Risk of tuberculosis in patients with solid cancers and haematological malignancies: a systematic review and meta-analysis

Claudia C. Dobler [1,2,3], Kelvin Cheung[1,2], John Nguyen[1,2] and Andrew Martin[4]

Affiliations: [1]Department of Respiratory Medicine, Liverpool Hospital, Liverpool (Sydney), NSW, Australia. [2]South Western Sydney Clinical School, University of New South Wales, Sydney, NSW, Australia. [3]Clinical Management Group, Woolcock Institute of Medical Research, University of Sydney, NSW, Australia. [4]NHMRC Clinical Trials Centre, University of Sydney, NSW, Australia.

Correspondence: Claudia C. Dobler, Department of Respiratory Medicine, Liverpool Hospital, Elizabeth Street, Liverpool, NSW 2170, Australia. E-mail: c.dobler@unsw.edu.au

@ERSpublications
Screening and treatment for latent tuberculosis infection should be considered in children with cancer
http://ow.ly/lpSQ30dxyam

Cite this article as: Dobler CC, Cheung K, Nguyen J, *et al*. Risk of tuberculosis in patients with solid cancers and haematological malignancies: a systematic review and meta-analysis. *Eur Respir J* 2017; 50: 1700157 [https://doi.org/10.1183/13993003.00157-2017].

ABSTRACT There is uncertainty regarding whether patients with cancer should be screened for latent tuberculosis infection (LTBI). We performed a systematic review and meta-analysis to estimate the relative incidence of tuberculosis (TB) in cancer.

We searched MEDLINE and Embase for studies published before December 21, 2016. We included studies that evaluated the incidence of TB in patients with solid cancers and haematological malignancies relative to a reference group (study control or general population). A pooled estimate of the incidence rate ratio (IRR) was obtained using standard meta-analysis methods.

The search strategy identified 13 unique studies including 921 464 patients with cancer. The IRR of TB for adult patients with cancer was 2.61 (95% CI 2.12–3.22; I^2=91%). In haematological cancers, the IRR was 3.53 (95% CI 1.63–7.64; I^2=96%); and in solid cancers in adults, it was 2.25 (95% CI 1.96–2.58; I^2=91%). The highest IRR was found in children with haematological malignancies or solid cancers (IRR 16.82, 95% CI 8.81–32.12; I^2=79%).

Considering the limited duration of maximum immunosuppression in cancer and reduced cumulative lifetime risk of TB because of reduced life expectancy, children, but not adults, appear to be at a sufficient level of risk to warrant systematic screening for LTBI.

This article has supplementary material available from erj.ersjournals.com

Received: Jan 23 2017 | Accepted after revision: May 26 2017

Support statement: C.C. Dobler was supported by an Australian National Health and Medical Research Council fellowship (APP1090198). The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication. Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: None declared

Introduction

Tuberculosis (TB) is one of the major infectious causes of disease and death globally [1]. There is currently a renewed interest in screening and treatment of latent tuberculosis infection (LTBI), as a possible means to achieve control of the global tuberculosis epidemic [2]. In most infected people, TB remains clinically asymptomatic and microbiologically inactive (latent). However, in approximately 5 to 10% of latently infected persons, the infection will cause active TB at some point during their lifetime [3]. The risk of TB reactivation is increased in persons with immunocompromising conditions, such as HIV infection [4], chronic renal failure [5] or diabetes mellitus [6], and in persons on immunocompromising medications, such as tumour necrosis factor-α (TNF-α) inhibitors [7, 8]. The World Health Organization (WHO) recommends targeted screening of high risk groups in high or upper middle income countries with a TB incidence of <100 per 100 000 per year [9], as preventive TB treatment can significantly reduce the risk of TB reactivation [10].

Patients with solid cancers and haematological malignancies are immunocompromised because of the disease itself, and as a consequence of chemotherapy. It is therefore reasonable to assume that the risk of TB reactivation would be increased in people with cancer, and consider LTBI screening and treatment in this group. There is, however, a paucity of information on whether patients with cancer should be screened for LTBI. The British National Institute for Health and Care Excellence (NICE) recommendations state that people who "have a haematological malignancy", "are having chemotherapy" and "have had a gastrectomy" (for gastric cancer or other reasons) are at increased risk of developing TB, but they do not provide any specific screening and treatment recommendations for these groups [11]. Joined guidelines of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC), endorsed by the Council of the Infectious Diseases Society of America (IDSA), identify persons with "some hematologic disorders (*e.g.*, leukemias and lymphomas)" and "other specific malignancies (*e.g.*, carcinoma of the head or neck and lung)" as high risk, and recommend the consideration of treatment of LTBI in these groups [12]. The evidence that has informed these guidelines was derived from an informal synthesis of individual studies conducted from the 1950s to 1970s that had important methodological limitations: the frequency of TB among patients with cancer was expressed as a proportion (cumulative incidence) rather than an incidence rate; thus not adjusting for the observation period/ time at risk. Relative risk estimates were calculated by dividing the cumulative incidence of TB in a cancer cohort by an incidence rate (per year) in the general population [13], or were not calculated at all [14].

A recently published systematic review and meta-analysis by Cheng *et al.* [15] on the risk of TB in patients with cancer also had significant methodological limitations. That analysis did not exclude studies that contained information on cumulative incidence of TB only, and used annual country-specific TB incidence rates that were unadjusted for potential confounders obtained from WHO for comparison [15]. Comparing the cumulative incidence of TB in patients with cancer (in one included study cumulated over a study period of 25 years [16]) with an annual TB incidence in the general population would have resulted in overestimation of the risk of TB in patients with cancer. Equally, using the general population as a comparator group, without any adjustment for potential confounders, particularly age, would have resulted in overestimation of the risk of TB in patients with cancer. The authors' conclusion of the study that individuals living in the United States with haematologic, head and neck, and lung cancers would benefit from targeted LTBI screening and therapy thus has to be questioned.

Another systematic review published in 2014 focused on lung cancer only, and evaluated the prevalence of TB in those patients [17]. It was not the goal of that review to establish causality (the authors were aware that there is a bidirectional causal link between lung cancer and TB [18]).

There remains considerable uncertainty about whether patients with cancer should be screened for LTBI, with the intention to offer preventive treatment, if there is evidence of LTBI. The risk of TB in cancer patients remains imprecisely quantified, despite the need for contemporary evidence to inform guidelines and public health policy on LTBI screening and treatment in this setting. We have consequently performed a systematic review and meta-analysis to estimate the relative incidence of TB in people with cancer (solid cancers as well as haematological malignancies) in comparison to the general population.

Methods

Search strategy and selection criteria

We searched the electronic databases MEDLINE, including Epub Ahead of Print, In-Process & Other Non-Indexed Citations (1946 to December 21, 2016) and Embase (1947 to December 21, 2016), through OVID for studies that examined the risk of TB in cancer (solid tumours and haematological malignancies). The search strategy was discussed and agreed upon by the authors, and advice was sought from an experienced research librarian. The following search terms were used to identify citations relevant to (1) tuberculosis, (2) risk and (3) cancer, respectively: (1) tuberculosis, *Mycobacterium tuberculosis*; (2)

risk, incidence, probability, proportion, frequency; and (3) neoplasm, cancer, malignancy, tumour, carcinoma, oncology and metastases. The detailed search strategy is available in the supporting information (S1 Appendix). Articles resulting from these searches and relevant references cited in those articles were reviewed. In addition, we screened reference lists of systematic reviews, literature reviews and meta-analyses identified through the search. Articles published in any language were included.

