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REVIEW ARTICLE

Air Pollution and Its Association with Cervical Cancer: A Scoping Review

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ABSTRAK

Kanser serviks adalah salah satu kanser wanita yang utama di dunia. Punca kanser serviks adalah 'human papillomavirus' (HPV), namun faktor risiko lain seperti faktor persekitaran turut mempunyai kaitan dengan penyakit ini. Pencemaran udara adalah penyebab utama kematian akibat kanser. Walaupun ia telah lama dikaitkan dengan kanser paru-paru, terdapat kajian-kajian yang telah membuktikan ianya merupakan faktor risiko untuk kanser lain di kalangan manusia, termasuklah kanser serviks. Kajian skop ini bertujuan untuk mengenal pasti dan meneliti literatur sedia ada yang mengkaji perkaitan antara pencemaran udara dengan perkembangan kanser serviks. Protokol 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews' (PRISMA-ScR) telah digunakan untuk membimbing kajian ini. Tujuh penerbitan yang membincangkan pencemaran udara dan kaitannya dengan kanser serviks telah dipilih berdasarkan kriteria tertentu. Huraian tentang punca pencemaran udara, jenis bahan pencemar udara, dan kesan pendedahannya terhadap kejadian kanser serviks telah dibincangkan. Beberapa bahan pencemar udara dikaitkan dengan pelbagai kesan pendedahannya yang berhubungkait dengan kanser serviks, termasuklah perkembangan pra-kanser serviks, serta peningkatan dalam kejadian dan kematian kanser serviks. Kajian ini menekankan perkaitan antara pencemar udara yang bertindak sebagai faktor risiko bersama dalam perkembangan kanser serviks. Dengan mengenalpasti bahan pencemar udara yang mempengaruhi perkembangan kanser serviks, kajian ini seterusnya dapat dijadikan panduan untuk penyelidikan berkaitan mekanisma faktor-faktor risiko pencemar udara yang menyebabkan kanser serviks di masa hadapan.

Kata kunci: bahan pencemar, kanser serviks, pencemaran udara

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ABSTRACT

Cervical cancer is one of the leading women cancer globally. The human papillomavirus (HPV) is the definite cause of cervical cancer, although other risk factors such as environmental variables, can also raise the likelihood of its development. The leading environmental cause of cancer death is air pollution. While it has long been linked to lung cancer, studies show that it is also a risk factor for other human cancers, including cervical cancer. This scoping review aims to identify and review published literature on the association of air pollution with the development of cervical cancer. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) protocol was applied to guide this review. Seven publications discussing air pollution and its association with cervical cancer were included based on specific criteria. The elaboration of the sources of air pollution, types of air pollutants, and the exposure-outcome related to cervical cancer were discussed. Several air pollutants were associated with different exposure outcomes pertaining to cervical cancer, including the development of cervical precancerous lesions, and the increment in cervical cancer incidence and mortality. This review emphasised the association of air pollution that acted as the co-risk factor in the development of cervical cancer. It identified the air pollutants that influenced cervical cancer development thus proposing future research to elucidate the mechanism of possible co-risk factors leading to cervical cancer.

Keywords: air pollution, cervical cancer, pollutant

INTRODUCTION

Cervical cancer is one of the most common and leading women cancer globally. Human papillomavirus (HPV) is the definite cause of the disease, accounting for more than 90% of all occurrences (Arbyn et al. 2014; Cohen et al. 2019; Wan Puteh et al. 2011). Another significant risk factor that causes cervical cancer is tobacco smoking (Fang et al. 2018; Nagelhout et al. 2021; Sugawara et al. 2019). Smokers have a two-fold increased risk of cervical cancer than non-smokers (Roura et al. 2014), while passive smokers were found to have an increased risk of cervical cancer, as indicated by a meta-analysis with a total of 384,995 participants (Su et al. 2018). In reality, the majority of women infected with HPV do not get cancer because the virus normally goes away on its own (Łaniewski et al. 2020). Gunnell et al. (2006) found a synergistic interaction between smoking and HPV infection, which may occur many years before cancer detection. The finding suggested that further exposure to other co-factors such as tobacco smoking, accompanied with or without a weakened immune system,

may increase the likelihood of cervical HPV infection which will progress to cervical cancer (Cohen et al. 2019; Gunnell et al. 2006).

