CASE REPORT

RISK FACTORS FOR PRIMARY LUNG CANCER IN PATIENTS WITH A HISTORY OF TUBERCULOSIS

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ABSTRACT

Background: Tuberculosis (TB) is an infectious disease with the highest mortality rate. TB infection can damage lung structure and trigger genetic mutations in lung parenchymal cells, as well as the role of immunosuppression and cellular DNA damage. This can be a risk factor for primary lung cancer.This EBCR aims to determine risk factors that increase the risk of primary lung cancer in patients with a history of TB.
Methods: A systematic search was performed on the PubMed, ScienceDirect, Cochrane, Scopus, and Clinical Key databases. Systematic cohort/meta-analysis studies, cohort studies, and case control studies were analyzed to answer etiological questions. Critical review using the Oxford Center of Evidence-Based Medicine (CEBM) etiology.
Result: There were 3 studies in the form of a systematic review/meta-analysis of cohorts. These three studies found that a history of TB infection within <2 years can increase the risk of primary lung cancer. In addition, a history of active or passive smoking, young age, being in a country with middle economic status, as well as East Asian and Pacific countries, increases the risk of experiencing primary lung cancer.
Conclusion: In this EBCR, we report the risk factors for primary lung cancer in patients with a history of TB. Based on a critical review, it was concluded that a history of duration of TB diagnosis, active and passive smoking, young age, being in a country with middle economic status, as well as East Asia and Pacific countries, increased the risk of experiencing primary lung cancer.

Keywords: tuberculosis, lung cancer, risk factor, smoking, age

ABSTRAK

Latar Belakang: Tuberkulosis (TB) merupakan penyakit infeksi dengan angka kematian tertinggi. Infeksi TB dapat merusak struktur paru-paru serta memicu mutasi genetik pada sel parenkim paru, serta peran imunosupresi dan kerusakan DNA seluler. Hal ini dapat menjadi salah satu faktor risiko terjadinya kanker paru primer. EBCR ini bertujuan untuk mengetahui faktor risiko yang meningkatkan risiko kejadian kanker paru primer pada pasien dengan riwayat TB.
Metode: Pencarian sistematis dilakukan pada database PubMed, ScienceDirect, Cochrane, Scopus, dan Clinical Key. Penelitian systematic cohort/meta-analysis, penelitian cohort, dan penelitian case control dianalisis untuk menjawab pertanyaan etiologik. Telaah kritis menggunakan Oxford Centre of Evidence-Based Medicine (CEBM) etiologik.
Hasil: Didapatkan 3 studi berupa systematic review/meta-analysis of cohort. Ketiga studi ini menemukan bahwa riwayat infeksi TB dalam waktu <2 tahun dapat meningkatkan risiko kejadian kanker paru primer. Selain itu, riwayat merokok aktif, pasif, usia muda, berada pada negara dengan status ekonomi menengah, serta negara asia timur dan pasifik, meningkatkan risiko mengalami kanker paru primer.
Kesimpulan: Dalam EBCR ini, kami melaporkan faktor risiko kanker paru primer pasien dengan riwayat TB. Berdasarkan telaah kritis, disimpulkan bahwa riwayat durasi terdiagnosis TB, merokok aktif, pasif, usia muda, berada pada negara dengan status ekonomi menengah, serta negara asia timur dan pasifik, meningkatkan risiko mengalami kanker paru primer.

Kata Kunci: Tuberkulosis, kanker paru primer, faktor risiko, merokok, usia

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INTRODUCTION

Case Illustration

A 59-year-old male patient presented to Dr. Cipto Mangunkusumo National General Hospital with complaints of dyspnea. The shortness of breath was triggered by physical activity and improved with rest. The dyspnea was accompanied by hemoptysis and fever reaching 39°C. The patient also experienced a weight loss of 7 kg over the past 3 months. Contrast-enhanced thoracic computed tomography (CT) scan and sputum examination were performed, revealing negative TB results on sputum testing. Thoracic CT scan demonstrated a mass in the right lung and multiple bilateral parotid gland cysts.

