Hubungan antara Pajanan Kadmium dan Kanker Prostat pada Pekerja: Laporan Kasus Berbasis Bukti

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Abstrak

Kadmium memiliki peranan penting karena banyak digunakan di berbagai macam industri. Kadmium dapat masuk dan terakumulasi dalam tubuh termasuk di prostat. Kadmium sangat toksik dan bisa menyebabkan kanker. Tujuan dari laporan kasus berbasis bukti ini adalah untuk mendapatkan jawaban yang tepat terkait hubungan antara pajanan kadmium di tempat kerja dan kanker prostat pada pekerja. Metode dengan pencarian literatur dilakukan melalui database PubMed, Scopus dan Cochrane Library. Kata kunci yang digunakan adalah cadmium, cancer, prostate, work* dan occupation*. Pemilihan artikel menggunakan kriteria inklusi dan eksklusi yang telah ditetapkan. Kemudian dilakukan penilaian kritis menggunakan kriteria yang relevan untuk studi etiologi atau systematic review berdasarkan Oxford Center for Evidence-Based Medicine. Terpilih dua artikel yang relevan dan valid dengan desain studi systematic review dan meta-analisis. Penelitian dari Ju-Kun, dkk menunjukkan rasio kematian terstandarisasi (standardized mortality ratio) antara pajanan Cd dan risiko terjadinya kanker prostat adalah 1.66 (95% CI 1.10–2.50) pada populasi pekerja yang terpajan Cd. Berdasarkan penelitian Chen, dkk menunjukkan bahwa pekerja dengan pajanan kadmium memiliki risiko terjadinya kanker prostat yang lebih tinggi dibandingkan populasi umum, namun secara statistik tidak signifikan yakni dengan nilai OR pada studi case-control 1.17 (95%CI [0.85-1.62]), dan standardized mortality ratio (*100) pada studi kohort adalah 98 (95%CI [75-126]). Hasil studi yang ada tidak menunjukkan bukti yang cukup untuk memastikan bahwa pajanan kadmium bisa menyebabkan kanker prostat pada pekerja.

Key words: Kadmium, kanker prostat, pekerja.

The Association Between Occupational Cadmium Exposure and Prostate Cancer in Worker: Evidence-Based Case Report

Abstract

Introduction. Cadmium has an important role because widely used in various industries. Cadmium penetrates and can be accumulated in human body including prostate. Cadmium is highly toxic and can cause human carcinogens. The aim of this evidence-based case report is to get an appropriate answer about the association between occupational cadmium exposure and prostate cancer in worker. **Method.** The literature searching was conducted through PubMed, Scopus and Cochrane Library. The keywords used were cadmium, cancer, prostate, work* and occupation*. The selection of articles was performed using the defined inclusion and exclusion criterias. Then, they were critically appraised using relevant criteria by the Oxford Center for Evidence-Based Medicine for etiological study or systematic review. **Result.** Two relevant and valid articles with systematic review and meta-analysis study design were included. Studies by Ju-Kun, et al. showed that the combined standardized mortality ratio of the association between Cd exposure and risk of prostate cancer was 1.66 (95% CI 1.10–2.50) in populations exposed to occupational Cd. While a study by Chen, et al. showed that workers with cadmium exposure have more risk for prostate cancer than general population but was not significant statistically with the weighted OR in case-control studies was 1.17 (95%CI [0.85-1.62]), and the weighted standardized mortality ratio (*100) in cohort studies was 98 (95%CI [75-126]). **Conclusion.** The current evidences do not show sufficient evidence to ensure that cadmium exposure can cause prostate cancer in worker.

Key words: Cadmium exposure, prostate cancer, worker.

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Introduction

Cadmium is one type of heavy metal that has an important role because this element is widely used in various industries including plating of steel, battery recycling, welding, mining and smelting works. Cadmium is also used as a plastic stabilizer, in production of pigments for paints, and in semi-conductors. Cadmium actually is a metallic element found naturally in low concentrations. Elevated

concentrations in air, water, and soil may occur close to industrial emission sources [1]. Heavy metal contamination from occupational origin is a cause for concern because of its potential accumulation in the environment and in living organisms leading to long term toxic effects [2].

