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Relationship between environmental factors and cancer: a systematic review on environmental carcinogens and lung cancer

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Abstract

The risk of lung cancer continues to elevate for both smokers and never-smokers. With the increasing morbidities and mortalities related to lung cancer, there is much interest on establishing other confounding factors that lead to lung cancer, other than smoking which is the most common cause. Some of the environmental factors have been identified as potential lung cancer causes. Therefore, the aim of this systematic review is to assess the relationship of environmental factors and lung cancer incidences by investigating various carcinogenic risks exposures that predispose an individual to lung cancer. The objective of this systematic review is thus to assess the evidence of relationship between environmental carcinogens and lung cancer incidence by systematically reviewing relevant studies. A standard criterion for the review methodology was formulated to guide the review process and data extraction. Online databases like PubMed, MEDLINE, Scopus (EMBASE), Google Scholar, Web of Science, and CINAHL were systematically searched for articles published between 2000 and 2021 that explored potential environmental carcinogens that were believed to expose occupational workers and individuals within the environment with lung cancer risks. 25 studies were eligible based on the selection criteria, and were finally included in the systematic review among which four were case-control studies, seven were cohorts, five was prospective, four were previous systematic reviews and four were systematic analysis. Chemical exposures like pesticides were analyzed for their carcinogenesis. Air pollution was also discussed with particulate and coal being the core of evidence of association with lung cancer. Second hand smoke, Asbestos, metal compounds like copper, PVC

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dust particles and ionizing radiations also provided evidence of environmental carcinogenesis associating to lung cancer cases.

Background

Lung cancer is among the most prevalent and deadliest chronic non-communicable disease globally. It's approximated that over 90,000 deaths are associated with cancer, with over 12,000 new cases reported annually worldwide.[1] Generally, cancer is the primary cause of death for most young and middle-aged populations aged between 20 and 64.[2] Research has it that the mortalities and morbidities associated with cancer are primarily due to the changing exposure risk factors. As perceived by Malki et al., the cancerous process is usually a result of disturbance of the cell function, majorly due to the accumulated genetic and epigenetic alterations in the cell chromosomes or molecules causing genetic instability.[3] In most instances, scholars agree that assessing the validity of specific etiological factors associated with cancer becomes difficult. However, it's unanimously concluded that almost all forms of cancer associate various risk factors not limited to environmental, endogenous, and exogenous factors and individual factors like genetic predisposition.[4] According to Anand and colleagues, close to 35% of the global death toll related to cancer is normally due to potential risk factors linked to lifestyle behaviors like smoking, alcoholism, exposure to radiation, dietary factors, and hormone therapy.[5]

Precisely for this review, the main focus is on exploring lung cancer. Most of the studies postulate that lung cancer is the most common malignant tumor globally, with its incidence increase rate at 2% percent every year worldwide.[6] For 2018 alone, the global estimate of the lung cancer incidence stood at 2.1 million for new cases and was accountable for an averagely of 18.4 % of all the global cancer mortalities.[7] In such a revelation, it's indisputable that lung cancer is among the deadliest form of cancer globally. For decades, smoking has been heavily presumed to be the major cause of lung cancer. However, the researcher has new concerns since smoking rates are declining, yet the incidences and mortalities of lung cancer continue to rise. This has triggered a shift from the perception that tobacco smoking is the primary vital risk factor for lung cancer, and interests have developed towards other environmental carcinogens. Considered one of the most environmentally-impacted malignancies, researchers assert that lung cancer can also result from physical and chemical environmental carcinogens.[8] For example, exposure to a compound mixture in a particulate matter (PM) is a potential carcinogenic factor propelling the development of lung cancer. Besides, other carcinogenic compounds like radon, asbestos, arsenic, silica, and coal are freely found in the environment or at the workplace, strongly associated with the escalating new incidence of lung cancer mortalities and morbidities, especially for the nonsmoking population. Accordingly, scholars argue that exposure to these compounds (asbestos, carbon, radon, nickel, etc.) is likely to induce a wider spreading of epigenetic and genetic alterations due to their strong carcinogenicity, independent of a person's smoking status.[9] The discoveries have recently been ascertained that 53 % of women and 15 % of women diagnosed with lung cancer are typically nonsmokers.[10] Hence, it has triggered more interest in lung cancer problems for both smokers and nonsmokers, with the view that environmental carcinogens are heavily taking shape and contributing to most lung cancer-related mortalities and mortifies, amid the decline of smoking rates. Therefore, this systematic review evaluates the relationship between environmental factors and cancer incidence by exploring various environmental carcinogens associated with the development of lung cancer.

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Methods

The present study was a systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al.). This review focused on assessing the relationship between environmental factors and cancer development by investigating relevant evidence on how environmental carcinogens propagated the incidence of lung cancer for both smoking and non-smoking population.

Search strategy

A systematic search was conducted in the critical electronic databases to establish the relevant studies that had full-text discussions of various carcinogenic compounds from either open or work-related environments that led to lung cancer among the respective populations. Valid online databases like PubMed, MEDLINE, Scopus (EMBASE), Google Scholar, Web of Science, and CINAHL were systematically searched for articles published between 2000 and 2021 that discussed the topic of interest. Key terms and free text words were used to establish relevant studies for inclusion. However, a hand search was not done due to time limits, and only the articles written in English were considered for inclusion. Some of the key terms used included "lung cancer, carcinogens, environmental factors, asbestos, radon, carcinogenic, cancer."

Eligibility: Inclusion and exclusion criteria

The inclusion criteria were based on the following characteristics;
Any English study published between 2000 and 2021 discusses environmental carcinogens and factors exposed to workers or non-workers that could lead to lung cancer carcinogenesis for smokers or never smokers. Articles that included cohorts, case-control, experimental, analysis, and systematic reviews were all eligible for inclusions. Studies that identified risks associated with using certain elements that potentially contained the environmental carcinogens were also included.
Studies were excluded if they were non-English articles, republished articles with similar contents and or results, or those with incomplete data. Studies were also excluded if they did not discuss the relevant topic of interest. Reports, opinion articles, dissertations were also excluded from this study.

