# OCURRENCIA DE CÁNCER DE PULMÓN DESPUÉS DE UN EPISODIO DE TUBERCULOSIS: REVISIÓN SISTEMÁTICA Y METAANÁLISIS

# LUNG CANCER OCCURRENCE AFTER AN EPISODE OF TUBERCULOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

TESIS PARA OPTAR POR EL TÍTULO PROFESIONAL DE MÉDICO CIRUJANO

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## DEDICATORIA

A nuestras familias.

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Los autores declaran no tener conflictos de interés

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**TABLA DE CONTENIDOS**

## RESUMEN

**Antecedentes:** La tuberculosis genera efectos de salud a largo plazo más allá de la cura, incluyendo enfermedades respiratorias crónicas. Investigamos si la tuberculosis es un factor de riesgo para el cáncer pulmonar posterior. **Métodos:** Buscamos en PubMed, Scopus, Cochrane, Latin American and Caribbean Health Sciences Literature y Scientific Electronic Library Online estudios de cohorte y casos-controles con estimados que midan la asociación entre tuberculosis y cáncer pulmonar posterior. Utilizamos el modelo de efectos aleatorios para el metaanálisis. El estudio se registró en Prospero (CDR42020178362). **Resultados:** De 6240 registros, incluimos 29 estudios de cohorte y 44 casos-controles. El metaanálisis de estimados ajustados por edad y tabaquismo (evaluados cuantitativamente) fue HR 1.51 (IC 95% 1.30–1.76, I2 = 81%; cinco estudios), OR 1.74 (IC 95% 1.42–2.13, I2 = 59%; 19 estudios). La ocurrencia de cáncer pulmonar aumentó en los 2 primeros años después del diagnóstico de tuberculosis (HR 5.01, IC 95% 3.64–6.89; dos estudios), pero luego disminuyó. La mayoría de estudios fueron retrospectivos, tuvieron un riesgo de sesgo moderado a alto y no controlaron para tabaquismo pasivo, exposición ambiental y estado socioeconómico. La heterogeneidad fue alta. **Conclusión:** Documentamos una asociación entre tuberculosis y la ocurrencia de cáncer pulmonar, particularmente en los primeros 2 años. Algunos casos de cáncer pudieron estar presentes durante el diagnóstico de tuberculosis y no se puede determinar causalidad. Se necesitan estudios prospectivos que controlen factores de confusión clave para identificar qué pacientes con tuberculosis tienen el mayor riesgo, así como enfoques rentables para mitigar dicho riesgo.



**Palabras clave:** tuberculosis, cáncer de pulmón, neoplasia de pulmón, revisión sistemática, metaanálisis

## ABSTRACT

**Background:** People with tuberculosis experience long-term health effects beyond cure, including chronic respiratory diseases. We investigated whether tuberculosis is a risk factor for subsequent lung cancer. **Methods:** We searched PubMed, Scopus, Cochrane, Latin American and Caribbean Health Sciences Literature and the Scientific Electronic Library Online for cohort and case–control studies providing effect estimates for the association between tuberculosis and subsequent lung cancer. We pooled estimates through random-effects meta-analysis. The study was registered in PROSPERO (CDR42020178362). **Results:** Out of 6240 records, we included 29 cohort and 44 case–control studies. Pooled estimates adjusted for age and smoking (assessed quantitatively) were hazard ratio (HR) 1.51 (95% CI 1.30–1.76, I2=81%; five studies) and OR 1.74 (95% CI 1.42–2.13, I2=59%; 19 studies). The occurrence of lung cancer was increased for 2 years after tuberculosis diagnosis (HR 5.01, 95% CI 3.64–6.89; two studies), but decreased thereafter. Most studies were retrospective, had moderate to high risk of bias, and did not control for passive smoking, environmental exposure and socioeconomic status. Heterogeneity was high. **Conclusion:** We document an association between tuberculosis and lung cancer occurrence, particularly in, but not limited to, the first 2 years after tuberculosis diagnosis. Some cancer cases may have been present at the time of tuberculosis diagnosis and therefore causality cannot be ascertained. Prospective studies controlling for key confounding factors are needed to identify which tuberculosis patients are at the highest risk, as well as cost-effective approaches to mitigate such risk.



**Keywords:** tuberculosis, lung cancer, lung neoplasm, systematic review, meta-analysis

# Lung cancer occurrence after an episode of tuberculosis: a systematic review and meta-analysis

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After an episode of tuberculosis, an individual is more likely to be diagnosed with lung cancer than a person in the general population. This is most marked within the first 2 years after a tuberculosis diagnosis, but a causal relation cannot be ascertained. https://bit.ly/38I4HMc

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## Abstract

*Introduction:* People with tuberculosis experience long-term health effects beyond cure, including chronic respiratory diseases. We investigated whether tuberculosis is a risk factor for subsequent lung cancer.

*Methods:* We searched PubMed, Scopus, Cochrane, Latin American and Caribbean Health Sciences Literature and the Scientific Electronic Library Online for cohort and case–control studies providing effect estimates for the association between tuberculosis and subsequent lung cancer. We pooled estimatesthrough random-effects meta-analysis. The study was registered in PROSPERO (CDR42020178362).

*Results:* Out of 6240 records, we included 29 cohort and 44 case–control studies. Pooled estimates adjusted for age and smoking (assessed quantitatively) were hazard ratio (HR) 1.51 (95% CI 1.30–1.76, $I^2$=81%; five studies) and OR 1.74 (95% CI 1.42–2.13, $I^2$=59%; 19 studies). The occurrence of lung cancer was increased for 2 years after tuberculosis diagnosis (HR 5.01, 95% CI 3.64–6.89; two studies),but decreased thereafter. Most studies were retrospective, had moderate to high risk of bias, and did not control for passive smoking, environmental exposure and socioeconomic status. Heterogeneity was high.

*Conclusion:* We document an association between tuberculosis and lung cancer occurrence, particularly in, but not limited to, the first 2 years after tuberculosis diagnosis. Some cancer cases may have been present at the time of tuberculosis diagnosis and therefore causality cannot be ascertained. Prospective studies controlling for key confounding factors are needed to identify which tuberculosis patients are at the highest risk, as well as cost-effective approaches to mitigate such risk.

## Introduction

Tuberculosis is a major health problem worldwide. Although the incidence is slowly declining, an estimated 10 million cases and 1.5 million tuberculosis deaths occurred in 2020 [1]. Its morbidity burden extends beyond cure, since people successfully treated for tuberculosis experience health problems in the long term. Tuberculosis has been associated with subsequent lung function impairment and other respiratory conditions such as bronchiectasis and COPD [2, 3]. All-cause mortality is significantly higher in people treated for tuberculosis compared to the general population [4].

The association between tuberculosis and lung cancer has received special interest. There were 2.2 million new cases and 1.8 million deaths from lung cancer in 2020 [5]. Chronic inflammation can promote tumour growth in different types of cancer and chronic inflammation in the lung has been hypothesised to promote carcinogenesis [6]. Chronic bronchitis and emphysema have been associated with increased risk of lung cancer, independently of tobacco use [7]. Inflammation from pulmonary tuberculosis has also been suspected to contribute to lung cancer development, but studies on the association between an episode of

tuberculosis and subsequent lung cancer have shown mixed results. Some found a positive association, while others did not [8, 9].

A 2009 systematic review of epidemiological studies on the subject found a significant increased risk of lung cancer among people with previous tuberculosis, especially for adenocarcinoma [10]. However, most included studies had a case–control design. During the past decade, several cohort studies assessing this relationship have been published. Still, establishing a causal relationship between tuberculosis and lung cancer is challenging, as it is difficult to control for cofounding due to shared risk factors, especially smoking [11]. It is also problematic to ascertain the absence of lung cancer upon tuberculosis diagnosis, at the start of the follow up. Therefore, reverse causation needs to be considered, the more so because lung cancer facilitates activation of latent tuberculosis infection [12].

We appraised in a systematic review the now available evidence that evaluates the association between tuberculosis and subsequent lung cancer occurrence and mortality.

## Methods

We conducted a systematic review and meta-analysis. The population, exposure, comparator, outcome framework was filled out as follows. Population: any population; exposure: tuberculosis; comparator: subjects without tuberculosis; outcomes: lung cancer diagnosis (the main outcome) and lung cancer mortality (the secondary outcome). The protocol was prospectively registered in PROSPERO (ID number: CDR420178362). We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 checklist to report our findings (appendix 1).

### *Search strategy and selection criteria*

We searched the literature in PubMed, Scopus, Cochrane, Latin American and Caribbean Health Sciences Literature and the Scientific Electronic Library Online using terms related to “tuberculosis” and “lung cancer” (the full search strategy can be found in appendix 2). We manually searched the references cited in the papers included. Full-text peer-reviewed papers reporting on cohort and case–control studies written in English, French or Spanish and published between 1 January 1980 and 1 September 2021 were eligible for inclusion. We withheld studies with a comparator group reporting an effect estimate for the association between tuberculosis and lung cancer diagnosis or lung cancer mortality. Retrieved articles were uploaded to Covidence 2.0. Title and abstract screening as well as full-text reviews were performed in duplicate by two reviewers ( J. Cabrera-Sanchez and V. Cuba). Discrepancies about the inclusion of a study were resolved by consensus or through discussion with a third reviewer (L. Otero).

### *Data extraction and risk-of-bias assessment*

We extracted data using a pilot-tested standardised form in Covidence. We extracted bibliographic information, study setting, population description, number of participants, methods to ascertain exposure (tuberculosis)/outcomes (lung cancer diagnosis and lung cancer mortality) and results, including number of events per exposure group and unadjusted and adjusted effect estimates of the association between tuberculosis and subsequent lung cancer diagnosis or mortality. We used the option “merge” in Covidence when data concerning the same study was reported in more than one paper, to treat multiple reports as one single study. In these cases, we extracted the effect estimate based on the larger study population. Authors were contacted by email when necessary to obtain relevant information.

To assess the risk of bias, we adapted the Newcastle–Ottawa scale for observational studies, maintaining three domains with a total of eight items: representativeness of the study population (four items), comparability of study groups (one item) and ascertainment of exposure (for cohorts), or outcome (for case–control studies) (three items). The full description of the adapted Newcastle–Ottawa scale, therationale for adaptations and the rules used to reach the overall risk of bias judgment can be found in the supplementary material (appendices 3 and 4). Both the data extraction and the risk of bias assessment were accomplished independently by two reviewers and disagreements were solved with a third reviewer.

### *Statistical analysis*

We performed a random-effects meta-analysis to pool unadjusted as well as adjusted estimates of the association between tuberculosis and subsequent lung cancer diagnosis or lung cancer mortality. We developed three models. In the first model, we pooled unadjusted estimates extracted from the included studies. In models two and three, we pooled adjusted estimates. Since the variables considered for adjustment varied widely between studies, we pre-defined (as proposed by Riley *et al.* [13]) a minimum set of variables for which studies had to adjust in order to be included in the latter models. These variables were age and smoking, for being associated with tuberculosis and constituting the strongest widespread risk factors for

lung cancer. Smoking could be assessed either qualitatively by smoking status categories (never-, former or current smoker), or quantitatively, when measured by intensity, duration or cumulative amount. In the second model, we pooled studies' estimates adjusted for at least age and any assessment of smoking. In the third model, we pooled estimates adjusted for at least age and any quantitative assessment of smoking. Estimates from studies restricted to never-smokers were considered to be quantitatively adjusted for smoking.

Thus, studies could contribute to more than one model depending on the estimates reported. If a study only reported results stratified by subgroups, we calculated a single pooled estimate. Studies that did not report unadjusted estimates nor estimates adjusted for at least age and smoking were not included in the meta-analyses, but are still part of the descriptive synthesis of the review, except when the data were available to calculate risk ratios or odds ratios for use in model 1. In view of their methodologicaldifferences, separate meta-analyses were performed for cohort and case–control studies. For cohort studies,risk ratios, incidence rate ratios and standardised ratios were pooled together with hazard ratios (HRs). We obtained estimates of pooled odds ratios for case–control studies.

To explore heterogeneity, we performed stratified meta-analyses. First, for all studies, stratified by overall risk of bias (as assessed by the review team) and then, conditional on data availability, by sex, smoking status and latency. Since effect estimates in never-smokers are free of residual confounding by active tobacco consumption, we did a subgroup analysis restricted to that subpopulation. We performed stratified analysis by time intervals between tuberculosis diagnosis and lung cancer detection (latency) aiming to decrease the possibility of lung cancer being present at time of tuberculosis diagnosis and deal with reverse causality bias. For this stratified analysis, we constructed categories accommodating the heterogeneity of the cut-offs reported.

We developed funnel plots and performed the Egger test to assess publication bias. Meta-analysis was done with the meta package version 4.16-2 using R Studio version 4.0.3. Effect measures were calculated with STATA 15.0 (Stata Corp, College Station, TX, USA) and OpenEpi (Centers for Disease Control and Prevention, Atlanta, GA, USA) when studies did not report them directly, but data to do so were available.

## Results

The search yielded 6240 records, 5106 of which we screened after removing duplicates (figure 1). We excluded 4718 records and retained 127 for retrieving the full text. 62 reports fulfilled the inclusion criteria and were included. We identified 18 eligible records from citation searching. Hence, we included a total of 80 records and 73 unique studies. Lung cancer diagnosis was reported in 62 studies: 19 were cohort studies [8, 9, 14–30 ] and 43 were case–control studies [31–72]. Lung cancer mortality was reported in 13 studies: 12 were cohort studies [9, 26, 73–82] and one was a case–control study [83]. Two studies [9, 26] reported both outcomes. Appendix 5 indicates the number of studies included in the different meta-analysis models that pooled the estimates of associations of tuberculosis with subsequent lung cancer diagnosis or mortality. 46 studies originated from Asia, predominantly from China, Taiwan and South Korea (appendix 6); 16 came from North America (USA and Canada); 10 from Europe; and one from Africa. No studies were conducted in Oceania, Latin America or the Caribbean. Only 39 out of 62 and three out of 13 studies addressing diagnosis or mortality, respectively, adjusted somehow for smoking. 12, 25 and 25 studies had low, moderate and high risk of bias, respectively, for the main outcome. Four, one and eight studies were at low, moderate and high risk of bias, respectively, for the secondary outcome. A full description of the included studies and their risk of bias across different domains can be found in the supplementary material (appendices 7 and 8).

Sample sizes ranged from 6699 to 15 219 024 (median 29 641, interquartile range (IQR) 304 977) in cohort studies and from 144 to 91 301 (median 1212, IQR 1983) in case–control studies reporting the main outcome. Sample size in studies reporting the secondary outcome ranged from 515 to 1 607 710 (median 19 497, IQR 39 782) in cohort studies and was 1046 in one case–control study. For lung cancer diagnosis,the minimum length of follow-up in cohort studies was 3.8 years and the maximum was 18.5 years(median 8 years, IQR 4 years); for lung cancer mortality, the minimum was 2 years and the maximum25 years (median 10 years, IQR 7 years). In most cohort studies, lung cancer was detected under routine medical care and coupled to tuberculosis diagnosis through record linkage or by using registries, except in one study [25], where chest radiography was performed systematically as part of the study's follow-up.

Individual results reported in the included studies are tabulated in appendix 9. Results from the meta-analysis are summarised in table 1. For lung cancer diagnosis, among cohort studies, the pooled adjusted hazard ratio for persons with a tuberculosis history *versus* nonexposed individuals was 1.87 (95% CI 1.29–2.70, $I^2$=94%; figure 2) in model 2 and 1.57 (95% CI 1.20–2.07, $I^2$=74%; figure 3) in model 3.

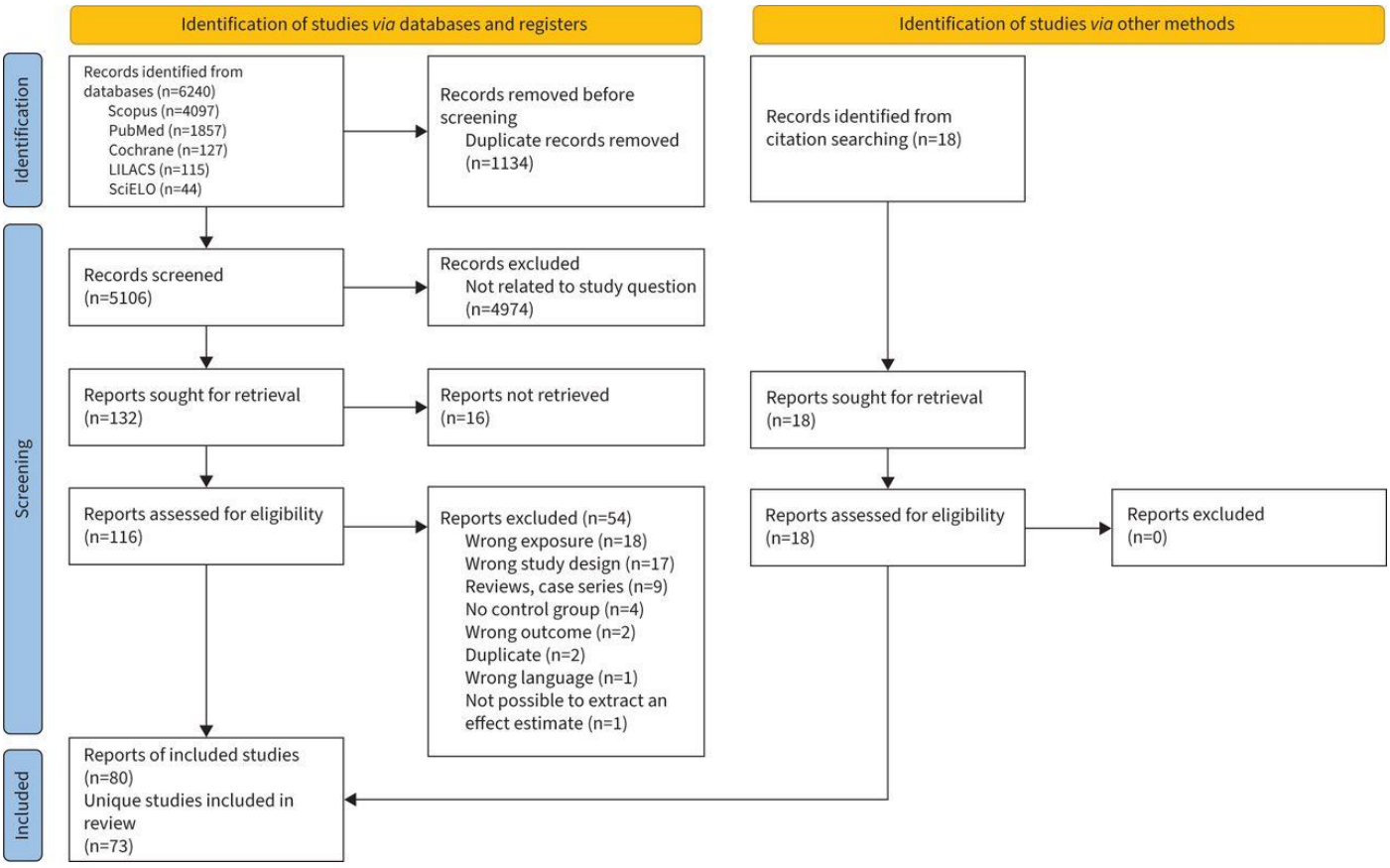


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flowchart. LILACS: Latin American and Caribbean Health Sciences Literature; SciELO: Scientific Electronic Library Online.

**TABLE 1** Pooled estimates of the association between tuberculosis and subsequent lung cancer diagnosis or mortality

| | Model 1[#] | | Model 2[¶] | | Model 3[+] | |
|---|---|---|---|---|---|---|
| | Studies n | Pooled estimate[§] (95% CI) | Studies n | Pooled estimate[§] (95% CI) | Studies n | Pooled estimate[§] (95% CI) |
| **Cohort studies** | | | | | | |
| Lung cancer diagnosis | 8[f] | 2.96 (2.28–3.83) | 7 | 1.77 (1.41–2.22) | 5 | 1.51 (1.30–1.76) |
| Adenocarcinoma | | NA | 3 | 2.00 (0.93–4.31) | 3 | 2.00 (0.93–4.31) |
| Small cell carcinoma | | NA | 3 | 0.88 (0.34–2.26) | 3 | 0.88 (0.34–2.26) |
| Squamous cell carcinoma | | NA | 3 | 2.01 (1.00–4.03) | 3 | 2.01 (1.00–4.03) |
| Lung cancer mortality | 7 | 2.97 (2.14–4.11) | 2 | 1.62 (1.18–2.21) | | NA |
| **Case–control studies** | | | | | | |
| Lung cancer diagnosis | 41 | 2.00 (1.65–2.41) | 23 | 1.76 (1.41–2.19) | 19 | 1.74 (1.42–2.13) |
| Adenocarcinoma | 10 | 2.27 (1.46–3.52) | 8 | 1.96 (1.20–3.21) | 6 | 1.51 (0.92–2.48) |
| Small cell carcinoma | 4 | 2.26 (1.13–4.52) | 3 | 1.50 (0.95–2.39) | 2 | 2.05 (0.42–10.03) |
| Squamous cell carcinoma | 3 | 4.51 (2.75–7.39) | 4 | 2.43 (1.34–4.41) | 3 | 2.23 (0.85–5.86) |
| Lung cancer mortality | 1 | 2.86 (1.87–4.45) | | NA | | NA |

NA: not applicable (no study reporting this estimate). [#]: unadjusted estimates of lung cancer and previous tuberculosis; [¶]: adjusted for age and any assessment of smoking; [+]: adjusted for age and quantitatively assessed smoking; [§]: hazard ratio for cohort studies and odds ratio for case–control studies; [f]: studies from Taiwan used the same database and duplication of information was possible, so we considered only the cohort with the largest sample size [14].

