Journal of Microbiology, Immunology and Infection 55 (2022) 266—272

Available online at www.sciencedirect.com

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journal homepage: www.e-jmii.com

Original Article

Global burden of tuberculosis attributable to cancer in 2019: Global, regional, and national estimates

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Received 18 November 2020; received in revised form 6 February 2021; accepted 21 February 2021
Available online 8 March 2021

KEYWORDS
Cancer;
Global burden of disease;
Population attributable fraction;
Tuberculosis

Abstract *Background:* Cancer is an independent risk factor for tuberculosis (TB). The global burden of incident TB attributable to cancer has never been explored. We aimed to evaluate the cancer-attributable burden of TB.
Methods: We estimated the population attributable fraction (PAF) by Levin's formula. The cancer prevalence rates were derived from the Institute for Health Metrics and Evaluation. The relative risk of TB in cancer patients was estimated by using the National Health Insurance Research Database in Taiwan. The global burden of incidence TB attributable to cancer was the weighted sum of PAFs multiplied by the incidence of TB retrieved from the World Health Organization.
Results: Worldwide, the total of incident TB cases attributable to cancer was 115,478 cases with a 95% confidence interval (CI), 110,482—123,007, in 2019. The global PAF of TB due to cancer was 1.85% (95% CI, 1.77—1.97%). The three countries with the highest PAFs were Greenland (7.77%), Canada (7.75%), and the United States of America (6.79%), while the three countries with the highest attributable TB cases due to cancer were China (25,240), India (21,629), and Indonesia (13,917). Cancer of respiratory system contributed to 60,257 of TB cases.

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https://doi.org/10.1016/j.jmii.2021.02.005

Conclusions: This study comprehensively explored the impact of cancer on the global burden of TB. Efforts to reduce cancer risk, delay the occurrence of cancer, or treat latent TB infection in the cancer population could potentially reduce the burden of TB and rely on formulating integrated strategies.

Introduction

Tuberculosis (TB) is an infectious disease that is a major cause of ill health; TB is one of the top 10 causes of death worldwide, and it is the leading cause of death from a single infectious pathogen.[1] Worldwide, there were an estimated 10.0 million incident TB cases and an estimated 1.2 million TB deaths in 2019. The TB incidence rate is decreasing gradually, but it is not falling fast enough to reach the goal of the End TB Strategy of the World Health Organization (WHO).[1]

Cancer is one of the independent risk factors for TB.[2] Globally, there were an estimated 18.1 million new cancer cases and an estimated 9.6 million cancer-related deaths in 2018.[3] By 2040, the global burden is expected to increase up to 27.5 million new cancer cases and 16.2 million cancer-related deaths. In the foreseeable decades, cancer will remain a risk factor adversely affecting the goal of TB control in the End TB Strategy.

There are several possible mechanisms that increase the risk of TB in the cancer population. Weight loss and immunodeficiency are cancer-related clinical symptoms evidently associated with increased risk of TB in the period around a cancer diagnosis.[4,5] During anticancer treatment, chemotherapy and radiotherapy may compromise host immunity. The interacted mechanisms could result in TB reactivation.[6]

Since the 1950s, the methods of population attributable fraction (PAF) and related measures were developed to answer the question that suppose each individual of a population who was not in the most favorable level of an exposure with relation to an adverse outcome and had been counterfactually shifted into that level.[7] The Global Burden of Disease (GBD) project, dating to the early 1990s, provided global estimates for systematic evaluation of the changes in population health which would result from eliminating the population distribution of exposure to a risk factor or a group of risk factors by utilizing consistent and comparable methods.[8] Using the comparative risk assessment framework of the GBD study, the burden of diseases attributable to risk exposure and substantial geographic variations can be estimated.

Incident TB is preventable and manageable if prevention strategies and treatments are introduced in a timely manner.[9] Intervention targeting the cancer population, which is one of the high-risk groups for TB, could be part of a reasonable and practical strategy to eliminate the global burden of TB. Given that the global burden of incident TB attributable to cancer has never been explored in the literature, we evaluate the burden of TB that can be attributed to having a cancer diagnosis.