Study selection

The selection of included studies was based on a two-step approach of title and abstract screening then a full-text analysis afterward. Two reviewers (GD and TR) independently selected all eligible studies by first screening their title and abstract for suitability based on the inclusion and exclusion criteria. After screening for the study titles and abstracts, all the selected articles were then examined on full-text analysis independently to ascertain their eligibility and suitability for inclusion. Any discrepancies and conflicting views or understandings between these two reviewers relating to selecting any included article were discussed among them to a consensus. In cases where a consensus was not possible, a third reviewer (JF) was consulted. An agreement value for screening the included studies was assessed and determined by Kappa scores. Finally, the data from the source articles were extracted and appraised by a third independent reviewer (JF) and then verified by their scientific advisory expert.

Data Quality Assessment

The quality of the studies was determined by evaluating their adherence to the (GRADE) approach. The framework focused on reporting how the studies were designed, analyzed, and interpreted. The checklist for the systematic reviewers focused on their relevance, validity, and appropriateness of methodology, quality of evidence from their results, and quality of reporting.

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Data collection and synthesis

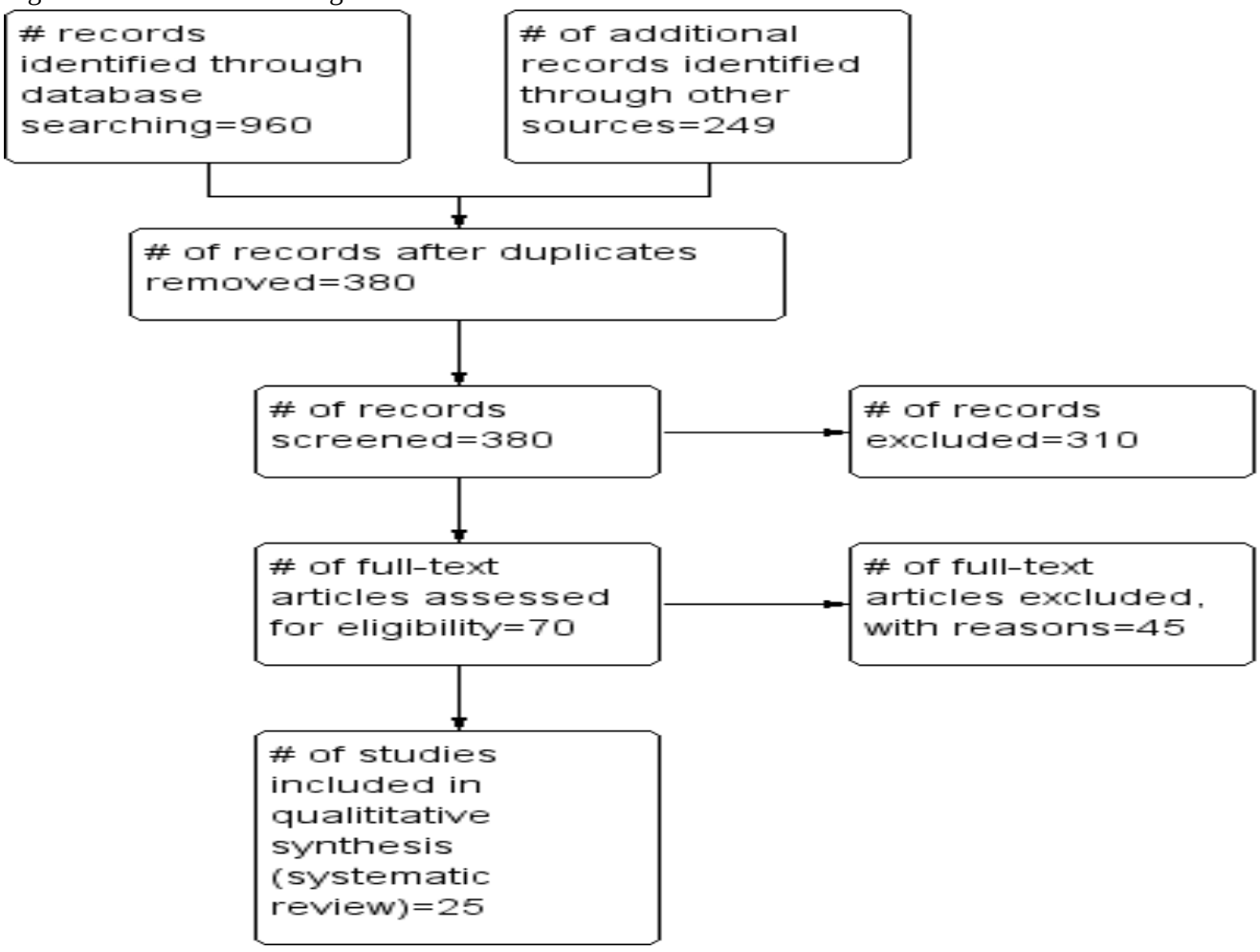
Relevant data were collected using a specially designed excel sheet that contained all the key study aspects. In adherence to Cochrane recommendation, a standardized pre-piloted data extraction form was designed and used to collect the necessary data from the eligible studies and recorded by the initial reviewers (GD and TR). It was further cross-checked by the third reviewer (JF) for the accuracy and validity of the obtained data. In the event of missing information, there were attempts to contact primary authors, but all the included studies had relevant information for this case. The following information was retrieved from the included studies and analyzed; first author, publication year, study design, cohort location, cohort size, follow-up duration, exposure subject, outcome results, measurement and conclusion, and evidence level.

Results

Search outcome

Indexes and key terms searched a total of 1209 articles through a combined electronic search of the databases including PubMed, MEDLINE, Scopus (EMBASE), Google Scholar, Web of Science, and CINAHL. After exclusion based on abstracts and titles, a full-text analysis of 70 studies was done for possible inclusion. A total of 25 studies and two studies remained for quantitative and qualitative analysis, respectively. Figure 1 summarizes the PRISMA flow chart of the search outcome of included studies.

