

Prevalence Lung Cancer in Former Tuberculosis Patients in Indonesia: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Indonesia faces a 14% increase in Tuberculosis (TB) cases, putting it 14 years behind the world's second-highest burden. This raises concerns about lung cancer risk, as studies outside Indonesia are limited. **Aim:** This study aims to determine the risk of lung cancer in TB patients in Indonesia.

Methods: This systematic review with meta-analysis according to PRISMA statement with various databases. We use PEOS framework for screening and select articles to be included. We exclude articles about co-infection TB with lung cancer and misdiagnose condition. We analyze risk of bias using JBI critical appraisal tools and we used R Studio and RevMan 5.4 with random-effect model for results of data that can be generalized on a wider population

Result: There are 3 out of 4210 articles with 1270 patients included in this study. The research came from different cities and extracted the number of patients that matched the criteria. A total of 101 (7.9%) of 1270 lung cancer patients had a history of tuberculosis. There are 8 out of 100 lung cancer patients in Indonesia had TB infection before and is dominated by the type of adenocarcinoma compared to squamous cell carcinoma (statistically not meaningful, $p=0.21$). This study was evaluated as heterogeneous among all inclusion studies. The risk rate of bias with the JBI was 76.6% above the risk limit of the bias agreement.

Conclusion: Patients with a history of TB need future attention and further evaluation before the occurrence of lung cancer.

Keywords: Former Tuberculosis, Lung Cancer, Meta-Analysis, Systematic Review, Tuberculosis

Prevalensi Kanker Paru Pada Pasien Riwayat Tuberkulosis di Indonesia: Sebuah Tinjauan Sistematis dan Meta-Analisis

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Abstrak

Pendahuluan: Indonesia menghadapi peningkatan kasus Tuberkulosis (TBC) sebesar 14%, yang menempatkan Indonesia 14 tahun lebih lambat dari negara dengan beban TBC tertinggi kedua di dunia. Hal ini menimbulkan kekhawatiran mengenai risiko kanker paru, karena penelitian di luar Indonesia masih terbatas. Tujuan: Penelitian ini bertujuan untuk mengetahui risiko kanker paru pada pasien TB di Indonesia.

Metode: Tinjauan sistematis dengan meta-analisis ini sesuai dengan pernyataan PRISMA dengan berbagai basis data. Kami menggunakan kerangka kerja PEOS untuk menyaring dan memilih artikel yang akan dimasukkan. Kami mengecualikan artikel tentang koinfeksi TB dengan kanker paru dan kondisi salah diagnosis. Menganalisis risiko bias menggunakan alat penilaian kritis JBI dan menggunakan R Studio dan RevMan 5.4 dengan model efek acak untuk hasil data yang dapat digeneralisasi pada populasi yang lebih luas.

Hasil: Terdapat 3 dari 4210 artikel dengan 1270 pasien yang termasuk dalam penelitian ini. Penelitian ini berasal dari berbagai kota dan mengambil jumlah pasien yang sesuai dengan kriteria. Sebanyak 101 (7,9%) dari 1270 pasien kanker paru memiliki riwayat tuberkulosis. Terdapat 8 dari 100 pasien kanker paru di Indonesia yang pernah menderita TB dan didominasi oleh jenis adenokarsinoma dibandingkan dengan karsinoma sel skuamosa (secara statistik tidak bermakna, $p=0,21$). Penelitian ini dievaluasi sebagai penelitian yang heterogen di antara semua penelitian inklusi. Tingkat risiko bias dengan JBI adalah 76,6% di atas batas risiko kesepakatan bias.

Kesimpulan: Pasien dengan riwayat TB memerlukan perhatian di masa depan dan evaluasi lebih lanjut sebelum terjadinya kanker paru

Kata Kunci: Kanker Paru, Meta-Analisis, Riwayat Tuberkulosis, Tinjauan Sistematis, Tuberkulosis

Introduction

Tuberculosis (TB) cases in the world totaled 10.6 million and Indonesia moved from third place to the second highest tuberculosis burden in the world. Not only that, the incidence of Tuberculosis in Indonesia increased by 14% with a total of 969,000 cases in 2021 according to the TB Global Report 2022.¹ This sets Indonesia back 14 years in the running for Tuberculosis elimination. Behind this increase in cases, there is a potentially increasing disease called lung cancer. As de-

scribed by the hallmark of cancer,² infectious diseases including Tuberculosis increase the risk of lung cancer growth, but these studies are mostly outside of Indonesia. For example, Meta-analysis by Sanchez., et al³ in 2022 demonstrated that the likelihood of developing lung cancer following a bout of TB decreased after the first two years following diagnosis. Cohort study by Ho., et al⁴ in 2021 revealed that 761 (10.97%) individuals with TB developed secondary lung cancer, and as TB is associated with an increased risk of secondary lung cancer metastasis among primary

cancers and comorbidities, TB patients should be assessed for this risk.