Methods

Following the framework of the GBD study, we evaluated the burden of TB that is attributable to having a cancer diagnosis nationally and globally by Levin's formula, calculating the PAF by integrating data of the proportion of risk exposure and risk functions connecting exposure and disease outcomes.[10] PAF represented the proportion of burden of disease in a given population that would be avoided if risk exposures of a population were shifted to an alternative or counterfactual distribution that would be more favorable for public health.[11] The global burden of TB disease attributable to cancer can be unbiasedly estimated by computing the global TB incidence and multiplying it by the PAF due to cancer.[12]

Estimation of relative risk

The relative risk of incident TB was estimated by conducting a matched cohort study to compare the cancer population with the noncancer population using the National Health Insurance Research Database in Taiwan. Based on the time-dependent association between cancer exposure and TB risk, the highest TB risk mainly clustered in the year before and the year after the time of cancer diagnosis (Fig. S1). Thus, we estimated the adjusted hazard ratio (HR) during the two-year period as the relative risk of incident TB in cancer exposure. The HRs were stratified in sex-age-specific groups corresponding to the cancer categories in the GBD study (Fig. S2). Focusing on the association between cancer diagnosis and incident TB, individuals under the age of 30, above the age of 90, or having any past cancer history were excluded. Parts of the HRs in the sex-age-cancer-specific categories were pooled to minimize the variation of risk estimates.

Data of proportion of risk exposure

We estimated the prevalence of cancer cases during the two-year period around a cancer diagnosis to be consistent with the estimation period for relative risk. Given that the peridiagnostic cancer consisted of a one-year prediagnostic period and one-year postdiagnotic period relative to the cancer diagnosis, the prevalence rate was estimated to be

two times the annual cancer incidence rate. The information of country-sex-age-specific cancer incidence in 2019 was retrieved from the Institute for Health Metrics and Evaluation (IHME).[13]

Estimation of burden of TB attributable to cancer

We estimated PAFs for TB due to cancer by integrating information of cancer prevalence and the associations between cancer and TB. The following generalized formula was used to calculate PAF:

$$\text{Population Attributable Fraction (PAF)} = \frac{P(RR-1)}{1+P(RR-1)}$$

where P was the proportion of risk exposure, and RR was the corresponding relative risk.

The global PAF for a specific cancer category was estimated by summation of weighted PAFs for country-sex-age-specific strata:

$$\text{Global PAF for Specific Cancer}\left(c\right) = \sum_r \sum_s \sum_a W_{r,s,a}\left(\frac{PR_{r,s,a,c}(HR_{s,a,c}-1)}{1+PR_{r,s,a,c}(HR_{s,a,c}-1)}\right)$$

where PR was the prevalence rate of cancer, HR was the adjusted hazard ratio for cancer and TB, and W was the weight of strata. The weighted strata were summed by a ratio of the country-sex-age-specific incidence number of TB divided by the global incidence number of TB. The symbols for each subgroup were defined as region r = {locations classified in GBD study}, sex group s = {male, female}, age group a = {30 to 34, 35 to 39, ..., 85 to 89}, and cancer category c = {cancer groups classified in GBD study}.

We estimated the global PAF for all cancer by joint attributable risks under the assumption of independence among cancer categories:

$$\text{Global PAF for All Cancer} = \sum_r \sum_s \sum_a W_{r,s,a}\left(1-\prod_c\left(1-\frac{PR_{r,s,a,c}(HR_{s,a,c}-1)}{1+PR_{r,s,a,c}(HR_{s,a,c}-1)}\right)\right)$$

To derive the cancer-attributable burden of TB cases at the country level, the incidence of TB for each country was multiplied by the PAF for each country. The incidence of TB for each country was retrieved from the WHO's TB data in 2019, including pulmonary TB and extra pulmonary TB.[14] We additionally imported native TB data in 2019 for Taiwan,[15] which were unavailable in WHO's data. The proportional relationships of sex and age groups within a country were concordant with the GBD study.[13] The estimate of global burden of TB attributable to cancer was calculated by multiplying the global TB cases by the weighted sum of the PAFs for all countries in 2019.

Uncertainty analyses

The uncertainty of PAF estimates due to sampling variability was handled with a statistical simulation approach. We randomly generated 100,000 pairs of risk exposure and relative risk from their distributions for each country-sex-age-cancer-specific stratum. Each pair of sampled risk exposure and relative risk was used to generate a PAF. When combining the strata of groups, we summed the weighted PAFs in their generating order. The resulting 100,000 PAFs were ranked, and the 2.5th and 97.5th percentiles were reported as the lower and the upper bounds of the 95% confidence interval (CI), respectively.