In 2013, the patient previously complained of dyspnea and sought treatment at Mayapada Hospital. At that time, he was informed that the right lung was compressed and contained pleural fluid. A chest tube was inserted into the right hemithorax for 2 weeks. Sputum examination indicated pulmonary TB, and the patient completed 9 months of anti-tuberculosis treatment with clinical improvement. In 2021, the patient developed recurrent dyspnea. Bronchoscopy findings suggested relapsed pulmonary TB, and the patient underwent another 6 months course of anti-tuberculosis treatment. Recurrent right pleural effusion was also identified, necessitating repeat tube thoracostomy of the right hemithorax. Approximately 800 mL of pleural fluid was drained over a 2-week period.

The patient had a significant smoking history, having smoked approximately two packs of cigarettes daily since adolescence until smoking cessation in 2010. He denied any history of diabetes mellitus, hypertension, asthma, or allergic disease. There was no known family history of similar respiratory complaints or malignancy. At present, the patient was hemodynamically stable, although laboratory examination demonstrated leukocytosis. The treating physician was aware that a prior history of TB infection may increase the risk of primary lung malignancy and sought to identify potential risk factors contributing to the development of primary lung cancer in this post-TB patient.

Background

Tuberculosis (TB) remains the leading cause of death from infectious diseases globally. [1] In 2018, approximately 10 million people were estimated to have TB worldwide. Despite being preventable and curable, TB continues to be associated with high mortality, with more than 3,500 deaths occurring daily and approximately 1.3 million deaths annually.[2]

Tuberculosis remains a major public health problem in Indonesia despite ongoing control efforts. The World Health Organization (WHO) classifies Indonesia as one of the 10 countries with the highest burden of TB and drug-resistant TB. Indonesia has the second-highest TB incidence globally, with an incidence rate of 312 cases per 100,000 population, contributing to 8.5% of TB cases worldwide. Indonesia also contributes substantially to the global burden of drug-sensitive TB and multidrug-resistant TB (MDR-TB). In 2021, approximately 845,000 individuals in Indonesia were estimated to have active TB, including 24,000 MDR-TB cases. However, only 570,000 cases were registered in the National Tuberculosis Program.[1]

A history of TB infection has also been identified as a risk factor for primary lung cancer. Previous TB infection may increase the risk of lung cancer by approximately twofold. Structural pulmonary changes and chronic inflammation caused by TB infection may trigger genetic mutations in pulmonary parenchymal cells, alongside the effects of immunosuppression and cellular DNA damage. These mechanisms are thought to contribute to an increased risk of lung cancer.[3]

The presence of lung cancer may result in various complications. Locally, lung cancer can obstruct the airways, leading to atelectasis, induce malignant pleural effusion, and compress the sympathetic nerves, resulting in Horner syndrome.[4] Systemically, lung cancer may metastasize to other organs,

including the brain, liver, adrenal glands, and bones. In addition, patients may experience symptoms such as fever, dyspnea, weight loss, and chest pain.[5] Identifying factors that increase the risk of primary lung cancer in patients with a history of TB may improve the management of patients following TB infection. Therefore, this evidence-based case report (EBCR) aims to evaluate factors associated with an increased risk of primary lung cancer among patients with a history of TB infection.

Clinical Question

In adult patients with a prior history of tuberculosis, does age, smoking history (active, passive, or vaping), comorbidities, family history of malignancy, and air exposure to pollutants significantly influence the risk of primary lung cancer?

METHODS

Search Strategy

A comprehensive literature search was performed across five major electronic databases: PubMed, Science Direct, Scopus, Clinical Key, and Cochrane, covering studies published up to June 26, 2023. The search strategy employed a combination of Medical Subject Headings (MeSH) and keywords related to the core clinical question, specifically: "tuberculosis," "lung cancer," and "risk factors." To refine the results, additional terms including "age," "smoking," "vaping," "genetics," "air pollution," "comorbid," and "cancer history" were integrated using Boolean operators. The search was restricted to articles published in English or Bahasa Indonesia. Only studies with available full-text versions were included for further evaluation. The detailed results of the search strategy are summarized in Table.

