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ASBESTOS EXPOSURE IN LUNG CANCER; A HOSPITAL-BASED CASE CONTROL STUDY IN INDONESIA

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ABBREVIATIONS

BPS	Badan Pusat Statistik
CT scan	Computed Tomography scan
DOMJEM	Dutch General Population Job Exposure Matrix
ILO	International Labor Organization
IARC	International Agency for Research on Cancer
ISIC*/IndSIC	Indonesian Standard of Industrial Classification
ISIC	International Standard of Industrial Classification
JEM	Job Exposure Matrix
GPJEM	General Population Job Exposure Matrix
KBLI	Kriteria Baku Lapangan Usaha Indonesia
KSCO	Korean Standard classification on Occupation
KSIC	Korean Standard of Industrial Classification
PAF	Population Attributable Fraction
WAM	Weight Average Mean
WHO	World Health Organization

LIST OF PUBLICATIONS

Anna Suraya, Dennis Nowak, Astrid Sulistomo, Aziza Ghanie Icksan, Elisna Syahruddin, Ursula Berger, Stephan Boese O'Reilly,
Asbestos-related Lung Cancer: A Hospital-Based Case-Control Study in Indonesia,
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Anna Suraya, Dennis Nowak, Astrid Sulistomo, Aziza Ghanie Icksan, Elisna Syahruddin, Ursula Berger, Stephan Boese O'Reilly,
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CONTRIBUTION TO THE PUBLICATIONS

Contribution to The Paper I

At the beginning of the study, the PhD candidate framed the study's concept and developed a research proposal. Having the accepted proposal in hand, the PhD candidate organized the study and built a team to conduct a data collection process. Following the end of data collection, the PhD candidate organized, analyzed, and interpreted the data. All the process was under the supervision of all supervisors of the study. After having the study results, the Ph.D. candidate started writing the original draft of the article and doing some revisions according to the co-authors' suggestions or comments. The article was submitted to the journal then, and the PhD candidate became a corresponding author to manage the publication process until the article was published.

The PhD candidate was also responsible for project administration and resources of the study.

Contribution to The Paper II

The second paper was developed using the same data as the first paper. The PhD candidate organized, analyzed, and interpreted the data under the supervision of all supervisors of the study. After having the study results, the Ph.D. candidate started writing the original draft of the article and doing some revisions according to the co-authors' suggestions or comments. The article was submitted to the journal then, and the PhD candidate became a corresponding author to manage the publication process until the article was published.

CHAPTER I

INTRODUCTORY SUMMARY

1 Introductory Summary

1.1 Introduction

Work-related diseases are matters of health and also matters for society and the economy because of their impact on the lives of employees and families. According to the “International Labor Organization” and the “World Health Organization”, 5-7% of total global deaths are attributable to work-related illnesses and occupational injuries (1). Globally, 2.78 million deaths are attributed to work annually, and more than 85% of the fatalities were due to occupational diseases. Asia contributed to around two-thirds of the deaths and occupational cancers accounted for more than a quarter of the global occupational mortality (2).

Indonesia, like other developing countries, faces serious problem in recognizing work-related diseases. During 2018-2019, the “National Social Security Agency” reported only 15 cases of work-related diseases compensation claims (3). Compared to the number of Indonesian workers being 125 million, the number of work-related diseases reported was considered to be far from accurate (4). The majority of occupational diseases either was not diagnosed or failed to be reported which leads to the inability to prioritize targeted interventions, allocate proper resources, and evaluate the effectiveness of those interventions that are most needed to protect workers’ health.

A large proportion of the confirmed “(International Agency for Research on Cancer Group”) carcinogens present at the workplaces, including asbestos, arsenic, beryllium, cadmium, silica, and diesel engine emissions (5,6). In addition to tobacco smoke, the majority of those occupational carcinogens are known risk factors for lung cancer. It is hardly surprising that the most common type of occupational cancer is primary lung cancer which contributed to 54-75% of all work-related cancer (2,7). Asbestos is responsible for up to 85% of occupational lung cancers (7).

“Indonesian Cancer Information and Support Centre” reported that lung cancer is the number one cancer among Indonesian men, which caused 14% of cancer deaths in Indonesia (8). It is public knowledge that tobacco smoking is the most established risk factor for lung cancer, therefore with more than 65% smokers among Indonesian males, the role of other risk factors is somewhat overlooked. Lung carcinogens like asbestos, silica, and fuel engine exhaust have never been an attractive substance to be investigated, even though asbestos, the primary cause of occupational lung cancer, has been used in massively in Indonesia (7).

Asbestos is a group of naturally occurring silicate mineral fibers, which are conventionally divided into two mineralogical groups. The first is the serpentine group, of which chrysotile (known as "white asbestos") is the sole variety. The second is the amphibole series, which includes five different types of asbestos that are less known in industrial applications. Asbestos and its carcinogenic risk prevail in all types of fibers wherever it is found. Since asbestos was discovered in the early 19th century, it has been fused into thousands of commercial, construction, and household products, including fire-retardant coatings, cement, concrete, pipes, bricks, insulation, gaskets, flooring, drywall, roofing, joint compound, paints, and sealants. It can be a component in plastics, electrical appliances, mattresses, rubber, flowerpots, lawn furniture, gloves, and hats (9,10).

In 1924, the first medical literature concerning the adverse effect of asbestos for the lungs was published by the "British Medical Journal" (11). In 1935, Gloyne reported the first instance of asbestos-related lung cancer, which were two cases of small-cell carcinoma in women with asbestosis (12,13). Later, in 1955, Doll proved the causal association between asbestosis and lung cancer (14). The carcinogenic nature and pneumoconiosis initiations of asbestos has subsequently alarmed the world which has led to a ban on its use in 65 countries in 2020 (15). Unfortunately, instead of banning the use of asbestos, Indonesia is still one of the biggest asbestos importing countries in the world (16).

According to the "British Geological Survey", the first asbestos import to Indonesia was in 1950 (17). The number of asbestos imports in the early years was around 39 tons and it has increased sharply within the last 20 years. The peak of consumption totaled 163,412 tons in 2012, making Indonesia the second-largest asbestos importing country in the world after India (18). The increasing amounts of asbestos being imported to Indonesia and other low- and middle-income countries took place simultaneously with the efforts to ban asbestos in high income countries. Asbestos producing countries changed their export from countries banning asbestos to countries that still permit its use. Shifting export direction means as well diverting the adverse effect of asbestos to countries with less advanced health care systems.

The number of mortalities from all forms of asbestos-related diseases in a country can be predicted by extrapolating the amount of asbestos processed. In a paper about the global asbestos disaster, Sugio et al. reported that one person will be die for every 20 tons of asbestos application (19). Based on the number of asbestos processed in Indonesia, the WHO estimated that in 2017 there were 1,500 asbestos-related deaths in Indonesia, although this was almost undetectable compared to the country's 1.5 million annual deaths (20). However, due to the massive consumption of asbestos since the 2010s, the estimated number of asbestos-related deaths will increase to around 8,000 per year in the 2030s and beyond, representing around 0.5% of all deaths in Indonesia (19,20). Without adequate elimination efforts, asbestos-related diseases will become a more relevant burden for Indonesia.

1.2 Rationale and Objectives

It is common knowledge that asbestos-related diseases are underdiagnosed, especially in low- and middle-income countries. After more than 65 years of asbestos use, asbestos-related diseases have never been an issue in Indonesia. Medical doctors received insufficient occupational health training so there have always been difficulties in linking the diseases to workplace hazard exposure. Workers, employers, and other stakeholders did and do not have adequate knowledge of asbestos-induced health effects and government policies were not strong enough to protect workers and the community. Without adequate efforts to increase knowledge and skills, asbestos-related diseases will continue to be under-detected, and the increasing number of asbestos-related diseases will not be recognized. The most likely outcome is that the cases of lung cancer and lung parenchymal fibrosis will increase without any notification of the cause.

It is critical to improve this situation, that bring substantial evidence for asbestos-related diseases in Indonesia is gained. Having reliable data and accurate studies is crucial for the country to encourage the government and other stakeholders to make more effort to protect workers and the communities from the health hazards of asbestos.

This PhD project is aimed at producing that evidence by investigating the role of asbestos in causing lung cancer among Indonesian workers. To approach the overall research, three detailed objectives were:

1.2.1 To establish the effect of occupational asbestos exposure to the risk of lung cancer development among Indonesian workers;

1.2.2 To establish the joined effect of asbestos exposure and tobacco smoking on the development of lung cancer; and

1.2.3 To establish the different risks of lung cancer development among workers according to the Indonesian Standard Industrial Classification (IndSIC) 2015.

1.3 Methods

1.3.1 *Design*

To achieve the study's aims, a hospital-based, case-control study at “Persahabatan Hospital”, a national respiratory hospital in Jakarta, was conducted.

1.3.2 *Participants*

The study was conducted from May 2018 to August 2019. The study population consisted of patients who performed a thoracic computerized tomography (CT) scan at Persahabatan hospital’s Radiology Department. The cases were the histologically confirmed lung cancer patients, and the controls were the patients with the negative thoracic CT for lung cancer.

1.3.3 Assignment of Exposure

Several trained interviewers conducted the interviews to obtain the exposure history using a standardized cancer questionnaire (21). The interviews obtained sociodemographic data, smoking habits, history of occupational employment, and non-occupational asbestos exposure. The author classified job titles and industries according to the “Indonesian Standard Industrial Classification (IndSIC) 2015,” and an experienced thoracic radiologist interpreted the thoracic CT scans. The cumulative work-related asbestos exposure was calculated by multiplying the fiber concentration in the workplace and work duration. The values of fiber concentration in the workplaces were adopted from the “Korean General Population Job Exposure Matrix (GPJEM)” (22).

1.3.4 *Analysis*

The risks of getting lung cancer among workers were analyzed using logistic regression. The chi-square (χ^2) test evaluated the categorical variables, and the t-test was used to determine the different means of the two groups. ANOVA was used to determine the mean difference of multiple groups. The main effects were reported as odds ratios and 95% confidence intervals. Statistical analyses were performed using SPSS Statistics version 25.

1.3.5 *Ethics*

The study protocol was approved by two ethical committees ("Persahabatan Hospital" # 18/KEPK-RSUPP/03/2018; "ethical committee at the medical faculty, LMU" # 18-632).

1.3.6 *Team*

The team consisted of the author as a principal investigator, six supervisors from Germany and Indonesia, several colleagues, and medical staff from "Persahabatan Hospital". All team members were involved in every step of the study according to their expertise.

This study also received influential support from expert from Korea (Prof. Domyung Paek and Prof. Kim Jeung Sook), Australia (Prof. Ken Takahashi and Dr. Kenneth Lee), and Germany (Dr. Kurt Hering and Dr. Martina Ferstl).

1.4 Results

The three objectives were successfully addressed. The majority of lung cancer patients were male, with a mean age of 58.1 years. The proportion of subjects who smoke "more than ten pack-years" was higher in the cases group than in the controls group. The majority of cases were adenocarcinoma type of lung cancer and the most common diagnosis in the control group was tuberculosis.

The article titled "*Asbestos-Related Lung Cancer: A Hospital-Based Case-Control Study in Indonesia,"* describes in detail the results of the investigation of study objectives number one and number two. Asbestos-exposed workers had twice the risk of developing lung cancer than non-exposed workers "(OR=2.04, 95% CI=1.21-3.42)". The lung cancer risk increased by three times among asbestos-exposed workers who were exposed to ten fiber-years or more "(OR=3.08, 95% CI= 1.01-9.46)". A synergy effect was found between cigarette smoking and asbestos exposure. Subjects exposed to both asbestos of "ten fiber-years or more" and "smoke ten pack-years or more" had a nine-fold increased risk of lung cancer than subjects who were absent of both cigarette smoking and asbestos exposure (23).

The study objective number three was addressed in the article titled "*Excess Risk of Lung Cancer Among Agriculture and Construction Workers in Indonesia."* When subjects were classified according to "IndSIC 2015", this study indicated an excess risk of lung cancer among subjects who worked in the "crop, animal production, and hunting" division and "construction" section with the Population Attributable Fraction (PAF) of "3.9%" and "5.4%" respectively (24).

1.5 Discussion

This study has succeeded in bringing new evidence on the relationship between workplace exposure to asbestos and lung cancer development among Indonesian workers. Moreover, the research delivered some fresh insights into Indonesia's occupational health research, at least in three aspects. First, it is the first case-control study investigating the relationship between occupational asbestos exposure and the risk of lung cancer in Indonesian workers. Second, this epidemiological study is the first to utilize the "Indonesian Standard Industrial Classification 2015" as a proxy of workplace exposure. Third, the method employed to quantify the amount of chemical exposure in this study which is to adopt the job exposure matrix (JEM) from another country is the first in Indonesia. In this study, we adopted the "Korean Asbestos JEM" to determine the amount of cumulative occupational asbestos exposure of each subject.