Figure 1. PRISMA Flow Diagram



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Characteristics of the included studies

The key characteristics of the studies included are summarized in table 1. Among the included studies majority were cohort studies (n=7), prospective studies (n=5), case-control (n=4) cohort/systematic analysis (n=4) and systematic reviews (n=4). All the included articles for systematic reviews were quantitative. Cumulatively, the estimated cohort size for the case-control and cohort studies included was 672493 participants. The publication year of the included studies ranged from 2000 to 2021, with the majority of the studies being published between 2010 and 2021 (68 %). The cohort location was also spread across the Asian and American regions. However, there were no sources from the African or sub-Saharan region. Most of the studies were from United States (n=7), and the rest sourced from China (n=4), India (n=2), Japan (n=2), Spain (n=1), Germany (n=1), Italy (n=1), Taiwan (n=1), and Sweden (n=1). The exposure subjects were categorized mainly as chemical compounds, air pollutants, second-hand smoke, metal compounds, asbestos, vinyl chloride and polymers, ionizing radiation (radon), red meat mutagens, and bisphenol.

For the chemical compounds, the included studies discussed potential carcinogens, including tetrachlorodibenzo-p-dioxin,[11] pesticide (dieldrin, parathion and pendimethalin),[12] dioxin chemical[13] and crystalline silica.[14,15] For the environmental carcinogens within the air pollutants, included studies touched on the indoor particulate matter[16] and household coal use.[17,18] With regards to second-hand smoke exposures, the subjects presented by studies were active and passive smoking,[19],[20,21] and cigarette smoking.[22] The included study presented the following as potential carcinogens; arsenic dust,[23] Chromium particles[24] , and nickel.[25] On the other hand, asbestos exposure subjects were discussed and analyzed by (Kishimoto et al.;[26] and Jarvholm.[27] The vinyl chloride and polymers were also discussed as potential lung cancer risk carcinogens[28] and subsequently styrene that also had carcinogenic elements.[29] Studies also discussed ionizing radiation as a carcinogenic risk factor for lung cancer development and thus quoted radon as a major subject for lung cancer incidence. [30,31,32] Finally, the other carcinogenic exposure subjects uncovered from the studies were red meat mutagens (Yang) and BPA (Li).[33,34]

The level of evidence was also given for each included study based on its methodological quality, as shown in table 2.

Table 2. Level of Evidence of Studies.

Evidence Level	**Description**
I	Evidence obtained from a systematic review of all relevant randomized controlled trials.
II	Evidence obtained from at least one properly deigned randomized controlled trial.
III.1	Evidence obtained from well-designed controlled trials, not randomized.
III.2	Evidence obtained from comparative studies such as cohort studies, case control studies preferably from more than one center or research group.
III.3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments.
IV	Evidence from opinion of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Risk of bias assessment

Two investigators independently assessed the quality of each included study, and the bias risk was assessed through the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) and summarized using Review Manager Software 5.4 version. The overall risk of bias is

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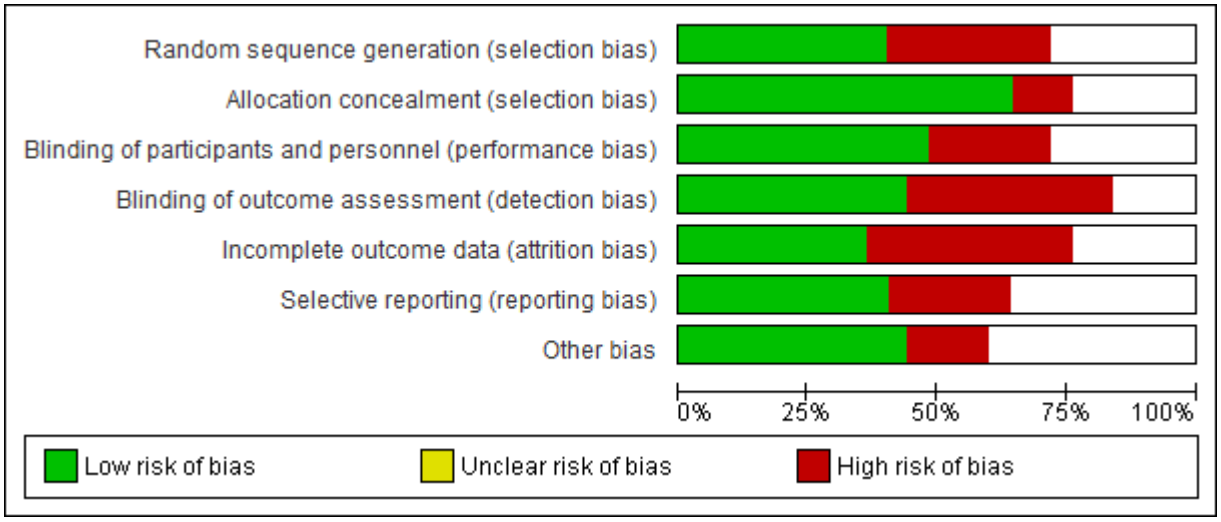
summarized in the risk of bias graph. The overall methodological quality of the included studies was moderate. This is because most of the participants in the studies were not blinded. Most of the studies also showed a high risk of bias in at least two categories.

