LUNG CANCER ASSOCIATED WITH CARBON BLACK EXPOSURE ON BRICK WORKERS

Evidence-Based Case Report

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ABSTRACT
Carbon black aerosol has potential risks to human health. It has been acknowledged to cause cardiovascular and respiratory diseases in humans. International Agency for Research on Cancer (IARC) 2010 stated that carbon black classification is 2b, which is carcinogenic. This research explains a case of lung cancer due to carbon black exposure and reviews the literature of occupational cases to get the answers about the effects of carbon black exposure and the increasing risk of lung cancer for workers exposed to carbon black. The literature review was performed to answer the clinical question via electronic databases: PubMed and Google Scholar. The keywords used were ‘carbon black’ and ‘lung cancer’ and ‘workers’. The inclusion criteria of this searching strategy were the workers which exposed to carbon black, meta-analysis, randomized controlled trial, systematic reviews, cohort. The exclusion criteria of this article were inaccessible articles, RCTs that have been used in the recent systematic reviews. The selected articles were then critically appraised using relevant criteria by the Oxford Center for Evidence-based Medicine. This study reviews the literature by Rota Matteo; The epidemiological evidence on the polyaromatic hydrocarbon (PAH) high exposed, perspective cohort study by Delli LD, and the control case study by Marie EP. All the researches above showed that carbon black carcinogenic potential is the same as the IARC monograph statement that the epidemiological studies of carbon black provide possible carcinogenicity (Group of 2B).

Keywords: carbon black, lung cancer, workers

INTRODUCTION
Carbon black, an important aerosol in the atmosphere, is generally produced by weathering of graphitic carbon in rocks and the incomplete combustion of fossil fuels, vegetation, biofuels, and biomass. Carbon black's nature has a distinctive form, with nanometer to micrometer particle size, and layered structure. Recently, carbon black has had an enormous contribution to global climate change and is related to a persistent organic pollutant and affects human health (Wu et al., 2018). Carbon black aerosol has potential risks to human health. It has been acknowledged to cause cardiovascular and respiratory diseases in humans. Carbon black potentially induces cardiovascular morbidity and mortality. Its particle size and its catastrophic effects are strongly connected. Polyaromatic hydrocarbon (PAH) carcinogenicity activity is primarily explained by the dioxepoxide process, i.e. the production of intermediate PAH metabolites (diols and dioxepoxides) as a result of DNA reaction and DNA adduct formation was known to be genotoxic and carcinogenic. (International Agency for Research on Cancer (IARC) Monographs on the evaluation of Carcinogenic Risks to Human volume, 2018). Other possible pathways include orthoquinone and the formation of reactive oxygen species, aryl-hydrocarbon, immunosuppression, and epigenetic processes (Sharma, 2010). Agency for Research on Cancer (IARC) stated that the carcinogenic effect of carbon black on human is still a controversy. Hence, it is important to research with literatures review to have the answer about carbon black exposure effects and the increasing risk of lung cancer among carbon
black exposed workers (Hancock DG, 2014).

The finding on this case explains the relationship of lung cancer with carbon black exposure through the literature review on the occupational case report.

The case description of this research was taken from a patient in A 47-year-old man who came to the hospital with complaints of breathing shortness and chest pain. The pain spread to the upper left abdomen. The patient felt pain and tight every time he breathed. Breath is felt rather tight. This complaint has been felt since approximately 3 months ago and started to get heavy in recent weeks. Coughing of blood since 6 months ago, history of completed tuberculosis treatment, diabetes, and hypertension were denied. History of the family with diabetes and hypertension was denied, smoking over 35 years, 1-2 packs/day. (index brickman: heavy). Based on the physical examination, there were signs of hypotension and uninodular firm elastic lymphatic node enlargement with 0,5 cm in diameter in the left neck. Based on the thorax examination, there were asymmetrical left and right chest, dimmed right lung percussion, and diminished vesicular breath sound. Based on the radiology examination, there were a quite massive right pleural effusion and swelling of antebrachial soft tissue with intact visualized bone and good joints. The biopsy result showed it as squamous cell carcinoma. The occupational history of this patient has been working as a brickmaker in his home industry since 20 years ago and works 8 hours per day, 6 days per week. For making much brick, he uses combustion material from charcoal which produces carbon black. He never uses personal protective equipment such as masks, boots, google glasses, and gloves. The clinical diagnosis for this patient is squamous cell carcinoma of lung cancer. Based on the 7 steps of occupational diagnosis, it was determined as lung cancer aggravated by work.