Air pollution is a global concern as its index rises year after year (Li et al. 2019). Humans are exposed to air pollution daily, whether at home, work or in public settings. Exposure to ambient air pollution is just as dangerous as direct tobacco smoke exposure (Pathak 2019), while indoor air pollution carries the risk of cancer to non-smokers as well (Mu et al. 2013). This data suggests that non-smokers exposed to air pollutants in the environment are also at risk of developing cancer. Despite extensive studies on its adverse effects on the environment and human health, air pollution's prevention and control efforts remain debatable (Feng & Liao 2016). Components of air pollutants include carbon monoxide (CO), lead, nitrogen oxides (NO_2), ozone (O_3), particulate matter (PM_{10}, $PM_{2.5}$), sulphur dioxide (SO_2), and other air pollutants such as acrolein, asbestos, benzene, fuel oils, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAH) and total petroleum hydrocarbons. Various air pollutants, such as benzene and PAHs, are cancer-causing substances or carcinogens (IARC 2021; WHO 2013).

According to the International Agency for Research on Cancer (IARC), air pollution is currently the leading environmental cause of cancer death. Air pollution by ambient $PM_{2.5}$ caused 265,267 lung cancer deaths globally in 2017, constituting 14.1% of global lung cancer deaths (Turner et al. 2020). When discussing the link between air pollution and cancer, many would describe its strong affiliation with lung cancer; however, air pollution is also the cause of other human cancers. There is strong evidence that air pollution increases the incidence of bladder cancer and is linked to a higher risk of death from various cancers such as liver, breast, and pancreatic cancer (Loomis et al. 2013; Turner et al. 2020). Recent and ongoing studies on other cancers are too being keenly done, including cervical cancer.

Studies on the association between cervical cancer and air pollution defined the presence of a mix of solid particles and gases that pollute the air and cause hazards to human health and the environment are needed. (Almetwally et al. 2020). While air pollution is a more extensive term that consists of more pollutant particles, findings on the association of general air pollutants with cervical cancer are still vague. Thus, the objective of this study is to review the association of air pollution with cervical cancer based on the existing literature.

MATERIALS AND METHODS

We used Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist to guide this current review (Tricco et al. 2018). Firstly, we started the review by determining the research question using PICO. It is based on three main conceptions: Problem (P), Interest (I), Context (C) and Outcome (O) (Lockwood et al. 2015). In this

review, we included air pollution as the problem (P), the association of air pollution and cervical cancer as the interest (I), and cervical cancer as the context (C) and outcome (O). Based on our PICO, we formulated the research question as 'Is there an association between air pollution and cervical cancer?'

Search Strategy and Selection Criteria

Search strategy and selection criteria include identification and screening of articles (Figure 1). In the identification phase, the literature search was done in four databases i.e. Web of Science (WoS), EBSCOhost, Ovid Medline and Google Scholar by authors SMA and MHJ. Boolean operators and phrase searching techniques were utilised. The search string that was used in WoS, EBSCOhost and Ovid Medline were: (('air pollution' OR 'air pollutant') AND ('cervical cancer' OR 'cervical dysplasia' OR 'cervical neoplasia') AND (factor OR cause OR influence OR determinant)). The Google Scholar platform was then used to search for additional relevant articles. There were also original articles identified in the reference lists of the screened full-text articles that were also searched using this platform. These articles would have been overlooked in the initial search via the three databases; therefore, a snowball search approach was adopted. This approach is frequently used to find pertinent primary studies and reduce the likelihood of missing relevant studies (Badampudi et al. 2015). We then moved on to the screening method by