Cadmium penetrates the human body through the principal routes of toxic matter absorption (through the lungs, gastrointestinal tract and skin). However, in the case of occupational exposure, the amount of cadmium absorption through ingestion and skin is considered to be much less important. Cadmium exposure can cause health problem in renal, musculoskeletal, lung, testes, prostate, hematopoietic system, and also cardiovascular system [1]. Cadmium and its compounds are highly toxic and exposure to this metal is known to be human carcinogens. Cadmium and cadmium compounds have been classified by the International Agency for Research on Cancer (IARC) as Group 1 human carcinogen, mainly on the basis of epidemiological studies showing a dose-response relationship between the level of cadmium exposure and the incidence of lung cancer in the human population. IARC also noted positive associations between occupational or environmental exposure to cadmium and risk of cancer in the prostate, kidney, bladder, breast, and endometrium [1,3,4]. Cadmium has a long biological half-life (>25 years), due to the flat kinetics of its excretion. The prostate is one of the organs with highest levels of cadmium accumulation [5]. In particular, numerous studies have been conducted on the relationship between cadmium exposure and prostate cancer. However, the role of cadmium and its derivatives in the induction of prostate cancer seems much more controversial. Several epidemiologic studies investigating the association between cadmium exposure and susceptibility to prostate cancer have yielded inconsistent findings. Some studies have demonstrated a significant correlation or little association between Cd exposure and risk of prostate cancer, but others failed to show any significant relationship [6]. Based on the reasons, it is necessary to conduct a review of the evidence in order to get an appropriate answer and to improved understanding of the association between cadmium exposure in the workplace and prostate cancer.

Case

A 49-year-old male patient came with a chief complaint of difficulty in urinating since 3 months ago. Patients sometimes have to wait a long time and struggle to urinate. When urinating, the urine stream becomes weak and he feels dissatisfaction when finish urinating. The patient also complained of frequent urination, especially in the middle of the night. There is no history of sandy urination and low back pain. There is no previous history of medical problem. There is no family history of suffering from the same disease. Based on the rectal toucher, it was found that the prostate is palpable enlarged with, hard consistency, protruding surface, and tenderness. This patient has prostate spesific antigen (PSA) level 12 ng/ml in the blood. From the histopathological examination, cancer cells were seen in the biopsy samples.

The patient works in welding workshop as a welder. This welding workshop is engaged in metal construction. Job duties of this patient include welding, cutting, and drilling. He works 8 hours/day, five days a week. Sometimes working time is longer if there are a lot of orders. He has been worked as a welder for approximately 20 years. The patient said that he usually use eye protection and sometimes use a respirator when working. He admitted that he often took off the respirator when working because of discomfort. As a welder, the patient is at risk for cadmium exposure. The patient asked the doctor for possible causes of his condition, whether it can be related to his job as a welder or not.

Method

The literature searching was performed to answer the clinical question via electronic databases from PubMed, Scopus, and Cochrane Library. The keywords used were cadmium, cancer, prostate, work* and occupation* (Table 1). The inclusion criteria of this searching strategy were Systematic Review, Meta-Analysis, Cohort Study, Case-control Study, Cross-sectional Study, worker with occupational cadmium exposure, and prostate cancer outcome. The exclusion criteria were inaccessible article, article is not

in English, and statistical value data is not available (Figure 1).

Table 1. Search Strategy Using Keywords

Database	*Keyword*	*Finding*
PubMed	(((cadmium) AND ((work*) OR (occupation*))) AND (prostate)) AND ((cancer) OR (carcinoma))	101
Scopus	(TITLE-ABS-KEY (cadmium) AND TITLE-ABS-KEY (work* OR occupation*) AND TITLE-ABS-KEY (prostate) AND TITLE-ABS-KEY (cancer OR carcinoma))	137
Cochrane Library	(((cadmium) AND ((work*) OR (occupation*))) AND (prostate)) AND ((cancer) OR (carcinoma))	1

