 (0.1%)	9,387 (0.9%)
85-94	1,408 (0.1%)	148 (0.0%)	1,556 (0.2%)
≥95	70 (0.0%)	4 (0.0%)	74 (0.0%)
Gender			
Female	497,883 (49.8%)	17,418 (1.7%)	515,301 (51.5%)
Male	473,433 (47.3%)	12,030 (1.2%)	485,463 (48.5%)
TB incidence by country of origin (per 100,000 population)			
0-30	158,280 (15.8%)	5,425 (0.5%)	163,705 (16.4%)
31-100	250,830 (25.1%)	6,018 (0.6%)	256,848 (25.7%)
101-200	310,359 (31.0%)	10,474 (1.0%)	320,833 (32.1%)
>200	251,821 (25.2%)	7,531 (0.8%)	259,352 (25.9%)
Immigration classification			
Refugee	76,919 (7.7%)	2,039 (0.2%)	78,958 (7.9%)
Family	321,328 (32.1%)	14,759 (1.5%)	336,087 (33.6%)
Economic	573,069 (57.3%)	12,650 (1.3%)	585,719 (58.5%)
Years in BC			
0-5	800,518 (80.0%)	22,769 (2.3%)	823,287 (82.3%)
>5	170,798 (17.1%)	6,679 (0.7%)	177,477 (17.7%)
Active TB contact	5,676 (0.6%)	248 (0.0%)	5,924 (0.6%)
Comorbidities†			
HIV	1,460 (0.1%)	109 (0.0%)	1,569 (0.2%)
Dialysis dependent end-stage kidney disease	1,671 (0.2%)	255 (0.0%)	1,926 (0.2%)
Immune-suppression*	22,715 (2.3%)	2,914 (0.3%)	25,629 (2.6%)
Diabetes	98,519 (9.8%)	7,025 (0.7%)	105,544 (10.5%)
Total	971,316 (97.1%)	29,448 (2.9%)	1,000,764 (100.0%)

Missing data (country of origin, n=26)

* Immune-suppression= Includes treatment with immune-suppressing drugs (TNFa inhibitors, DMARDS, or high-dose steroids or post-transplant)

†Includes incident and prevalent cases

ǂ Includes incident cases only

In the study population, 29,448 people (2.9%) were diagnosed with cancer (Table 2). The most frequently noted malignancies were breast (n = 5,918), gastrointestinal (n = 5,688), gynecologic (n = 4,450), lung (n = 2,421), lymphoma (n = 1,252), and leukemia (n =1,139) cancers. Table 2 provides details on cancer types. In the entire study cohort, 2,585 people developed active TB, with 91 people (0.3%) diagnosed with active TB within 5 years of a cancer diagnosis. Unadjusted active TB rates were as follows: lung cancer (525.1 per 100,000 person-years (PY)), sarcoma (174.4 per 100,000 PY), lymphoma (268.2 per 100,000 PY), leukemia (284.9 per 100,000 PY), gastrointestinal (107.9 per 100,000 PY), and head/neck cancer (31.3 per 100,000 PY) (Table 2). Figure 1 shows a scatter plot with timing of TB diagnosis against timing of cancer diagnosis for each cancer type.

Table 2: Incidence of active TB in patients newly diagnosed with cancer

Cancer type ǂ	n (%)	Median age at cancer diagnosis, years (Q1,Q3)	Median time from cancer to TB diagnosis, years (Q1,Q3)*	# active TB diagnoses		# active TB cases per 100,000 person-years at-risk†
				Up to 5 years after cancer diagnosis	From 6 months to 5 years after cancer diagnosis ("potentially preventable TB")	
Lung	2,421 (0.2)	68 (57, 77)	0.4 (0.3, 0.7)	25	9	525.1
Sarcoma	725 (0.1)	47 (36, 58)	1.6 (0.7, 1.9)	5	<5	174.4
Leukemia	1,139 (0.1)	62 (47, 74)	1.2 (0.8, 1.9)	11	8	284.9
Lymphoma	1,252 (0.1)	58 (45, 71)	0.5 (0.3, 1.6)	12	6	268.2
Breast	5,918 (0.6)	51 (44, 61)	4.7 (1.7, 5.8)	6	5	23.3
Head and Neck	840 (0.1)	55 (45, 67)	5.3 (2.5, 11.3)	<5	<5	31.3
Gastro-Intestinal	5,688 (0.6)	65 (54, 75)	1.8 (1.1, 5.1)	17	14	107.9
Skin / Melanoma	1,196 (0.1)	56 (45, 71)	3.1 (1.7, 6)	<5	<5	39.1
Prostate	3,012 (0.3)	68 (61, 75)	5.5 (2.1, 8.1)	10	8	78.6
Gynecologic	4,450 (0.4)	43 (35, 54)	6.2 (3.5, 13.8)	<5	<5	10.6
Gastro-Urinary	1,742 (0.2)	63 (49, 75)	0.9 (0.9, 0.9)	<5	<5	15.5
Neural	457 (0.1)	55 (45, 71)	2.1 (2.1, 2.1)	<5	<5	94.5
Other/Unknown	1,890 (0.2)	53 (41, 69)	1.3 (0.4, 7.0)	<5	<5	48.6
Any cancer	29,448 (2.9)	57 (45, 70)	1.6 (0.4, 4.9)	91	60	83.3

* Among people diagnosed with active TB on or after their cancer diagnosis date, up to 5 years after the cancer diagnosis date
† person-years at-risk includes up to 5 years after cancer diagnosis
ǂ Includes incident cases only

Potentially preventable TB cases were identified as those occurring >6 months after the diagnosis of cancer, as these cases could be potentially amenable to LTBI screening and therapy at the time of cancer diagnosis. Amongst 2,421 people with lung cancer, 25 people (1.0%) were diagnosed with active TB within 5 years. Of these, 9 (42.9%) had active TB diagnosed >6 months after cancer diagnosis. Similarly, 8 (72.7%) with leukemia, 6 (50%) with lymphoma, and 14 (82.4%) with gastrointestinal cancers were diagnosed with active TB >6 months post cancer diagnosis (Table 2). Overall, 60 out of 91 (65.9%) diagnosed active TB cases were classified as potentially preventable.

Figure 2 shows results from multivariable Cox regression analyses by cancer type. People with lung cancer and sarcoma had the highest risk of active TB, with adjusted hazard ratios (aHR) of 11.2 (95%CI: 7.4,16.9) for lung, and 8.1 (95%CI: 3.3,19.5) for sarcoma. This was followed by leukemia (aHR 5.6 (95%CI: 3.1,10.2)), lymphoma (aHR 4.9 (95% CI: 2.7, 8.7)), and gastrointestinal cancers (aHR 2.7 (95%CI: 1.7,4.4)). The full multivariable Cox model for lung cancer is shown in Table 3.

Table 3: TB risk in people diagnosed with lung cancer, univariable and multivariable hazard ratios

	# TB cases per 100,000 person-years	Univariate HR (95% CI)	Multivariable HR (95% CI)
Cancer, lung			
Yes	525.1	25.2 (17.0, 37.6)	11.2 (7.4, 16.9)
No	22.4	1.0	1.0
Age group (years)			
15-24	16.5	1.0	1.0
25-34	19.4	1.4 (1.2, 1.6)	1.1 (1.0, 1.3)
35-44	17.0	1.2 (1.1, 1.4)	1.1 (1.0, 1.3)
45-54	15.5	1.3 (1.1, 1.5)	1.2 (1.0, 1.4)
55-64	25.3	2.1 (1.8, 2.5)	1.7 (1.4, 2.0)
65-74	51.5	4.2 (3.5, 4.9)	3.0 (2.5, 3.6)
75-84	88.7	7.7 (6.5, 9.1)	5.6 (4.6, 6.8)
85-94	109.1	10.1 (8.0, 12.8)	8.4 (6.5, 10.9)
≥95	91.2	9.0 (4.4, 18.2)	8.4 (4.1, 17.2)
Sex			
Male	24.3	1.1 (1.1, 1.2)	1.2 (1.1, 1.2)
Female	21.1	1.0	1.0
TB incidence in country of origin			
0-30	2.4	1.0	1.0
31-100	9.9	4.2 (3.0, 5.8)	4.2 (3.0, 5.9)
101-200	21.0	9.2 (6.6, 12.6)	9.4 (6.8, 12.9)
>200/ 100,000 population	45.2	19.7 (14.3, 27.1)	18.6 (13.5, 25.6)
Immigration type			
Refugee	29.8	2.1 (1.9, 2.4)	2.0 (1.7, 2.3)

Family	33.5	2.4 (2.2, 2.6)	1.2 (1.1, 1.4)
Economic	14.4	1.0	1.0
Years in BC			
0-5	29.8	1.4 (1.3, 1.7)	1.6 (1.4, 1.9)
>5	19.8	1.0	1.0
Active TB contact			
Yes	298.5	12.8 (9.0, 18.4)	9.0 (6.2, 12.9)
No	22.4	1.0	1.0
HIV			
Yes	442.8	21.3 (16.1, 28.2)	20.3 (15.1, 27.2)
No	22.2	1.0	1.0
Dialysis dependent end stage kidney disease			
Yes	553.6	27.1 (20.0, 36.8)	8.2 (5.9, 11.5)
No	22.3	1.0	1.0
Immune-suppression*			
Yes	253.5	12.5 (10.3, 15.3)	7.0 (5.6, 8.6)
No	21.8	1.0	1.0
Diabetes			
Yes	48.0	2.7 (2.4, 3.0)	1.3 (1.2, 1.5)
No	20.5	1.0	1.0

*Includes treatment with immune-suppressing drugs (TNF-alpha inhibitors, DMARDS, or high-dose steroids), or post-transplant

DISCUSSION

Our province-wide, retrospective cohort study demonstrates that migrants with cancer are at higher risk for active TB than migrants without cancer, with TB risk varying by tumour type. The highest risk of TB was observed among migrants with lung cancer, followed by sarcoma, leukemia, lymphoma, and gastrointestinal malignancies. Head and neck, neural, skin, prostate, and breast cancers all had an elevated point estimate for TB risk, however, the increase was not significant in multivariable analysis. Notably, the majority of active TB cases were clustered immediately before or after cancer diagnosis, but an appreciable number of people developed TB more than 6 months post-cancer diagnosis. This represents a population of people with potentially preventable TB.

To our knowledge, our study is the first to provide risk estimates for TB due to various cancer types in a cohort of migrants within a low incidence region. As latent TB screening of all immigrants has previously been shown to be economically challenging, understanding the selective impact of various malignancies becomes crucial to help clinicians identify migrants at highest risk of active TB. Significant strengths of our study include large population cohort, risk estimates adjusted for other commonly recognized TB risk factors, stratification of TB risk by cancer type, and long follow up time. Given the wide capture of immigrant population over a 19 year follow up period, we believe that our results may be applicable at other low incidence areas including other Canadian provinces, and regions within United States.

The elevated TB risk observed in immigrants with lung and hematologic cancers are in concordance with those noted in the non-immigrant populace as reported by Cheng et. al 2016 and Simonsen et. al. 2017, with some variations which may reflect differences in study populations and cancer treatments amongst

different regions (12,35). The mechanism through which malignancies increases TB risk is speculated to be multifactorial, including immunosuppression by both local and systemic effects. For lung cancer, mass effect and inflammation may disrupt local barriers to infection, increasing TB risk (35). Furthermore, infiltration of dormant TB granulomas by local tumour peptides in lung cancer may further increase re-activation risk (36). Importantly, our observed TB risk amongst lung cancer may be influenced by shared lifestyle variables, including smoking and ethanol use, which were not accounted for in our study (37–39). For hematologic malignancies, immunosuppression may be due to multiple factors including bone marrow infiltration, impaired T cell mediated immunity, and superimposed chemotherapy (40–42). Although we were unable to account for chemotherapy regimens, we found no significant impact of radiotherapy on active TB risk (Appendix Table A2).

Importantly, in contrast to previously assessed TB risk estimates within the general population, we found that head/neck cancer within the immigrant population resulted in a non-statistically significant elevated TB risk. The low incidence of head and neck cancer within our cohort resulted in wide confidence intervals. We suspect that our observed lower TB risk amongst head/neck malignancies may reflect evolution in treatment and care of head/neck cancer which may secondarily lower TB risk by reducing systemic immunosuppression and malnutrition. This includes transition to directed beam therapy, improved nutritional supplementation, and closer surveillance (43). This is consistent with the systematic review conducted by Cheng et. al. 2016, which described a decrease in TB incidence amongst head and neck cancers after 1980 compared to pre 1980 period. In addition to changes in treatments, they speculated that decreased TB incidence may also reflect changes in the underlying etiology of head/neck cancers, from non-HPV associated Head and Neck cancer, which are typically related to heavy smoking and alcohol use, to HPV related Head and Neck malignancies (12,43).

Furthermore, to our knowledge, this study is the first to show increased adjusted TB risk in individuals with sarcomas. The link between sarcoma and TB has been described in rare case reports, and remains poorly understood (44,45). While our risk estimates account for concurrent immunosuppression in sarcoma patients, namely HIV and post-transplant state, we were unable to adjust for chemotherapy which may result in the observed elevated risk of active TB amongst individuals with sarcoma. Additionally, similar to head/neck cancers, the low incidence of sarcoma within our cohort accounts for the wide confidence intervals observed. Literature also remains sparse on the association of gastrointestinal malignancies and TB. While other authors have shown increased risk of TB with aerodigestive cancers(35,46), our study shows an elevated active TB risk amongst gastrointestinal malignancies independent from lung and head/neck cancers. It is speculated that concurrent comorbidities including significant weight loss and malnutrition may result in increased susceptibility to TB reactivation amongst GI cancers (44,47).

The clustering of active TB around time of cancer diagnoses as noted in Figure 1, may point to higher susceptibility to TB amongst cancer patients, either by primary acquisition or latent TB re-activation. As mentioned, early identification and treatment of LTBI in high risk cancer patients is crucial to prevent active TB and the possibility of ongoing transmission, most importantly in oncology clinics and inpatient services (48). We observed that amongst cancers noted to increase active TB risk, including sarcoma, leukemia, lymphoma, gastrointestinal malignancies, an appreciable proportion of migrants were diagnosed with active TB greater than six months post cancer diagnosis. These people represent potentially preventable TB as they could benefit from LTBI screening and treatment at the time of cancer diagnosis. In contrast to other malignancies, a lower proportion (approximately 1/3rd) of active TB in immigrants with lung cancer was diagnosed greater than six months post-cancer diagnosis. This phenomenon has been described by other authors and may be explained by the similar care pathways; TB can often produce masses or nodules which can imitate neoplasms in the lung, and therefore, similar imaging and diagnostic strategies involved for work-up of both entities may explain this close association of lung cancer with TB (44,49–51). At present, in BC, province-wide screening and treatment for LTBI in cancer patients is not routine. Our data provide

strong support for LTBI testing amongst migrants with sarcoma, leukemia, lymphoma, lung, and gastrointestinal cancers.

Limitations

Our study has several limitations. First, we did not have access to certain variables such as smoking history, alcohol use and specific chemotherapeutic regimens, all of which are associated with increased active TB risk (35,37–39). Second, we were unable to account for contact to TB outside of BC, however, we expect these numbers to be low, given the overall low TB incidence rate in Canada. Third, the high rate of active TB in cancer patients noted in our study may reflect the high level of care which cancer patients require. Importantly, we conducted sensitivity analysis to account for individuals screened for LTBI and this did not reveal any significant differences in our observed risk estimates (Appendix Table A1). Despite the stated limitations in understanding the causal role of malignancy in TB risk, we do note that people with certain malignancies have high rates of active TB, and may potentially benefit from LTBI screening and treatment, regardless of the underlying causal pathway.

CONCLUSION

In people that migrate to BC, specific cancers increase active TB risk, with highest risk noted in lung, sarcoma, leukemia, lymphoma, and gastrointestinal malignancies. An appreciable number of active TB cases are diagnosed more than six months after cancer diagnoses and may be potentially preventable with vigilant LTBI screening and therapy. While current Canadian TB guidelines recommend LTBI screening in migrants with hematologic or head/neck cancer, our data provide evidence of the preventable burden of active TB in migrants with other malignancies who could be considered for LTBI screening and therapy.

Notes: The corresponding author (Dr. J. Johnston) has full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of analysis.

Author contributions:

Study concept and design: JCJ, VJC, LR
Data acquisition, analysis, and interpretation: LR,CR, DSK, JCJ, HPS
Manuscript drafting: DSK, LR, JCJ
Critical revision of manuscript: DSK, LR, CR, KR, VCJ, JCJ, HPS
Statistical analysis: LR, CR, HPS
Funding acquisition: JCJ
Administrative and technical support: KR
Study supervision: VJC, JCJ

Conflicts of Interest Disclosure: None reported

Disclaimer: All inferences, opinions, and conclusions drawn in this study are those of the authors, and do not reflect the opinions or policies of the Data Steward(s)

Funding support: Michael Smith Foundation for Health Research and Canadian Institutes for Health Research (Grant: 377364)

Approval: This study received ethical approval from the University of BC Clinical Ethics Review Board (H16 -00625).

Previous presentation: Preliminary findings from this study were presented as a podium presentation at the 49th Union World conference on Lung Health, October 24-27th, 2018 at The Hague, Netherlands.

Data sharing: Data were extracted as deidentified datasets from several linked health administrative databases, including a national immigration database (Population Data BC and IRCC), a provincial health insurance registry, hospitalization, physician billing, outpatient pharmacy, vital statistics, HIV, and End-Stage Renal Disease (ESRD) registries. Additional data was extracted from the BC Provincial TB and BC Cancer Agency registries. Data are not publicly available. Data may be obtained upon authorized request to the respective data stewards as detailed in the study protocol.

REFERENCES

1. Ronald LA, Campbell JR, Balshaw RF, et al. Predicting tuberculosis risk in the foreign-born population of British Columbia, Canada: study protocol for a retrospective population-based cohort study. BMJ Open. 2016 Nov 1;6(11):e013488.

2. World Health Organization. Global tuberculosis report 2018 [Internet]. 2018. Available from: https://www.who.int/tb/publications/global_report/en/

3. World Health Organization, End TB Strategy. Global strategy and targets for tuberculosis prevention, care and control after 2015 [Internet]. World Health Organization. 2015 [cited 2019 Feb 27]. Available from: https://www.who.int/tb/strategy/End_TB_Strategy.pdf?ua=1

4. Lönnroth K, Migliori GB, Abubakar I, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. European Respiratory Journal. 2015 Mar 18;ERJ-02140-2014.