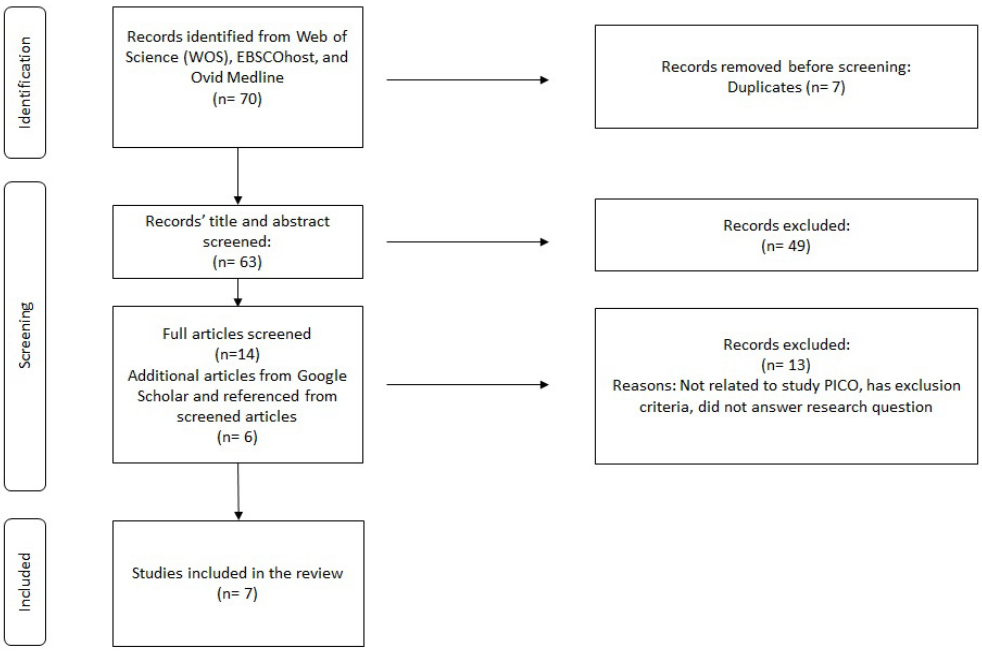

Figure 1: The PRISMA-ScR flow diagram

looking at the inclusion and exclusion criteria that had been predetermined for this review. The inclusion criteria were original articles published in English between the year 2010 to 2021; we excluded conference and meeting abstracts, letters to the editor, working papers, and book chapters. Articles that fulfilled these criteria were chosen for the review. Subsequently, data from the chosen articles was extracted and presented in a table for better viewing. The charted data were then summarised, and we looked for relevant data that may answer the research question of this review.

RESULTS

There were 70 records found during the initial search in the three databases (WoS, EBSCOhost, Ovid Medline), but seven were removed because they were duplicates, leaving 63 articles to be screened by the title and abstract. Through title and abstract screening, 49 articles were excluded, which left 14 to be read in full text. Another six articles were found through the snowballing method and were added for full-text screening. Out of the 20 full-text articles that had been screened, 13 articles were excluded as they were found to be unrelated to the study PICO and did not answer the current research question. We ended up with seven articles chosen and included in our review.

Characteristics of Included Studies

Following the screening phase, we identified seven studies that were looking at the association of air pollution with cervical cancer development (Al-Ahmadi & Al-Zahrani 2013; Lee et al. 2010; Liang et al. 2020; Liu et al. 2020; Raaschou-Nielsen et al. 2011; Scheurer et al. 2014; Yu et al. 2021; Zhang et al. 2022). Table 1 showed the summary of the included studies. For each study, the following data were extracted: first author, year of publication, country, study design, sample size, source of air pollution, type of air pollutants, cervical cancer-related outcome, and study findings. There were two articles from China, and one each from Iran, Denmark, the USA, Arab Saudi, and Taiwan. Three studies used a case-control design, two used cross-sectional, and one used prospective and retrospective cohorts. The sample size ranged from 113 to 228,795 women. Five articles studied outdoor air pollution, while two were on indoor air pollution. The types of pollutants were varied in all studies, likewise for the outcome related to cervical cancer development.

DISCUSSION

Included studies used either outdoor or indoor air pollutants as the sources of possible carcinogens. Five studies focused on the association between outdoor air pollution and cervical cancer, whereas two studied indoor air pollution. Outdoor air pollution was researched through traffic-related pollutants in the studies by Raaschou-Nielsen et al. (2011) and Scheurer et al. (2014). NO_x, SO_2, O_3, CO, hydrocarbons (HC) and particulate matter (PM) make up the majority of