Database retrieval, statistical analysis, and preparation of tables and figures were carried out in R version 3.6.3 and associated statistical and graphical packages.[16] This study was approved by the Research Ethics Committee of National Taiwan University Hospital, Taiwan (201808 105RINC).

Results

The estimated global PAF of TB due to cancer was 1.85% (95% CI, 1.77–1.97%) in 2019 (Table 1). The global PAF in the male population was 1.76% (95% CI, 1.70–1.84%), whereas the global PAF in the female population was 2.02% (95% CI, 1.83–2.35%). There was an approximately three-fold difference of PAFs within the WHO regions, among which the two highest PAFs were in the Western Pacific Region (PAF = 3.03%; 95% CI, 2.82–3.32%) and the European Region (PAF = 2.96%; 95% CI, 2.81–3.20%), while the lowest PAF was in the African Region (PAF = 1.10%; 95% CI, 1.04–1.19%).

The total of incident TB attributable to cancer was 115,478 (95% CI, 110,482–123,007) worldwide (Table 2). The attributable cases were dominant in the male population 72,822 (95% CI, 70,204–76,098) compared with the female population 42,519 (95% CI, 38,513–49,514). The majority of attributable TB cases due to cancer originated from the South-East Asia Region (n = 47,205; 95% CI, 43,503–53,904) and the Western Pacific Region (n = 39,072; 95% CI, 36,468–42,897). These two regions accounted for 86,277 cases, which is the majority (74.71%) of TB cases attributable to cancer in the world.

At the country level, the PAFs and the attributable numbers varied among countries (Fig. 1). The three

Table 1 Estimated population attributable fractions of tuberculosis associated with cancer in 2019 by the WHO region.

	Male population		Female population		Total population	
	PAF (%)	95% CI	PAF (%)	95% CI	PAF (%)	95% CI
African Region	1.07	1.01–1.14	1.17	1.05–1.40	1.10	1.04–1.19
Region of the Americas	1.73	1.65–1.83	2.56	2.33–2.95	2.01	1.91–2.15
Eastern Mediterranean Region	1.77	1.59–2.10	1.93	1.60–2.63	1.84	1.66–2.16
European Region	3.08	2.91–3.35	2.68	2.40–3.19	2.96	2.81–3.20
South-East Asia Region	1.40	1.32–1.52	1.78	1.50–2.35	1.54	1.42–1.76
Western Pacific Region	2.94	2.75–3.18	3.21	2.75–4.06	3.03	2.82–3.32
Global	**1.76**	**1.70–1.84**	**2.02**	**1.83–2.35**	**1.85**	**1.77–1.97**

Abbreviations: WHO, World Health Organization; PAF, population attributable fraction; CI, confidence interval.

countries with the highest PAFs were Greenland (PAF = 7.77%; 95% CI, 6.93–8.74%), Canada (PAF = 7.75%; 95% CI, 6.70–8.97%), and the United States of America (PAF = 6.79%; 95% CI, 6.00–7.67%). By contrast, the three countries with the highest attributable TB cases due to cancer were China (n = 25,240; 95% CI, 22,955–28,788), India (n = 21,629; 95% CI, 18,981–27,402), and Indonesia (n = 13,917; 95% CI, 12,065–17,642). The results of estimated PAFs and attributable TB cases for all countries were detailed in the supplementary materials (Table S1 and Table S2).

The two highest cancer categories for global PAFs among the major cancer categories (Table 3) were the respiratory system (PAF = 0.97%; 95% CI, 0.91–1.04%) and hematology (PAF = 0.42%; 95% CI, 0.37–0.52%). There were 60,257 (95% CI, 56,796–65,137) TB cases attributable to the former category, and 26,304 (95% CI, 23,193–32,654) TB cases attributable to the latter (Table 4). The results of estimated PAFs and attributable TB cases for the GBD cancer categories were detailed in the supplementary materials (Table S3 and Table S4).

Discussion

In this study, we estimated the global burden of TB attributable to cancer, based on the distributive property quantitatively partitioned or distributed into exposure-category-specific attributable fractions.[17] We found that a total of 115,478 incident TB cases were attributable to cancer globally, accounting for a PAF of 1.85%. The PAF varied among countries, and the excess risk was as high as 6.79% to 7.77% in some of the major countries in North America. In contrast to the high PAFs noted in North America, most of the TB cases attributable to cancer originated from the Western Pacific Region and the South-East Asia Region. China, India, and Indonesia accounted for a total of 60,786 (52.64%) attributable TB cases due to cancer, which is more than half of the global total.