5. World Health Organization and European Respiratory Society, Framework towards TB elimination in low incidence countries [Internet]. 2014 [cited 2019 Feb 27]. Available from: https://www.who.int/tb/publications/Towards_TB_Eliminationfactsheet.pdf

6. Campbell JR, Chen W, Johnston J, et al. Latent Tuberculosis Infection Screening in Immigrants to Low-Incidence Countries: A Meta-Analysis. Mol Diagn Ther. 2015 Apr 1;19(2):107–17.

7. Campbell J, Marra F, Cook V, et al. Screening immigrants for latent tuberculosis: Do we have the resources? Canadian Medical Association Journal: CMAJ; Ottawa. 2014 Mar 4;186(4):246–7.

8. Pareek M, Watson JP, Ormerod LP, et al. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. The Lancet Infectious Diseases. 2011 Jun;11(6):435–44.

9. Public Health Agency of Canada. Canadian Tuberculosis Standards 7th Edition [Internet]. 2014 [cited 2016 Apr 21]. Available from: http://www.phac-aspc.gc.ca/tbpc-latb/pubs/tb-canada-7/index-eng.php

10. Public Health Agency of Canada. Canadian Tuberculosis Standards 7th Edition: 2014 [Internet]. aem. 2014 [cited 2017 Dec 17]. Available from: https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition.html

11. American Thoracic Society and Centers of Disease Control and Prevention. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. Am J Respir Crit Care Med. 2000 Apr 1;161(supplement_3):S221–47.

12. Cheng MP, Abou Chakra CN, Yansouni CP, et al. Risk of Active Tuberculosis in Patients with Cancer: A Systematic Review and Meta-Analysis. Clinical Infectious Diseases. 2016 Dec 16;ciw838.

13. Statistics Canada. Population size and growth rate, Canada, provinces and territories, 2006 to 2011 and 2011 to 2016 [Internet]. 2017 [cited 2019 Feb 27]. Available from: https://www150.statcan.gc.ca/n1/daily-quotidien/170208/t002a-eng.htm

14. Statistics Canada. Number and proportion of foreign-born population in Canada, 1871 to 2036 [Internet]. 2017 [cited 2019 Feb 27]. Available from: https://www.statcan.gc.ca/eng/dai/btd/othervisuals/other006

15. Public Health Agency of Canada. Tuberculosis in Canada 2016 [Internet]. 2018 [cited 2019 Feb 27]. Available from: https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2018-44/issue-3-4-march-1-2018/article-1-tuberculosis-2016.html

16. Population Data BC [Internet]. [cited 2016 Apr 20]. Available from: https://www.popdata.bc.ca

17. Immigration Statistics Canada. [cited 2016 Sep 26]. Available from: http://epe.lac-bac.gc.ca/100/202/301/immigration_statistics-ef/index.html

18. Immigration, Refugees, and Citizenship Canada (IRCC) [creator] (2014). Permanent Resident database [Internet]. Population Data BC [publisher]. Data Extract. IRCC; 2015. Available from: http://www.popdata.bc.ca/data

19. Statistics Canada (2009) [creator]. Statistics Canada Income Band Data. Catalogue Number: 13C0016 [Internet]. Population Data BC [publisher]. Data Extract; 2014. Available from: http://www.popdata.bc.ca/data

20. Canadian Institute for Health Information [creator] (2015). Discharge Abstract Database (Hospital Separations) [Internet]. Population Data BC [publisher]. Data Extract. MOH; 2014. Available from: http://www.popdata.bc.ca/data

21. BC Renal Agency [creator] (2015). BC Provincial Renal Agency Database (PROMIS) [Internet]. Population Data BC [publisher]. Data Extract. PROMIS; 2014. Available from: http://www.popdata.bc.ca/data

22. BC Vital Statistics Agency [creator] (2015). BC Vital Statistics Deaths [Internet]. Population Data BC [publisher]. Data Extract. BC Vital Statistics Agency; 2014. Available from: http://www.popdata.bc.ca/data

23. British Columbia Ministry of Health [creator] (2015). Consolidation File (MSP Registration & Premium Billing) [Internet]. Population Data BC [publisher]. Data Extract. MOH; 2015. Available from: http://www.popdata.bc.ca/data

24. BC Ministry of Health [creator] (2015). PharmaNet [Internet]. BC Ministry of Health Data Stewardship Committee [publisher]. Data Extract. MOH Data Stewardship Committee; 2014. Available from: http://www.popdata.bc.ca/data

25. BC Centre for Disease Control [creator] (2015). BC Provincial HIV/AIDS Surveillance Database (BCCDC-HAISIS) [Internet]. Population Data BC [publisher]. Data Extract. BCCDC; 2014. Available from: http://www.popdata.bc.ca/data

26. BC Centre of Disease Control [creator] (2015). BC Provincial TB Registry (BCCDC-iPHIS). Population Data BC [publisher] Data Extract BCCDC [Internet]. 2014; Available from: http://www.popdata.bc.ca/data

27. BC Cancer Agency. BC Cancer Registry [Internet]. [cited 2016 May 30]. Available from: http://www.bccancer.bc.ca/health-professionals/professional-resources/bc-cancer-registry

28. BC Cancer Agency [creator] (2015). BC Cancer Agency Registry Data [Internet]. Population Data BC [publisher]. Data Extract. BCCA; 2014. Available from: http://www.popdata.bc.ca/data

29. British Columbia Ministry of Health [creator] (2015). Medical Services Plan (MSP) Payment Information File [Internet]. Population Data BC [publisher]. Data Extract. MOH; 2014. Available from: http://www.popdata.bc.ca/data

30. Ministry of Health. MSP for B.C. Residents - Province of British Columbia [Internet]. [cited 2016 Apr 22]. Available from: https://www2.gov.bc.ca/gov/content/health/health-drug-coverage/msp/bc-residents

31. Public Health Agency of Canada. Canadian Tuberculosis Reporting System: Reporting Form Completion Guidelines, Version 1.9. January 1, 2011. http://www.phac-aspc.gc.ca/tbpc-latb/pdf/guidelinesform-eng.pdf. Accessed May 30, 2016.

32. WHO World TB Database (http://www.who.int/tb/country/data/download/en/). Accessed April 22, 2016.

33. Ronald LA, Campbell JR, Rose C, et al. Estimated Impact of World Health Organization Latent Tuberculosis Screening Guidelines in a Region With a Low Tuberculosis Incidence: Retrospective Cohort Study. Clin Infect Dis [Internet]. [cited 2019 Jul 27]; Available from: https://academic-oup-com.ezproxy.library.ubc.ca/cid/advance-article/doi/10.1093/cid/ciz188/5374592

34. Thomas P, Foley R, Kosowicz L. Reactivation of pulmonary tuberculosis following local radiation therapy of prostate cancer. Connecticut Medicine. 2014 Feb;78(2):77–80.

35. Simonsen DF, Farkas DK, Horsburgh CR, et al. Increased risk of active tuberculosis after cancer diagnosis. Journal of Infection. 2017 Jun;74(6):590–8.

36. Suzuki Y, Imokawa S, Sato J, et al. Cumulative incidence of tuberculosis in lung cancer patients in Japan: A 6-year observational study. Respiratory Investigation. 2016 May;54(3):179–83.

37. Maurya V, Vijayan V. K, Shah A. Smoking and tuberculosis: an association overlooked. The International Journal of Tuberculosis and Lung Disease. 2002 Nov 1;6(11):942–51.

38. Boon S den, Lill SWP van, Borgdorff MW, et al. Association between smoking and tuberculosis infection: a population survey in a high tuberculosis incidence area. Thorax. 2005 Jul 1;60(7):555–7.

39. Rehm J, Samokhvalov AV, Neuman MG, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC Public Health. 2009 Dec 5;9:450.

40. Advani SH, Banavali SD. Pattern of Infection in Hematologic Malignancies: An Indian Experience. Reviews of Infectious Diseases. 1989;11:S1621–8.

41. Au WY, Kwong YL, Ma SK, et al. Hairy cell leukemia in Hong Kong Chinese: a 12-year retrospective survey. Hematol Oncol. 2000 Dec 1;18(4):155–9.

42. Liu C-J, Hong Y-C, Teng C-J, et al. Risk and impact of tuberculosis in patients with chronic myeloid leukemia: A nationwide population-based study in Taiwan. Int J Cancer. 2015 Apr 15;136(8):1881–7.

43. Marur S, Forastiere AA. Head and Neck Squamous Cell Carcinoma: Update on Epidemiology, Diagnosis, and Treatment. Mayo Clinic Proceedings. 2016 Mar 1;91(3):386–96.

44. Kaplan MH, Armstrong D, Rosen P. Tuberculosis complicating neoplastic disease. A review of 201 cases. Cancer. 1974 Mar 1;33(3):850–8.

45. Aggarwal R, Rao S. Coexistence of tuberculosis with histiocytic sarcoma: A rare association. Journal of Cancer Research and Therapeutics. 2015;11(3):658.

46. Wu C-Y, Hu H-Y, Pu C-Y, et al. Aerodigestive tract, lung and haematological cancers are risk factors for tuberculosis: an 8-year population-based study. Int J Tuberc Lung Dis. 2011 Jan;15(1):125–30.

47. Vento S, Lanzafame M. Tuberculosis and cancer: a complex and dangerous liaison. The Lancet Oncology. 2011 Jun;12(6):520–2.

48. Parry C, Kent EE, Mariotto AB, et al. Cancer Survivors: A Booming Population. Cancer Epidemiology Biomarkers & Prevention. 2011 Oct 1;20(10):1996–2005.

49. Chen C-Y, Wang J-Y, Chien Y-C, et al. Lung cancer mimicking pulmonary tuberculosis in a TB-endemic country: the role of early invasive diagnostic procedures. Lung Cancer Management. 2015 Feb;4(1):9–16.

50. Ciftci F, Shimbori N, Karnak D. Concurrent central nervous system and endobronchial tuberculosis mimicking a metastatic lung cancer. The Clinical Respiratory Journal. 2017 Jan 1;11(1):98–102.

51. Davies PDO, Pai M. The diagnosis and misdiagnosis of tuberculosis [State of the art series. Tuberculosis. Edited by I. D. Rusen. Number 1 in the series]. The International Journal of Tuberculosis and Lung Disease. 2008 Nov 1;12(11):1226–34.

FIGURE LEGENDS:

Figure 1 Legend:
GI: Gastro-Intestinal; **HN:** Head and Neck; **GYN:** Gynecological; **GU:** Genito-Urinary; **Oth/Unk:** other and unknown;
∘ Active TB diagnosis

Figure 2 Legend:
Hazard Ratios adjusted for*: age at follow up, sex, time since arrival in BC (0-5 yrs and >5 yrs), immigration classification type (refugee, family or economic), high risk medical comorbidities (HIV, Dialysis dependent end stage kidney disease, Immune Suppression, Diabetes), and TB incidence by country of origin.

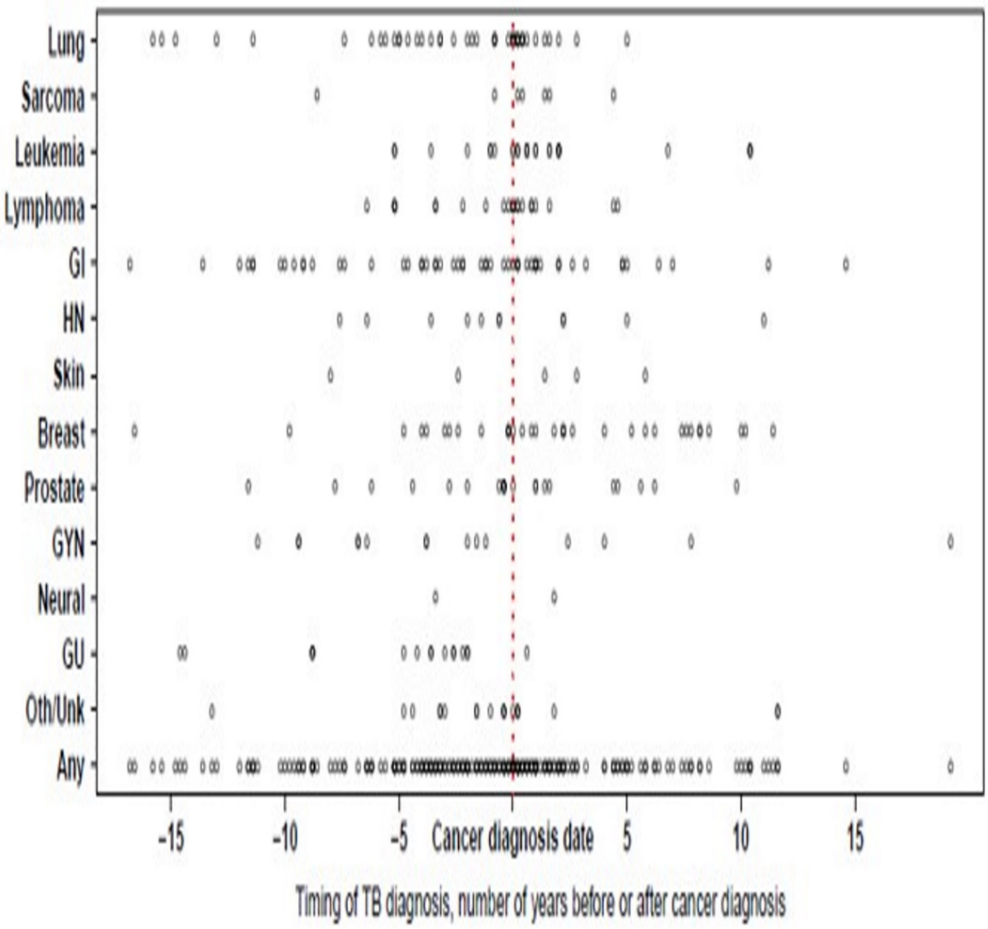


Figure 1: Timing of active TB diagnoses, number of years before and after cancer diagnoses

90x90mm (300 x 300 DPI)

Cancer	Active TB (cancer)	Active TB (control)	HR (95% CI)
Lung	25	2560	11.2 (7.4, 16.9)
Sarcoma	5	2580	8.1 (3.3, 19.5)
Leukemia	11	2574	5.6 (3.1, 10.2)
Lymphoma	12	2573	4.9 (2.7, 8.7)
GI	17	2568	2.7 (1.7, 4.4)
Neural	<5	2584	2.5 (0.3, 18.7)
HN	<5	2582	1.1 (0.2, 7.9)
Breast	6	1258	1.2 (0.5, 2.6)
Prostate	10	1310	1.2 (0.6, 2.2)
Skin	<5	2583	1.1 (0.2, 4.6)
GYN	<5	1262	0.5 (0.1, 2.1)
GU	<5	2584	0.3 (0.0, 2.4)
Other	<5	2584	1.2 (0.4, 3.8)
Any	91	2484	2.5 (2.0, 3.1)

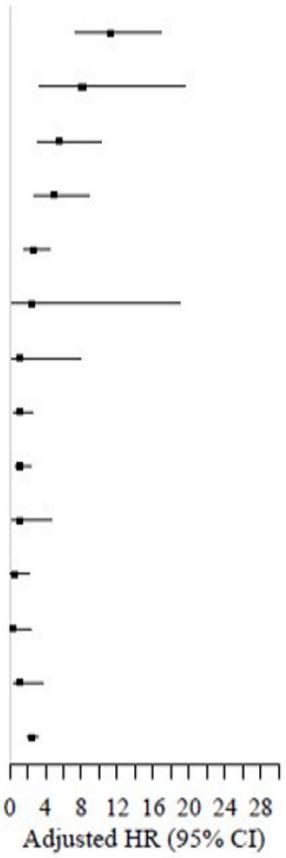


Figure 2: TB risk (multivariable hazard ratios*) in immigrants diagnosed with different cancer types

90x90mm (300 x 300 DPI)

APPENDIX

Table A1: Sensitivity analysis, testing models with different population inclusion criteria

Model #	Model description	# people deleted (w/ prevalent cancers)	# people included in analysis	# TB cases included in analysis	Adj HR, Lung cancer
1*	Age 15+	2,014	1,000,764	2,585	11.2 (7.4-16.9)
2	Age 30+	2,558	800,489	2,071	11.2 (7.4-16.9)
3	All ages	1,961	1,046,759	2,634	11.5 (7.6-17.4)
4	Age 15+, excluding LTBI	2,010	995,828	2,575	11.4 (7.5-17.1)

*Base-case model

Table A2: Total BCCA Registry cancer episodes identified as having radiation (n=1078)*†§

BCCA Cancer type	Total episodes	% with radiation therapy‡
Breast	5630	1.0
GI	5375	1.3
GU/GYN	5928	3.6
Head and Neck	1834	31.5
Hematological	2578	1.4
Lung	2297	3.1
Prostate	2824	6.0
Other/Unknown	3577	1.8
Total	30043	3.6

*Of all primary cancers reported to BC Cancer Registry between 1985-2012
†Radiation defined as occurring any time 1 year before cancer registry date or anytime after
‡ There were no cases of active TB diagnosed in people with cancer and radiation therapy
§ Codes used to identify inpatient radiation therapy:

System	Code	Code description
ICD9	V580	Encounter for radiotherapy
ICD10	Z510	Encounter for anti-neoplastic radiation therapy
CCP	06.21	Radioisotopic teleradiotherapy
	06.34	Implantation or insertion of radioactive elements
	06.35	Injection or installation of radioisotopes
	06.39	Other radiotherapeutic procedure
CCI	1.FU.59.CA-V1	Destruction, thyroid gland, using oral approach radioactive pharma agent
	1.FU.59.HA-V1	Destruction, thyroid gland, using percutaneous approach radioactive pharma agent
	1.FU.59.DA-AW	Destruction, liver, endoscopic approach using radiofrequency
	1.ZZ.35.HA-V1	Pharmacotherapy, total body, percutaneous approach, using radioactive pharma agent
	x.xx.26	Brachytherapy, on any section of body
	x.xx.27	Radiation, on any section of body

Sources: "Concept: Overview of the Manitoba Cancer Registry and Treatment Data"; CCI to CCP crosswalk; CCP manual; CCI manual

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3, 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3, 4
Participants	6	**(*a*) *Cohort study*—**Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	a) 4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3, Reference 1
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	5

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	5
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, 6
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5, 6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7, 8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7, 8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9, 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9, 10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Risk of active tuberculosis in migrants diagnosed with cancer in British Columbia, Canada

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-037827.R1
Article Type:	Original research
Date Submitted by the Author:	07-Sep-2020
Complete List of Authors:	Kumar, Divjot; The University of British Columbia Faculty of Medicine, Respiratory Medicine Ronald, Lisa; BC Centre for Disease Control Romanowski, Kamila; The University of British Columbia Department of Medicine; BC Centre for Disease Control Rose, Caren; BC Centre for Disease Control Shulha, Hennady; BC Centre for Disease Control Cook, Victoria; The University of British Columbia Faculty of Medicine, Respiratory Medicine; BC Centre for Disease Control Johnston, James; The University of British Columbia Faculty of Medicine, Respiratory Medicine; BC Centre for Disease Control,
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Epidemiology, Global health, Infectious diseases, Public health, Health policy
Keywords:	Tuberculosis < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Respiratory tract tumours < ONCOLOGY, PREVENTIVE MEDICINE, ONCOLOGY, EPIDEMIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Risk of active tuberculosis in migrants diagnosed with cancer in British Columbia, Canada

Divjot S. Kumar[1], B.Sc., MD, Lisa A. Ronald[2], PhD, Kamila Romanowski[2,3], MSc, Caren Rose[2], PhD, Hennady P. Shulha[2], PhD ,Victoria J. Cook[1,2], MD, FRCPC, James C. Johnston[1,2], MD, MPH, FRCPC

[1]Division of Respiratory Medicine, Faculty of Medicine, University of British Columbia, Vancouver, Canada,[2] British Columbia Centre for Disease Control, Vancouver, British Columbia, Canada, Department of Medicine, University of British Columbia, Vancouver, Canada[3]

Corresponding Author information:
James Johnston, MD, MPH, FRCPC
British Columbia Centre of Disease Control
655 W 12th Avenue Vancouver, BC, V5Z 4R4
James.Johnston@bccdc.ca

The authors have no conflicts of interest to declare.