This case control study discovered an increased lung cancer risk for workers exposed to asbestos that has never been an issue in Indonesia. The excess risk of lung cancer among construction workers intensified the role of asbestos in causing primary lung cancer among Indonesian workers. It is because around 90% of asbestos containing materials professionally used in Indonesia are construction materials. The increased risks found in this study was consistent with previous studies found in other countries (25–27).

Asbestos imports to Indonesia increased dramatically around the 1990s when high income countries started banning the product. Once some countries banned the use of asbestos, asbestos companies moved to other countries, particularly into low- and middle-income countries that still allowed the use of asbestos. Choi at al. gave an example of the asbestos industry's transfer in four countries, Germany, Japan, Korea and Indonesia. They reported, that, when asbestos was banned in Germany, the companies moved to Korea. When the Korean government became aware of the negative health effects of asbestos and banned it, companies were transferred to Indonesia. The industry transfers essentially have shifted the risk of asbestos-related diseases from one country to another country. Additionally, Choi's study also observed, that the health and safety measures, that should have accompanied the transfer, were actually not conveyed. Therefore, the risk of asbestos-related diseases will repeatedly occur in other countries after certain time after such transfers (22).

Moreover, this study showed the synergy interaction of cigarette smoking and asbestos exposure that was also similar with the results of previous studies (28). Since more than 65% of

Indonesian males smoke, further research should be conducted to discover whether the interaction effect has an important role to the earlier stage of the lung cancer incidence among Indonesian (22–24).

Like JEM and the industrial classification, some reliable methods have been identified to represent occupational exposure assessment (30). This study has brought evidence of the effectiveness of employing proxies of occupational exposure to occupational health research in Indonesia. This research has successfully employed the "Korean Asbestos GPJEM" and "IndSIC 2015" in discovering the risk of lung cancer among workers in Indonesia. It is an important finding considering that employing a proxy for occupational exposure has never been acknowledged in studies or practices connected with occupational health in Indonesia. This crucial research can be a model for Indonesia to identify work-related diseases among workers.

Some limitations that commonly existed in a case-control study were addressed with no substantial effect in this study. The odds ratios found in this study were around the range of the odds ratios of the risks of asbestos-related lung cancer resulting in previous research worldwide.

Along with the study, the research team performed some activities to increase awareness on the asbestos issue and its health effects among Indonesian people. In April 2018, at the beginning of the study, supported by Prof. Dr. med. Dennis Nowak, we held three seminars in Jakarta: a seminar to increase awareness about asbestos-related diseases for medical staff and other hospital stakeholders was held at Persahabatan Hospital; a seminar for students aimed to introduce the health effects of asbestos in construction work was organized at the Department of Civil Engineering, Universitas Indonesia; thirdly, in collaboration with the Occupational Medicine Department of the Medical Faculty, Universitas Indonesia, we held a seminar about asbestos management and research in Indonesia attended by academicians, researchers, government agencies, NGOs, and occupational health practitioners. In October 2018, we invited Prof. Kim Jeung Sook, an expert from Korea, to introduce asbestos-related diseases radiology imaging for Indonesian doctors (31). Furthermore, in June 2019, the "Indonesian Radiologists Association" arranged a special symposium on asbestos-related disease imaging during a national conference of the "Indonesian Radiologist Association". Many more seminars, workshops, and conferences on asbestos-related diseases have taken place since then. In October 2019, a workshop on how to histologically diagnose interstitial lung disease and mesothelioma was held for pathologists from several cancer referral hospitals in Indonesia.

Concurrently with this study, the Indonesian government has issued several new regulations regarding work-related diseases. A Presidential Decree was issued in 2019 to update the list of compensated occupational diseases and revise the reporting system (32). The "Ministry of Health" issued the list of specific occupational diseases that all Indonesian doctors should be able to recognize and included asbestos-related diseases among them. Further, the asbestos issue has become sufficiently prominent in Indonesia to encourage Indonesia, e.g. in February 2020, Indonesia launched a national movement of lung cancer care , and for the first time, asbestos was introduced broadly as one of the lung cancer risk factors that should be avoided elsewhere (33).

Some additional research has been following the work presented in this thesis. A study is being conducted to investigate the existence of pleural and lung parenchymal abnormality in the thoracic CT scans of patients who had a history of asbestos exposure. Another study to identify the range of asbestos-containing materials distributed in Indonesia is also being prepared. More research should also be conducted to build on the initial findings in this thesis study to provide more information on occupational diseases among Indonesian workers.

What can the world learn from this study? Finding an increased risk of asbestos-related lung cancer among workers is not a new topic in research. However, the fact that in one part of the world, people are saved from a particularly hazardous material, whilst in other parts of the world, people are still struggling to prove the existence of its ill-health effects is really unfair. It is a tragedy of humanity where people are seen to be viewed differently in front of the same hazardous substances. The world should use one common language for hazardous substances; whenever they are declared to be dangerous, all parts of the world should take the same action for the sake of humanity.

1.6 Reference

1. Rushton L. The Global Burden of Occupational Disease. Curr Environ Health Rep [Internet]. 2017 [cited 2019 Jan 30];4(3):340–8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5591369/
2. Päivi Hämäläinen . Jukka Takala . Tan Boon Kiat. Global Estimates of Occupational Accidents and Work-Related Illnesses 2017. Workplace Safety and Health Institute; 2017.
3. BPJS Ketenagakerjaan [Internet]. [cited 2019 Oct 13]. Available from: https://www.bpjsketenagakerjaan.go.id/
4. Badan Pusat Statistik. Penduduk Indonesia, Hasil Survey Penduduk Antar sensus. 2015.
5. Siemiatycki J, Richardson L, Straif K, Latreille B, Lakhani R, Campbell S, et al. Listing Occupational Carcinogens. Environmental Health Perspectives [Internet]. 2004 [cited 2020 Apr 16];112(15):1447–59. Available from: https://www.jstor.org/stable/3435600
6. Loomis D, Guha N, Hall AL, Straif K. Identifying occupational carcinogens: an update from the IARC Monographs. Occup Environ Med [Internet]. 2018 Aug 1 [cited 2020 Apr 3];75(8):593–603. Available from: https://oem.bmj.com/content/75/8/593
7. TAKALA J. Eliminating occupational cancer. Ind Health [Internet]. 2015 Jul [cited 2019 Jan 5];53(4):307–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4551060/
8. Beranda [Internet]. CISC. [cited 2021 Feb 19]. Available from: https://cancerclubcisc.org/id/beranda/
9. Craighead JE, Gibbs AR. Asbestos and Its Diseases. Oxford University Press, USA; 2008. 424 p.
10. Asbestos, its Chemical and Physical Properties: Second in a series of articles on asbestos: Its history, chemical and physical properties, uses, health hazards and the legal implications of asbestosis & mesothelioma. (EnvironmentalChemistry.com) [Internet]. [cited 2019 Jan 29]. Available from: https://environmentalchemistry.com/yogi/environmental/asbestosproperties2004.html
11. Cooke WE. Fibrosis of the Lungs Due to the Inhalation of Asbestos Dust. Br Med J [Internet]. 1924 Jul 26 [cited 2019 Jan 30];2(3317):147–140. Available from: https://www.bmj.com/content/2/3317/147
12. Bartrip P. History of asbestos related disease. Postgrad Med J [Internet]. 2004 Feb [cited 2019 Jan 29];80(940):72–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1742940/
13. Gloyne SR. Two Cases of Squamous Carcinoma of the Lung Occurring in Asbestosis. Tubercle [Internet]. 1935 [cited 2019 Jan 5];17:5–10. Available from: https://www.cabdirect.org/cabdirect/abstract/19362700526

14. Doll R. Mortality from lung cancer in asbestos workers 1955. Br J Ind Med [Internet]. 1993 Jun [cited 2019 Jan 30];50(6):485–90. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1035472/

15. Current Asbestos Bans [Internet]. [cited 2020 Jul 10]. Available from: http://www.ibasecretariat.org/alpha_ban_list.php

16. Asbestos imports in Indonesia from China, Asbestos imports data of Indonesia from China-Voleba.com [Internet]. [cited 2020 Jun 12]. Available from: https://www.voleba.com/china/indonesia-product-asbestos-imports-data.html

17. Colonial Geological Surveys, Mineral Resources Division. Statistical Summary of The Mineral Industry Production, Exports and Imports, 1950-1955. Her Majesty's Stationary Office;

18. Indonesia | Imports and Exports | World | Asbestos | Netweight (kg); Quantity and Value (US$) | 2010 - 2018 [Internet]. [cited 2020 Jun 14]. Available from: https://trendeconomy.com/data/h2/Indonesia/2524

19. Furuya S, Chimed-Ochir O, Takahashi K, David A, Takala J. Global Asbestos Disaster. Int J Environ Res Public Health [Internet]. 2018 May [cited 2019 Jan 30];15(5). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5982039/

20. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians [Internet]. 2018 Nov 1 [cited 2020 Jul 18];68(6):394–424. Available from: https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21492

21. Tsim S, Kelly C, Alexander L, Shaw A, Paul J, Woodward R, et al. The DIAPHRAGM study: Diagnostic and prognostic biomarkers in the rational assessment of Mesothelioma. European Respiratory Journal [Internet]. 2018 Sep 15 [cited 2019 Jun 1];52(suppl 62):OA493. Available from: https://erj.ersjournals.com/content/52/suppl_62/OA493

22. Choi S, Kang D, Park D, Lee H, Choi B. Developing Asbestos Job Exposure Matrix Using Occupation and Industry Specific Exposure Data (1984–2008) in Republic of Korea. Saf Health Work [Internet]. 2017 Mar [cited 2017 Sep 10];8(1):105–15. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5355542/

23. Suraya A, Nowak D, Sulistomo AW, Ghanie Icksan A, Syahruddin E, Berger U, et al. Asbestos-Related Lung Cancer: A Hospital-Based Case-Control Study in Indonesia. International Journal of Environmental Research and Public Health [Internet]. 2020 Jan [cited 2020 Jan 20];17(2):591. Available from: https://www.mdpi.com/1660-4601/17/2/591

24. Suraya A, Nowak D, Sulistomo AW, Icksan AG, Berger U, Syahruddin E, et al. Excess Risk of Lung Cancer Among Agriculture and Construction Workers in Indonesia. Annals of Global Health [Internet]. 2021 Jan 6 [cited 2021 Jan 25];87(1):8. Available from: http://www.annalsofglobalhealth.org/articles/10.5334/aogh.3155/

25. Case BW, Dufresne A. Asbestos, asbestosis, and lung cancer: observations in Quebec chrysotile workers. Environmental Health Perspectives [Internet]. 1997 Sep [cited 2017 Aug 8];105(Suppl 5):1113. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1470135/

26. Gustavsson P, Nyberg F, Pershagen G, Schéele P, Jakobsson R, Plato N. Low-Dose Exposure to Asbestos and Lung Cancer: Dose-Response Relations and Interaction with Smoking in a Population-based Case-Referent Study in Stockholm, Sweden. Am J Epidemiol [Internet]. 2002 Jun 1 [cited 2019 Sep 17];155(11):1016–22. Available from: https://academic.oup.com/aje/article/155/11/1016/57233

27. Pohlabeln H, Wild P, Schill W, Ahrens W, Jahn I, Bolm-Audorff U, et al. Asbestos fibreyears and lung cancer: a two phase case–control study with expert exposure assessment. Occupational and Environmental Medicine [Internet]. 2002 Jun 1 [cited 2019 May 29];59(6):410–4. Available from: https://oem.bmj.com/content/59/6/410

28. Ngamwong Y, Tangamornsuksan W, Lohitnavy O, Chaiyakunapruk N, Scholfield CN, Reisfeld B, et al. Additive Synergism between Asbestos and Smoking in Lung Cancer Risk: A Systematic Review and Meta-Analysis. PLOS ONE [Internet]. 2015 Agu [cited 2017 Jan 1];10(8):e0135798. Available from: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0135798

29. Tamura A, Funakoshi M, J-P NA, Hasegawa K, Ishimine A, Koike A, et al. Potential asbestos exposure among patients with primary lung cancer in Japan. J Occup Health [Internet]. 2018 May 20 [cited 2019 Apr 19];60(3):236–45. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5985347/

30. Teschke K, Olshan AF, Daniels JL, Roos AJD, Parks CG, Schulz M, et al. Occupational exposure assessment in case–control studies: opportunities for improvement. Occupational and Environmental Medicine [Internet]. 2002 Sep 1 [cited 2019 Aug 30];59(9):575–94. Available from: https://oem.bmj.com/content/59/9/575