Tabel 1. Article Search Strategy

Database	Search Strategy	Hits
Pubmed	(((tuberculosis) AND (lung cancer)) AND (risk factor)) AND (((((((age) OR (smoking)) OR (vaping)) OR (genetics)) OR (air pollution)) OR (comorbid)) OR (cancer history)) Filters: Systematic review, Meta-Analysis, Observational studies	21
Science direct	(tuberculosis history) AND (primary lung cancer) AND (risk factor) and ((age) OR (smoking) OR (vaping) OR (genetics) OR (air pollution) OR (comorbid) OR (cancer history))	2455
Scopus	("tuberculosis" OR "TB") AND "primary lung cancer" AND "risk factor" AND ("age" OR "smoking" OR "vaping" OR "genetics" OR "air pollution" OR "comorbid" OR " cancer history")	20
Clinical Key	(Tuberculosis history) AND (primary lung cancer) AND (risk factor) and ((age) OR (smoking) OR (vaping) OR (genetics) OR (air pollution) OR (comorbid) OR (cancer history))	572
Cochrane	"tuberculosis" in Title Abstract Keyword AND "lung cancer" in Title Abstract Keyword AND "risk factors" in Title Abstract Keyword AND "age" OR "smoking" OR "vaping" OR "genetics" OR "air pollution" OR "comorbid" OR "cancer history" in Title Abstract Keyword	13

Eligibility Criteria

Eligible articles were articles fulfilling our PICO framework and reporting effect measures, including odds ratio (OR), relative risk (RR), or number needed to harm (NNH). Systematic reviews and/or meta-analyses of cohort studies, cohort studies, or case-control studies were included. Studies were excluded if they were published as letters, editorials, opinion papers, conference abstracts, narrative reviews, or clinical guidelines, were not available in either English or Indonesian, or if the full-text article could not be accessed.

Critical Appraisal Tool and Level of Evidence

The levels of evidence for the included studies ranged from Level 1 (for the systematic reviews and meta-analyses) to Level 2 (for the prospective cohort study), according to the Oxford Centre for Evidence-Based Medicine (CEBM) guidelines.

Article Selection

A total of 2,495 records were initially identified through database searching (PubMed: 21, ScienceDirect: 2,455, and Scopus: 20). After removing 28 duplicates, 2,468 records were screened, resulting in the exclusion of 2,450 records based on title and abstract. Sixteen reports were sought for full-text retrieval, all of which were successfully retrieved. Upon eligibility assessment of these

RESULTS

Study Characteristics

A total of three studies met the eligibility criteria for this Evidence-Based Case Report (EBCR). The included literature comprises three systematic reviews/meta-analyses and one prospective cohort study. All three studies evaluated the association between a history of tuberculosis (TB) and the