This research aims to get the answers about the effects of carbon black exposure and the increasing risk of lung cancer for workers exposed to carbon black.

**METHODS**

The literature search was performed to answer the clinical question via electronic databases: PubMed and Google Scholar. The keywords used were 'carbon black' AND 'lung cancer' AND 'workers' (table 1). The inclusion criteria of this searching strategy were the workers which exposed to carbon black, meta analysis, randomized controlled trial, systematic reviews, cohort. The exclusion criteria of this article were inaccessible articles, RCTs that have been used in the recent systematic review (figure1). The searching was done on March 23th 2019.

The selected articles were then critically appraised to determine whether the article is valid, important, and applicable to the patient using relevant criteria for etiological study by the Oxford Center for Evidence-based Medicine. (Oxford Centre for Evidence-Based Medicine (CEBM). Critical Appraisal Tools., 2019).

From online search results, three selected articles fit the inclusion and exclusion criteria: A systematic review; Occupational exposures to polycyclic aromatic hydrocarbons and respiratory and urinary tract cancers: an updated systematic review and a meta-analysis to 2014 (Rota et al., 2014), a prospective cohort study; Cohort Study of Carbon Black Exposure and Risk of Malignant and Nonmalignant Respiratory Disease Mortality in the US Carbon Black Industry (Dell et al., 2015), and case-control study; Case-Control Study of Exposure to Carbon Black in the Occupational Setting and Risk of Lung Cancer (Marie EP, 1996).
Figure 1. Literature searching chart

Table 1. Searching strategy using the database from PubMed AND Google Scholar

| Database          | Search strategy                                      | Hits  | Selection |
|-------------------|------------------------------------------------------|-------|-----------|
| PubMed            | Carbon black AND Lung cancer AND workers             | 22    | 2         |
| Google Scholar    | Carbon black AND Lung cancer AND workers             | 3550  | 3         |
| Additional Search | Carbon black AND Lung cancer AND workers             | 2     | 1         |

Searching date: March 23<sup>rd</sup> 2019
RESULT

The first study Rota et al., (2014) found 62 out of 474 non-specific journals identified through eligibility standard for literature searching and a complete text evaluation, 49 out of 62 articles are not included because of different occupation or peculiar cancer, control case study, investigated mortality or incident quantitative estimation, or several publications on the same cohort. Thus, there are 13 articles assessed in this review.

This systematic review assessed 13 articles that showed that polycyclic aromatic hydrocarbons (PAH) exposure among the aluminium workers was showed insignificantly related to lung cancer (including other non-specified respiratory cancers) (RR 1.08 95% CI 0.95 to 1.23). The study shows that the iron and steel factory workers were insignificantly related with lung cancer (including other non-specified respiratory cancers) (RR 1.31 95% CI 1.08 to 1.59), in three cohort studies on asphalt workers, showed insignificant results with RR for lung cancer was 1.59 (95% CI 0.68–3.76).

Table 2. Critical appraisal checklist for systematic review

| Article | Occupational exposures to polycyclic aromatic hydrocarbons and respiratory and urinary tract cancers: an updated systematic review and a meta-analysis to 2014 | Level: 1a (Systematic review of clinical trials, meta-analysis) |
|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| Question | What question (PICO) did the systematic review address? | Yes according to the abstract and the final paragraph of the introduction the article, the PICO was P: the workers in selected industries; I: polycyclic hydrocarbons; C: unexposed workers; O: respiratory and urinary tract cancers |
| find | Is it unlikely that important, relevant studies were missed? | The search technique, including the words used, is evidence in some detail. The number of titles and abstracts checked, the number of full-text studies retrieved, the number of omitted studies and the exclusion grounds. |
| Appraise | Were the criteria used to select articles for inclusion appropriate? | Yes, they were appropriate. Inclusion criteria; cohort studies, the study of workers from selected industries characterized by PAH exposure, providing standardized mortality ratios (SMRs) and/or standardized incidence ratios |
Synthesize | Were the included studies sufficiently valid for the type of question asked | Unclear | The description of how the quality of each study was assessed using predetermined quality criteria relevant to a clinical questioning method (e.g. randomization, blinding and thorough investigation) was not found in the method or result section.

| Were the results similar from study to study? | No | The assessment of heterogeneity between studies was focused on the chi-square test, according to the method portion. The findings of the numerous cohort studies under review were substantially heterogeneous in many cases.

