Clinical Infectious Diseases

MAJOR ARTICLE

Risk of Active Tuberculosis in Patients With Cancer: A Systematic Review and Metaanalysis

Matthew P. Cheng,[1] Claire Nour Abou Chakra,[2] Cedric P. Yansouni,[1] Sonya Cnossen,[2] Ian Shrier,[2] Dick Menzies,[3] and Christina Greenaway[2,4]

[1]Division of Infectious Diseases and Department of Medical Microbiology, McGill University Health Centre, [2]Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Jewish General Hospital, [3]Respiratory Epidemiology Unit, McGill University Health Centre, and [4]Division of Infectious Diseases, Jewish General Hospital, McGill University, Montreal, Quebec, Canada

Background. Cancer is a known risk factor for developing active tuberculosis. We determined the incidence and relative risk of active tuberculosis in cancer patients compared to the general population.

Methods. Medline, Medline InProcess, EMBASE, PubMed, the Cochrane Database of Systematic Reviews, Cancerlit, and Web of Science were searched up to December 1, 2015. Studies of pathologically confirmed cancer cases were included if active tuberculosis was identified concurrently or after diagnosis. Cumulative incidence rate/100 000 population (CIR) of new cases of tuberculosis occurring in cancer patients and comparative incidence rate ratios (IRRs) to the general population from the same country of origin were estimated. A random effect meta-analysis was conducted on the CIR and IRR.

Results. A total of 23 studies reporting 593 tuberculosis cases occurring in 324 041 cancer patients between 1950 and 2011 were identified. In a meta-analysis of 6 studies conducted in the United States in 317 243 cancer patients (98% of all patients), the CIR of tuberculosis decreased by 3-fold and 6.5-fold in hematologic and solid cancers, respectively, before and after 1980. After 1980 the CIR of tuberculosis was highest in hematologic (219/100 000 population; IRR = 26), head and neck (143; 16), lung cancers (83; 9) and was lowest in breast and other solid cancers (38; 4).

Conclusions. Individuals living in the United States with hematologic, head and neck, and lung cancers had a 9-fold higher rate of developing active tuberculosis compared to those without cancer and would benefit from targeted latent tuberculosis screening and therapy.

Keywords. tuberculosis; active; cancer; malignancy; reactivation.

Identification and treatment of persons with latent *Mycobacterium tuberculosis* infection is an essential component of tuberculosis control in low tuberculosis–incidence countries [1]. Cancer has been a well-recognized risk factor for developing active *M. tuberculosis* infection since the 1970s; however, the absolute and relative risk for different cancer types and the change in risk over time has not been well defined. US and Canadian guidelines identify immunosuppression due to human immunodeficiency virus, organ transplant, prolonged therapy with corticosteroids, tumor necrosis factor-alpha inhibitors, hematologic malignancies, and head and neck cancers as important risk factors for developing active tuberculosis [2, 3]. The magnitude of risk due to hematologic malignancies is not mentioned nor is the risk due to common cancers such as cancer of the breast, prostate, lung, and colon addressed, although they account for half of all new cancer diagnoses annually [4, 5]. Patients with cancer are a growing group at increased risk of tuberculosis given that almost 40% of North American's will develop cancer in their lifetime, cancer survival is steadily improving, and the number of foreign-born persons from tuberculosis-endemic countries living in low tuberculosis–incidence countries is increasing [4, 5]. The risk of tuberculosis reactivation due to immunosuppression from cancer therapies has changed over time and is also different between cancer types. Treatments for hematologic cancer such as combination therapies, purine analogues, targeted monoclonal antibodies, and hematopoietic stem cell transplantation are more deeply immunosuppressive compared to therapies that were available prior to the 1970s, whereas local damage due to radiotherapy in head and neck cancers has decreased with newer radiation modalities [6, 7].

Targeted screening and treatment of latent tuberculosis infection (LTBI) is an important strategy for groups at high risk of developing active tuberculosis. We conducted a systematic review and metaanalysis of studies that assessed the risk of developing active tuberculosis in cancer patients. These estimates were stratified by important predictors, including cancer type and tuberculosis incidence in the country of study in order to determine which patients would benefit most from LTBI screening and treatment.

METHODS

Data Sources and Searches

In preparing this work, we followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analysis Of Observational Studies in Epidemiology)

Received 12 August 2016; editorial decision 30 November 2016; accepted 7 December 2016; published online December 13, 2016.

Correspondence: C. Greenaway, Jewish General Hospital, Division of Infectious Diseases, 3755 Cote St. Catherine Road, Montreal, PQ H3T 1E2 Canada (ca.greenaway@mcgill.ca).

Clinical Infectious Diseases® 2017;64(5):635–44

DOI: 10.1093/cid/ciw838

guidelines [8, 9]. The following 7 electronic databases were searched from database inception to 1 December 2015: Medline, Medline In-Process, EMBASE, PubMed, the Cochrane Database of Systematic Reviews, Cancerlit, and Web of Science. Search terms combined MESH terms, text words, and exploded terms including "*Mycobacterium tuberculosis*," "tuberculosis," "cancer," "cancerous," "neoplasms," "epidemiological studies," "seroepidemiology studies," "risk factors," "odds ratio," "prevalence," "incidence," "risk," and "multivariate analysis." The strategy and search terms for Medline are listed in Appendix Table 1. The searches were limited to human studies published in English or French. Additional studies were identified by hand-searching references from relevant articles.

Study Selection

We included studies that reported new cases of tuberculosis that occurred concurrently or after the diagnosis of cancer and that provided the number of cancer patients at risk during the study period. A subset of 13 studies also reported the follow-up time of the entire cohort. Neoplasms were diagnosed pathologically and tuberculosis was diagnosed bacteriologically or pathologically and, in a few studies cases, were identified clinically. Studies where isoniazid prophylaxis was provided to the entire study population or certain subgroups were excluded.