Current main text word count: **3,741**
Current abstract word count: **254**

ABSTRACT

Objectives: To describe the association between types of cancer and active TB risk in migrants. Additionally, in order to better inform Latent TB infection (LTBI) screening protocols, we assessed proportion of active TB cases potentially preventable through LTBI screening and treatment in migrants with cancer.

Design: Population based, retrospective cohort study

Setting: British Columbia (BC), Canada

Participants: 1,000,764 individuals who immigrated to Canada from 1985 to 2012 and established residency in BC at any point up to 2015.

Primary and secondary outcome measures: Using linked health administrative databases and disease registries, data on demographics, comorbidities, cancer type, TB exposure and active TB diagnosis were extracted. Primary outcomes included: time to first active TB diagnoses, and risks of active TB following cancer diagnoses which were estimated using Cox extended hazard regression models. Potentially preventable TB was defined as active TB diagnosed greater than 6 months post cancer diagnoses.

Results: Active TB risk was increased in migrants with cancer [(HR (95% CI))= 2.5 (2.0, 3.1)], after adjustment for age, sex, TB incidence in country of origin, immigration classification, contact status, and comorbidities. Highest risk was observed with lung cancer [HR=11.2 (7.4, 16.9)] and sarcoma [HR=8.1 (3.3, 19.5)], followed by leukemia [HR=5.6 (3.1, 10.2)], lymphoma [HR=4.9 (2.7, 8.7)], and gastrointestinal cancers [HR=2.7 (1.7, 4.4)]. The majority (65.9%) of active TB cases were diagnosed greater than 6 months post cancer diagnosis.

Conclusion: Specific cancers increase active TB risk to varying degrees in the migrant population of BC, with approximately two-thirds of active TB cases identified as potentially preventable.

Strengths and Limitations of study:

- Our study included a large cohort with >1 million people over 19 year period
- First study to assess risk of active TB amongst different malignancies in an immigrant population, and include other common malignancies such as prostate, breast, and gastrointestinal cancers.
- Risk of active TB amongst different malignancies were adjusted for other commonly recognized TB risk factors
- Unable to account for impact of smoking, alcohol use, and chemotherapy
- Unable to account for TB contact outside of British Columbia.

Original study protocol: Refer to Ronald et al. 2016

External funding: This work was supported by the Michael Smith Foundation for Health Research and the Canadian Institutes for Health Research [Grant: 377364].

Keywords: Tuberculosis, Cancer, Malignancy, Prevention, Immigrant

INTRODUCTION

Tuberculosis (TB) remains the top single infectious disease cause of death worldwide, with an estimated 10 million cases and 1.4 million deaths in 2018 (1). Recognizing this, the World Health Organization (WHO) created the EndTB Strategy with a vision of global TB elimination (2). A core part of the EndTB strategy is identification and treatment of latent tuberculosis infection (LTBI) in regions with low TB incidence (2–5). In many low incidence regions, such as Canada, efforts to meet EndTB elimination goals have been hindered by high TB rates in specific populations (5–7). People that migrate to Canada, in particular, experience rates of TB over 20 times greater than the Canadian-born non-Indigenous population (2,8). There are also clear links between certain comorbidities and TB risk (8). New strategies to identify and treat people at highest risk for TB are required to accelerate TB elimination in Canada.

The association between cancer and TB risk is increasingly recognized in peer-reviewed literature and national TB guidelines. At present, Canadian and American guidelines recognize hematologic and head/neck malignancies as risk factors for TB (8,9), and a recent systematic review and meta-analysis conducted by Cheng *et. al* identified up to a nine-fold increased risk of TB amongst patients with hematologic, head and neck, and lung cancers (10). In migrant populations, the risk of active TB associated with different malignancies has not been well studied and may represent an additive risk. Furthermore, literature is sparse on TB risk in people with many common malignancies such as gastrointestinal, breast, prostate and gynecologic cancers.

In this study, we used linked health administrative data on migrants to the province of British Columbia (BC), Canada to describe the association between different malignancies and active TB risk within foreign born individuals. Furthermore, we aimed to assess the proportion of immigrants with cancer in whom active TB was potentially preventable through LTBI screening and treatment.

METHODOLOGY

Study Setting and Data Sources

This study is part of a larger project (11) that describes TB epidemiology in people that migrate to BC, a Canadian province with a population of 5.0 million people and TB incidence of 4.7 per 100,000 persons (12,13). In 2016, approximately 22% of the population of BC, and 85% of people diagnosed with active TB, were born outside of Canada (14).

Descriptions of the databases and methods to identify the cohort have been described in detail in previous publications (11). Briefly, data were extracted from several linked health administrative databases, including a national immigration database, a provincial health insurance registry, hospitalization, physician billing, outpatient pharmacy, vital statistics, HIV, and End-Stage Renal Disease (ESRD) registries (15–27). Extracted data were provided as de-identifiable datasets linked using unique scrambled identification numbers. Full details on this linkage are described in a protocol publication (11).

TB diagnosis and treatment data were obtained from the BC Provincial TB Registry, housed at the BC Centre for Disease Control (BCCDC). The BCCDC is responsible for treatment of all people with active TB and LTBI in the province, and maintains a provincial TB registry that includes data on all people with a history of TB contact, LTBI and active TB diagnosis, and treatment (25). Data on cancer diagnosis were obtained from the BC Cancer Agency (BCCA) registry. The BCCA is a government organization that provides comprehensive cancer care to the people of BC in partnership with regional health authorities. The BCCA registry houses data on all primary cancers diagnosed in BC, with diagnoses confirmed based on pathology, cytology, lab results, cancer centre admissions, and death certificates (26).

Study population and follow-up

Our source population included all foreign-born individuals that obtained permanent residency in Canada between January 1, 1985 and December 31, 2012 and established residency in BC at any point until December 31, 2015. BC residents were identified when they registered in the provincial Medical Services Plan (MSP), a universal health insurance program administered by the BC government. Depending on a household's income, MSP coverage may be free, or may require monthly premiums. Thus, we believe that MSP coverage may be a surrogate marker of residency status in BC (28,29). Individuals who did not acquire an MSP number (e.g. temporary visitors, students, short-term workers or undocumented residents of BC) were not included in the cohort.

We limited the cohort to 1996 onward when community pharmacy data became available. Furthermore, we limited the analysis cohort to individuals aged ≥15 years as there were few cancer cases at younger ages. Calculation of follow-up time began for all individuals at their index event, which was identified as occurring at 90 days before first MSP registration date or at an individual's first health service record in BC, whichever date was earliest. The 90 day window was selected to account for the mandatory 90-day waiting period required for starting MSP after arrival in BC. The follow-up period ended at first active TB diagnosis, end of MSP coverage, death or end of study period (December 31st, 2015), whichever date was earliest.

Definitions of outcome and risk factor variables

The primary outcome measured was time to first active TB diagnosis. TB diagnosis was identified based on BCCDC TB Registry data, and included all TB sites (i.e., pulmonary and extra-pulmonary TB) that were either microbiologically or clinically confirmed. TB diagnosis was established in the BCCDC registry based on the Canadian TB Reporting System Guidelines (30).

The exposure of interest was incident cancer diagnosis occurring after study entry. Specific cancers were identified based on the site of primary malignancy, as reported in the BCCA Registry. Specific cancers identified for this analysis included: lung; breast; gastrointestinal (GI); hematologic cancers (lymphoma and leukemia); head and neck (HN); genitourinary (GU); gynecologic (GYN); prostate; sarcoma; skin (including melanoma and other skin cancers); neural; and other/unknown cancers.

TB incidence rate per 100,000 person-years (PYs) was calculated in people with and without a diagnosis of cancer. We identified the cancer risk start date as 90 days before the recorded cancer diagnosis date, and the cancer risk end date occurring 5 years after cancer diagnosis, at which time patients who were alive and without TB contributed time to the non-cancer group. If there were multiple overlapping cancer episodes of the same type, we tied these together and counted them as one episode only, with the first cancer diagnosis date identified as the start date of the episode. We also limited our analysis to incident cancers occurring after study entry (i.e. 2,014 people with prevalent cancers at the index date were excluded from analyses).

Other risk variables included sex, age (10-year age categories), time since arrival in BC (0-5 years and >5 years), immigration classification (refugee, family or economic), high-risk medical co-morbidities, and TB incidence in country of origin (8). For the TB incidence in country of origin, we used country-level WHO TB incidence data at year of arrival to Canada from 1990-2012 (31). For years prior to 1990, we applied 1990 TB incidence rates.

For medical co-morbidities, we established diagnosis dates of the following conditions: HIV, dialysis dependent end stage kidney disease (ESKD), diabetes, and medical immune-suppression (including use of TNF-alpha inhibitors, high-dose steroids, high-risk DMARDS, or receipt of solid organ or bone marrow transplantation). We also identified if an individual was a known contact of a person diagnosed with active TB in BC. Disease registries were used as the gold standard for disease diagnoses, supplemented with data

from health administrative databases using validated algorithms (11). Detailed definitions and exposure risk periods for each comorbidity have been described previously (11,32).

Statistical analysis

Analyses were conducted in R (version 3.6.0; The R Project for Statistical Computing) and SAS/STAT (V.9.4, SAS Institute, Cary, USA). This study received ethical approval from the University of BC Clinical Ethics Review Board (H16 -00625).

We produced descriptive statistics for our study cohort at the time of cohort entry, defined by index date. Rates of active TB and median years from cancer diagnosis to active TB were calculated for each cancer subtype. Cancer diagnoses may occur with or after a diagnosis of active TB, and therefore, to understand the potential impact of LTBI screening and prevention amongst people with cancer, we plotted the time of active TB diagnoses against the time of cancer diagnoses for each cancer type. The proportion of active TB cases that were potentially preventable was then calculated as those occurring more than 6 months after cancer diagnosis. This time point was set to capture preventable TB cases amenable to LTBI testing and treatment at cancer diagnosis.

We used extended Cox regression to model the risk of active TB. We ran separate models based on site of primary malignancy. For sex-predominant cancers, we restricted models by sex (i.e. breast and gynecologic cancer models were restricted to females; the prostate cancer model was restricted to males). We included all identified risk variables in multivariable models, determined *a priori* based on clinical relevance. Schoenfeld residuals were used to test extended Cox model parameters.

Model assumptions were tested through sensitivity analyses, including testing different age at risk for cancer thresholds and the time window for the cancer at-risk period. We examined whether radiotherapy during cancer treatment increased the risk of active TB, as this has previously been suspected to be a risk factor for active TB (33,34). As an additional sensitivity analysis, we assessed for impact of LTBI screening within our cohort. Furthermore, we conducted sensitivity analysis assessing active TB risk stratified by TB incidence of country of origin in foreign born individuals with cancer. Results of sensitivity analyses are reported in the Appendix. Incomplete data was identified as "missing data" in results.

Patient and Public Involvement:

Patients or public were not involved in the methodology, conduct, analyses, or reporting of this research.

RESULTS

Population characteristics:

Our study population included 1,000,764 individuals aged ≥15 years, with a mean of 13.4 person-years of total follow-up time per individual. Population characteristics are outlined in Table 1. Median age was 32.3 years, 48.5% were male, and 58.0% migrated from countries with TB incidence >100 per 100,000 persons. In terms of WHO regions, 54.8% of individuals migrated from Western Pacific, 14.5% from South East Asia, and 13.2% from Europe. A small proportion of individuals (0.6%) were contacts of people diagnosed with active TB at any time in BC.

Table 1: Cohort characteristics at entry and co-morbidities over study follow-up (N=1,000,764)

Cohort Characteristics	Without Cancer [n (%)]	Cancer ǂ [n (%)]	Total [n (%)]
Age group at baseline (years)			
15-24	311,087 (31.1%)	1,747 (0.2%)	312,834 (31.3%)
25-34	255,477 (25.5%)	4,431 (0.4%)	259,908 (26.0%)
35-44	214,955 (21.5%)	6,997 (0.7%)	221,952 (22.2%)
45-54	101,959 (10.2%)	5,402 (0.5%)	107,361 (10.7%)
55-64	50,987 (5.1%)	5,235 (0.5%)	56,222 (5.6%)
65-74	27,322 (2.7%)	4,148 (0.4%)	31,470 (3.1%)
75-84	8,051 (0.8%)	1,336 (0.1%)	9,387 (0.9%)
85-94	1,408 (0.1%)	148 (0.0%)	1,556 (0.2%)
≥95	70 (0.0%)	4 (0.0%)	74 (0.0%)
Gender			
Female	497,883 (49.8%)	17,418 (1.7%)	515,301 (51.5%)
Male	473,433 (47.3%)	12,030 (1.2%)	485,463 (48.5%)
TB incidence by country of origin (per 100,000 population)			
0-30	158,280 (15.8%)	5,425 (0.5%)	163,705 (16.4%)
31-100	250,830 (25.1%)	6,018 (0.6%)	256,848 (25.7%)
101-200	310,359 (31.0%)	10,474 (1.0%)	320,833 (32.1%)
>200	251,821 (25.2%)	7,531 (0.8%)	259,352 (25.9%)
WHO Region			
Western Pacific	532,415 (53.2%)	15,981 (1.6%)	548,396 (54.8%)
South-East Asia	141,507 (14.2%)	3,483 (0.4%)	144,990 (14.5%)
Europe	126,952 (12.7%)	5,054 (0.5%)	132,006 (13.2%)
Eastern Mediterranean	75,265 (7.5%)	1,674 (0.2%)	76,939 (7.7%)
Americas	67,583 (6.8%)	2,303 (0.2%)	69,886 (7.0%)
Africa	27,242 (2.7%)	935 (0.1%)	28,177 (2.8%)
Immigration classification			
Refugee	76,919 (7.7%)	2,039 (0.2%)	78,958 (7.9%)
Family	321,328 (32.1%)	14,759 (1.5%)	336,087 (33.6%)
Economic	573,069 (57.3%)	12,650 (1.3%)	585,719 (58.5%)
Years in BC			
0-5	800,518 (80.0%)	22,769 (2.3%)	823,287 (82.3%)
>5	170,798 (17.1%)	6,679 (0.7%)	177,477 (17.7%)
Active TB contact	5,676 (0.6%)	248 (0.0%)	5,924 (0.6%)
Comorbidities†			
HIV	1,460 (0.1%)	109 (0.0%)	1,569 (0.2%)

Dialysis dependent end-stage kidney disease	1,671 (0.2%)	255 (0.0%)	1,926 (0.2%)
Immune-suppression*	22,715 (2.3%)	2,914 (0.3%)	25,629 (2.6%)
Diabetes	98,519 (9.8%)	7,025 (0.7%)	105,544 (10.5%)
Total	971,316 (97.1%)	29,448 (2.9%)	1,000,764 (100.0%)

Missing data (country of origin, n=26, WHO region n = 370)
* Immune-suppression= Includes treatment with immune-suppressing drugs (TNFa inhibitors, DMARDS, or high-dose steroids or post-transplant)
†Includes incident and prevalent cases
ǂ Includes incident cases only

In the study population, 29,448 people (2.9%) were diagnosed with cancer (Table 2). The most frequently noted malignancies were breast (n = 5,918), gastrointestinal (n = 5,688), gynecologic (n = 4,450), lung (n = 2,421), lymphoma (n = 1,252), and leukemia (n =1,139) cancers. Table 2 provides details on cancer types. In the entire study cohort, 2,585 people developed active TB, with 91 people (0.3%) diagnosed with active TB within 5 years of a cancer diagnosis. Unadjusted active TB rates were as follows: lung cancer (525.1 per 100,000 person-years (PY)), sarcoma (174.4 per 100,000 PY), lymphoma (268.2 per 100,000 PY), leukemia (284.9 per 100,000 PY), gastrointestinal (107.9 per 100,000 PY), and head/neck cancer (31.3 per 100,000 PY) (Table 2). Figure 1 shows a scatter plot with timing of TB diagnosis against timing of cancer diagnosis for each cancer type.