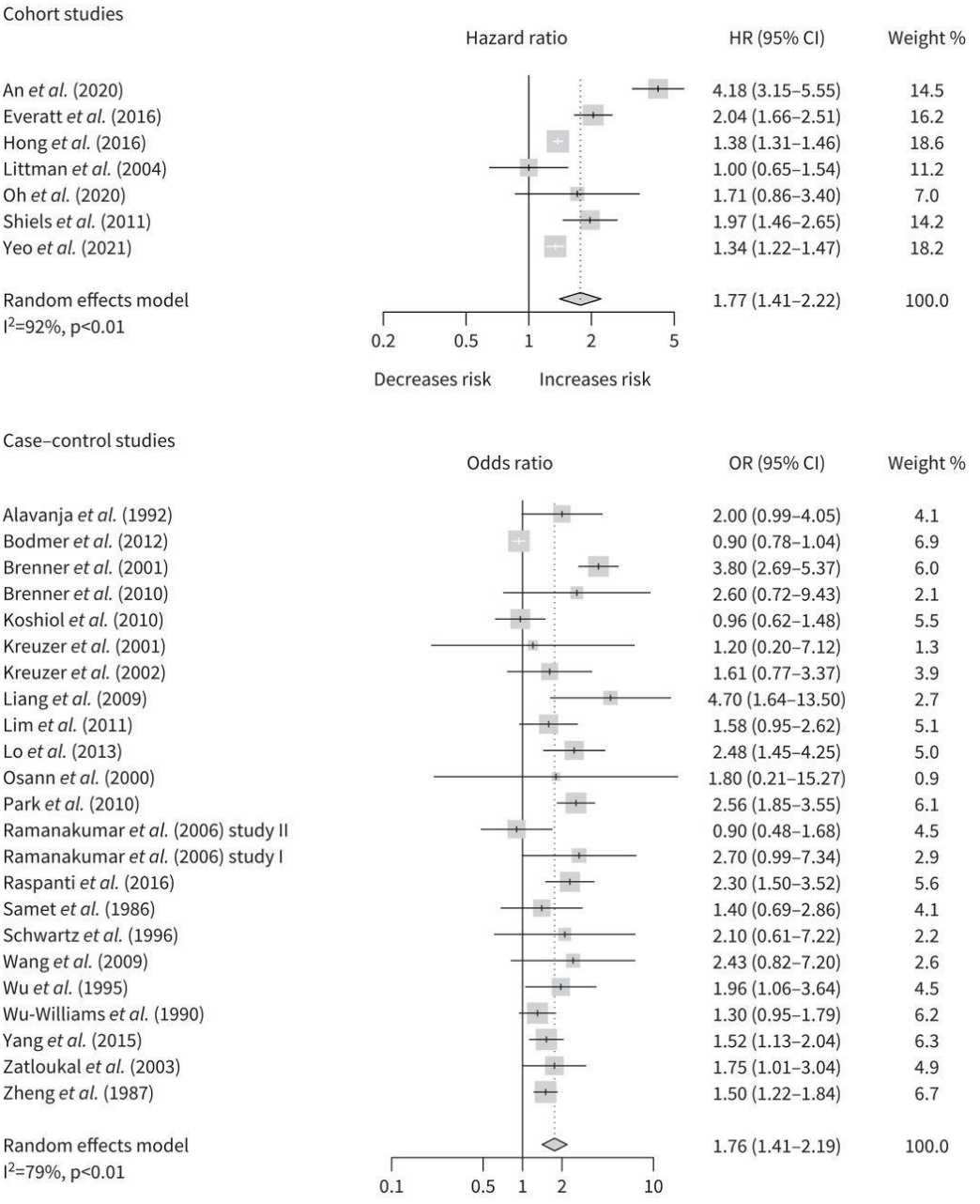


FIGURE 2 Forest plots showing the association between tuberculosis and subsequent lung cancer diagnosis in studies with adjustment for age and any assessment of smoking (model 2). HR: hazard ratio.

There exists heterogeneity, but six out of seven studies that controlled for smoking documented a positive association. Among case–control studies, the pooled adjusted odds ratio was 1.76 (95% CI 1.41–2.19, $I^2$=79%; figure 2) in model 2 and 1.74 (95% CI 1.42–2.13, $I^2$=59%; figure 3) in model 3. Moderate heterogeneity was found, with 20 out of 23 studies included in model 2 documenting a positive association between tuberculosis and subsequent lung cancer diagnosis. The pooled model 2 estimate for lung cancer mortality subsequent to tuberculosis was significant in cohort studies (HR 1.62, 95% CI 1.18–2.21;$I^2$=68%; appendix 10). The pooled estimates of the associations between tuberculosis and specific lung cancer subtypes (table 1) are generally in line with the overall results above, but lack precision.

We restricted stratified analyses (table 2) to the main outcome, lung cancer diagnosis, due to the small number of studies (n=2) eligible for inclusion in adjusted models of the secondary outcome. The estimates in the risk of bias strata differ between themselves, but still remain broadly in line with the nonstratified

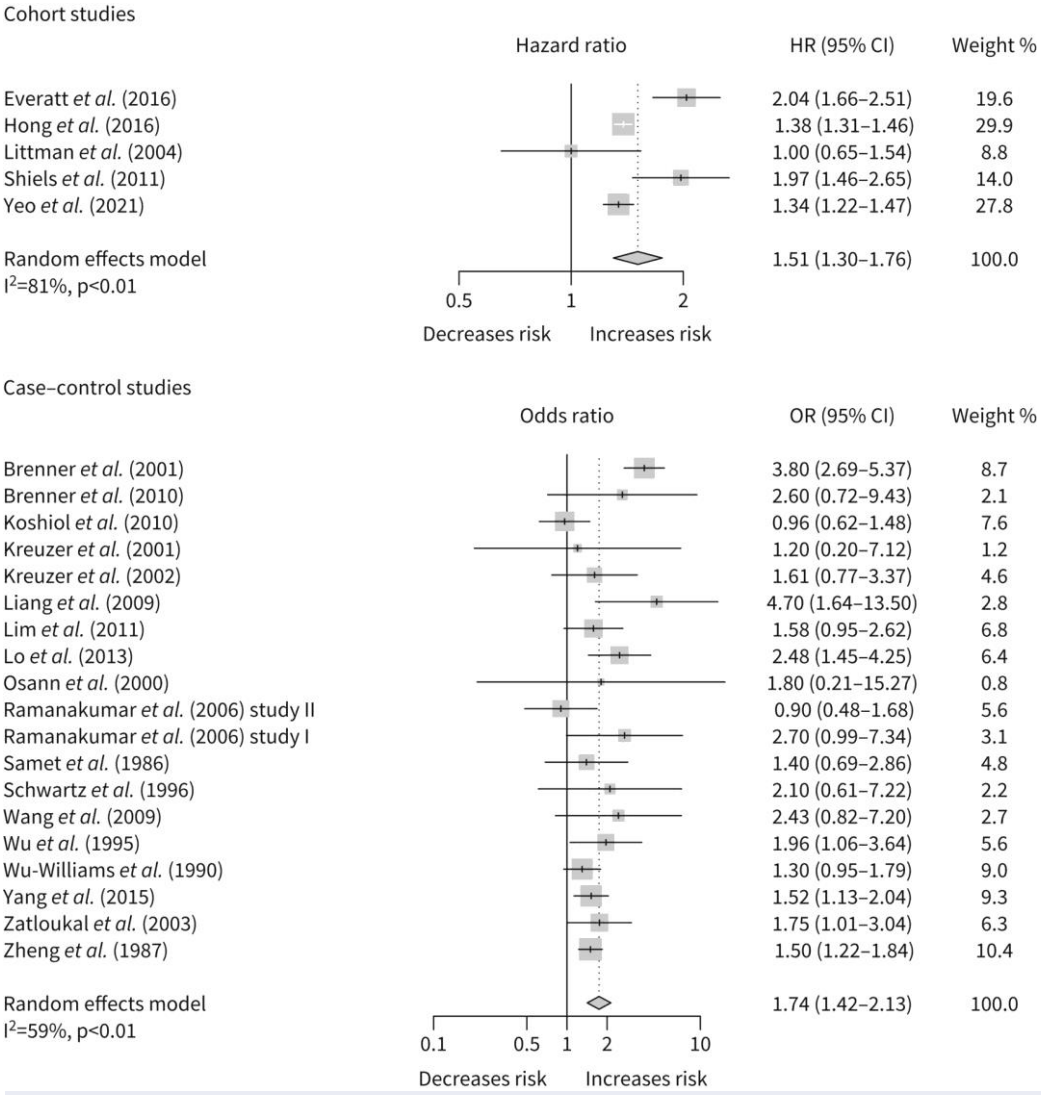


FIGURE 3 Forest plots showing the association between tuberculosis and subsequent lung cancer diagnosis in studies with adjustment for age and quantitatively assessed smoking (model 3). HR: hazard ratio.

results reported earlier. Results by sex were comparable for men and women. The estimates in never-smokers were significant in both cohort and case–control studies and close to the earlier-obtained estimates in the models including studies that adjusted for smoking. We observed that the risk of lung cancer diagnosis was high in the first years after tuberculosis diagnosis (table 2 and appendix 11), but decreased and became moderate-to-weak over time.

Out of the 19 cohort studies reporting the main outcome, 10 did not perform stratified analysis accordingto the interval between tuberculosis diagnosis and detection of lung cancer nor exclude lung cancer cases detected in the first years of follow-up. Those that did so used variable cut-off points, which constrained our stratified pooled analysis by latency. The pooled hazard ratio adjusted for smoking and age for patients that developed cancer beyond 2 years of tuberculosis diagnosis from the only two studies reporting such effect estimate [17, 25] was 1.44 (95% CI 1.06–1.96; table 2). When we pooled study estimates that excluded lung cancer cases detected within 1 [15] or 2 years [17, 25] of tuberculosis diagnosis the pooled hazard ratio was 1.47 (95% CI 1.10–1.97) (appendix 12). Among the two cohort studies [18, 79] that reported adjusted results for the secondary outcome (lung cancer mortality), one [79] excluded patientswho died within the first 2 years of follow-up alongside patients with unconfirmed suspected malignancy (or with recent weight loss) at enrolment. Its adjusted hazard ratio for tuberculosis and death from lung cancer was 2.01 (95% CI 1.40–2.89).

**TABLE 2** Stratified pooled analysis of the association between tuberculosis and subsequent lung cancer diagnosis

| | Model 1[#] | | Model 2[¶] | | Model 3[+] | |
|---|---|---|---|---|---|---|
| | Studies n | Pooled estimate[§] (95% CI) | Studies n | Pooled estimate[§] (95% CI) | Studies n | Pooled estimate[§] (95% CI) |
| Cohort studies | | | | | | |
| Risk of bias[f] | | | | | | |
| Low | 4 | 2.27 (1.58–3.26) | 4 | 2.16 (1.35–3.44) | 3 | 1.72 (1.25–2.38) |
| Moderate | 7 | 3.68 (2.57–5.27) | 2 | 1.38 (1.31–1.46) | 1 | 1.38 (1.31–1.46) |
| High | 1 | 5.86 (3.03–11.37) | 1 | 1.00 (0.65–1.54) | 1 | 1.00 (0.65–1.54) |
| Sex | | | | | | |
| Male | 4 | 1.95 (1.43–2.67) | 2 | 1.59 (1.12–2.26) | 2 | 1.59 (1.12–2.26) |
| Female | 3 | 2.37 (1.92–2.92) | 1 | 1.49 (1.28–1.74) | 1 | 1.49 (1.28–1.74) |
| Smoking status[f] | | | | | | |
| Never-smokers | 1 | 2.45 (2.21–2.72) | 2 | 1.69 (1.21–2.38) | 2 | 1.69 (1.21–2.38) |
| Latency period[f] | | | | | | |
| Up to 1 year | 1 | 12.5 (7.17–21.73) | 2 | 8.50 (4.09–17.67) | 2 | 8.50 (4.09–17.67) |
| Up to 2 years | | NA | 2 | 5.01 (3.64–6.89) | 2 | 5.01 (3.64–6.89) |
| Up to 5 years | 2 | 7.69 (4.79–12.34) | | NA | | NA |
| ⩾2 years | | NA | 2 | 1.44 (1.06–1.96) | 2 | 1.44 (1.06–1.96) |
| ⩾4 years | | NA | 2 | 0.82 (0.53–1.26) | 2 | 0.82 (0.53–1.26) |
| ⩾5 years | 2 | 2.36 (0.90–6.19) | | NA | | NA |
| ⩾7 years | 2 | 1.61 (0.88–2.95) | 1 | 1.69 (0.62–4.65) | 1 | 1.69 (0.62–4.65) |
| ⩾10 years | | NA | 2 | 1.15 (0.40–3.29) | 2 | 1.15 (0.40–3.29) |
| Case–control studies | | | | | | |
| Risk of bias[f] | | | | | | |
| Low | 5 | 1.92 (0.82–4.51) | 2 | 0.91 (0.79–1.04) | 1 | 0.96 (0.62–1.48) |
| Moderate | 15 | 1.89 (1.38–2.58) | 10 | 1.94 (1.48–2.55) | 10 | 1.94 (1.48–2.55) |
| High | 21 | 2.18 (1.83–2.59) | 11 | 1.87 (1.47–2.39) | 8 | 1.48 (1.16–1.87) |
| Sex | | | | | | |
| Male | 10 | 2.34 (1.81–3.03) | 6 | 2.07 (1.57–2.71) | 5 | 1.87 (1.31–2.66) |
| Female | 23 | 2.04 (1.67–2.50) | 13 | 1.84 (1.49–2.29) | 11 | 1.78 (1.39–2.28) |
| Smoking status[f] | | | | | | |
| Never-smokers | 18 | 1.69 (1.20–2.36) | 13 | 1.90 (1.51–2.39) | 13 | 1.90 (1.51–2.39) |
| Latency period[f] | | | | | | |
| 1–5 years | | NA | 2 | 7.20 (0.52–99.19) | 2 | 7.20 (0.52–99.19) |
| ⩾5 years | | NA | 2 | 3.03 (1.30–7.04) | 2 | 3.03 (1.30–7.04) |
| ⩾10 years | | NA | 3 | 1.57 (1.13–2.16) | 3 | 1.57 (1.13–2.16) |
| ⩾20 years | | NA | 3 | 1.54 (0.97–2.44) | 3 | 1.54 (0.97–2.44) |

NA: not applicable (no study reporting this estimate). [#]: unadjusted estimates of lung cancer and previous tuberculosis; [¶]: adjusted for age and any assessment of smoking; [+]: adjusted for age and quantitatively assessed smoking; [§]: hazard ratio for cohort studies and odds ratio for case–control studies; [f]: pre-specified subgroup analysis.

Funnel plots of the main outcome do not indicate small-study effects (appendix 13). Egger test was not significant for the main outcome in cohort ( p=0.61) and case–control studies ( p=0.37). These analyses were not performed for the secondary outcome due to the small number of included studies. The Gradingof Recommendations, Assessment, Development and Evaluation (GRADE) assessment of the evidence (appendix 14) reveals overall low certainty for cohort studies and very low certainty for case–control studies.

## Discussion

This systematic review and meta-analysis found moderate pooled effect estimates for being diagnosed with lung cancer after a tuberculosis episode: adjusted for age and smoking, a hazard ratio of 1.51 (95% CI 1.30–1.76) in cohort studies and an odds ratio of 1.74 (95% CI 1.42–2.13) in case–control studies. In addition, we found a compatible pooled hazard ratio of 1.62 (95% CI 1.18–2.21) of dying from lungcancer. The pooled hazard ratios and odds ratios for lung cancer occurrence remained consistent with the overall result in a stratified meta-analysis by risk of study bias and sex, and when restricted to never-smokers. The hazard ratio was positive for incidence of adenocarcinoma and squamous cell carcinoma diagnosis but not of small cell carcinoma. Importantly, in cohort studies we found, adjusted for age and smoking, a substantially increased occurrence of being diagnosed with lung cancer within the first2 years after tuberculosis diagnosis (HR 5.01, 95% CI 3.64–6.89) that waned after year two (HR 1.44,95% CI 1.06–1.96) and disappeared after 4 years.

Our crude results are comparable with the overall risk ratio adjusted for smoking (1.74, 95% CI 1.48–2.03) found in a previous review [10], which included 37 case–control and four cohort studies publishedbetween 1966 and 2008. However, that review concluded that, while declining much in the first 5 years, lung cancer risk ratio remained at ~2 for >20 years after a diagnosis of tuberculosis. The overall certainty of evidence provided by the 43 case–control studies included in our review is very low, but most of the 19 cohort studies have moderate risk of bias, good precision and consistent effect estimates. However, the certainty of their accumulated evidence is rated low in the GRADE framework due to their observational nature. While almost all studies included in our review report effect estimates of the association between tuberculosis and subsequent lung cancer greater than one, there exists quite some heterogeneity that is possibly explained by the presence of (residual) confounding. It is of note that 31 out of the 73 studies did not even control for smoking status, while tobacco consumption increases the risk of developing lung cancer >10-fold [84]. However, when limiting our meta-analysis to the studies that controlled at least for smoking and age, or that selected never-smokers, we still found significant, moderately positive pooled hazard ratios and odds ratios.

The increased risk of lung cancer thus seems to be independent of active tobacco consumption, but we cannot exclude residual confounding by passive smoking, which has a weaker association to tuberculosis [85]. Furthermore, the studies did generally not adjust for socioeconomic status and environmental pollution, which have also been associated with tuberculosis and lung cancer [11]. Low socioeconomic status is a risk factor for tuberculosis [86] and may be associated with higher exposure to environmental pollution or occupational carcinogens. A meta-analysis found low socioeconomic status to mildly increase the risk of developing lung cancer after adjustment for smoking [87], and the authors hypothesised thatboth aforementioned exposures were overrepresented among people with lower socioeconomic status. Unfortunately, only two studies included in our review [26, 51] adjusted jointly for the three key confounders: age, smoking and socioeconomic status. Another limitation is that most studies did not conclusively rule out lung cancer upon tuberculosis diagnosis. Not surprisingly, since there are no effective screening methods to detect early or occult lung cancer, with chest radiographs lacking sensitivity and low-dose computed tomography being plagued by false positives [88]. Notwithstanding, the likelihood that occult cancer is present before the tuberculosis diagnoses can be high in retrospective designs and only two included studies were prospective. Furthermore, few studies reported estimates by latency to cancer diagnosis and among those that did, the time category cut-off points used were heterogeneous. This limited our scope for stratified meta-analysis by latency.

The substantially higher occurrence of lung cancer we uncovered in the first year (HR 8.50) and first 2 years (HR 5.0) following tuberculosis diagnosis, which fades out thereafter, raises the question whether cancer latency can be that short. The results could be explained by different mechanisms. Firstly, due to shared clinical and radiological characteristics lung cancer can initially be misdiagnosed as tuberculosis, as illustrated by a study in Taiwan [89] that found 1% of such misclassifications. Studies that include tuberculosis cases without bacteriological confirmation may be more prone to this error and most cohort studies in our review selected the exposed comparison group from large national databases or tuberculosis registries but do not clarify what percentage had bacteriological confirmation. Secondly, it is conceivable that occult cancer triggers active tuberculosis occurrence. A recent systematic review found that lungcancer patients are at nine-fold increased risk of developing active tuberculosis [12] and attributed most of the excess risk to the immunosuppressive cancer treatment. Still, people with undiagnosed lung cancer might be at increased risk of active tuberculosis due to cancer by itself having immunomodulatory effects. Excluding lung cancer cases diagnosed within the first 2 years of tuberculosis decreases, but not totally excludes the possibility of lung cancer prevalent cases being already present at the time of tuberculosis diagnosis. In our pooled analysis by latency (table 2), the adjusted hazard ratio for lung cancer diagnosis after ⩾2 years of tuberculosis was 1.44 (95% CI 1.06–1.96). However, it was not significant at ⩾7 years and ⩾10 years. In the three cohort studies [15, 17, 25] that report adjusted stratified analysis according to latency for lung cancer diagnosis, the risk decreased as latency increases (appendix 11).

Thirdly, surveillance bias exists if tuberculosis patients are offered, or demand, more medical imaging after diagnosis and further lung conditions may be more likely to be diagnosed. However, regular chest radiography does not seem to increase the diagnostic yield when screening the general population [90]. In the prospective study by Shiels *et al.* [25] included in our review, a thorough medical examination with chest radiography was performed at baseline and all participants underwent regular repeat examinationsand chest radiography at the same interval during 5–8 years' follow-up [91]. The overall hazard ratio for lung cancer adjusted for age and smoking in this study was significant and decreased with time after tuberculosis diagnosis. Temporal ambiguity in retrospective designs coupled to the scarcity of prospective studies demonstrating a decreasing relative risk over time has been interpreted as absence of genuine

relationship between tuberculosis and lung cancer [18]. However, a credible alternative hypothesis wouldbe that the risk dwindles after tuberculosis is cured, analogous to lung cancer hazard progressively decreasing after smoking cessation.