Data Extraction and Quality Assessment

Two independent reviewers screened the title and abstract of potentially relevant studies and assessed their eligibility and quality. Data extraction was performed independently by 2 authors who used a standardized data-extraction tool. Discrepancies were resolved at all stages by consensus or with a third author when necessary. Patient characteristics included age, sex, type of malignancy, site of tuberculosis, and diagnostic methods used. Data was stratified by specific cancer type and then grouped as either hematologic or solid malignancies. Studies that included both types of malignancies were classified as mixed, but data was stratified if reported separately. Study characteristics included design type, recruitment methods, site, as well as type and length of follow-up.

Study quality was assessed with a standardized tool based on a modified version of the Newcastle-Ottawa scale [10], where selection, exposure, detection, and attrition bias were assessed. We did not assess small study effects (eg, publication bias) as this is not reliable for studies of cumulative incidence (proportions) [11].

Data Synthesis and Analyses

The main outcome was cumulative incidence rate (CIR) of tuberculosis calculated by the number of new tuberculosis cases/number of cancer patients at risk occurring during the study period per 100 000. To explore heterogeneity, the data were stratified by tuberculosis incidence in the study country, cancer type (hematologic and solid and mixed types), and in the pre- and post-1980 time periods. Six studies from the United States accounted for 98% of all cancer cases and were of higher quality. The main metaanalysis was performed on these studies in order to reduce differences due to varying tuberculosis incidence, diagnostic capacity, therapeutic regimens, and access to healthcare within different countries. For all studies the CIRs were transformed with arcsine to minimize the effect of standard error variance and pooled with a random effects model using the *metaprop* and *metagen* default commands of the meta package (3.4-1) in R (version 3.1.3) [12, 13]. These estimates were backtransformed, and results were presented as CIR. Arcsine and logarithmic transformations were compared in a sensitivity analysis. Heterogeneity was estimated with I^2 and classified as low, moderate, and high level corresponding to I^2 values of 25%, 50%, and 75%, respectively [14].

To adjust for risk of prior tuberculosis exposure, incidence rate ratios (IRRs) and 95% confidence intervals were estimated by tuberculosis incidence in cancer patients from each study/tuberculosis incidence in the general population of the country. Tuberculosis incidence rates (IRs) in the general population were calculated as the mean tuberculosis IRs/year during the study period ± 1 year from the country in which each study was conducted. Annual country-specific tuberculosis IRs were obtained from World Health Organization estimates from 1990 to 2015 or published national reports on tuberculosis incidence for years prior to 1990 [15]. Given that tuberculosis is a reportable disease in most countries and the majority of tuberculosis cases are symptomatic and diagnosed, these data are considered to be the most accurate estimates of tuberculosis in the general population. Tuberculosis incidence in study countries were defined as high incidence >100/100 000, intermediate 30–100/100 000, or low <30/100 000 [16]. This category was assigned to studies based on reported tuberculosis incidence after 1980 as the United States had tuberculosis incidence rates >30/100 000 in the years prior to 1980. Studies were stratified into pre- and post-1980s because tuberculosis rates in the United States were much higher before (up to 90/100 000) compared to after the 1980s (<12/100 000) and because there was 1 large study from both Sloan Kettering [17, 18] and MD Anderson [19, 20] before and after the 1980s.

A sensitivity analysis of a subset of 13 of the 23 studies that had included person-time of follow-up to determine the risk of tuberculosis over time after diagnosis. Tuberculosis IR per 100 000 persons/year during study follow-up among cancer patients was calculated by the number of incident tuberculosis cases/mean follow-up × N. For studies that reported a median and/or range of follow-up, the median was used to estimate follow-up time.

RESULTS

Included Studies

Electronic database and hand searching yielded 6843 unique articles. After screening titles and abstracts, the full texts of 260 articles were reviewed (Appendix Figure 1). A total of 23 studies reporting 593 tuberculosis cases occurring in 324 041 cancer patients over 7 decades were included. The CIRs of tuberculosis in these studies, stratified by tuberculosis incidence in study country and cancer type, were described (Table 1 and Table 2 and

Table 1. Cumulative Tuberculosis Incidence and Incidence Rate Ratios by Cancer Type and Country Tuberculosis Incidence, 1950–2011

Study, Country, Duration	Age Range, a y	Cancer Type	Follow-up Time, mo	N cancer	N Tuberculosis	General Population IR/100,000 (95% CI)	Overall CIR/100,000 (95% CI) /IRR	Hematologic Cancers (CIR /IRR)						Solid Cancers (CIR/IRR)				
								Overall (95%CI)	Acute Leukemia	Chronic Leukemia	Hodgkin's Lymphoma	Non-Hodgkin's Lymphoma	Other	Overall IRR (95%CI)	Head or Neck	Lung	Breast	Other
High tuberculosis incidence																		
Au et al 2000 [28] Hong Kong; 1988–1999	56 (33–83)	H	72	18	3	124 (105, 142)		16667 (3578–41418) 134										
Advani and Banavali 1989 [21] India; 1986–1987	NR	H		441	20	217[a] (216–217)		4535 (2792–6918) 21	2247[b] 10		6818 31	1905 8.8	50000[c] 230					
Liu et al 2015 [33] Taiwan; 1998–2011	48 (36–61)	H	47	1082	19	1079 (107, 108)		1756 (106–2729) 16										
Khan et al 2005 [25] India; 2001–2002	34 (8–80)	H		188[d]	30	216 (215–216)		15957 (11033–21990) 74	19231 89	122445 53	7692 36	25581 118	12903 60					
Mishra et al 2006 [23] India; 2003–2004	36[e] 2 (6–48)	H		128[f]	7	213 (212, 231.2)			5469 26									
Kumar et al 2003 [32] India; 1990–2002	52 (26–65)	Auto-HSCT Multiple myeloma	26	50	1	168 (125, 210)		2000 (51–10647) 12										
Raza et al 2008 [34] Pakistan; 2002–2007	28 (7–54)	Allo-HSCT Myeloid leukemia	47 42–53	37	2	231 (185, 278)		5405 (661–18195) 23										
Singh et al 2013 [38] India; 2008–2011	47[e] ± 16	S Lung	NR	662	6	188 (179197)								906 5.0				
Stefan et al 2008 [26] South Africa; 1991–2005	3.8 (0–15)	M		625	57	407 (406, 407)	9120[g] (6981–11655) 22											
Wessels et al 1992 [39] South Africa; 1983–1990	6[e] (0–14)	M		278	13	301 (213, 422)[h]	4676 (2513–7864) 16											
Intermediate tuberculosis incidence																		
Colonna et al 1987 [29] Algeria; 1980–1985	28 (4–66)	H	36 8–78	82	1	38 (23, 54)		1220 (31–60610) 32										
Ibrahim et al 1996 [30] Saudi Arabia; 1985–1994	42[a] (16–74)	H	32 4–98	73	4	31 (21, 41)		5479 (1513–13440) 177										
Silva et al 2005 [22] Brazil; 1990–2000	48 (10–9)	H		917	24	72 (71–73)		2617 (1684–3869) 37	535 7.5	4762 67	1724 24	3548 50	2247 31					