Table 2: Incidence of active TB in patients newly diagnosed with cancer

Cancer type ǂ	n (%)	Median age at cancer diagnosis, years (Q1,Q3)	Median time from cancer to TB diagnosis, years (Q1,Q3)*	# active TB diagnoses		# active TB cases per 100,000 person-years at-risk†
				Up to 5 years after cancer diagnosis	From 6 months to 5 years after cancer diagnosis ("potentially preventable TB")	
Lung	2,421 (0.2)	68 (57, 77)	0.4 (0.3, 0.7)	25	9	525.1
Sarcoma	725 (0.1)	47 (36, 58)	1.6 (0.7, 1.9)	5	<5	174.4
Leukemia	1,139 (0.1)	62 (47, 74)	1.2 (0.8, 1.9)	11	8	284.9
Lymphoma	1,252 (0.1)	58 (45, 71)	0.5 (0.3, 1.6)	12	6	268.2
Breast	5,918 (0.6)	51 (44, 61)	4.7 (1.7, 5.8)	6	5	23.3
Head and Neck	840 (0.1)	55 (45, 67)	5.3 (2.5, 11.3)	<5	<5	31.3
Gastro-Intestinal	5,688 (0.6)	65 (54, 75)	1.8 (1.1, 5.1)	17	14	107.9
Skin / Melanoma	1,196 (0.1)	56 (45, 71)	3.1 (1.7, 6)	<5	<5	39.1
Prostate	3,012 (0.3)	68 (61, 75)	5.5 (2.1, 8.1)	10	8	78.6

Gynecologic	4,450 (0.4)	43 (35, 54)	6.2 (3.5, 13.8)	<5	<5	10.6
Gastro-Urinary	1,742 (0.2)	63 (49, 75)	0.9 (0.9, 0.9)	<5	<5	15.5
Neural	457 (0.1)	55 (45, 71)	2.1 (2.1, 2.1)	<5	<5	94.5
Other/Unknown	1,890 (0.2)	53 (41, 69)	1.3 (0.4, 7.0)	<5	<5	48.6
Any cancer	29,448 (2.9)	57 (45, 70)	1.6 (0.4, 4.9)	91	60	83.3

* Among people diagnosed with active TB on or after their cancer diagnosis date, up to 5 years after the cancer diagnosis date

† person-years at-risk includes up to 5 years after cancer diagnosis

ǂ Includes incident cases only

Potentially preventable TB cases were identified as those occurring >6 months after the diagnosis of cancer, as these cases could be potentially amenable to LTBI screening and therapy at the time of cancer diagnosis. Amongst 2,421 people with lung cancer, 25 people (1.0%) were diagnosed with active TB within 5 years. Of these, 9 (42.9%) had active TB diagnosed >6 months after cancer diagnosis. Similarly, 8 (72.7%) with leukemia, 6 (50%) with lymphoma, and 14 (82.4%) with gastrointestinal cancers were diagnosed with active TB >6 months post cancer diagnosis (Table 2). Overall, 60 out of 91 (65.9%) diagnosed active TB cases were classified as potentially preventable.

Figure 2 shows results from multivariable Cox regression analyses by cancer type. People with lung cancer and sarcoma had the highest risk of active TB, with adjusted hazard ratios (aHR) of 11.2 (95%CI: 7.4,16.9) for lung, and 8.1 (95%CI: 3.3,19.5) for sarcoma. This was followed by leukemia (aHR 5.6 (95%CI: 3.1,10.2)), lymphoma (aHR 4.9 (95% CI: 2.7, 8.7)), and gastrointestinal cancers (aHR 2.7 (95%CI: 1.7,4.4)). The full multivariable Cox model for lung cancer is shown in Table 3.

Table 3: TB risk in people diagnosed with lung cancer, univariable and multivariable hazard ratios

	# TB cases per 100,000 person-years	Univariate HR (95% CI)	Multivariable HR (95% CI)
Cancer, lung			
Yes	525.1	25.2 (17.0, 37.6)	11.2 (7.4, 16.9)
No	22.4	1.0	1.0
Age group (years)			
15-24	16.5	1.0	1.0
25-34	19.4	1.4 (1.2, 1.6)	1.1 (1.0, 1.3)
35-44	17.0	1.2 (1.1, 1.4)	1.1 (1.0, 1.3)
45-54	15.5	1.3 (1.1, 1.5)	1.2 (1.0, 1.4)
55-64	25.3	2.1 (1.8, 2.5)	1.7 (1.4, 2.0)
65-74	51.5	4.2 (3.5, 4.9)	3.0 (2.5, 3.6)
75-84	88.7	7.7 (6.5, 9.1)	5.6 (4.6, 6.8)
85-94	109.1	10.1 (8.0, 12.8)	8.4 (6.5, 10.9)
≥95	91.2	9.0 (4.4, 18.2)	8.4 (4.1, 17.2)
Sex			

Male	24.3	1.1 (1.1, 1.2)	1.2 (1.1, 1.2)
Female	21.1	1.0	1.0
TB incidence in country of origin			
0-30	2.4	1.0	1.0
31-100	9.9	4.2 (3.0, 5.8)	4.2 (3.0, 5.9)
101-200	21.0	9.2 (6.6, 12.6)	9.4 (6.8, 12.9)
>200/ 100,000 population	45.2	19.7 (14.3, 27.1)	18.6 (13.5, 25.6)
Immigration type			
Refugee	29.8	2.1 (1.9, 2.4)	2.0 (1.7, 2.3)
Family	33.5	2.4 (2.2, 2.6)	1.2 (1.1, 1.4)
Economic	14.4	1.0	1.0
Years in BC			
0-5	29.8	1.4 (1.3, 1.7)	1.6 (1.4, 1.9)
>5	19.8	1.0	1.0
Active TB contact			
Yes	298.5	12.8 (9.0, 18.4)	9.0 (6.2, 12.9)
No	22.4	1.0	1.0
HIV			
Yes	442.8	21.3 (16.1, 28.2)	20.3 (15.1, 27.2)
No	22.2	1.0	1.0
Dialysis dependent end stage kidney disease			
Yes	553.6	27.1 (20.0, 36.8)	8.2 (5.9, 11.5)
No	22.3	1.0	1.0
Immune-suppression*			
Yes	253.5	12.5 (10.3, 15.3)	7.0 (5.6, 8.6)
No	21.8	1.0	1.0
Diabetes			
Yes	48.0	2.7 (2.4, 3.0)	1.3 (1.2, 1.5)
No	20.5	1.0	1.0

*Includes treatment with immune-suppressing drugs (TNF-alpha inhibitors, DMARDS, or high-dose steroids), or post-transplant

DISCUSSION

Our province-wide, retrospective cohort study demonstrates that migrants with cancer are at higher risk for active TB than migrants without cancer, with TB risk varying by tumour type. The highest risk of TB was observed among migrants with lung cancer, followed by sarcoma, leukemia, lymphoma, and gastrointestinal malignancies. Head and neck, neural, skin, prostate, and breast cancers all had an elevated point estimate for TB risk, however, the increase was not significant in multivariable analysis. Notably, the majority of active TB cases were clustered immediately before or after cancer diagnosis, but an appreciable number of people developed TB more than 6 months post-cancer diagnosis. This represents a population of people with potentially preventable TB.

To our knowledge, our study is the first to provide risk estimates for TB due to various cancer types in a cohort of migrants within a low incidence region. As latent TB screening of all immigrants has previously been shown to be economically challenging, understanding the selective impact of various malignancies becomes crucial to help clinicians identify migrants at highest risk of active TB. Significant strengths of our study include large population cohort, risk estimates adjusted for other commonly recognized TB risk factors, stratification of TB risk by cancer type, and long follow up time. Given the wide capture of immigrant population over a 19 year follow up period, we believe that our results may be applicable at other low incidence areas including other Canadian provinces, and regions within United States.

The elevated TB risk observed in immigrants with lung and hematologic cancers are in concordance with those noted in the non-immigrant populace as reported by Cheng et. al 2016 and Simonsen et. al. 2017, with some variations which may reflect differences in study populations and cancer treatments amongst different regions (10,34). The mechanism through which malignancies increases TB risk is speculated to be multifactorial, including immunosuppression by both local and systemic effects. For lung cancer, mass effect and inflammation may disrupt local barriers to infection, increasing TB risk (34). Furthermore, infiltration of dormant TB granulomas by local tumour peptides in lung cancer may further increase re-activation risk (35). Importantly, our observed TB risk amongst lung cancer may be influenced by shared lifestyle variables, including smoking and alcohol use, which were not accounted for in our study (36–38). For hematologic malignancies, immunosuppression may be due to multiple factors including bone marrow infiltration, impaired T cell mediated immunity, and superimposed chemotherapy (39–41). Although we were unable to account for chemotherapy regimens, we found no significant impact of radiotherapy on active TB risk (Appendix Table A1).

Importantly, in contrast to previously assessed TB risk estimates within the general population, we found that head/neck cancer within the immigrant population resulted in a non-statistically significant elevated TB risk. The low incidence of head and neck cancer within our cohort resulted in wide confidence intervals. We suspect that our observed lower TB risk amongst head/neck malignancies may reflect evolution in treatment and care of head/neck cancer which may secondarily lower TB risk by reducing systemic immunosuppression and malnutrition. This includes transition to directed beam therapy, improved nutritional supplementation, and closer surveillance (42). This is consistent with the systematic review conducted by Cheng et. al. 2016, which described a decrease in TB incidence amongst head and neck cancers after 1980 compared to pre 1980 period. In addition to changes in treatments, they speculated that decreased TB incidence may also reflect changes in the underlying etiology of head/neck cancers, from non-HPV associated Head and Neck cancer, which are typically related to heavy smoking and alcohol use, to HPV related Head and Neck malignancies (10,42).

Furthermore, to our knowledge, this study is the first to show increased adjusted TB risk in individuals with sarcomas. The link between sarcoma and TB has been described in rare case reports, and remains poorly understood (43,44). While our risk estimates account for concurrent immunosuppression in sarcoma patients, namely HIV and post-transplant state, we were unable to adjust for chemotherapy which may

result in the observed elevated risk of active TB amongst individuals with sarcoma. Additionally, similar to head/neck cancers, the low incidence of sarcoma within our cohort accounts for the wide confidence intervals observed. Literature also remains sparse on the association of gastrointestinal malignancies and TB. While other authors have shown increased risk of TB with aerodigestive cancers(34,45), our study shows an elevated active TB risk amongst gastrointestinal malignancies independent from lung and head/neck cancers. It is speculated that concurrent comorbidities including significant weight loss and malnutrition may result in increased susceptibility to TB reactivation amongst GI cancers (43,46).

The clustering of active TB around time of cancer diagnoses as noted in Figure 1, may point to higher susceptibility to TB amongst cancer patients, either by primary acquisition or latent TB re-activation. As mentioned, early identification and treatment of LTBI in high risk cancer patients is crucial to prevent active TB and the possibility of ongoing transmission, most importantly in oncology clinics and inpatient services (47). We observed that amongst cancers noted to increase active TB risk, including sarcoma, leukemia, lymphoma, gastrointestinal malignancies, an appreciable proportion of migrants were diagnosed with active TB greater than six months post cancer diagnosis. These people represent potentially preventable TB as they could benefit from LTBI screening and treatment at the time of cancer diagnosis. In contrast to other malignancies, a lower proportion (approximately 1/3rd) of active TB in immigrants with lung cancer was diagnosed greater than six months post-cancer diagnosis. This phenomenon has been described by other authors and may be explained by the similar care pathways; TB can often produce masses or nodules which can imitate neoplasms in the lung, and therefore, similar imaging and diagnostic strategies involved for work-up of both entities may explain this close association of lung cancer with TB (43,48–50). At present, in BC, province-wide screening and treatment for LTBI in cancer patients is not routine. Our data provide strong support for LTBI testing amongst migrants with sarcoma, leukemia, lymphoma, lung, and gastrointestinal cancers.

Limitations

Our study has several limitations. First, we did not have access to smoking history, alcohol use and specific chemotherapeutic regimens, all of which increase active TB risk (34,36–38). Certainly, the lack of smoking history likely confounds the relationship between smoking-related malignancies (i.e. head/neck, lung cancer) and active TB risk. In a systematic review of smoking and TB risk, active smokers had a pooled risk estimate of 2.66 (95%CI: 2.15-3.28) for TB disease compared with non-smokers; this falls below the lower bounds of our 95%CI on multivariate analysis for lung cancer(51). Therefore, smoking alone is unlikely to be the sole driver of TB risk in people with lung cancer.

Second, we were unable to account for contact to TB outside of BC, however, we expect these numbers to be low, given the overall low TB incidence rate in Canada. Third, the high rate of active TB in cancer patients noted in our study may reflect the high level of care which cancer patients require. While frequent follows ups for cancer patients may lead to earlier diagnosis of Tuberculosis by clinicians, the frequent visits to different health care by cancer patients may result in varied exposure to Tuberculosis based on specific hospitals and local city prevalence. However, we do believe that endemic spread is uncommon in BC, as shown by prior genomic epidemiology studies (52). Lastly, while our study population is large, the overall low number of active TB results in limited statistical power of our analyses.

Importantly, we conducted sensitivity analysis to account for individuals screened for LTBI and this did not reveal any significant differences in our observed risk estimates (Appendix Table A2). Further sensitivity analysis examining for effect modification by TB incidence in country of birth was performed (Appendix Table A3). The relationship between cancer subtype and TB risk varied between low and high incidence regions, but the overlap in confidence intervals makes the data difficult to interpret further. Despite our stated limitations in understanding the causal role of malignancy in TB risk, we do note that people with certain malignancies have high rates of active TB, and may potentially benefit from LTBI screening and treatment, regardless of the underlying causal pathway.

CONCLUSION

In people that migrate to BC, specific cancers increase active TB risk, with highest risk noted in lung, sarcoma, leukemia, lymphoma, and gastrointestinal malignancies. An appreciable number of active TB cases are diagnosed more than six months after cancer diagnoses and may be potentially preventable with vigilant LTBI screening and therapy. While current Canadian TB guidelines recommend LTBI screening in migrants with hematologic or head/neck cancer, our data provide evidence of the preventable burden of active TB in migrants with other malignancies who could be considered for LTBI screening and therapy.

Notes: The corresponding author (Dr. J. Johnston) has full access to all data in the study and takes responsibility for the integrity of the data and accuracy of analysis.

Author contributions:

All authors contributed equally to study conception, manuscript drafting and critical review, data analyses, and provided final approval of the manuscript. JCJ and VJC were involved in study design, funding acquisition, statistical analysis, critical revision, and supervision of the project. DSK, LR, KR, HPS, CR participated in manuscript drafting, statistical analysis, critical revision, and data interpretation.

Conflicts of Interest Disclosure: None reported

Disclaimer: All inferences, opinions, and conclusions drawn in this study are those of the authors, and do not reflect the opinions or policies of the Data Steward(s)

Funding support: Michael Smith Foundation for Health Research and Canadian Institutes for Health Research (Grant: 377364)

Approval: This study received ethical approval from the University of BC Clinical Ethics Review Board (H16 -00625).

Previous presentation: Preliminary findings from this study were presented as a podium presentation at the 49th Union World conference on Lung Health, October 24-27th, 2018 at The Hague, Netherlands.

Data sharing: Data were extracted as deidentified datasets from several linked health administrative databases, including a national immigration database (Population Data BC and IRCC), a provincial health insurance registry, hospitalization, physician billing, outpatient pharmacy, vital statistics, HIV, and End-Stage Renal Disease (ESRD) registries. Additional data was extracted from the BC Provincial TB and BC Cancer Agency registries. Data are not publicly available. Data may be obtained upon authorized request to the respective data stewards as detailed in the study protocol.

REFERENCES

1. WHO World TB Database. Global tuberculosis report 2019 [Internet]. 2019. Available from: https://www.who.int/tb/publications/global_report/en/

2. World Health Organization, End TB Strategy. Global strategy and targets for tuberculosis prevention, care and control after 2015 [Internet]. World Health Organization. 2015 [cited 2019 Feb 27]. Available from: https://www.who.int/tb/strategy/End_TB_Strategy.pdf?ua=1

3. Lönnroth K, Migliori GB, Abubakar I, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. European Respiratory Journal. 2015 Mar 18;ERJ-02140-2014.

4. World Health Organization and European Respiratory Society, Framework towards TB elimination in low incidence countries [Internet]. 2014 [cited 2019 Feb 27]. Available from: https://www.who.int/tb/publications/Towards_TB_Eliminationfactsheet.pdf

5. Campbell JR, Chen W, Johnston J, et al. Latent Tuberculosis Infection Screening in Immigrants to Low-Incidence Countries: A Meta-Analysis. Mol Diagn Ther. 2015 Apr 1;19(2):107–17.

6. Campbell J, Marra F, Cook V, et al. Screening immigrants for latent tuberculosis: Do we have the resources? Canadian Medical Association Journal: CMAJ; Ottawa. 2014 Mar 4;186(4):246–7.

7. Pareek M, Watson JP, Ormerod LP, et al. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. The Lancet Infectious Diseases. 2011 Jun;11(6):435–44.

8. Public Health Agency of Canada. Canadian Tuberculosis Standards 7th Edition: 2014 [Internet]. aem. 2014 [cited 2017 Dec 17]. Available from: https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition.html

9. American Thoracic Society and Centers of Disease Control and Prevention. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. Am J Respir Crit Care Med. 2000 Apr 1;161(supplement_3):S221–47.

10. Cheng MP, Abou Chakra CN, Yansouni CP, et al. Risk of Active Tuberculosis in Patients with Cancer: A Systematic Review and Meta-Analysis. Clinical Infectious Diseases. 2016 Dec 16;ciw838.

11. Ronald LA, Campbell JR, Balshaw RF, et al. Predicting tuberculosis risk in the foreign-born population of British Columbia, Canada: study protocol for a retrospective population-based cohort study. BMJ Open. 2016 Nov 1;6(11):e013488.