Eligible studies evaluated the incidence of TB in patients with cancer, relative to a reference group (control group specified for the study, or general population with or without adjustment for potential confounding factors), allowing for estimation of the relative risk of TB in cancer. We included studies reporting on pulmonary, as well as extra-pulmonary TB. A diagnosis of TB could either have been based on microbiological results, or symptoms and chest radiographic findings consistent with TB. Studies were included that reported on solid cancers or haematological malignancies in any age group. Studies that reported on the risk of TB in patients who received a stem cell transplant were excluded. We excluded cross-sectional (prevalence) studies, studies that used cumulative incidence (incidence proportion) without adjustment for the time at risk, studies in which a diagnosis of TB preceded the cancer diagnosis and studies in which the temporal relationship between TB and cancer was not specified. Furthermore, we excluded studies that only examined the risk of TB in pre-defined subgroups of cancer patients that were considered to have an increased pre-test probability of TB infection (*e.g.* because of abnormal chest radiographs). Abstracts, editorials, case reports, conference abstracts, systematic reviews, literature reviews and meta-analyses were not included. Three reviewers (C.C. Dobler, K. Cheung and J. Nguyen) independently screened titles and abstracts and then the full text of papers identified as potentially eligible by at least one reviewer. Disagreements between the reviewers were resolved by discussion. This systematic review follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for reporting meta-analyses and systematic reviews of observational studies [19].

Data analysis

Three reviewers (C.C. Dobler, K. Cheung and J. Nguyen) independently extracted data from included studies onto a standardised data sheet. Variables recorded from each article included the following:

Publication year, country, study design, number of patients, incidence of TB in the cancer group, incidence of TB in the reference group (*i.e.* a control sample or applicable general population statistic), time of follow-up, demographic and clinical characteristics of patients, previous TB (based on history, chest radiographs, *etc.*), prevalence of LTBI based on the tuberculin skin test (TST) or interferon gamma release assay (IGRA) and treatment of LTBI, type of cancer, information on chemotherapy and TB definition for the purpose of the study. Risk of bias in the included studies was evaluated using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies [20].

For studies in which an IRR was not specifically reported, the IRR was calculated by dividing the incidence of TB in cancer patients by the incidence of TB in the reference group. If not reported, a 95% CI for the IRR was determined, assuming the frequency of observed cases followed a Poisson distribution [21]. We accepted hazard ratios (HRs), the ratio of the hazard (*i.e.* the "instantaneous" rate) in cancer patients compared to a control group or the general population, as estimates of IRRs [22]. For studies that reported a crude IRR, as well as an adjusted or standardised IRR, we included the adjusted or standardised IRR (aIRR and standardised incidence ratio (SIR), respectively) in the meta-analysis. We used DerSimonian and Laird random effects meta-analyses [23] with the Comprehensive Meta-Analysis v3.0 software (Biostat, Englewood, NJ, USA) to estimate pooled IRRs and 95% CIs. We assessed the magnitude of heterogeneity using the I^2 statistic, and tested for its statistical significance using the Q-statistic. Subgroup analysis was pre-specified for age groups (adults *versus* children), as well as for any specific solid tumours or haematological malignancies.

As there was a maximum of one event (TB diagnosis) per patient or control in the included studies, the IRR expressed the relative risk for TB, and the terms were thus used interchangeably.

Results

The search strategy identified 11 006 unique citations, of which 42 were included for full-text review and 13 studies met the inclusion and exclusion criteria, involving a total of 921 464 patients with cancer (figure 1). Table 1 summarises the characteristics of the included studies [24–36].

Study characteristics

All 13 studies were observational and retrospective. Five studies were based on information from national databases and eight were cohort studies at a single hospital site. Five studies were from Taiwan, five from South Korea, two from South Africa, and one from the USA. Four studies included patients with different haematological and solid cancers; one study each, reported only on the risk of TB in patients with

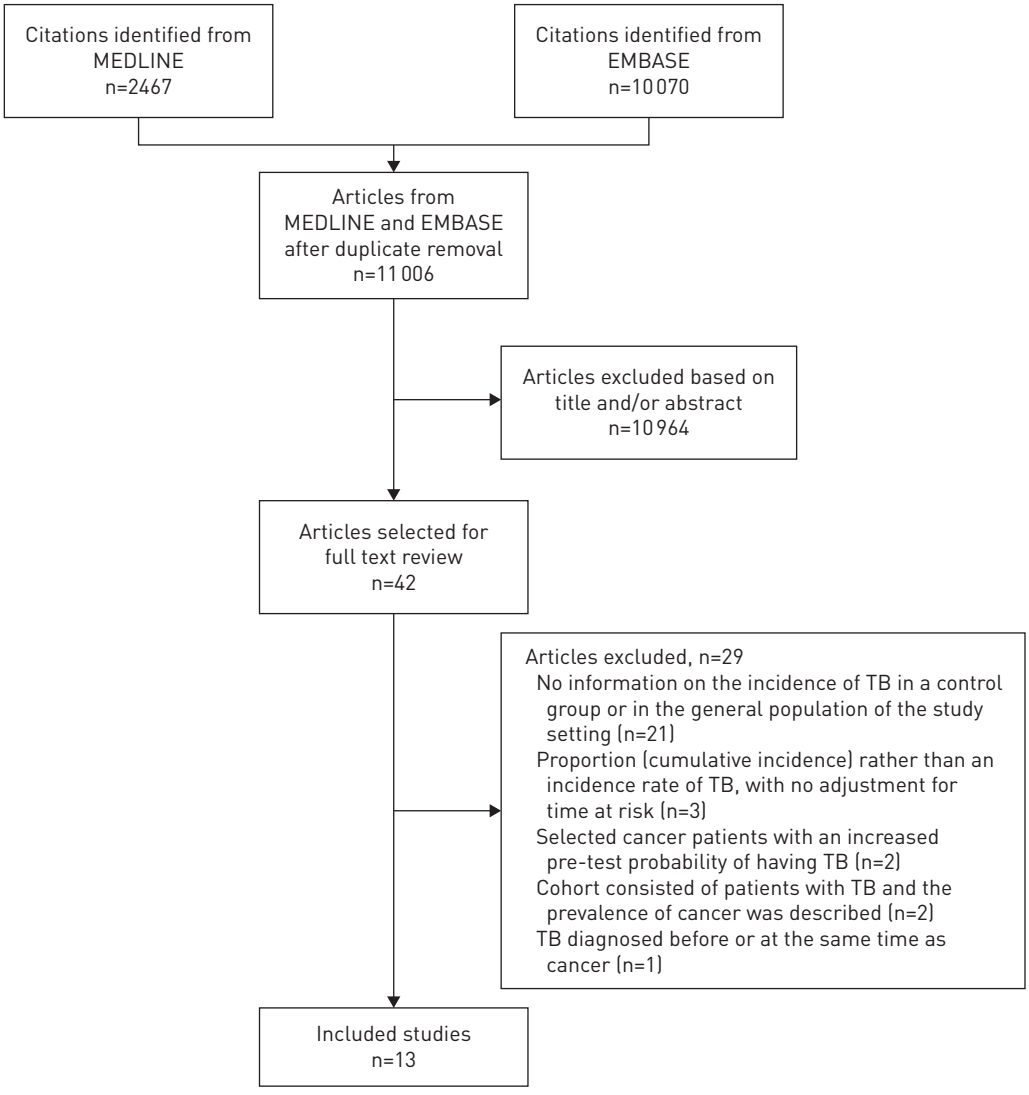

FIGURE 1 Flowchart of study selection.

different haematological or solid cancers, respectively; and seven studies included only patients with a specific cancer type (five studies on gastric cancer, one study on lung cancer and one study on chronic myeloid leukaemia (CML)). Two studies from South Africa focused on children (aged up to 15 years) with different haematological and solid malignancies. Study size ranged from 257 to 855 382 participants.