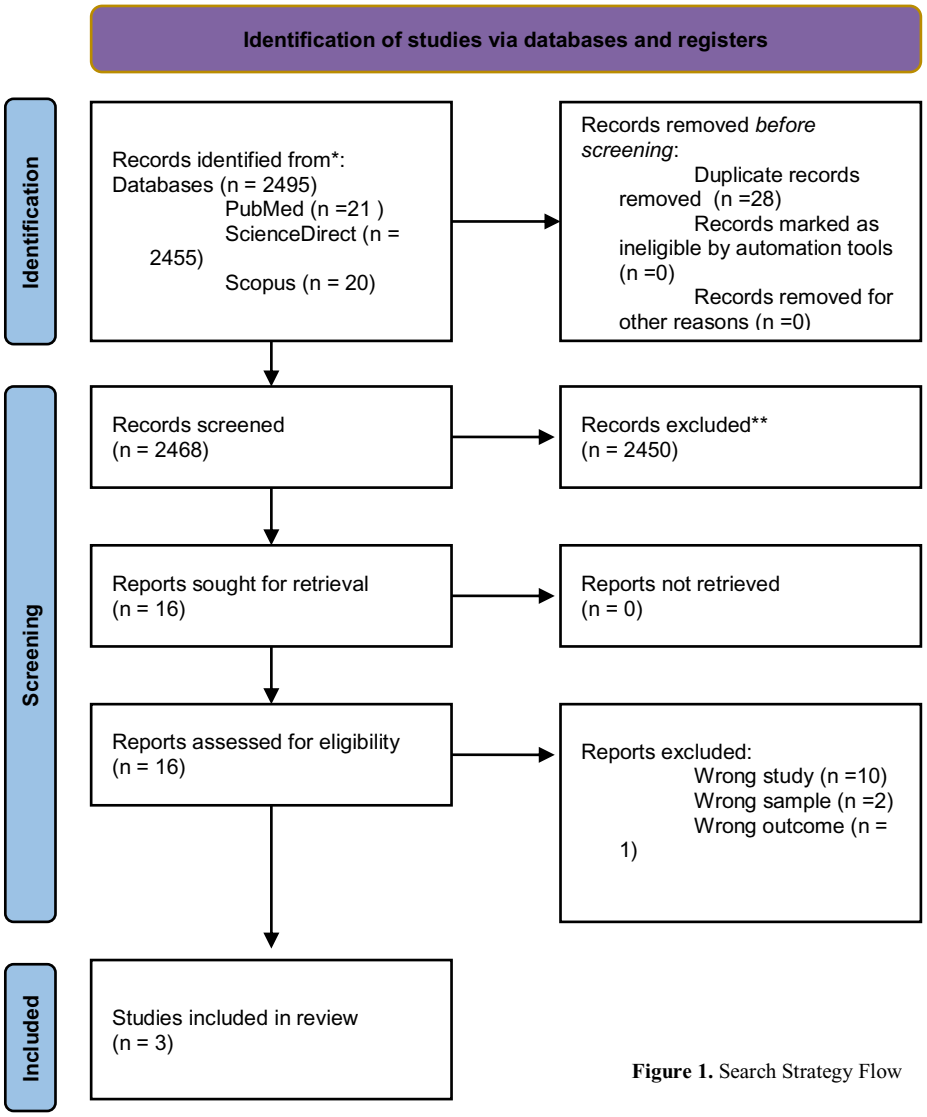

Figure 1. Search Strategy Flow

16 reports, 13 were excluded due to incorrect study design (n=10), inappropriate sample (n=2), and unsuitable outcomes (n=1). Finally, three studies were included in this evidence-based case report (Figure 1). Consequently, three articles were selected for final inclusion. Figure 1 provides a visual representation of the systematic literature search and selection process.

subsequent development of primary lung cancer, as well as the specific risk factors influencing this relationship.

Critical appraisal

In this evidence-based case report, the selected studies underwent a rigorous critical appraisal process. The systematic reviews and meta-analyses were evaluated using the Oxford Centre for Evidence-Based Medicine (CEBM) Critical Appraisal Worksheet for

Systematic Reviews. For the prospective cohort study, the appraisal was conducted using the Oxford CEBM Worksheet for Prognosis/Incidence studies. These tools were utilized to assess the validity, clinical importance, and applicability of the evidence to our specific patient case.

Validity and Importance

The validity and importance assessment of the included studies are presented in the following Table 1 and 2.

Tabel 2. Validity of three studies based on the Oxford Centre for Evidence-Based Medicine worksheet

Critical Appraisal Question	Sanchez et al. (2022)[6]	Hwang et al.(2022)[3]	Ang et al. (2009)[7]
Is it unlikely that important, relevant studies were missed?	**Yes.** Multiple major databases were searched with broad language and publication-year coverage.	**Yes.** Major databases were searched with limited exclusion criteria.	**Yes**. Comprehensive database searches were conducted from 1966–2008.
Were the criteria used to select articles for inclusion appropriate?	**Yes.** Included cohort and case-control studies evaluating TB and lung cancer risk.	**Yes**. Included observational studies and excluded non-relevant designs.	**Yes**. Included studies reporting RR/OR estimates related to lung cancer risk.
Were the included studies sufficiently valid for the type of question asked?	**Yes.** Risk of bias was assessed using the Newcastle–Ottawa Scale.	**Yes**. Risk of bias and subgroup analyses were performed.	**Unclear**. Publication bias was assessed, but risk-of-bias methods were not clearly described.
Were the results similar from study to study?	**Yes.** Despite high heterogeneity, pooled estimates were consistently above 1.	**No**. Heterogeneity remained very high across analyses.	**Yes**. Heterogeneity decreased after subgroup analysis, with consistent pooled estimates above 1.