31. PERHATIAN DARI DUNIA AKAN ASBES DI INDONESIA MAKIN TINGGI • INDONESIA BAN ASBESTOS NETWORK [Internet]. INDONESIA BAN ASBESTOS NETWORK. 2018 [cited 2021 Jan 13]. Available from: http://inaban.org/perhatian-dari-dunia-akan-asbes-di-indonesia-makin-tinggi/

32. Peraturan Presiden Nomor 7 Tahun 2019 [Internet]. hukumonline.com/pusatdata. [cited 2020 Nov 3]. Available from: https://www.hukumonline.com/pusatdata/detail/lt5c6280db02a31/node/183/peraturan-presiden-nomor-7-tahun-2019

33. Antara. Atap Asbes Disebut Bisa Tingkatkan Risiko Kanker Paru-paru [Internet]. tirto.id. [cited 2020 Aug 29]. Available from: https://tirto.id/atap-asbes-disebut-bisa-tingkatkan-risiko-kanker-paru-paru-eyiA

CHAPTER II

ASBESTOS-RELATED LUNG CANCER: A HOSPITAL-BASED CASE CONTROL STUDY IN INDONESIA

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2 Asbestos-Related Lung Cancer: A Hospital-Based Case-Control Study in Indonesia

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Abstract: Indonesia has limited data on asbestos-related diseases despite abundant using. This study investigated the risk of occupational asbestos exposure for lung cancer development, utilizing a hospital-based case-control study. Subjects were patients who received a thoracic CT scan at Persahabatan Hospital, Jakarta. The cases had primary lung cancer confirmed by histology, the controls were negative for lung cancer. The cumulative occupational asbestos exposure was calculated by multiplying the exposure intensity by the years of exposure. The exposure intensity was obtained by adopting the weighted arithmetic mean value of asbestos exposure from a job-exposure matrix developed in Korea. The primary data analysis was based on logistic regression. The study included 696 subjects, with 336 cases and 360 controls. The chance of lung cancer for subjects exposed to asbestos was doubled (OR=2.04, 95% CI=1.21-3.42) compared with unexposed, and subjects with a cumulative asbestos exposure of 10 fiber-years or more even showed an OR of 3.08 (95% CI= 1.01-9.46). The OR of the combined effect between smoking and asbestos was 8.7 (95% CI=1.71-44.39); the interaction was consistent with an

additive and multiplicative risk model. Asbestos exposure is associated with a higher chance of lung cancer. Improved policies are needed to protect the population from asbestos hazards.

Keywords: lung cancer; asbestos; Indonesia

2.1 Introduction

Lung cancer is the most common cancer in Indonesian men and the third most common in women, causing a total of 26,095 fatalities in 2018 (1). With approximately 63% of Indonesian males smoking, it is an attractive risk factors for a lung cancer investigation (2). However, studies have demonstrated that other risk factors such as asbestos, radon and diesel engine particulates, increase the risk of lung cancer (3). It has been estimated that occupational lung cancer is responsible for 17-29% of all lung cancer deaths in men and asbestos is the most significant occupational carcinogen accounting for around 55-85% of all occupational lung cancer cases (4).

Asbestos is a general term for a family of fibrous silicate minerals with a crystalline structure that mesmerized the industrial world in the 1900's because of its unique chemical and physical characteristics (5). Asbestos is strong, flexible, stable, durable and resistant to heat, chemical, and biological degradation. For over a century it was used in more than 3000 different products, including construction materials, brake pads, insulation, textiles, plastic, paper and many others (6,7). Health consequences related to asbestos arose following its extensive use. The first suspected asbestos-related lung cancers were reported by Gloyne in 1935 upon autopsies of two female asbestos textile factory workers who were found to suffer from asbestosis and lung cancer (8). More cases of asbestos-related cancers have been diagnosed since that time and since 1987 asbestos has been classified by the International Agency for Research on Cancer of the World Health Organization as being carcinogenic to humans (9,10).

Indonesia started importing asbestos in 1950 and recently it joined the top five asbestos-importing countries in the world (11,12). In the past ten years, more than one million tons of asbestos have been brought into Indonesia, mainly as a raw material for roofing, cement, ceilings, partitions, and in lesser amounts for brake systems, insulation, and heat-resistant textiles (13). Consumption of asbestos increased from 20,000 tons in the 1980s to 50,000 tons in the 1990s and continued to increase to roughly 150,000 tons in the 2000s. Based on the amount of asbestos processed, in 2017 the WHO estimated that there should be approximately 1000 lung cancer cases and 400 mesothelioma cases in Indonesia in that year (14). In reality, until 2019, there were no confirmed reports of asbestos-related lung cancer or mesothelioma. In addition, occupational and environmental asbestos exposure data is very limited in the country.

Considering the extensive use of asbestos in Indonesia, an investigation of its health effects is necessary. This study is the first case-control study in Indonesia comparing occupational asbestos exposure to the risk of lung cancer development and the combined effect with smoking. This study is also the first to adopt the asbestos Job Exposure Matrix (JEM) from a neighboring country: The General Population Job Exposure Matrix (GPJEM) from the Republic of South Korea. It was developed by Choi et al. (15) to quantify the amount of asbestos exposure in various job classifications in that country. We have adopted it due to the lack of data on workplace asbestos exposure for Indonesia. Improved scientific information about asbestos and its health effects may facilitate the development of asbestos management policies in Indonesia.

2.2 Materials and Methods

2.2.1 Study Population

This study was conducted at the National Respiratory Hospital, a 585-bed public hospital in Jakarta, Indonesia (16). A case-control study was performed to identify the association between asbestos exposure and the risk of developing lung cancer. Inpatients and outpatients aged 35 years or older who had received a thoracic CT scan at the radiology department between May 2018 and August 2019 were recruited. The reasons for a thoracic CT scan were lung infection, mediastinal mass, lung nodule or mass, trauma, evaluation of pleural diseases and malignancies, and other conditions.

The cases had primary lung cancer confirmed by histology regardless of the type of cancer. The controls were negative for lung cancer selected from the same group of patients receiving thoracic CT. Patients were excluded as controls if they had one of these conditions: mesothelioma, pleural plaques, asbestosis, and interstitial lung diseases.

2.2.2 Assignment of Exposure

An occupational medicine physician evaluated the occupational and non-occupational asbestos exposures blind to the patient's grouping as a case or control.

Occupational asbestos exposure was defined as a history of occupational contact with asbestos fibers at least ten years prior to the time of interview. The description of occupational asbestos exposure in the workplace was obtained from a questionnaire adapted from Cancer

Research UK (17). It included industry category, type of job, time of first contact, duration of work, the number of work hours in a day and the number of workdays per week. Subjects' occupations were coded according to 5-digit Indonesian Standard Industrial Classification (ISIC*) 2015.

The cumulative occupational asbestos exposure was expressed in fiber-years, which was fiber concentration in weighted arithmetic mean (WAM), expressed in fiber/milliliter (f/mL) of air multiplied by the total duration of exposure in years. A year was defined as exposure during 8-hour shift over 240 workdays and spread over 48 weeks. Fiber concentration in WAM was obtained from the Korean GPJEM by linking the five-digit ISIC* 2015 to the Korean Standard Industrial Classification (KSIC, 9th edition) and Korean Standards Classification of Occupation code (6th edition) to the asbestos exposure levels in the Korean GPJEM (15).

Non-occupational asbestos exposure was identified separately because individuals often had multiple exposure circumstances. Exposures unrelated to work included living in proximity to industrial or natural sources of airborne asbestos (environmental exposures), sharing a home with individuals occupationally exposed to asbestos (familial exposure), having experienced a fire or an earthquake that destroyed buildings in the neighborhood and living close to a public garbage dump. Detailed information was also collected from all subjects for several potential risk factors including sociodemographic data, smoking, and exposure to second-hand smoke. Smoking was expressed in pack-years which was the number years of smoking an average of 20 cigarettes per day.

2.2.3 Statistical Analysis

The questionnaire data, tumor histology, and CT scan results collected from the study participants were entered into an electronic database using Epi-info software. Statistical analyses were performed using IBM SPSS Statistics 23 software. The primary data analyses were based on logistic regression, adjusting all models for gender, age, ethnicity, education, house ownership, smoking, and environmental asbestos exposure. Effects were reported as odds ratios and 95% confidence intervals and considered as significant at a level of 5%.

The combined effect of asbestos exposure and smoking on the risk of lung cancer was examined by cross-classification of the two variables with the categories "not exposed to asbestos" or "exposed less than 10 fiber-years ($_{A(-)}$)" versus "exposed to asbestos 10 fiber-years or more ($_{A(+)}$)" and, "not smoking or smoking less than 10 pack-years ($_{Sm(-)}$)" versus "smoking 10 pack-years or more ($_{Sm(+)}$)". The interaction effect was evaluated using the synergy index (S) and multiplicativity (V) risk model. The synergy index measured the extent to which the risk ratio for smoking and asbestos together exceeds 1 and whether this is greater than the sum of the extent to which each of the risk ratios considered separately each exceed 1. If S>1, the additive interaction is said to be positive and if S<1, the additive interaction is said to be negative. The synergy index was calculated using derived odd ratios (ORs) as follows (22):

$$S = (OR_{A(+)Sm(+)} - 1) / [(OR_{A(+)Sm(-)} - 1) + (OR_{A(-)Sm(+)} - 1)]$$

The multiplicativity index measured the extent to which, on the risk ratio scale, the effect of asbestos and smoking together exceeds the product of the effects of the two exposures considered separately. If V> 1, the multiplicative interaction is said to be positive. If V< 1, the interaction is said to be negative. The multiplicativity was calculated using derived ORs as follows (18):

$$V = OR_{A(+)Sm(+)} / [OR_{A(+)Sm(-)} \times OR_{A(-)Sm(+)}]$$

2.2.4 Ethics Approval

The Ethical Committee of Ludwig Maximilian University, Munich, Germany and the Ethics Committee of Persahabatan Hospital, Jakarta, Indonesia approved the study protocol. Subjects were informed about all aspect of the study, and they provided written consent for participation in the study.

2.3 Results

A total of 710 subjects were interviewed between May 2018 and August 2019. Among them, 336 subjects were eligible for cases, and 360 were eligible for the controls. Fourteen patients were excluded. Two subjects were not confirmed histologically of having lung cancer. Two subjects were excluded because of metastatic cancer from other organs to the lung, five subjects were suspected mesothelioma cases, three subjects were suspected asbestosis, and two subjects were suspected interstitial lung diseases.

Table 2.1 presents the characteristics of the subjects. The mean age for cases was 58.1 years, and for control was 54.8 years. About 40% of the subjects reported more than 10 package-years smoking. The proportions of males, of house owners and of smokers was higher in cases than in controls.

Table 2.1 Characteristics of subjects.

	Cases (n=336)		Controls (n=360)		
	Mean (SD)	**No. of Subjects (%)**	**Mean (SD)**	**No. of Subjects (%)**	P Value *
Mean Age	58.19 (9.79)		54.68 (10.35)		0.00
Gender					
Female		125 (37.2)		165 (45.8)	0.02
Male		211 (62.8)		195 (54.3)	
Ethnicity					
Javanese		115 (34.2)		111 (30.8)	0.65
Sundanese		57 (17.0)		54 (15.0)	
Sumatran		63 (18.8)		68 (18.9)	
Sulawesi		7 (2.1)		10 (2.8)	
Kalimantan		0 (0)		2 (0.6)	
Papuan/East Indonesia		4 (1.2)		5 (1.4)	
Others		90 (26.8)		110 (30.6)	
Education					
Illiterate		10 (3.0)		10 (3.0)	0.09
Elementary		76 (22.6)		64 (17.8)	
Junior High School		31 (9.2)		40 (11.1)	
Senior High School		130 (38.7)		170 (47.4)	
Bachelor		78 (23.3)		71 (19.8)	
Postgraduate		11 (3,3)		5 (1.4)	
Homeownership					
Renting		48 (14.3)		69 (19.2)	0.01
Own house		234 (69.6)		195 (54.3)	
Family house		54 (16.1)		96 (26.7)	
Smoking					
0 to 10 pack-years		172 (51.2)		236 (65.6)	0.001
>10 to 40 pack-years		106 (31.5)		80 (22.2)	
>40 pack-years		58 (17.3)		44 (12.3)	

*The t-test was used for continuous variables and $\chi 2$ test for categorical variables.

A total of 1,095 work histories were collected from 710 individuals, 84 (12%) of the subjects, including 55 cases and 29 controls, reported that they worked at the industries or the occupations with asbestos exposures from the Korean GPJEM. Occupational asbestos exposure levels were between 0.03 fiber-years and 61.20 fiber-years with a mean exposure of 0.86 fiber-years in cases and 0.43 fiber-years in controls (p= 0.14). Only eight subjects were exposed to more than 25 fiber-years of asbestos. The most common occupation was technical workers in constructions, second was automobile mechanic and the rest were in other industries that handled asbestos-containing material (Table 2.2).