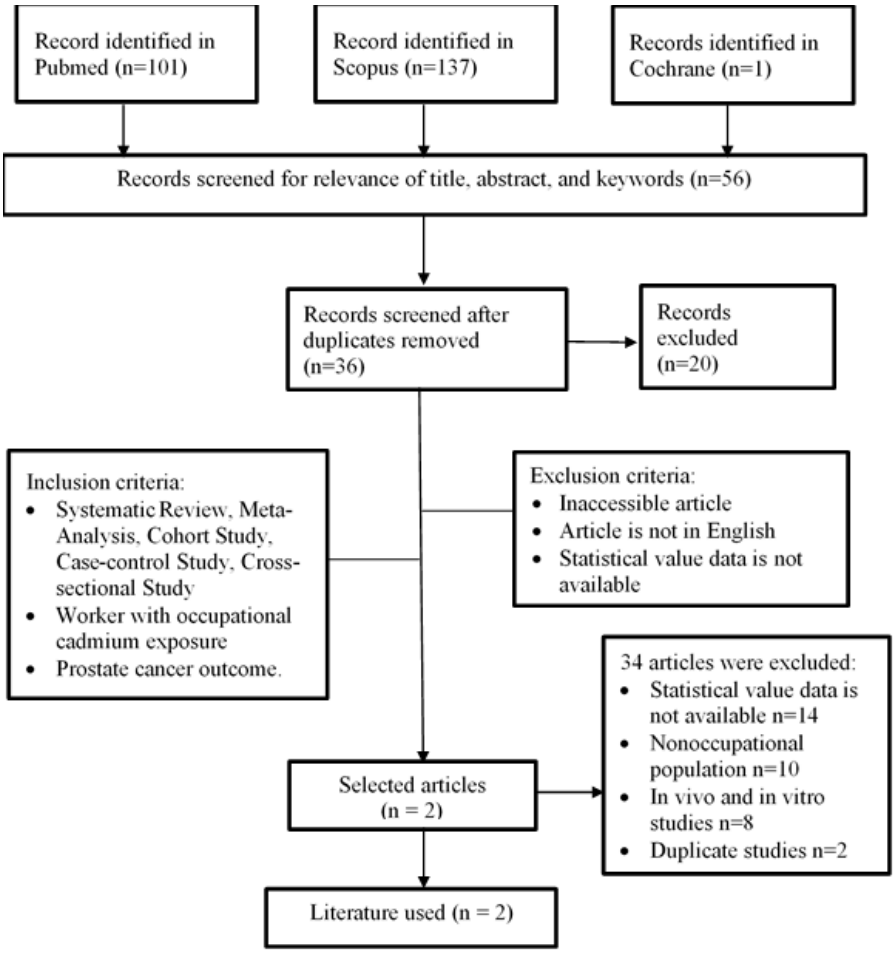

Figure 1. The Process of Article Selection

Result

The online searching resulted two selected articles that fit the inclusion and exclusion criteria, i.e systematic review and meta-analysis studies by Ju-Kun et al. [6] and Chen, et al. [7] . The characteristics from each study can be seen in Table 2 and the results of the critical appraisal from each study can be seen in Table 3. The study conducted by Ju-Kun, et al. was a systematic review and meta-analysis study that aimed to investigate the association between cadmium exposure and risk of prostate cancer. Relevant studies in PubMed and Embase databases were retrieved until October 2015 with proper inclusion and exclusion criteria. They manually searched the reference lists of previous reviews and related article references to

identify other potentially eligible studies. A total of 22 studies, comprising 8 case-control and 14 cohort studies with 137,998 participants, contributed to the meta-analysis. Twelve studies reported an association between occupational Cd exposure and prostate cancer risk, whereas 10 studies used nonoccupational populations. Most of the studies were controlled for some conventional risk factors, including age (n=6) and smoking (n=6). Some studies were also controlled for body mass index (n=3) and alcohol consumption (n=2), but few studies were adjusted for beef intake, dairy product consumption (n=1), and intake of vegetable and fruit (n=1). None of the studies were adjusted for other heavy metals, trace elements of organic pollutants, and intake of grains.

This study shows the standardized mortality ratio (SMR) estimates and 95% CI from each study, as well as the pooled SMR estimate based on a random effects model. The standardized mortality ratio is the ratio of observed deaths in the study group to expected deaths in the population. The SMR may be quoted as either a ratio or a percentage. If the SMR is quoted as a ratio and is equal to 1.0, then this means the number of observed deaths equals that of expected cases. If higher than 1.0, then there is a higher number of deaths than is expected. The SMR can be expressed as a percentage simply by multiplying by 100 (*100). Results from the 8 cohort studies indicated that the pooled SMR was 1.66 (95% CI 1.10–2.50) with moderate heterogeneity (p for heterogeneity=0.002; I^2=69.9%). In subgroup analyses for exposure type, they restricted each analysis to 7 occupational exposure studies, resulting in a summary SMR of prostate cancer of 1.65 (95% CI 1.03–2.64). This study also shows the OR estimates, 95% CI from individual studies, and pooled OR estimate based on a random-effects model. Results from the 14 studies, comprising 9 case-control studies and 6 cohort studies, indicated that the pooled OR was 1.23 (95% CI 0.81–1.88) with significant heterogeneity (p for heterogeneity = 0.000; I^2=96.2%). In subgroup analyses for exposure type, they restricted each analysis to 5 occupational exposure case-control studies. Five studies reported an association between occupational Cd exposure and prostate cancer risk; however, the association was not significant in the occupational exposure population (OR=1.31, 95% CI 0.79–2.19).