We document a modestly increased risk of developing lung cancer after a tuberculosis episode and observe consistency: hazard ratio and odds ratio between 1.5 and 2 in our overall and stratified analyses. Methodological limitations of the reviewed studies warrant a plea for cautious interpretation and preclude a causal reading, but tuberculosis being a risk factor for lung cancer is plausible and coherent. Chronic inflammation in the lung promotes carcinogenesis, in which macrophages may play a role by producing inflammatory cytokines and nitrogen reactive species [92]. This is illustrated by the carcinogenesis in mycobacterium-infected rats depending on the activity of macrophages [93]. Chronic inflammation may also damage DNA and increase mutation rates in key genes that promote malignant cell proliferation and angiogenesis. A study in South Korean patients with pulmonary adenocarcinoma found that the presence of pre-existing tuberculosis lesions was associated with significantly more epidermal growth factor receptor gene mutations [94]. The fragile histidine triad diadenoside triphosphate gene, a tumour suppressor gene, has also been found to be more frequently affected in lung cancer patients with a tuberculosis infection [95].

Evidence is growing on the long-term health consequences of having tuberculosis [96]. This reviewsuggests a potential higher risk of developing lung cancer, which tuberculosis program managers and clinicians ought to be aware of. However, the finding of increased occurrence of lung cancer in the first2 years after tuberculosis diagnosis could also indicate that some lung cancer cases may have been present at the time of tuberculosis diagnosis, and therefore it is not possible to ascertain causality. Yet, no concrete hard recommendations can be made relating to the programme's organisation for routine post-cure follow-up, screening and early detection. Notwithstanding, in particular in patients with other risk factors for lung cancer, our result prompt sharpening up clinical suspicion during fortuitous re-encounters and reinforcing the possible ensuing diagnostic work-up.

### Questions for future research

Further basic research is recommended to better understand the biological mechanisms behind the tuberculosis-subsequent lung cancer association. Linking routine tuberculosis programme databases and cancer registers in countries with reliable health information systems, as well as setting up methodologicallyrigorous longitudinal clinical–epidemiological studies that permit adequate control of potential confounding factors, could enable the identification of which tuberculosis patients (if any) are at the highest risk andfor how long. Eventually, operational research will be needed to sort out how health services can cost-effectively contribute to mitigating that risk.

Provenance: Submitted article, peer reviewed.

Author contributors: J. Cabrera-Sanchez, V. Cuba and L. Otero conceived the study idea. J. Cabrera-Sanchez, V. Cuba, P. Van der Stuyft and L. Otero designed the protocol. J. Cabrera-Sanchez and V. Cuba did the literature search, extracted data and assessed the risk of bias. J. Cabrera-Sanchez and V. Cuba performed the statistical analysis with support from V. Vega and P. Van der Stuyft. J. Cabrera-Sanchez wrote the initial draft of the manuscript. All authors critically revised, provided important conceptual input, and approved the final version of the manuscript. All authors had access to the data.

Data sharing: The data supporting this meta-analysis are from previously reported studies and datasets, which have been cited. The extracted data are available in the supplementary material.

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# SUPPLEMENTARY MATERIAL

LUNG CANCER OCCURRENCE AFTER AN EPISODE OF TUBERCULOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS


## AUTHORS

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**Appendix 1. PRISMA checklist**

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | Tittle |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Summary |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | Introduction |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Introduction |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Methods (Search strategy and inclusion criteria) |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Methods (Search strategy and inclusion criteria) |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Appendix 2 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Methods (Search strategy and inclusion criteria) |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Methods (Data extraction and risk of bias assessment) |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Methods (Data extraction and risk of bias assessment) |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Methods (Data extraction and risk of bias assessment) |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Methods (Data extraction and risk of bias assessment), Appendix 3 and 4 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Methods (Statistic analysis) |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Methods (Statistic analysis) |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Methods (Statistic analysis) |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Methods (Statistic analysis) |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Methods (Statistic analysis) |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Methods (Statistic analysis) |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Methods (Statistic analysis) |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Methods (Statistic analysis) |
| Certainty | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Methods |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| assessment | | | (Statistic analysis) |
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Results, figure 1; Appendix 6 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Appendix 16 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Results; Appendix 7 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Appendix 8 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Appendix 9 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Results; Discussion |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Results; Tables 1 and 2; Appendix 10 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Table 2 |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Tables 1 and 2 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Appendix 12 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Appendix 13 |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Discussion |
| | 23b | Discuss any limitations of the evidence included in the review. | Discussion |
| | 23c | Discuss any limitations of the review processes used. | Discussion |
| | 23d | Discuss implications of the results for practice, policy, and future research. | Discussion |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Methods |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Methods |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Appendix 15 |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Role of the funding source |
| Competing interests | 26 | Declare any competing interests of review authors. | Declaration of interests |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Data sharing |

**Appendix 2. Search strategy**

Search strategy: PubMed

1. Search **tuberculosis[MeSH Terms]**
2. Search **tuberculosis[Title/Abstract]**
3. Search **mycobacterium[Title/Abstract]**
4. Search **"tb"[Title/Abstract]**
5. Search **"tbc"[Title/Abstract]**
6. 1 OR 2 OR 3 OR 4 OR 5
7. Search **lung neoplasm[MeSH Terms]**
8. Search **lung cancer[MeSH Terms]**
9. Search **lung cancer*[Title/Abstract]**
10. Search **lung neoplasm*[Title/Abstract]**
11. Search **lung carcinoma*[Title/Abstract]**
12. Search **lung tumor*[Title/Abstract]**
13. Search **pulmonary cancer*[Title/Abstract]**
14. Search **pulmonary neoplasm*[Title/Abstract]**
15. Search **pulmonary carcinoma*[Title/Abstract]**
16. Search **pulmonary tumor*[Title/Abstract**
17. Search **"cancer of the lung"[Title/Abstract]**
18. Search **"neoplasm of the lung"[Title/Abstract]**
19. Search **"tumor of the lung"[Title/Abstract]**
20. 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21. 6 AND 20
22. Search **("case reports"[Publication Type] OR "comment*"[Publication Type] OR "Autobiography"[Publication Type] OR "Biography"[Publication Type] OR "legal case"[Publication Type])**
23. 21 NOT 22

Filters: **Publication date from 1980/01/01 to 2020/06/24; English; French; Spanish**

Search strategy: Scopus

1. TITLE-ABS-KEY ( "tuberculosis" )
2. TITLE-ABS-KEY ( "mycobacterium infection" )
3. 1 OR 2
4. TITLE-ABS-KEY ( "lung cancer" )
5. TITLE-ABS-KEY ( "lung neoplasm" )
6. TITLE-ABS-KEY ( "lung tumor" )
7. TITLE-ABS-KEY ( "lung carcinoma" )
8. TITLE-ABS-KEY ( "lung adenocarcinoma" )
9. TITLE-ABS-KEY ( "pulmonary cancer" )
10. TITLE-ABS-KEY ( "pulmonary neoplasm" )
11. TITLE-ABS-KEY ( "pulmonary tumor" )
12. TITLE-ABS-KEY ( "pulmonary carcinoma" )
13. TITLE-ABS-KEY ( "pulmonary adenocarcinoma" )
14. TITLE-ABS-KEY ( "cancer of the lung" )
15. TITLE-ABS-KEY ( "cancer of lung" )
16. TITLE-ABS-KEY ( "neoplasm of the lung" )
17. TITLE-ABS-KEY ( "neoplasm of lung" )
18. TITLE-ABS-KEY ( "tumor of lung" )
19. TITLE-ABS-KEY ( "tumor of the lung" ) ) )
20. 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21. 3 AND 20

Filters:

22. LIMIT-TO ( DOCTYPE , "ar" )
23. LIMIT-TO ( DOCTYPE , "re" )
24. LIMIT-TO ( DOCTYPE , "le" )
25. 22 OR 23 OR 24
26. LIMIT-TO ( SUBJAREA , "MEDI" )
27. LIMIT-TO ( SUBJAREA , "BIOC" )
28. LIMIT-TO ( SUBJAREA , "IMMU" )
29. 26 OR 27 OR 28
30. LIMIT-TO ( LANGUAGE , "English" )
31. LIMIT-TO ( LANGUAGE , "French" )
32. LIMIT-TO ( LANGUAGE , "Spanish" )
33. 30 OR 31 OR 32
34. LIMIT-TO ( PUBYEAR , 1980-2021)
35. 25 AND 29 AND 33 AND 34

Search strategy: Lilacs

1. tw:(tuberculosis) OR
2. tw:(mycobacterium tuberculosis) OR
3. tw:("TB") OR
4. tw:(mycobacterium infection)
5. 1 OR 2 OR 3 OR 4
6. tw:(lung cancer) OR
7. tw:(lung neoplasm) OR
8. tw:(small cell carcinoma) OR
9. tw:(lung tumor) OR
10. tw:(lung malignancy) OR
11. tw:("cancer of the lung") OR
12. tw:(non-small cell carcinoma)
13. 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
14. 5 AND 13

Search strategy: Scielo

1. ti:(tuberculosis) OR
2. ab:(tuberculosis) OR
3. ti:(TB) OR
4. ab:(TB) OR
5. ti:(mycobacterium infection)
6. ab:(mycobacterium infection)
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. ti:(lung cancer)
9. ab:(lung cancer)
10. ti:(lung neoplasm)
11. ab:(lung neoplasm)
12. ti:(lung tumor)
13. ab:(lung tumor)
14. ti:(lung malignancy)
15. ab:(lung malignancy)
16. 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15

Search strategy: Cochrane

#1: (tuberculosis):ti,ab,kw OR (TB):ti,ab,kw OR ("Mycobacterium"):ti,ab,kw
#2: ("lung cancer"):ti,ab,kw OR ("lung neoplasm"):ti,ab,kw OR ("lung adenocarcinoma cell"):ti,ab,kw OR ("small cell lung cancer"):ti,ab,kw OR ("non small cell lung cancer"):ti,ab,kw
#3: #1 AND #2

The search strategy was developed by LO (MD, PhD), JACS (medical student) and VC (medical student).

**Appendix 3. Modified Newcastle-Ottawa Quality Assessment Scale (NOS)**
**Modified Newcastle - Ottawa Quality Assessment Scale**
**Cohort Studies**

**Selection**
1) Representativeness of the exposed cohort
a) truly representative **(one star)**
b) somewhat representative **(one star)**
c) selected group of users
d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
a) drawn from the same community as the exposed cohort **(one star)**
b) drawn from a different source
c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
a) Bacteriologically confirmed TB episode, from NTP/medical records **(two stars)**
b) Bacteriologically confirmed episode, from a structured interview **(one star)**
c) Clinically diagnosed TB episode from NTP/medical records **(one star)**
d) Structured interview with no information on bacteriological diagnosis
e) Self-report
f) No description
g) Other

4) Attempt to Demonstrate that outcome of interest was not present at start of study
a) yes (excluded cases occurring in the first year after the tuberculosis diagnosis or performed latency analysis) **(one star)**
b) no

**Comparability**
1) Comparability of cohorts on the basis of the design or analysis
a) study controls age AND smoking **(two stars)**
b) study controls for age OR smoking **(one star)**

**Outcome**
1) Assessment of outcome
a) Pathological (histological or cytological) diagnosis (for at least 80% of all lung cancer cases) **(one star)**
b) No pathological diagnosis in more than 80% cases.
c) No description
d) Other

2) Was follow-up long enough for outcomes to occur
a) yes (>5 years) **(one star)**
b) no

3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for **(one star)**
b) subjects lost to follow up unlikely to introduce bias – number lost less than or equal to 20%, or description of those lost suggested no difference from those followed-up **(one star)**
c) Evidence of selective losses
d) Follow-up rate less than 80% and no description of those lost
e) No statement

Overall risk of bias for cohort studies:

| | |
|---|---|
| Low risk of bias | 4 or 5 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain |
| Moderate risk of bias | 2 or 3 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain |
| High risk of bias | 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome domain |

**Newcastle - Ottawa Quality Assessment Scale**
**Case Control Studies**

**Selection**
1) Is the case definition adequate?
a) Yes, with pathological evidence **(one star)**
b) No pathological evidence
c) No description

2) Representativeness of the cases
a) consecutive or obviously representative series of cases **(one star)**
b) potential for selection biases or not stated

3) Selection of Controls
a) community controls **(one star)**
b) hospital controls
c) no description

4) Definition of Controls
a) no history of disease (lung cancer) **(one star)**
b) no description of source

**Comparability**
1) Comparability of cases and controls on the basis of the design or analysis
a) study controls age AND smoking **(two stars)**
b) study controls for age OR smoking **(one star)**

**Exposure**
1) Ascertainment of exposure
a) Linked record with NTP database with bacteriological confirmation (>80%) **(two stars)**
b) Linked record with NTP database without bacteriological confirmation **(one star)**
c) Structured interview where blind to case-control status **(one star)**
d) Interview not blinded or written self-report
e) No description

2) Same method of ascertainment for cases and controls
a) yes **(one star)**
b) no

3) Non-Response rate
a) Similar for both groups and total response rate >80% **(one star)**
b) Non-response selective to one group
c) Total response rate <80%
d) No description

Overall risk of bias for case-control studies:

| | |
|---|---|
| Low risk of bias | 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 3 or 4 stars in exposure domain |
| Moderate risk of bias | 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 stars in exposure domain |
| High risk of bias | 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in exposure domain |

**Appendix 4. Rationale for changes to the Newcastle-Ottawa Scale**

| | **Cohort studies** | | |
|---|---|---|---|
| | Original scale | Adapted scale | Rationale for changes |
| | | | |
| Selection | | | |
| 1 | Representativeness of the exposed cohort<br><br>A. Truly representative **(one star)**<br>B. Somewhat representative **(one star)**<br>C. Selected group<br>D. No description of the derivation of the cohort | No changes made | |
| 2 | Selection of the non-exposed cohort<br><br>A. Drawn from the same community as the exposed cohort (**one star**)<br>B. Drawn from a different source<br>C. No description of the derivation of the non-exposed cohort | No changes made | |
| 3 | Ascertainment of exposure<br><br>A. Secure record (e.g., surgical record) (**one star**)<br>B. Structured interview (**one star**)<br>C. Written self-report<br>D. No description<br>E. Other | Ascertainment of exposure<br><br>A. Bacteriologically confirmed TB episode, from NTP/medical records (**two star**)<br>B. Bacteriologically confirmed TB episode, from structured interview (**one star**)<br>C. Clinically diagnosed TB episode from NTP/medical records (**one star**)<br>D. Structured interview with no information on bacteriological diagnosis<br>E. Self-report with no further information on the TB symptoms or diagnosis<br>F. No description<br>G. Other | When the episode of TB is bacteriologically confirmed, we can be almost certain that it was active TB and not an early manifestation of lung cancer.<br>This is more reliable if it has been ascertained from a NTP or medical record.<br>An interview is less reliable to ascertain if a diagnosis was made bacteriologically<br>Clinical or radiological TB diagnosis is less accurate since TB and lung cancer may share symptoms and radiological findings. |
| 4 | Demonstration that outcome of interest was not present at start of study<br><br>A. Yes, no history of endpoint (**one star**)<br>B. No | 4) <u>Attempt to Demonstrate that outcome of interest was not present at start of study</u><br>A. Yes (excluded cases occurring in the first year after the tuberculosis diagnosis or performed latency analysis) **(one star)**<br>B) No | Ascertain that a TB patient did not have lung cancer is very difficult to even using imaging. Therefore, we allow for a period one years between the TB diagnosis and the cancer diagnosis. If less, the cancer could have been present. |
| Comparability | | | |

| | | | |
|---|---|---|---|
| 1 | Comparability of cohorts on the basis of the design or analysis controlled for confounders<br><br>A. The study controls for the most important factor (**one star**)<br>B. Study controls for any additional important factor (list) (**one star**)<br>C. Cohorts are not comparable on the basis of the design or analysis controlled for confounders | Comparability of cohorts on the basis of the design or analysis controlled for confounders<br><br>A. The study controls for age AND smoking (**two star**)<br>B. The study controls for age OR smoking (**one star**)<br>C. The study controls for other factors only)<br>D. Cohorts are not comparable on the basis of the design or analysis controlled for confounders | We considered a study should control for age and smoking for it to be pooled in the adjusted effects meta-analysis. These variables were chosen from a larger list of potential cofounders after considering epidemiological evidence (see "DAG and references")<br><br>Smoking and age are the main (ref) risk factors for lung cancer. Studies controlling for both, have more comparable cohorts, than those controlling for age or for other factors only. |
| Outcome | | | |
| 1 | Assessment of outcome<br><br>A. Independent blind assessment (**one star**)<br>B. Record linkage (**one star**)<br>C. Self-report<br>D. No description<br>E. Other | Assessment of outcome<br><br>A. Pathological diagnosis (for at least 80% of all lung cancer diagnoses) (**one star**)<br>B. No pathological diagnosis<br>F. No description<br>G. Other | Since TB and lung cancer may share clinical features, we consider it necessary that the diagnosis of lung cancer is made based on pathological evidence. Otherwise, a recurrence or sequel of TB may be misdiagnosed as lung cancer. |
| 2 | Was follow-up long enough for outcomes to occur<br><br>A. Yes (**one star**)<br>B. No Indicate the median duration of follow-up and a brief rationale for the assessment above:_____ | Was follow-up long enough for outcomes to occur<br>A. Yes (>= 5 years on average) (**one star**)<br>B. No | |

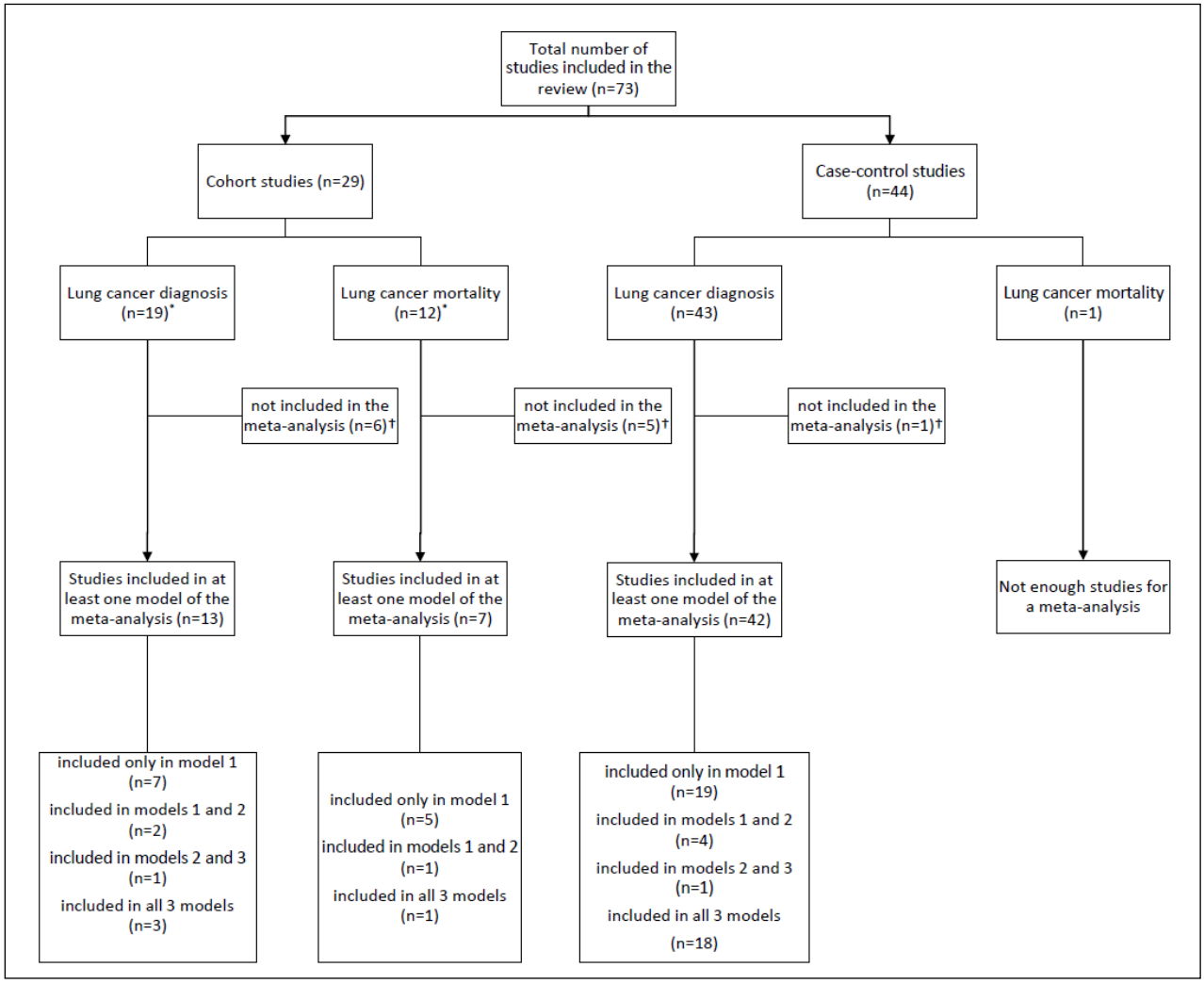
| | | | |
|---|---|---|---|
| 3 | Adequacy of follow-up of cohorts<br><br>A. Complete follow-up- all subject accounted for (**one star**)<br>B. Subjects lost to follow-up unlikely to introduce bias – number lost less than or equal to 20% or description of those lost suggested no different from those followed. (**one star**)<br>C. Follow-up rate less than 80% and no description of those lost<br>D. No statement | Adequacy of follow-up of cohorts<br><br>A. Complete follow-up- all subject accounted for (**one star**)<br>B. Subjects lost to follow-up unlikely to introduce bias - number lost less than or equal to 20%. (**one star**)<br>C. losses are clearly selective to one group<br>D. Follow-up rate less than 80% and no description of those lost<br>E. No statement | A study where losses are relatively small but selective to one group may also introduce bias. |
| Overall risk of bias | | | |
| | Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain<br><br>Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain<br><br>Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome domain | Low risk of bias: 4 or 5 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain<br><br>Moderate risk of bias: 2 or 3 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain<br><br>High risk of bias: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome domain | Adapted to the changes in stars assigned to ascertainment of exposure (because this item can receive up to two stars instead of only one in the original scale).<br><br>We substituted the terms related to “quality” for “risk of bias” as suggested by current systematic review guidelines. |