More than 40% of subjects reported having been exposed environmentally to asbestos roofing and a few to other environmental exposures (table 2.3)

Table 2.2 Distribution of occupations with an exposure to asbestos based on Indonesian Standard Industrial Classification (ISIC*) 2015 and Korean Standard Industrial Classification (KSIC) Rev 9.

				Cases	Controls
ISIC*	**KSIC**	**Industrial Classification**	**Occupation**	**n**	**n**
		Handling asbestos containing product during working			
410	41112	Construction	Technical worker	33	19
4520	95212	Car repair and maintenance	Automobile mechanic	9	4
28160	29169	Manufacture of lifting and transferring equipment	General machinery assembler	1	0
29200	30399	Four wheeled or more vehicles carrosserie industry	Automobile paint mechanic	1	0
6110	6022	Telecommunication activities with cables	Technician	2	1
25920	25921	Industrial services for metal and non-metal processing	Heat treatment operator	2	1
25952	25924	Manufacture of other fabricated metal products	Machine operator	1	0
2392	23229	Manufacture of other refractory ceramic products	Operator	1	0
33151	95119	Ship, boat and floating building repair services	Ship mechanic	2	0
3011	30111	Ship, boat and floating building industries	Ship assembler	0	1
		Handling asbestos-containing product in manufacturing process			
23955	23994	Manufacture of construction material from asbestos	Machine operator	0	1
17021	17129	Manufacture of paper and corrugated paper board	Machine operator	1	0
20131	20302	Manufacture of synthetic resin and other plastic materials	Machine operator	0	1
22230	22250	Manufacture of plastic pipe and equipment	Machine operator	2	1

Exposure group in Korean GPJEM. ISIC*: Indonesian Standard Industrial Classification 2015; KSIC: Korean Standard Industrial Classification rev.9.

Table 2.3 Distribution of environmental exposure.

Environmental exposure	cases	control
	N (%)	N (%)
Unexposed	187 (55.6)	182 (50.6)
Asbestos roof	144 (42.8)	168 (46.7)
Demolition	1 (0.3)	2 (0.6)
Earthquake	2 (0.6(	0 (0)
Fire	1 (0.3)	1 (0.3)
Combination of two or more environmental exposures	1 (0.3)	7 (1.9)

Table 2.4 Histological cell type of case group and the underlying diagnosis of control group according to occupational asbestos exposure

	Number (%)	Occupational Exposure (%)	No occupational exposure (%)	P value*
Histological cell type of cases				
Adenocarcinoma	188 (55.9)	34 (61.8)	154 (54.8)	0.255
Squamous cell	72 (21.3)	13 (23.6)	59 (20.8)	
Small cell	13 (3.8)	3 (5.5)	10 (3.5)	
Large cell	16 (4.7)	0 (0)	16 (5.7)	
Others	44 (13.3)	4 (7.3)	40 (14.5)	
Unidentified	3 (0.9)	1 (1.8)	2 (0.7)	
	336 (100)	55 (100)	281(100)	
Underlying diagnosis of controls				
Tuberculosis and other lung infections	197 (54.9)	19 (65.5)	178 (54.1)	0.856
Chronic lung diseases	62 (17)	5 (16.7)	57 (17.0)	
Mediastinal mass and other malignancies	40 (11.1)	1 (3.4)	39 (11.6)	
Other diseases	31 (8.6)	2 (6.7)	29 (8.8)	
No abnormality	30 (8.4)	2 (6.7)	28 (8.5)	
	360 (100)	29 (100)	331(100)	

*χ^2 test used for categorical variables

Table 2.4 shows the histological cell type of the lung cancer and the underlying diagnoses of the control group. The most frequent histological type was adenocarcinoma, and the most frequent underlying non-malignant diagnosis was tuberculosis. No significant association have been found between asbestos exposure and the histological cell type within the case group nor between exposure and the underlying diagnosis within the control group.

The odds ratio of lung cancer in exposed subjects was 2.04-fold compared to unexposed subjects after adjusting for age, gender, home ownership, education, and smoking (OR=2.04, 95% CI=1.21-3.42). It increased 3-fold for subjects with cumulative asbestos exposure of 10 fiber-years or more (OR=3.08, 95% CI=1.01-9.46)). When the exposure was categorized into unexposed, exposed by less than 25 f-year and exposed 25 f-year or more, the ORs showed a dose response relationship but did not achieve a 5 % significance level. Concerning the duration, exposure to asbestos for more than 10 years doubled the chance of lung cancer (OR=2.31, 95% CI= 1.26-4.26). The OR of a latency period between 10 to 30 years was 2.47 (95% CI= 1.10-5.55). No significant effect of environmental asbestos exposure was observed (Table 2.5)

Table 2.5 Odds ratios and adjusted odds ratios of the association between asbestos exposure and lung cancer.

	Cases (n=336) **No of subjects (%)**	**Controls (n=360)** **No of subjects (%)**	**OR (95% CI)**	**Adjusted OR (95%CI) [b]**
Occupational asbestos exposure				
Unexposed	281 (83.6)	331 (91.9)	1	1
Ever exposed	55 (16.4)	29 (8.1)	2.23 (1.39-3.60)	2.04 (1.21-3.42)
Categorical of exposure by fiber-years				
Unexposed	281 (83.6)	331 (92.5)	1	1
Exposed <10 fiber-years	44 (13.1)	24 (6.7)	2.16 (1.28-3.64)	1.85 (1.05-3.24)
Exposed ≥10 fiber-years	11 (3)	5 (0.8)	2.59 (0.89-7.55)	3.08 (1.01-9.46)
Duration of Exposure				
0 years	281 (83.6)	331 (91.9)	1	1
< 10 years	13 (3.9)	10 (2.8)	1.53 (0.66-3.55)	1.34 (0.56-3.20)
≥10 years	42 (12.5)	19 (5)	2.60 (1.48-4.58)	2.31 (1.26-4.26)
Latency period from first exposure				
Never contact	281 (83.6)	331 (91.9)	1	1
10 to 30 years	22 (6.5)	10 (2.8)	2.59 (1.21-5.56)	2.47 (1.10-5.55)
>30 years	33 (9.8)	19 (4.7)	2.05 (1.14-3.68)	1.85 (0.98-3.50)
Environmental asbestos exposure				
Unexposed	187 (55.7)	181 (50.5)	1	1
Ever exposed	149 (44.3)	178 (49.6)	0.8 (0.60-1.09)	0.77 (0.56-1.05)

The OR was calculated using logistic regression. [b] adjusted for age, gender, homeownership and smoking

Smoking significantly doubled the chance of getting lung cancer (OR=1.88, 95%CI=1.25-2.83). The combined effect of asbestos exposure and smoking in the development of lung cancer is shown in Table 2.6. After adjusting for age, gender, education and home ownership, subjects with cumulative asbestos exposure 10 fiber-years or more combined with smoking 10 pack-years or more had an 8.7-fold increased risk of lung cancer compared to the reference (OR=8.70, 95%

CI=1.71-44.39). The synergy index for the association of smoking and asbestos exposure was 6.2 and the multiplicativity index was 3.4. Those results supported the positive additive and multiplicative interaction between smoking and asbestos.

Table 2.6 Odds ratios and adjusted odds ratios of the association between the combination of occupational asbestos exposure and smoking with lung cancer.

	Cases (n=336)	**Controls (n=360)**	**OR (95% CI)**	**Adjusted OR (95% CI)[c]**
	No of subjects (%)	**No of subjects (%)**		
A(-) Sm(-)	169 (50.3)	233 (64.7)	1	1
A(+) Sm(-)	3 (0.9)	3 (0.9)	1.38 (0.28-6.92)	1.38 (0.25-7.62)
A(-) Sm(+)	156 (46.4)	122 (33.9)	1.76 (1.30-2.40)	1.85 (1.20-2.85)
A(+) Sm(+)	8 (2.4)	2 (0.6)	5.52 (1.16-26.30)	8.70 (1.71-44.39)
S				6.2[d]
V				3.4[e]

The OR was calculated using logistic regression. [c] Adjusted for age, gender and homeownership; $_{A(-)}$: Unexposed and exposed to asbestos less than 10 fiber-years; $_{A(+)}$: Exposed to asbestos 10 fiber-years or more; $_{Sm(-)}$: Smoking 0-10 pack-years; $_{Sm(+)}$: Smoking 10 pack-years or more; [d] $S = (OR_{A(+)Sm(+)} - 1) / [(OR_{A(+)Sm(-)} - 1) + (OR_{A(-)Sm(+)} - 1)]$; [e] $V = OR_{A(+)Sm(+)} / [OR_{A(+)Sm(-)} \times OR_{A(-)Sm(+)}]$.

2.4 Discussion

The present study proves our hypothesis that exposure to asbestos is associated with an increased risk of lung cancer among Indonesian workers. This association persisted after adjusting for age, sex, education, home ownership, and smoking. The increased risk is consistent with a dose-response relationship. This study shows that asbestos exposure contributes to lung cancer burden in Indonesia.

Unfortunately, Indonesia does not have national figures for lung cancer diagnosis. Our study was performed at the National Respiratory Referral Hospital in Jakarta, that is the national referral hospital for respiratory diseases and the most prominent center for lung cancer management in Indonesia, which allows us to assume that we obtained a representative sample of the lung cancer patients of Indonesia for the aim of our study.

We observed that the chance of getting lung cancer more than doubled among exposed subjects compared with unexposed subjects and it was comparable to the findings of Hardt et al. (19). In their case-control study, those who were grouped as exposed subjects by DOM-JEM assessment had an odds ratio of 1.9 (95% CI=1.3-2.7) compared to those with no exposure. Our study was similar to the study of Hardt et al. because both defined asbestos exposures using the job-exposure matrix from a neighboring country.

The dose-response relationship was explored in this study by employing fiber-years, categorized into unexposed, exposed to less than 10 fiber-years and exposed to 10 fiber-years or more. While the risk of lung cancer increased with an exposure of up to 10 fiber-years by 85%, we found an increase of 200% for subjects exposed to 10 fiber-years or more. It was somewhat lower than the effect reported by Yano et al. for high asbestos exposure in a study of asbestos textile workers in China (OR: 3.66, 95% CI 1.61 to 8.29), however the confidence interval of OR between this study and Yano's study are in the range of adjacent intervals (20).

Other published studies reported lower ORs for the risk of asbestos exposure leading to lung cancer. Villeneuve et al., in a population-based case-control study in Canada, reported the OR 1.28 (95% CI: 1.02-1.61) for generally exposed subjects and when the exposure categorized into low and medium or high exposure the ORs was 1.17 (95%CI: 0.92-0.50) and 2.16 (95% CI: 1.21-3.88) respectively (21). In a meta-analysis, Moon et al. concluded that the great variety of asbestos exposures between nations may arise from differences in culture, technology, legislation, and attitude toward the risk (22). The prevalence of smokers in the different countries also strongly influenced the risk of lung cancer.

This present study found a significant association between the duration of asbestos exposure measured in years and the risk of lung cancer that supported the results from previous studies (19,23). This association is slightly weaker as it does not take the intensity into account. However, given the limited information regarding actual asbestos exposure levels in many studies, the duration of exposure can be presumed to be a valid proxy measure of cumulative exposure.

The combined effect of smoking and asbestos exposure is of special interest in a country like Indonesia where smoking prevalence is very high. The combination of high exposure to asbestos and smoking increased the chances of lung cancer by 770%. The same effect was found by Ngamwong et al. in a meta-analysis (24). The combined effect between smoking and asbestos exhibited a positive additive and multiplicative interaction. The strong interaction of both risk factors pointed out the need for lung cancer prevention efforts, especially in Indonesia.

Indonesia is one of the countries in Asia that has no comprehensive reporting of asbestos-related diseases despite its widespread use. Having no available exposure data made estimates of asbestos exposure challenging. In this situation, adopting the JEM from another Asian country as a reference to estimate the exposure was more reasonable than other methods such as exposure self-reports by study subjects or qualitative estimates of exposures. The General Population JEM from Korea was the best choice for several reasons. First, the Korean GPJEM grouped exposures based on international industrial classifications that linked to Indonesian classifications (15,25). Second, asbestos processing companies and the asbestos-containing material used are similar in both countries; in fact several asbestos industries were transferred from Korea to Indonesia (2). The GPJEM brought more certainty and consistency to the asbestos exposure values for each industry and that led to more precise classification of exposure.

However, differences in workplace conditions, culture, policy regarding asbestos management and the perception toward hazards between Indonesia and Korea could be a potential bias in our risk estimate. Yet, this would not refute the general results that asbestos exposure is associated with a significantly increased risk of lung cancer, which has also been confirmed by regarding the duration of exposure and is consistent with other similar studies in the epidemiological literature.