A common reason for the exclusion (from this systematic review) of studies that evaluated the risk of TB in patients with cancer after a full-text review was the lack of information on the incidence of TB in an appropriate reference group. Furthermore, several studies were excluded because they expressed TB cases among cancer patients as a proportion (cumulative incidence) rather than an incidence rate, with no adjustment for the time at risk [16, 37, 38]. Two studies were excluded after full-text review because they reported the risk of TB in cancer patients with an increased pre-test probability of having TB (based on the assessment of clinicians [39] or chest radiographic abnormalities suspicious for TB [40]). Another study was excluded because TB was diagnosed simultaneously with cancer in the majority of cases [41]. In two excluded studies, the examined cohort consisted of patients with TB, and the prevalence of cancer was described [42, 43].

Adjustments for confounding in studies included in the meta-analysis are outlined in table 1.

Relative risk of TB in patients with cancer

The overall IRR of TB among adult persons with cancer was 2.61 (95% CI, 2.12–3.22) (figure 2). There was considerable heterogeneity between studies (Q-statistic, p<0.001, I^2=91%). The pooled IRR of the two

TABLE 1 Characteristics of included studies

Study, year of publication [ref.] Study period	Population and setting	Cancer type	Cancer treatment	Control/general population	TB cases and incidence in cancer group	TB cases and incidence in control group	Rate ratio (95% CI)	Adjustment for potential confounders
Wu 2011 [24] 2000–2007	n=16 487 cancer patients in Taiwan (no age restriction) Taiwan national population (NHI database)	All solid organ cancers and haematological malignancies, IRRs given for cancer subgroups	not specified	n=65 948 controls from the NHI database without cancer, matched for age and sex	205 cases out of 16 487 patients; no information on median follow-up time TB incidence: 339/100 000 person-years	489 cases out of 65 948 controls TB incidence: 202/100 000 person-years	aIRR 1.67 (1.42–1.96)	controls matched for age and sex, and IRR adjusted for age, sex and comorbidities in multivariate analysis
Seo 2016 [25] 2008–2012	n=855 382 patients with newly diagnosed cancer in Korea, aged 20 to 99 years, identified from the National Health Insurance Review Assessment Service (HIRA) excluded: patients with lung cancer	thyroid cancer (n=170 597), gastric cancer (n=253 158), hepatocellular carcinoma (n=83 512), colon cancer (n=77 903), breast cancer (n=75 801), haematological malignancy (n=32 026), pancreatic cancer (n=22 822), biliary tract cancer (n=20 452), other cancers (n=219 111)	not specified	General population of Korea aged 20 to 99 years	5745 cases out of 855 382 patients (1 589 876 patient-years of follow-up), median follow-up time: 1.6 years TB incidence 361.3/100 000 person-years of follow-up	230 247 cases in the general population TB incidence: 125.3/100 000 person-years	SIR 2.22 (2.17–2.27)	TB incidence was standardised for age and sex
Chen 2011 [26] 1996–2009	n=2984 adult cancer patients (>18 years) HIV+ excluded National Taiwan University Hospital, Taiwan	haematological malignancies AML (n=1011), ALL (n=276), lymphoma (n=956), MM (n=307), CML/CLL (n=169), SAA/MDS (n=265)	not specified	general population of Taiwan	53 cases out of 2984 patients; no information on median follow-up time TB incidence: 120/100 000 per year	number of TB cases and size of control population not given TB incidence: 62/ 100 000 in 2008	IRR 1.94[#] (1.48–2.53)[¶]	no adjustment
Liu 2015 [27] 1998–2011	n=1082 patients with newly diagnosed CML, aged 20 years and older, identified from NHI database in Taiwan	CML	4.5% had a haematopoietic stem cell transplantation, 23.3% received interferon-alpha, all CML patients received at least one type of Bcr-Abl tyrosine kinase inhibitor	Subjects without CML from the NHI database in Taiwan, matched for age, sex and comorbidities	19 cases out of 1082 patients, median follow-up time: 3.9 years TB incidence: 401/100 000 person-years	59 cases out of 10 820 matched subjects in the control cohort TB incidence: 105/100 000 person-years	Crude HR 3.65 (2.18–6.12) aHR 3.76 (2.24–6.31)	controls matched by age, sex and comorbidities, and HR adjusted for age, sex and comorbidities in multivariate analysis

Continued

TABLE 1 Continued

Study, year of publication [ref.] Study period	Population and setting	Cancer type	Cancer treatment	Control/general population	TB cases and incidence in cancer group	TB cases and incidence in control group	Rate ratio (95% CI)	Adjustment for potential confounders
Kim 2008 [28] 2001	n=1809 cancer patients in a tertiary hospital in South Korea median age 58 years (range, 15–90) excluded: HIV+, silicosis, immunosuppressive therapy other than corticosteroids for cancer treatment	gastric cancer (n=663), liver cancer (n=382), lung cancer(n=348), colon cancer (n=277) and breast cancer (n=139) IRRs can be calculated for cancer subgroups based on information provided	n=1132 (62.6%) had surgery, n=757 (41.8%) had chemo therapy, of gastric cancer patients, 459 out of 663 (69%) had gastrectomy	n=1809 controls, patients attending the same hospital during the same time period for the treatment of hypertension, or benign breast or gynaecological tumours	11 cases out of 1809 patients, median follow-up time 29 (range 0–47) months TB incidence: 307/100 000 person-years	5 cases out of 1809 patients TB incidence: 77/100 000 person-years	IRR 4.69 (1.52–14.46)	controls matched for age, sex and comorbidities, and IRR adjusted for sex, comorbidity and presence of old healed TB
Huang 2011 [29] 2000–2006	n=2177 cancer patients at Cancer Center of Taipei Veterans General Hospital, Taiwan median or mean age and age range were not specified; excluded: prior gastrectomy, prior TB treatment, active TB within 6 months before the diagnosis of gastric cancer and receiving anti-TB treatment, concurrent TB with gastric cancer treatment (+/−2 months)	gastric cancer (subtypes: adenocarcinoma, signet cell carcinoma, mucinous adenocarcinoma, GIST, others)	not specified	general population in Taiwan in 2006	44 cases out of 2177 patients (5578 person-years), follow-up time ranged from 0 to 10 years Crude incidence: 788/100 000 person-years Standardised incidence: 134.3 (80.9–187.6)/ 100 000 person-years	TB incidence: 63.7/100 000 population in 2006	SIR 2.11 (1.57–2.84)[¶]	TB incidence was standardised for age and sex
Kim 2014 [30] 2003–2009	n=2684 patients who underwent gastrectomy for gastric cancer, at a tertiary referral hospital in South Korea; excluded: diagnosis of concurrent pulmonary TB, on TB treatment for 3 months before gastrectomy	gastric cancer: adenocarcinoma (81%), signet-ring cell carcinoma (17%), mucinous adenocarcinoma (2%), mixed carcinoma (0.4%), GIST (0.1%)	Information on chemotherapy was not available	General population of South Korea	35 cases out of 2684 patients, median duration of follow-up: 4 years Crude incidence: 327/100 000 person-years Age-standardised incidence: 404/100 000 person-years	TB incidence in the general population: 78/100 000 in 2010	SIR 5.2 (4.08–6.62)	TB incidence was standardised for age