| | **Adapted Newcastle-Ottawa Scale for case-control studies** | | |
|---|---|---|---|
| | Original scale | Adapted scale | Rationale for changes |
| Selection | | | |
| 1 | Is the case definition adequate?<br><br>A. Yes, with independent validation **(one star)**<br>B. Based on record linkage or based on self-reports<br>C. No description | Is the case definition adequate?<br><br>A. Yes, with pathological evidence **(one star)**<br>B. Attempt to independently validate but not enough pathological evidence<br>C. Based on record linkage<br>D. Based on self-reports<br>E. No description | Since TB and lung cancer may share clinical and radiological features, we consider it necessary that the diagnosis of lung cancer is made based on pathological evidence. Otherwise, a recurrence or sequel of TB may be misdiagnosed. |

| | | | |
|---|---|---|---|
| 2 | Representativeness of the cases<br><br>A. Consecutive or obviously representative series of cases (**one star**)<br>B. Potential for selection biases or not stated | No changes made | |
| 3 | Selection of Controls<br><br>This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.<br><br>A. Community controls (**one star**)<br>B. Hospital controls or other health service controls<br>C. No description | No changes made | |
| 4 | Definition of Controls<br><br>A. No history of disease (endpoint) (**one star**)<br>B. No description of source | Definition of Controls<br><br>A. No history of lung cancer (**one star**)<br>B. No description of source | |
| Comparability | | | |
| 1 | Comparability of cases and controls on the basis of the design or analysis controlled for confounders<br><br>A. The study controls for the most important factor (**one star**)<br>B. Study controls for any additional important factor (list) (**one star**)<br>C. Cases and controls are not comparable on the basis of the design or analysis controlled for confounders | Comparability of cases and controls on the basis of the design or analysis controlled for confounders<br><br>A. The study controls* for age AND smoking (**two star**)<br>B. The study controls* for age OR smoking (**one star**)<br>C. Study controls* for other predefined factors (socioeconomic status, passive smoking, chronic bronchitis or emphysema)<br>D. Cases and controls are not comparable on the basis of the design or analysis controlled for confounders<br><br>*if controls were matched to cases, matched analysis needs to be conducted, in order for the factors to be controlled.(not for frequency matching) | We considered a study should control for age, and smoking for it to be pooled in the adjusted effects meta-analysis. These variables were chosen from a larger list of potential cofounders after considering epidemiological evidence |
| Exposure | | | |
| 1 | Assessment of exposure<br><br>A. Secure record (**one star**)<br>B. Structured interview where blind to case/control status (**one star**)<br>C. Interview not blinded<br>D. Written self-report or medical record only | Assessment of exposure<br><br>A. Linked record with NTP database with bacteriological confirmation (>80%) (**two star**)<br>B. Linked record with NTP database without | When the episode of TB is bacteriologically confirmed, we can be almost certain that it was active TB and not an early manifestation of lung cancer misdiagnosed as TB. Diagnosis of TB based on clinical or radiological criteria is less accurate since TB and lung cancer |

| | | | |
|---|---|---|---|
| | E. No description | bacteriological confirmation (**one star**).<br>**C.** Structured interview where blind to case/control status (**one star)**<br>D. Interview not blinded or written self-report<br>E. No description<br><br>(bacteriological confirmation of exposure would be ideal, but unlikely to be complete for all) | may share symptoms and radiological findings.<br>An interview is less reliable to ascertain if a diagnosis was made bacteriologically and it is also prone to recall bias |
| 2 | Same method of ascertainment for cases and controls<br><br>A. Yes (**one star**)<br>B. No | No changes made | |
| 3 | Non-response rate<br><br>A. Same for both groups (**one star**)<br>B. Non respondents described<br>C. Rate different and no designation | Non-response rate (or not **possible** to link? Which is different to "not linked")<br><br>A. Similar for both groups and total response rate >80% and description of non-respondents suggests no difference from respondents. (**one star**)<br>B. Non-response selective to one group<br>C. Total response rate <80%<br>C. No description | A study where overall non-response rate is relatively small but selective to either cases or controls may introduce bias. |
| Overall risk of bias | | | |
| | Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in exposure domain<br><br>Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in exposure domain<br><br>Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in exposure domain | Low risk of bias: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 3 or 4 stars in exposure domain<br><br>Moderate risk of bias: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 stars in exposure domain<br><br>High risk of bias: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in exposure domain | |

**Appendix 5**. Flow diagram of study selection into the meta-analysis models



**Appendix 6**. Summary of the characteristic of the studies included in the systematic review
*The variables controlled for in each individual study as well as the number of times each variable was adjusted for by the included studies can be found in appendix 9 and 15. †Either income, education or occupation

| | **Cohorts studies (n)** | **Case-control studies (n)** |
|---|---|---|
| **Lung cancer diagnosis** | 19 studies | 43 studies |
| Study setting | Taiwan (8), South Korea (5), USA (2), China (1), Denmark (1), Finland (1), Lithuania (1) | China (16), USA (9), Taiwan (6), Canada (3), Singapore (2), Germany (2), South Korea (1), Nepal (1), Czech Republic (1), Italy (1), United Kingdom (1) |
| Publication date | 1980-1999 (0), 2000-2009 (3), 2010-2021 (16) | 1980-1999 (14), 2000-2009 (15), 2010-2021 (14) |
| Risk of bias | Low (7), moderate (10), high (2) | Low (5), moderate (15), high (23) |
| Main variables adjusted for* | Smoking (7), age (18), sex (18), any socioeconomic status indicator† (6), any comorbidity (10), passive smoking (0) | Smoking (32), age (25), sex (32), any socioeconomic status indicator* (2), any comorbidity (6), passive smoking (6) |
| **Lung cancer mortality** | 12 studies | 1 study |
| Study setting | China (5), USA (2), Denmark (2), Japan (1), South Korea (1), Italy (1) | China (1) |
| Publication date | 1980-1999 (7), 2000-2009 (1), 2010-2021 (4) | 1980-1999 (1), 2000-2009 (0), 2010-2021 (0) |
| Risk of bias | Low (4), moderate (1), high (7) | Low (0), moderate (0), high (1) |
| Main variables adjusted for* | Smoking (3), age (2), sex (8), any socioeconomic status indicator† (2), any comorbidity (6), passive smoking (1) | None |

**Appendix 7. Characteristics of included studies**

Table 1. Characteristic of included cohort studies that report lung cancer diagnosis as the outcome

| Study | Study setting (location, country) | Study population | Number of participants | Ascertainment of TB / source | Comparator group | Ascertainment of lung cancer / source | Recruitment period | Follow-up duration | Factors adjusted for |
|---|---|---|---|---|---|---|---|---|---|
| An et al (2020) | South Korea | General population, A representative sample established by the National Health Insurance Service (NHIS) | 22 656 | Only record linkage / NHIS database | Five matched people without TB according to the same database | Only record linkage / NHIS database | 2003-2013 | Follow-up until 2013 | Adjustment for smoking status (ever smoker, ex-smoker or current smoker), age, sex and household income |
| Bae et al (2013) | Seoul, South Korea | Representative sample of current male smokers | 7 009 | Interview / Seoul Male Cancer Cohort (SMCC) | Males without history of TB from the same cohort | Only record linkage / Seoul Regional Cancer Registry (SRCR), the Korea Central Cancer Registry (KCCR) and death certificates at Statistics Korea | 1992-1993 | 99 965 person-years; follow-up until 2008 | Adjustment for age, intake of tomatoes and coffee |
| Engels et al (2009) | Xuanwei, China | Farmers | 42 422 | Interview | Farmers without history of TB from the same community | Death records from hospitals, public security bureaus and public health bureaus | 1976-1992 | Follow-up until 1996 | None |
| Everatt et al (2016) | Lithuania | General population | 21 986 | Record linkage / Lithuanian Tuberculosis Registry | Estimates from the general population | Record linkage ( 66.9% were microscopically confirmed) / Lithuanian Cancer Registry (LCR) | 1998-2012 | 138 811.1 person years; 6.3 years (mean) | Standardization for age and sex |

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|---|---|---|---|---|---|---|---|---|---|
| Hong et al (2016) | South Korea | General population, participants of the Korean Cancer Prevention Study (KCPS) | 1 607 710 | Chest x-ray or past hospitalization for TB / National Health Insurance Service (NHIS) | Participants without TB that participated in the same study | Two or more hospitalizations for lung cancer / NHIS | 1997-2000 | 23 379 734 person-years; 14.5 years (mean) | Adjustment for smoking status (current smokers, exsmokers and never-smokers), amount of cigarettes per day (1-9, 10-19 and >=20 ), age, sex, socioeconomic status, alcohol consumption, hospitalizations for respiratory diseases |
| Huang et al (2015) | Taiwan | General population | 15 219 024 | Record linkage and more than two outpatient visits or one admission for TB / National Health Insurance Research Database (NHIRD) | People without history of TB from the same database | Record linkage with histological confirmation / NHIRD, Taiwan Cancer Registry Database (TCRD) | 2001-2003 | Follow-up until 2008 | Adjustment for age, sex, low income, urbanization, geographical area, asthma, COPD, diabetes, hyperlipidaemia, chronic kidney disease, smoking-related cancers |
| Jian et al (2016) | Taiwan | Asthma patients | 54 520 | Record linkage and more than two outpatient visits or one admission for TB / NHIRD | Asthma patients without history of TB | Record linkage with histological confirmation / NHIRD, Taiwan Cancer Registry Database (TCRD) | 2001-2005 | Follow-up until 2010 | Adjustment for age, sex, urbanization, COPD, pneumonia, diabetes, hyperlipidaemia, liver cirrhosis, chronic kidney disease, autoimmune disease, atopy dermatitis, rhinosinusitis, inhaled corticosteroids use, smoking-related cancers |
| Kuo et al (2013) | Taiwan | General population | 6 699 | Record linkage including prescription of at least two ant tuberculosis drugs for 2 months / NHIRD | Estimates from the general population | Record linkage – with histological confirmation / NHIRD, Catastrophic Illness Taiwan Database | 2000-2010 | 28 866 person-years; 3.8 years (median) | Standardization for age and sex |

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|---|---|---|---|---|---|---|---|---|---|
| Lai et al (2012) | Taiwan | Diabetes Mellitus patients and matched controls (aim of the study was to study diabetes as a risk factor for lung cancer) | 98 120 | Only record linkage / NHIRD | People without history of TB from the same sample | Only record linkage / NHIRD | 1995-2005 | 442 237 and 108 214 person-years for the DM and non-DM cohort respectively; follow-up until 2008 | Adjustment for age, sex, COPD, diabetes mellitus |
| Littman et al (2004) | USA | Heavy smokers and asbestos-exposed workers that participated in a cancer prevention trial (CARET trial). | 17 698 | Interview | Subjects without history of TB from the same trial | Review of clinical records and pathology reports from the diagnosing physician or hospital to confirm the tumor origin, location, and histology | 1985-1993 | 9.1 years (median); follow-up until 2002 | Adjustment for years smoked and years smoked squared, average number of cigarettes smoked per day and average number of cigarettes smoked per day squared, smoking status (former or current), age, sex, body mass index, trial intervention, asbestosis, asthma, chronic bronchitis or emphysema, pneumonia |
| Liu et al (2017) | Taiwan | Female COPD patients | 13 686 | Only record linkage / NHIRD | Female COPD patients without history of TB from the same database | Only record linkage / NHIRD | 1997-2011 | 9.78 years (median); follow-up until 2011 | Adjustment for age, income, pneumonia, bronchiectasis, pulmonary fibrosis, hypertension, diabetes mellitus, inhaled corticosteroids use |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Oh et al (2020) | South Korea | General population older than 40 years that participated in a nationwide survey (KNHANES study) | 20 252 | Interview / conducted as part of the survey | People without history of TB from the same survey | Record linkage with pathological confirmation / Korea Central Cancer Registry | 2008-2013 | 3.85 years (mean) for the TB group, 4 years (mean) for the control group; follow-up until 2014 | Adjustment for smoking status (current smokers, ex-smokers or never-smokers), age, sex, income level, education, body mass index, physical activity |
| Shebl et al (2010) | USA | AIDS patients | 322 675 | History of TB / HIV/AIDS registries | AIDS patients without TB from the same registry | Only record linkage / cancer registries in 11 US regions | 1977-2002 | 1 032 256 person-years; 10 years (not clear if mean or median) | Adjustment for age, sex, race, mode of HIV acquisition, CD4 count at AIDS onset, calendar year of AIDS onset |
| Shiels et al (2011) | Southwestern regions of Finland | Male smokers, aged 50 to 69 years old, that participated in a cancer prevention trial (ATBC trial) | 29 133 | Only record linkage / available from the National Hospital Discharge Register | Participants without history of TB from the same trial | Record linkage with histology known for 62% cases / Finnish Cancer Registry | 1985-1988 | Follow-up until 2005 | Adjustment for smoking measured with log cig-years (log [cigarettes smoked per day + 1] x number of years smoked) and age |
| Simonsen et al (2014) | Denmark | General population | 15 024 | Record linkage (58% cultured-confirmed) / Danish National Registry of Patients (DNRP) | Estimates from the general population | Record linkage with 89% cases verified morphologically / Danish Cancer Registry, Danish Pathology Register | 1978-2011 | 150 400 person-years; 8.5 years (median) | Standardization for age and sex |
| Wu et al (2011) | Taiwan | General population | 29 641 | Record linkage and prescriptions of at least 2 anti-tuberculosis medications for >28 day | Four matched control subjects with no TB record matched to each TB patient from the same database | Record linkage – with histological confirmation / NHIRD, Catastrophic Illness Taiwan Database | 1997-2008 | 5.86 years (mean) for TB patients, 6.22 years (mean) for controls | Adjustment for age, sex, COPD, diabetes mellitus, chronic renal failure, autoimmune disease |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Wu et al (2016) | Taiwan | COPD patients | 44 065 | Record linkage and either 2 outpatients visits or one admission for TB / NHIRD | COPD patients without history of TB from the same database | Record linkage – with histological confirmation / NHIRD, Taiwan Cancer Registry | 2001-2005 | (4.2 + 17.4) x $10^5$ person-months; follow-up until 2010 | Adjustment for age, sex, urbanization, number of visits for respiratory diseases within 2 years after index date, pneumonia, chronic kidney disease, diabetes mellitus, hyperlipidaemia, liver cirrhosis, autoimmune disease, atopy dermatitis, rhinosinusitis, inhaled corticosteroids use, oral corticosteroids use, bronchodilators use, statins and aspirin use |
| Yeo et al (2021) | South Korea | Random sample from the general population that participated in health examinations | 1 875 846 | Record linkage / Korean National Health Insurance (KNHI) database | People without history of TB from the same sample | Record linkage – with histological confirmation /KNHI database | 2009 | 15 341 796 person years; 8.2 years (mean) | Adjustment for smoking (pack-years), age, sex, BMI, COPD, diabetes mellitus, alcohol consumption, insurance coverage |
| Yu et al (2011) | Taiwan | General population | 716 872 | Only record linkage / NHIRD | People without history of TB from the same database | Record linkage / NHIRD | 1998-2000 | 37 951 person-years for the TB group and 6 571 088 person-years for the control group; follow-up until 2007 | Adjustment for age, sex, occupation, COPD, diabetes mellitus, hypertension, dyslipidaemia, smoking-related cancers |

Table 2. Characteristic of included case-control studies that report lung cancer diagnosis as the outcome

| Study | Study setting (location, country) | Number of participants | Case description | Control description | Type of controls | Ascertainment of lung cancer | Ascertainment of TB /source | Recruitment period | Factors adjusted for |
|---|---|---|---|---|---|---|---|---|---|
| Alavanja et al (1992) | Missouri, USA | 2 015 | Nonsmoking women from Missouri Cancer Registry | Nonsmoking women randomly sampled from driver's license files and the HCFA | Community controls | 76% histologically confirmed, others were cytologically confirmed (percentage no available) | Structured interview | 1986-1991 | Smoking history (lifetime nonsmoker or former smoker), age |
| Bodmer et al (2012) | United Kingdom | 91 301 | Subjects from the General Practice Research Database | Randomly sampled subjects without lung cancer from the General Practice Research Database | Community controls | Record linkage | Record linkage | 1995-2009 | Smoking status (non-smoker, current, past or unknown), age, sex, COPD, BMI, congestive heart failure, ischemic heart disease, stroke/transient ischemic attack, hypertension, dyslipidaemia, diabetes mellitus |
| Brenner et al (2001) | Pingliang and Qingyang, China | 2 650 | Subjects from 2 prefecture hospitals, a company hospital,15 county hospitals and local clinics | Randomly sampled subjects from a population census list | Community controls | 60% clinical-radiological diagnosis, 40% pathologically confirmed | Structured interview | 1994-1998 | Smoking category (heavy, moderate, light o never-smokers), age, sex, prefecture |
| Brenner et al (2010) | Toronto, Canada | 1 393 | Subjects from 4 major tertiary care hospitals in metropolitan Toronto | Subjects without any cancer and randomly sampled from property tax assessment files (45%) and the Mount Sinai Hospital Family Medicine Clinic (55%) | Community and hospital controls | 100% histology confirmed | Interview | 1997-2002 | Smoking (pack-years), age, sex, education, ethnicity |
| Brownson et al (2000) | Missouri, USA | 1 376 | Women from the Missouri Cancer Registry | Randomly sampled subjects from state driver's license files and from the HCFA | Community controls | 74% histologically confirmed, others were cytologically confirmed (percentage no available) | Interview | 1993-1994 | Smoking (pack-years) |
| Chan-yeung et al (2003) | Hong Kong, China | 661 | Subjects from the Queen Mary Hospital | Subjects without lung cancer from the Queen Mary Hospital | Hospital or other health service controls | 100% pathologically confirmed | Interview | 1999-2001 | Smoking duration and amount of cigarettes smoked (<20, 20-39, >40 pack-years), sex |
| Cheng et al (2012) | Taiwan | 1 485 | Women from the NHRI | Women from the NHRI hospitalized for orthopedic conditions, trauma, and other health conditions | Hospital or other health service controls | Record linkage | Record linkage | 2005-2008 | None |
| Chen et al (2021) | Xinjian, China | 16 884 | Subjects from a Cancer hospital | Subjects treated for benign tumors | Hospital controls | 100% histologically confirmed | Medical records | 2016-2018 | Age and sex |