Table 1: Table of evidence

No	Author, year of publication	Country	Study design	Sample size (N)	Source of air pollution	Types of pollutant(s)	Outcome related to cervical cancer	Findings
1	Zhang et al. 2022	Iran	Case-control	133	Outdoor	Lead (Pb)	Cervical intraepithelial neoplasia (CIN)	There is a direct association between Pb accumulation and the presence of CIN.
2	Raaschou-Nielsen et al. 2011	Denmark	Retrospective cohort	54,304	Outdoor (Traffic-related)	Nitrogen oxides (NO_x)	Risk of cervical cancer (incidence rate ratio)	This study found an exposure-response relationship between NOx levels in the home and the risk of cervical cancer, as well as relationships with traffic-related markers.
3	Scheurer et al. 2014	USA	Cross-sectional	736	Outdoor (Traffic-related)	Ambient benzene, diesel particulate matter (DPM), and polycyclic aromatic hydrocarbons (PAHs)	Cervical dysplasia	The presence of benzene, DPM, and PAH in the environment has been linked to cervical dysplasia. The combined effect of exposure to high levels of several hazardous air pollutants (HAPs) is positively associated with the prevalence of cervical dysplasia.
4	Yu et al. 2021	China	Case-control	35,989	Outdoor	$PM_{2.5}$, CO, O_3, SO_2	Risk of gynecologic cancer – including cervical cancer	The study suggests that exposure to more significant air pollution increases the risk of gynecologic cancer, including cervical cancer.
5.	Al Ahmadi et al. 2013	Arab Saudi	Cross-sectional	45,532	Outdoor	NO_2	Cervical cancer incidences	NO_2 concentration and lung and breast cancer occurrences had high coefficients of determination, followed by prostate, bladder, cervical, and ovarian cancers.
6.	Lee et al. 2010	Taiwan	Case-control	324	Indoor	Cooking oil fumes	Development of cervical precancerous lesions	Indoor exposure to cooking fumes from heated oil has been linked to the late development of cervical precancerous lesions.
7.	Liu et al. 2020	China	Prospective cohort	228,795	Indoor	Indoor solid fuels for heating	Cervical cancer mortality	The use of solid fuels for heating in the home was associated with a greater risk of cervical cancer mortality. The significance of the association grew more robust over time, and it was influenced by age and menopause status.

outdoor air pollutants. These pollutants are generated primarily by road vehicles in urban areas, but other sources like power plants, industrial boilers, incinerators, petrochemical plants, aircraft, and ships contribute. Outdoor air pollutants are also a contributor to indoor pollution, affecting indoor air quality through mechanical aeration, natural ventilation, and infiltration (Fung et al. 2014; Leung 2015).

Indoor air pollutants include PM, SO_2, NO_2, CO, O_3, VOCs, radon, and biological air pollutants (gasses and airborne particulates such as pets' dander, dust from human skin flakes and decomposed hair, and dust mites). These pollutants are mainly formed from cooking stoves, fireplaces, building materials, and even outdoor air (Leung 2015). Two of the included studies by Lee et al. (2010) and Liu et al. (2020) used indoor air pollution in cooking oil fumes and heated solid fuels as the source of air pollutants.

In the included studies, two articles focused on NO_x (Al-Ahmadi & Al-Zahrani 2013; Raaschou-Nielsen et al. 2011), one study on lead (Zhang et al. 2021), and one study on ambient benzene, diesel particulate matter (DPM), and PAHs (Scheurer et al. 2014). One article studied several different types of pollutants, including PM ($PM_{2.5}$ and PM_{10}), CO, SO_2 and O_3 (Liang et al. 2020; Yu et al. 2021). Lee et al. (2010) studied exposure to cooking oil fumes, which have been identified to contain PAH compounds (Chiang et al. 1999; Lee et al. 2010). Liu et al. (2020) investigated the indoor combustion of solid fuels such as coal and wood heating, which are known to emit high amounts of carcinogens. CO, SO_2, NO_2, alkanes, alkenes, aromatics, and PAHs are the principal chemical constituents of solid fuel smoke (IARC 2010). Burning wood in an unventilated stove produces more PM than coal, while coal combustion produces a higher concentration of SO_2 compared to wood (Hendryx et al. 2020; Hu et al. 2014).

Among these studied air pollutants, benzene, DPM, PAHs, and indoor emissions from coal combustion are classified as Group 1, which is carcinogenic to humans (IARC 2021). Cooking oil emissions from high-temperature frying, which include several PAHs and PAN, have been classified as carcinogens in Group 2A, which means there is sufficient evidence that they are probably carcinogenic to humans. Lead is in Group 2B, indicating there is sufficient evidence that it is possibly carcinogenic to humans. CO, NO_2, and SO_2 are in Group 3, which are not classifiable as carcinogenic to humans (IARC 2021).

For cervical cancer to happen, it began with cellular changes over the transformation zone of the cervix (the place where two cell types of the cervix, glandular and squamous cells, met). Cells in the transformation zone do not become cancerous instantly. Instead, precancerous lesions will develop from one phase to another over ten to 30 years (Cohen et al. 2019; Ghim et al. 2002). Precancerous lesions, also known as cervical intraepithelial neoplasia (CIN), squamous intraepithelial lesion (SIL), or dysplasia, occur when the normal cells of the cervix develop

atypical changes over time (American Cancer Society 2020). From here, we consider that any changes in cervical cancer development are classed as an outcome that leads to invasive cervical cancer.