Result | What is The result of the articles? | The forest plot shows that the exposure to polycyclic hydrocarbons amid aluminium workers was negligible concerning lung cancer (including other non-specified respiratory cancers) (RR 1.08 95 percent CI 0.95 to 1.23) and significant to lung cancer (including other non-specified respiratory cancers) among iron and steel smelting workers (including other non-specified respiratory cancers) (RR 1.31 95 percent CI 1.08 to 1.59)

The second study (Dell et al., 2015) found that there was no clear association in the full-time or hourly worker community between the mortality risk of lung cancer and carbon black exposure.

Even though there is no excess lung cancer mortality in this cohort study, the lack of connection between carbon black exposure and lung cancer is persistent with the studies of the same field in the UK and Germany.

Cancer mortality in this cohort is different (RR: 2.781 CI 95%1.923 to 4.022). Concerning carbon black exposure estimates, this study concluded that no clear trends of increased lung cancer were found. No clear association was found between the risk of mortality from lung cancer with lagged or lugged carbon black exposure in the full cohort or the entry cohort of hourly male workers.
Table 3. Critical appraisal checklist for a prospective cohort study

| Article | Cohort Study of Carbon Black Exposure and Risk of Malignant and Nonmalignant Respiratory Disease Mortality in the US Carbon Black Industry | Level: (3) prospective cohort study |
|---------|----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| Validity | Was the objective of the study clearly stated? | To know if there was a correlation between cumulative inhalable carbon black exposure and lung cancer and respiratory disease mortality among 6634 US carbon black employees. |
| | Were exposures and results measured in the same method in the patient groups? | The measurement is the same method for exposure of black carbon and the result (standardized mortality ratio) for each group of patients. |
| | were there clearly defined groups of patients. similar in all important ways other than exposure to the treatment or other cause? | Employees at 18 carbon black facilities in the United States are groups of patients (of a total of 20 that were working with carbon black as of January 1, 2000) |
| | was the investigation of the patients complete and long enough? | Yes, the investigation of the patients is complete and long enough. The analysis aimed to determine whether carbon black exposures were predictive of risk in the 15 years preceding the death of lung cancer to allow for direct comparisons of outcomes between the cohorts. |
| | did the study have a sufficiently large sample size? | The sample size is 6634 subjects. It is sufficient. |
| | was there a statistical adjustment for the important difference between patient groups? | Cumulative inhalable carbon black exposure was modeled as both a continuous and a categorical component. Continuous cumulative inhalable carbon black exposure was modeled in increments of 100 mg/m3.yr. |
is it clear that the exposure preceded the onset of the outcome?  | The onset of the outcome was preceded by exposure.
---|---
is there a dose-response gradient?  | Yes
is the association consistent from study to study?  | Yes
is the biological relationship plausible?  | Yes

| Clinical importance | how strong is the association between exposure and outcome, and how precise? | Total patient for lung cancer : 184  
Total patient : 6634  
Total reference patient : 2565  
Relative Risk for kohort: 2,781  
CI 95% (1,923 – 4,022) |
|---|---|---|
| Aplicability | were the study patient and their management similar to those in my practice ? | Yes |
| | This patient has the same exposure, the other risk factor are similar |

The result of the third study Marie EP, 1996) is compatible with the hypothesis of the high risk of lung cancer due to black carbon exposure, yet only in the “higher” exposure group. Moreover, this study provides evidence on the risk that can occur from carbon black exposure in a wide range of occupations, compared to cohort studies carried out in specific industries. The results from the present in-depth analyses are compatible with the hypothesis of excess risk of lung cancer with exposure to carbon black, but only in the "higher" exposure group. These findings must be interpreted cautiously, given the limited number of exposed cases in this exposure category.
The conclusion is that the evidence for carbon black’s role is inadequate and contradictory. This study provides some additional evidence for an association between exposure to carbon black and lung cancer.