The distributive property in PAF calculation is that the sum of the PAFs from two or more strata of the population equals the PAF calculated from combining those strata into a single stratum, regardless of the number and the divisions of the strata that are formed. The proportion of risk exposure for each sex-age-specific population, the corresponding relative risk, and the composition of the population in each country were distinct and dissimilar. Since heterogeneities of cancer prevalence and relative risk existed among country-sex-age-specific groups for each cancer category, we calculated respective PAFs and summed the weighted PAFs to yield the combined PAFs. The combined PAFs represented the excess fraction of diseases without confounding by heterogeneous compositions of sex and age groups in distinct populations. Furthermore, we regarded separate cancer categories as multiple independent risk factors within a single stratum. To avoid overestimation, we calculated a joint risk of PAFs for all cancer categories instead of approximately summing the PAFs for all cancer categories.

We adjusted confounding effects of possible risk factors between cancer and TB to ensure that the relative risks of TB we identified in the cancer population compared with the noncancer population were robust effects for respective country-sex-age-specific groups in adults (Fig. S2).

Table 2 Estimated numbers of tuberculosis attributable to cancer in 2019 by the WHO region.

	Male population		Female population		Total population	
	n	95% CI	n	95% CI	n	95% CI
African Region	8,048	7,652–8,610	4,039	3,617–4,813	12,113	11,494–13,038
Region of the Americas	2,119	2,021–2,242	1,554	1,412–1,791	3,678	3,499–3,938
Eastern Mediterranean Region	4,694	4,226–5,576	2,885	2,393–3,921	7,629	6,882–8,944
European Region	3,866	3,653–4,210	1,566	1,402–1,858	5,445	5,158–5,882
South-East Asia Region	27,364	25,695–29,736	19,708	16,608–26,110	47,205	43,503–53,904
Western Pacific Region	26,569	24,882–28,759	12,393	10,621–15,702	39,072	36,468–42,897
Global	**72,822**	**70,204–76,098**	**42,519**	**38,513–49,514**	**115,478**	**110,482–123,007**

Abbreviations: WHO, World Health Organization; CI, confidence interval.