For the current review, not all included studies convey their findings directly to the incidence of cervical cancer. Three studies were looking at the development of precancerous lesions (Lee et al. 2010; Scheurer et al. 2014; Zhang et al. 2022), three on cervical cancer risk and incidences (Al-Ahmadi & Al-Zahrani 2013; Raaschou-Nielsen et al. 2011; Yu et al. 2021), and one studied on the association of air pollution to cervical cancer mortality (Liu et al. 2020). Among the articles that studied the development of precancerous lesions, Lee et al. (2010) identified the dysplasia changes by using Pap smear screening and biopsy examination methods. Scheurer et al. (2014) used secondary data from an earlier trial that identified women with CIN through Pap smear testing, HPV testing, colposcopy, and biopsy examination (Pham et al. 2012). Zhang et al. (2022) also used secondary data from the earlier published article that had performed histopathological analyses to identify CIN-positive women (Sohrabi et al. 2014).

Three different studies found the association of various air pollutants to CIN's development. Firstly, Lee et al. (2010) found the association through indoor air pollution exposure in the form of cooking oil fumes, and Scheurer et al. (2014) found the same outcome through exposure to ambient benzene, DPM and PAHs. On the other hand, Zhang et al. (2022) studied the association through exposure to lead, another toxic air pollutant agent (Lee et al. 2010; Scheurer et al. 2014; Zhang et al. 2022). Women exposed to heated cooking oil fumes with insufficient gas ventilation were more likely to develop CIN, corresponding to prior research findings indicating cooking oil fumes components can be distributed and metabolised into the cervix. Subsequently, it causes oxidative DNA damage, which causes carcinogenic effects (Cherng et al. 2002; Pan et al. 2008).

Meanwhile, in the workplace setting, occupational exposure to diesel engine fumes leads to an increased risk of cervical cancer, subjected to a dose-response relationship (Boffetta et al. 2001). Studies on lead exposure found that the accumulation of lead in organs leads to DNA and chromosomal damages; its genotoxicity element leads to impairment of the DNA repair system in the cervix (García-Lestón et al. 2010; Sanders et al. 2015). The increased lead level in pathological CIN tissues confirms the possibility of lead accumulation in cervical tissues after being exposed (Rzymski et al. 2016).

Raaschou-Nielsen et al. (2011) discovered a link between cervical cancer incidence and NO_x exposure, further verified by Al-Ahmadi & Al-Zahrani in 2013 by looking at the NO_2 exposure in urban and industrial localities (Al-Ahmadi & Al-Zahrani 2013; Raaschou-Nielsen et al. 2011). However, neither study addressed the likely mechanism of cervical cancer formation as a result of NO_2 exposure.

In the case of lung cancer, NO_2 exposure increases the inflammatory markers in lung tissues, leading to reduced lung function (Knibbs et al. 2018). Another research study that involved healthy and non-smoking adults supported these findings on the same exposure (Dauchet et al. 2018). Further research is indeed needed to determine the mechanism behind NO_2 exposure and the incidence of cervical cancer.

Yu et al. (2021) studied the relation between $PM_{2.5}$, CO, O_3 and SO_2 exposure and gynecologic cancer risk, including cervical cancer risk. After adjusting confounders, the study discovered an association between these air pollutants and cervical cancer (Yu et al. 2021). Prolonged exposure to hazardous settings like cigarette smoke, can cause oxidative stress in cervical cancer cells, resulting in DNA damage (Moktar et al. 2011). Despite these findings, the role of environmental elements in the pathogenesis of cervical cancer, or vulnerability to it, is still uncertain. In fact, in a review article using a classical twin design, the authors found a possible association between genetic cause and cervical cancer pathogenesis; however unable to relate it to any environmental factors (Moore et al. 2012).

This review potentially benefits future research on cervical cancer's environmental risk factors, especially on different air pollutants. Most of the included studies applied large numbers of sample sizes. The use of cohort and case-control studies could show the causal relationship between air pollutants exposure and the development of cervical cancer. There were, however, some limitations to this review. To begin with, we only chose English papers; there were likely to be research findings from non-English articles that were not included. Another drawback is that while this study looked at a range of outcomes, not all of them (for example, cervical dysplasia) were proven to be the definitive causes of invasive cervical cancer incidence or mortality.

CONCLUSION

Cervical cancer is linked to chronic HPV infection as the leading cause of the disease; however, many co-factors could aggravate the development of the disease. This review showed that there were associations between air pollution and cervical cancer development. Exposure to different air pollutants was related to various exposure outcomes of cervical cancer; however, its definite mechanism is still unclear. Future studies on the pathways of this mechanism are needed for a better understanding of the association between air pollution and cervical cancer.

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