The study conducted by Chen, et al. (2016) was also a systematic review and meta-analysis study that aimed to evaluate the association of cadmium exposure with the risk of prostate cancer in both the general and occupational populations. Relevant studies in PubMed database were retrieved until June 2015. Eight additional articles were identified through Google Scholar or reference lists of articles. In sum, 21 studies (5 cohort and 3 case-control studies in the general population, and 7 cohort and 6 case-control studies in occupational populations) met the criteria and were included in this meta-analysis. Five/seven cohort studies in the general/occupational populations consist of 78,263/13,434 participants (4,731/83 events). Three/six case-control studies in the general/occupational populations include 334/1,315 cases and 670/4,477 controls.

Among the case-control studies conducted in the occupational population, the weighted OR did not reveal an association between cadmium exposure and the risk of prostate cancer (weighted OR = 1.17; 95% CI 0.85-1.62). The pooled association persisted when omitting any single study at each time. Evidence on heterogeneity (I^2 = 0.0%, p = 0.59) and publication bias (p = 0.61) were not found. In addition, the weighted SMR (*100) among occupational cohort studies did not indicate any significant association (SMR = 98; 95% CI 75-126). The result was not materially influenced by any single study. Heterogeneity (I^2 = 22.8%, p= 0.26) and publication bias (p= 0.35) were not detected.

Table 2. The Characteristic of The Study

Author	Study Design	Subject	Occupation	Intervention	Outcome and Result	Proper Inclusion Criteria	Level of Evidence
Ju-Kun et al (2016)[6]	Systematic review and Meta-analysis	22 studies: • 9 case-control (5 occupational, 4 general) • 13 cohort (7 occupational, 6 general) With 137,998 participants	• Nickel cadmium battery worker • Cadmium-copper alloy worker • Smelter • Metal worker • Atomic energy authority worker	Cadmium exposure	Outcome: The risk of prostate cancer (incidence and mortality) : in occupational population Result: **Incidence:** OR = 1.27 95% CI (0.87-1.87) p=0.217 **Mortality:** SMR = 1.65; 95%CI (1.03-2.64) p=0.038	Yes	1
Chen et al (2016)[7]	Systematic review and Meta-analysis	21 studies: • 12 cohort (5 general, 7 occupational populations) • 9 case-control (3 general, 6 occupational populations). **Cohort:** 5/7 cohort studies in the general and occupational populations consist of 78,263/13,434 participants **Case-control:** 334 cases/670 controls in the general population, and 1,315 cases/4,477 controls in occupational populations.	• Nickel cadmium battery worker • Cadmium-copper alloy worker • Smelter • Tool and die maker • Jeweler • Pipe fitter • Plumber • Cd production worker	Cadmium exposure	Outcome: The risk of prostate cancer (incidence and mortality): in occupational population Result: **Case-control (incidence in occupational population)** • OR = 1.17 • 95%CI (0.85, 1.62) **Cohort (mortality in occupational population)** • SMR (*100) = 98 • 95%CI (75, 126)	Yes	1

Table 3. The Critical Appraisal of The Study

	Study by Ju-Kun et al[6]	Study by Chen et al[7]
Title	Association between Cd Exposure and Risk of Prostate Cancer: A PRISMA-Compliant Systematic Review and Meta-Analysis	Cadmium Exposure and Risk of Prostate Cancer: a Meta-analysis of Cohort and Case Control Studies among The General and Occupational Populations
Study Design	Meta analysis	Meta analysis
Population	General and occupational population	General and occupational populations
Intervention	Cadmium exposure	Cadmium exposure
Comparison	-	-
Outcome	The risk of prostate cancer	The risk of prostate cancer

Question	Study by Ju-Kun et al	Study by Chen et al
Is the result of this harm study valid?		
Does the systematic review address a focused question (PICO)?	Yes	Yes
….and use it to direct the search and select articles for inclusion?	Yes	Yes
Did the search find all the relevant evidence?	Yes	Yes
Have the studies been critically appraised?	Yes	Yes
…and was the overall quality adequate?	Yes	Yes
Have the results been synthesized with appropriate summary tables and plots?	Yes	Yes
…and were the results similar between studies?	No	Yes
Does this meta-analysis clinically importance?		
What measure was used? How large was the effect?	**Incidence:** OR = 1.27 95% CI (0.87-1.87) p=0.217 **Mortality:** SMR = 1.65; 95%CI (1.03-2.64) p=0.038	**Incidence:** OR = 1.17 95% CI (0.85-1.62) **Mortality:** SMR (100) = 98; 95%CI (75-126)
Do the result can be applied to our patient?		
Do the results apply to our patient?	Yes	Yes
Are our patient characteristics similar to those of patients in meta-analysis?	Yes	Yes
What are our patient's preferences, concerns and expectations from this treatment?	Patient concern: how much cadmium exposure can effect prostate cancer.	Patient concern: how much cadmium exposure can effect prostate cancer.