Figure 2. Risk of bias graph



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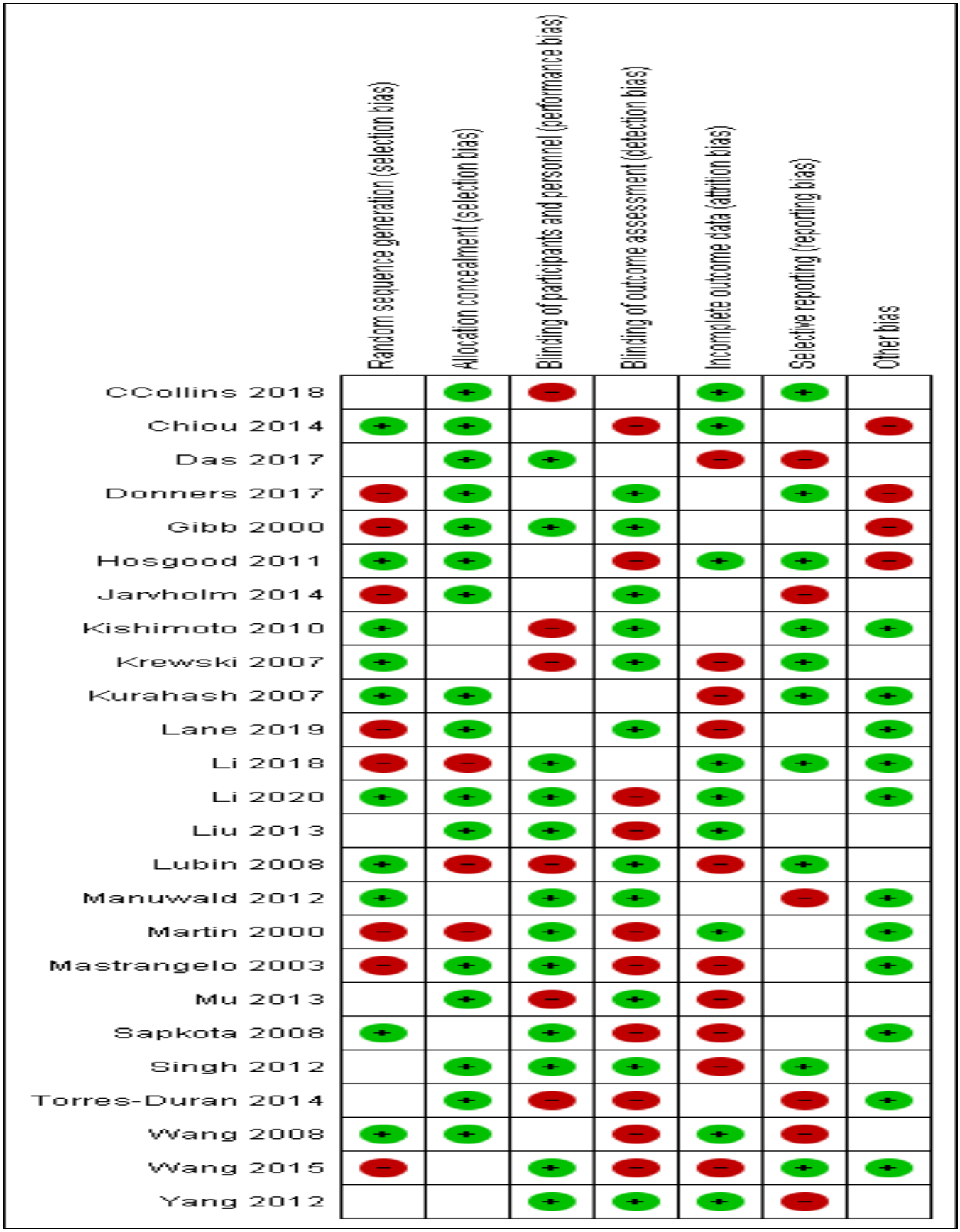

Figure 3. Risk of Bias Summary

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Thematic Analysis of Environmental Carcinogens and Lung Cancer Risk

Chemical exposure

There is strong evidence supporting that exposure to chemical components in pesticides or aflatoxins can cause cancer triggering factors within the environment. Environmental contaminant like TCDD (2, 3, 7, 8-tetrachlorodibenzo-p-dioxin) is known to induce chronic and acute toxicity for individuals exposed and further thymic atrophy effects and alteration T cell differentiation. In the study by Singh et al., [11] findings showed that prenatal exposure to TCDD mediated changes in the microRNAs by altering them and thus propagating high toxicity levels that lead to lung cancer. On the other hand, Bonner et al.[12] evaluated occupational pesticides (dieldrin, parathion, and pendimethalin) association with lung cancer risks. The prospective cohort study comprised 57,310 pesticide users followed up for over ten years, and the results exhibited higher lung cancer risk rations in the order use of pendimethalin (1.50; 95% CI: 0.98, 2.31), dieldrin (1.93; 95% CI: 0.70, 5.30), and chlorimuron ethyl (1.74; 95% CI: 1.02, 2.96). These results provided evidence of a carcinogenic association between dieldrin, pendimethalin, and parathion use with the escalated risks of lung cancer incidences. In another similar evaluation of chemical exposure, Manuwald et al.[13] conducted a cohort study of 1191 men and 398 women through a follow-up duration of 23 years. Based on the findings, the authors realized an increase in overall cancer-associated mortalities due to long-term exposure to dioxin chemicals, which signified another strong evidence for the carcinogenic effects of dioxin compounds towards lung cancer-associated mortalities. Moreover, crystalline silica was investigated for its possible association with the development of lung cancer.[14] Crystalline silica is one of the common particulate matter pollutants in the living environment, especially in metal and coal mining industries or even the clay or construction industries. Based on the results, categorical analysis confirmed an increasing hazard ratio with increasing quartiles of cumulative silica exposure (hazard ratios = 1.26, 1.54, 1.68, and 1.70, respectively). Unlike the unexposed group, the silica exposed workers exhibited an overall 44% (95% confidence interval (CI): 18%, 76%) increase in lung cancer development risk. For the factory workers exposed from 20 to 65 years to silica 0.1 mg/m3, there was an estimated excess risk of lung cancer incidence of 0.51%. Suggestively, these findings confirmed that crystalline silica was a potential carcinogenic factor for lung cancer prevalence. In another related study, Martin et al.[15] performed a case-control survey in a cohort of active workers. Their analysis showed significant increase of lung cancer risks linked to exposure of crystalline silica (highest exposure class: odds ratio = 2.27; 95% confidence interval: 1.10, 4.68) and creosotes (highest exposure level: odds ratio = 2.14; 95% confidence interval: 1.06, 4.31).[15]