12. Statistics Canada. Population size and growth rate, Canada, provinces and territories, 2006 to 2011 and 2011 to 2016 [Internet]. 2017 [cited 2019 Feb 27]. Available from: https://www150.statcan.gc.ca/n1/daily-quotidien/170208/t002a-eng.htm

13. Statistics Canada. Number and proportion of foreign-born population in Canada, 1871 to 2036 [Internet]. 2017 [cited 2019 Feb 27]. Available from: https://www.statcan.gc.ca/eng/dai/btd/othervisuals/other006

14. Public Health Agency of Canada. Tuberculosis in Canada 2016 [Internet]. 2018 [cited 2019 Feb 27]. Available from: https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2018-44/issue-3-4-march-1-2018/article-1-tuberculosis-2016.html

15. Population Data BC [Internet]. [cited 2016 Apr 20]. Available from: https://www.popdata.bc.ca

16. Immigration Statistics Canada. [cited 2016 Sep 26]. Available from: http://epe.lac-bac.gc.ca/100/202/301/immigration_statistics-ef/index.html

17. Immigration, Refugees, and Citizenship Canada (IRCC) [creator] (2014). Permanent Resident database [Internet]. Population Data BC [publisher]. Data Extract. IRCC; 2015. Available from: http://www.popdata.bc.ca/data

18. Statistics Canada (2009) [creator]. Statistics Canada Income Band Data. Catalogue Number: 13C0016 [Internet]. Population Data BC [publisher]. Data Extract; 2014. Available from: http://www.popdata.bc.ca/data

19. Canadian Institute for Health Information [creator] (2015). Discharge Abstract Database (Hospital Separations) [Internet]. Population Data BC [publisher]. Data Extract. MOH; 2014. Available from: http://www.popdata.bc.ca/data

20. BC Renal Agency [creator] (2015). BC Provincial Renal Agency Database (PROMIS) [Internet]. Population Data BC [publisher]. Data Extract. PROMIS; 2014. Available from: http://www.popdata.bc.ca/data

21. BC Vital Statistics Agency [creator] (2015). BC Vital Statistics Deaths [Internet]. Population Data BC [publisher]. Data Extract. BC Vital Statistics Agency; 2014. Available from: http://www.popdata.bc.ca/data

22. British Columbia Ministry of Health [creator] (2015). Consolidation File (MSP Registration & Premium Billing) [Internet]. Population Data BC [publisher]. Data Extract. MOH; 2015. Available from: http://www.popdata.bc.ca/data

23. BC Ministry of Health [creator] (2015). PharmaNet [Internet]. BC Ministry of Health Data Stewardship Committee [publisher]. Data Extract. MOH Data Stewardship Committee; 2014. Available from: http://www.popdata.bc.ca/data

24. BC Centre for Disease Control [creator] (2015). BC Provincial HIV/AIDS Surveillance Database (BCCDC-HAISIS) [Internet]. Population Data BC [publisher]. Data Extract. BCCDC; 2014. Available from: http://www.popdata.bc.ca/data

25. BC Centre of Disease Control [creator] (2015). BC Provincial TB Registry (BCCDC-iPHIS). Population Data BC [publisher] Data Extract BCCDC [Internet]. 2014; Available from: http://www.popdata.bc.ca/data

26. BC Cancer Agency. BC Cancer Registry [Internet]. [cited 2016 May 30]. Available from: http://www.bccancer.bc.ca/health-professionals/professional-resources/bc-cancer-registry

27. BC Cancer Agency [creator] (2015). BC Cancer Agency Registry Data [Internet]. Population Data BC [publisher]. Data Extract. BCCA; 2014. Available from: http://www.popdata.bc.ca/data

28. British Columbia Ministry of Health [creator] (2015). Medical Services Plan (MSP) Payment Information File [Internet]. Population Data BC [publisher]. Data Extract. MOH; 2014. Available from: http://www.popdata.bc.ca/data

29. Ministry of Health. MSP for B.C. Residents - Province of British Columbia [Internet]. [cited 2016 Apr 22]. Available from: https://www2.gov.bc.ca/gov/content/health/health-drug-coverage/msp/bc-residents

30. Public Health Agency of Canada. Canadian Tuberculosis Reporting System: Reporting Form Completion Guidelines, Version 1.9. January 1, 2011. http://www.phac-aspc.gc.ca/tbpc-latb/pdf/guidelinesform-eng.pdf. Accessed May 30, 2016.

31. WHO World TB Database (http://www.who.int/tb/country/data/download/en/). Accessed April 22, 2016.

32. Ronald LA, Campbell JR, Rose C, et al. Estimated Impact of World Health Organization Latent Tuberculosis Screening Guidelines in a Region With a Low Tuberculosis Incidence: Retrospective Cohort Study. Clin Infect Dis [Internet]. [cited 2019 Jul 27]; Available from: https://academic-oup-com.ezproxy.library.ubc.ca/cid/advance-article/doi/10.1093/cid/ciz188/5374592

33. Thomas P, Foley R, Kosowicz L. Reactivation of pulmonary tuberculosis following local radiation therapy of prostate cancer. Connecticut Medicine. 2014 Feb;78(2):77–80.

34. Simonsen DF, Farkas DK, Horsburgh CR, et al. Increased risk of active tuberculosis after cancer diagnosis. Journal of Infection. 2017 Jun;74(6):590–8.

35. Suzuki Y, Imokawa S, Sato J, et al. Cumulative incidence of tuberculosis in lung cancer patients in Japan: A 6-year observational study. Respiratory Investigation. 2016 May;54(3):179–83.

36. Maurya V, Vijayan V. K, Shah A. Smoking and tuberculosis: an association overlooked. The International Journal of Tuberculosis and Lung Disease. 2002 Nov 1;6(11):942–51.

37. Boon S den, Lill SWP van, Borgdorff MW, et al. Association between smoking and tuberculosis infection: a population survey in a high tuberculosis incidence area. Thorax. 2005 Jul 1;60(7):555–7.

38. Rehm J, Samokhvalov AV, Neuman MG, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC Public Health. 2009 Dec 5;9:450.

39. Advani SH, Banavali SD. Pattern of Infection in Hematologic Malignancies: An Indian Experience. Reviews of Infectious Diseases. 1989;11:S1621–8.

40. Au WY, Kwong YL, Ma SK, et al. Hairy cell leukemia in Hong Kong Chinese: a 12-year retrospective survey. Hematol Oncol. 2000 Dec 1;18(4):155–9.

41. Liu C-J, Hong Y-C, Teng C-J, et al. Risk and impact of tuberculosis in patients with chronic myeloid leukemia: A nationwide population-based study in Taiwan. Int J Cancer. 2015 Apr 15;136(8):1881–7.

42. Marur S, Forastiere AA. Head and Neck Squamous Cell Carcinoma: Update on Epidemiology, Diagnosis, and Treatment. Mayo Clinic Proceedings. 2016 Mar 1;91(3):386–96.

43. Kaplan MH, Armstrong D, Rosen P. Tuberculosis complicating neoplastic disease. A review of 201 cases. Cancer. 1974 Mar 1;33(3):850–8.

44. Aggarwal R, Rao S. Coexistence of tuberculosis with histiocytic sarcoma: A rare association. Journal of Cancer Research and Therapeutics. 2015;11(3):658.

45. Wu C-Y, Hu H-Y, Pu C-Y, et al. Aerodigestive tract, lung and haematological cancers are risk factors for tuberculosis: an 8-year population-based study. Int J Tuberc Lung Dis. 2011 Jan;15(1):125–30.

46. Vento S, Lanzafame M. Tuberculosis and cancer: a complex and dangerous liaison. The Lancet Oncology. 2011 Jun;12(6):520–2.

47. Parry C, Kent EE, Mariotto AB, et al. Cancer Survivors: A Booming Population. Cancer Epidemiology Biomarkers & Prevention. 2011 Oct 1;20(10):1996–2005.

48. Chen C-Y, Wang J-Y, Chien Y-C, et al. Lung cancer mimicking pulmonary tuberculosis in a TB-endemic country: the role of early invasive diagnostic procedures. Lung Cancer Management. 2015 Feb;4(1):9–16.

49. Ciftci F, Shimbori N, Karnak D. Concurrent central nervous system and endobronchial tuberculosis mimicking a metastatic lung cancer. The Clinical Respiratory Journal. 2017 Jan 1;11(1):98–102.

50. Davies PDO, Pai M. The diagnosis and misdiagnosis of tuberculosis [State of the art series. Tuberculosis. Edited by I. D. Rusen. Number 1 in the series]. The International Journal of Tuberculosis and Lung Disease. 2008 Nov 1;12(11):1226–34.

51. Bates MN. Risk of Tuberculosis From Exposure to Tobacco Smoke: A Systematic Review and Meta-analysis. Arch Intern Med. 2007 Feb 26;167(4):335.

52. Guthrie JL, Kong C, Roth D, Jorgensen D, Rodrigues M, Hoang L, et al. Molecular Epidemiology of Tuberculosis in British Columbia, Canada: A 10-Year Retrospective Study. Clinical Infectious Diseases. 2018 Mar 5;66(6):849–56.

FIGURE LEGENDS:

Figure 1 Legend:
GI: Gastro-Intestinal; **HN:** Head and Neck; **GYN:** Gynecological; **GU:** Genito-Urinary; **Oth/Unk:** other and unknown;
∘ Active TB diagnosis

Figure 2 Legend:
Hazard Ratios adjusted for*: age at follow up (age at which TB acquired), sex, time since arrival in BC (0-5 yrs and >5 yrs), immigration classification type (refugee, family or economic), high risk medical comorbidities (HIV, Dialysis dependent end stage kidney disease, Immune Suppression, Diabetes), and TB incidence by country of origin.

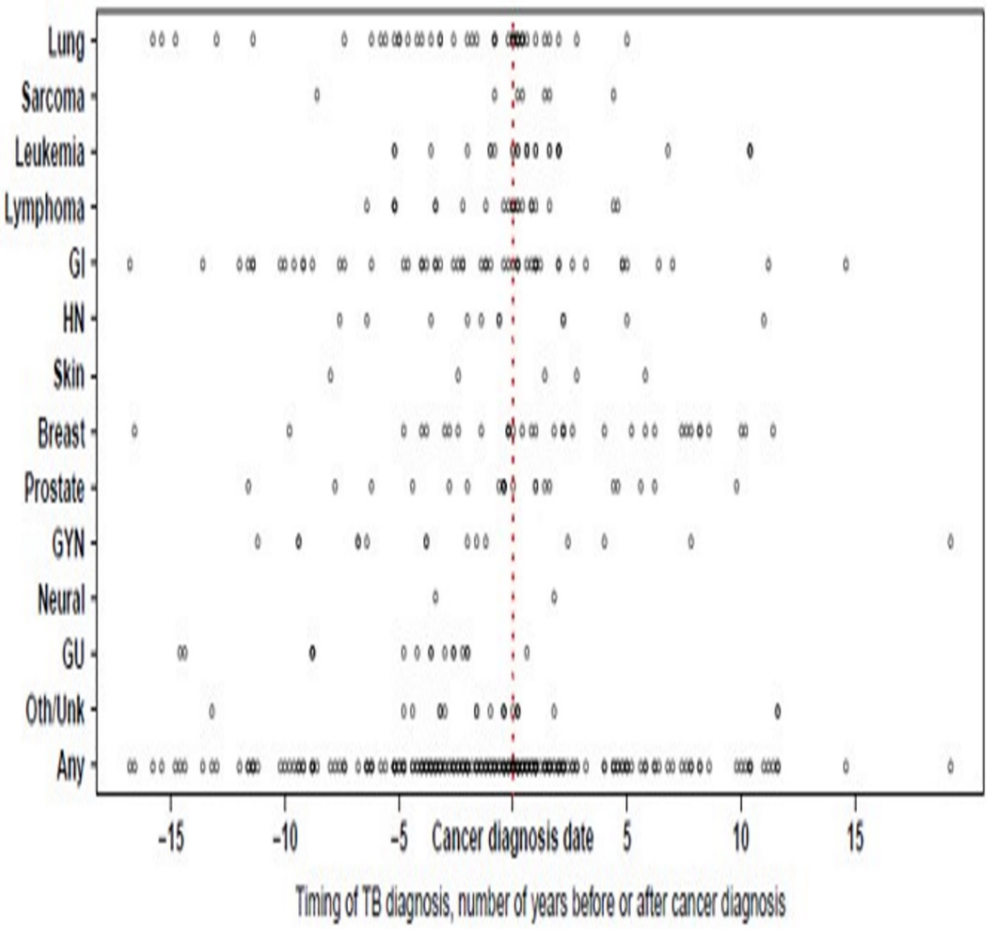
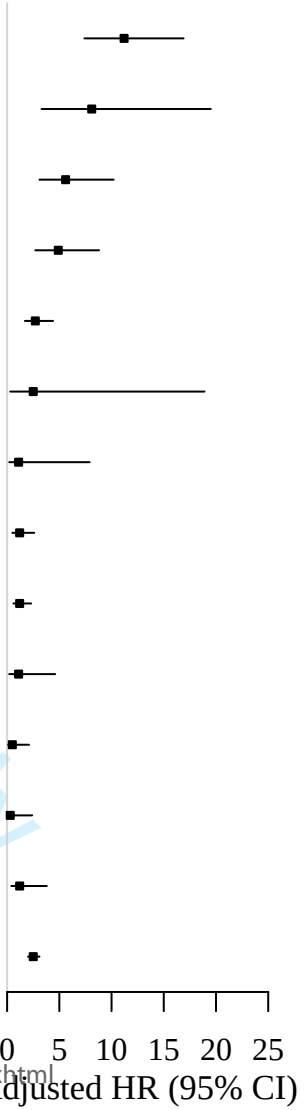


Figure 1: Timing of active TB diagnoses, number of years before and after cancer diagnoses

90x90mm (300 x 300 DPI)

Cancer	Active TB (cancer)	Active TB (without cancer)	HR (95% CI)
Lung	25	2560	11.2 (7.4, 16.9)
Sarcoma	5	2580	8.1 (3.3, 19.5)
Leukemia	11	2574	5.6 (3.1, 10.2)
Lymphoma	12	2573	4.9 (2.7, 8.7)
GI	17	2568	2.7 (1.7, 4.4)
Neural	<5	2584	2.5 (0.3, 18.7)
HN	<5	2582	1.1 (0.2, 7.9)
Breast	6	1258	1.2 (0.5, 2.6)
Prostate	10	1310	1.2 (0.6, 2.2)
Skin	<5	2583	1.1 (0.2, 4.6)
GYN	<5	1262	0.5 (0.1, 2.1)
GU	<5	2584	0.3 (0.0, 2.4)
Other	<5	2584	1.2 (0.4, 3.8)
Any	91	2484	2.5 (2.0, 3.1)



APPENDIX

Table A1: Total BCCA Registry cancer episodes identified as having radiation (n=1078)*†§

BCCA Cancer type	Total episodes	% with radiation therapy‡
Breast	5630	1.0
GI	5375	1.3
GU/GYN	5928	3.6
Head and Neck	1834	31.5
Hematological	2578	1.4
Lung	2297	3.1
Prostate	2824	6.0
Other/Unknown	3577	1.8
Total	30043	3.6

*Of all primary cancers reported to BC Cancer Registry between 1985-2012
†Radiation defined as occurring any time 1 year before cancer registry date or anytime after
‡ There were no cases of active TB diagnosed in people with cancer and radiation therapy
§ Codes used to identify inpatient radiation therapy:

System	Code	Code description
ICD9	V580	Encounter for radiotherapy
ICD10	Z510	Encounter for anti-neoplastic radiation therapy
CCP	06.21	Radioisotopic teleradiotherapy
	06.34	Implantation or insertion of radioactive elements
	06.35	Injection or installation of radioisotopes
	06.39	Other radiotherapeutic procedure
CCI	1.FU.59.CA-V1	Destruction, thyroid gland, using oral approach radioactive pharma agent
	1.FU.59.HA-V1	Destruction, thyroid gland, using percutaneous approach radioactive pharma agent
	1.FU.59.DA-AW	Destruction, liver, endoscopic approach using radiofrequency
	1.ZZ.35.HA-V1	Pharmacotherapy, total body, percutaneous approach, using radioactive pharma agent
	x.xx.26	Brachytherapy, on any section of body
	x.xx.27	Radiation, on any section of body

Sources: "Concept: Overview of the Manitoba Cancer Registry and Treatment Data"; CCI to CCP crosswalk; CCP manual; CCI manual

Table A2: Sensitivity analysis, testing models with different population inclusion criteria

Model #	Model description	# people deleted (w/ prevalent cancers)	# people included in analysis	# TB cases included in analysis	Adj HR, Lung cancer
1	Age 15+	2,014	1,000,764	2,585	11.2 (7.4-16.9)
2	Age 30+	2,558	800,489	2,071	11.2 (7.4-16.9)
3	All ages	1,961	1,046,759	2,634	11.5 (7.6-17.4)
4	Age 15+, excluding LTBI	2,010	995,828	2,575	11.4 (7.5-17.1)

Table A3: Active TB risk stratified by TB incidence of country of origin in foreign born individuals with cancer

Cancer Type	TB Incidence 0 -100 HR (95% CI)	TB Incidence > 100 HR (95% CI)	All Regions HR (95% CI)
Lung	3.1 (0.4, 23.2)	12.4 (8.1, 18.8)	11.2 (7.4, 16.9)
Gastrointestinal	3.8 (1.2, 12.4)	2.5 (1.5, 4.3)	2.7 (1.7, 4.4)
Leukemia	3.9 (0.5, 29.3)	5.9 (3.1, 11.0)	5.6 (3.1, 10.2)
Lymphoma	6.5 (1.5, 27.9)	4.7 (2.5, 8.8)	4.9 (2.7, 8.8)
Head and Neck	NA	1.2 (0.2, 8.8)	1.1 (0.2, 7.9)
GU	NA	0.4 (0.1, 2.8)	0.3 (0.0, 2.4)
Other	NA	1.3 (0.4, 4.1)	1.2 (0.4, 3.8)
Sarcoma	15.3 (2.1, 109.3)	7.2 (2.7, 19.3)	8.1 (3.3, 19.5)
Skin	NA	1.4 (0.3, 6.0)	1.1 (0.2, 4.6)
Neural	NA	2.9 (0.4, 22.1)	2.5 (0.3, 18.9)
Breast	NA	1.4 (0.6, 3.1)	1.2 (0.5, 2.6)
Gyn	4.2 (1.0, 17.1)	NA	0.5 (0.1, 2.1)
Prostate	2.9 (0.7, 11.7)	1.1 (0.5, 2.1)	1.2 (0.6, 2.3)
Any Cancer	2.7 (1.5, 4.9)	2.4 (1.9, 3.1)	2.5 (2.0, 3.1)

Other: other/unknown cancer type

NA: Not applicable as 0 ATB cases recorded.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3, 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3, 4
Participants	6	**(*a*) *Cohort study*—**Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	a) 4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3, Reference 1
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	5

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	5
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, 6
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5, 6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7, 8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7, 8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9, 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9, 10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Risk of active tuberculosis in migrants diagnosed with cancer: a retrospective cohort study in British Columbia, Canada

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-037827.R2
Article Type:	Original research
Date Submitted by the Author:	15-Jan-2021
Complete List of Authors:	Kumar, Divjot; The University of British Columbia Faculty of Medicine, Respiratory Medicine Ronald, Lisa; BC Centre for Disease Control Romanowski, Kamila; The University of British Columbia Department of Medicine; BC Centre for Disease Control Rose, Caren; BC Centre for Disease Control Shulha, Hennady; BC Centre for Disease Control Cook, Victoria; The University of British Columbia Faculty of Medicine, Respiratory Medicine; BC Centre for Disease Control Johnston, James; The University of British Columbia Faculty of Medicine, Respiratory Medicine; BC Centre for Disease Control,
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Epidemiology, Global health, Infectious diseases, Public health, Health policy
Keywords:	Tuberculosis < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Respiratory tract tumours < ONCOLOGY, PREVENTIVE MEDICINE, ONCOLOGY, EPIDEMIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Risk of active tuberculosis in migrants diagnosed with cancer: a retrospective cohort study in British Columbia, Canada

Divjot S. Kumar[1], B.Sc., MD, Lisa A. Ronald[2], PhD, Kamila Romanowski[2,3], MSc, Caren Rose[2], PhD, Hennady P. Shulha[2], PhD ,Victoria J. Cook[1,2], MD, FRCPC, James C. Johnston[1,2], MD, MPH, FRCPC

[1]Division of Respiratory Medicine, Faculty of Medicine, University of British Columbia, Vancouver, Canada,[2] British Columbia Centre for Disease Control, Vancouver, British Columbia, Canada, Department of Medicine, University of British Columbia, Vancouver, Canada[3]

Corresponding Author information:
James Johnston, MD, MPH, FRCPC
British Columbia Centre of Disease Control
655 W 12th Avenue Vancouver, BC, V5Z 4R4
James.Johnston@bccdc.ca

The authors have no conflicts of interest to declare.