Table 1. Continued

Study, Country, Duration	Age Range, a y	Cancer Type	Follow-up Time, mo	N cancer	N Tuberculosis	General Population IR/100,000 (95% CI)	Overall CIR/100,000 (95% CI) /IRR	Hematologic Cancers (CIR /IRR)						Solid Cancers (CIR/IRR)				
								Overall (95%CI)	Acute Leukemia	Chronic Leukemia	Hodgkin's Lymphoma	Non-Hodgkin's Lymphoma	Other	Overall IRR (95%CI)	Head or Neck	Lung	Breast	Other
Kim et al 2008 [31] South Korea; 2001–2004	58 (15–90)	S	36 0–47	1809	11	82 (71, 92)								608 (304–1085) 7.4				
Low tuberculosis incidence																		
Saarinen 1984 [36] Finland; 1975–1983	0–15	H	60 24–102	100	1	18 (15, 22)		1000 (25–5446) 56										
Rödel et al 2005 [35] Germany; 1992–1995	39 16–73	H	122 11–135	22	1	19 (16, 22)		4545 (115–22 844) 239										
Siracusano et al 2004 [37] Italy; 1999–2001	56 32–69	H	44 2–50	29	1	9 (8, 10)		3448 (87–17 764) 383										
Papac 1985 [24] United States; 1968–1982	54 (34–84)	S	NR	191	6	14.95 (14, 15)									3141 210			
Alhashimi et al 1988 [27] United States; 1975–1982	59[e] (40–69)	S		257	2	13 (10, 15)								778 (94–2783) 60				
Kaplan et al 1974 [17] United States; 1950–1971	54[e]	M		58 245[i]	195	36 (35–36)	335 (290–385) 9.4	728 (502–1021) 21	318 9.0		957 27	828 23		307 (262–358) 8.6	512 14	916 26	190 5.3	177 5.0
Feld et al 1976 [19] United States; 1968–1973	60 (17–73)	M		10 033[j]	30	18 (17–18)	300 (202–427) 17		374 21		87 4.9			322 (210–471) 18	732 42	321 18	51 2.9	314 18
Kamboj and Sepkowitz 2006 [18] United States; 1980–2004	58 (9mo–82)	M		186 843	103	8.6 (8–9)	55 (45–67) 6.3	205 (144–282) 24	120 14	61 7.0	204 24	231 27		39 (30–49) 4.5	135 16	52 6.1	41 4.8	30 3.5
Libshitz et al 1997 [20] United States; 1989–1994	55[e] (21–88)	M		61 931	56	10 (9, 10)	90 (68–117) 9.1	255 (154–398) 26	504 51	172 17	321 32	178 18		68 (48–94) 6.8	155 16	136 14		50 5.1

Tuberculosis incidence was defined as high if >100/100 000, as intermediate if 30–100/100 000, and as low if <30/100 000 after 1980 [16]. Confidence intervals (CIs) for population incidence rate were calculated using the formula: log(IR) ± (1.96*√1/tuberculosis cases), where IR is mean of IRs during study duration ±1 year and tuberculosis cases where mean of cases during study duration ±1 year. CIs for cumulative incidence rates were calculated using the Clopper-Pearson method ("exact" binomial interval). CIs for cancer subtypes are shown in forest plots (Appendix Figures 3, 4, and 5).

Abbreviations: CI, confidence interval; CIR, cumulative incidence rate; HSCT, hematopoietic stem cell transplantation; IR, incidence rate; IRR, incidence rate ratio. Cancer type: H, hematologic; S, solid; M, mixed; NR, not reported.

[a]Data on tuberculosis cases and rates for 1986–1987 in India could not be found; data on 1990 were used.

[b]Acute leukemia included patients with acutely lymphoblastic leukemia (n = 45) and acute nonlymphoblastic leukemia (n = 44). Tuberculosis was found in 2 patients, 1 in each type of leukemia.

[c]Among 10 patients with hairy cell leukemia, 5 experienced tuberculosis infection.

[d]The total number of patients in this study was 213; however, we removed 25 bone marrow transplant (BMT) for noncancer hematologic malignancies, thus 188 patients with a hematologic malignancies were included.

[e]Age is reported as median (years) unless indicated as mean.

[f]The total number of patients in this study was stated as 130; however, 2 patients (both with tuberculosis) were removed from our calculations since tuberculosis was diagnosed before cancer diagnosis.

[g]The annual cumulative incidence reported in the study was of 9135/100 000.

[h]The authors estimated the population rate to be 360/100 000 and a standardized morbidity ratio of 11.5 for tuberculosis in children with cancer (or incidence of tuberculosis 4150/100 000 in children with cancer).

[i]Calculated only for cancers for which the total number of cancer cases was available.

[j]The total number of patients in this study was stated as 90 022; however, only 10 033 patients with a particular cancer were described. Since no additional information was given for the other 79 989 cases, we used 10 033 in our calculation of total cumulative incidence.