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|---|---|---|---|---|---|---|---|---|---|
| Galeone et al (2008) | Harbin, China | 651 | Hospitalized subjects from the department of cardiothoracic surgery of the hospitals | Subjects without lung cancer from the cardiothoracic, urological and general surgery departments of the same hospitals as cases | Hospital or other health service controls | 100% histologically confirmed | Structured interview | 1987-1990 | Smoking status (never, current or exsmokers), smoking duration (for current smokers: <25, 25-35 and >35 years; for exsmokers: <5 and > 5 years from the last cigarette) and amount of smoking (for current cmokers: <10, 10-15 and >=15 cigarettes per day; for exsmokers: <15 and >=15 cigarettes per day), income, family history of lung and other cancers, occupational exposure to lung carcinogens |
| Hinds et al (1982) | Hawaii, USA | 629 | Women from Hawaii Tumor Registry | Women from a representative sample of 38 000 adults in Hawaii | Community controls | No information (tumor registry) | Medical records | 1968-1978 | None |
| Hosgood lll et al (2013) | Xuanwei, China | 996 | Subjects from 4 hospitals in Xuanwei | Randomly sampled subjects from the general population | Community controls | 61% clinical-radiological diagnosis, 39% pathologically confirmed | Interview | 1985-1990 | Smoking (never users; sole users of other types of tobacco or cigarettes smoked with a water pipe, ≤20 pack-years of cigarettes smoked without a water pipe; >20 pack-years of cigarettes smoked without a water pipe), sex, educational status, passive smoking, fuel type, family history of lung cancer |
| Ko et al (1997) | Kaohsiung, Taiwan | 210 | Women from Kaohsiung Medical College Hospital | Women with non-smoking related disease from a health check or ophthalmic department in the Kaohsiung Medical College Hospital | Hospital or other health service controls | 100% pathologically confirmed | Structured interview | 1992-1993 | Socioeconomic status, education residential area, industrial district, cooking fuels, fume extractor, vegetable consumption |
| Koshiol et al (2010) | Lombardia, Italy | 3 883 | Subjects from 13 hospitales in Lombardia | Randomly sampled subjects from the Regional Health Service database | Community controls | 95% pathologically confirmed, 5% clinical-radiological diagnosis | Structured interview | 2002-2005 | Smoking (pack-years and average packs/day), age, sex, region |
| Kreuzer et al (2001) | Germany | 857 | Men who were never-smokers from 15 study clinics in defined regions of East and West Germany | Men who were never-smokers and randomly sampled from mandatory registries or by a modified random-digit dialing from the same regions as cases | Community controls | 100% pathologically confirmed | Structured interview | 1990-1996 | Age, region |
| Kreuzer et al (2002) | Germany | 762 | Women who were never-smokers from | Women who were never-smokers and | Community controls | 100% pathologically confirmed | Structured interview | 1991-1996 | Age, region |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 15 study clinics in defined regions of East and West Germany | randomly sampled from mandatory registries or by a modified random-digit dialing from the same regions as cases | | | | | |
| Lai et al (2013) | Taiwan | 14 110 | Subjects from NHI | Subjects without lung cancer from NIH | Community controls | Record linkage | Record linkage | 2000-2009 | Smoking (ICD-9 codes, NIH is not reliable for this variable), age, sex, parkinson's disease, COPD, pneumoconiosis, asbestosis, alcoholism |
| Lai et al (2013) | Taiwan | 11 450 | Men from NHI | Randomly sampled men from NIH | Community controls | Record linkage | Record linkage | 2000-2010 | Smoking (ICD-9 codes, NIH is not reliable for this variable, COPD, asbestosis |
| Lee et al (2001) | Kaohsiung, Taiwan | 473 | Hospitalized subjects in the chest or oncology from Kaohsiung Medical University Hospital | Hospitalized subjects with conditions unrelated to tobacco use from Kaohsiung Medical University Hospital | Hospital or other health service controls | 100% histologically confirmed | Structured interview | 1993-1999 | Smoking (cumulative pack-years), sex, socioeconomic status, education, residential area |
| Liang et al (2009) | Shenyang, China | 505 | Women who were never-smokers from 18 hospitals in Shenyang. | Women who were never-smokers and randomly sampled from the general population using the Residential Registry in Shenyang | Community controls | 68% histologically confirmed, others were cytologically confirmed (percentage no available) | Structured interview | 2004-2007 | Age, passive smoking, years of schooling, marital status- - ethnicity, 5 years ago BMI, coal use, exposure to coal smoke and cooking fumes |
| Lim et al (2011) | Singapore | 1 808 | Women from the five major public sector hospitals in Singapore | Hospitalized women for conditions other than cancer at the same hospital as cases | Hospital or other health service controls | 96% pathologically confirmed | Structured interview | 1996-1998 and 2005-2008 | Age, passive smoking, number of years in school, family history of cancer, fruit and vegetable consumption, country of origin, dialect group, housing type |
| Liu et al (1993) | Guangzhou, China | 632 | Subjects from 8 major hospitals in Guangzhou | Inpatients of the surgery departments at 6 of the same hospitals as cases | Hospital or other health service controls | 32% pathologically confirmed | Structured interview | 1983-1984 | Smoking (not clear how, but they measured cigarettes smoked per day), sex, education, occupation, living area |
| Lo et al (2013) | Taiwan | 3 055 | Never-smokers from 6 tertiary medical centres in Taiwan | Never-smokers without lung cancer and randomly selected from the health-examination departments of the same six hospitals as cases | Hospital or other health service controls | 100% histologically confirmed | Structured interview | 2002-2009 | Age, sex, years of education |
| Luo et al (1996) | Fuzhou, China | 408 | Subjects from a special reporting system designed to cover all lung cancers in hospitals in urban Fuzhou | Subjects randomly sampled of the general population of urban Fuzhou | Community controls | 100% histologically confirmed | Structured interview | 1990-1991 | None |
| Mayne et | New York, | 868 | Nonsmoking subjects | Nonsmoking subjects | Community | 99% histologically | Structured | 1982-1984 | None |

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|---|---|---|---|---|---|---|---|---|---|
| al (1999) | USA | | from a special system established to rapid ascertainment of lung cancer in New York | randomly sampled from the New York State Department of Motor Vehicles' file of licensed drivers | controls | confirmed | interview | | |
| Osann et al (2000) | California, USA | 302 | Women with small cell carcinoma from 28 hospitals in Orange County and neighbouring areas | Women identified through a random digit dialling in the same region as cases | Community controls | 100% pathologically confirmed | Interview | 1990-1993 | Smoking (pack-years), years since quitting smoking, age, education |
| Park et al (2010) | South Korea | 2 615 | Subjects from 50 Korean general hospitals recruited in the nationwide KATRD study | Subjects from Chungju in the KMCC, a prospective cohort, who were voluntary participants in cancer screening surveys | Hospital or other health service controls | 100% histologically confirmed | Interview | 1996-2004 | Smoking status (ever or never smoker), age, sex |
| Ramanakumar et al (2006) – study I | Montreal, Canada | 2 746 | Subjects from 18 large hospitals in Metropolitan Montreal | Randomly sampled subjects from population based electoral lists in Metropolitan Montreal | Community controls * | 100% histologically confirmed | Structured interview | 1995-2001 | Smoking status (ever or never smoker), log of cigarettes-year, number of years since quitting smoking (0-2, 2-5, 5-10, 10-15 or >15 years), age, family income, year of schooling, ethnicity, type of respondent |
| Ramanakumar et al (2006) – study II | Montreal, Canada | 1 287 | Men from 18 large hospitals in Metropolitan Montreal | Randomly sampled men from population based electoral lists in Metropolitan Montreal | Community controls * | 100% histologically confirmed | Structured interview | 1979-1986 | Smoking status (ever or never smoker), log of cigarettes- year, number of years since quitting smoking (0-2, 2-5, 5-10, 10-15 or >15 years), age, sex, family income, years of school attendance, ethnicity, type of respondent |
| Raspanti et al (2016) | Chitwan, Nepal | 1 212 | Subjects from Koirala Memorial Cancer Hospital | Visitors of non-lung cancer patients from Koirala Memorial Cancer Hospital | Hospital or other health service controls | 92% histologically confirmed for a group of 209 cases, no data for the other 397 cases | Structured interview | 2009-2012 | Smoking status (ever or never smoker; they also calculated pack-years of smoking but it is not clear if this was included in the model), age, sex, socioeconomic status, passive smoking, household air pollution exposure |
| Samet et al (1986) | New Mexico, USA | 1 287 | Subjects from New Mexico Tumor Registry | Subjects randomly sampled from a list of residential telephone numbers and the New Mexico Medicare Financing Administration | Community controls | No information (tumor registry) | Interview | 1980-1982 | Smoking (duration of smoking in years, number of cigarettes smoked per day on average, duration of cessation in years, and a product term of smoking duration with an indication variable for age above and age below 65), age, sex, ethnicity |

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|---|---|---|---|---|---|---|---|---|---|
| Schwartz et al (1996) | Detroit, USA | 534 | Subjects who were never-smokers from the OCISS | Subjects without any cancer who were never-smokers and were sampled by random-digit dialling in the OCISS | Community controls | 86% histologically confirmed | Interview | 1984-1987 | Age, gender, race |
| Seow et al (2002) | Singapore | 1 066 | Women from 3 major hospitals in Singapore | Women without lung cancer from the same hospitals as cases | Hospital or other health service controls | 100% pathologically confirmed | Structured interview | 1996-1998 | None |
| Wang et al (1996) a | Guangzhou, China | 780 | Inpatients from 5 hospitals in Guangzhou | Inpatients without any cancer from the same hospitals as cases | Hospital or other health service controls | 100% pathologically confirmed | Interview | 1990-1993 | Smoking status (no more details), passive smoking, chronic bronchitis/emphysema, family history of tumors, consumption of pickled and cured foods |
| Wang et al (1996) b | Shenyang, China | 270 | Women who were never-smokers from 18 hospitals in Shenyang | Women who were never-smokers and randomly sampled from the general population in urban areas of Shenyang | Community controls | 57% pathologically confirmed, 43% clinical-radiological diagnosis | Structured interview | 1992-1994 | None |
| Wang et al (2009) | Hong Kong, China | 504 | Women who were never-smokers from the largest oncology centre in Hong Kong | Women who were never-smokers and randomly sampled using the residential telephone in Hong Kong | Community controls | 100% pathologically confirmed | Structured interview | 2002-2004 | Age, employment, total dish year, intake of yellow/orange vegetables, dark green vegetables, multivitamins |
| Wang et al (2014) | Changchun, China | 1 000 | Subjects from a hospital (not specified) in Changchun | Randomly selected subjects with routine physical examinations in the same hospital as cases | Hospital or other health service controls | 100% histologically confirmed | Structured interview | 2010-2012 | Smoking (pack-years), COPD, family history of cancer |
| Wu et al (1988) | California, USA | 672 | Women with adenocarcinoma from the Cancer Surveillance Program, a population-based tumour registry, in Los Angeles County | Women selected from each case's neighbourhood in Los Angeles County | Community controls | 100% histologically confirmed | Structured interview | 1983-1986 | Smoking (pack-years), years since smoking stopped, depth of inhalation, social class according to father occupation (blues or white collar worker) |
| Wu et al (1995) | USA | 1 633 | Women who were never-smokers from 5 major metropolitan areas in USA | Women who were never-smokers and randomly selected through digit dialing and from the HCFA from the same areas as cases | Community controls | Microscopically confirmed diagnosis | Interview | 1985-1990 | Age-area-ethnicity-education-passive smoking |
| Wu-Williams et al (1990) | Harbin and Shenyang, China | 1 924 | Women from cancer registries of Harbin and Shenyang | Randomly sample women of the general population in the same location as cases | Community controls | 42% histologically confirmed, 32% cytology confirmed, 26% clinical- | Structured interview | 1985-1987 | Smoking (non-smoker, smoked 1-9 cigarettes per day and 1-29 years, 2-19 and 30-39 years, 1-19 and >40 years, >20 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | radiological diagnosis | | | cigarettes per day and 1-29 years >20 and 30-39 years, >20 and >40 years), age, education, study area |
| Yang et al (2015) | Guangzhou and Suzhou, China | 3 238 | Subjects from urban hospitals and one suburb hospital in Guangzhou and Suzhou | Subjects without any cancer from healthy check-up programs in the community health stations in the same city as cases | Hospital or other health service controls | 100% histologically confirmed | Structured interview | 2007-2010 | Smoking status (ever or never smoker), pack-years of smoking (low, 0-5; moderate, 6-20; or high, >20), age, sex, passive smoking, emphysema, education, BMI, educational experience, centre, packs-years occupational exposure to metallic toxicant, housing ventilation, biomass burning, cured meat, vegetables/fruits |
| Zatloukal et al (2003) | Czech Republic | 1 990 | Women admitted to Prague University Hospital Na Bulovce | Women who were spouses, relatives, or friends of other patients hospitalized at Prague University Hospital Na Bulovce | Hospital or other health service controls | 100% histologically confirmed | Structured interview | 1998-2002 | Smoking (pack-years), age, education, residence, residence |
| Zheng et al (1987) | Shanghai, China | 2 863 | Men from Shanghai Cancer Registry and a specially established lung cancer rapid-reporting system operated by the Shanghai Cancer Institute | Randomly sampled subjects from the general population in Shanghai urban area | Community controls | 62% histologically confirmed, 30% cytology confirmed, 7% clinical-radiological diagnosis | Structured interview | 1984-1986 | Smoking category (non-smoker, light, moderate or heavy smoker), age, sex, education |
| Zhou et al (2000) | Shenyang, China | 144 | Women with adenocarcinoma from 18 major hospitals in Shenyang | Randomly selected women from the general population in various areas of Shenyang | Community controls | 100% histologically confirmed | Structured interview | 1991-1995 | None |

When the setting is not specified below the country level, the participants were selected nationwide or from a large area of the corresponding country. Non-smokers include never and former smokers. Some studies report a nonsmoking definition that matches corresponding to a never-smokers definition, those studies were considered to only as never-smokers due to uniformity criteria. Pathologically confirmed lung cancer includes histological AND / OR cytological confirmation. HCFA: Health Care Financing Administration. NHRI: National Health Research Institutes from Taiwan. NHI: National Health Insurance from Taiwan. KARTD: Korean academy of tuberculosis and respiratory disease. KMCC: Korean Multi-Center Cancer Cohort. OCISS: Occupational Cancer Incidence Surveillance Study. COPD: chronic obstructive pulmonary disease. BMI: body mass index

Table 3. Characteristic of included cohort studies that report lung cancer mortality as the outcome

| Study | Study setting (location, country) | Study population | Number of participants | Ascertainment of TB / source | Comparator group | Ascertainment of lung cancer death / source | Recruitment period | Follow-up duration | Factors adjusted for |
|---|---|---|---|---|---|---|---|---|---|
| Boice et al (1980) | Massachusetts, USA | General population, only females, treated for TB before availability of isoniazid | 1090 | Medical records / 2 Massachusetts hospitals | Estimates from females in the general population | Death certificates / hospitals | 1930-1954 | 23 094 person-years; 21.2 years (mean); follow-up until 1975 | Standardizes for age |
| Chen et al (1990) | Hebein province, China | Males mine workers with silicosis | 5406 | Interview | Workers without history of TB from the same mine | Death records / pension department | 1970-1982 | 6102.7 person-years for the TB group and 61633.7 person-years for the non-TB group | None |
| Christensen et al (2014) | Denmark | General population | 25608 | Record linkage with 82.6 % microbiological confirmation / Danish Tuberculosis Registry, Danish National Patient Registry (DNPR) | Matched people randomly sampled from the general population | Death certificates / Danish Registry of Causes of Death | 1977-2008 | TB group: 64 212 person-years; 8.1 years (median) Control group: 234 484 person-years; 10.5 years (median) Total population: 298 696 person-years | Matched on age and sex |
| Davis et al (1989) | Massachusetts, USA | General population | 13 385 | Medical records / 12 hospitals | Estimates from the general population | Death certificates / hospitals | 1925-1954 | 25 years (mean); follow-up until 1986 | Standardizes for age and sex |

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|---|---|---|---|---|---|---|---|---|---|
| Engels et al (2009) | Xuanwei, China | Farmers | 42 422 | Interview | Farmers without history of TB from the same community | Death records / hospitals, public security bureaus and public health bureaus | 1976-1992 | Follow-up until 1996 | They adjust one variable at a time: smoking per day (cigarettes per day), age, sex, education level, use of smoky coal, asthma, chronic bronchitis, emphysema, family history of tuberculosis, walking hours spent indoors, number of rooms in house) |
| Floe et al (2018) | Denmark | General population | 42 140 | Only record linkage / National Patient Registry | Matched controls randomly sampled from the general population | No description | 1998-2010 | Follow-up until 2010 | None |
| Gao et al (1992) | Shangai, China | General population | 30 373 | There is only and exposed group | Estimates from the general population | No description | 1972-1986 | Follow-up until 1986 | Standardizes for age and sex |
| Hong et al (2016) | South Korea | General population, participants of the Korean Cancer Prevention Study (KCPS) | 1 607 710 | Chest x-ray or past hospitalization for TB / National Health Insurance Service (NHIS) | Participants without TB that participated in the same study | Death certificates / National Statistical Office in Korea | 1997-2000 | 23 379 734 person-years; 14.5 years (mean) | Adjusts for smoking status (current smokers, exsmokers and never-smokers), amount of cigarettes per day (1-9, 10-19 and >=20), age, sex, alcohol consumption-socioeconomic status-diabetes mellitus and respiratory diseases hospitalizations |
| Leung et al (2013) | Hong Kong, China | Clients enrolled at the 18 health centers for the elderly | 61 239 | Medical records (49.2% bacteriologically confirmed – 50.8% clinical, radiological and/or histological plus appropriate response to anti-TB | Elderly without history of TB from the same centers | Death registry / statistical section of the Department of Health | 2000-2011 | 490 258 person-years | Adjusts for smoking status, age, sex, passive smoking, language, education level, marital status, housing situation, public means, tested financial assistance status, alcohol use, body mass index, COPD, asthma and |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | treatment) / territory-wide TB notification registry | | | | | family history of malignancy |
| Merlo et al (1995) | Genoa, Italy | People with silicosis | 515 | No description | People with silicosis without history of TB | No description | 1961-1980 | 11.56 years (mean); follow-up until 1981 | None |
| Ng et al (1990) | Hong Kong, China | Men with silicosis | 1 419 | Interview | Those without history of TB from the same sample | Death records / Registry of Persons, Registry of Deaths | 1980 | 7 429.8 person-years; follow-up until 1986 | None |
| Sasaki et al (1992) | Nagoya, Japan | General population | 3 580 | Medical records / Nagoya TB Registry | Estimates from the general population | Death certificates and/or medical records | 1979-1981 | 12 702 person-years; follow-up until 1983 | Standardizes for age and sex |

Table 4. Characteristic of included case-control studies that report lung cancer mortality as the outcome

| Study | Study setting (location, country) | Number of participants | Case description | Control description | Type of controls | Ascertainment of lung cancer mortality | Ascertainment of TB /source | Recruitment period | Factors adjusted for |
|---|---|---|---|---|---|---|---|---|---|
| Fu et al (1984) | Harbin, China | 1 046 | Lung cancer deaths from medical certificates, held by the police substation in each of 3 districts in Harbin, and data from death reports held by each district's Sanitation and Antiepidemic Station | Non-respiratory deaths in the same district of residence held by the same source as cases | Community controls | Death certificates | Interview with relatives of the dead | 1977-1979 | None |

**Appendix 8. Assessment of Risk of Bias in included studies**

| | Selection | | | | Comparability | Outcome | | | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|
| | Representativeness of the exposed cohort (maximum 1 star) | Selection of the non-exposed cohort (maximum 1 star) | Ascertainment of exposure (maximum 2 stars) | Dealing with reverse causation bias (maximum 1 star) | Comparability of the cohorts on the basis of the design or analysis (maximum 2 stars) | Assessment of outcome (maximum 1 star) | Was follow-up long enough for outcomes to occur (maximum 1 star) | Adequacy of follow-up (maximum 1 star) | |
| An et al (2020) | 1 star | 1 star | 1 star | 1 star | 2 stars | none | 1 star | 1 star | LOW |
| Bae et al (2013) | 1 star | 1 star | none | none | 1 star | none | 1 star | 1 star | MODERATE |
| Engels et al (2009) | 1 star | 1 star | none | 1 star | none | none | 1 star | none | HIGH |
| Everatt et al (2016) | 1 star | 1 star | 2 stars | 1 star | 2 stars | none | 1 star | 1 star | LOW |
| Hong et al (2016) | 1 star | 1 star | 1 star | none | 2 stars | none | 1 star | 1 star | MODERATE |
| Huang et al (2015) | 1 star | 1 star | 1 star | none | 1 star | 1 star | 1 star | 1 star | MODERATE |
| Jian et al (2016) | none | 1 star | 1 star | none | 1 star | 1 star | 1 star | 1 star | MODERATE |
| Kuo et al (2013) | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | LOW |
| Lai et al (2012) | none | 1 star | 1 star | none | 1 star | none | 1 star | 1 star | MODERATE |
| Littman et al (2004) | none | 1 star | none | none | 2 stars | 1 star | 1 star | 1 star | HIGH |
| Liu et al (2017) | none | 1 star | 1 star | none | 1 star | none | 1 star | 1 star | MODERATE |
| Oh et al (2020) | 1 star | 1 star | none | none | 2 stars | 1 star | none | 1 star | MODERATE |
| Shebl et al (2010) | none | 1 star | 1 star | 1 star | 1 star | none | 1 star | 1 star | MODERATE |
| Shiels et al (2011) | 1 star | 1 star | 1 star | 1 star | 2 stars | none | 1 star | 1 star | LOW |
| Simonsen et al (2014) | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | LOW |
| Wu et al (2011) | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | LOW |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Wu et al (2016) | none | 1 star | 1 star | none | 1 star | 1 star | 1 star | 1 star | MODERATE |
| Yeo et al (2021) | 1 star | 1 star | 1 star | 1 star | 2 stars | 1 star | 1 star | 1 star | LOW |
| Yu et al (2011) | 1 star | 1 star | 1 star | none | 1 star | none | 1 star | 1 star | MODERATE |

Table 1. Risk of bias in included cohort studies for the lung cancer diagnosis outcome