Current main text word count: **3,685**
Current abstract word count: **254**

ABSTRACT

Objectives: To describe the association between types of cancer and active TB risk in migrants. Additionally, in order to better inform Latent TB infection (LTBI) screening protocols, we assessed proportion of active TB cases potentially preventable through LTBI screening and treatment in migrants with cancer.

Design: Population based, retrospective cohort study

Setting: British Columbia (BC), Canada

Participants: 1,000,764 individuals who immigrated to Canada from 1985 to 2012 and established residency in BC at any point up to 2015.

Primary and secondary outcome measures: Using linked health administrative databases and disease registries, data on demographics, comorbidities, cancer type, TB exposure and active TB diagnosis were extracted. Primary outcomes included: time to first active TB diagnoses, and risks of active TB following cancer diagnoses which were estimated using Cox extended hazard regression models. Potentially preventable TB was defined as active TB diagnosed greater than 6 months post cancer diagnoses.

Results: Active TB risk was increased in migrants with cancer [(HR (95% CI))= 2.5 (2.0, 3.1)], after adjustment for age, sex, TB incidence in country of origin, immigration classification, contact status, and comorbidities. Highest risk was observed with lung cancer [HR=11.2 (7.4, 16.9)] and sarcoma [HR=8.1 (3.3, 19.5)], followed by leukemia [HR=5.6 (3.1, 10.2)], lymphoma [HR=4.9 (2.7, 8.7)], and gastrointestinal cancers [HR=2.7 (1.7, 4.4)]. The majority (65.9%) of active TB cases were diagnosed greater than 6 months post cancer diagnosis.

Conclusion: Specific cancers increase active TB risk to varying degrees in the migrant population of BC, with approximately two-thirds of active TB cases identified as potentially preventable.

Strengths and Limitations of study:

- Our study included a large cohort with >1 million people over 19 year period
- First study to assess risk of active TB amongst different malignancies in an immigrant population, and include other common malignancies such as prostate, breast, and gastrointestinal cancers.
- Risk of active TB amongst different malignancies were adjusted for other commonly recognized TB risk factors
- Unable to account for impact of smoking, alcohol use, and chemotherapy
- Unable to account for TB contact outside of British Columbia.

Original study protocol: Refer to Ronald et al. 2016

External funding: This work was supported by the Michael Smith Foundation for Health Research and the Canadian Institutes for Health Research [Grant: 377364].

Keywords: Tuberculosis, Cancer, Malignancy, Prevention, Immigrant

INTRODUCTION

Tuberculosis (TB) remains the top single infectious disease cause of death worldwide, with an estimated 10 million cases and 1.4 million deaths in 2018 (1). Recognizing this, the World Health Organization (WHO) created the EndTB Strategy with a vision of global TB elimination (2). A core part of the EndTB strategy is identification and treatment of latent tuberculosis infection (LTBI) in regions with low TB incidence (2–5). In many low incidence regions, such as Canada, efforts to meet EndTB elimination goals have been hindered by high TB rates in specific populations (5–7). People that migrate to Canada, in particular, experience rates of TB over 20 times greater than the Canadian-born non-Indigenous population (2,8). There are also clear links between certain comorbidities and TB risk (8). New strategies to identify and treat people at highest risk for TB are required to accelerate TB elimination in Canada.

The association between cancer and TB risk is increasingly recognized in peer-reviewed literature and national TB guidelines. At present, Canadian and American guidelines recognize hematologic and head/neck malignancies as risk factors for TB (8,9), and a recent systematic review and meta-analysis conducted by Cheng *et. al* identified up to a nine-fold increased risk of TB amongst patients with hematologic, head and neck, and lung cancers (10). In migrant populations, the risk of active TB associated with different malignancies has not been well studied and may represent an additive risk. Furthermore, literature is limited on TB risk in people with many common malignancies such as gastrointestinal, breast, prostate and gynecologic cancers.

In this study, we used linked health administrative data on migrants to the province of British Columbia (BC), Canada to describe the association between different malignancies and active TB risk within foreign born individuals. Furthermore, we aimed to assess the proportion of immigrants with cancer in whom active TB was potentially preventable through LTBI screening and treatment.

METHODOLOGY

Study Setting and Data Sources

This study is part of a larger project (11) that describes TB epidemiology in people that migrate to BC, a Canadian province with a population of 5.0 million people and TB incidence of 4.7 per 100,000 persons (12,13). In 2016, approximately 22% of the population of BC, and 85% of people diagnosed with active TB, were born outside of Canada (14).

Descriptions of the databases, linkages, and methods to identify the cohort have been described in detail in previous publication (11). Briefly, data were extracted from several linked health administrative databases, including a national immigration database, a provincial health insurance registry, hospitalization, physician billing, outpatient pharmacy, vital statistics, HIV, and End-Stage Renal Disease (ESRD) registries (15–27). Extracted data were provided as de-identifiable datasets linked using unique scrambled identification numbers. Full details on this linkage are described in a protocol publication (11).

TB diagnosis and treatment data were obtained from the BC Provincial TB Registry, housed at the BC Centre for Disease Control (BCCDC). The BCCDC is responsible for treatment of all people with active TB and LTBI in the province, and maintains a provincial TB registry that includes data on all people with a history of TB contact, LTBI and active TB diagnosis, and treatment (25). Data on cancer diagnosis were obtained from the BC Cancer Agency (BCCA) registry. The BCCA is a government organization that provides comprehensive cancer care to the people of BC in partnership with regional health authorities. The BCCA registry houses data on all primary cancers diagnosed in BC, with diagnoses confirmed based on pathology, cytology, lab results, cancer centre admissions, and death certificates (26).

Study population and follow-up

Our source population included all foreign-born individuals that obtained permanent residency in Canada between January 1, 1985 and December 31, 2012 and established residency in BC at any point until December 31, 2015. BC residents were identified when they registered in the provincial Medical Services Plan (MSP), a universal health insurance program administered by the BC government. Depending on a household's income, MSP coverage may be free, or may require monthly premiums. Thus, we believe that MSP coverage may be a surrogate marker of residency status in BC (28,29). Individuals who did not acquire an MSP number (e.g. temporary visitors, students, short-term workers or undocumented residents of BC) were not included in the cohort.

We limited the cohort to 1996 onward when community pharmacy data became available. Furthermore, we limited the analysis cohort to individuals aged ≥15 years as there were few cancer cases at younger ages. Calculation of follow-up time began for all individuals at their index event, which was identified as occurring at 90 days before first MSP registration date or at an individual's first health service record in BC, whichever date was earliest. The 90 day window was selected to account for the mandatory 90-day waiting period required for starting MSP after arrival in BC. The follow-up period ended at first active TB diagnosis, end of MSP coverage, death or end of study period (December 31st, 2015), whichever date was earliest.

Definitions of outcome and risk factor variables

The primary outcome measured was time to first active TB diagnosis. TB diagnosis was identified based on BCCDC TB Registry data, and included all TB sites (i.e., pulmonary and extra-pulmonary TB) that were either microbiologically or clinically confirmed. TB diagnosis was established in the BCCDC registry based on the Canadian TB Reporting System Guidelines (30).

The exposure of interest was incident cancer diagnosis occurring after study entry. Cancers were identified based on the site of primary malignancy, as reported in the BCCA Registry. This dataset encompassed cancer diagnoses between Jan 1st, 1985 to Dec 31st, 2014. Specific cancers identified for this analysis included: lung; breast; gastrointestinal (GI); hematologic cancers (lymphoma and leukemia); head and neck (HN); genitourinary (GU); gynecologic (GYN); prostate; sarcoma; skin (including melanoma and other skin cancers); neural; and other/unknown cancers. For HN cancers, thyroid malignancies were excluded due to significant differences in prognosis and management compared to other HN malignancies.

TB incidence rate per 100,000 person-years (PYs) was calculated in people with and without a diagnosis of cancer. We identified the cancer risk start date as 90 days before the recorded cancer diagnosis date, and the cancer risk end date occurring 5 years after cancer diagnosis, at which time patients who were alive and without TB contributed time to the non-cancer group. If there were multiple overlapping cancer episodes of the same type, we tied these together and counted them as one episode only, with the first cancer diagnosis date identified as the start date of the episode. We also limited our analysis to incident cancers occurring after study entry (i.e. 2,014 people with prevalent cancers at the index date were excluded from analyses).

Other risk variables included sex, age (10-year age categories), time since arrival in BC (0-5 years and >5 years), immigration classification (refugee, family or economic), high-risk medical co-morbidities, and TB incidence in country of origin (8). For the TB incidence in country of origin, we used country-level WHO TB incidence data at year of arrival to Canada from 1990-2012 (31). For years prior to 1990, we applied 1990 TB incidence rates.

For medical co-morbidities, we established diagnosis dates of the following conditions: HIV, dialysis dependent end stage kidney disease (ESKD), diabetes, and medical immune-suppression (including use of TNF-alpha inhibitors, high-dose steroids, high-risk DMARDS, or receipt of solid organ or bone marrow

transplantation). We also identified if an individual was a known contact of a person diagnosed with active TB in BC. Disease registries were used as the gold standard for disease diagnoses, supplemented with data from health administrative databases using validated algorithms (11). Detailed definitions and exposure risk periods for each comorbidity have been described previously (11,32).

Statistical analysis

Analyses were conducted in R (version 3.6.0; The R Project for Statistical Computing) and SAS/STAT (V.9.4, SAS Institute, Cary, USA). This study received ethical approval from the University of BC Clinical Ethics Review Board (H16 -00625).

We produced descriptive statistics for our study cohort at the time of cohort entry, defined by index date. Rates of active TB and median years from cancer diagnosis to active TB were calculated for each cancer subtype. Cancer diagnoses may occur with or after a diagnosis of active TB, and therefore, to understand the potential impact of LTBI screening and prevention amongst people with cancer, we plotted the time of active TB diagnoses against the time of cancer diagnoses for each cancer type. The proportion of active TB cases that were potentially preventable was then calculated as those occurring more than 6 months after cancer diagnosis. This time point was set to capture preventable TB cases amenable to LTBI testing and treatment at cancer diagnosis.

We used extended Cox regression to model the risk of active TB. We ran separate models based on site of primary malignancy. For sex-predominant cancers, we restricted models by sex (i.e. breast and gynecologic cancer models were restricted to females; the prostate cancer model was restricted to males). We included all identified risk variables in multivariable models, determined *a priori* based on clinical relevance. Schoenfeld residuals were used to test extended Cox model parameters.

Model assumptions were tested through sensitivity analyses, including testing different age at risk for cancer thresholds and the time window for the cancer at-risk period. We examined whether radiotherapy during cancer treatment increased the risk of active TB, as this has previously been suspected to be a risk factor for active TB (33,34). As an additional sensitivity analysis, we assessed for impact of LTBI screening within our cohort. Furthermore, we conducted sensitivity analysis assessing active TB risk stratified by TB incidence of country of origin in foreign born individuals with cancer. Lastly, we provided breakdown of pulmonary/mix TB and extrapulmonary TB amongst immigrants diagnosed with cancer. Results of sensitivity analyses are reported in the Appendix. Incomplete data was identified as "missing data" in results.

Patient and Public Involvement:

Patients or public were not involved in the methodology, conduct, analyses, or reporting of this research.

RESULTS

Population characteristics:

Our study population included 1,000,764 individuals aged ≥15 years, with a mean of 13.4 person-years of total follow-up time per individual. Population characteristics are outlined in Table 1. Median age was 32.3 years, 48.5% were male, and 58.0% migrated from countries with TB incidence >100 per 100,000 persons. In terms of WHO regions, 54.8% of individuals migrated from Western Pacific, 14.5% from South East Asia, and 13.2% from Europe. A small proportion of individuals (0.6%) were contacts of people diagnosed with active TB at any time in BC.

Table 1: Cohort characteristics at entry and co-morbidities over study follow-up (N=1,000,764)

Cohort Characteristics	Without Cancer [N (%)]	Cancer ‡ [N (%)]	Total [N (%)]
Age group at baseline (years)			
15-24	311,087 (32.0%)	1,747 (5.9%)	312,834 (31.3%)
25-34	255,477 (26.3%)	4,431 (15.0%)	259,908 (26.0%)
35-44	214,955 (22.1%)	6,997 (23.8%)	221,952 (22.2%)
45-54	101,959 (10.5%)	5,402 (18.3%)	107,361 (10.7%)
55-64	50,987 (5.2%)	5,235 (17.8%)	56,222 (5.6%)
65-74	27,322 (2.8%)	4,148 (14.1%)	31,470 (3.1%)
75-84	8,051 (0.8%)	1,336 (4.5%)	9,387 (0.9%)
85-94	1,408 (0.1%)	148 (0.5%)	1,556 (0.2%)
≥95	70 (0.0%)	4 (0.0%)	74 (0.0%)
Gender			
Female	497,883 (51.3%)	17,418 (59.1%)	515,301 (51.5%)
Male	473,433 (48.7%)	12,030 (40.9%)	485,463 (48.5%)
TB incidence by country of origin (per 100,000 population)			
0-30	158,280 (16.3%)	5,425 (18.4%)	163,705 (16.4%)
31-100	250,830 (25.8%)	6,018 (20.4%)	256,848 (25.7%)
101-200	310,359 (32.0%)	10,474 (35.6%)	320,833 (32.1%)
>200	251,821 (25.9%)	7,531 (25.6%)	259,352 (25.9%)
WHO Region			
Western Pacific	532,415 (54.8%)	15,981 (54.3%)	548,396 (54.8%)
South-East Asia	141,507 (14.6%)	3,483 (11.8%)	144,990 (14.5%)
Europe	126,952 (13.1%)	5,054 (17.2%)	132,006 (13.2%)
Eastern Mediterranean	75,265 (7.7%)	1,674 (5.7%)	76,939 (7.7%)
Americas	67,583 (7.0%)	2,303 (7.8%)	69,886 (7.0%)
Africa	27,242 (2.8%)	935 (3.2%)	28,177 (2.8%)
Immigration classification			
Refugee	76,919 (7.9%)	2,039 (6.9%)	78,958 (7.9%)
Family	321,328 (33.1%)	14,759 (50.1%)	336,087 (33.6%)
Economic	573,069 (59.0%)	12,650 (43.0%)	585,719 (58.5%)
Years in BC			
0-5	800,518 (82.4%)	22,769 (77.3%)	823,287 (82.3%)
>5	170,798 (17.6%)	6,679 (22.7%)	177,477 (17.7%)
Active TB contact	5,676 (0.6%)	248 (0.8%)	5,924 (0.6%)
Comorbidities†			

HIV	1,460 (0.2%)	109 (0.4%)	1,569 (0.2%)
Dialysis dependent end-stage kidney disease	1,671 (0.2%)	255 (0.9%)	1,926 (0.2%)
Immune-suppression*	22,715 (2.3%)	2,914 (9.9%)	25,629 (2.6%)
Diabetes	98,519 (10.1%)	7,025 (23.9%)	105,544 (10.5%)
Total	971,316 (100.0%)	29,448 (100.0%)	1,000,764 (100.0%)

Missing data (country of origin, n=26, WHO region n = 370)

* Immune-suppression= Includes treatment with immune-suppressing drugs (TNFa inhibitors, DMARDS, or high-dose steroids or post-transplant)

†Includes incident and prevalent cases

ǂ Includes incident cases only

In the study population, 29,448 people (2.9%) were diagnosed with cancer (Table 2). The most frequently noted malignancies were breast (n = 5,918), gastrointestinal (n = 5,688), gynecologic (n = 4,450), lung (n = 2,421), lymphoma (n = 1,252), and leukemia (n =1,139) cancers. Table 2 provides details on cancer types. In the entire study cohort, 2,585 people developed active TB, with 91 people (3.5%) diagnosed with active TB within 5 years of a cancer diagnosis. Unadjusted active TB rates were as follows: lung cancer (525.1 per 100,000 person-years (PY)), sarcoma (174.4 per 100,000 PY), lymphoma (268.2 per 100,000 PY), leukemia (284.9 per 100,000 PY), gastrointestinal (107.9 per 100,000 PY), and head/neck cancer (31.3 per 100,000 PY) (Table 2). Figure 1 shows a scatter plot with timing of TB diagnosis against timing of cancer diagnosis for each cancer type.