Table 2. Summary of Cumulative Incidence Rates and Incidence Rate Ratios of Tuberculosis

Stratification	No. of Studies	Tuberculosis Cases	No. of Cancer Patients	Pooled CIR/100 000 (95% CI)	I2 for CIR (%) (95% CI)	P Value	Pooled IRR (95% CI)
All studies (N = 23)							
Overall	23	590	324 729	1432 (1069–1847)	97 (97–98)	<0.001	25 (17–37)
High tuberculosis incidence	10	156	3509	5080 (2564–8390)	92 (88–95)	<0.001	22 (14–37)
Intermediate	4	40	2881	1884 (510–4101)	86 (67–94)	<0.001	34 (10–122)
Low	12	394	319 329	316 (173–501)	97 (96–98)	<0.001	25 (15–42)
Cancer type and tuberculosis incidence							
Hematologic	14	198	33 119	2505 (1514–3736)	95 (93–96)	<0.001	39 (26–57)
High tuberculosis incidence	5	77	1857	6873 (2530-13 130)	93 (86–96)	<0.001	34 (16–75)
Intermediate	3	29	1072	2686 (1449–4288)	19 (0–92)	0.291	62 (19–201)
Low	6	92	30190	418 (187–742)	83 (63–92)	<0.001	31 (19–49)
Solid	8	319	290 620	334 (169–554)	98 (96–98)	<0.001	12 (8–22)
High tuberculosis incidence	1	6	662	906 (328–1770)	N/A	-	5 (2–11)
Intermediate	1	11	1809	608 (302–1019)	N/A	-	7 (4–13)
Low	6	302	288 149	244 (97–457)	98 (97–99)	<0.001	17 (9–32)
Hematopoietic stem cell transplantation High tuberculosis incidence	2	3	87	3253 (581–7981)	0	-	19 (6–58)
Mixed cancers High tuberculosis incidence	2	70	903	6869 (3146–11890)	84 (N/A)[a]	-	20 (15–28)
US studies only (N = 6) [17-20, 24, 27]							
Overall	6	392	318 188	254 (111–456)	98 (97–99)	<0.001	17 (10–29)
<1980	4	233	74 212	407 (230–633)	76 (33–91)	0.006	34 (12–97)
>1980	2	159	251 419	71 (41–109)	88 (N/A)	0.0045	8 (5–11)
Hematologic cancers	3	89	30 039	291 (186–420)	70 (45–83)	<0.001	25 (20–31)
<1980	1	33	4532	728 (502–997)	N/A	N/A	21 (12–34)
>1980	2	56	25 508	219 (165–280)	0[a]	0.444	26 (20–34)
Acute leukemia	3	14	5146	276 (92–558)	60 (0–89)	0.082	19 (6–60)
<1980	1	4	1258	318 (83–705)	N/A	N/A	9 (3–24)
>1980	2	10	3888	268 (26–761)	79 (N/A)[a]	0.030	29 (8- 101)
Chronic leukemia	2	4	3379	111 (27–252)	0[a]	0.330	14 (5–37)
Hodgkin's lymphoma	3	22	4848	439 (107–994)	81 (40–94)	0.006	27 (17–41)
<1980	1	14	1463	957 (523–1520)	N/A	N/A	27 (16–46)
>1980	2	8	3385	234 (99–425)	0[a]	0.550	27 (13–53)
Non-Hodgkin's lymphoma	3	38	12 554	345 (119–689)	84 (54–95)	0.002	24 (17–33)
<1980	1	15	1811	828 (463–1298)	N/A	N/A	23 (14–39)
>1980	2	23	10 743	213 (135–310)	0[a]	0.572	24 (16–36)
Other (>1980)	1	11	4113	267 (133–449)	N/A	N/A	31 (17–56)
Solid cancers	6	302	288 149	212 (132–310)	95 (93–96)	<0.001	12.8 (8–20)
<1980	4	196	62 237	413 (241–631)	91 (84–94)		19 (10–36)
>1980	2	103	225 912	64 (40–94)	0[a]		7 (5–12)
Breast	3	42	48 398	87 (13–227)	91 (76–97)	<0.001	5 (4–7)
<1980	2	29	16 702	128 (25–309)	67 (N/A)	0.081	5 (4–7)
>1980	1	13	31 696	41 (22–66)	N/A		5 (3–8)
Head and neck	5	78	22 245	447 (182–830)	90 (80–95)	<0.001	31 (13–71)
<1980	3	61	10 338	884 (350–1686)	78 (29–93)	0.010	48 (11–210)
>1980	2	17	11 907	143 (83–218)	0[a]	0.784	16 (10–25)
Lung	5	68	31 355	326 (63–795)	95 (92–97)	<0.001	17 (9–34)
<1980	3	50	6309	645 (259–1204)	67 (0–91)	0.048	26 (20–34)
>1980	2	18	25 046	83 (23–179)	72 (N/A)[a]	0.060	9 (4–20)
Other	4	111	186 151	106 (38–208)	96 (92–98)	<0.001	6 (4–10)
<1980	2	56	28 888	220 (115–358)	58 (N/A)[a]	0.122	9 (3–32)
>1980	2	55	157 263	38 (20–60)	72 (N/A)[a]	0.060	4 (4–6)

Tuberculosis incidence was defined as high if >100/100 000, as intermediate if 30–100/100 000, and as low if <30/100 000 after 1980 [16].

Abbreviations: CI, confidence interval; CIR, cumulative incidence rate; IRR, incidence rate ratio.

[a] Confidence interval for I^2 could not be estimated for fewer than 3 studies [14].