There has been no research that determines the risk of lung cancer in Indonesia caused by Tuberculosis even though Tuberculosis cases in Indonesia have not ended until now. There is no study that clearly shows how stratified the risk of lung cancer is in tuberculosis patients in Indonesia. This study is important to be the basis for making health regulations regarding the examination of patients with Tuberculosis for lung cancer screening. This regulation does not seem to have been made due to the lack of scientific evidence. Therefore, the purpose of this study is to determine the number of lung cancer cases with a previous history of TB and determine the risk of lung cancer in TB patients in Indonesia.

Methods

We registered and publish our protocol, which contains details of the literature search strategy in PROSPERO and accepted with number register: [CRD42023438456]. Our systematic review and meta-analysis manuscript is written accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) Statement for reporting systematic reviews and meta-analyses.⁵ The primary outcome of this study is to determine the prevalence and risk of lung cancer among former tuberculosis patients in Indonesia. Secondary outcome of this study is to determine the risk of the type of lung cancer suffered by former tuberculosis patients in Indonesia.

Data Sources and Selection

We searched the literature using Google Scholar and ResearchGate. This choice was made because research in Indonesia in the form of cancer patient profiles or cancer risk factors is published in campus journals as a thesis and commonly found in both search engines. Inclusion criteria were: (1) Full-text, (2) Last 10 years, (3) Using Indonesian or English language, and (4) Observational study. We excluded articles with co-infection of tuberculosis and lung cancer, and lung cancer that was misdiagnosed as tuberculosis. We selected articles using PEOS framework such as: Patients, History of Tuberculosis Infection (Exposure), Incidence or Risk of Lung Cancer (Outcome), Observational Study (Study design). We used keywords as “Risk” AND “Lung Cancer OR Lung Malignancy OR Lung

Cancer” AND “Tuberculosis OR Former Tuberculosis”.

Data Extraction and Quality Assessment

Data were independently extracted by all authors using the PRISMA schema, and any disagreements were resolved through discussion. First author, year of publication, total sample size, number of patients with a history of tuberculosis, number of patients without tuberculosis, and type of lung cancer were extracted from each article. Each included article was analyzed by all authors to assess the risk of bias and we used the Joanna-Briggs Institute (JBI) Critical Appraisal tool. The JBI critical appraisal tool consists of several questions and each yes answer gets a score of 1 and each no answer gets a score of 0. The average score is obtained by dividing the score obtained by the total score multiplied by 100. It was agreed that a score below 75% was considered as an article with a high risk of bias.

Statistical Analysis

The total number of lung cancer patients, the number of cancer patients with a history of tuberculosis and the amount of non-tuberculosis cancer patients in the extraction as the primary outcome. The total number of lung cancer patients with a history of tuberculosis, the number of patients with adenocarcinoma and the amount of patient with squamous cell carcinoma are extracted as a secondary outcome. All the data that has been extracted is then inserted into the statistical analysis machine. This meta-analysis is carried out using R Studio 2024.04.2 Build 764 program in the implementation of proportional meta-analysis. We used Review Manager (RevMan) 5.4 program in the implementation of statistical analysis for the risk based on type of lung cancer. The proportion assessment is used to determine the probability of occurrence based on the results of the data obtained with the interpretation of the probability of occurrence x of the total population. To determine the type of lung cancer that is more likely to appear in patients with Scar TB Carcinoma, the Odds Ratio (OR) assessment was used to determine the odds of occurrence. To evaluate heterogeneity between studies included using Chi-square values and inconsistency index (I²). If the chi-square value has a p value <0.05 , then there is heterogeneity between the studies.