Table 2: Incidence of active TB in patients newly diagnosed with cancer

Cancer type ǂ	n (%)	Median age at cancer diagnosis, years (Q1,Q3)	Median time from cancer to TB diagnosis, years (Q1,Q3)*	# active TB diagnoses		# active TB cases per 100,000 person-years at-risk†
				Up to 5 years after cancer diagnosis	From 6 months to 5 years after cancer diagnosis ("potentially preventable TB")	
Lung	2,421 (0.2)	68 (57, 77)	0.4 (0.3, 0.7)	25	9	525.1
Sarcoma	725 (0.1)	47 (36, 58)	1.6 (0.7, 1.9)	5	<5	174.4
Leukemia	1,139 (0.1)	62 (47, 74)	1.2 (0.8, 1.9)	11	8	284.9
Lymphoma	1,252 (0.1)	58 (45, 71)	0.5 (0.3, 1.6)	12	6	268.2
Breast	5,918 (0.6)	51 (44, 61)	4.7 (1.7, 5.8)	6	5	23.3
Head and Neck€	840 (0.1)	55 (45, 67)	5.3 (2.5, 11.3)	<5	<5	31.3
Gastro-Intestinal	5,688 (0.6)	65 (54, 75)	1.8 (1.1, 5.1)	17	14	107.9
Skin / Melanoma	1,196 (0.1)	56 (45, 71)	3.1 (1.7, 6)	<5	<5	39.1

Prostate	3,012 (0.3)	68 (61, 75)	5.5 (2.1, 8.1)	10	8	78.6
Gynecologic	4,450 (0.4)	43 (35, 54)	6.2 (3.5, 13.8)	<5	<5	10.6
Genito-Urinary	1,742 (0.2)	63 (49, 75)	0.9 (0.9, 0.9)	<5	<5	15.5
Neural	457 (0.1)	55 (45, 71)	2.1 (2.1, 2.1)	<5	<5	94.5
Other/Unknown	1,890 (0.2)	53 (41, 69)	1.3 (0.4, 7.0)	<5	<5	48.6
Any cancer	29,448 (2.9)	57 (45, 70)	1.6 (0.4, 4.9)	91	60	83.3

* Among people diagnosed with active TB on or after their cancer diagnosis date, up to 5 years after the cancer diagnosis date

† person-years at-risk includes up to 5 years after cancer diagnosis

ǂ Includes incident cases only

€ Excludes thyroid cancers

Potentially preventable TB cases were identified as those occurring >6 months after the diagnosis of cancer, as these cases could be potentially amenable to LTBI screening and therapy at the time of cancer diagnosis. Amongst 2,421 people with lung cancer, 25 people (1.0%) were diagnosed with active TB within 5 years. Of these, 9 (42.9%) had active TB diagnosed >6 months after cancer diagnosis. Similarly, 8 (72.7%) with leukemia, 6 (50%) with lymphoma, and 14 (82.4%) with gastrointestinal cancers were diagnosed with active TB >6 months post cancer diagnosis (Table 2). Overall, 60 out of 91 (65.9%) diagnosed active TB cases were classified as potentially preventable.

Figure 2 shows results from multivariable Cox regression analyses by cancer type. People with lung cancer and sarcoma had the highest risk of active TB, with adjusted hazard ratios (aHR) of 11.2 (95%CI: 7.4,16.9) for lung, and 8.1 (95%CI: 3.3,19.5) for sarcoma. This was followed by leukemia (aHR 5.6 (95%CI: 3.1,10.2)), lymphoma (aHR 4.9 (95% CI: 2.7, 8.7)), and gastrointestinal cancers (aHR 2.7 (95%CI: 1.7,4.4)). The full multivariable Cox model for lung cancer is shown in Table 3.

Table 3: TB risk in people diagnosed with lung cancer, univariable and multivariable hazard ratios

	# TB cases per 100,000 person-years	Univariate HR (95% CI)	Multivariable HR (95% CI)
Cancer, lung			
Yes	525.1	25.2 (17.0, 37.6)	11.2 (7.4, 16.9)
No	22.4	1.0	1.0
Age group (years)			
15-24	16.5	1.0	1.0
25-34	19.4	1.4 (1.2, 1.6)	1.1 (1.0, 1.3)
35-44	17.0	1.2 (1.1, 1.4)	1.1 (1.0, 1.3)
45-54	15.5	1.3 (1.1, 1.5)	1.2 (1.0, 1.4)
55-64	25.3	2.1 (1.8, 2.5)	1.7 (1.4, 2.0)
65-74	51.5	4.2 (3.5, 4.9)	3.0 (2.5, 3.6)
75-84	88.7	7.7 (6.5, 9.1)	5.6 (4.6, 6.8)

85-94	109.1	10.1 (8.0, 12.8)	8.4 (6.5, 10.9)
≥95	91.2	9.0 (4.4, 18.2)	8.4 (4.1, 17.2)
Sex			
Male	24.3	1.1 (1.1, 1.2)	1.2 (1.1, 1.2)
Female	21.1	1.0	1.0
TB incidence in country of origin			
0-30	2.4	1.0	1.0
31-100	9.9	4.2 (3.0, 5.8)	4.2 (3.0, 5.9)
101-200	21.0	9.2 (6.6, 12.6)	9.4 (6.8, 12.9)
>200/ 100,000 population	45.2	19.7 (14.3, 27.1)	18.6 (13.5, 25.6)
Immigration type			
Refugee	29.8	2.1 (1.9, 2.4)	2.0 (1.7, 2.3)
Family	33.5	2.4 (2.2, 2.6)	1.2 (1.1, 1.4)
Economic	14.4	1.0	1.0
Years in BC			
0-5	29.8	1.4 (1.3, 1.7)	1.6 (1.4, 1.9)
>5	19.8	1.0	1.0
Active TB contact			
Yes	298.5	12.8 (9.0, 18.4)	9.0 (6.2, 12.9)
No	22.4	1.0	1.0
HIV			
Yes	442.8	21.3 (16.1, 28.2)	20.3 (15.1, 27.2)
No	22.2	1.0	1.0
Dialysis dependent end stage kidney disease			
Yes	553.6	27.1 (20.0, 36.8)	8.2 (5.9, 11.5)
No	22.3	1.0	1.0
Immune-suppression*			
Yes	253.5	12.5 (10.3, 15.3)	7.0 (5.6, 8.6)
No	21.8	1.0	1.0
Diabetes			
Yes	48.0	2.7 (2.4, 3.0)	1.3 (1.2, 1.5)
No	20.5	1.0	1.0

*Includes treatment with immune-suppressing drugs (TNF-alpha inhibitors, DMARDS, or high-dose steroids), or post-transplant

DISCUSSION

Our province-wide, retrospective cohort study demonstrates that migrants with cancer are at higher risk for active TB than migrants without cancer, with TB risk varying by tumour type. The highest risk of TB was observed among migrants with lung cancer, followed by sarcoma, leukemia, lymphoma, and gastrointestinal malignancies. Head and neck, neural, skin, prostate, and breast cancers all had an elevated point estimate for TB risk, however, the increase was not significant in multivariable analysis. Notably, the majority of active TB cases were clustered immediately before or after cancer diagnosis, but an appreciable number of people developed TB more than 6 months post-cancer diagnosis. This represents a population of people with potentially preventable TB.

To our knowledge, our study is the first to provide risk estimates for TB due to various cancer types in a cohort of migrants within a low incidence region. As latent TB screening of all immigrants has previously been shown to be economically challenging, understanding the selective impact of various malignancies becomes crucial to help clinicians identify migrants at highest risk of active TB. Significant strengths of our study include large population cohort, risk estimates adjusted for other commonly recognized TB risk factors, stratification of TB risk by cancer type, and long follow up time. Given the wide capture of immigrant population over a 19 year follow up period, we believe that our results may be applicable at other low incidence areas including other Canadian provinces, and regions within United States.

The elevated TB risk observed in immigrants with lung and hematologic cancers are in concordance with those noted in the non-immigrant populace as reported by Cheng et al. 2016, Simonsen et al. 2017, and Shu et al. 2019, with some variations which may reflect differences in study populations and cancer treatments amongst different regions (10,34,35). The mechanism through which malignancies increases TB risk is speculated to be multifactorial, including immunosuppression by both local and systemic effects. For lung cancer, mass effect and inflammation may disrupt local barriers to infection, increasing TB risk (34). Furthermore, infiltration of dormant TB granulomas by local tumour peptides in lung cancer may further increase re-activation risk (36). Importantly, our observed TB risk amongst lung cancer may be influenced by shared lifestyle variables, including smoking and alcohol use, which were not accounted for in our study (37–39). For hematologic malignancies, immunosuppression may be due to multiple factors including bone marrow infiltration, impaired T cell mediated immunity, and superimposed chemotherapy (40–42). Although we were unable to account for chemotherapy regimens, sensitivity analyses examining effect of radiotherapy did not reveal any significant impact on active TB risk within our cohort.

Importantly, in contrast to previously assessed TB risk estimates within the general population, we found that head/neck cancer (excluding thyroid cancers) within the immigrant population resulted in a non-statistically significant elevated TB risk. The low incidence of head and neck cancer within our cohort resulted in wide confidence intervals. We suspect that our observed lower TB risk amongst head/neck malignancies may reflect evolution in treatment and care of head/neck cancer which may secondarily lower TB risk by reducing systemic immunosuppression and malnutrition. This includes transition to directed beam therapy, improved nutritional supplementation, and closer surveillance (43). This is consistent with the systematic review conducted by Cheng et. al. 2016, which described a decrease in TB incidence amongst head and neck cancers after 1980 compared to pre 1980 period. In addition to changes in treatments, they speculated that decreased TB incidence may also reflect changes in the underlying etiology of head/neck cancers, from non-HPV associated Head and Neck cancer, which are typically related to heavy smoking and alcohol use, to HPV related Head and Neck malignancies (10,43).

Furthermore, to our knowledge, this study is the first to show increased adjusted TB risk in individuals with sarcomas. The link between sarcoma and TB has been described in rare case reports, and remains poorly understood (44,45). While our risk estimates account for concurrent immunosuppression in sarcoma patients, namely HIV and post-transplant state, we were unable to adjust for chemotherapy which may

result in the observed elevated risk of active TB amongst individuals with sarcoma. Additionally, similar to head/neck cancers, the low incidence of sarcoma within our cohort accounts for the wide confidence intervals observed. Literature also remains sparse on the association of gastrointestinal malignancies and TB. While other authors have shown increased risk of TB with aerodigestive cancers(34,46), our study shows an elevated active TB risk amongst gastrointestinal malignancies independent from lung and head/neck cancers. After further stratifying GI cancer subtypes into smoking associated (including esophageal and gastric) and non-smoking associated gastrointestinal cancers, we did not observe significant difference in active TB risk (Appendix Table A1). It is speculated that concurrent comorbidities including significant weight loss and malnutrition may result in increased susceptibility to TB reactivation amongst GI cancers (44,47).

The clustering of active TB around time of cancer diagnoses as noted in Figure 1, may point to higher susceptibility to TB amongst cancer patients, either by primary acquisition or latent TB re-activation. As mentioned, early identification and treatment of LTBI in high risk cancer patients is crucial to prevent active TB and the possibility of ongoing transmission, most importantly in oncology clinics and inpatient services (48). We observed that amongst cancers noted to increase active TB risk, including sarcoma, leukemia, lymphoma, gastrointestinal malignancies, an appreciable proportion of migrants were diagnosed with active TB greater than six months post cancer diagnosis. These people represent potentially preventable TB as they could benefit from LTBI screening and treatment at the time of cancer diagnosis. In contrast to other malignancies, a lower proportion (approximately 1/3rd) of active TB in immigrants with lung cancer was diagnosed greater than six months post-cancer diagnosis. This phenomenon has been described by other authors and may be explained by the similar care pathways; TB can often produce masses or nodules which can imitate neoplasms in the lung, and therefore, similar imaging and diagnostic strategies involved for work-up of both entities may explain this close association of lung cancer with TB (44,49–51). At present, in BC, province-wide screening and treatment for LTBI in cancer patients is not routine. Our data provide strong support for LTBI testing amongst migrants with sarcoma, leukemia, lymphoma, lung, and gastrointestinal cancers.

Limitations

Our study has several limitations. First, we did not have access to smoking history, alcohol use and specific chemotherapeutic regimens, all of which increase active TB risk (34,37–39). Certainly, the lack of smoking history likely confounds the relationship between smoking-related malignancies (i.e. head/neck, lung cancer) and active TB risk. In a systematic review of smoking and TB risk, active smokers had a pooled risk estimate of 2.66 (95%CI: 2.15-3.28) for TB disease compared with non-smokers; this falls below the lower bounds of our 95%CI on multivariate analysis for lung cancer(52). Therefore, smoking alone is unlikely to be the sole driver of TB risk in people with lung cancer.

Second, we were unable to account for contact to TB outside of BC, however, we expect these numbers to be low, given the overall low TB incidence rate in Canada. Third, the high rate of active TB in cancer patients noted in our study may reflect the high level of care which cancer patients require. While frequent follows ups for cancer patients may lead to earlier diagnosis of Tuberculosis by clinicians, the frequent visits to different health care by cancer patients may result in varied exposure to Tuberculosis based on specific hospitals and local city prevalence. However, we do believe that endemic spread is uncommon in BC, as shown by prior genomic epidemiology studies (53). Lastly, while our study population is large, the overall low number of active TB results in limited statistical power of our analyses.

Importantly, we conducted sensitivity analysis to account for individuals screened for LTBI and this did not reveal any significant differences in our observed risk estimates (Appendix Table A2). Further sensitivity analysis examining for effect modification by TB incidence in country of birth was performed (Appendix Table A3). The relationship between cancer subtype and TB risk varied between low and high incidence regions, but the overlap in confidence intervals makes the data difficult to interpret further. Lastly,

amongst immigrants with different malignancies, varying presentations of active TB (pulmonary and extrapulmonary) were noted. While lung cancer and lymphoma exhibited higher pulmonary TB diagnoses, limited numbers of active TB amongst other malignancies make it challenging to further discern relationship between cancer and type of TB presentation (Appendix Table A4). Despite our stated limitations in understanding the causal role of malignancy in TB risk, we do note that people with certain malignancies have high rates of active TB, and may potentially benefit from LTBI screening and treatment, regardless of the underlying causal pathway.

CONCLUSION

In people that migrate to BC, specific cancers increase active TB risk, with highest risk noted in lung, sarcoma, leukemia, lymphoma, and gastrointestinal malignancies. An appreciable number of active TB cases are diagnosed more than six months after cancer diagnoses and may be potentially preventable with vigilant LTBI screening and therapy. While current Canadian TB guidelines recommend LTBI screening in migrants with hematologic or head/neck cancer, our data provide evidence of the preventable burden of active TB in migrants with other malignancies who could be considered for LTBI screening and therapy.

Notes: The corresponding author (Dr. J. Johnston) has full access to all data in the study and takes responsibility for the integrity of the data and accuracy of analysis.

Author contributions:

All authors contributed equally to study conception, manuscript drafting and critical review, data analyses, and provided final approval of the manuscript. JCJ and VJC were involved in study design, funding acquisition, statistical analysis, critical revision, and supervision of the project. DSK, LR, KR, HPS, CR participated in manuscript drafting, statistical analysis, critical revision, and data interpretation.

Conflicts of Interest Disclosure: None reported

Disclaimer: All inferences, opinions, and conclusions drawn in this study are those of the authors, and do not reflect the opinions or policies of the Data Steward(s)

Funding support: Michael Smith Foundation for Health Research and Canadian Institutes for Health Research (Grant: 377364)

Approval: This study received ethical approval from the University of BC Clinical Ethics Review Board (H16 -00625).

Previous presentation: Preliminary findings from this study were presented as a podium presentation at the 49th Union World conference on Lung Health, October 24-27th, 2018 at The Hague, Netherlands.

Data sharing: Data were extracted as deidentified datasets from several linked health administrative databases, including a national immigration database (Population Data BC and IRCC), a provincial health insurance registry, hospitalization, physician billing, outpatient pharmacy, vital statistics, HIV, and End-Stage Renal Disease (ESRD) registries. Additional data was extracted from the BC Provincial TB and BC Cancer Agency registries. Data are not publicly available. Data may be obtained upon authorized request to the respective data stewards as detailed in the study protocol.

REFERENCES

1. WHO World TB Database. Global tuberculosis report 2019 [Internet]. 2019. Available from: https://www.who.int/tb/publications/global_report/en/

2. World Health Organization, End TB Strategy. Global strategy and targets for tuberculosis prevention, care and control after 2015 [Internet]. World Health Organization. 2015 [cited 2019 Feb 27]. Available from: https://www.who.int/tb/strategy/End_TB_Strategy.pdf?ua=1

3. Lönnroth K, Migliori GB, Abubakar I, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. European Respiratory Journal. 2015 Mar 18;ERJ-02140-2014.

4. World Health Organization and European Respiratory Society, Framework towards TB elimination in low incidence countries [Internet]. 2014 [cited 2019 Feb 27]. Available from: https://www.who.int/tb/publications/Towards_TB_Eliminationfactsheet.pdf

5. Campbell JR, Chen W, Johnston J, et al. Latent Tuberculosis Infection Screening in Immigrants to Low-Incidence Countries: A Meta-Analysis. Mol Diagn Ther. 2015 Apr 1;19(2):107–17.

6. Campbell J, Marra F, Cook V, et al. Screening immigrants for latent tuberculosis: Do we have the resources? Canadian Medical Association Journal: CMAJ; Ottawa. 2014 Mar 4;186(4):246–7.

7. Pareek M, Watson JP, Ormerod LP, et al. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. The Lancet Infectious Diseases. 2011 Jun;11(6):435–44.

8. Public Health Agency of Canada. Canadian Tuberculosis Standards 7th Edition: 2014 [Internet]. aem. 2014 [cited 2017 Dec 17]. Available from: https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition.html

9. American Thoracic Society and Centers of Disease Control and Prevention. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. Am J Respir Crit Care Med. 2000 Apr 1;161(supplement_3):S221–47.

10. Cheng MP, Abou Chakra CN, Yansouni CP, et al. Risk of Active Tuberculosis in Patients with Cancer: A Systematic Review and Meta-Analysis. Clinical Infectious Diseases. 2016 Dec 16;ciw838.