Table 3. Overall Quality Assessment of Included Studies

Number of Studies	Type of Bias Risk of Bias	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Quality	Importance
US Studies include in Meta-analysis*							
6/6	Selection Low/Moderate	Low/Moderate	Low	Low	Low	Moderate	Important
6/6	Exposure Low						
6/6	Detection Low						
All studies*							
20/23	Selection Low/Moderate	Moderate	Moderate	Low	Moderate/High	Low/Moderate	Important
23/23	Exposure Low						
6/10 7/13	Detection Low Moderate/High						
Person-time estimation studies							
10/13	Selection Moderate	Moderate	Moderate	Low	High	Low	Important
13/13	Exposure Low						
6/13 7/13	Detection Low Moderate/High						
13	Attrition Low						

Selection Bias: *Low:* Recruited in a setting that is likely to include all eligible cancer patients. *Moderate:* Recruited in a specific setting that is unlikely to include all eligible cancer patients. *High:* Recruited in a highly specialized setting that will not include all eligible cancer patients.

Exposure Bias: *Low:* Subjects had a pathological diagnosis of cancer. *High:* Subjects had a clinical diagnosis of cancer or had an unclear or unspecified method of diagnosis for their cancer.

Detection Bias: *Low:* Subjects tested had a bacteriological or pathological diagnosis of TB. *Moderate:* Some subjects had a clinical diagnosis of TB.

High: There was no mention of how TB cases were diagnosed.

Attrition Bias: *Low:* All subjects were followed up. Moderate: Only study duration was reported.

Appendix Figure 2) [17–39]. Cancer patients from 6 US studies accounted for 98% of all cancer patients at risk (n = 317 243) [17–20, 24, 27]. Metaanalyses of these studies, overall and stratified by cancer type and study period, are reported in Table 2 and in Appendix Figures 3 and 4.

The study quality of all 23 identified studies and the 4 types of bias are summarized in Table 3 and detailed in Appendix Table 2. The overall quality of the data was judged to be low to moderate because all studies recruited patients from a single center and there was moderate to high detection bias in one third of studies (7/23) given that cases were detected clinically (response to tuberculosis treatment) in 3 studies, and there was no description of how tuberculosis cases were diagnosed in another 4 studies [17–39]. The quality of the 6 US studies was better and was estimated to be moderate. The body of data from the person-time studies (n = 13) was judged to be low due to moderate to high detection bias in half the studies and serious imprecision due to small study size and very low numbers of tuberculosis cases [27–39].

Tuberculosis Cumulative Incidence

In all 23 studies, the CIR of tuberculosis in patients with hematologic malignancies reflected the incidence in the country of origin, which was highest in high tuberculosis–incidence countries (6873/100 000 population) and lower in intermediate- and low-incidence countries (2686 and 418/100 000 population, respectively). There was a similar decreasing gradient of tuberculosis incidence by country tuberculosis incidence for solid cancers (Table 2). Despite stratification by cancer type, tuberculosis incidence in study country and study period among the 23 studies, there was a residual high level of heterogeneity.

In the metaanalysis of the 6 US studies, CIR decreased significantly and by 3-fold for hematologic cancers pre- and post-1980 (728 vs 219/100 000 population) but the IRR remained similar (21 vs 26; Table 2, Appendix Figures 3 and 4). Rates in acute leukemia did not change over the study period, whereas rates decreased among those with lymphoma (Table 2, Figure 1). The CIR for solid cancers decreased by more than 6-fold over the study period from 413 to 64/100 000 in the pre- vs post-1980 studies (Table 2, Figure 2). The IRR decreased from 19 to 7 over this time period, with an overall estimate of 12.8. The greatest decrease in rates occurred in those with head and neck cancers (884 to 143/100 000) and lung cancer (645 to 83/100 000; Table 2, Figure 2). Head and neck and lung cancers had an IRR of 16 and 9 compared to the general population, respectively, post-1980. Incidence rates of breast and other tumors after 1980 were much lower, with a CIR of 41/100 000 and an IRR

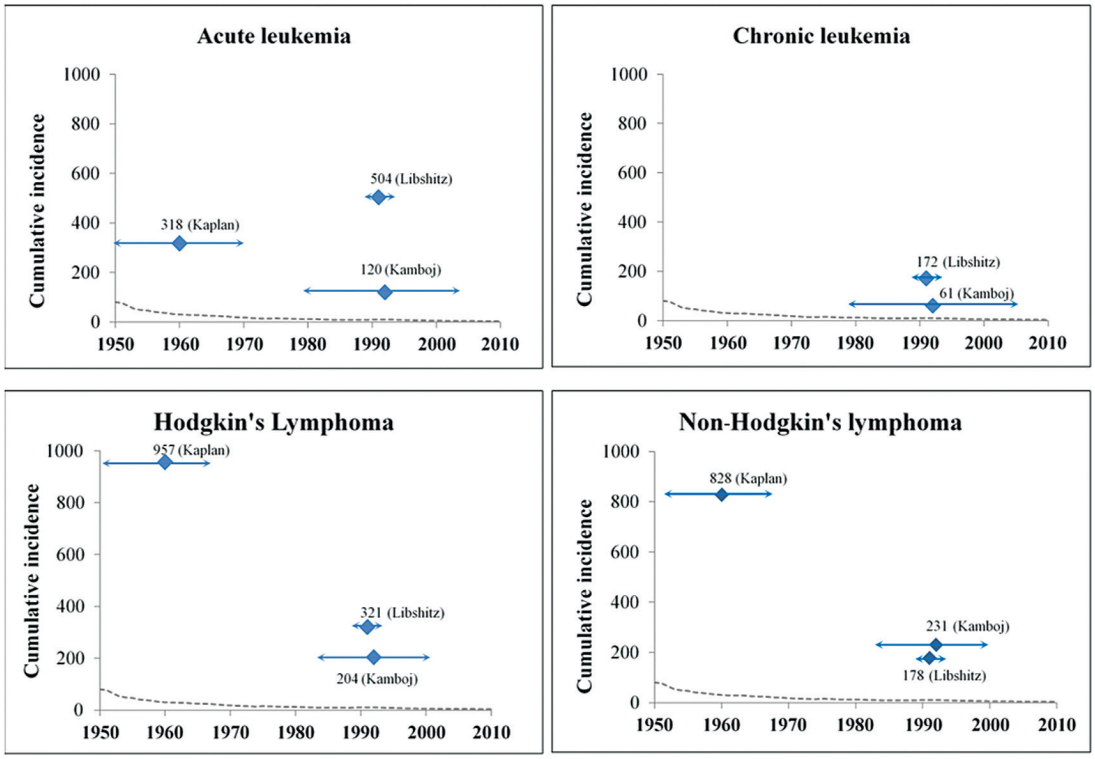

Figure 1. Cumulative tuberculosis incidence rates stratified by hematologic cancer type in the US population over time (1950–2004). Symbols represent the cumulative incidence rate for each study per 100 000. The studies' periods were centered; arrows show the beginning and end of each study inclusion period. The dashed line represents the US tuberculosis incidence rate per 100 000 population. The studies included are Kamboj et al 2006 [18], Kaplan et al 1974 [17], and Libshitz et al 1997 [20].