Outdoor and indoor air pollution

Various research studies found an association between air pollution and lung cancer development due to various carcinogenic compounds released into the environment. In a case-control study of a particular Chinese cohort, the indoor particulate matter was evaluated for its association with lung cancer incidences among non-smoking Chinese women. Inclusive of the 399 lung cancer cases and 466 controls, the indoor particulate matter emerged strongly associated with lung cancer development for nonsmokers.[16] Household coal use was another considerable form of air pollution perceived to be carcinogenic. A systematic review of selective case-control studies investigated coal use relation with lung cancer among the included studies. With a total of 10142 cases and 13416 controls, the results showed that household coal use is associated with risks of lung cancer incidences and thus strengthened the evidence on the carcinogenic impacts of coal use.[17] Similarly, a multicentric case-control study by Sapkota et al. identified coal use as a potential environmental carcinogen.[18] Compared with coal non-users, the authors realized that individuals using coal experienced increased lung cancer incidence risks [odds ratio (OR) 3.76, 95% confidence interval (CI) 1.64–8.63].

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Second-hand smoke

Tobacco smoke or active smoking, and second-hand smoke are known human-environmental carcinogens associated with lung cancer incidences in human beings for a long time. For the included studies, Wang et al.[19] conducted a prospective cohort study to evaluate the association of active and passive smoking with lung cancer incidence. On their results, the lung cancer incidence was significantly higher for the current smokers hazard ratio (HR) 13.44, 95% confidence interval (CI) 10.80–16.75] and former smokers (FS; HR 4.20, 95% CI 3.48–5.08). The authors remarked that active smoking substantially increased lung cancer incidence, and current smokers experienced higher risks than former smokers. For nonsmokers, prolonged passive smoking is positively associated with lung cancer development. On a similar note, a prospective study of 279214 men and 184623 women also evaluated the associated risks between cigarette smoking and lung carcinoma.[22] The result showed that lung carcinoma developed in 4097 men and 2237 women. As showed in their results, incidence rates were 20.3 per 100,000 person-years (95% CI: 16.3–24.3) in never-smoking men (99 carcinomas) and 25.3, 95% CI: 21.3–29.3 in never-smoking women (152 carcinomas). Ideally, it provided evidence that smoking was positively associated with lung carcinoma risk increase for both men and women. Nevertheless, the prospective study of the Japanese cohort was done by Kurahashi et al.[20] on passive smoking and lung cancer. As per the results, compared to the women married to non-smoking husbands, those who were exposed to passive smoking exhibited a hazard ratio (HR) [95% confidence interval (CI)] for all lung cancer incidence of 1.34 (95% CI 0.81–2.21). The findings confirm that passive smoking is a carcinogenic risk factor for lung cancer incidences, especially for nonsmokers. Another prospective study confirmed the association between lung cancer and second-hand smoke, as nonsmokers exhibited an increasing trend of lung cancer development than smokers themselves.[21]

Metal compounds

Arsenic compounds are classified as occupational and environmental lung cancer carcinogens existing as arsenates when workers are exposed to dust particles from gold, lead, and copper. The other carcinogenic metal elements are nickel or chromium metals. A cohort study was performed at Montana Copper smelter to investigate the relationship between respiratory lung cancer deaths and inhaled arsenic exposure for the copper smelters, alongside the varied impact on arsenic concentration levels.[23] The findings showed a consistent linear relationship between respiratory cancer and arsenic exposure, suggesting a positive association between lung cancer mortalities and exposure to arsenic carcinogens. The increase in arsenic concentration cumulatively increased the risk of lung cancer incidences and mortalities. Gibbet al.[24,] on the other hand, assessed lung cancer incidence in chromium chemical production sites (trivalent and hexavalent carcinogenic compounds). A cohort of 2357 workers in the chromate production plant showed a positive dose-response relationship between hexavalent chromium exposure and lung cancer. However, the study found no association between trivalent chromium exposure and lung cancer. The formerly provided evidence of the association between lung cancer risks and hexavalent chromium exposure, not confounded by smoking. Another cohort study was performed in Taiwan, which examined whether nickel exposure potentially increased the actions of P53 mutations through the inhibition of DNA repair by nickel compounds.[25] Nickel exposure levels in p53 mutant patients were substantially higher than those in p53 wild-type patients. The odds ratio (OR) for p53 mutation risk of lifetime nonsmokers in the high-nickel exposure group was greater than that in the low-nickel subgroup. The results thus suggested a significant relationship of high nickel exposure with an increased risk of lung cancer development.

Asbestos

Exposure to occupational asbestos is argued to be carcinogenic and thus highly associated with the development of lung cancer. One further investigated the relationship between lung cancer and asbestos exposure in a Japanese cohort. According to the findings, close to 62% of those with

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asbestos-related cancers had more than ten years of industrial exposure to asbestos through their working environment.[26] Again, for the autopsied patients who exhibited asbestos-related cancers, 62% contained more than 5000 particles per gram, unlike non-asbestos-related cancer cases with less than 5000 per gram in their lungs. This study strengthened the association between lung cancer incidence and asbestos carcinogenic components. In another investigation, the study by Jarvholm and Astrom on lung cancer risks on asbestos exposure discovered a significant relation. Based on the study results, the highly exposed workers to asbestos consequently experienced increased lung cancer incidence risks (relative risks =1.74; 95% confidence interval, 1.25 to 2.41).[27]