Continued

TABLE 1 Continued

Study, year of publication [ref.] Study period	Population and setting	Cancer type	Cancer treatment	Control/general population	TB cases and incidence in cancer group	TB cases and incidence in control group	Rate ratio (95% CI)	Adjustment for potential confounders
Choi 2015 [31] 2001–2008	n=1935 patients with early gastric cancer stage IA, aged 24 to 88 years, identified from the database of the Center for Gastric Cancer of the National Cancer Center, Korea; excluded: cases with TB before or within 3 months after gastrectomy	gastric cancer, stage IA	77.3% had a gastrectomy and 22.7% had an endoscopic resection of the gastric cancer	General population of Korea in the same age group as the patients with gastric cancer	31 cases out of 1935 patients (9272 patient-years of follow-up), median follow-up time: 4.9 years TB incidence: 334/100 000 person-years	TB incidence: 87/100 000 in 2013	IRR whole cohort 3.84[#] (2.70–5.46)[¶]	TB incidence was standardised for age
Fang 2015 [32] 2000–2011	n=36 972 patients newly diagnosed with gastric cancer, aged 20 years and older, identified from the NHI database in Taiwan; excluded: patients whose diagnosis of TB occurred before enrolment, patients who were diagnosed with TB within 30 days of the diagnosis of gastric cancer	gastric cancer	66.9% of patients had major surgery, 52.2% received chemotherapy, 14.3% received radiotherapy	36 972 subjects identified from the NHI database, matched by age, sex and presence of comorbidities	521 cases out of 36 972 patients; no information on median follow-up time TB incidence: 523/100 000 person-years	640 cases out of 36 972 matched subjects in the control cohort TB incidence: 344/100 000 person-years	Crude HR 1.50 (1.33–1.68) aHR 1.59 (1.41–1.79)	controls matched by age, sex and comorbidities, and HR adjusted for age, sex and comorbidities in multivariate analysis
Jung 2016 [33] 2007–2009	n=1776 patients who underwent gastrectomy for gastric cancer, aged 20 to 89 years, at a tertiary referral hospital in Seoul, South Korea; excluded: patients who received chemotherapy after gastrectomy, patients who had a history of previous gastrectomy, patients who were treated for TB within 6 months before surgery or developed TB within 2 months after surgery, patients who visited the hospital only once after surgery	gastric cancer	Patients who received chemotherapy after gastrectomy were excluded	General population of South Korea	16 cases out of 1776 patients (7152.5 patient-years), mean duration of follow-up: 4 years TB incidence: 423.7/100 000 person-years	TB incidence: 89.4/100 000 person-years in 2008	SIR 2.22 (1.27–3.60)	TB incidence was standardised for age and sex

Continued

TABLE 1 Continued

Study, year of publication [ref.] Study period	Population and setting	Cancer type	Cancer treatment	Control/general population	TB cases and incidence in cancer group	TB cases and incidence in control group	Rate ratio (95% CI)	Adjustment for potential confounders
Alhashimi 1988 [34] 1975–82	n=257 cancer patients (89 (35%) with latent TB infection based on TST⩾10 mm) without isoniazid prophylaxis, mean age 58.5 years (range 40–69 years) VA Medical Center, Washington DC, USA	lung cancer	all patients received chemotherapy with or without radiotherapy, corticosteroid therapy or both	residents of Washington, DC, USA, ⩾45 years	3 cases out of 257 patients; no information on median follow-up time TB incidence: 1100/100 000/year	number of TB cases and size of control population not given TB incidence: 73/100 000/ year	IRR 15.00[#] (4.84–46.51)[¶]	used the same or a similar age group in the general population for comparison
Wessels 1992 [35] 1983–1990	n=278 patients registered in the Tygerberg Hospital's children's cancer registry (below the age of 15 years); excluded: children with brain tumours and those who died within 6 weeks of cancer diagnosis	haematological and solid (excluding brain tumours)	not specified	general population of South Africa and the Western Cape in 1986	13 cases out of 278 patients (277.5 patient-years of follow-up); no information on median follow-up time TB incidence: 4150/100 000 person-years of follow-up	TB incidence: 360/100 000 among children aged below 15 years	SIR 11.53 (6.69–19.85)[¶]	used the same or a similar age group in the general population for comparison
Stefan 2008 [36] 1991–2005	n=625 children (0–15 years old) undergoing cancer therapy at Tygerberg Hospital, located in a Cape Town area with high TB prevalence; mean age at cancer diagnosis was 5.1 years (median 3.8, range 0–15); excluded: children who completed TB treatment before the cancer diagnosis	haematological and solid	not specified	general population of South Africa aged 0–15 years	57 cases out of 625 patients; no information on median follow-up time Crude incidence: 9135/100 000/year	TB incidence: 407/100 000/ year among children aged 0–15 years	IRR 22.44 (17.31–29.10)[¶]	used the same or a similar age group in the general population for comparison

TB: tuberculosis; NHI: National Health Insurance; IRR: incidence rate ratio; aIRR: adjusted incidence rate ratio; SIR: standardised incidence ratio; CML: chronic myeloid leukaemia; CLL: chronic lymphocytic leukaemia; SAA: severe aplastic anaemia; MDS: myelodysplastic syndrome; HR: hazard ratio; aHR: adjusted hazard ratio; GIST: gastrointestinal stromal tumour; TST: tuberculin skin test.[#]: IRR was not specified in the original study, but was calculated by dividing the incidence of TB in cancer patients by the incidence of TB in the reference group. [¶]: Confidence interval was estimated using the Poisson assumption.

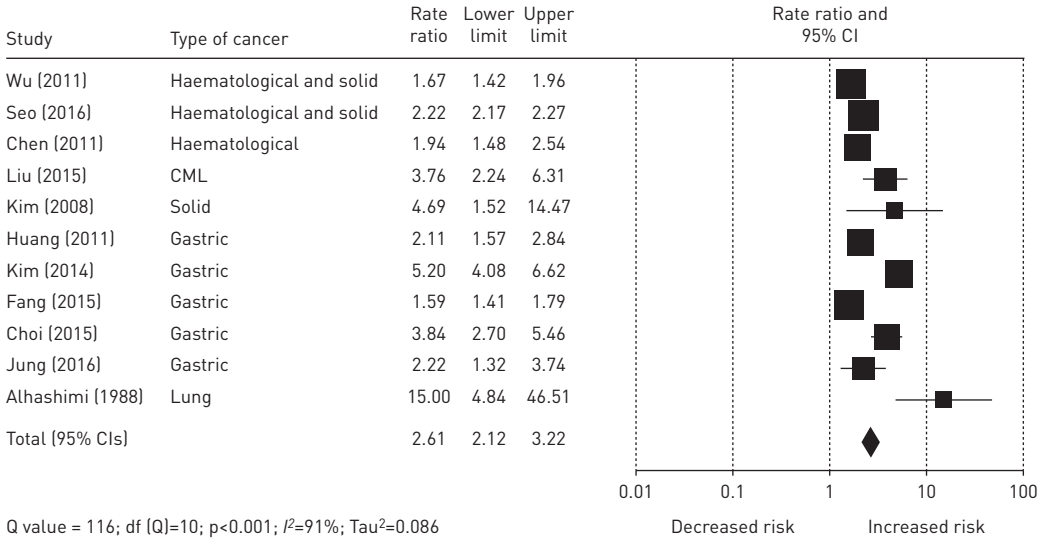

FIGURE 2 Forest plot of relative risk of tuberculosis in all adult cancer studies. CML: chronic myeloid leukaemia.

studies performed in children with haematological and solid malignancies was 16.82 (95% CI 8.81–32.12; Q=5, df=1, p=0.030; I^2=79%) (figure 3).