of 5. After 1980, hematologic cancer patients had the highest rate of active tuberculosis, with a CIR/100 000 of 219 and an IRR of 26 followed by head and neck (143 vs 16), lung (83 vs 9), and breast and other solids cancers (40 vs4). There was high residual heterogeneity across all estimates for cumulative incidence despite stratification by cancer subtype and year of study (Table 2).

Sensitivity Analysis

The descriptive characteristics of the 13 studies that reported on median or mean follow-up time are listed in Table 1 [27–39]. A total of 65 cases of tuberculosis were identified in 4499 cancer patients from 11 countries and spanned 4 decades (1975–2013) (Appendix Table 3 and Figure 5). Included studies were small, with a mean of 285 study participants (range, 18–1809) and a mean of 5 tuberculosis cases (range, 1–19) (Table 1). Median length of follow-up ranged from 26 to 122 months (median of medians = 46 months). The majority of studies reported on hematologic malignancies [27, 31, 38]. The tuberculosis incidence was higher in high tuberculosis–incidence countries and higher in hematologic vs solid tumors, consistent with results from the cumulative incidence studies (Appendix Table 3). The annual tuberculosis incidence per year after cancer diagnosis could not be estimated from the data, thus the time to tuberculosis diagnosis after cancer diagnosis and the time period at greatest risk could not be estimated.

DISCUSSION

This metaanalysis in the 6 US studies showed that rates of active tuberculosis decreased significantly among all cancer types over the 6-decade study period in a low tuberculosis–incidence setting. Hematologic cancer patients had the highest rates of active tuberculosis, followed by head and neck cancers, lung cancer, and breast cancer patients. Our study results support the contention that all types of cancer increase the risk of the development of active tuberculosis, but with varying degrees. This is likely due to both intrinsic immunosuppression due to the cancer itself, the immunosuppressive effects of chemotherapy, or other host factors that may increase the susceptibility to both cancer and tuberculosis.

Although the rate of tuberculosis in patients with hematologic malignancy decreased over the study period, the relative risk compared to the US general population remained high. The magnitude of active tuberculosis risk supports the importance of targeted LTBI therapy for this group with a lower threshold of tuberculin skin testing (TST) of 5 mm. In the review of all studies the risk of developing active tuberculosis in those with hematologic malignancies was highest in high tuberculosis–incidence countries, which is likely due to the risk of recent

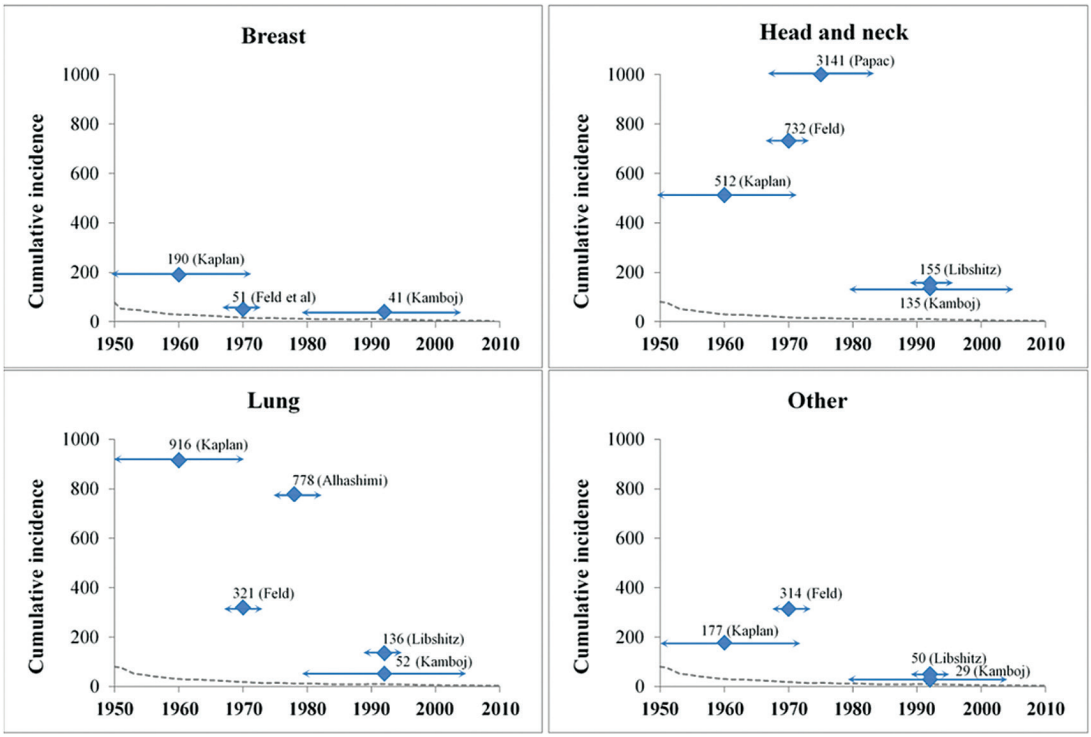

Figure 2. Cumulative tuberculosis incidence rates stratified by solid cancer type in the US population over time (1950–2004). Symbols represent the cumulative incidence rate per 100 000 for each study. The studies' periods were centered; arrows show the beginning and end of each study inclusion period. The dashed line represents the US tuberculosis incidence rate per 100 000 population. The studies included are Alhashimi et al 1988 [27], Feld et al 1976 [19], Kamboj et al 2006 [18], Kaplan et al. 1974 [17], Libshitz et al 1997 [20], and Papac et al 1985 [24]. Other cancers included the following: Feld et al: cervix, skin, prostate, testicle, bladder; Kaplan et al: cervix, ovary, vulva, uterus, stomach, colon, basal cell, prostate, bladder, kidney, thyroid, thymus, and fibrosarcoma; Kamboj et al: prostate, testicle, cervix, colorectal, and other; and Libshitz et al: not specified.

infection as well as latent tuberculosis reactivation during immune suppression in this setting.