Tabel 3. Importance of three studies based on the Oxford Centre for Evidence-Based Medicine worksheet

Author	Patient Group	Intervention / Variables	Outcome	Key Results
Sanchez et al. (2022)[6]	Patients with a history of tuberculosis diagnosis	Sex - Male - Female Smoking status - Non-Smoker Post-treatment period - First year - First 2 years - ≥2 years - ≥4 years	Adjusted HR (95% CI) for primary lung cancer incidence	This study found that a history of tuberculosis significantly increased the risk of primary lung cancer, with an HR of 2.96 (95% CI: 2.28–3.83). Sex - Male: HR = 1.59 (1.12–2.26) - Female: HR = 1.49 (1.28–1.74) Smoking status - Non-smoker: HR = 1.69 (1.21–2.38) Post-treatment period - First year: HR = 8.50 (4.09–17.67) - First 2 years: HR = 5.01 (3.64–6.89) - ≥2 years: HR = 1.44 (1.06–1.96) - ≥4 years: HR = 0.82 (0.53–1.26)
Hwang et al. (2022)[3]	Patients with a history of tuberculosis diagnosis	- Age - Smoking - Diabetes - Hypertension - Pulmonary comorbidities - National economic status Geographic region	- Regression coefficient and p-value Adjusted OR for primary lung cancer incidence	This study demonstrated that a history of tuberculosis significantly increased the risk of primary lung cancer, with an OR of 2.09 (1.62–2.69). -Younger age: Regression coefficient = 0.949; p-value <0.001 - Smoking: OR = 2.03 (1.51–2.73) - Diabetes: OR = 1.72 (0.48–6.20) -Hypertension: OR = 1.92 (0.66–5.57) -Pulmonary comorbidities: OR = 1.32 (0.93–1.86) -Middle-income countries: OR = 2.57 (1.68–3.93) -East Asia and Pacific region: OR = 2.49 (1.83–3.39)
Ang et al. (2009)[7]	Patients with a history of tuberculosis diagnosis		Adjusted RR	This study found that a history of tuberculosis significantly increased the risk of primary lung cancer, with an RR of 1.97 (1.60–2.41). -Smoking history: RR = 1.74 (1.48–2.03) -Passive smoking: RR = 2.93 (1.63–5.26)

Applicability

These three studies are applicable to the patients in the clinical scenario of this EBCR, as all studies included populations of patients with a history of tuberculosis who subsequently developed primary lung cancer. In Indonesia, the highest incidence of TB occurs among individuals aged 15–24 years and those aged >65 years. The demographic characteristics of the populations included in these studies, in which the majority of participants were aged 60–70 years, are consistent with the Indonesian population and the clinical scenario addressed in this EBCR.

Furthermore, the study conducted by Hwang et al. performed subgroup analyses in middle-income countries and Asian countries, increasing the relevance of the findings to the Indonesian setting. The comorbidities analyzed by Hwang et al., including diabetes and hypertension, are also commonly observed in the Indonesian population. In addition, all three studies evaluated the impact of smoking on the increased risk of lung cancer among patients with a history of TB, which is likewise highly relevant to Indonesia. Therefore, the findings of these three studies are considered applicable to this EBCR.

DISCUSSION

In this EBCR, we identified three systematic reviews/meta-analyses of cohort studies that analyzed factors associated with an increased risk of lung cancer in patients with a history of tuberculosis (TB). Overall, these studies demonstrated that patients with a prior history of TB had a 2–3-fold higher risk of developing lung cancer compared with those without a history of TB. A prospective cohort study conducted by Yu et al. also reported that the incidence of lung cancer in patients with TB was 11 times higher than in patients without TB (26.3 vs. 2.41 per 10,000 person-years).[8]

One proposed mechanism underlying this increased risk is chronic inflammation and lung damage caused by TB, which may lead to the development of Post-Tuberculosis Obstructive Syndrome (PTOS).[9] PTOS has been recognized as a significant risk factor for lung cancer.[10] In addition, TB-associated inflammation and fibrotic changes may induce genetic damage, thereby increasing the likelihood of lung cancer development.