Vinyl chloride and polymers

Exposure to polyvinyl chloride and vinyl chloride dust is also a potential carcinogenic risk for lung cancer within the environment. However, researchers attribute that the exposure levels tend to be quite low. A nested case-referent cohort study was performed in an Italian-based cohort by Mastrangelo et al. to estimate the lung cancer risks on polyvinyl chloride and or vinyl chloride monomer. In the result findings, those exposed to high levels of respirable polyvinyl chloride particles had an increased odds ratio risk of lung cancer by 20% ((OR = 1.2003; 95% CI 1.0772 to 1.3469; p = 0.0010).[28] This cohort study provided evidence that exposure to vinyl chloride monomer or polyvinyl chloride dust was carcinogenic, potentially increasing the risk of lung cancer incidence. Styrene (C6H5CH=CH2) is also another vital chemical in the manufacture of polymers and copolymers, and its exposure association with lung cancer risks is a major concern. Collins and Delzell performed a systematic review of epidemiological studies to this effect. Based on the results, the meta-relative risk of the analysed epidemiological studies stood at 1.14 (95% confidence interval (CI), 0.91–1.43) for NHL, 1.00 (95% CI, 0.80–1.26) for multiple myeloma, 0.98 (95% CI, 0.87–1.09) for all leukemia, 1.03 (95% CI, 0.92–1.15) for esophageal cancer, 1.02 (95% CI, 0.93–1.12) for pancreatic cancer, 1.09 (95% CI, 0.95–1.24) for lung cancer and 1.10 (95% CI, 0.99–1.22) for kidney cancer.[29] The research findings showed a shred of epidemiologic evidence on the possible carcinogenicity of styrene towards the occurrence of lung cancer.

Ionizing radiation

Unlike natural radiation that comes from naturally occurring radioactive materials, ionizing radiation comes from radon, gamma rays, and x-rays. Radon is a uranium degradation by-product that propagates lung cancer development, mostly in uranium mining workplaces. Radon produces alpha particles and potentially damages the DNA in the respiratory epithelial cells. Thus, radon exposure is associated with increased lung cancer incidence due to its carcinogenicity. One of the included studies investigated radon exposure to the never-smokers population as a potential factor for lung cancer incidence for the Galicia population.[30] In a data set 0f 192 cases and 329 controls, the investigators observed an odds ratio of 2.42 (95% CI 1.45–4.06) for individuals exposed to radon components, and the risk was even more to those who were further exposed to environmental tobacco smoke. Radon exposure was higher for the group cases than controls, and 48% of cases had residential radon exposure >200 Bq·m−3 compared with 29.4% for the controls. In line with the above, another study by Krewski et al.[31] performed a combined systematic analysis of data pooled from the case-control studies of the North American cohort investigating the association of residual radon and lung cancer. In the data set that included 4081 cases and 5281 controls, the results showed that the odds ratio (OR) trend was consistent with linearity (p = .10), and the excess OR (EOR) was 0.10 per Bq/m3 with 95% confidence limits (−0.01, 0.26). These results provided thus provided conclusive evidence on the association between residual radon exposure and lung cancer development. A statistically significant relationship between lung cancer mortality and radon exposure was established in another joint cohort study by Lane and colleagues for the French, Czech, and Canadian uranium miners.[32] This study also

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contributed solid evidence for the increased lung cancer risks and mortality for even the low occupational radon exposure.

Red meat mutagens exposure

One of the included studies also discussed red meat mutagen exposure as a potential carcinogenic risk for the development of lung cancer. A study by Yang and colleagues involving 23 case-control and 11 cohort studies for the non-smoking population showed evidence of an association between red meat mutagens and lung cancer incidence. Based on the findings, the relative risk (RR) of lung cancer incidence for high intake of meat was at 1.35 (95% confidence intervals (CI) of 1.08 to 1.69) and 1.34 (95% CI 1.18–1.52) for red meat.[33] The finding suggested that the relationship between meat consumption and lung cancer development depended on the type of meat consumed, and red meat arguably increased the risk of lung cancer incidences by about 35%. The former association is due to saturated fats, heme iron compounds, and potent mutagens. Significantly, the likes of other compounds like heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs), and N-nitroso compounds (NOCs) also play a vital role in the development of lung cancer as a result of red meat consumption.

Bisphenol A exposure

Bisphenol A (BPA) was also investigated for its potential relationship with the occurrence of lung cancer in exposed individuals.[34] Ideally, BPA is an endocrine disruptor believed to promote invasion and mitigation of the lung cancer cells. According to the results, the creatinine-adjusted BPA levels were higher for the exposed non-small cell lung cancer group than the controlled population. Therefore, there was a significant positive association between the exposure levels of BPA and the incidence of non-small cell lung cancer (OR = 1.91, 95%CI: 1.39–2.62).[34] Moreover, through interaction analysis, bisphenol A exposure exhibited a multiplicative interaction with the rs2046210 in estrogen receptor, leading to the incidence of non-small cell lung cancer (NSCLC). Therefore, from a general perspective, the study confirmed that exposure to bisphenol components was carcinogenic to develop non-small cell lung cancer for the exposed population.

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Study	Year	Cohort Location	Study design/ type	Cohort size	Follow up duration	Exposure Subject	Results on Mortality rates/& Lung Cancer incidence rates	Outcome measures & conclusions	Evidence Quality
Mu et al.	2013	Urban Chinese cohort	Case-control study	865 participants; 399 cases and 466 controls, of which 164 cases and 218 controls were female non-smokers	Not mentioned	Indoor particulate matter & indoor air pollution	Subjects who only used solid fuel for cooking (coal, honeycomb, and wood) had a 4-fold risk of lung cancer. Solid fuel for heating, including coal furnaces, coke stoves and heated brick beds, was also associated with higher risk of lung cancer.	A strong relationship was found between solid fuel usage for cooking and heating. The study concluded that indoor air pollution played a critical role in the development of lung cancer among non-smoking females. Indoor PM levels were associated with pollutants exposure and might serve as a good measurement of indoor air quality	III.2