Table 2. Risk of bias in included case-control studies for the lung cancer diagnosis outcome

| | **Selection** | | | | **Comparability** | **Exposure** | | | **Overall risk of bias** |
|---|---|---|---|---|---|---|---|---|---|
| | Is the case definition adequate? (maximum 1 star) | Representativeness of the cases (maximum 1 star) | Selection of controls (maximum 1 star) | Definition of controls (maximum 1 star) | Comparability of cases and controls on the basis of the design or analysis (maximum 2 stars) | Assessment of exposure (maximum 2 stars) | Same method of ascertainment for cases and controls (maximum 1 star) | Non-response rate (maximum 1 star) | |
| Alavanja et al (1992) | 1 star | 1 star | 1 star | 1 star | 2 stars | none | 1 star | none | HIGH |
| Bodmer et al (2012) | none | 1 star | 1 star | 1 star | 2 stars | 1 star | 1 star | 1 star | LOW |
| Brenner et al (2001) | none | 1 star | 1 star | none | 2 stars | none | 1 star | 1 star | MODERATE |
| Brenner et al (2010) | 1 star | none | none | 1 star | 2 stars | none | 1 star | none | HIGH |
| Brownson et al (2000) | 1 star | 1 star | 1 star | 1 star | 1 star | none | 1 star | 1 star | MODERATE |
| Chan-yeung et al (2003) | 1 star | none | none | 1 star | 1 star | none | 1 star | none | HIGH |
| Cheng et al (2012) | none | 1 star | none | 1 star | none | 1 star | 1 star | 1 star | HIGH |
| Galeone et al (2008) | 1 star | none | none | none | 1 star | none | 1 star | none | HIGH |
| Chen et al (2021) | 1 star | 1 star | none | 1 star | 1 star | 1 star | 1 star | 1 star | LOW |
| Hinds et al (1982) | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | LOW |
| Hosgood lll et al (2013) | none | 1 star | 1 star | none | 1 star | none | 1 star | 1 star | MODERATE |
| Ko et al (1997) | 1 star | 1 star | none | 1 star | 1 star | 1 star | 1 star | 1 star | LOW |
| Koshiol et al (2010) | 1 star | 1 star | 1 star | none | 2 stars | 1 star | 1 star | 1 star | LOW |
| Kreuzer et al (2001) | 1 star | none | 1 star | none | 2 stars | none | 1 star | 1 star | MODERATE |
| Kreuzer et al (2002) | 1 star | none | 1 star | none | 2 stars | none | 1 star | 1 star | MODERATE |
| Lai et al (2013) | none | none | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | MODERATE |
| Lai et al (2013) | none | none | 1 star | 1 star | none | 1 star | 1 star | 1 star | HIGH |
| Lee et al (2001) | 1 star | 1 star | none | 1 star | 1 star | none | 1 star | 1 star | MODERATE |
| Liang et al (2009) | none | 1 star | 1 star | none | 2 stars | none | 1 star | 1 star | MODERATE |
| Lim et al (2011) | 1 star | 1 star | none | 1 star | 2 stars | none | 1 star | 1 star | MODERAT |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | E |
| Liu et al (1993) | none | 1 star | none | none | 1 star | none | 1 star | 1 star | HIGH |
| Lo et al (2013) | 1 star | 1 star | none | 1 star | 2 stars | none | 1 star | 1 star | MODERATE |
| Luo et al (1996) | 1 star | 1 star | 1 star | 1 star | none | none | 1 star | none | HIGH |
| Mayne et al (1999) | 1 star | none | 1 star | none | none | none | 1 star | none | HIGH |
| Osann et al (200) | 1 star | none | 1 star | none | 2 stars | none | 1 star | none | HIGH |
| Park et al (2010) | 1 star | none | none | 1 star | 2 stars | none | none | 1 star | HIGH |
| Ramanakumar et al (2006) – study I | 1 star | 1 star | 1 star | none | 2 stars | none | 1 star | none | HIGH |
| Ramanakumar et al (2006) – study II | 1 star | 1 star | 1 star | none | 2 stars | none | 1 star | none | HIGH |
| Raspanti et al (2016) | 1 star | 1 star | none | none | 2 stars | none | 1 star | none | HIGH |
| Samet et al (1986) | none | 1 star | 1 star | 1 star | 2 stars | none | 1 star | 1 star | MODERATE |
| Schwartz et al (1996) | 1 star | 1 star | 1 star | 1 star | 2 stars | none | 1 star | none | HIGH |
| Seow et al (2002) | 1 star | 1 star | none | 1 star | 1 star | none | 1 star | 1 star | MODERATE |
| Wang et al (1996) a | 1 star | none | none | 1 star | 1 star | none | 1 star | none | HIGH |
| Wang et al (1996) b | none | 1 star | 1 star | none | 1 star | none | 1 star | none | HIGH |
| Wang et al (2009) | 1 star | 1 star | 1 star | 1 star | 2 stars | none | 1 star | none | HIGH |
| Wang et al (2014) | 1 star | none | none | 1 star | 1 star | none | 1 star | none | HIGH |
| Wu et al (1988) | 1 star | none | 1 star | none | 1 star | none | 1 star | none | HIGH |
| Wu et al (1995) | 1 star | 1 star | 1 star | none | 2 stars | none | 1 star | none | HIGH |
| Wu-Williams et al (1990) | none | 1 star | 1 star | 1 star | 2 stars | none | 1 star | none | HIGH |
| Yang et al (2015) | 1 star | 1 star | none | 1 star | 2 stars | none | 1 star | 1 star | MODERATE |
| Zatloukal et al (2003) | 1 star | 1 star | none | none | 2 stars | none | 1 star | 1 star | MODERATE |
| Zheng et al (1987) | 1 star | 1 star | 1 star | 1 star | 2 stars | none | 1 star | 1 star | MODERATE |
| Zhou et al (2000) | 1 star | none | 1 star | none | none | none | 1 star | none | HIGH |

Table 3. Risk of bias in included cohort studies for the lung cancer mortality outcome

| | Selection | | | | Comparability | Outcome | | | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|
| | Representativeness of the exposed cohort (maximum 1 star) | Selection of the non-exposed cohort (maximum 1 star) | Ascertainment of exposure (maximum 2 stars) | Dealing with reverse causation bias (maximum 1 star) | Comparability of the cohorts on the basis of the design or analysis (maximum 2 stars) | Assessment of outcome (maximum 1 star) | Was follow-up long enough for outcomes to occur (maximum 1 star) | Adequacy of follow-up (maximum 1 star) | |
| Boice et al (1980) | 1 star | 1 star | 1 star | none | 1 star | 1 star | 1 star | 1 star | MODERATE |
| Chen et al (1990) | none | 1 star | none | none | none | 1 star | 1 star | none | HIGH |
| Christensen et al (2014) | 1 star | 1 star | 2 stars | none | none | 1 star | 1 star | 1 star | HIGH |
| Davis et al (1989) | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | LOW |
| Engels et al (2009) | 1 star | 1 star | none | 1 star | none | 1 star | 1 star | none | HIGH |
| Floe et al (2018) | 1 star | 1 star | 1 star | none | none | none | 1 star | 1 star | HIGH |
| Gao et al (1992) | 1 star | 1 star | 1 star | 1 star | 1 star | none | 1 star | none | HIGH |
| Hong et al (2016) | 1 star | 1 star | 1 star | 1 star | 2 stars | 1 star | 1 star | none | LOW |
| Leung et al (2013) | 1 star | 1 star | 2 stars | 1 star | 2 stars | 1 star | 1 star | 1 star | LOW |
| Merlo et al (1995) | none | 1 star | none | none | none | none | 1 star | none | HIGH |
| Ng et al (1990) | none | 1 star | none | none | none | 1 star | none | 1 star | HIGH |
| Sasaki et al (1992) | 1 star | 1 star | 1 star | 1 star | 1 star | 1 star | none | 1 star | LOW |

Table 4. Risk of bias in included case-control studies for the lung cancer mortality outcome

| Study | Selection | | | | Comparability | Outcome | | | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|
| | Case definition (maximum 1 star) | Representativeness of the cases (maximum 1 star) | Selection of controls (maximum 1 stars) | Definition of controls (maximum 1 star) | Comparability of cases and controls on the basis of the design or analysis (maximum 2 stars) | Ascertainment of exposure (maximum 2 stars) | Same method of ascertainment for cases and controls (maximum 1 star) | Non-response rate (maximum 1 star) | |
| Fu et al (1984) | 1 star | none | 1 star | none | none | none | 1 star | none | HIGH |

**Appendix 9. Results of individual studies**

Table 1. Effect size estimates of lung cancer diagnosis risk among persons with a previous episode of TB in cohort studies

| Study | Unadjusted effect measure | Unadjusted effect estimate | Lower CI | Upper CI | 2 x 2 table* | | | | Adjusted effect measure | Adjusted effect estimate | Lower CI | Upper CI | Factors adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | A | B | C | D | | | | | |
| An et al (2020) | HR | 4.1 | 3.09 | 5.45 | 86 | 3690 | 108 | 18772 | HR | 4.18 | 3.15 | 5.56 | Smoking status (ever smoker, ex-smoker or current smoker), age, sex, household income |
| Bae et al (2013) | RR | 2.01 | 1.09 | 3.47 | 16 | 77 | 642 | 6274 | RR | 1.85 | 1.08 | 3.19 | Age, intake of tomatoes, coffee |
| Engels et al (2009) | HR† | 5.86 | 3.03 | 11.37 | - | - | - | - | - | - | - | - | - |
| Everatt et al (2016) | - | not applicable § | - | - | 477 | 21509 | - | - | SIR | 3.83 | 3.49 | 4.19 | Standardization based on age and sex |
| Hong et al (2016) | RR‡ | 2.70 | 2.56 | 2.84 | 1573 | 77725 | 11246 | 1517166 | HR¶ | 1.38 | 1.31 | 1.46 | Smoking status (current smokers, ex-smokers and never-smokers), amount of cigarettes per day (1-9, 10-19 and >=20), age, sex, socioeconomic status, alcohol consumption, diabetes mellitus, respiratory diseases hospitalizations |
| Huang et al (2015) | RR‡ | 4.49 | 4.23 | 4.78 | 1052 | 110469 | 31707 | 15075796 | HR¶ | 1.62 | 1.12 | 2.35 | Age, sex, asthma, chronic obstructive pulmonary disease, low income, urbanization, geographical area, diabetes, hyperlipidaemia, chronic kidney disease, smoking related cancers |
| Jian et al (2016) | - | - | - | - | - | - | - | - | HR | 1.08 | 0.57 | 2.03 | Age, sex, urbanization, inhaled corticosteroids use, medication, chronic obstructive pulmonary disease, smoking related cancers, diabetes, hyperlipidaemia, liver cirrhosis, chronic kidney disease, autoimmune disease, atopy dermatitis, rhinosinusitis, pneumonia |
| Kuo et al (2013) | - | not applicable § | - | - | 159 | 6540 | - | - | SIR | 4.09 | 3.48 | 4.78 | Standardization based on age and sex |
| Lai et al (2012) | HR | 2.96 | 2.17 | 4.03 | - | - | - | - | HR | 1.60 | 1.16 | 2.20 | Age, sex, diabetes mellitus, chronic obstructive pulmonary disease |
| Littman et al (2004) | - | - | - | - | - | - | - | - | HR | 1.00 | 0.65 | 1.54 | Years smoked and years smoked squared, average number of cigarettes smoked per day and average number of cigarettes smoked per day squared, smoking status (former or current), age, sex, body mass index, study arm, asbestosis, asthma, chronic bronchitis or emphysema, pneumonia |
| Liu et al (2017) | HR | 2.87 | 2.15 | 3.83 | 57 | 926 | 248 | 12455 | HR | 2.65 | 1.95 | 3.59 | Age, income, pneumonia, bronchiectasis, pulmonary fibrosis, hypertension, diabetes, inhaled corticosteroids use |
| Oh et al (2020) | HR | 2.84 | 1.41 | 5.71 | - | - | - | - | HR | 1.71 | 0.86 | 3.39 | Smoking status (current smokers, ex- smokers or never-smokers), age, sex, education, income level, body mass index, moderate or vigorous |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | physical activity |
| Shebl et al (2010) | - | - | - | - | - | - | - | - | HR | 1.11 | 0.81 | 1.51 | Age, sex, race, mode of HIV acquisition, CD4 count at AIDS onset, calendar year of AIDS onset |
| Shiels et al (2011) | RR | 1.52‡ | 1.16 | 2.00 | 44 | 229 | 3058 | 25802 | HR | 1.97 | 1.5 | 2.65 | Smoking measured with log cig-years (log [cigarettes smoked per day + 1] x number of years smoked), age |
| Simonsen et al (2014) | - | not applicable § | - | - | 429 | 14595 | - | - | SIR | 3.40 | 3.09 | 3.74 | Standardization based on age and sex |
| Wu et al (2011) | RR | 1.64‡ | 1.26 | 2.14 | 74 | 5583 | 191 | 23793 | HR | 1.64 | 1.24 | 2.15 | Age, gender, chronic obstructive pulmonary disease, diabetes, chronic renal failure, autoimmune disease |
| Wu et al (2016) | - | - | - | - | - | - | - | - | HR | 1.42 | 0.89 | 2.26 | Age, sex, pneumonia, urbanization, inhaled corticosteroids, oral corticosteroids, long-acting agonists, short-acting beta agonists, theophylline, statins, aspirin, chronic kidney disease, diabetes, hyperlipidaemia, liver cirrhosis, smoking-related cancers, autoimmune disease, atopy dermatitis, rhinosinusitis, number of visits for respiratory diseases within 2 years after index data |
| Yeo et al (2021) | HR | 2.57 | 2.35 | 2.81 | 485 | 22083 | 16262 | 1837016 | HR | 1.34 | 1.22 | 1.47 | Smoking (pack-years), age, sex, BMI, COPD, diabetes mellitus, alcohol consumption, insurance coverage |
| Yu et al (2011) | HR | 11.9 | 9.73 | 14.6 | 100 | 4380 | 1584 | 710808 | HR | 3.32 | 2.7 | 4.09 | Age, sex, occupation, diabetes, hypertension, dyslipidaemia, chronic obstructive pulmonary disease, smoking related cancers |

*A: number of exposed with outcome, B: exposed without outcome, C: unexposed with outcome, D: unexposed without outcome reported in the paper. † Unadjusted effect estimate and confidence intervals calculated from unadjusted effect estimates reported separately for lung cancer diagnosis 0-4.9 and >5 years after tuberculosis diagnosis. ‡ Unadjusted effect estimates and confidence intervals calculated from the 2 x 2 table. § The study reports SIR using lung cancer incidence in the general population. ¶Adjusted effect estimate and confidence intervals calculated from adjusted effect estimates reported separately for males and females.

Table 2. Effect size estimates of lung cancer diagnosis risk among persons with a previous episode of TB in case-control studies

| Study | Unadjusted effect measure | Unadjusted effect estimate | Lower CI | Upper CI | 2 x 2 table* | | | | Adjusted effect measure | Adjusted effect estimate | Lower CI | Upper CI | Set of factors adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | A | B | C | D | | | | | |
| Alavanja et al (1992) | OR | 1.82† | 0.85 | 1.12 | 15 | 19 | 600 | 1381 | OR | 2.0 | 1.0 | 4.1 | Smoking history (lifetime nonsmoker or former smoker), age |
| Bodmer et al (2012) | OR | 0.97 | 0.84 | 1.12 | 226 | 1395 | 12817 | 76863 | OR | 0.9 | 0.8 | 1.05 | Smoking status (non-smoker, current, past or unknown), age, sex, body mass index, congestive heart failure, ischemic heart disease-stroke/transient ischemic attack, hypertension, dyslipidaemia, diabetes mellitus, chronic obstructive pulmonary disease |
| Brenner et al (2001) | OR | 3.8† | 2.7 | 5.38 | 103 | 59 | 783 | 1705 | OR | 3.8 | 2.7 | 5.4 | Smoking category (heavy, moderate, light o never-smokers), age, sex, prefecture |
| Brenner et al (2010) | OR | 2.58† | 0.65 | 10.73 | 6 | 5 | 439 | 943 | OR | 2.6 | 0.7 | 9.2 | Pack-years of smoking, age, sex, education and ethnicity |
| Brownson et al (2000) | OR | 0.86† | 0.33 | 2.19 | 10 | 12 | 666 | 688 | OR | 0.9 | 0.4 | 2.2 | Pack-years of smoking |
| Chan-yeung et al (2003) | OR | 1.78† | 1.05 | 3.06 | 45 | 27 | 285 | 304 | OR | 1.83‡ | 1.1 | 3.19 | Smoking duration and amount of cigarettes smoked (<20, 20-39, >40 pack-years), sex |
| Cheng et al (2012) | OR | 3.03 | 1.79 | 5.13 | 26 | 37 | 271 | 1151 | - | - | - | - | - |
| Chen et al (2021) | OR | 4.34† | 3.53 | 5.33 | 233 | 175 | 3745 | 12741 | OR | 1.44 | 1.06 | 1.95 | Age and sex |
| Galeone et al (2008) | OR | 3.97† | 2.05 | 7.85 | 30 | 17 | 186 | 418 | OR | 3.82 | 1.97 | 7.41 | Smoking status (never, current or ex-smokers), duration of smoking (for current smokers <25, 25-35 and >35 years; for ex-smokers <5 and > 5 years from the last cigarette), amount of smoking (for current smokers: <10, 10-15 and ≥ 15 cigarettes per day; for ex-smokers: <15 and ≥ 15 cigarettes per day), income, family history of lung cancer and other cancers, occupational exposure to lung carcinogens |
| Hinds et al (1982) | OR | 1.6 | 0.6 | 4.3 | 7 | 9 | 203 | 410 | - | - | - | - | - |
| HosgoodIII et al (2013) | OR | 12.56† | 3.08 | 110 | 24 | 2 | 474 | 496 | OR | 83.70 | 11.00 | 634.70 | Smoking (never users; sole users of other types of tobacco or cigarettes smoked with a water pipe, ≤20 pack-years of cigarettes smoked without a water pipe; >20 pack-years of cigarettes smoked without a water pipe), passive smoking, sex, fuel type, educational status, family history of lung cancer |
| Ko et al (1997) | OR | 4.54† | 1.39 | 19.2 | 16 | 4 | 89 | 101 | OR | 5.9 | 1.3 | 25.9 | Socioeconomic status, residential area, education, industrial district, cooking fuels, fume extractor, vegetable consumption |
| Koshiol et al | OR | 1.1† | 0.75 | 1.6 | 60 | 61 | 1777 | 1985 | OR | 0.96 | 0.62 | 1.48 | Pack-years and smoking intensity (average packs/day) , |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (2010) | | | | | | | | | | | | | age, gender, region |
| Kreuzer et al (2001) | OR | 1.19† | 0.23 | 3.97 | 3 | 35 | 55 | 764 | OR | 1.2 | 0.04 | 1.41 | Age, area |
| Kreuzer et al (2002) | OR | 1.7† | 0.75 | 3.74 | 13 | 18 | 218 | 513 | OR | 1.61 | 0.77 | 3.37 | Age, region |
| Lai et al (2013) | OR | 3.66 | 3.23 | 4.14 | 516 | 655 | 2306 | 10633 | OR | 2.96 | 2.60 | 3.37 | Smoking (ICD-9 codes, the NIH database is not reliable for this variable), age, sex, Parkinson's disease, chronic obstructive pulmonary disease, pneumoconiosis, asbestosis, alcoholism |
| Lai et al (2013) | OR | 3.31 | 2.73 | 4.02 | 193 | 248 | | | OR | 2.42 | 1.98 | 2.95 | Smoking (ICD-9 codes, the NIH database is not reliable for this variable), chronic obstructive pulmonary disease, asbestosis |
| Lee et al (2001) | OR | 1.4† | 0.87 | 2.25 | 45 | 51 | 146 | 231 | OR | 6.88‡ | 3.03 | 15.63 | Smoking (cumulative pack-years), residential area, education, socioeconomic status, sex |
| Liang et al (2009) | OR | 4.18† | 1.43 | 14.77 | 16 | 5 | 210 | 274 | OR | 4.7 | 1.6 | 13.2 | Age, passive smoking, marital status, years of schooling, ethnicity, 5 year ago body mass index, coal use, exposure to coal smoke and cooking fumes |
| Lim et al (2011) | OR | 1.66† | 0.99 | 2.73 | 27 | 53 | 406 | 1322 | OR | 1.58 | 0.95 | 2.62 | Age, passive smoking, family history of cancer, fruit and vegetable consumption, country of origin, dialect group, housing type, number of years in school |
| Liu et al (1993) | OR | 2.23 | 1.51 | 3.31 | 101 | 55 | 215 | 261 | OR | 2.10‡ | 1.2 | 3.67 | Smoking (not clear how, but they measured cigarettes smoked per day), sex, education, occupation, living area |
| Lo et al (2013) | OR | 2.35† | 1.58 | 3.55 | 88 | 39 | 1433 | 1495 | OR | 2.48‡ | 1.45 | 4.25 | Age, sex, years of education |
| Luo et al (1996) | OR | 2.4 | 1.2 | 4.7 | 16 | 23 | 86 | 283 | - | - | - | - | - |
| Mayne et al (1999) | OR | 1.20 | 0.52 | 2.79 | 12 | 10 | 421 | 425 | - | - | - | - | - |
| Osann et al (2000) | OR | 1.26† | 0.19 | 6.61 | 3 | 5 | 95 | 199 | OR | 1.8 | 0.2 | 14.4 | Pack-years of smoking, years since quitting smoking, age, education |
| Park et al (2010) | OR | 2.96† | 2.25 | 3.93 | 276 | 74 | 1262 | 1003 | OR | 2.56‡ | 1.85 | 3.56 | Smoking status (ever or never smoker), age, sex |
| Ramanakumar et al (2006) study I | OR | 2.93† | 1.17 | 8.75 | 26 | 6 | 749 | 506 | OR | 2.7 | 1.0 | 7.4 | Smoking status (ever or never smoker), log of cigarettes-year, number of years since quitting smoking (0-2, 2-5, 5-10, 10-15 or >15 years), age, ethnicity, type of respondent (self or surrogate), year of schooling, family income |
| Ramanakumar et al (2006) study II | OR | 1.2† | 0.68 | 2.1 | 27 | 29 | 1178 | 1512 | OR‡ | 0.90 | 0.48 | 1.67 | Smoking status (ever or never smoker), log of cigarettes-year, number of years since quitting smoking (0-2, 2-5, 5-10, 10-15 or >15 years), age, sex, ethnicity, type of respondent (self or surrogate), year of schooling, family income |
| Raspanti et al (2016) | OR | 2.17† | 1.46 | 3.25 | 88 | 44 | 518 | 562 | OR | 2.30 | 1.50 | 3.51 | Smoking status (ever or never smoker; they also calculated pack-years of smoking but it is not clear if this was included in the model), age, sex, household air pollution exposure, socioeconomic status, passive |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | smoking |
| Samet et al (1986) | OR | 1.24 | 0.66 | 2.29 | 27 | 22 | 491 | 747 | OR | 1.40 | 0.69 | 2.87 | Smoking (duration of smoking in years, number of cigarettes smoked per day on average, duration of cessation in years, and a product term of smoking duration with an indication variable for age above and age below 65), age, sex, ethnicity |
| Schwartz et al (1996) | OR | 2.19 | 0.58 | 10.06 | 8 | 4 | 249 | 273 | OR | 2.1 | 0.6 | 7.1 | Age, sex, race |
| Seow et al (2002) | OR | 1.92† | 1.10 | 3.31 | 27 | 37 | 276 | 726 | - | - | - | - | - |
| Wang et al (1996) | - | - | - | - | - | - | - | - | OR | 2.57 | 1.37 | 4.80 | Smoking status (no more details), chronic bronchitis/emphysema, family history of tumours, passive smoking, consumption of pickled and cured foods |
| Wang et al (1996_2) | OR | 1.39 | 0.94 | 3.04 | - | - | - | - | - | - | - | - | - |
| Wang et al (2009) | OR | 1.76† | 0.61 | 5.21 | 10 | 8 | 202 | 284 | OR | 2.43 | 0.82 | 7.20 | Age, employment, total dish year, intake of yellow/orange vegetables, dark green vegetables, multivitamins |
| Wang et al (2014) | OR | 2.22† | 1.12 | 4.58 | 30 | 14 | 470 | 486 | - | - | - | - | - |
| Wu et al (1988) | OR | 7.1† | 0.91 | 322.12 | 7 | 1 | 329 | 335 | RR | 10.0 | 1.1 | 90.1 | Pack-years of smoking, years since smoking stopped, depth of inhalation, social class according to father occupation (blues or white-collar worker) |
| Wu et al (1995) | OR | 1.63† | 0.87 | 2.95 | 19 | 37 | 378 | 1199 | OR | 1.96 | 0.9 | 3.1 | Age, passive smoking, area, ethnicity, education |
| Wu-Williams (1990) | - | - | - | - | 103 | 83 | - | - | RR | 1.3 | 0.9 | 1.7 | Age, smoking (non-smoker, smoked 1-9 cigarettes per day and 1-29 years, 2-19 and 30-39 years, 1-19 and >40 years, >20 cigarettes per day and 1-29 years, >20 and 30-39 years, >20 and >40 years), education, study area |
| Yang et al (2015) | OR | 1.74† | 1.3 | 2.34 | 131 | 84 | 1428 | 1595 | OR | 1.52 | 1.13 | 2.04 | Smoking status (ever or never smoker), pack-years of smoking (low, 0-5; moderate, 6-20; or high, >20), age, passive smoking, sex, emphysema, education, body mass index, educational experience, centre, packs-years occupational exposure to metallic toxicant, housing ventilation, biomass burning, cured meat, vegetables/fruits consumption |
| Zatloukal et al (2003) | OR | 0.81 | 0.47 | 1.34 | 20 | 108 | 346 | 1516 | OR | 1.75‡ | 1.01 | 3.05 | Smoking (pack-years), age, residence, education, residence |
| Zheng et al (1987) | OR | 1.45† | 1.18 | 1.77 | 266 | 213 | 1105 | 1279 | OR | 1.5 | 1.2 | 1.8 | Smoking category (non-smoker, light, moderate or heavy smoker), age, sex, education |
| Zhou et al (2000) | OR | 1.63 | 0.63 | 4.29 | 15 | 10 | 57 | 62 | - | - | - | - | - |