Subgroup analysis in adult cancer patients

Separate analysis of haematological malignancies and solid tumours (excluding studies that did not present measures of effect size for these two groups separately) yielded an IRR of 3.53 (95% CI 1.63–7.64; Q=82, df=3, p<0.001; I^2=96%) (figure 4) for haematological malignancies, and an IRR of 2.25 (95% CI 1.96–2.58; Q= 341, df=29, p<0.001; I^2=91%) (figure 5) for solid cancers.

Of the solid tumours for which data was available from at least three studies, lung cancer had an IRR of 6.14 (95% CI 1.97–19.20; I^2=76%) (figure 6a), gastric cancer had an IRR of 2.63 (95% CI 1.96–3.52; I^2=93%) (figure 6b), breast cancer had an IRR of 2.17 (95% CI 1.98–2.38; I^2=0%) (figure 6c), liver cancer had an IRR of 2.02 (95% CI 0.83–4.91; I^2=83%) (figure 6d) and colon cancer had an IRR of 2.00 (95% CI 1.16–3.43; I^2=75%) (figure 6e).

Effect of surgery, chemotherapy and/or radiotherapy on TB risk

The majority of reviewed studies provided no detailed information on the number of patients with cancer who had undergone surgery, chemotherapy and/or radiotherapy, and the temporal relationship between treatment and a diagnosis of TB.

Treatment details were available for a number of studies in gastric cancer. A nationwide study from Taiwan did not establish any treatment modality (gastrectomy, chemotherapy or radiotherapy) as an independent risk factor for TB in patients with gastric cancer [32]. Another study from Taiwan found that chemotherapy was associated with a higher risk for TB, compared to gastrectomy and palliative therapy in patients with gastric cancer (SIR 2.91, 2.50 and 1.19, respectively) [29]. A nationwide Korean study in patients with early gastric cancer showed that patients who underwent endoscopic resection showed no increase in the relative risk of TB, compared to the general population; whereas patients who underwent gastrectomy had a hazard ratio of 7.92 (95% CI 1.08–58.16) for the risk of developing TB [31]. Another Korean study found that patients undergoing total gastrectomy had an OR of 3.48 (95% CI 1.25–9.66) for the risk of developing TB, compared to patients who underwent subtotal gastrectomy [33].

Assessment of risk of bias of included studies

The risk of bias assessment, using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies [20], showed that this risk was moderate to low (supplementary Table S1). Risk of bias was mainly related to selection of the reference group (control cohort, not drawn from the same community, during the same period as the cancer cohort), as well as the comparability of the reference group (lack of adjustment/stratification for the most important confounders) and uncertainties regarding the reporting of follow-up. Heterogeneity between studies for all outcomes under evaluation was high, although it was reduced during sub-group analysis for different solid organ tumours (but remained high for most subgroups).

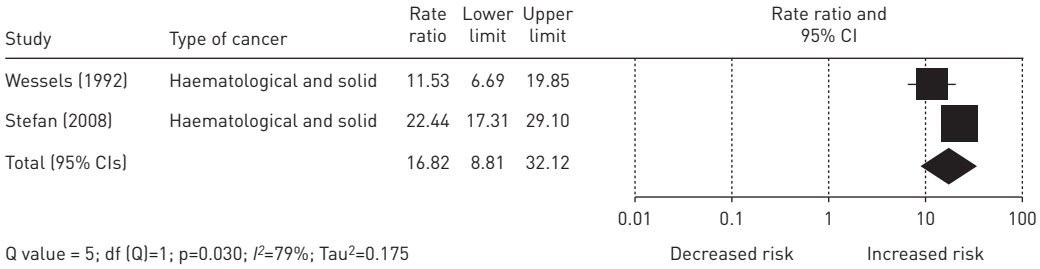

FIGURE 3 Forest plot of relative risk of tuberculosis in children with cancer.

Only one study provided a prevalence estimate of LTBI, based on the TST/IGRA in the study cohort (89/257, 35%), and stated that five patients received LTBI treatment [34]. These patients were, however, excluded from the analysis. No other study indicated whether participants received treatment for LTBI. Six studies, four of which evaluated TB exclusively in gastric cancer, included information on the history of TB treatment and/or radiological evidence of previously healed TB [28–31, 33, 34], with a prevalence of previous TB on chest radiographs ranging from 7% [34] to 17% [28] in the study population. There was a paucity of available information on HIV status. One paediatric study from South Africa reported that six out of 57 children with cancer and TB (11%) were infected with HIV [36]. Two studies excluded HIV-positive individuals [26, 28]. The remainder of the studies disclosed no information on HIV status.

Discussion

The meta-analysis showed a statistically significantly increased risk of TB in cancer patients, compared to the general population. Most solid cancers, for which data from three or more studies were available, were associated with an approximately two-fold increase in the risk of developing TB, compared to the general population. This increase was significant for gastric, breast and colon cancer, but not for liver cancer (IRR 2.02; 95% CI 0.83–4.91). Lung cancer was associated with a six-fold increase in TB. The relative risk of TB in gastric cancer (IRR 2.63, 95% CI 1.96–3.52), which is often treated with gastrectomy (associated with malnutrition [44], a risk factor for TB [45, 46]), was not markedly different from the relative risk in other solid cancers. The relative risk of TB in haematological cancers in adults (IRR 3.53; 95% CI 1.63–7.64) was only moderately higher than that in adults with solid cancers (IRR 2.25; 95% CI 1.96–2.58). The highest relative risk of TB was found in children with haematological malignancies or solid cancers (IRR 16.82, 95% CI 8.81–32.12).

To our knowledge, this is the first meta-analysis to assess the relative risk of TB in haematological malignancies and solid cancers, among studies that include information on a comparator group (controls or general population of the study setting and period). Although significant heterogeneity was noted between included studies, the random effects model that was applied yields estimates that appropriately reflect this variation (*i.e. via* the 95% CIs). Thus, the pooled estimate is not as important as the upper and lower 95% CI of the estimates, in consideration of whether the relative risk is too low (based on the upper 95% CI) to warrant LTBI screening, or sufficiently high (based on the lower 95% CI) to consider LTBI screening.

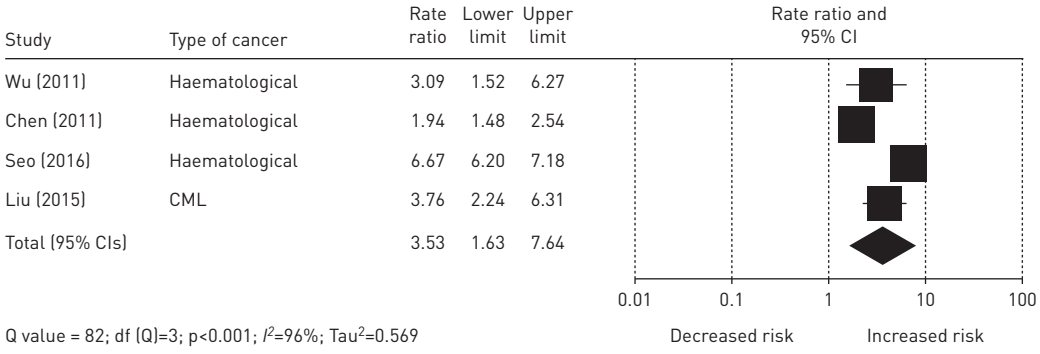

FIGURE 4 Forest plot of relative risk of tuberculosis in adults with haematological malignancies. CML: chronic myeloid leukaemia.