Discussion

Cadmium is prevalent heavy metal in the environment, but exposure to this metal primarily occurs as a result of human activities. Occupational cadmium exposure is widely used in various industries. Cadmium is classified as a human carcinogen by the International Agency for Research on Cancer and the National Toxicology Program. The prostate is a potential target for cadmium carcinogenesis[1,8]. Early

epidemiological studies found elevated prostate cancer mortality among cadmium exposed workers, whereas later studies failed to confirm this positive association. The studies conducted by Ju-Kun et al.[6] and Chen et al.[7] are meta-analysis studies that aimed to evaluate the association of cadmium exposure with the risk of prostate cancer in both the general and occupational populations.

Both meta-analysis studies found no convincing evidence of a link between cadmium exposure and prostate cancer risk in the general or occupational populations. Although a positive connection between high Cd exposure and the risk of prostate cancer was discovered in a meta-analysis by Ju-Kun et al., this finding should be regarded with caution due to significant heterogeneity. The research undertaken by Ju-Kun et al. had various advantages. The enormous sample size of this meta-analysis is its hallmark. Because of the huge number of total cases, the association between Cd exposure and prostate cancer risk could be objectively evaluated. Little evidence of publication bias was detected in this meta-analysis. In addition to its strengths, this meta-analysis has certain flaws to consider. They can't rule out the possibility that the observed positive relationship between Cd exposure and prostate cancer risk is attributed to confounding factors. The majority of the studies in this meta-analysis were corrected for potential confounding factors, but not all of them were. The majority of studies were corrected for several common risk factors, such as age and smoking status, and some studies were also controlled for BMI and alcohol intake. Few studies were adjusted for other dietary factors or nutrients, and none of the studies included in this review were tested for additional heavy metals, trace elements, or organic contaminants[6].

Another weakness of this study is about an accurate evaluation of Cd exposure. The majority of studies used questionnaires to quantify Cd exposure, whereas others relied on interviews, corporate records, and self-reports to estimate Cd levels. The imprecise measurement of Cd content may have diluted the true connections due to increasing measurement errors. Subgroup analyses revealed that one sort of probable source of variability is type of exposure, according to the findings of this study. Despite this, they employed meta-regression and sensitivity analysis to look into the causes of heterogeneity between studies. Covariates of type of Cd exposure were not identified as sources of heterogeneity in this meta-regression study[6].

Finally, despite using the highest multivariable-adjusted effect estimates in this meta-analysis, they cannot rule out the possibility that the observed increase in the association between Cd exposure and prostate cancer risk among occupational populations is due to unmeasured or residual confounding factors. In both occupational and environmental groups, the results were inconclusive, indicating that additional relevant publications are needed to further investigate this link. In conclusion, high Cd exposure appears to be a risk factor for prostate cancer in occupational populations but not in nonoccupational ones, according to Ju-Kun's meta-analysis. However, due of the high heterogeneity among researches, these findings should be regarded with caution[6].

The study conducted by Chen et al.[7] also have some limitations. Although Egger's regression asymmetry test did not suggest publication bias in the current meta-analysis when pooling studies ≥6, a potential publication bias resulting from the exclusion of articles published in languages other than English or any unpublished result could not be completely ruled out. They also looked at the English abstracts of the excluded papers that were published in other languages (if available), but none of them matched the inclusion criteria. Several experimental researches have established the carcinogenic activity of cadmium on human prostate in vivo and in vitro, in contradiction to epidemiological data. The inaccuracy in assessing cadmium exposure could be one cause for the contradictory data. Recall bias, information bias, and/or misclassification are all possible outcomes of occupational studies that rely on job history rather than objective measurements of cadmium exposure. Because occupational studies did not account for other carcinogens, determining the risk of cadmium exposure alone may be challenging. Furthermore, the link between cadmium exposure and prostate cancer risk may be

masked by the concurrent risk of lung cancer, the most common and lethal malignancy[7].