*A: number of exposed cases, B: exposed controls, C: unexposed cases, D: unexposed controls reported in the paper. †Unadjusted effect estimate and confidence intervals calculated from the 2 x 2 table. ‡ Adjusted effect estimate and confidence intervals calculated from adjusted effect estimates reported by subgroups (e.g.: males and females or lung cancer subtypes).

Table 3. Effect size estimates of lung cancer mortality risk among persons with a previous episode of TB in cohort studies

| Study | Unadjusted effect measure | Unadjusted effect estimate | Lower CI | Upper CI | 2 x 2 table* | | | | Adjusted effect measure | Adjusted effect estimate | Lower CI | Upper CI | Set of factors adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | A | B | C | D | | | | | |
| Boice et al (1980) | - | not applicable ‡ | - | - | 3 | - | | - | SMR | 1.54§ | 0.29 | 3.14 | Standardization based on age and sex |
| Chen et al (1990) | RR | 2.72† | 1.17 | 6.33 | 7 | 560 | 22 | 4817 | - | - | - | - | - |
| Christensen et al (2014) | RR | not applicable | | | 171 | 6231 | 278 | 18928 | RR | 2.25 | 1.86 | 2.72 | Age and sex |
| Davis et al (1989) | - | not applicable ‡ | - | - | - | - | - | - | SMR | 1.05§ | 0.71 | 1.55 | Standardization based on age and sex |
| Engels et al (2009) | HR | 6.1 | 4.3 | 8.7 | 31 | 215 | 2428 | 39748 | HR | 9.70<br>4.30 | 4.8<br>1.8 | 19<br>10 | Smoking per day (cigarettes per day). Other variables separately adjusted for (results not shown): age, sex, education level, use of smoky coal, asthma, chronic bronchitis, emphysema, family history of tuberculosis, walking hours spent indoors, number of rooms in house |
| Floe et al (2018) | RR | 4.76† | 3.81 | 5.93 | 165 | 6536 | 146 | 28055 | - | - | - | - | - |
| Gao et al (1992) | - | not applicable ‡ | - | - | - | - | - | - | SMR | 1.91§ | 0.98 | 3.73 | Standardization based on age and sex |
| Hong et al (2016) | RR | 3.07† | 2.90 | 3.26 | 1315 | 77983 | 8247 | 1520165 | HR | 1.44¶ | 1.36 | 1.53 | Smoking (current smokers, ex-smokers and never-smokers), amount of cigarettes per day (1-9, 10-19 and >=20), age, sex, alcohol consumption, socioeconomic status, diabetes mellitus, respiratory diseases hospitalizations |
| Leung et al (2013) | RR | 2.61 | 1.82 | 3.74 | 30 | 486 | 1314 | 59409 | HR | 2.01 | 1.40 | 2.90 | Smoking status (never-smokers and ever-smokers), age, sex, passive smoking, language, education level, marital status, housing situation, public means, tested financial assistance status, alcohol use, body mass index, chronic obstructive pulmonary disease, asthma, family history of malignancy |
| Merlo et al (1995) | RR | 0.71† | 0.32 | 1.59 | 7 | 110 | 28 | 305 | - | - | - | - | - |
| Ng et al (1990) | RR | 1.64† | 0.75 | 3.59 | 19 | 758 | 9 | 593 | - | - | - | - | - |
| Sasaki et al (1992) | - | not applicable ‡ | - | - | - | - | - | - | SMR | 4.57§ | 2.81 | 7.42 | standardization based on age and sex |

*A: number of exposed with outcome, B: exposed without outcome, C: unexposed with outcome, D: unexposed without outcome reported in the paper. † Unadjusted effect estimate and confidence intervals calculated from the 2 x 2 table. ‡ The study reports SMR using lung cancer death rates in the general population. § Adjusted SMR and confidence intervals calculated from data reported in the paper. ¶ Adjusted effect estimate and confidence intervals calculated from adjusted effect estimates reported separately for males and females.

Table 4. Effect size estimates of lung cancer mortality risk among persons with a previous episode of TB in case-control studies

| Study | Unadjusted effect measure | Unadjusted effect estimate | Lower CI | Upper CI | numerators and denominators * | | | | Adjusted effect measure | Adjusted effect estimate | Lower CI | Upper CI | Set of factors adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | A | B | C | D | | | | | |
| Fu et al (1984) | OR | 2.86† | 1.87 | 4.45 | 89 | 35 | 434 | 488 | - | - | - | - | - |

*A: number of exposed cases, B: exposed controls, C: unexposed cases, D: unexposed controls reported in the paper. † Unadjusted OR and confidence intervals calculated from the 2 x 2 table (the study reports an unadjusted RR).

**Appendix 10. Additional forest plots**

Figure 1. Forest plot for the association between tuberculosis and subsequent lung cancer diagnosis among cohort studies (model 1)

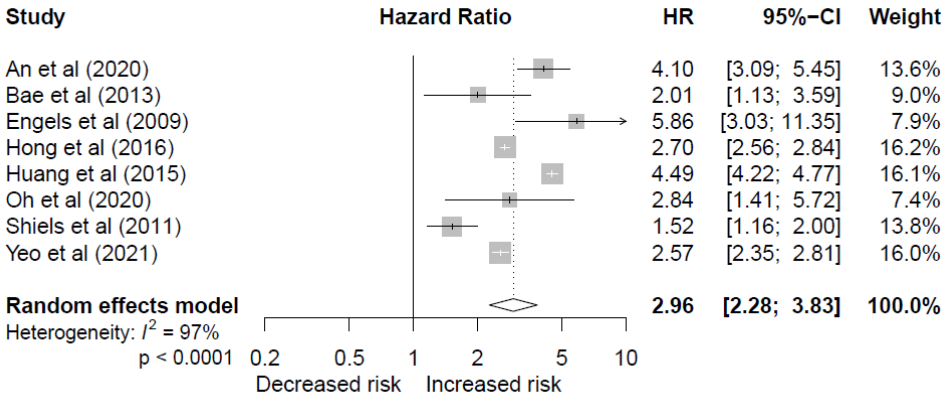


Figure 2. Forest plot for the association between tuberculosis and subsequent lung cancer diagnosis among case-control studies (model 1)

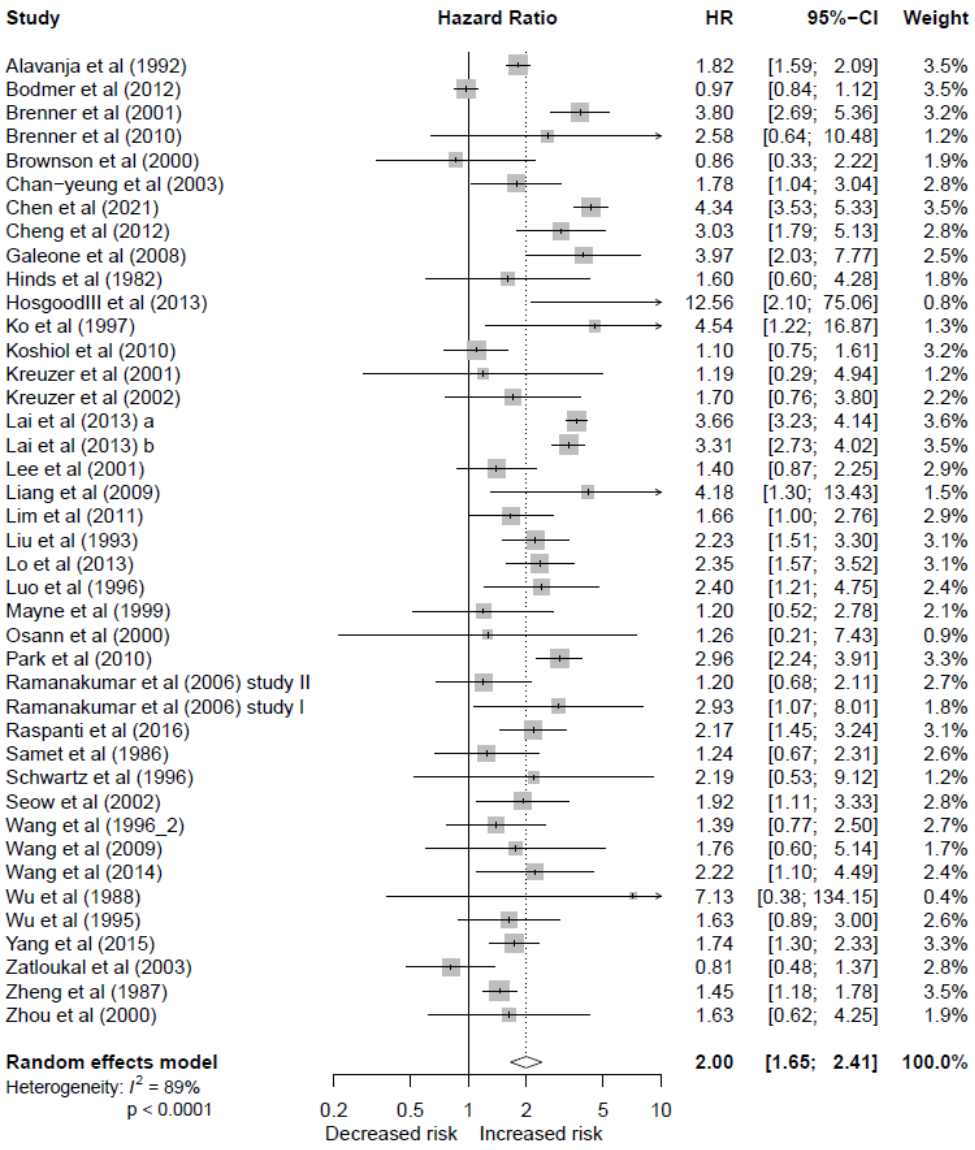


Figure 3. Forest plot for the association between tuberculosis and subsequent lung cancer mortality among cohort studies (model 1)

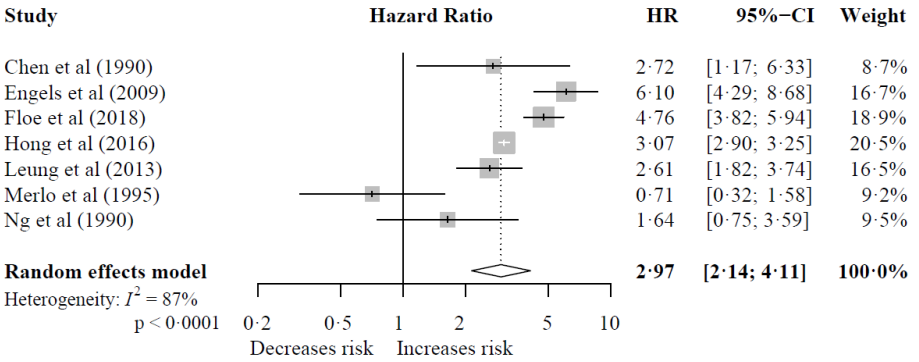
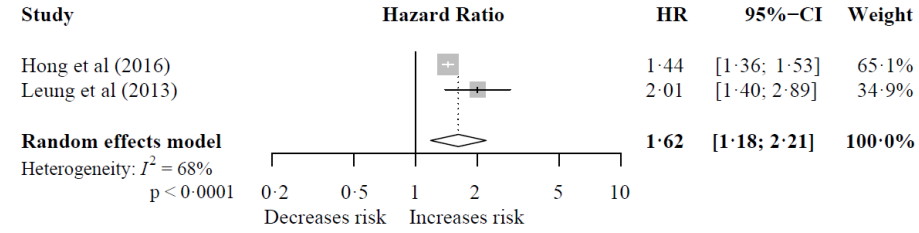
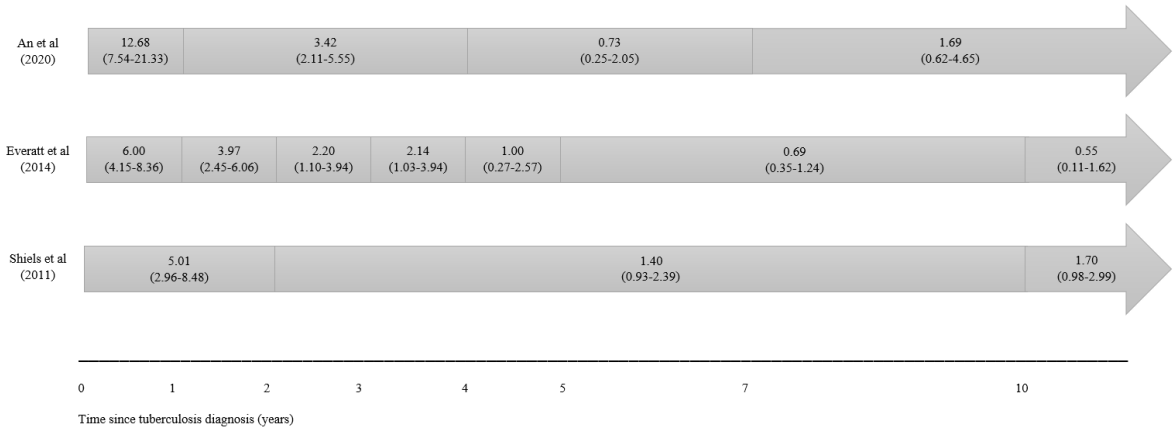


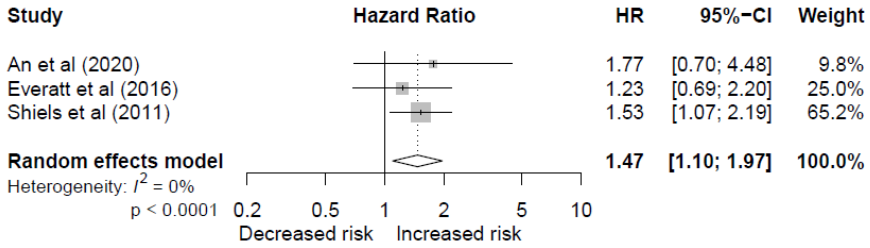

Figure 4. Forest plot for the association between tuberculosis and subsequent lung cancer mortality among cohort studies (model 2)



**Appendix 11.** Effect estimates by time between tuberculosis diagnosis and lung cancer diagnosis from the three cohort studies reporting by latency strata.



**Appendix 12. Pooled adjusted estimates from cohort studies excluding lung cancer cases detected within one or two years of tuberculosis diagnosis**




All the studies included in this analysis controlled for age and any assessment of smoking (model 2). The HR from Shiels et al (2011) and Everatt et al (2016) was calculated after excluding lung cancer cases detected within the first two years of tuberculosis diagnosis. In the study by An et al (2020), cancer cases within the first year of tuberculosis diagnosis were excluded.