A study conducted by Sanchez et al. evaluated several risk factors, including sex, smoking status, and recovery period in patients with a previous history of TB. The study found that a prior history of TB increased the risk of lung cancer by approximately threefold (HR = 2.96 [2.28–3.83]), with non-small cell lung carcinoma (NSCLC) showing the highest risk (HR = 2.01 [1.00–4.03]).[6] These findings are consistent with those reported by Brenner et al., who found that the incidence of NSCLC was highest among patients with a history of TB. Furthermore, the highest risk of lung cancer was observed during the first year after TB recovery (HR = 8.50 [4.09–17.67]) and the second year after recovery (HR = 5.01 [3.64–6.89]). In contrast, a recovery period of more than two years was not identified as a significant risk factor for lung cancer in patients with a prior history of TB (HR = 1.44 [1.06–1.96]). Patients with never-smoking status were also found to have an increased risk of lung cancer (HR = 1.69 [1.21–2.38]). However, sex was not identified as a significant risk factor.[11]

A study conducted by Hwang et al. analyzed several factors, including age, smoking, diabetes, hypertension, pulmonary comorbidities, national economic status, and geographic region. The study found that a history of TB significantly increased the risk of lung cancer (OR = 2.09 [1.62–2.69]). Younger age was also associated with lung cancer occurrence (regression coefficient = 0.949; p-value < 0.001). In addition, the risk of lung cancer was higher among patients with a history of smoking (OR = 2.03 [1.51–2.73]), those from middle-income countries (OR = 2.57 [1.68–3.93]), and those residing in East Asia and Pacific regions (OR = 2.49 [1.83–3.39]).[3] However, diabetes, hypertension, and pulmonary comorbidities were not identified as significant risk factors.

A study conducted by Ang et al. evaluated factors such as active smoking, passive smoking, and duration after TB diagnosis. The study found that patients with a prior history of TB had a twofold higher risk of developing lung cancer (RR = 1.97 [1.60–2.41]). The risk of lung cancer was also higher among patients with a history of active smoking (RR = 1.74 [1.48–2.03]) and passive smoking (RR = 2.93 [1.63–5.26]). A shorter duration after TB diagnosis was likewise associated with an increased risk of lung cancer, with the first 1–5 years showing an 11-fold increased risk (RR = 11.14 [7.57–16.41]), 6–10 years showing a 4-fold

increased risk (RR = 3.96 [1.80–8.71]), 11–20 years showing a 2.32-fold increased risk (RR = 2.32 [1.59–3.38]), and more than 20 years showing a 2-fold increased risk (RR = 1.99 [1.32–2.99]).[7]

Taken together, these studies suggest that patients with a history of TB have a higher risk of developing lung cancer, particularly within the first two years after recovery or within the first five years after TB diagnosis. Histories of active and passive smoking, as well as younger age, may further increase this risk. In addition, residing in middle-income countries and in East Asia and Pacific regions was associated with a higher risk of lung cancer. However, factors such as sex, diabetes, hypertension, and pulmonary comorbidities were not identified as significant risk factors. To date, no previous studies have evaluated the effects of family history of tumors, vaping, and air pollution on lung cancer occurrence in patients with a history of TB.

This EBCR has several strengths. First, the included studies were systematic reviews/meta-analyses that synthesized evidence from multiple cohort studies, thereby providing a high level of evidence. Second, the included studies evaluated multiple risk factors through subgroup analyses, allowing assessment of adjusted ORs, RRs, and HRs. However, several limitations should also be acknowledged. The included studies demonstrated substantial heterogeneity, which may have influenced the overall findings. In addition, factors such as family history of tumors, vaping, and air pollution could not be evaluated because no eligible studies investigating these factors were identified, representing important gaps in the current literature. Furthermore, the association between PTOS and lung cancer could not be assessed because of the lack of available studies examining this relationship.

CONCLUSION

In this EBCR, we report a 59-year-old male patient with a history of relapsed tuberculosis in 2021 who was diagnosed with a right lung mass. The patient had a smoking history since junior high school, consuming two packs of cigarettes per day, as well as multiple bilateral parotid gland cysts and pleural effusion. This EBCR highlights that patients with a history of TB have a higher risk of developing primary lung cancer, particularly within the first two years after recovery. Histories of active and passive smoking, as well as younger age, are also associated with an increased risk of lung cancer. Therefore, this patient had several risk factors for lung cancer, including a history of TB within the past three years and long-term smoking since adolescence. However, pulmonary comorbidities in this patient were not found to influence the occurrence of lung cancer.

This EBCR suggests that younger patients with a history of active or passive smoking who have recently recovered from TB within the previous two years should undergo monitoring and receive education regarding their increased risk of primary lung cancer. Future studies investigating the effects of vaping, air pollution, and prior tumor history are also warranted. In addition, further understanding of therapies that may reduce the risk of primary lung cancer in patients with a history of TB is needed.

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