2.5 Conclusions

The findings of the present case-control study are consistent with other previous studies that supported the association of asbestos exposure and lung cancer. The disease risk is consistent with a dose-response relationship. It brought crucial new information regarding asbestos as the cause of lung cancer in Indonesia. Furthermore, there is a strong interaction of positive additive and multiplicative effects between asbestos and smoking that has to be taken into account in the prevention of lung cancer efforts in the future.

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2.6 References

1. IACR - GLOBOCAN [Internet]. [cited 2019 Jun 1]. Available from: http://www.iacr.com.fr/index.php?option=com_content&view=article&id=101&Itemid=578
2. Kementerian Kesehatan Republik Indonesia [Internet]. [cited 2019 Jun 1]. Available from: http://www.depkes.go.id/article/view/18091700002/penguatan-upaya-pengendalian-konsumsi-rokok-sangat-dibutuhkan.html
3. Malhotra J, Malvezzi M, Negri E, Vecchia CL, Boffetta P. Risk factors for lung cancer worldwide. European Respiratory Journal. 2016 Sep 1;48(3):889–902.
4. TAKALA J. Eliminating occupational cancer. Ind Health. 2015 Jul;53(4):307–9.
5. Craighead JE, Gibbs AR. Asbestos and Its Diseases. Oxford University Press, USA; 2008. 424 p.
6. Roggli VL, Coin P. Mineralogy of Asbestos. In: Roggli VL, Sporn TA, Oury TD, editors. Pathology of Asbestos-Associated Diseases [Internet]. New York, NY: Springer New York; 2004 [cited 2019 Jan 31]. p. 1–16. Available from: https://doi.org/10.1007/0-387-21819-X_1
7. The History of Asbestos - Importing, Exporting & Worldwide Use [Internet]. Mesothelioma Center - Vital Services for Cancer Patients & Families. [cited 2017 Aug 7]. Available from: https://www.asbestos.com/asbestos/history/
8. Gloyne SR. Two Cases of Squamous Carcinoma of the Lung Occurring in Asbestosis. Tubercle. 1935; 17:5–10.
9. Marsili D, Terracini B, Santana VS, Ramos-Bonilla JP, Pasetto R, Mazzeo A, et al. Prevention of Asbestos-Related Disease in Countries Currently Using Asbestos. Int J Environ Res Public Health [Internet]. 2016 May [cited 2019 Feb 4];13(5). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4881119/
10. IARC. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1–42 [Internet]. [cited 2019 Aug 30]. Available from: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-Supplements/Overall-Evaluations-Of-Carcinogenicity-An-Updating-Of-IARC-Monographs-Volumes-1%E2%80%9342-1987
11. Frank AL, Joshi TK. The Global Spread of Asbestos. Annals of Global Health. 2014 Jul 1;80(4):257–62.
12. Colonial Geological Surveys, Mineral Resources Division. Statistical Summary of The Mineral Industry Production, Exports and Imports, 1950-1955. Her Majesty’s Stationary Office;
13. Badan Pusat Statistik [Internet]. [cited 2017 Aug 8]. Available from: https://www.bps.go.id/
14. GBD Compare | IHME Viz Hub [Internet]. [cited 2017 Jan 22]. Available from: http://vizhub.healthdata.org/gbd-compare

15. Choi S, Kang D, Park D, Lee H, Choi B. Developing Asbestos Job Exposure Matrix Using Occupation and Industry Specific Exposure Data (1984–2008) in Republic of Korea. Saf Health Work. 2017 Mar;8(1):105–15.
16. Home - RSUP PERSAHABATAN [Internet]. [cited 2019 Jun 1]. Available from: https://rsuppersahabatan.co.id/
17. Tsim S, Kelly C, Alexander L, Shaw A, Paul J, Woodward R, et al. The DIAPHRAGM study: Diagnostic and prognostic biomarkers in the rational assessment of Mesothelioma. European Respiratory Journal. 2018 Sep 15;52(suppl 62): OA493.
18. VanderWeele TJ, Knol MJ. A Tutorial on Interaction. Epidemiologic Methods [Internet]. 2014 Jan 1 [cited 2019 Sep 22];3(1). Available from: https://www.degruyter.com/view/j/em.2014.3.issue-1/em-2013-0005/em-2013-0005.xml
19. Hardt JS, Vermeulen R, Peters S, Kromhout H, McLaughlin JR, Demers PA. A comparison of exposure assessment approaches: lung cancer and occupational asbestos exposure in a population-based case-control study. Occup Environ Med. 2014 Apr;71(4):282–8.
20. Yano E, Wang X, Wang M, Qiu H, Wang Z. Lung cancer mortality from exposure to chrysotile asbestos and smoking: a case–control study within a cohort in China. Occup Environ Med. 2010 Dec;67(12):867–71.
21. Villeneuve PJ, Parent M-É, Harris SA, Johnson KC. Occupational exposure to asbestos and lung cancer in men: evidence from a population-based case-control study in eight Canadian provinces. BMC Cancer. 2012;12:595.
22. Olsson AC, Vermeulen R, Schüz J, Kromhout H, Pesch B, Peters S, et al. Exposure–Response Analyses of Asbestos and Lung Cancer Subtypes in a Pooled Analysis of Case–Control Studies. Epidemiology. 2017 Mar;28(2):288–299.
23. Moon EK, Son M, Jin Y-W, Park S, Lee WJ. Variations of lung cancer risk from asbestos exposure: impact on estimation of population attributable fraction. Ind Health. 2013;51(1):128–33.
24. Ngamwong Y, Tangamornsuksan W, Lohitnavy O, Chaiyakunapruk N, Scholfield CN, Reisfeld B, et al. Additive Synergism between Asbestos and Smoking in Lung Cancer Risk: A Systematic Review and Meta-Analysis. PLOS ONE. 2015 Agu;10(8):e0135798.
25. 20151123 KBLI 2015 Merge.pdf - KBLI-2015.pdf [Internet]. [cited 2017 Aug 5]. Available from: http://www2.bkpm.go.id/images/uploads/prosedur_investasi/file_upload/KBLI-2015.pdf
26. Choi Y, Lim S, Paek D. Trades of dangers: a study of asbestos industry transfer cases in Asia. Am J Ind Med. 2013 Mar;56(3):335–46.

CHAPTER III

EXCESS RISK OF LUNG CANCER AMONG AGRICULTURE AND CONSTRUCTION WORKERS IN INDONESIA

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3 Excess Risk of Lung Cancer Among Agriculture and Construction Workers in Indonesia

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Abstract

Background: In Indonesia, many occupations and industries involve a variety of hazardous and toxic materials. The ILO estimates that about 21.1% of the tracheal, bronchial, and lung cancer deaths among men were attributable to workplace hazardous substances. This study investigated the relationship between occupations or workplace exposure and the risk of lung cancer in the country. The results will help determine how Indonesia can best mitigate the risk for its workers.

Objectives: This case-control study utilizes the Indonesian Standard of Industrial Classification (IndSIC) 2015 with the aim of exploring the risk of lung cancer among Indonesian workers.

Methods: The study included patients aged 35 years old or older receiving thoracic CT at the radiology department of Persahabatan Hospital. The cases were histological confirmed primary lung cancers, while the controls were negative thoracic CT scan for lung cancer. The subjects' job titles and industries were classified according to IndSIC 2015 and blind to the patient's grouping as a case or control. Logistic regression was used to determine the odds ratios for lung cancer among all sections and some divisions or groups of IndSIC 2015.

Findings: The mean age was 58.1 (±10.23) years for lung cancer patients and 54.5 (±10.23) years for controls. The majority of subjects (19.6%) worked in Section G (Wholesale and retail trade; repair of motor vehicles and motorcycle). After adjusting for age, gender, level of education, and smoking habit, the risk of lung cancer was nearly three-times higher (OR = 2.8, 95% CI = 1.11–7.02) in workers of Division A01 (crop, animal production, and hunting) and two-times higher (OR = 1.9, 95% CI = 1.05–3.46) in workers of Section F (construction) compared to the workers in other sections or divisions.

Conclusions: The excess risk of lung cancer among certain categories of workers confirms the need for improved policy, monitoring, and control of occupational exposure for primary cancer prevention and workers' compensation purposes.

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3.1 Introduction

The International Agency for Research on Cancer has listed 19 substances with sufficient evidence for lung carcinogenicity in humans (Group 1) [1, 2]. Many occupations and industries in Indonesia involve a variety of carcinogenic materials, such as asbestos and silica in construction and renovation work, welding fumes in steel processing industries, and diesel exhaust for truck drivers and operators of machine engines [2, 3]. Epidemiological studies have reported the increased risk of lung cancer development in several occupations [4–6]. According to the global estimates of occupational accidents and work-related illnesses reported in 2017, about 21.1% of the tracheal, bronchial, and lung cancer deaths among men were attributable to workplace hazardous substances including dust, vapors, and fumes [7].

The number of lung cancer incidents in Indonesia has increased over time and occurs at a younger age compared to other countries [8]. In 2018, the WHO reported 30,023 new cases of lung cancer in Indonesia and 26,095 deaths, making up around 2.6% of Indonesia's total deaths [9]. Unfortunately, a limited number of studies have been conducted regarding the relationship between occupations or workplace exposure and the risk of lung cancer in the country [10, 11]. Until 2020, occupational lung cancer had not been reported to the Indonesian government, and the occupational risks for lung cancer among Indonesian workers remained unclear [12].

Approaching the relationship between workplace exposure and lung cancer is very challenging. The most notable intricacies in recognizing the relationship is the long latency period of lung cancer and strong confounding factors, like smoking. Indonesia also lacks data on occupational exposure. This further complicates identifying the relationship between occupational agents and lung cancer.

The International Standard Industrial Classification (ISIC) is the system established by the United Nations to classify economic activities [13]. In 1977, Indonesia adopted a system called the "Indonesian Standard Industrial Classification" (IndSIC) or "Klasifikasi Baku Lapangan Usaha Indonesia" (KBLI) [14]. The extensive use of the classification has made it a tool for when studying the economic phenomena as well as employment, health data, and other matters [13, 15]. Amid limited occupational exposure data, IndSIC can be used as a proxy for different exposures for each classification [16]. When implementing the ISIC, many studies have successfully discovered the risk of lung cancer among workers in many countries [3, 17].

This study set out to determine the association between occupational exposure proxied by IndSIC and the risk of developing lung cancer among Indonesian workers. Having health information based on the economic activities' classification may bring new insight into occupational health research and cancer prevention programs in Indonesia.

3.2 Materials and methods

We conducted this study with the review and approval of the Ethical Committee of Persahabatan Hospital, Indonesia, (number 18/KEPK-RSUPP/03/2018) and the Ethical Committee at the medical facility, Ludwig-Maximilians University in Munich, Germany (number 18–632). All subjects signed an informed consent form after receiving the participants' information on all aspects of the study.

3.2.1 Study population

For 17 months between May 2018 and September 2019, we performed a case-control study at the National Respiratory Hospital in Jakarta, Indonesia. The recruitment of cases and controls in this study followed a protocol similar to what was utilized in a previously published study by the same authors on asbestos-related lung cancer in a hospital-based case-control study in Indonesia [18]. The study population consisted of all patients aged 35 years old or older who received a thoracic computerized tomography (CT) scan for a range of indications including lung infection, mediastinal mass, lung nodule or mass, trauma, and evaluation of pleural diseases. The cut off age of the subjects, 35 years, was chosen based on the assumption that the youngest working- age in Indonesia is 15 years old and the average latency period for developing lung cancer is around 20 years; therefore, it is estimated that the youngest occupational lung cancer develops around the age of 35 years [19, 20].

The cases were primary lung cancers that were confirmed by histology, and the controls were recruited from the same as those who had the thoracic CT scan but returned images with no evidence of lung cancer. The CT scans were interpreted by a thoracic radiologist, and the histological information was obtained from the hospital's pathology department.

Trained interviewers carried out the interviews using a standardized questionnaire adapted from Cancer Research UK [21] and were translated by a certified translator into Bahasa, Indonesia. We obtained the information on demographic data, smoking habits, and lifetime occupational history including industry category, job titles, and the start and end dates of each job episode.

The occupational physician classified job titles and industries according to IndSIC 2015 were blind to the patient's grouping as a case or as a control. Subjects who worked in more than one of IndSIC's sections were grouped into the section that reflected the longest period of work.

3.2.2 Indonesian Standard of Industrial Classification (IndSIC) 2015 Version

The original version of ISIC was developed in 1948, and since that time, the majority of countries around the world have used ISIC as their national activity classification or have developed a national classification derived from ISIC [22]. The latest version of ISIC is ISIC revision four (ISIC rev.4), which comprises of 21 sections, 88 divisions, 238 groups, and 419 classes [8].