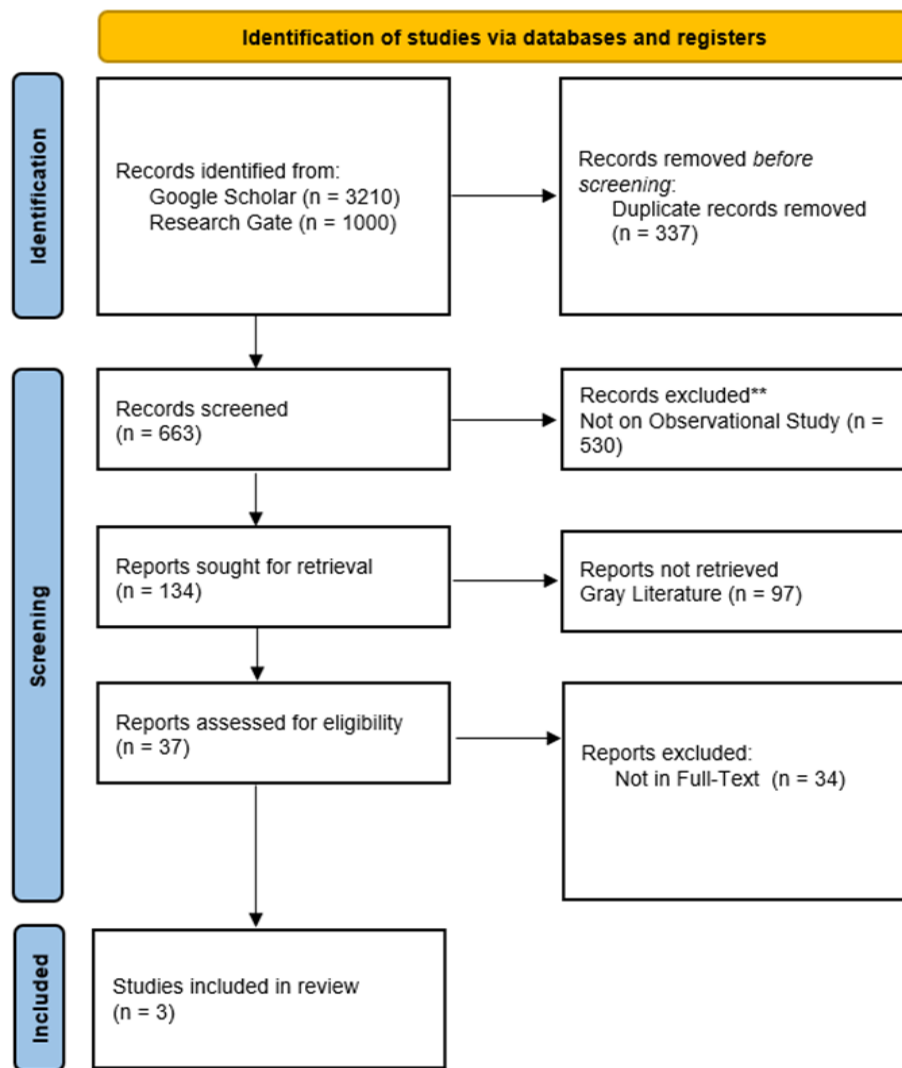


Figure 1. PRISMA Flow Chart for Identification of Study

Result

Systematic Review and Characteristics of Included Studies

From various literature databases, we found 4210 articles. 8 articles were deemed suitable for further evaluation after excluding duplicate articles through abstract screening and 3 articles were further analyzed after 5 articles could not be accessed in full-text (Figure 1). A total of 1270 patients were included in this study and came from three cities namely Padang, Pekanbaru and Surabaya. Table 1 displays the characteristics of the articles that have been included and have been extracted and organized into a table. From these three articles, data was extracted in the form of the total number of patients, the number of pa-

tients with a history or without a history of tuberculosis. The type of lung cancer could be extracted from two studies and one did not have information on the type of lung cancer suffered by lung cancer patients with a history of tuberculosis.