**Table 4.** Critical checklist for case control study

| Article | Case-Control Study of Exposure to Carbon Black in the Occupational Setting and Risk of Lung Cancer |
|---------|------------------------------------------------------------------------------------------------------------------|
| Validity | Level: (3a) a case control study                                                                                   |
| were exposures and outcomes measured in the same way in the patient groups | Yes |
| were there clearly defined groups of patients, similar in all important ways other than exposure to the treatment or other cause? | Yes |
| was the follow-up of study unclear patients complete and long enough? | Male residents from the greater Montreal area aged 35-70 years were recently diagnosed with one of 19 histologically confirmed cancer types comprised the case series. The ascertainment of cases was carried out in all large hospitals in the area over 6 years |
| did the study have a sufficiently large sample size? | The follow-up study is complete but it wasn't mentioned about the duration of follow up |
| was there a statistical adjustment for important differences between patient groups? | Exposure of carbon black was expressed in three categories, that is, unexposed, lower, and higher exposure, corresponding to the lower two-thirds and upper third of the distribution of the index of cumulative exposure described previously. This allowed for an examination of the exposure-response relationship. Adjusted regression models included linear terms for age, socioeconomic status as measured |
It is clear that the exposure preceded the onset of the outcome?

Yes

It is shown in TABLE 5. Odds Ratio between exposure to carbon black and Lung cancer for the main histologic Subtypes, using two control groups, Montreal, 1979-1985

Table 5: Odds Ratio between Exposure to Carbon Black and Lung Cancer for the Main Histologic Subtypes, Using Two Control Groups, Montreal, 1979-1985

| Clinical importance | how strong is the association between exposure and outcome, and how precise? |
|---------------------|----------------------------------------------------------------------------|
| Low Exposure        | OR 1.08 CI95% 0.66 – 1.76. Higher exposure: OR 2.17 CI95% 0.95 – 4.91. The association is not strong enough. |

According to some research, carbon black exposure is related to non-carcinogenic diseases of the respiratory system. [Gardiner et al., 1993; Gardiner, 1995; IARC, 19841, while other studies have found no such deleterious effect [Crosbie, 1986; Robertson and Ingalls, 1989; Indirect evidence pointing to carbon black as a lung carcinogen comes from studies focusing on industries.

Some researchers mentioned that carbon black exposures are related to non malignant diseases of the respiratory system.

is there a dose-response gradient?

Yes

is the association persistent from research to research?

Yes

is the association consistent from study to study?

Yes

is it clear that the exposure preceded the onset of the outcome?

Yes

Clinical importance

Applicability

were the study patient and their management similar to those in my practice?

This patient has the same exposure, the other risk factor are similar

by self-reported income, job dirtiness, and alcohol intake, and categorical terms for ethnicity (French, Anglo, other) and respondent status (self, proxy). Asbestos and chromium compounds are recognized lung carcinogens and were incorporated as continuous variables, using the same type of synthetic index described earlier for carbon black.
DISCUSSION

The studies above showed that the relation between carbon black and lung cancer was still not clear. A systematic review about occupational exposures to polycyclic aromatic hydrocarbons and the health effect on respiratory and urinary tract cancers showed that carbon black which is a group of polyaromatic hydrocarbon (PAH) has an insignificant related to lung cancer for aluminium workers (RR 1.08 95%CI 0.095 T0 1.23), the iron and steel foundry workers (RR 1.31 95%CI 1.08 to 1.59), asphalt worker (RR 1.59 95%CI 0.68-3.76). The conclusion is there is no indication of high risk discovered in coal tar and carbon black employees.

In the study of meta-analysis, coal gasification, coke production, and carbon electrode production were observed to find the high risk of respiratory tract cancer among workers in these sectors. It revealed that there was no high risk of respiratory tract cancers in employees. The study of meta-analysis confirmed workers engaged in the manufacturing of carbon electrodes had a potential excess risk of respiratory cancer. (Rota et al., 2014).