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Singh et al.	2012	Not mentioned	Experimental cohort study	608 experimental mice	Not mentioned	TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin); the pathophysiological role of MicroRNAs (miRs)	Of the 608 mouse miRs screened, 78 miRs were altered more than 1.5-fold and 28 miRs were changed more than 2-fold in fetal thymocytes post-TCDD exposure when compared to vehicle controls	The study revealed that TCDD-mediated alterations in miR expression may be involved in the regulation of its toxicity including cancer.	III.2
Yang et al.	2012	N/A	Systematic review (case control & cohort studies)	23 case–control and 11 cohort studies	N/A	Red meat mutagens (heme iron, heterocycle amine compounds (HCAs), polycyclic aromatic hydrocarbons (PAHs) & N-nitroso compounds (NOCs))	The analysis of the studies on red meat consumption yielded a summary relative risk (RRs) of lung cancer for the highest versus lowest intake categories were 1.35 (95% confidence interval (CI) 1.08–1.69) for total meat, 1.34 (95% CI 1.18–1.52) for red	Based on the study results, there was an established relationship between meat consumption and lung cancer; high intake of red meat increased the risk of developing lung cancer by 35%. Specifically, high red meat consumption, but not processed meat,	I

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							meat, and 1.06 (95% CI 0.90–1.25) for processed meat	was observed to increase the risk of lung carcinoma; while a higher consumption of poultry, but not total white meat or fish intake, was observed to decrease the risk of lung carcinoma. The mutagenic byproducts like HCAs and PAHs that an individual get exposed while cooking or eating red meat is likely to cause lung carcinogenesis leading to cancer development.	
Torres-Duran et al.	2014	Galocia, Spain	Multicenter hospital-based case–control study in radon prone areas	521 participants; 192 cases and 329 controls (21% women), all non-smokers	January 2011 to June 2013	Radon	On the effect of residential radon exposure on lung cancer, an OR of 2.42 (95% CI 1.45–4.06) for	The study showed that residential radon compounds increased the risks of lung	III.2

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							individuals exposed to concentrations >200 Bq·$^{m-3}$. When the analysis was restricted to only female, n OR 2.84 (95% CI 1.58–5.09) for those exposed >200 Bq·$^{m-3}$ was observed. For individuals who had lived for ≥20 years in the same dwelling, there was a 1.83 OR (95% CI 1.01–3.30) when patients were exposed to ≥200 Bq·m−3 compared with those exposed to <100 Bq·m−3.	cancer incidences for the exposed population regardless of their smoking status. The study also concluded that there might be an association between radon exposure and environmental tobacco smoke.	
Li et al.	2020	Wuhan, central China	Case-control	615 non-small cell lung cancer (NSCLC) cases and 615 healthy controls were enrolled.	Not mentioned	Bisphenol A [BPA; (CH3)2C(C6H4OH)2]	The creatinine-adjusted BPA levels were significantly higher in NSCLC cases	Based on the results observed, the study concluded that exposure to high BPA	III.2

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				than that in healthy controls (median: 0.97 vs 0.73 μg/L, P < 0.001). Exposure to high levels of BPA was significantly associated with NSCLC (adjusted OR = 1.91, 95%CI: 1.39–2.62, P < 0.001 for the highest quartile). Further result showed a close response association of BPA and NSCLC, and more observation indicating that BPA exposure could potentially interact with rs2046210 (estrogen receptor gene) to facilitate	concentration contributed to the development of lung cancer, and the relationship could be further modified by a person's genetic polymorphism.

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							development of non-small cell lung cancer.		
Liu et al.	2013	Chinese silica cohort	Cohort	34018 workers who worked at metal mines and pottery factories for 1 year or more	1960 to 2003	Crystalline silica	At the end of the study period, 85.95 of the participants had died or retired and only 4% were still working. A total of 11377 deaths were recorded, among which 546 were from lung cancer and 418 of them were continuously exposed to silica. Generally, there were 5297 cases of silicosis identified during the follow-up period. Comparing to the unexposed group, ever-exposed	The analysis results suggested a positive exposure response relationship between crystalline silica exposure and development of lung cancer. For workers exposed from ages 20 to 65 years at 0.1 mg/m3 of silica exposure, the estimated excess lifetime risk (through age 75 years) was 0.51%. The above findings confirmed that crystalline silica was a human environmental carcinogen that highly exposed	III.2

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							workers had an overall 44% (95% confidence interval (CI): 18%, 76%) increase in lung cancer risk, and adjustment for smoking did not change the association.	workers to lung cancer mortalities owing to its high risk levels.	
Kishimoto et al.	2010	Japan	Clinical retrospective study	152 patients with asbestos-related lung cancer & 431 patients with non-asbestos-related lung cancer	2000 to 2008 (asbestos related patients) & 1997 to 2007 (non-asbestos related lung cancer cases)	Asbestos	Results on the 152 patients with asbestos recorded 34% cases of asbestosis and a relative 81% exhibiting pleural plagues. For the autopsied patients, 62% had more than 5000 asbestos particles per gram compared to non-asbestos patients who recorded below 500 particles per gram. One hundred and	Based on the result findings, the number of asbestos particles in the lungs for the exposed were significantly higher than the patients with non-asbestos related cancers. Besides, for the patients diagnosed with asbestosis, there was a diagnosis of asbestos related lung cancer cases of up to 34%. The studies	III.1

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							fifty (98%) of 152 patients whose occupational histories were ascertained had occupational exposure to asbestos. The overall survival rate for the 152 patients with asbestos-related lung cancer was 17.4 months with 25% having 5 year-survival.	therefore concluded that asbestos exposure was a potential carcinogenic risk factor for developing lung cancer within the environment	
Jarvholm and Astrom	2014	Swedish construction industry cohort	Analysis of cohort study	189,896 workers data	20 years	Asbestos exposure	2835 cases of lung cancer were reported. Workers heavily exposed to asbestos had an increased risk of lung cancer (relative risks = 1.74; 95% confidence interval, 1.25 to 2.41) before exposure ended and a similar risk to those	The study concluded that workers highly exposed to asbestos had similar risk of lung cancer development, but the risk reduced 20 years after exposure ended.	III.2