Statistical Result

Prevalence and Risk of Lung Cancer in Former Tuberculosis Patients in Indonesia

The articles included in this forest plot (Fig.2) are said to be heterogeneous with a moderate I^2 value (52%). Of the 1270 cancer patients included in this study, there were 8% ($n = 101$) patients who had a history of tuberculosis. Fig.2 shows the proportion of lung cancer incidence in patients with a previous history of Tuberculosis infection. In

Table 1. Baseline Characteristics of Included Studies

Author,- Year	Province/ District	N	With Histo- ry of Tuber- culosis	Without History of Tuberculosis	Type of Lung Cancer
Ernawa- ti,2019 ⁶	South Sumatra/ Padang	23	1	22	NA 12 (50%) Adenocarcinoma 9 (37.5%) Squamous Cell Carci- noma
Martari- ta,2024 ⁷	Riau/ Pe- kanbaru	203	24	180	3 (12.5%) Others 69 (90.7%) Adenocarcinoma
Nasti- ti,2023 ⁸	West Java/ Surabaya	1044	76	968	7 (9.2%) Squamous Cell Carcinoma

this study, it was found that in the Indonesian population, there is a chance of 8 out of 100 cancer patients having a previous history of tuberculosis, this chance can be greater or smaller. the 95%CI results in this study also show numbers 0.06 to 0.09 which can be said to be narrow so we can believe that the results of this proportion are reliable in the Indonesian population.

culosis, 81% (n = 81) with adenocarcinoma type and 16% (n = 16) with squamous cell carcinoma type. The articles included in this forest plot (Fig.3) are said to be heterogenous with a Chi-square p value <0.05 and a large I² value (96%). The statistical value of Fig.3 is not statistically significant because the P value is <0.05 (p=0.21) and the 95% Confidence Interval (95%CI) intersects the center line. The odds of squamous cell carcinoma

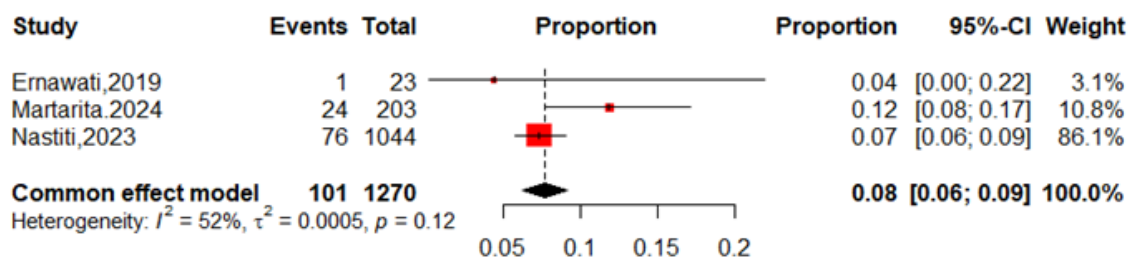


Figure 2. Forest Plot of Meta Proportion for Lung Cancer in Former TB Patients in Indonesia.

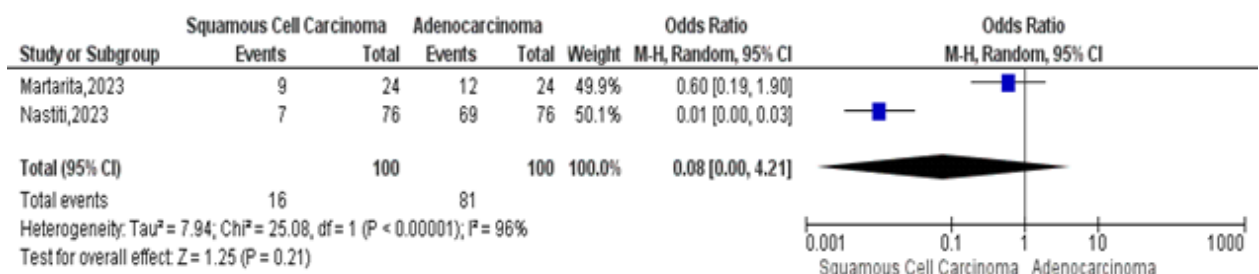


Figure 3. Risk of Lung Cancer Type in Patients with a History of Tuberculosis.