The other paper, a prospective cohort (Dell et al., 2015), concluded that to estimate carbon black exposure, there were no clear trends of increased lung cancer. There was no direct connection between lagged or lugged carbon black exposure and lung cancer mortality in the full cohort or the entry cohort of hourly male workers.

The last article of case control study (Marie EP, 1996), reported that the results from the present in-depth analyses are compatible with the hypothesis of excess risk of lung cancer with exposure to carbon black, but only in the “higher” exposure group. The quality of job histories may differ depending on whether they are obtained directly from the subjects or by proxy interviews. The interviews had to be carried out for some lung cancer cases as well as for an appreciable proportion of cancer controls. Since there was little difference (10%) in the proportions of proxies in the two groups, there was little opportunity for bias in the comparison. The inclusion of proxies may have resulted in some misclassification and have minimized the differences between groups, but not in an inflation of the risk estimates. Along with inaccurate recall of work histories and misclassification in the attribution of exposures by chemists, the use of proxy respondents is one of the factors that may have attenuated the relationships observed if there was a true association (Sorahan and Harrington, 2007).

The result from these three studies is contributed for several reasons that in the West where the three studies had been done, especially in US and UK where they have standard regulation of harmful exposure effect protection. They use standard engineering control to limit the exposure and also management early detecting management for workers’ health. However, it is important to remember that each country has its medical regulation on a surveillance system that can influence the implementation, accessibility ,and effectiveness of lung cancer prevention, such as the quantity examination of polyaromatic hydrocarbon (PAH) especially carbon black in the working environment and workers health by biological monitoring of carbon black exposure (Sorahan and Harrington, 2007).

The eminence of this study is a large number of research samples in a systematic review, prospective cohort study, and control cases. The study is complete with adequate quantitative data and cost-efficient data collecting by compiling cohort studies from original articles. Of course, there are weaknesses of this research, such as the heterogeneous data that reflects the varied pattern of exposure in some cohorts and the difference of period that can be a bias and confounding factor. This study did not analyze the dose–response relation between carbon black and lung cancer.

Information from the above literature study on the review of this patient
case explains that carbon black exposure causing lung cancer is still not clear. Moreover, for his patient, Other factors can contribute to lung diseases (especially lung cancer) such as smoking habits, other working process exposure, and pollutant from where he lives in.

It is important to manage carbon black exposure by medical surveillance especially in home industries in Indonesia where there is a lack of regulation, controlling and protection from exposure. Home industries like as charcoal industries, tofu industries, extraction of nutmeg oils and clove oils, food industries which are exposed by carbon black should get attention for safe and healthy workers with the hierarchy of control such as: 1) Elimination or substitution by change charcoal burning to gas which is healthier and safe. 2) If elimination and substitution can’t be realized, get engineering control to enclose operations and/or provide appropriate local exhaust ventilation at machinery and at places where dust can be generated to flow away air pollutant direction and make a chimney or closed burn setting/isolating operation. 3) Administration control to lead the regulation of job procedure, health promotion to prevent the health risk for the workers, Medical surveillance to determinate the quantity of carbon black in air workplace, early detection by biomonitoring of carbon black to the workers; by examining the metabolic of hydroxypyrene (in urine) by using the high performance of liquid chromatography (HPLC) and enzyme-linked immunosorbent assay (ELISA) and periodic medical examination (Angerer J, Mannschreck C, 1997). 4) Personal protective equipment (carbon black; 1750 mg/m³) by using respirators such as respirators operated in a pressure-demand or other positive-pressure mode. For research; Advanced studies of the carbon black exposure to lung cancer in Indonesia, and the research of grading dose cumulative inhalable carbon black exposure as cancer’s variable cause to human’s other organs, especially in workers (Borm and Driscoll, 2019)(McJunney RJ.et al, 2012).

CONCLUSION

This research showed there was no strong relation between carbon black and lung cancer risk. The three types of research showed that carbon black carcinogenic potential is the same as the IARC monograph statement that the epidemiological studies of carbon black provide lack indication to the notation of carcinogenicity (Group of 2B).

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