The "Indonesian Standard of Industrial Classification" IndSIC was developed by the Centre of Statistical Bureau, or Badan Pusat Statistik (BPS) of Indonesia, which was derived from the ISIC rev. 4. This study used the IndSIC 2015 version which consists of 21 sections (A to U), 88 divisions, 240 groups, 520 subgroups, and 1573 classes. Each item is coded as one letter plus five digits. For example, the code A 01111 can be interpreted as follows: A represents Section A (agriculture, forestry, and fishing), A 01 indicates Division A 01 (crop and animal production, hunting and related service activities), A 011 indicates Group A 011 (crowing of non-perennial crops), A 0111 indicates subgroups A 0111 (growing of cereals (except rice), leguminous crops and oil seeds), and A 01111 indicates Class A 01111 (corn farming) [15].

Among the 21 sections of IndSIC, some sections include a variety of work processes, materials, and substances among their divisions or groups; whereas, in some other sections, they are almost similar. For example, Section C (manufacturing) has 33 divisions such as cement, plastic, chemical, and food industries that are very different when it comes to work processes and exposures, while Section F (construction) has only three nearly similar divisions. These differences can lead to different lung cancer risks among workers in the different divisions of the manufacturing section [16].

3.2.3 *Statistical analysis*

The differences in the proportions of demographic characteristics between cases and controls were evaluated using the chi-square test. We calculated the odds ratio (OR) to investigate the association between different occupational sections of IndSIC 2015 and lung cancer. To control the confounding factors, a multivariate unconditional logistic regression was performed to obtain odds ratio estimates together with 95% confidence intervals (CI) that were adjusted for gender, age, level of education, and smoking habits.

We employed three analysis models to verify the appropriateness of assumptions made in this study and to validate study findings. “Model 1” analysis discovered the ORs among all IndSIC sections using “housewife” as “Reference 1” and Section S (Other services as member of organization, repair of household) as “Reference 2”. Housewives, the “Reference 1”, were considered to have the most similar tasks in all settings, less probability of contact to workplace exposures, the majority of them being non-smokers, and them being at a lower risk of lung cancer compared to other occupations [24–28]. The limitation of this reference group is that they were not part of IndSIC and that they were all females. Section S (Other services as member of organization, repair of household) was chosen to be “Reference 2” because it had the most similar OR to “Reference 1”.

“Model 2” analysis was developed to discover the possible hidden risk of lung cancers in some divisions or groups. We subdivided Sections A (Agriculture, forestry and fishing), B (Mining and quarrying), C (Manufacturing), G (Wholesale and retail trade; repair of motor vehicles and motorcycle), H (Transportation and storage), and Q (Human health and social work activities) into divisions or groups. The remaining sections were not redivided into divisions because most of their divisions are not so different in terms of workplace exposure or work processes. The new classification consisted of the combinations of the sections and divisions or groups. The investigation of ORs was similar to the “Model 1” analysis.

Following the “Model 1” and “Model 2” analysis, sections with significantly increased lung cancer odds ratios were compared to other sections in a third model (“Model 3”). A one-way ANOVA was conducted to compare the mean of ORs among the three models of analyses.

We calculated the population attributable fraction (PAF) for any section or division that had significant OR to estimate the proportion of lung cancer cases that would be prevented if the risk factor was eliminated [23]. Our estimate was made by using the formula, PAF = P(EC) × (OR-1)/OR where OR is the adjusted odds ratio and P(EC) is the proportion of exposed cases [6]. All test decisions were performed at a significance level of 5%. IBM SPSS Statistic for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data.

3.3 Results

For 17 months between May 2018 and August 2019, 710 subjects were interviewed, of which 340 subjects were eligible for cases and 370 were eligible for controls. The mean age for lung cancer patients was 58.1 (10.23) years, and the mean age for the controls was 54.5 (10.23) years. The proportion of male smokers who had a smoking history of more than ten pack-years and of workers who had worked for more than ten years was higher in the cases than in the controls. Among the cases, adenocarcinoma dominated the histological cell type (55.9%), and, among controls, tuberculosis (54.6%) was the most prominent diagnosis (Table 3.1).

Table 3.1 Characteristics of subjects.

	Cases (n=340)	Controls (n=370)	
	No. of Subjects (%)	No. of Subjects (%)	P Value *
Age			
Mean (SD)	58.1 (10.23)	54.8 (10.23)	0.00
Age categories			
<45 years	35 (10.3)	82 (22.2)	0.00
45-55 years	97 (28.5)	106 (28.6)	
56-65 years	126 (37.1)	117 (31.6)	
66 -75 years	68 (20)	52 (14.1)	
>75 years	14 (4.1)	13 (3.5)	
Gender			
Female	128 (37.8)	164 (44.3)	0.08
Male	212 (62.2)	206 (55.7)	
Duration of work			
<10 years	49 (14.4)	87 (23.5)	0.003
10-30 years	156 (45.9)	168 (45.4)	
> 30 years	135 (39.7)	115 (31.1)	
Education			
Illiterate	10 (2.9)	10 (2.7)	0.09
Elementary	77 (22.6)	67 (18.1)	
Junior High School	32 (9.4)	40 (10.8)	
Senior High School	132 (38.8)	177 (47.8)	
Bachelor	78 (22.9)	71 (19.2)	
Postgraduate	11 (3.2)	5 (1.4)	
Smoking			
0 to 10 pack-years	174 (51.2)	240 (64.9)	0.001
>10 to 40 pack-years	107 (31.5)	85 (23.0)	
>40 pack-years	59 (17.4)	45 (12.2)	
Histological cell type			
Adenocarcinoma	190 (55.9)		
Large cell	16 (4.7)		
Squamous cell	73 (21.5)		
Unidentified	3 (0.9)		
Small cell	13 (3.8)		
Others	45 (13.2)		
Diagnoses of controls			
No abnormality		30 (8.1)	
Tuberculosis and other lung infections		202 (54.6)	
Chronic lung diseases		66 (17.8)	
Mediastinal mass and other malignancies		40 (10.8)	
Other diseases		32 (8.6)	

* The t test was used for continues variables and $\chi 2$ test for categorical variables.

In total, 1,095 work histories were collected. Table 3.2 shows the distribution of subjects for each section of IndSIC, housewife, and unemployment, all of which were stratified by gender. The highest proportion of all subjects was working in Section G (wholesale and retail trade; repair of motor vehicles and motorcycle), followed by Section C (manufacturing). Among female subjects, the highest proportion was in housewives. In almost all sections of IndSIC 2015, the proportion of males was dominant except for Section C (manufacturing), Section K (financial and insurance activities), Section P (education), and Section T (activities of a household as employers; undifferentiated goods and services-producing activities of households for own use).

Table 3.2 Distribution of gender in each section of Indonesian Standard of Industrial Classification 2015.

	Female (292)	**Male (418)**	**Total (710)**
IndSIC 2015	n (%)	n (%)	n (%)
Housewife	83 (28.4)	0 (0)	83 (11.7)
Unemployed	3 (1.0)	2 (0.5)	5 (0.7)
A: Agriculture, forestry and fishing	6 (2.1)	23 (5.5)	29 (4.1)
B: Mining and quarrying	1 (1.3)	8 (1.9)	9 (1.3)
C: Manufacturing	47 (16.1)	47 (11.3)	94 (13.2)
D: Electricity, gas, steam and air conditioning supply	0 (0)	5 (1.2)	5 (0.7)
E: Water supply; sewage, waste management, material recovery	0 (0)	3 (0.7)	3 (0.4)
F: Construction	5 (1.7)	50 (12.0)	55 (7.7)
G: Wholesale and retail trade; repair of motor vehicles and motorcycle	48 (16.4)	91 (21.8)	139 (19.6)
H: Transportation and storage	2 (0.7)	64 (15.3)	67 (9.4)
I: Accommodation and food service activity	6 (2.1)	11 (2.6)	17 (2.4)
J: Information and communication	5 (1.7)	6 (1.4)	11 (1.5)
K: Financial and insurance activities	12 (4.1)	8 (1.9)	20 (2.8)
L: Real estate activities	3 (1.0)	0 (0)	3 (0.4)
M: Professional, scientific and technical activities	2 (0.7)	4 (1.0))	6 (0.8)
O: Public administration and defense; compulsory social security	10 (3.4)	35 (8.4)	45 (6.3)
P: Education	17 (5.8)	18 (4.3)	35 (4.9)
Q: Human health and social work activities	15 (5.1)	8 (1.9)	23 (3.2)
R: Arts, sports and recreation related services	2 (0.7)	7 (1.7)	9 (1.3)
S: Membership organization, repair and other personal services	13 (4.5)	27 (6.5)	40 (5.6)
T: Activities of household as employers; undifferentiated goods- and services-producing activities of households for own use	12 (4.1)	0 (0)	12 (1.6)

"Model 1" analysis found that, compared to "Reference 1", the adjusted OR for workers in Section A (agriculture, forestry, and fishing) was 3.8 (95% CI = 1.42–10.6), and Section F (Construction) was 2.9 (95% CI = 1.27–6.54). In comparison to "Reference 2", the adjusted OR for workers in Section A (Agriculture, forestry, and fishing) was 3.6 (95% CI = 1.20–10.43), and Section F (Construction) was 2.6 (95% CI = 1.06–6.20) (Table 3.3).

Table 3.3 Adjusted odds ratios of the association between occupational backgrounds in sections of the Indonesian Standard of Industrial Classification 2015 and lung cancer.

	Cases (340)	Controls (370)	Adjusted OR (95%CI) #	Adjusted OR (95% CI) ##
IndSIC 2015	n (%)	n (%)		
Housewife	31 (9.1)	52 (14.1)	Reference	Not included
Unemployed	1 (0.3)	4 (1.1)	0.6 (0.05-5.81)	Not included
A: Agriculture, forestry and fishing	21 (6.2)	8 (2.2)	3.8 (1.42-10.6) *	3.6 (1.20-10.43) *
B: Mining and quarrying	5 (1.5)	4 (1.1)	3.7 (0.82-16.90)	2.6 (0.56-11.95)
C: Manufacturing	42 (12.4)	52 (14.1)	2.8 (0.64-12.86)	1.7 (0.76-3.70)
D: Electricity, gas, steam and air conditioning supply	2 (0.6)	3 (0.8)	1.9 (0.96-3.66)	1.1 (0.16-7.93)
E: Water supply; sewage, waste management, material recovery	2 (0.6)	1 (0.3)	4.2 (0.33-54.53)	3.8 (0.29-48.75)
F: Construction	35 (10.3)	20 (5.4)	2.9 (1.27-6.54) *	2.6 (1.06-6.20) *
G: Wholesale and retail trade; repair of motor vehicles and motorcycle	61 (17.9)	79 (21.4)	1.4 (0.75-2.67)	1.3 (0.60-2.67)
H: Transportation and storage	32 (9.4)	33 (8.9)	1.7 (0.75-3.78)	1.5 (0.65-3.44)
I: Accommodation and food service activity	7 (2.1)	10 (2.7)	1.2 (0.39-3.82)	1.1 (0.33-3.59)
J: Information and communication	4 (1.2)	7 (1.9)	1.3 (0.33-5.16)	1.2 (0.28-4.93)
K: Financial and insurance activities	12 (3.5)	8 (2.2)	2.8 (0.98-8.28)	2.6 (0.82-8.10)
L: Real estate activities	0 (0)	3 (0.8)	0	0
M: Professional, scientific and technical activities	2 (0.6)	4 (1.1)	0.5 (0.09-4.02)	0.5 (0.08-3.83)
O: Public administration and defense; compulsory social security	25 (7.4)	21 (5.7)	1.7 (0.71-3.95)	1.5 (0.61-3.86)
P: Education	17 (5.0)	18 (4.9)	1.3 (0.53-3.43)	1.2 (0.44-3.40)
Q: Human health and social work activities	15 (4.4)	8 (2.2)	2.8 (0.89-8.5)	2.8 (0.89-8.51)
R: Arts, sports and recreation related services	5 (1.5)	4 (1.1)	2.5 (0.58-11.13)	2.3 (0.51-10.35)
S: Membership organization, repair computer and household, and other personal services	15 (4.4)	25 (6.8)	1.1 (0.48-2.62)	Reference
T: Activities of household as employers; undifferentiated goods- and services-producing activities of households for own use	6 (1.8)	6 (1.6)	1.8 (0.53-6.51)	1.7 (0.41-6.55)

The OR was calculated using logistic regression adjusted for age, gender, education and smoking.
Reference group: "Housewife"
Reference group: Section S (Membership organization, repair computer and household, and other personal services)
* Statistically significant, i.e. p ≤ 0.05

When several sections were subdivided into divisions or groups in "Model 2", subjects who had worked in Division A01 (crop, animal production, and hunting) (OR = 3.9, 95% CI = 1.36–11.25), Division C20 (chemical and chemical product) (OR = 4.8, 95% CI = 1.09–21.60), and Section F (construction) (OR = 2.8, 95% CI = 1.20–6.37) had a significantly higher chance of developing lung cancer compared to "Reference 1". Division A 02 and 03 (forestry and fishing) of Section A did not show an increased chance of developing lung cancer. Compared to "Reference 2", subjects in Division A01 (crop, animal production, and hunting) (OR = 3.7, 95% CI = 1.20–11.32) and Section F (construction) (OR = 2.6, 95% CI = 1.07–6.14) maintained a higher chance of developing lung cancer, while subjects working in Division C20 (chemical and chemical product) did not show a statistically significant odds ratio (Table 3.4).