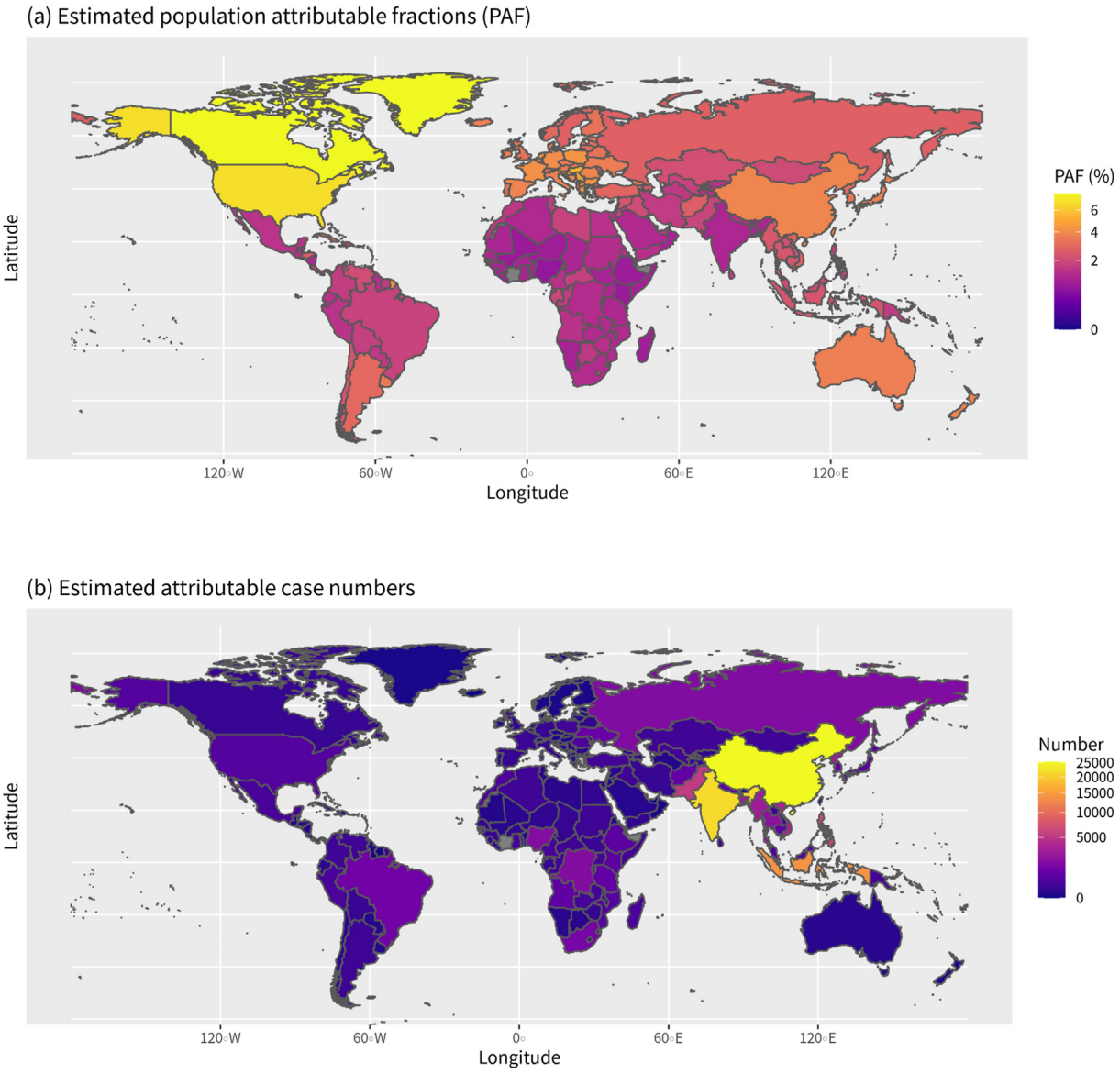

Figure 1. Estimated burden of tuberculosis attributable to cancer in 2019 by country.

Table 3 Estimated population attributable fractions of tuberculosis associated with cancer in 2019 by major cancer category.

	Male population		Female population		Total population	
	PAF (%)	95% CI	PAF (%)	95% CI	PAF (%)	95% CI
Head and neck	0.14	0.13–0.15	0.06	0.06–0.06	0.11	0.11–0.12
Respiratory system	0.92	0.87–0.99	1.06	0.94–1.25	0.97	0.91–1.04
Digestive system	0.24	0.22–0.25	0.12	0.11–0.13	0.20	0.19–0.21
Central nervous system	0.02	0.01–0.02	0.01	0.01–0.01	0.01	0.01–0.02
Breast	0.00	0.00–0.00	0.05	0.05–0.06	0.02	0.02–0.02
Skin	0.02	0.02–0.03	0.02	0.01–0.02	0.02	0.02–0.02
Genitourinary system	0.02	0.02–0.03	0.04	0.04–0.05	0.03	0.03–0.03
Hematology	0.32	0.30–0.36	0.61	0.48–0.90	0.42	0.37–0.52
Others	0.10	0.09–0.11	0.05	0.05–0.05	0.08	0.08–0.09

Abbreviations: PAF, population attributable fraction; CI, confidence interval.

Table 4 Estimated numbers of tuberculosis attributable to cancer in 2019 by major cancer category.

	Male population		Female population		Total population	
	n	95% CI	n	95% CI	n	95% CI
Head and neck	5,822	5,460—6,239	1,290	1,216—1,370	7,113	6,743—7,535
Respiratory system	37,875	35,714—40,810	22,255	19,774—26,377	60,257	56,796—65,137
Digestive system	9,697	9,211—10,239	2,523	2,323—2,765	12,227	11,692—12,811
Central nervous system	629	555—719	237	210—270	867	787—961
Breast	0	0—0	1,156	1,064—1,255	1,156	1,064—1,255
Skin	915	807—1,035	318	284—354	1,234	1,120—1,358
Genitourinary system	985	885—1,105	929	784—1,151	1,919	1,734—2,163
Hematology	13,372	12,200—14,951	12,827	10,122—19,061	26,304	23,193—32,654
Others	4,048	3,788—4,341	1,047	957—1,150	5,096	4,821—5,405

Abbreviations: CI, confidence interval.

While comparing with the PAFs of TB due to diabetes mellitus (11.9% to 19.7%) and human immunodeficiency (9%),[18,19] the PAFs of TB due to cancer could not be neglected in some major countries, which were as high as 6.79% to 7.77%. The time-dependent risk of TB, with the highest risk observed around the time of cancer diagnosis, provides timing for intervention strategies clearer than other chronic TB risk factors (Fig. S1).