Risk of Lung Cancer Type (Adenocarcinoma or Squamous Cell Carcinoma) in Former Tuberculosis Patients in Indonesia

From an inclusion study involving 100 lung cancer patients with a history of tuber-

culosis, 81% (n = 81) with adenocarcinoma type and 16% (n = 16) with squamous cell carcinoma type. This can be interpreted as the incidence of a history of tuberculosis is potentially often lung cancer with adenocarcinoma type than squamous cell carcinoma. However, it's not statistical-

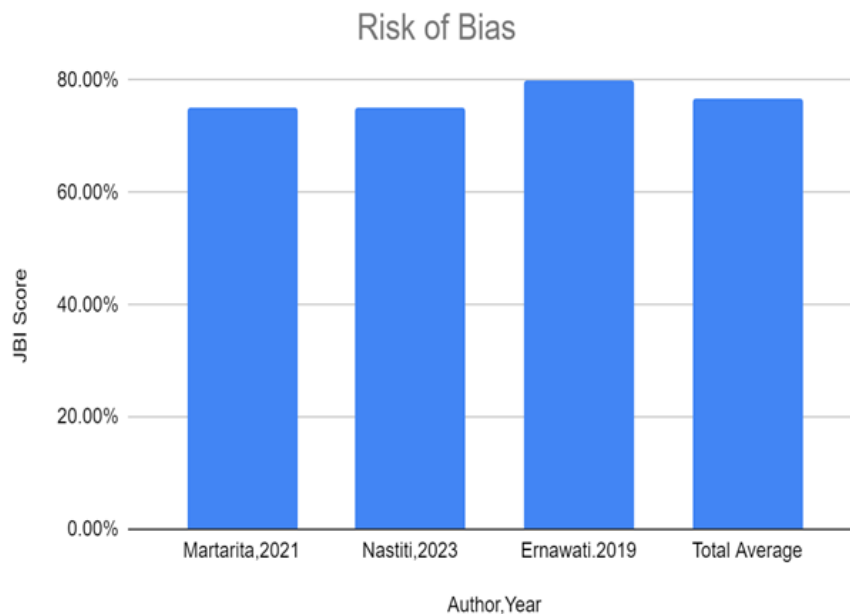


Figure 4. Risk of Bias Score with Joanna-Briggs Institute (JBI) Score.

ly significant, therefore more data required to confirmed the actual common type of lung cancer prior to TB. Interpretation of this data in clinical practice in the field requires special attention not to be misinterpreted as for lung cancer patients to be dominated by adenocarcinoma, the patient must have been infected with tuberculosis beforehand.

Risk of Bias

All authors analyze risk of bias from every included studies. Any disagreement resolved by discussion. With JBI Critical Appraisal tools, total average score for risk of bias is 76.6%. This value exceeds the uniform limit previously determined by all authors. All studies do not discuss co-funding factors and do not show strategies in dealing with these co-founding factors ahead so that such things make the value of risk of bias lower. This can happen when observational studies only pay attention to the data obtained without analyzing each data subject on the factors that may influence the results.

Discussion

Summary and Interpretation of Findings

There were 3 studies with 1270 patients included in this study. Of the 1270 cancer patients in Indonesia, 8% ($n = 101$) of them had a history of TB. This meta-analysis showed that 8 out of 100 lung cancer patients

had a previous history of tuberculosis in Indonesia with a narrow 95%CI so we can be confident in the precision of the study results.

Of the 100 lung cancer patients who have a history of tuberculosis and there is information about the type of lung cancer they have, 81 (81%) of them are adenocarcinomas and 16 (16%) are squamous cell carcinomas. This meta-analysis result was assessed as statistically insignificant ($p=0.21$) with a 95% CI overall test value cutting line 1 (95%CI: 0.00 - 4.21). These data need to be interpreted carefully, not to reduce the incidence of squamous cell carcinoma so the patient is recommended to be infected with tuberculosis. That is a wrong interpretation. Tuberculosis is more likely to become an adenocarcinoma than a squamous cell carcinoma. The occurrence of tuberculosis can be either adenocarcinoma or squamous cell carcinoma but proportionally the risk is greater to adenocarcinoma. To support future confidence, more data required to ensure the potential type of lung cancer.

Implication for Practice

Tuberculosis cases in Indonesia are quite large and survive as eight countries with the largest burden of tuberculosis in the world. Indonesia currently ranks second with a 14% increase in cases of tuberculosis, with 969,000 cases in 2022, according to TB Global Report. The risk of cancer in former tuberculosis sufferers has been found in other countries but in Indonesia only three articles conducted an

observational study of the incidence of the cancer in patients with Tuberculosis with 101 cancer patients with a history of TB in Indonesia. This shows his minimum study concerned about the matter as if this case was “ignored”. While the number of cases of tuberculosis in Indonesia is hundreds of thousands, it is hypothesized that this occurrence should be directly correlated with an increase in cases of lung cancer.