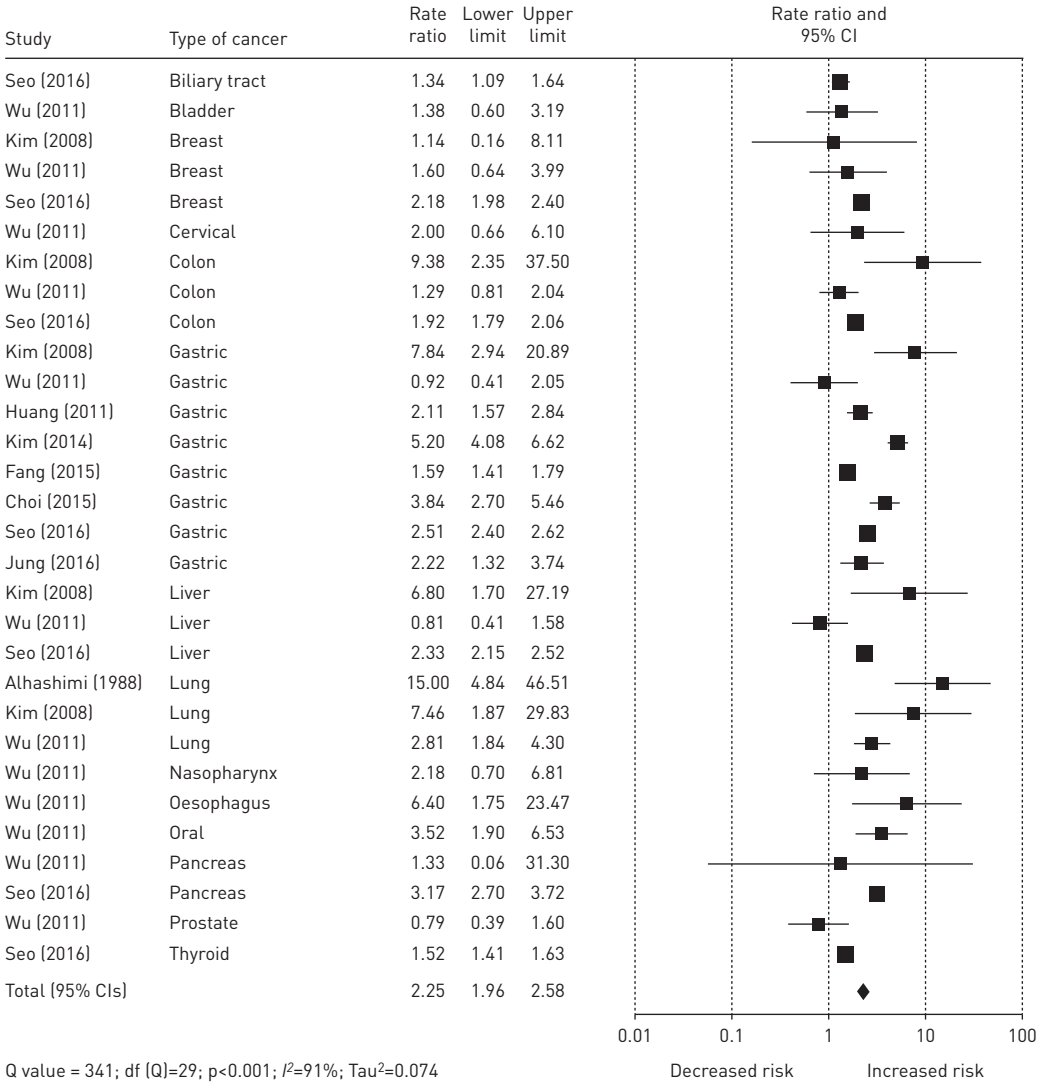

FIGURE 5 Forest plot of relative risk of tuberculosis in adults with different solid tumours.

Children with solid cancers and haematological malignancies have a high relative risk of developing TB, and should be considered for systematic screening and treatment of LTBI. Although both of the included paediatric studies were conducted in South Africa, a setting with a high risk for reinfection with TB, this should not have affected the estimated relative risk of TB, as the control population shared the same risk of exposure. The implementation of LTBI screening and treatment, however, depending on the setting and our recommendations, only applies to high or upper middle income countries with a TB incidence of <100 per 100 000 per year [9].

The findings of this meta-analysis facilitate comparison with the relative risk of TB among other groups with an increased risk of developing TB, and inform screening recommendations for latent TB infection and TB chemoprophylaxis in patients with cancer. The upper 95% CI of the relative risk (RR) of TB in cancer (3.22) is lower than the relative risk in groups currently targeted for LTBI screening and treatment, such as patients with HIV (RR of 50–110 [47, 48]), contacts of patients with active TB (RR of 10.4 during follow-up of 90 days to 2 years after initial healthcare contact, with 1.5% of all TB contacts already diagnosed with TB at initial screening [49]), patients with chronic renal failure (RR of 7.8[5]) and patients being treated with TNF-α inhibitors (RR 1.8–29.3 [50]). The reactivation of TB can occur at any time after initial infection [3], and the estimated cumulative lifetime risk to develop TB is therefore important to inform decisions about LTBI screening and treatment. In chronic conditions, such as diabetes and chronic renal failure, the increased risk associated with the disease can be expected to last a lifetime, without any considerable reduction in life expectancy due to the underlying disease. In cancer, however, immunosuppressive states are more likely to be temporary (*e.g.* during chemotherapy). In addition, life