Our patient is a welder in the welding workshop and exposed to cadmium every day at workplace and has prostate cancer. Those studies use a similar population, workers with cadmium exposure in the workplace. Both studies with systematic review and meta-analysis design showed no significant relationship between cadmium exposure in the workplace and the risk of prostate cancer in workers. Thus, that indicates that the current evidences have not shown sufficient evidence to be able to ensure that cadmium exposure can cause prostate cancer in worker.

Although based on these meta-analysis studies there were no evidence about association between cadmium and prostate cancer, several in vivo and in vitro studies suggest otherwise. In vitro studies have reported malignant transformation of non-tumorigenic human prostate epithelial cells following cadmium exposure. The cells transformed by cadmium demonstrate morphological alterations, anchorage-independent growth in soft agar, and formation of tumors when transplanted into severe combined immune deficient (SCID) mice. In addition, cadmium chloride has been shown to produce premalignant and/or invasive epithelial lesions in the rat ventral prostate when administered in drinking water. Interestingly, patients with prostate cancer appear to have higher levels of cadmium both in the circulation and in prostatic tissues. Aberrant gene expression resulting in increased cell proliferation or blockade of apoptosis may be the mechanisms responsible for cadmium-mediated carcinogenesis[5].

Induction of oxidative stress, suppression of DNA repair, changes in DNA methylation, inhibition of apoptosis proto-oncogene activation, tumor suppressor gene inactivation, and cell adhesion disruption are all involved in the carcinogenesis of Cd exposure. Cd can also have estrogenic effects, which can contribute to the development of prostate cancer. Cd is thought to have estrogenic properties, and estrogen's direct receptor-mediated effects on the prostate are possible. Excessive estrogen exposure has been shown in studies to induce prostate cancer. d has estrogenic effects in human prostate epithelial cells, causing prostate cell growth and activation of the estrogen receptor-a. There was substantial evidence of a link between Cd exposure and the risk of endometrial and breast malignancies. As a result, excessive Cd exposure may raise the risk of prostate cancer[6].

Based on the existing literature, the null association found in these meta-analysis studies should not alter ongoing public health efforts to eliminate cadmium exposure of industrial workers and cadmium contamination in the environment, which may have a negative impact on human health, particularly at high exposure levels. Some recommendation can be applied for practices, such as minimizing the cadmium exposure at workplace by maximizing the use of personal protective equipment properly when working; conducting biological monitoring as an important tool to protect workers from the possible health effects of hazardous industrial chemicals, especially cadmium; and looking for other possible causes of prostate cancer in workers who exposed to cadmium directly. All employees who are or may be exposed to cadmium must also be subjected to a medical surveillance program. An initial examination for each employee is the start of medical surveillance. The evaluation includes not only a medical and employment history, but also biochemical monitoring[9].

Cadmium levels in blood, urine, feces, liver, kidney, hair, and other tissues have been used to assess cadmium exposure. Cadmium levels in whole blood are widely utilized as a diagnostic for current exposure. It also reflects long-term exposures, but it is vulnerable to shift based on current exposure, because a significant portion of blood cadmium, even in long-term exposures, is dependent on a bodily compartment with a very quick turnover rate (half-life 100 days). Cadmium levels in urine are commonly acknowledged as a marker of body burden and kidney accumulation. There is no single biological biomarker for cadmium toxicity that is completely adequate when used alone at this time. The presence of cadmium in diverse biological components can indicate recent or complete cadmium exposure, but the likelihood of harmful effects cannot be predicted with certainty[10]. Based on The American Conference of Governmental Industrial Hygienists (ACGIH), biological

exposure index (BEI) of cadmium in urine is 5 ug/g creatinine and BEI of cadmium in blood is 5 ug/L. Blood monitoring should be preferred during the initial year of exposure and whenever changes in the degree of exposure are suspected[11].

Conclusion

One systematic review and meta-analysis study did not show a significant association statistically between cadmium exposure and prostate cancer in workers. Another study with systematic review and meta-analysis design did show a significant association statistically between cadmium exposure and prostate cancer in workers but there is a high heterogeneity among researches. The current studies do not show sufficient evidence to ensure that cadmium exposure can cause prostate cancer in worker. But public health efforts to minimize negative health effect caused by cadmium exposure of industrial workers and cadmium contamination in the environment still have to be implemented. Further researches are recommended with better quality, larger sample sizes and objective measurement of occupational cadmium exposure.

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