Table 3.4 Adjusted odds ratios of the association between occupational backgrounds classified in sections, divisions or groups based on the Indonesian Standard of Industrial Classification 2015 and lung cancer.

	Cases (340)	Controls (370)	Adjusted OR (95%CI) #	Adjusted OR (95% CI) ##
IndSIC 2015	n (%)	n (%)		
Housewife	31 (9.1)	52 (14.1)	Reference	Not included
Unemployed	1 (0.3)	4 (1.1)	0.6 (0.05-5.86)	Not included
A: Agriculture, forestry and fishing				
A 01: Crop, animal production and hunting	19 (5.6)	7 (1.9)	3.9 (1.36-11.25) *	3.7 (1.20-11.31) *
A 02 & 03: Forestry and fishing	2 (0.6)	1 (0.3)	2.8 (0.22-35.52)	2.5 (0.20-32.35)
B: Mining and quarrying				
B 610: Oil and gas mining	4 (1.2)	(0.0)	~	~
B 510: Coal and lignite mining	1 (0.3)	4 (1.1)	0.5 (0.05-4.80)	0.4 (0.04-4.53)
C: Manufacturing				
C 10: Food industry	5 (1.4)	5 (1.4)	2.5 (0.63-9.80)	2.3 (0.54-9.65)
C 14: Manufacture of wearing apparel	12 (3.5)	17 (4.6)	1.6 (0.67-4.06)	1.5 (0.54-4.10)
C 15: Industry of leather, synthetic, footwear	1 (0.3)	4 (1.2)	0.7 (0.07-6.98)	0.7 (0.07-6.58)
C 17: Industry of pulp, paper, paper board	4 (1.2)	0 (0.0)	~	~
C 20: Chemical and chemical product	7 (2.1)	3 (0.8)	4.8 (1.09-21.60) *	4.5 (0.96 (20.73)
C 21: Pharmaceuticals, medicinal chemical and botanical products	3 (0.9)	0 (0.0)	~	~
C 23: Non-metal mining goods	3 (0.9	4 (1.2)	1.7 (0.32-8.50)	1.6 (0.29-8.39)
C 24: Industry of iron and steel	4 (1.2)	5 (1.4)	1.8 (0.41-8.30)	1.7 (0.37-7.81)
C 26: Computer, electronic and optic industry, semiconductor, and other electronic components	1 (0.3)	4 (1.2)	0.5 (0.05-4.52)	0.4 (0.04-4.36)
C 2910: Four Wheels vehicle industry	4 (1.2)	0 (0)	0	0
C 31: Furniture industry	1 (0.3)	3 (0.8)	0.6 (0.06-6.80)	0.6 (0.05-0.38)
C 32: Other industries	1 (0.3)	3 (0.8)	0.9 (0.09-9.73)	0.8 (0.07-9.02)
D: Electricity, gas, steam and AC supply	2 (0.6)	3 (0.8)	1.2 (0.18-8.68)	1.1 (0.16-7.82)
E: Water supply; sewage, waste management, material recovery	2 (0.6)	1 (0.3)	4.2 (0.34-53.69)	3.8 (0.29-49.51)
F: Construction	35 (10.3)	20 (5.4)	2.8 (1.20-6.37) *	2.6 (1.07-6.14) *
G: Wholesale and retail trade; repair of motor vehicles and motorcycle				
G 45: Repair of motor vehicles	9 (2.6)	9 (2.4)	1.8 (0.57-5.52)	1.6 (0.51-5.23)
G 47: Retail trade	52 (15.3)	70 (18.9)	1.3 (0.69-2.54)	1.2 (0.57-2.59)
H: Transportation and storage				
H 49: Railroad transportation	25 (7.4)	23 (6.2)	1.8 (0.75-4.23)	1.6 (0.66-3.94)
H 501: Sea and air transport and warehouse, transportation support	7 (2.1)	10 (2.7)	1.3 (0.39-4.20)	1.1 (0.34-3.83)
I: Accommodation and food service activity	7 (2.1)	10 (2.7)	1.2 (0.37-4.01)	1.1 (0.33-3.56)
J: Information and communication	4 (1.2)	7 (1.9)	1.3 (0.32-5.07)	1.2 (0.28-4.95)
K: Financial and insurance activities	12 (3.5)	8 (2.2)	2.8 (0.95-8.13)	2.5 (0.81-8.11)
L: Real estate activities	0 (0)	3 (0.8)	0	0
M: Professional, scientific and technical activities	2 (0.6)	4 (1.2)	0.6 (0.08-3.86)	0.5 (0.07-3.75)
O: Public administration and defense; compulsory social security	25 (7.4)	21 (5.7)	1.6 (0.66-3.78)	1.5 (0.59-3.78)
P: Education	17 (5.0)	18 (4.9)	1.3(0.50-3.36)	1.2 (0.43-3.39)
Q: Human health and social work activities				
Q 861: Hospital and medical activities	11 (3.2)	6 (1.6)	2.7 (0.83-8.68)	2.5 (0.72-8.67)
Q 869: Nonhospital health-related activities	4 (1.2)	2 (0.6)	3.9 (0.64-23.5)	3.5 (0.54-22.85)
R: Arts, sports and recreation related services	5 (1.5)	4 (1.2)	2.5 (0.56-10.9)	2.3 (0.50-10.38)
S: Membership organization, repair and other personal services	15 (4.4)	25 (6.8)	1.1 (0.46-2.59)	Reference
T: Activities of household as employers; undifferentiated goods-and services-producing activities of households for own use	6 (1.8)	6 (1.6)	1.9 (0.54-6.70)	1.7 (0.44-6.92)

The OR was calculated using logistic regression *adjusted for age, gender, education and smoking habits.

~ is infinite

Reference group: “Housewife”

Reference group: Section S (Membership organization, repair computer and household, and other personal services)

* Statistically significant, i.e. p ≤ 0.05

Table 3.5 Adjusted odds ratio of the association between lung cancer and occupational backgrounds in division A01, division C20, and section F of the Indonesian Standard of Industrial Classification 2015.

	Cases (308)	**Controls (314)**	**Adjusted OR (95% CI)**
IndSIC 2015	n (%)	n (%)	
Reference	236 (76.6)	278 (88.5)	1
A 01: Crop, animal production and hunting	19 (6.2)	7 (2.2)	2.7 (1.05-6.76) *
F: Construction	35 (11.4)	20 (6.4)	1.9 (1.03-3.40) *
C 20: Chemical and chemical products	7 (2.3)	3 (1.0)	3.2 (0.79-12.79)

The OR was calculated using logistic regression adjusted for age, gender, education and smoking.

* Statistically significant, i.e. p ≤ 0.05

Table 3.5 shows the association between occupational backgrounds in division A01, division C20, section F, and the remaining sections of IndSIC 2015 and lung cancer (“Model 3”). The chance of developing lung cancer for workers in division A01 (Crop, animal production and hunting) (OR=2.7, 95% CI=1.05-6.76) and section F (Construction) (OR=1.9, 95% CI= 1.03-3.40) consistently higher compared to workers of the remaining sections.

The ANOVA showed that there was no statistically significant difference of the mean of ORs among the three models (F (4,103) = 0.44, p = 0.78). The PAF for workers in Division A 01 (crop, animal production, and hunting) was 3.9% and for workers in Section F (Construction) was 5.4%. Two divisions in Section C (C17: pulp, paper, and paper products and C21: pharmaceuticals, medicinal chemical, and botanical products) and a division in Section B (B610: oil and gas mining) were the only divisions that had cases without controls.

3.4 Discussion

The present study succeeds in bringing evidence of the excess risk of lung cancer for workers that can be classified under the IndSIC's Division A01 (Crop, animal production and hunting) and Section F (Construction). The PAF for crop, animal, and hunting workers was 3.9% and construction workers was 5.2%, showing that the contribution of occupational carcinogens contributed to the lung cancer burden in Indonesia. Applying the PAF to the 30,023 incident cases of lung cancer in Indonesia in 2018, we estimated that 1,170 cases were attributable to occupation in crop, animal, and hunting division and 1,561 cases were attributable to occupations in the construction section in 2018 [9]. The increased risk of lung cancer for agriculture and construction workers was similar to a study performed by Baser, et al. in Turkey. They identified the increased risk of lung cancer among agriculture workers (OR = 1.89, 95% Cl = 1.17−2.98) and workers exposed to inorganic dust (ceramic and pottery workers, construction, and mining) (OR = 1.81, 95% Cl = 1.0−3.25) compared to office workers. They also discovered that the elevated risk for agriculture workers was associated with pesticide use [29]. The odds ratio in our study was slightly higher than in the Baser study but comparable with a cohort study by Alavanja et al [30]. Many other studies have proved that pesticides are associated with an increased risk of lung cancer in agriculture workers [30–34].

Tse et al., after applying the ISIC rev.4 to investigate the risk of lung cancer in Chinese workers, reported that construction workers have a significantly increased risk of having lung cancer compared to workers from other sections (OR = 1.37, 95% CI: 1.01–1.89). Tse et al. further identified that occupational carcinogens associated with the development of lung cancer were caused by silica dust (1.75, 95% CI: 1.16–2.62), welding fumes (1.74, 95% CI: 1.13–2.68), diesel exhaust (2.18, 95% CI: 1.23–3.84), and man-made mineral fibers (7.45, 95% CI: 1.63–34.00) [3]. In addition to the increased risk of lung cancer, a study in California by Calvert et al. indicated that lung cancer in construction workers was diagnosed at an earlier age, at a more advanced stage, and had significantly lower survival rates by three years compared to non-construction workers. The odds ratio in this study was comparable with Calvert et al.'s findings [17].

Bianco and Demers, in a publication about trends in compensation for occupational cancer in Ontario, Canada, noted that lung cancer was the most frequently compensated occupational cancer, especially in the construction, manufacturing, and mining industries [35]. Occupational lung cancer in Korea, reported by Yeon-Soon Ahn and Kyong Sook Jeong, was primarily associated with manufacturing and construction work and were the most common occupations compensating for lung cancer [19]. Both studies indicated that asbestos was responsible for the elevated risks of lung cancer, especially among construction workers.

It is common knowledge that construction workers face a lack of protection and have a high rate of occupational accidents, especially in developing countries. An inspection report in 2018 revealed that up to 80% of construction projects in Jakarta, the capital of Indonesia, did not have health and safety regulations in place and that there were a lack of trained workers [36]. On the other hand, most agriculture workers are informal workers who do not have enough knowledge and resources to protect themselves. Several studies have reported a high prevalence of chronic pesticide intoxication in farmers [37], and other researchers reported that most agricultural workers in Indonesia have been working without personal protective equipment when using pesticides [38].

Siemiatycki et al. and Loomis et al. listed lung carcinogens (Group A) with the occupations or industries in which the carcinogen substances are found [1, 39]. This study only identified the elevated risks of lung cancer for Division A01 (crop, animal production, and hunting) and Section F (construction) and could not discover potential increased risk for other occupations or industries that have occupational carcinogens. However, we can observe possible increased risks coming from Division C17 (pulp, paper, and paper products), Division C21 (pharmaceuticals, medicinal chemical, and botanical products), and Division B (oil and gas). Unfortunately, the number of subjects was not sufficient to obtain enough controls. This meant that those divisions did not have controls, only some cases. Therefore, we could not indicate the OR. We were also careful with the increased OR for chemical and chemical product divisions compared to the housewife as a reference. The increased OR was not significant when the reference was from Section S and the other remaining sections. Further research should be conducted to investigate the risks of lung cancer by having a sufficient number of subjects.

There are some limitations in this study, especially of methodological nature. A major limitation is the explorative character of this case-control study, such as the lack of conducting multiple tests for different subgroups. As there are limited studies and data on the risks of lung cancer in Indonesia available, this explorative research has nonetheless added an important first insight into this public health issue, proving that further research in this area is indispensable. Unmatched subjects, possible misclassification of the subjects’ occupations, and recall bias were other limitations of this study. However, the increased chances for agriculture and construction workers to develop lung cancer found in this study were comparable to other previous studies of other countries and indicated no substantial effect of the limitations. Selection bias was also a concern for the hospital-based case-control study. However, almost all of the proportioning of subjects in each section of IndSIC were comparable with the proportion of Indonesian workers based on IndSIC, and this allowed us to assume that the subjects represented the Indonesian population [20, 40]. Moreover, the study's location was the national referral hospital for respiratory diseases and the most prominent center for lung cancer management in Indonesia. This allowed us to assume that we had obtained a representative sample of the lung cancer patients of Indonesia for our study's aim.