The proportion of risk exposure will increase in the foreseeable decades. A 50% increase in the estimated 18.1 million global cancer cases in 2018 is expected, resulting in 27.5 million new cancer cases per year by 2040.[3] Increases in the cancer incidence burden will occur in all countries. From 2018 to 2040 using demographic changes, the predicted increases will be proportionately greatest in countries with low and medium Human Development Index (HDI). A 48.65% increase in the global PAF of TB due to cancer is expected to increase the excess risk from 1.85% to 2.75% solely due to a 50% increase of global cancer burden. Since the global burden of TB case number has been slowly declining in recent years, the global burden of TB attributable to cancer is expected to increase, especially in the South-East Asia Region and the Western Pacific Region, which contribute to approximately three quarters of TB cases attributable to cancer in the world.

In addition to genetic and environmental factors, age is coincidentally associated with preventable chronic conditions, avoidable exposures, and modifiable health habits that are causally associated with cancer.[20,21] During midlife, the prevalence of multiple cancer risk factors is high and incidence rates begin to increase for many types of cancer. Changing individual behaviors, multilevel system and environmental interventions addressing multiple diseases and risk factors could reduce cancer risk or delay the occurrence of cancer and other age-related diseases. Since the global burden is expected to reach 27.5 million new cancer cases due to growth and aging of the population by 2040, an alternative counterfactual distribution of cancer would not be realized effortlessly.[22]

Prevention strategies targeting the cancer population with latent TB infection provide an opportunity for TB control. Using mathematical modeling, approximately one fourth of the global population was estimated to be infected with *Mycobacterium tuberculosis*.[23] Most infected persons were asymptomatic and classified as having latent TB infection. Tuberculin testing and treatment of latent TB infection in high-risk groups including cancer patients were recommended.[24] Treatment of latent TB infection was effective in preventing TB reactivation.[25] Targeting the cancer population at the time of a new cancer diagnosis, screening programs for latent TB infection are expected to catch one fourth of the cancer population who are at risk for TB reactivation. Though it is difficult to achieve an alternative counterfactual distribution of cancer, an alternative counterfactual outcome of TB occurrence in the cancer population is possibly achievable.

The global impact of cancers on TB disease burden has not yet been addressed in the literature. This integrated analysis has critical implications on sustainable development goals (SDGs).[26] By analyzing the global impact of cancer on TB diseases, we informed development of intervention strategies across different SDGs and offered synergistic benefits on noncommunicable diseases and communicable diseases.[27,28] Globally and nationally, the risk of dying from various communicable diseases is marked by huge diversity in terms of magnitude and changes over time. No country should aim to achieve the goal of TB control in the End TB Strategy by addressing a single disease. It is essential to reduce premature mortality not only from preventing incident TB in the cancer population but also from preventing interruption of cancer management due to occurrences of incident TB around a cancer diagnosis.

There are limitations and uncertainties of our global assessment. First, the relative risk of TB in cancer patients was estimated from a single country. The adjusted sex-age-cancer-specific risks may vary among different countries since the genetic variations and environmental factors were not all measurable. The external validity needs to be globally verified. Second, the incidence and prevalence of cancer might be underestimated globally. Medical services are unevenly distributed and inequalities increased in some parts of the world, which were related with a portion of low-to-medium HDI countries recording proportionately slower gains for cancers.[29,30] Due to a lack of appropriate monitoring systems, low rates of cancer mortality could actually result from inadequate screening and cancer treatment instead of good access to cancer detection and excellent cancer management. Third, many TB cases worldwide clearly remain undiagnosed, resulting in

underestimation of TB burden.[31] Many TB cases receive no or inadequate treatment when diagnosed outside national TB programs. Better information would enable better assessment of TB control achievements, in turn challenging countries to improve their control efforts. Based on the information of incident TB cases retrieved from WHO's data and the proportion of cancer exposures derived from the GBD study, we assumed low risk by overestimating the global burden of incident TB attributable to cancer.

In conclusion, this study comprehensively explored the impact of cancer on global burden of incident TB. Efforts to reduce cancer risk, delay the occurrence of cancer, or treat latent TB infection in the cancer population would potentially synergistically benefit TB burden reduction, particularly in endemic areas. The study provided insights into advanced research to recognize the potential of individual countries to formulate integrated strategies and policies for the prevention of cancer and TB.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2021.02.005.