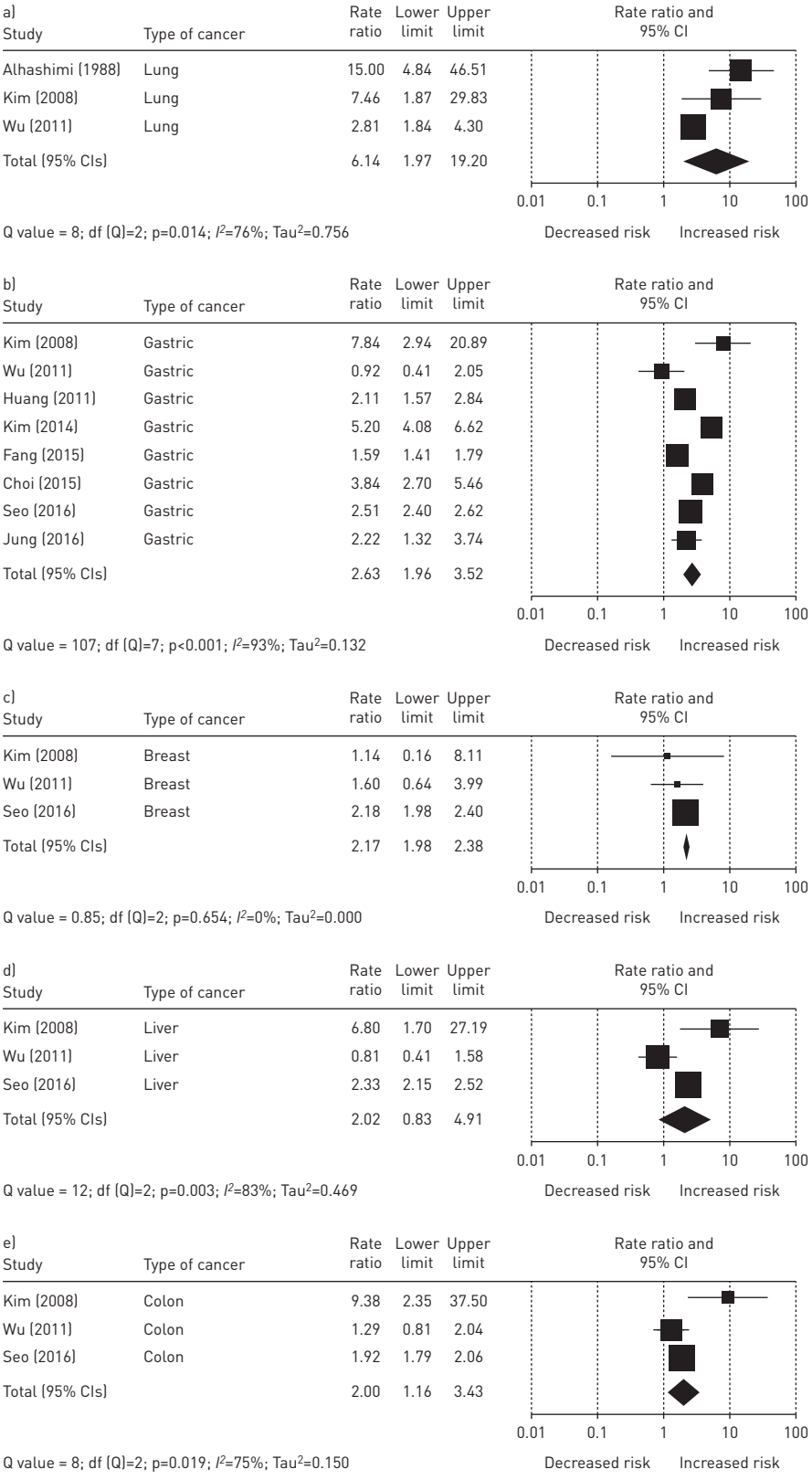

FIGURE 6 a) Forest plot of relative risk of tuberculosis in persons with lung cancer. b) Forest plot of relative risk of tuberculosis in persons with gastric cancer. c) Forest plot of relative risk of tuberculosis in persons with breast cancer. d) Forest plot of relative risk of tuberculosis in persons with liver cancer. e) Forest plot of relative risk of tuberculosis in persons with colon cancer.

expectancy is markedly reduced in many cancers, which reduces the cumulative lifetime risk of developing TB. This has to be considered when comparing the relative risk of TB in cancer patients with that in other immunocompromised groups. Based on these considerations, we suggest that in adult patients with cancer, there is not a sufficiently increased risk of TB to recommend systematic screening and treatment for LTBI, independent of other risk factors. As outlined in the WHO guidelines, the potential harms and benefits of LTBI treatment will need to be weighed on an individual patient basis [9]. The introduction of systematic screening and treatment of LTBI in any group needs to take into account the local context, accessibility, equity, cost and implementation aspects [9]; however, discussion of these aspects is beyond the scope of the present research.

The overall incidence rate (per year) of TB decreases with the time that has elapsed since the diagnosis of cancer (associated with early treatment). This was demonstrated in the largest study that was included in the present meta-analysis (including 855 382 patients with cancer), which showed that the relative risk of TB was highest, immediately after the diagnosis of cancer, and gradually declined over time with a SIR of 3.70 (95% CI 3.57–3.83) for the first 6 months; SIR of 2.19 (95% CI 2.08–2.30) for months 6 to 11; SIR of 1.75 (95% CI 1.67–1.84) for months 12 to 23; and SIR of 1.43 (95% CI 1.36–1.51) for greater than 24 months after diagnosis [25]. In addition to the impaired immunity due to cancer and cancer treatment, more intense medical follow-up and examinations early in the course of cancer disease might result in an increase in the number of diagnosed TB cases. This might result in overestimation of the risk of TB in cancer patients.

Considerations regarding the relative risk of TB during different periods following the diagnosis of cancer are also relevant for interpretation of the present results. Studies with a prolonged follow-up of cancer patients will yield a lower incidence estimate per person-years of follow-up, as the risk of TB would decline with time elapsed since diagnosis. This risk reduction over time was especially prominent in haematological malignancies in the aforementioned large cohort study, in which the SIR was 12.01 (95% CI 10.81–13.30) for the first 6 months following diagnosis, and decreased to a SIR of 2.70 (2.12–3.39) for greater than 24 months after diagnosis [25]. In the present meta-analysis, the pooled IRR in haematological malignancies (in patients aged 15 years or above) of 3.53 (95% CI 1.63–7.64) might have been lower than expected, because of a prolonged follow-up. The TB incidence rates showed a decline with increased follow-up duration, reflecting the reduction in TB risk after initial diagnosis and completion of chemotherapy [51].

One strength of our systematic review was its rigorous methodology, in terms of the inclusion only of studies that provided an incidence rate of TB (rather than a cumulative incidence or prevalence) in patients with cancer, as well as a TB incidence rate in a control/general population. One limitation of the present systematic review was its inability to differentiate between risk arising from cancer per se and that from cancer treatment. The available data also did not allow us to consider the impact of cancer stage. As treatment modalities are chosen based on the cancer stage and expected prognosis, and the follow-up period is shorter in patients with advanced cancer, it is very difficult, if not impossible, to establish the independent effect of treatment modalities and cancer stage on the risk of TB reactivation from cohort studies. As outlined above, variable follow-up times in different studies are likely to have contributed to differences in estimates of TB risk. The included studies did not distinguish between TB caused by recent transmission and TB secondary to reactivation, with only the latter being an indication for LTBI screening.

The use of different reference groups (ranging from matched controls to the unadjusted general population of the study setting) could have added to the heterogeneity identified in the meta-analysis. The lowest quality reference group was the general population of the study setting, without adjustment for potential confounders, particularly age. This could have led to overestimation of the relative risk of TB in populations with a higher incidence of TB among older people (the more likely scenario), or underestimation of the relative risk of TB in populations with a higher incidence of TB among younger people. However, only one study did not adjust for age as a potential confounder [26].

In summary, this meta-analysis showed that patients with cancer have an increased risk of developing TB, compared to the general population. Children with solid cancers or haematological malignancies have a high relative risk of developing TB, and should be considered for systematic screening and treatment of LTBI, especially when they originate from settings with a high TB incidence. In adults with cancer, the relative risk of TB was only modestly increased. The slightly increased risk, paired with the fact that, in many instances, the risk decreases over time since the initial cancer diagnosis, and/or the cumulative lifetime risk is reduced because of reduced life expectancy, suggests that adult patients with cancer do not require systematic screening and treatment for LTBI, independent of other risk factors. Adults with cancer, especially those with haematological malignancies, who have additional risk factors (such as being a migrant from a country with a high TB burden), should be considered for LTBI screening and treatment

on a case-by-case basis. Among the solid cancers, lung cancer has one of the highest risks of TB, but prognosis is often poor [52], and a short mean expected survival might suggest that the benefits of LTBI treatment do not outweigh the associated inconvenience and risks in many patients. While current guidelines describe patients with gastrectomy as a high-risk group for TB, our analysis (which included a number of recent studies on gastric cancer and gastrectomy) showed no marked difference in the risk of TB in patients with gastric cancer, with or without gastrectomy, compared to patients with other solid cancers.