The incidence of active tuberculosis in patients with head and neck cancers (HNSCC) decreased by more than 6-fold over the study period in the United States, while the relative risk decreased but remained very high. The increased tuberculosis risk in these patients may be confounded by the association of heavy smoking and drinking as they are independent risk factors for developing active tuberculosis. It is unclear if risk of HNSCC is principally through the direct impairment of antituberculosis immunity by cigarette smoking or alcohol consumption or the association of these risk factors with poverty, malnutrition, and low socioeconomic status (SES). The dramatic decrease in incidence of tuberculosis in those with head and neck cancers in the pre- and post-1980 period may be due to decreasing tuberculosis rates, as well as the change in etiology of head and neck cancers associated risk factors and treatment modalities. Non-human papillomavirus (HPV)–associated HNSCC typically occurs in low- to middle-class males who are heavy smokers and drinkers, whereas HPV-associated HNSCC occurs in young nonsmoking males of high SES. Between 1998 and 2004, the incidence of HPV-positive HNSCC in the United States increased by 225%, whereas HPV-negative cancers decreased by 50% [40]. Treatment modalities for head and neck cancer evolved from using intensive radiotherapeutic regimens to directed beam therapy over the study period [7]. Improved supportive care over the study period led to decreased risk of severe malnutrition, which is another known risk factor for tuberculosis reactivation and may be another factor leading to decreased HNSCC rates.

The incidence of tuberculosis in lung cancer patients decreased dramatically over the study period in the United States, with the relative risk decreasing but remaining high after 1980. The increased risk of tuberculosis in those with lung cancer may be due to local immunologic effect of the cancer but also to confounders such as heavy cigarette smoking and alcohol consumption. We do not have an explanation for the dramatic decreased risk of tuberculosis in lung cancer patients over the study period other than lower exposure to active tuberculosis after 1980. Active tuberculosis occurred concurrently or soon after the cancer diagnosis in more than half of the patients with head and neck and lung cancer in 2 large studies included in our metaanalysis [17, 20]. This highlights the importance of screening these patients for active tuberculosis at diagnosis and, if absent, to screen and treat for LTBI.

In our metaanalysis, breast cancer and other solid tumors had a risk of developing active tuberculosis of 41/100 000 and an IRR of 5 compared to the US population. Although the risk is

not as high as for hematologic, head and neck, and lung cancers, the number of patients at risk is very large. In the Kamboj et al study, the risk of developing active tuberculosis in the United States compared to the foreign-born population was 25 vs 100/100 000 population [18]. Based on this finding, the authors recommended that the US-born population with solid tumors other than head and neck cancers should not be screened for LTBI due, in part, to the associated risk of hepatotoxicity with LTBI therapy. While the mean age of developing solid cancer is between 50 and 60 years, the emergence of shorter-course rifampin-based therapies without age-related hepatotoxicity may justify LTBI screening and therapy for foreign-born populations with solid cancers.

The strength of our systematic review and metaanalysis is that it included a large number of cancer patients over 6 decades and there was sufficient detail to stratify the results by cancer type. The majority of patients in the included studies (98%) were from the United States, which reduced heterogeneity. The results of this study should be generalizable to other low tuberculosis–incidence settings with a moderate level of migration. One important limitation of our study is that follow-up time was not reported in most studies and we were unable to estimate the annual risk of developing active tuberculosis after cancer diagnosis or to estimate the time period at greatest risk for developing active tuberculosis. Some studies spanned 25 years during which tuberculosis rates decreased and cancer therapies evolved, but we were not able to estimate the risk of tuberculosis by decade. There was potential differential tuberculosis case detection bias between those with and without cancer. Case detection may have been higher among cancer patients as a result of closer monitoring and lower in the general population due to missed undiagnosed cases who died or self-healed. We were unable to stratify for important variables, as there is limited data available on TST status, country of birth, and underlying co-morbidities including smoking, alcohol, and human immunodeficiency virus status.

CONCLUSIONS

Our study results highlight the increased risk of active tuberculosis in all patients with cancer. Those with hematologic malignancies and head and neck are at the highest risk and should be targeted for LTBI screening and treatment as per published guidelines [2, 3]. Other groups to consider for screening for LTBI and treatment are all lung cancer patients as they are at high risk and the foreign born population with breast and other cancers as they have a moderate increased risk of developing active tuberculosis.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Financial support. C. P. Y. is supported by a Chercheur-boursier clinicien career award from the Fonds de recherche du Québec–Santé (FRQS).