**Appendix 13. Funnel plots**

Figure 1. Adjusted estimates from cohort studies that report the association between tuberculosis and lung cancer diagnosis

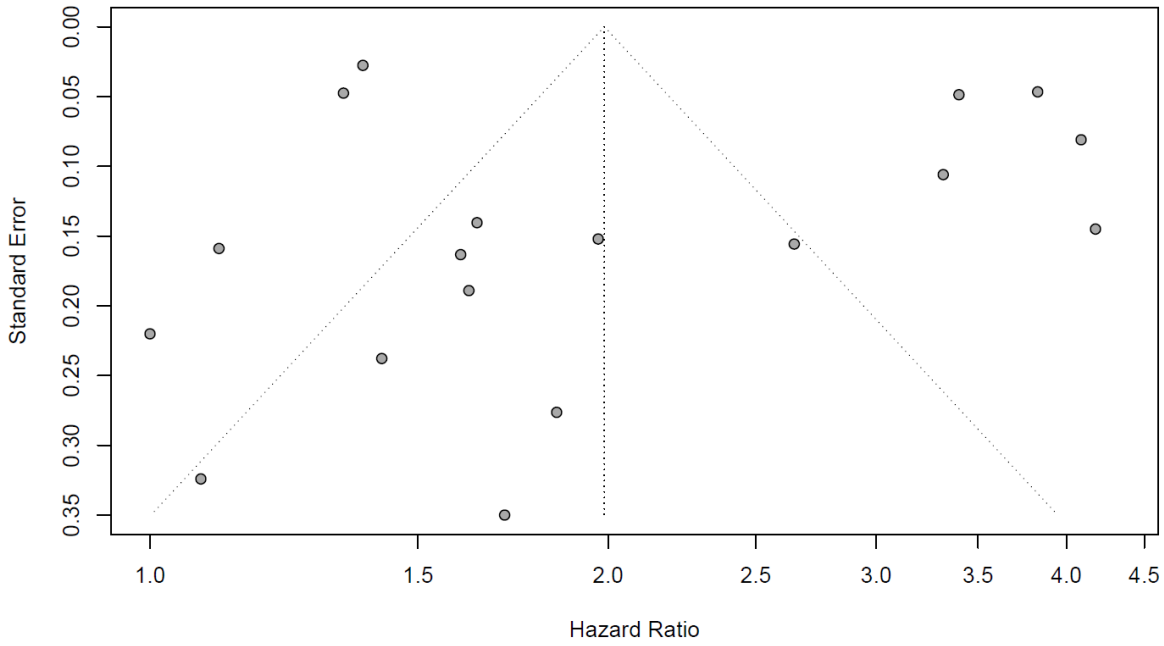
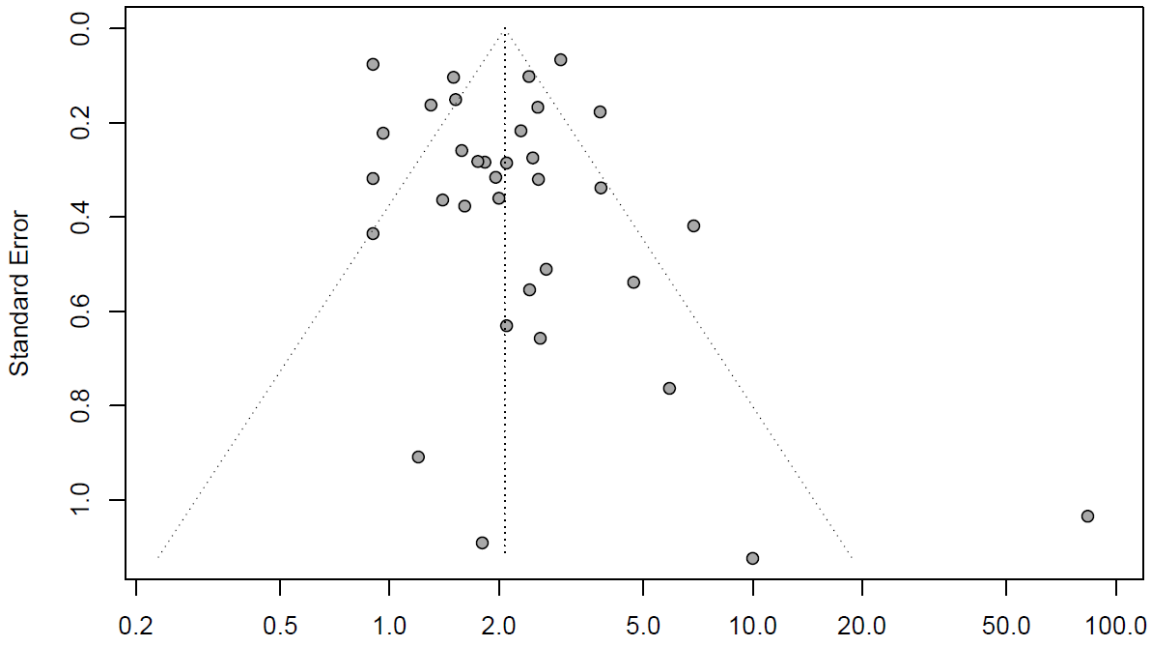


Figure 2. Adjusted estimates from case-control studies that report the association between tuberculosis and lung cancer diagnosis



**Appendix 14. GRADE assessment of the evidence**

| Cohort studies | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Certainty assessment | | | | | | Effect | | |
| Number of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Pooled HR* (95% CI) | Certainty | Importance |
| **Lung cancer diagnosis** | | | | | | | | | |
| 5 | Observational | Not serious† | Not serious | Not serious | Not serious | None | 1.51 (1.30-1.76) | ⨁⨁◯◯ Low | Important |
| **Lung cancer mortality** | | | | | | | | | |
| 2 | Observational | Serious‡ | Not serious | Not serious | Not serious | None | 1.62 (1.18-2.21) | ⨁◯◯◯ Very low | Important |

HR: Hazard ratio. *Here we considered the pooled estimates form the available model with the most rigorous adjustment for smoking. For lung cancer diagnosis, model 3 provides the most accurate pooled estimate (HR adjusted for age and quantitatively assessed smoking=1.51). For lung cancer mortality, model 3 was not performed so the most accurate estimate is provided by model 2 (HR adjusted for age and any assessment of smoking=1.62). †Three of the five studies included in this meta-analysis had low risk of bias. Furthermore, stratified analysis to the three cohorts with low risk of bias yielded consistent results (HR=1.72, 95% CI 1.25-2.38). ‡Only two studies included in this meta-analysis and therefore not possible to perform an analysis restricted to studies with low risk of bias.

| Case-control studies | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Certainty assessment | | | | | | Effect | | |
| Number of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Pooled OR* (95% CI) | Certainty | Importance |
| **Lung cancer diagnosis** | | | | | | | | | |
| 19 | Observational | Serious† | Not serious | Not serious | Not serious | None | 1.74 (1.42-2.13) | ⨁◯◯◯ Very low | Important |

OR=Odds ratio. *Here we considered the pooled estimates form the available model with the most rigorous adjustment for smoking (model 3, table 2 in the main manuscript). †Only one out of the 19 case-control studies in model 3 had low risk of bias. Ten and eight had moderate and high risk of bias, respectively.

**Appendix 15. List of variables adjusted for in the included studies**

| Adjustment for | Lung cancer diagnosis | | Lung cancer mortality |
|---|---|---|---|
| | Cohort studies (n=19) | Case-control studies (n=43) | Cohort studies (n=12) |
| **Smoking** | 7* | 32¶ | 3 |
| **Age** | 18 | 25 | 7 |
| **Sex** | 18† | 32# | 9** |
| Any socioeconomic status indicator (income, education or occupation) | 6 | 18 | 2 |
| Ethnicity | 1 | 4 | 0 |
| Location (urbanization, area, residence or prefecture) | 3 | 10 | 0 |
| Passive smoking | 0 | 6 | 1 |
| **Comorbidities** | | | |
| Any comorbidity | 10 | 6 | 4 |
| COPD | 8‡ | 4 | 1 |
| Diabetes | 7 | 1 | 1 |
| Pneumonia | 4 | 0 | 0 |
| Dyslipidaemia | 4 | 1 | 0 |
| Chronic kidney disease/failure | 4 | 4 | 0 |
| Asthma | 3§ | 0 | 1 |
| Smoking-related cancers | 3 | 0 | 0 |
| Autoimmune disease | 3 | 0 | 0 |
| Hypertension | 2 | 1 | 0 |
| Liver cirrhosis | 2 | 0 | 0 |
| Atopy dermatitis | 2 | 0 | 0 |
| Rhinosinusitis | 2 | 0 | 0 |
| Chronic bronchitis/emphysema | 1 | 3 | 0 |
| Bronchiectasis | 1 | 0 | 0 |
| Pulmonary fibrosis | 1 | 0 | 0 |
| Asbestosis | 1 | 2 | 0 |
| Silicosis | 0 | 0 | 2†† |
| Pneumoconiosis | 0 | 1 | 0 |
| AIDS | 1 | 0 | 0 |
| Congestive heart failure | 0 | 1 | 0 |
| Ischemic heart disease | 0 | 1 | 0 |
| Stroke/transient ischemic attack | 0 | 1 | 0 |
| Inhaled corticosteroids use | 3 | 0 | 0 |
| Oral corticosteroids use | 1 | 0 | 0 |
| Body mass index | 3 | 3 | 1 |
| Physical activity | 1 | 0 | 0 |
| Alcohol | 2 | 1 | 1 |
| Hospitalizations for respiratory diseases | 1 | 0 | 1 |
| Any adjustment for diet | 1 | 5 | 0 |
| Family history of lung cancer | 0 | 4 | 1 |

*Everatt et al (2016) reports an adjusted estimate for "non-smokers" equivalent to "never-smokers" definition. † Bae et al (2013), Liu et al (2017), and Shiels et al (2011) restricted intake to one sex (females or males). Huang et al (2015) reported adjusted estimates stratified by sex. ‡ Liu et al (2017) and Wu et al (2016) restricted intake to COPD patients. § Jian et al (2016) restricted intake to asthma patients. ¶ Kreuzer et al (2001), Kreuzer et al (2002), Liang et al (2009), Lo et al (2013), Schwartz et al (1996), Wang et al (1996) b, Wang et al (2009), and Wu et al (1995) restricted intake to never-smokers. # Alavanja et al (1992), Brownson et al (2000), Cheng et al (2012), Hinds et al (1982), Ko et al (1997), Kreuzer et al (2001), Kreuzer et al (2002), Lai et al (2013), Liang et al (2009), Lim et al (2011), Osann et al (2000), Ramanakumar et al (2006) – study l, Seow et al (2002), Wang et al (1996) b, Wang et al (2009), Wu et al (1988), Wu et al (1995), Wu-Williams et al (1990), Zatloukal et al (2003), and Zhou et al (2000) restricted intake to one sex (females or males). Chan-Yeung et al (2003), Lee et al (2001), Liu et al (1993), Lo et al (2013), Park et al (2010), Ramanakumar et al (2006) – study ll reported results stratified by sex. ** Boice et al (1980), Chen et al (1990), and Ng et al (1990) restricted intake to one sex (females or males). ††Merlo et al (1995) and Ng et al (1990) restricted to patients with silicosis.

**Appendix 16. Amendments to the protocol**

The study was prospectively registered in PROSPERO. A first version of the protocol was published in PROSPERO on 05/07/2020. The start of the review was delayed due to the COVID-19 outbreak in Peru, and the authors uploaded a new version of the protocol before starting the data extraction. We added a secondary outcome (lung cancer mortality), further databases to search (Scopus, conference abstracts) to make the review more comprehensive, and pre-specified the subgroup analysis (available online on 26/02/2021). No more versions of the protocol were published.

Some details of the analysis could not possibly be pre-specified in the protocols. We had to define the core set of factors for the meta-analysis of adjusted effect estimates after ascertaining, during data extraction, adjustment approaches used in the studies. We then also established the different methods studies used to control for smoking and decided to develop two models to pool adjusted estimates. Importantly, we defined these details before starting the statistical analysis. Apart from that, all further not pre-specified analyses are labelled as such in the manuscript.

**Appendix 17. List of excluded studies with reasons**

| Study ID | Reason for exclusion and study reference |
|---|---|
| Abou et al (2017) | Wrong study design: Systematic Review<br>Abou Chakra C, Cheng M, Cnossen S, et al. Risk of Active Tuberculosis in Patients with Cancer: A Systematic Review and Meta-Analysis. Clin Infect Dis 2017; 64: 635–44. |
| Aerts et al (2012) | Wrong study design<br>Aerts J, Bakker M, Hegmans, et al. History of tuberculosis as an independent prognostic factor for lung cancersurvival. Lung Cancer 2012; 76: 452–6. |
| Ahmed et al (2014) | Exposure of active TB cannot be determined<br>Ahmed F, Al Emran A, Bin Imran I, et al. Score based risk assessment of lung cancer and its evaluation for Bangladeshipeople. Asian Pac J Cancer Prev 2014; 15: 7021–7. |
| Ahrens et al (2014) | This article was a pooled analysis of case-control studies<br>Ahrens W, Behrens T, Bencko V, Boffetta P, DR B, Bruning T, et al. Is previous respiratory disease a risk factor for lung cancer? Am J Respir Crit Care Med [Internet]. 2014;190(5 PG-549–59):549–59. |
| An et al (2020) | Wrong study design: Genetic study<br>An S, Ashikawa K, Bassig B, et al. Tuberculosis infection and lung adenocarcinoma: Mendelian randomization andpathway analysis of genome-wide association study data from never-smoking Asianwomen. Genomics 2020; 112: 1223–32. |
| Andrew et al (2012) | This article was a pooled analysis of observational studies<br>Andrew A, Bencko V, Bickeboller H, et al. Previous lung diseases and lung cancer risk: a pooled analysis from theInternational Lung Cancer Consortium. Am J Epidemiol 2012; 176: 573–85. |
| Ariannia et al (2020) | Wrong study design<br>Ariannia A, Ashaari M, Fazel A, Ferlay J, Ghasemi-Kebria F, Ghayoriardahaei H, et al. Increasing trends of lung cancer in Golestan province, Northern Iran (2004-2016). Cancer Epidemiol [Internet]. 2020;65(PG-101687):101687. |
| Au et al (2012) | Exposure of interest was asbestosis and previous history of TB<br>Au R, Chen M, Tse L, Wang F, XR W, IT Y. Pulmonary tuberculosis and lung cancer mortality in a historical cohort ofworkers with asbestosis. Public Health 2012; 126: 1013–6. |
| Ba et al (2019) | No control group<br>Ba O, Baddredine H, Cisse M, et al. [Epidemiology of primary lung cancer among non-smokers in Senegal]. Rev Mal Respir 2019; 36: 15–21. |
| Boffetta et al (2012) | Wrong study design: Review<br>Boffetta P, Sisti J. What proportion of lung cancer in never-smokers can be attributed to known riskfactors? Int J Cancer [Internet]. 2012;131(2 PG-265–75):265–75. |
| Boice et al (2019) | Exposure of active TB cannot be determined<br>Boice Jr J, Cohen S, Ellis E, Golden A, Mumma M, Zablotska L. Sex-specific lung cancer risk among radiation workers in the million-person studyand patients TB-Fluoroscopy. Int J Radiat Biol 2019; : 1–12. |
| Brenner et al (2011) | Wrong study design: Systematic Review<br>Brenner D, Hung R, McLaughlin J. Previous lung diseases and lung cancer risk: a systematic review andmeta-analysis. PLoS One 2011; 6: e17479. |
| Caporaso et al (2006) | Exposure of active TB cannot be determined<br>Caporaso N, Consonni D, Gao Y, et al. Family history of cancer and nonmalignant lung diseases as risk factors for lung cancer. Int J Cancer 2009; 125: 146–52. |
| Cha et al (2009) | Wrong study design<br>Cha S, Jung T, Kim C, et al. The clinical course of respiratory tuberculosis in lung cancer patients. Int J Tuberc Lung Dis 2009; 13: 1002–7. |
| Chang et al (2009) | Exposure of active TB cannot be determined<br>Chang YL, Chul MA, Jeong HJ, Hyung JK, Se KK, Chang J, et al. Association of insulin receptor substrate-1 G972R variant with non-small cell lung cancer risk. Tuberc Respir Dis [Internet]. 2009;67(1 PG-8–13):8–13. |
| Chen et al (2007) | Exposure of active TB cannot be determined<br>Chen W, Yang J, Chen J, Bruch J. Exposures to silica mixed dust and cohort mortality study in tin mines: Exposure-response analysis and risk assessment of lung cancer. Am J Ind Med [Internet]. 2006;49(2 PG-67–76):67–76. |
| Chia et al (2014) | Wrong study design<br>Chia K, Lim W, Loy E, Omkar Prasad R, Seow A, Tan C. Lung cancer incidence in Singapore: ethnic and gender differences. Lung Cancer 2014; 84: 23–30. |
| Chou et al (2011) | Duplicate article<br>Chou Y, Hu H, Huang N, et al. Pulmonary tuberculosis increases the risk of lung cancer: a population-basedcohort study. Cancer 2011; 117: 618–24. |
| Christopoulos et al (2014) | Wrong study design: Systematic Review<br>Christopoulos A, Saif M, Sarris E, Syrigos K. Epidemiology of active tuberculosis in lung cancer patients: a systematic review. Clin Respir J 2014; 8: 375–81. |
| Colletti et al (2015) | No control group<br>Colletti P, Fellner F, Gabriel M, et al. Malignant disease as an incidental finding at (1)(8)F-FDG-PET/CT scanning inpatients with granulomatous lung disease. Nucl Med Commun 2015; 36: 430–7. |
| Cukic et al (2017) | No control group<br>Cukic V. The Association Between Lung Carcinoma and Tuberculosis. Med Arch [Internet]. 2017;71(3 PG-212–214):212–4. |
| Dong et al (2009) | Exposure of active TB cannot be determined<br>Dong D, Hu P, Sun Y, Xu G. Lung cancer among workers exposed to silica dust in Chinese refractory plants. Scand J Work Env Heal [Internet]. 1995;21 Suppl 2(PG-69-72):69–72. |
| Esfahani et al (2018) | Wrong type of publication: Letter to the editor<br>Esfahani B, Keikha M. The Relationship between Tuberculosis and Lung Cancer. Adv Biomed Res 2018; 7: 58. |

| | |
|---|---|
| Figueroa et al (2018) | Exposure of active TB cannot be determined<br>Figueroa CGS, Plata RF, Briseño DM, de la Garza SR, Pizano AM, Marina FF, et al. Analysis of a routine database to identify risk factors of the host and the environment associated with respiratory diseases . Rev Inst Nac Enferm Respir [Internet]. 2012;71(1 PG-11–20):11–20. |
| Fol et al (2021) | Wrong study design: Review<br>Fol M, Koziński P, Kulesza J, Białecki P, Druszczyńska M. Dual Nature of Relationship between Mycobacteria and Cancer. Int J Mol Sci [Internet]. 2021;22(15 PG-). |
| Fukami et al (2020) | Wrong study design<br>Fukami T, Hebisawa A, Takahashi F, Tamura A. Recent trends in the incidence of latent tuberculosis infection in Japanesepatients with lung cancer: A small retrospective study. J Infect Chemother [Internet]. 2020;26(3 PG-315–317):315–7. |
| Furlow et al (2018) | Wrong type of publication: Brief discussion<br>Furlow B. Tobacco control, lung cancer, and tuberculosis in Singapore. Lancet Respir Med [Internet]. 2018;6(10 PG-741–742):741–2. |
| Golsha et al (2009) | No control group<br>Golsha R, Rezaei SR, Shafiee A, Najafi L, Dashti M, Roshandel G. Pulmonary tuberculosis and some underlying conditions in Golestan Province of Iran, during 2001-2005. J Clin Diagn Res [Internet]. 2009;3(1 PG-1302–1306):1302–6. |
| Goo et al (2006) | Exposure of active TB cannot be determined<br>Goo J, Kim H, Kim H, Kim Y. Lung Cancer CT Screening and Lung-RADS in a Tuberculosis-endemic Country: TheKorean Lung Cancer Screening Project (K-LUCAS). Radiology 2020; : 192283. |
| Guan et al (2009) | Wrong study design: Systematic Review<br>Guan P, He Q, Li X, et al. Facts and fiction of the relationship between preexisting tuberculosis and lungcancer risk: a systematic review. Int J Cancer 2009; 125: 2936–44. |
| Han et al (2018) | Wrong study design<br>Han K, Hong S, Kim S, et al. Effect of pre existing respiratory conditions on survival of lung cancerpatients: A nationwide population-based cohort study. Asia Pac J Clin Oncol 2018; 14: e71–80. |
| Ho et al (2014) | Duplicate article<br>Ho C, Huang J, Jan S, et al. The coexistence of common pulmonary diseases on the histologic type of lungcancer in both genders in Taiwan: a STROBE-compliant article. Med 2014; 93: e127. |
| Ho et al (2015) | Wrong study design<br>Ho C, Huang J, Jan S, et al. Impact of coexisting pulmonary diseases on survival of patients with lungadenocarcinoma: a STROBE-compliant article. Med 2015; 94: e443. |
| Ho et al (2020) | Lung cancer as outcome cannot be determined<br>Ho L, Yang H, Chung C, et al. Increased risk of secondary lung cancer in patients with tuberculosis: A nationwide, population-based cohort study. PLoS One 2021; 16: e0250531. |
| Hoshuyama et al (1995) | Exposure of active TB cannot be determined<br>Hoshuyama T, Pan G, Tanaka C, Feng Y, Yu L, Liu T, et al. Mortality of iron-steel workers in Anshan, China: A retrospective cohort study. int J Occup Environ Heal [Internet]. 2006;12(3 PG-193–202):193–202. |
| Hughes et al (2001) | Exposure of active TB cannot be determined<br>Hughes J, McDonald A, McDonald J, RJ R, Shi R, Weill H. Cohort mortality study of North American industrial sand workers. II.Case-referent analysis of lung cancer and silicosis deaths. Ann Occup Hyg 2001; 45: 201–7. |
| Jo et al (2015) | Wrong study design<br>Jo YS, Choi SM, Lee J, Park YS, Lee S-M, Yim J-J, et al. The relationship between chronic obstructive pulmonary disease and comorbidities: A cross-sectional study using data from KNHANES 2010-2012. Respir Med [Internet]. 2015;109(1 PG-96–104):96–104. |
| Kikuchi et al (2007) | Exposure of active TB cannot be determined<br>Kikuchi S. Family history and mortality in the Japan Collaborative Cohort Study forEvaluation of Cancer (JACC). Asian Pac J Cancer Prev [Internet]. 2007;8 Suppl(PG-21-4):21–4. |
| Kinlen et al (1988) | Exposure of active TB cannot be determined<br>Kinlen L, Willows A. Decline in the lung cancer hazard: a prospective study of the mortality of ironore miners in Cumbria. Br J Ind Med 1988; 45: 219–24. |
| Marsh et al (2017) | Exposure of active TB cannot be determined<br>Marsh GM, Buchanich JM, Zimmerman S, Liu Y, Balmert LC, Esmen NA, et al. Mortality among Hardmetal Production Workers: US Cohort and Nested Case-Control Studies. J Occup Environ Med [Internet]. 2017;59(12 PG-306–326):e306–26. |
| Moshammer et al (2004) | Exposure of active TB cannot be determined<br>Moshammer H, Neuberger M. Lung cancer and dust exposure: Results of a prospective cohort study following 3260 workers for 50 years. Occup Environ Med [Internet]. 2004;61(2 PG-157–162):157–62. |
| Ording et al (2018) | Exposure of active TB cannot be determined<br>Ording AG, Veres K, Farkas DK, Adelborg K, Sørensen HT. Risk of cancer in patients with epistaxis and haemoptysis. Br J Cancer [Internet]. 2018;118(6 PG-913–919):913–9. |
| Pira et al (2017) | Exposure of active TB cannot be determined<br>Pira E, Romano C, Donato F, Pelucchi C, Vecchia CL, Boffetta P. Mortality from cancer and other causes among Italian chrysotile asbestos miners. Occup Environ Med [Internet]. 2017;74(8 PG-558–563):558–63. |
| Rodescu et al (1981) | Wrong type of publication: Case reports or case series;<br>Rodescu D, Abeles H, Zelefsky M, Henry Williams Jr. M. Accelerated growth of lung cancer in asociation with rifampicin administration for tuberculosis. Lancet [Internet]. 1981;318(8253 PG-983):983. |
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