The study showed 8 out of 100 lung cancer in patients who had been infected with tuberculosis. therefore, the implications on field practice should pay attention to patients who have completed tuberculosis treatment to be evaluated accordingly. Patients should also be informed that their condition requires medical attention in advance, the patient should be aware to check for health and also reduce the risk of causing lung cancer. Other study from Taiwan by Kuang-Ming Liao et al., 2023 evaluate lung cancer patients from Taiwan Cancer Registry from 2011 to 2015 and showed 1.211 (2.79%) out of 43.472 prior to TB infection.⁹ Simonsen et al., 2014 observed 1747 cancers in 15.024 TB patients, the incidence rate for TB to developed lung cancer was 3.40 (95%CI: 1.22 – 1.36).¹⁰ Sanchez et al., in 2022 meta-analysis also showed odds ratio of 1.74 among TB patients associated with lung cancer occurrence.¹¹

The previously presented data, apart from Indonesia, supports the evidence that Tuberculosis has a risk of future lung cancer incidence. However, it is important to note that research on this subject is still minimal in Indonesia, even though TB cases in Indonesia continue to be the top 3 highest in the world. The fear is that if this is not a concern, the high incidence of Tuberculosis in Indonesia will be followed by an increase in lung cancer cases in Indonesia, but it does not seem to be realized that these two cases do not stand alone, but are interconnected.

In addition to the attention of the clinician and also patients, it is necessary to cooperate with public officials to draft regulations that facilitate the condition of post-tuberculosis patients to be able to check their health regularly so that they hope if the patient is suspected of having a mass in the lungs with a history of having been infected with tuberculosis to immediately be further examined on the mass whether it is a pulmonary violence. When regular early screening in post-tuberculosis patients can be done and obtain mass in the lungs as soon as possible, then the patient can be treated as quickly as possible so as to

reduce the cost of long-term lung cancer treatment and reduce the incidence and mortality of future lung cancer patients.

How Can Tuberculosis Being Risk of Lung Cancer?

Tuberculosis increases lung cancer risk through inflammatory mechanisms that drive carcinogenesis. Neutrophil-activated reactive oxygen and nitrogen species cause DNA damage and neoplastic transformation,^{12,13} while persistent TB infections correlate with fragile histidine triad gene mutations^{14,15} and pulmonary fibrosis that enhances epithelial sensitivity to metaplasia.¹⁶ Reactive oxygen species (ROS) are pivotal in this process, serving as macrophages’ defense against *Mycobacterium tuberculosis* while simultaneously damaging chromosomal structures and mitochondrial DNA.¹⁷ These ROS-induced processes trigger comprehensive cellular damage affecting DNA, mitochondrial function, and apoptosis regulation. The release of danger-associated molecular patterns from ROS-activated cells contributes to fibrosis, while elevated ROS increases oncogene production, suppresses P21 expression, and disrupts cell cycle regulation, accelerating cell division and promoting mutations that significantly heighten carcinogenesis risk.¹⁷

Limitation, Strength, and Future Research Directions

The limitations of this study are only a few articles found and expose the number of cancer patients with a history of tuberculosis in Indonesia. Therefore the heterogeneity index (I² Value) could be a bias and should be interpreted carefully.¹⁸ The strength of this study is to summarize and analyze the risk of lung cancer in patients with a history of tuberculosis in Indonesia for the first time with available data. Instructions for his future research to conduct more observational studies on the risk of lung cancer in tuberculosis patients. Do not forget that patients with a history of tuberculosis need to be diagnosed to check their health regularly and also reduce the risk of lung cancer. Further research guidelines are also needed on the cost-benefit of early screening of lung cancer in patients with a history of tuberculosis compared with without early screening. This is necessary to support scientific evidence that early screening is necessary in the hope of its future regu-

lation and facilitation for tuberculosis patients to check their health.

Conclusion

As many as 8 out of 100 lung cancer patients in Indonesia have a previous history of tuberculosis. The most frequent type of lung cancer is adenocarcinoma compared to squamous cell carcinoma but more data required to increase confidence to conclude it. Patients who have completed treatment for tuberculosis should be checked to regularly check their health and to reduce the risk of lung cancer.

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