11. Ronald LA, Campbell JR, Balshaw RF, et al. Predicting tuberculosis risk in the foreign-born population of British Columbia, Canada: study protocol for a retrospective population-based cohort study. BMJ Open. 2016 Nov 1;6(11):e013488.

12. Statistics Canada. Population size and growth rate, Canada, provinces and territories, 2006 to 2011 and 2011 to 2016 [Internet]. 2017 [cited 2019 Feb 27]. Available from: https://www150.statcan.gc.ca/n1/daily-quotidien/170208/t002a-eng.htm

13. Statistics Canada. Number and proportion of foreign-born population in Canada, 1871 to 2036 [Internet]. 2017 [cited 2019 Feb 27]. Available from: https://www.statcan.gc.ca/eng/dai/btd/othervisuals/other006

14. Public Health Agency of Canada. Tuberculosis in Canada 2016 [Internet]. 2018 [cited 2019 Feb 27]. Available from: https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2018-44/issue-3-4-march-1-2018/article-1-tuberculosis-2016.html

15. Population Data BC [Internet]. [cited 2016 Apr 20]. Available from: https://www.popdata.bc.ca

16. Immigration Statistics Canada. [cited 2016 Sep 26]. Available from: http://epe.lac-bac.gc.ca/100/202/301/immigration_statistics-ef/index.html

17. Immigration, Refugees, and Citizenship Canada (IRCC) [creator] (2014). Permanent Resident database [Internet]. Population Data BC [publisher]. Data Extract. IRCC; 2015. Available from: http://www.popdata.bc.ca/data

18. Statistics Canada (2009) [creator]. Statistics Canada Income Band Data. Catalogue Number: 13C0016 [Internet]. Population Data BC [publisher]. Data Extract; 2014. Available from: http://www.popdata.bc.ca/data

19. Canadian Institute for Health Information [creator] (2015). Discharge Abstract Database (Hospital Separations) [Internet]. Population Data BC [publisher]. Data Extract. MOH; 2014. Available from: http://www.popdata.bc.ca/data

20. BC Renal Agency [creator] (2015). BC Provincial Renal Agency Database (PROMIS) [Internet]. Population Data BC [publisher]. Data Extract. PROMIS; 2014. Available from: http://www.popdata.bc.ca/data

21. BC Vital Statistics Agency [creator] (2015). BC Vital Statistics Deaths [Internet]. Population Data BC [publisher]. Data Extract. BC Vital Statistics Agency; 2014. Available from: http://www.popdata.bc.ca/data

22. British Columbia Ministry of Health [creator] (2015). Consolidation File (MSP Registration & Premium Billing) [Internet]. Population Data BC [publisher]. Data Extract. MOH; 2015. Available from: http://www.popdata.bc.ca/data

23. BC Ministry of Health [creator] (2015). PharmaNet [Internet]. BC Ministry of Health Data Stewardship Committee [publisher]. Data Extract. MOH Data Stewardship Committee; 2014. Available from: http://www.popdata.bc.ca/data

24. BC Centre for Disease Control [creator] (2015). BC Provincial HIV/AIDS Surveillance Database (BCCDC-HAISIS) [Internet]. Population Data BC [publisher]. Data Extract. BCCDC; 2014. Available from: http://www.popdata.bc.ca/data

25. BC Centre of Disease Control [creator] (2015). BC Provincial TB Registry (BCCDC-iPHIS). Population Data BC [publisher] Data Extract BCCDC [Internet]. 2014; Available from: http://www.popdata.bc.ca/data

26. BC Cancer Agency. BC Cancer Registry [Internet]. [cited 2016 May 30]. Available from: http://www.bccancer.bc.ca/health-professionals/professional-resources/bc-cancer-registry

27. BC Cancer Agency [creator] (2015). BC Cancer Agency Registry Data [Internet]. Population Data BC [publisher]. Data Extract. BCCA; 2014. Available from: http://www.popdata.bc.ca/data

28. British Columbia Ministry of Health [creator] (2015). Medical Services Plan (MSP) Payment Information File [Internet]. Population Data BC [publisher]. Data Extract. MOH; 2014. Available from: http://www.popdata.bc.ca/data

29. Ministry of Health. MSP for B.C. Residents - Province of British Columbia [Internet]. [cited 2016 Apr 22]. Available from: https://www2.gov.bc.ca/gov/content/health/health-drug-coverage/msp/bc-residents

30. Public Health Agency of Canada. Canadian Tuberculosis Reporting System: Reporting Form Completion Guidelines, Version 1.9. January 1, 2011. http://www.phac-aspc.gc.ca/tbpc-latb/pdf/guidelinesform-eng.pdf. Accessed May 30, 2016.

31. WHO World TB Database (http://www.who.int/tb/country/data/download/en/). Accessed April 22, 2016.

32. Ronald LA, Campbell JR, Rose C, et al. Estimated Impact of World Health Organization Latent Tuberculosis Screening Guidelines in a Region With a Low Tuberculosis Incidence: Retrospective Cohort Study. Clin Infect Dis [Internet]. [cited 2019 Jul 27]; Available from: https://academic-oup-com.ezproxy.library.ubc.ca/cid/advance-article/doi/10.1093/cid/ciz188/5374592

33. Thomas P, Foley R, Kosowicz L. Reactivation of pulmonary tuberculosis following local radiation therapy of prostate cancer. Connecticut Medicine. 2014 Feb;78(2):77–80.

34. Simonsen DF, Farkas DK, Horsburgh CR, et al. Increased risk of active tuberculosis after cancer diagnosis. Journal of Infection. 2017 Jun;74(6):590–8.

35. Shu C-C, Liao K-M, Chen Y-C, Wang J-J, Ho C-H. The burdens of tuberculosis on patients with malignancy: incidence, mortality and relapse. Sci Rep. 2019 Dec;9(1):11901.

36. Suzuki Y, Imokawa S, Sato J, et al. Cumulative incidence of tuberculosis in lung cancer patients in Japan: A 6-year observational study. Respiratory Investigation. 2016 May;54(3):179–83.

37. Maurya V, Vijayan V. K, Shah A. Smoking and tuberculosis: an association overlooked. The International Journal of Tuberculosis and Lung Disease. 2002 Nov 1;6(11):942–51.

38. Boon S den, Lill SWP van, Borgdorff MW, et al. Association between smoking and tuberculosis infection: a population survey in a high tuberculosis incidence area. Thorax. 2005 Jul 1;60(7):555–7.

39. Rehm J, Samokhvalov AV, Neuman MG, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC Public Health. 2009 Dec 5;9:450.

40. Advani SH, Banavali SD. Pattern of Infection in Hematologic Malignancies: An Indian Experience. Reviews of Infectious Diseases. 1989;11:S1621–8.

41. Au WY, Kwong YL, Ma SK, et al. Hairy cell leukemia in Hong Kong Chinese: a 12-year retrospective survey. Hematol Oncol. 2000 Dec 1;18(4):155–9.

42. Liu C-J, Hong Y-C, Teng C-J, et al. Risk and impact of tuberculosis in patients with chronic myeloid leukemia: A nationwide population-based study in Taiwan. Int J Cancer. 2015 Apr 15;136(8):1881–7.

43. Marur S, Forastiere AA. Head and Neck Squamous Cell Carcinoma: Update on Epidemiology, Diagnosis, and Treatment. Mayo Clinic Proceedings. 2016 Mar 1;91(3):386–96.

44. Kaplan MH, Armstrong D, Rosen P. Tuberculosis complicating neoplastic disease. A review of 201 cases. Cancer. 1974 Mar 1;33(3):850–8.

45. Aggarwal R, Rao S. Coexistence of tuberculosis with histiocytic sarcoma: A rare association. Journal of Cancer Research and Therapeutics. 2015;11(3):658.

46. Wu C-Y, Hu H-Y, Pu C-Y, et al. Aerodigestive tract, lung and haematological cancers are risk factors for tuberculosis: an 8-year population-based study. Int J Tuberc Lung Dis. 2011 Jan;15(1):125–30.

47. Vento S, Lanzafame M. Tuberculosis and cancer: a complex and dangerous liaison. The Lancet Oncology. 2011 Jun;12(6):520–2.

48. Parry C, Kent EE, Mariotto AB, et al. Cancer Survivors: A Booming Population. Cancer Epidemiology Biomarkers & Prevention. 2011 Oct 1;20(10):1996–2005.

49. Chen C-Y, Wang J-Y, Chien Y-C, et al. Lung cancer mimicking pulmonary tuberculosis in a TB-endemic country: the role of early invasive diagnostic procedures. Lung Cancer Management. 2015 Feb;4(1):9–16.

50. Ciftci F, Shimbori N, Karnak D. Concurrent central nervous system and endobronchial tuberculosis mimicking a metastatic lung cancer. The Clinical Respiratory Journal. 2017 Jan 1;11(1):98–102.

51. Davies PDO, Pai M. The diagnosis and misdiagnosis of tuberculosis [State of the art series. Tuberculosis. Edited by I. D. Rusen. Number 1 in the series]. The International Journal of Tuberculosis and Lung Disease. 2008 Nov 1;12(11):1226–34.

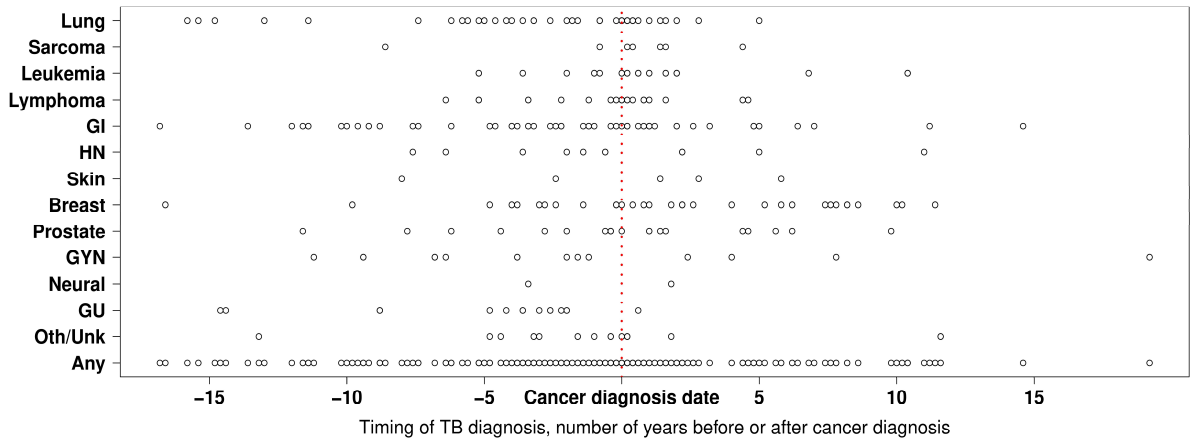
52. Bates MN. Risk of Tuberculosis From Exposure to Tobacco Smoke: A Systematic Review and Meta-analysis. Arch Intern Med. 2007 Feb 26;167(4):335.

53. Guthrie JL, Kong C, Roth D, Jorgensen D, Rodrigues M, Hoang L, et al. Molecular Epidemiology of Tuberculosis in British Columbia, Canada: A 10-Year Retrospective Study. Clinical Infectious Diseases. 2018 Mar 5;66(6):849–56.

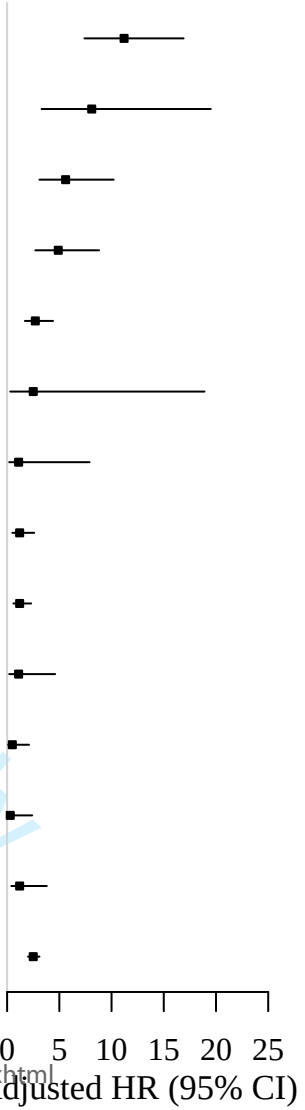
FIGURE LEGENDS:

Figure 1 Legend:
GI: Gastro-Intestinal; **HN:** Head and Neck; **GYN:** Gynecological; **GU:** Genito-Urinary; **Oth/Unk:** other and unknown;
∘ Active TB diagnosis

Figure 2 Legend:
Hazard Ratios adjusted for*: age at follow up (age at which TB acquired), sex, time since arrival in BC (0-5 yrs and >5 yrs), immigration classification type (refugee, family or economic), high risk medical comorbidities (HIV, Dialysis dependent end stage kidney disease, Immune Suppression, Diabetes), and TB incidence by country of origin.



Cancer	Active TB (cancer)	Active TB (without cancer)	HR (95% CI)
Lung	25	2560	11.2 (7.4, 16.9)
Sarcoma	5	2580	8.1 (3.3, 19.5)
Leukemia	11	2574	5.6 (3.1, 10.2)
Lymphoma	12	2573	4.9 (2.7, 8.7)
GI	17	2568	2.7 (1.7, 4.4)
Neural	<5	2584	2.5 (0.3, 18.7)
HN	<5	2582	1.1 (0.2, 7.9)
Breast	6	1258	1.2 (0.5, 2.6)
Prostate	10	1310	1.2 (0.6, 2.2)
Skin	<5	2583	1.1 (0.2, 4.6)
GYN	<5	1262	0.5 (0.1, 2.1)
GU	<5	2584	0.3 (0.0, 2.4)
Other	<5	2584	1.2 (0.4, 3.8)
Any	91	2484	2.5 (2.0, 3.1)



APPENDIX

Table A1: Active TB risk amongst patients with Genito-urinary and Gastrointestinal cancers

TUMOUR SUBGROUP	Number with Cancer	Number with Active TB	Adjusted HR (95% CI)
Genito-Urinary			
Bladder	855	0	NA
Prostate	3012	10	1.2 (0.6, 2.3)
Kidney	607	1	1.1 (0.2, 7.8)
Gastrointestinal*			
Esophagus and stomach	918	2	2 (0.5, 8.1)
Large intestine and rectum	3020	9	2.3 (1.2, 4.4)

*Liver, Pancreas, Gallbladder, and small intestinal malignancies not shown.

Table A2: Sensitivity analysis, testing models with different population inclusion criteria

Model #	Model description	# people deleted (w/ prevalent cancers)	# people included in analysis	# TB cases included in analysis	Adj HR, Lung cancer
1	Age 15+	2,014	1,000,764	2,585	11.2 (7.4-16.9)
2	Age 30+	2,558	800,489	2,071	11.2 (7.4-16.9)
3	All ages	1,961	1,046,759	2,634	11.5 (7.6-17.4)
4	Age 15+, excluding LTBI	2,010	995,828	2,575	11.4 (7.5-17.1)

Table A3: Active TB risk stratified by TB incidence of country of origin in foreign born individuals with cancer

Cancer Type	TB Incidence 0 -100 HR (95% CI)	TB Incidence > 100 HR (95% CI)	All Regions HR (95% CI)
Lung	3.1 (0.4, 23.2)	12.4 (8.1, 18.8)	11.2 (7.4, 16.9)
Gastrointestinal	3.8 (1.2, 12.4)	2.5 (1.5, 4.3)	2.7 (1.7, 4.4)
Leukemia	3.9 (0.5, 29.3)	5.9 (3.1, 11.0)	5.6 (3.1, 10.2)
Lymphoma	6.5 (1.5, 27.9)	4.7 (2.5, 8.8)	4.9 (2.7, 8.8)
Head and Neck	NA	1.2 (0.2, 8.8)	1.1 (0.2, 7.9)
Genitourinary	NA	0.4 (0.1, 2.8)	0.3 (0.0, 2.4)
Other	NA	1.3 (0.4, 4.1)	1.2 (0.4, 3.8)
Sarcoma	15.3 (2.1, 109.3)	7.2 (2.7, 19.3)	8.1 (3.3, 19.5)
Skin	NA	1.4 (0.3, 6.0)	1.1 (0.2, 4.6)
Neural	NA	2.9 (0.4, 22.1)	2.5 (0.3, 18.9)
Breast	NA	1.4 (0.6, 3.1)	1.2 (0.5, 2.6)
Gynecologic	4.2 (1.0, 17.1)	NA	0.5 (0.1, 2.1)
Prostate	2.9 (0.7, 11.7)	1.1 (0.5, 2.1)	1.2 (0.6, 2.3)
Any Cancer	2.7 (1.5, 4.9)	2.4 (1.9, 3.1)	2.5 (2.0, 3.1)

Other: other/unknown cancer type

NA: Not applicable as 0 ATB cases recorded.

Table A4: Active TB (ATB) stratified by Pulmonary/Mix and Extrapulmonary TB amongst foreign born individuals with cancer

Cancer Type	Total ATB within 5 years	Pulmonary or Mix ATB	Extrapulmonary ATB
Lung	25	16 (64.0%)	9 (36.0%)
Sarcoma	5	<5 (20%)	<5 (80.0%)
Leukemia	11	5 (45.5%)	6 (54.5%)
Lymphoma	12	10 (83.3%)	<5 (16.7%)
Breast	6	<5 (50%)	<5 (50.0%)
Head and Neck	<5	<5 (0%)	<5 (100%)
Gastro-Intestinal	17	9 (52.9%)	8 (47.1%)
Skin / Melanoma	<5	<5 (50%)	<5 (50.0%)
Prostate	10	7 (70.0 %)	<5 (30.0%)
Gynecologic	<5	<5 (50.0 %)	<5 (50.0%)
Genito-Urinary	<5	<5 (100%)	<5 (0.0%)
Neural	<5	<5 (0.0%)	<5 (100%)
Other/Unknown	<5	<5 (0.0 %)	<5 (100%)
Any cancer	91	51 (56.0%)	40 (43.9%)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3, 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3, 4
Participants	6	***(a) Cohort study***—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	a) 4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3, Reference 1
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	5

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	5
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, 6
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5, 6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7, 8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7, 8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9, 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9, 10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.