References

1 World Health Organization. Global Tuberculosis Report 2016. www.who.int/tb/publications/global_report/en/ Date last accessed: January 3, 2017.
2 Lonnroth K, Migliori GB, Abubakar I, *et al.* Towards tuberculosis elimination: an action framework for low-incidence countries. *Eur Respir J* 2015; 45: 928–952.
3 American Thoracic Society. Diagnostic standards and classification of tuberculosis. *Am Rev Respir Dis* 1990; 142: 725–735.
4 Getahun H, Gunneberg C, Granich R, *et al.* HIV infection-associated tuberculosis: the epidemiology and the response. *Clin Infect Dis* 2010; 50: Suppl. 3, S201–S207.
5 Dobler CC, McDonald SP, Marks GB. Risk of tuberculosis in dialysis patients: a nationwide cohort study. *PLoS One* 2011; 6: e29563.
6 Dobler CC, Flack JR, Marks GB. Risk of tuberculosis among people with diabetes mellitus: an Australian nationwide cohort study. *BMJ Open* 2012; 2: e000666.
7 Dobler CC. Biologic agents and tuberculosis. *Microbiol Spectr* 2016; 4. doi: 10.1128/microbiolspec.TNMI7-0026-2016
8 Dobler CC. Biological agents and tuberculosis: risk estimates and screening strategies. *Int J Rheum Dis* 2015; 18: 264–267.
9 Getahun H, Matteelli A, Abubakar I, *et al.* Management of latent *Mycobacterium tuberculosis* infection: WHO guidelines for low tuberculosis burden countries. *Eur Respir J* 2015; 46: 1563–1576.
10 Smieja MJ, Marchetti CA, Cook DJ, *et al.* Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database Syst Rev* 2000; (2): CD001363.
11 National Institute for Health and Care Excellence (NICE). Tuberculosis [NG33], section 1.2.4 Managing latent TB in all age groups. January 2016. www.nice.org.uk/guidance/ng33/chapter/Recommendations#latent-tb Date last accessed: January 3, 2017. Date last updated: May, 2016.
12 Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000; 161: S221–S247.
13 Feld R, Bodey GP, Groschel D. Mycobacteriosis in patients with malignant disease. *Arch Intern Med* 1976; 136: 67–70.
14 Kaplan MH, Armstrong D, Rosen P. Tuberculosis complicating neoplastic disease. A review of 201 cases. *Cancer* 1974; 33: 850–858.
15 Cheng MP, Abou Chakra CN, Yansouni CP, *et al.* Risk of active tuberculosis in patients with cancer: a systematic review and meta-analysis. *Clin Infect Dis* 2017; 64: 635–644.
16 Kamboj M, Sepkowitz KA. The risk of tuberculosis in patients with cancer. *Clin Infect Dis* 2006; 42: 1592–1595.
17 Christopoulos A, Saif MW, Sarris EG, *et al.* Epidemiology of active tuberculosis in lung cancer patients: a systematic review. *Clin Respir J* 2014; 8: 375–381.
18 Liang HY, Li XL, Yu XS, *et al.* Facts and fiction of the relationship between preexisting tuberculosis and lung cancer risk: a systematic review. *Int J Cancer* 2009; 125: 2936–2944.
19 Liberati A, Altman DG, Tetzlaff J, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009; 6: e1000100.
20 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
21 Rothman, KJ., Greenland, S. Modern Epidemiology. 2nd Edn. Philadelphia, Lippincott, 1998.
22 Hernan MA. The hazards of hazard ratios. *Epidemiology* 2010; 21: 13–15.
23 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177–188.
24 Wu CY, Hu HY, Pu CY, *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; 15: 125–130.
25 Seo GH, Kim MJ, Seo S, *et al.* Cancer-specific incidence rates of tuberculosis: A 5-year nationwide population-based study in a country with an intermediate tuberculosis burden. *Medicine (Baltim)* 2016; 95: e4919.
26 Chen CY, Sheng WH, Cheng A, *et al.* Clinical characteristics and outcomes of Mycobacterium tuberculosis disease in adult patients with hematological malignancies. *BMC Infect Dis* 2011; 11: 324.
27 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: 1881–1887.
28 Kim HR, Hwang SS, Ro YK, *et al.* Solid-organ malignancy as a risk factor for tuberculosis. *Respirology* 2008; 13: 413–419.
29 Huang SF, Li CP, Feng JY, *et al.* Increased risk of tuberculosis after gastrectomy and chemotherapy in gastric cancer: a 7-year cohort study. *Gastric Cancer* 2011; 14: 257–265.
30 Kim CH, Im KH, Yoo SS, *et al.* Comparison of the incidence between tuberculosis and nontuberculous mycobacterial disease after gastrectomy. *Infection* 2014; 42: 697–704.
31 Choi IJ, Kim YW, Lee HS, *et al.* Risk factors for TB in patients with early gastric cancer: Is gastrectomy a significant risk factor for TB? *Chest* 2015; 148: 774–783.
32 Fang WL, Hung YP, Liu CJ, *et al.* Incidence of and risk factors for tuberculosis (TB) in gastric cancer patients in an area endemic for TB: A nationwide population-based matched cohort study. *Medicine (Baltim)* 2015; 94: e2163.

33 Jung WJ, Park YM, Song JH, *et al.* Risk factors for tuberculosis after gastrectomy in gastric cancer. *World J Gastroenterol* 2016; 22: 2585–2591.
34 Alhashimi MM, Citron ML, Fossieck BE, Jr, *et al.* Lung cancer, tuberculin reactivity, and isoniazid. *South Med J* 1988; 81: 337–340.
35 Wessels G, Hesseling PB, Gie RP, *et al.* The increased risk of developing tuberculosis in children with malignancy. *Ann Trop Paediatr* 1992; 12: 277–281.
36 Stefan DC, Kruis AL, Schaaf HS, *et al.* Tuberculosis in oncology patients. *Ann Trop Paediatr* 2008; 28: 111–116.
37 Libshitz HI, Pannu HK, Elting LS, *et al.* Tuberculosis in cancer patients: an update. *J Thorac Imaging* 1997; 12: 41–46.
38 Ibrahim EM, Uwaydah A, al-Mulhim FA, *et al.* Tuberculosis in patients with malignant disease. *Indian J Cancer* 1989; 26: 53–57.
39 El-Sharif A, Afifi S, El-Dahshan R, *et al.* Characterization of *Mycobacterium tuberculosis* isolated from cancer patients with suspected tuberculosis infection in Egypt: identification, prevalence, risk factors and resistance pattern. *Clin Microbiol Infect* 2012; 18: E438–E445.
40 Karnak D, Kayacan O, Beder S. Reactivation of pulmonary tuberculosis in malignancy. *Tumori* 2002; 88: 251–254.
41 Suzuki Y, Imokawa S, Sato J, *et al.* Cumulative incidence of tuberculosis in lung cancer patients in Japan: A 6-year observational study. *Respir Investig* 2016; 54: 179–183.
42 Ortbals DW, Marr JJ. A comparative study of tuberculous and other mycobacterial infections and their associations with malignancy. *Am Rev Respir Dis* 1978; 117: 39–45.
43 Simonsen DF, Farkas DK, Sogaard M, *et al.* Tuberculosis and risk of cancer: a Danish nationwide cohort study. *Int J Tuberc Lung Dis* 2014; 18: 1211–1219.
44 Scholmerich J. Postgastrectomy syndromes – diagnosis and treatment. *Best Pract Res Clin Gastroenterol* 2004; 18: 917–933.
45 Dai G, Phalen S, McMurray DN. Nutritional modulation of host responses to mycobacteria. *Front Biosci* 1998; 3: e110–e122.
46 Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. *Int J Tuberc Lung Dis* 2004; 8: 286–298.
47 Wood R, Maartens G, Lombard CJ. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. *J Acquir Immune Defic Syndr* 2000; 23: 75–80.
48 Selwyn PA, Hartel D, Lewis VA, *et al.* A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med* 1989; 320: 545–550.
49 Dobler CC, Marks GB. Risk of tuberculosis among contacts in a low-incidence setting. *Eur Respir J* 2013; 41: 1459–1461.
50 Tubach F, Salmon D, Ravaud P, *et al.* Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry. *Arthritis Rheum* 2009; 60: 1884–1894.
51 Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. *Cancer* 2004; 100: 228–237.
52 Goldstraw P, Chansky K, Crowley J, *et al.* The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2016; 11: 39–51.