Potential conflicts of interest. All authors: No potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Getahun H, Matteelli A, Abubakar I, et al. Management of latent *Mycobacterium tuberculosis* infection: guidelines for low tuberculosis burden countries. Eur Respir J **2015**; 46:1563–76.
2. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recomm Rep **2000**;49:1–51.
3. Menzies D, Alvarez G, Khan K. Treatment of latent tuberculosis infection. Canadian Tuberculosis Standards 7th Edition **2014**; http://www.respiratory-guidelines.ca/sites/all/files/CTB_Standards_EN_Chapter%206.pdf
4. American Cancer Society. Cancer Facts & Figures 2016. **2016**. Accessed 2016-02-20.
5. Canadian Cancer Society. Cancer statistics at a glance. http://www.cancer.ca/en/cancer-information/cancer-101/cancer-statistics-at-a-glance/?region=qc. Accessed 2016-02-20.
6. Morrison VA. Immunosuppression associated with novel chemotherapy agents and monoclonal antibodies. Clin Infect Dis **2014**; 59:S360–4.
7. Cognetti DM, Weber RS, Lai SY. Head and neck cancer: an evolving treatment paradigm. Cancer **2008**; 113:1911–32.
8. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg **2010**; 8:336–41.
9. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA **2000**; 283:2008–12.
10. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
11. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. J Clin Epidemiol **2014**; 67:897–903.
12. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. J Epidemiol Community Health **2013**; 67:974–8.
13. Rücker G, Schwarzer G, Carpenter J, Olkin I. Why add anything to nothing? The arcsine difference as a measure of treatment effect in meta-analysis with zero cells. Stat Med **2009**; 28:721–38.
14. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med **2002**; 21:1539–58.
15. TB burden estimate. http://www.who.int/tb/country/data/download/en/.
16. World Health Organization. Global Tuberculosis Report. **2015**.
17. Kaplan MH, Armstrong D, Rosen P. Tuberculosis complicating neoplastic disease. A review of 201 cases. Cancer **1974**; 33:850–8.
18. Kamboj M, Sepkowitz KA. The risk of tuberculosis in patients with cancer. Clin Infect Dis **2006**; 42:1592–5.
19. Feld R, Bodey GP, Gröschel D. Mycobacteriosis in patients with malignant disease. Arch Intern Med **1976**; 136:67–70.
20. Libshitz HI, Pannu HK, Elting LS, Cooksley CD. Tuberculosis in cancer patients: an update. J Thorac Imaging **1997**; 12:41–6.
21. Advani SH, Banavali SD. Pattern of infection in hematologic malignancies: an Indian experience. Rev Infect Dis **1989**; 11:S1621–8.
22. Silva FA, Matos JO, de Q Mello FC, Nucci M. Risk factors for and attributable mortality from tuberculosis in patients with hematologic malignances. Haematologica **2005**; 90:1110–5.
23. Mishra P, Kumar R, Mahapatra M, et al. Tuberculosis in acute leukemia: a clinico-hematological profile. Hematology **2006**; 11:335–40.
24. Papac RJ. Medical aspects of head and neck cancer. Cancer Invest **1985**; 3:435–44.
25. Khan B, Ahmed P, Ullah K, Hussain CA, Hussain I, Raza S. Frequency of tuberculosis in haematological malignancies and stem cell transplant recipients. J Coll Physicians Surg Pak **2005**; 15:30–3.
26. Stefan DC, Kruis AL, Schaaf HS, Wessels G. Tuberculosis in oncology patients. Ann Trop Paediatr **2008**; 28:111–6.
27. Alhashimi MM, Citron ML, Fossieck BE Jr, et al. Lung cancer, tuberculin reactivity, and isoniazid. South Med J **1988**; 81:337–40.
28. Au WY, Kwong YL, Ma SK, et al. Hairy cell leukemia in Hong Kong Chinese: a 12-year retrospective survey. Hematol Oncol **2000**; 18:155–9.

29. Colonna P, Andrieu JM, Ghouadni R, et al. Hodgkin's disease, clinical stages IA to IIIB: combined modality therapy (3 MOPP followed by curative and prophylactic radiotherapy including the spleen). Six-year results. Eur J Haematol **1987**; 39:356–61.
30. Ibrahim EM, Bunyan RF, al-Mulhim FA, al-Nabhan AA, Ibrahim RE. Chemotherapy with MECOP-B for intermediate-grade and high-grade non-Hodgkin's lymphoma in Saudi Arabia: clinical results and analysis of prognostic factors. Acta Haematol **1996**; 96:126–34.
31. Kim HR, Hwang SS, Ro YK, et al. Solid-organ malignancy as a risk factor for tuberculosis. Respirology **2008**; 13:413–9.
32. Kumar L, Raju GM, Ganessan K, et al. High dose chemotherapy followed by autologous haemopoietic stem cell transplant in multiple myeloma. Natl Med J India **2003**; 16:16–21.
33. Liu CJ, Hong YC, Teng CJ, et al. Risk and impact of tuberculosis in patients with chronic myeloid leukemia: a nationwide population-based study in Taiwan. Int J Cancer **2015**; 136:1881–7.
34. Raza S, Ullah K, Ahmed P, Khan B, Kamal MK. Post-transplant outcome in chronic myeloid leukaemia. J Coll Physicians Surg Pak **2008**; 18:615–9.
35. Rödel S, Engert A, Diehl V, Reiser M. Combination chemotherapy with adriamycin, cyclophosphamide, vincristine, methotrexate, etoposide and dexamethasone (ACOMED) followed by involved field radiotherapy induces high remission rates and durable long-term survival in patients with aggressive malignant non-Hodgkin's lymphomas: long-term follow-up of a pilot study. Leuk Lymphoma **2005**; 46:1729–34.
36. Saarinen UM. Severe infections in childhood leukemia. A follow-up study of 100 consecutive ALL patients. Acta Paediatr Scand **1984**; 73:515–22.
37. Siracusano L, Balzarotti M, Magagnoli M, et al. FluCyD combination in low-grade lymphomas: an active regimen for selected patients. Haema **2004**;7:357–62.
38. Singh N, Madan K, Aggarwal AN, Gupta N, Das A, Behera D. Pleuropulmonary tuberculosis following chemotherapy for lung cancer at a tertiary care center in India. JPMER **2013**;47:177–80.
39. Wessels G, Hesseling PB, Gie RP, Nel E. The increased risk of developing tuberculosis in children with malignancy. Ann Trop Paediatr **1992**; 12:277–81.
40. Marur S, Forastiere AA. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. Mayo Clin Proc **2016**; 91:386–96.