As far as we know, this is the first study in Indonesia to approach occupational lung cancer through the IndSIC classification system. This approach is most convenient since the country has insufficient data on the effects of exposure. For more detailed information, further investigations, to the level of division or even classes that may identify risk that had not appeared at the section level, should be performed. The approach could be extended further by increasing the number of subjects or directly investigating the occupational agents causing lung cancer by using a job exposure matrix.

3.5 Conclusions

This study filled in the gap of knowledge by bringing significant evidence of how occupational roles correlate with the development of lung cancer among Indonesian workers. It shows the excess risk of lung cancer among workers in Section F (construction) and Division A01 (crop, animal husbandry, and hunting) which could be an early hint of association of some carcinogens with lung cancer development among Indonesian workers. This study confirms the need for improved policy, monitoring, and control of occupational exposure for primary cancer prevention and workers' compensation purposes. It is needed to ensure that people with work-related lung cancer are diagnosed. Therefore, more training about workplace exposures risk to workers at high risk and training on diagnosing occupational lung cancer need to be provided to health care professionals. Our study results demand further investigations to unravel the possibility that there are even more risk factors for lung cancer among workers in Indonesia in existence. Moreover, this study succeeded in employing IndSIC 2015 as the proxy of occupational exposure to discover occupational disease which can be applied in future occupational health research in Indonesia.

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Conceptualization and methodology A.S., D.N, S.B.O., and A.W.S.; software, A.S.; validation, S.B.O., U.B, and D.N.; formal analysis, A.S, U.B., S.B.O. and D.N.; investigation, A.S., A.G.I and E.S.; resources, A.G.I. and E.S.; writing—original draft preparation, A.S.; writing—review and editing, D.N., S.B.O. U.B, A.W.S; supervision, A.W.S., D.N., and S.B.O.; project administration, A.S.

All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

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3.6 References

1. **Loomis D, Guha N, Hall AL, Straif K.** Identifying occupational carcinogens: an update from the IARC monographs. *Occup Environ Med*. 2018; 75(8): 593–603. DOI: *https://doi.org/10.1136/oemed-2017-104944*
2. **Algranti E, Buschinelli JTP, De Capitani EM.** Occupational lung cancer. *Jornal Brasileiro de Pneumologia*. 2010; 36(6): 784–794. DOI: *https://doi.org/10.1590/S1806-37132010000600017*
3. **Tse LA, Yu IT, Qiu H, Au JSK, Wang X.** Occupational risks and lung cancer burden for Chinese men: A population-based case-referent study. *Cancer Causes Control*. 2012; 23(1): 121–131. DOI: *https://doi. org/10.1007/s10552-011-9861-1*
4. **Bovio N, Richardson DB, Guseva Canu I.** Sex-specific risks and trends in lung cancer mortality across occupations and economic activities in Switzerland (1990–2014). *Occup Environ Med*. 2020; 77(8): 540–548. DOI: *https://doi.org/10.1136/oemed-2019-106356*
5. **Matrat M, Guida F, Cénée S,** et al. Occupational exposure to diesel motor exhaust and lung cancer: A dose-response relationship hidden by asbestos exposure adjustment? *The ICARE study*. *J Cancer Epidemiol*. 2015; 2015. DOI: *https://doi.org/10.1155/2015/879302*

6. **Consonni D, De Matteis S, Lubin JH,** et al. Lung cancer and occupation in a population-based case- control study. *Am J Epidemiol*. 2010; 171(3): 323–333. DOI: *https://doi.org/10.1093/aje/kwp391*
7. **Hämäläinen P, Takala J, Kiat TB.** Global estimates of occupational accidents and work-related illnesses. 2017. Published online September 2017.
8. **Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A.** Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2018; 68(6): 394–424. DOI: *https://doi.org/10.3322/caac.21492*
9. **IACR – GLOBOCAN.** *http://www.iacr.com.fr/index.php?option=com_content&view=article&id=101&Itemid=578*. Accessed June 1, 2019.
10. **Mahendradhata Y, Trisnantoro L, Listyadewi S, Soewondo P, Marthias T,** et al. The Republic of Indonesia Health System Review. WHO Regional Office for South-East Asia; 2017. *https://apps.who.int/ iris/handle/10665/254716*. Accessed November 28, 2020.
11. **Tjindarbumi D, Mangunkusumo R.** Cancer in Indonesia, present and future. *Japanese Journal of Clinical Oncology*. 2002; 32(suppl 1): S17–S21. DOI: *https://doi.org/10.1093/jjco/hye123*
12. **BPJS Ketenagakerjaan.** *https://www.bpjsketenagakerjaan.go.id/*. Accessed October 13, 2019.
13. **International Standard Industrial Classification of All Economic Activities (ISIC).** ILOSTAT. *https:// ilostat.ilo.org/resources/methods/classification-economic-activities/*. Accessed March 27, 2020.
14. **Bantuan dan Tutorial | SPK Online – Sistem Pencarian Kode Klasifikasi Online.** *https://spkonline.bps.go.id/spkonline/help/klasifikasi/2*. Accessed November 30, 2020.
15. **20151123 KBLI 2015 Merge.pdf – KBLI-2015.pdf.** *http://www2.bkpm.go.id/images/uploads/prosedur_investasi/file_upload/KBLI-2015.pdf*. Accessed August 5, 2017.
16. **Mannetje A ‘t, Kromhout H.** The use of occupation and industry classifications in general population studies. *Int J Epidemiol*. 2003; 32(3): 419–428. DOI: *https://doi.org/10.1093/ije/dyg080*
17. **Calvert GM, Luckhaupt S, Lee S-J,** et al. Lung cancer risk among construction workers in California, 1988–2007. *Am J Ind Med*. 2012; 55(5): 412–422. DOI: *https://doi.org/10.1002/ajim.22010*
18. **Suraya A, Nowak D, Sulistomo AW,** et al. Asbestos-related lung cancer: A hospital-based case-control study in Indonesia. *International Journal of Environmental Research and Public Health*. 2020; 17(2): 591. DOI: *https://doi.org/10.3390/ijerph17020591*
19. **Ahn Y-S, Jeong KS.** Epidemiologic characteristics of compensated occupational lung cancers among Korean workers. *Journal of Korean Medical Science*. 2014; 29(11): 1473–1481. DOI: *https://doi.org/10.3346/jkms.2014.29.11.1473*

20. **Sicca SP.** BPS: Jumlah penduduk bekerja triwulan I 2018 sebanyak 127,07 juta. tirto.id. *https://tirto.id/bps-jumlah-penduduk-bekerja-triwulan-i-2018-sebanyak-12707-juta-cJ5D*. Accessed June 2, 2020.
21. **Tsim S, Kelly C, Alexander L,** et al. Diagnostic and prognostic biomarkers in the rational assessment of mesothelioma (DIAPHRAGM) study: protocol of a prospective, multicentre, observational study. *BMJ Open*. 2016; 6(11): e013324. DOI: *https://doi.org/10.1136/bmjopen-2016-013324*
22. **United Nations,** ed. International Standard Industrial Classification of All Economic Activities (ISIC). Rev. 4. United Nations; 2008.
23. **Rezende LFM de, Eluf-Neto J, Rezende LFM de, Eluf-Neto J.** Population attributable fraction: planning of diseases prevention actions in Brazil. *Revista de Saúde Pública*. 2016; 50. DOI: *https://doi.org/10.1590/ S1518-8787.2016050006269*
24. **Quinn MM, Smith PM.** Gender, work, and health. *Ann Work Expo Health*. 2018; 62(4): 389–392. DOI: *https://doi.org/10.1093/annweh/wxy019*
25. **Scarselli A, Corfiati M, Di Marzio D, Marinaccio A, Iavicoli S.** Gender differences in occupational exposure to carcinogens among Italian workers. *BMC Public Health*. 2018; 18. DOI: *https://doi. org/10.1186/s12889-018-5332-x*
26. **Sutandyo N, Suratman E.** Non-small cell lung carcinoma in women: A retrospective cohort study in Indonesia. *Acta Med Indones*. 2018; 50(4): 291–298.
27. **Robinson CF, Sullivan PA, Li J, Walker JT.** Occupational lung cancer in US women, 1984–1998. *Am J Ind Med*. 2011; 54(2): 102–117. DOI: *https://doi.org/10.1002/ajim.20905*
28. **Joshi SK, Bråtveit M, Moen B.** Possible occupational lung cancer in Nepal. *JNMA; Journal of the Nepal Medical Association*. 2003; 42: 1–5. DOI: *https://doi.org/10.31729/jnma.659*
29. **Baser S, Duzce O, Evyapan F, Akdag B, Ozkurt S, Kiter G.** Occupational exposure and thoracic malignancies, is there a relationship? *J Occup Health*. 2013; 55(4): 301–306. DOI: *https://doi.org/10.1539/ joh.13-0097-FS*
30. **Alavanja MCR, Dosemeci M, Samanic C,** et al. Pesticides and lung cancer risk in the agricultural health study cohort. *Am J Epidemiol*. 2004; 160(9): 876–885. DOI: *https://doi.org/10.1093/aje/kwh290*
31. **Barthel E.** Increased risk of lung cancer in pesticideχ-exposed male agricultural workers. *Journal of Toxicology and Environmental Health*. 1981; 8(5–6): 1027–1040. DOI: *https://doi. org/10.1080/15287398109530135*
32. **Bonner MR, Freeman LEB, Hoppin JA,** et al. Occupational exposure to pesticides and the incidence of lung cancer in the agricultural health study. *Environ Health Perspect*. 2017; 125(4): 544–551. DOI: *https:// doi.org/10.1289/EHP456*
33. **Weichenthal S, Moase C, Chan P.** A review of pesticide exposure and cancer incidence in the agricultural health study cohort. *Ciência & Saúde Coletiva*. 2012; 17(1): 255–270. DOI: *https://doi.org/10.1590/S1413- 81232012000100028*
34. **Boulanger M, Tual S, Lemarchand C,** et al. Lung cancer risk and occupational exposures in crop farming: results from the AGRIculture and CANcer (AGRICAN) cohort. *Occup Environ Med*. 2018; 75(11): 776–785. DOI: *https://doi.org/10.1136/oemed-2017-104976*

35. **Del Bianco A, Demers PA.** Trends in compensation for deaths from occupational cancer in Canada: A descriptive study. *CMAJ Open*. 2013; 1(3): E91–96. DOI: *https://doi.org/10.9778/cmajo.20130015*
36. **Gloal Construction Review.** 80% of Jakarta projects unsafe, says official report 2018. *http://www. globalconstructionreview.com/news/80-jakarta-projects-unsafe-says-official-report/*. Accessed June 18, 2020.
37. **Yuantari MC, Setiani O, Nurjazuli N.** Studi ekonomi lingkungan Ppnggunaan pestisida dan dampaknya pada kesehatan petani di area pertanian hortikultura desa sumber rejo kecamatan ngablak kabupaten magelang. *Jurnal Kesehatan Lingkungan Indonesia*. 2009; 8(2): 63–69. DOI: *https://doi.org/10.14710/ jkli.8.2.63-69*
38. **Yuantari MGC, Widianarko B, Sunoko HR.** Analisis risiko pajanan pestisida terhadap kesehatan petani. *KEMAS: Jurnal Kesehatan Masyarakat*. 2015; 10(2): 239–245. DOI: *https://doi.org/10.15294/kemas. v10i2.3387*
39. **Siemiatycki J, Richardson L, Straif K,** et al. Listing occupational carcinogens. *Environmental Health Perspectives*. 2004; 112(15): 1447–1459. *https://www.jstor.org/stable/3435600*. Accessed April 16, 2020. DOI: *https://doi.org/10.1289/ehp.7047*
40. **Badan Pusat Statistik.** *https://www.bps.go.id/*. Accessed August 8, 2017.

CHAPTER IV

CONCLUSION

4 Conclusion

This study successfully addressed the study's objectives by establishing the increased risk of lung cancer among workers exposed to asbestos and among workers classified under the IndSIC's Division A01 (crop, animal production and hunting) and Section F (construction). The study also established the synergy effect of asbestos and smoking habits in increasing the risk of lung cancer.

Report from this study urges the need to eliminate the use of asbestos to protect people from asbestos-related diseases. The country needs to review the policy of the use of asbestos and to prepare a national plan to eliminate asbestos-related diseases. Without a substantial commitment of prevention programs, people continue to live in danger of asbestos.

Besides, this study presented applicable methodology that can be followed by other researcher in Indonesia to define occupational diseases. Case-control study design is a suitable method within limited resources and adopting proxy to define occupational exposures is a thoughtful solution of limited exposure data in Indonesia.

CHAPTER V

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