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							with low exposure 20 years after the exposure had ceased (relative risks = 0.94; 95% confidence interval, 0.77 to 1.15).		
Lin et al.	2018	Not specified	Systematic review	20 RCTs(total of 13004 case group and 11199 control group population)	Not specified	Environmental tobacco smoke (EVT) for nonsmokers	9 studies with 13520 adults (8156 cases and 5364 controls) reported on the relationship between EVT exposure and lung cancer risk incidence and result demonstrated that the risk of lung cancer incidence was higher for the exposed (OR: 1.64, 95% CI: 1.34–2.01) than the non-exposed population. Again for the male population	In summary the study results showed a significant incident risks of lung cancer or the EVT exposure group (OR: 1.53, 95% CI: 1.01–2.33). Generally, the study found that EVT exposure was prospectively associated with significant increased risk of lung cancer incidence.	I

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			of 12526 adults ((case group, 7966; control group, 4560), there was a significantly higher lung cancer incidence risk (OR: 1.62, 95% CI: 1.16–2.28) than then non-exposed male. The same was recorded for the adult female of 15718 population (case group, 9199; control group, 6519) where the exposed group had higher incidence rates of lung cancer risks (OR: 1.57, 95% CI: 1.43–1.72). Regarding the EVT exposure in the workplaces, 3 studies with

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			2024 adults (case group = 637, control group = 1387) reported the association between EVT exposure at workplace and risk of lung cancer incidence. The incidence risk was significantly higher at OR: 1.78, 95% CI: 1.29–2.44. 3 other studies with 2413 adults (case group, 769; control group, 1644) reported the association between EVT exposure at home and risk of LC incidence, and results showed a significant higher incidence

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							rations (OR: 1.53, 95% CI: 1.01–2.33) for the exposure than the non-exposed group.		
Collins & Delzell	2018	Not specified	Systematic review	Not specified	Articles from 1 January 1975, through 30 June 2017	Styrene (C6H5CH=CH2)	5 cohort studies investigating the non-Hodgkin lymphoma (NHL) mortalities showed a standardized mortality ratio (SMR) of 0.77 (with 12 deaths; 95% CI, 0.40–1.34). Similarly, further studies on styrene production environment reported an increase in NHL with expected death value of 0.087 and expected cancer incidence at 0.4 (SMR = 7.5;	Although styrene has been associated with cancer, the results were not highly conclusive to provide evidence for a potential carcinogenicity of styrene on its association with any form of human cancer.	I

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							95% CI, 1.9–20.4). In the synthetic rubber Industry exposed to styrene, the the SMR for NHL was 0.98 (69 deaths; 95% CI, 0.77–1.25). In 6 studies of plastics workers, lung cancer SMRs or SIRs were 1.34 (any exposure: 556 deaths; 95% CI, 1.23–1.46)		
Hosgood et al.	2011	China based cohort	Systematic review	25 case–control studies (10 142 cases and 13 416 controls) to summarize the association between household coal use and lung cancer risk	Not specified	Household coal	Household coal use was found to associate with lung cancer incidence risk among all studies throughout the world [odds ratio (OR) = 2.15; 95% confidence interval (CI) = 1.61–	The study result give an evidence of the carcinogenic effect of household coal use that elevated the risks of lung cancer development, although the risk varied based on location.	I

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							2.89, $N_{studies} = 25$], and particularly among those studies carried out in mainland China and Taiwan (OR = 2.27; 95% CI = 1.65–3.12, $N_{studies} = 20$).		
Bonner et al.	2017	Lowa, North Carolina-USA	Cohort	57,310 restricted-use pesticide applicators	1993 to 1997	Pesticides (pendimethalin, dieldrin, and parathion)	Hazard ratios were elevated in the highest exposure category of lifetime days of use for pendimethalin (1.50; 95% CI: 0.98, 2.31), dieldrin (1.93; 95% CI: 0.70, 5.30), and chlorimuron ethyl (1.74; 95% CI: 1.02, 2.96), although monotonic exposure–response gradients were not evident.	The analyses providedl evidence for an association between pendimethalin, dieldrin, and parathion use and lung cancer risk.	III.2

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Manuwald et al.	2012	(Hamburg, Germany).	Cohort study	1589 male and female workers	1989 - 2007 (23 years)	Dioxin exposure	For men, there was an increase in overall mortality (ICD-9 1e999) (SMR¼1.14, 95% CI 1.06 to 1.23), all-cancer mortality (SMR¼1.37, 95% CI 1.21 to 1.56) and specific mortality from respiratory cancer (ICD-9 161, 162, 163) (SMR¼1.64, 95% CI 1.32 to 2.03)	Findings support the carcinogenic effect of dioxin compounds.	III.2
Sapkota et al.	2008	India	Multicentric case–control study	1062 incident hypopharyngeal/laryngeal cancer cases, 799 incident lung cancer case and 718 controls	From 2001 to 2004	Indoor air pollution from solid fuels (coal)	Unlike the non-coal users, consistent coal users l had an increased risk of lung cancer [odds ratio (OR) 3.76, 95% confidence interval (CI) 1.64–8.63].	The findings provided an evidence of differential lung cancer with indoor air pollution from coal and wood burning.	III.2

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Wang et al.	2015	U.S.A.	Prospective cohort study (observational)	76 304 postmenopausal women aged 50–79	Over 10.5 average years of follow-up through August 2009	Active smoking	901 lung cancer cases were identified. Compared with never smokers (NS), lung cancer incidence was much higher in current [hazard ratio (HR) 13.44, 95% confidence interval (CI) 10.80–16.75] and former smokers (FS; HR 4.20, 95% CI 3.48–5.08) in a dose-dependent manner.	Based on the findings, active smoking significantly increased risk of all lung cancer subtypes.	III.2
Wang et al.	2008	U.S based cohort	prospective cohort study	279,214 men and 184,623	October 13, 1995 and May 6, 1996 until December 31, 2003	Cigarette smoking	Lung carcinomas occurred in 4,097 men and 2,237 women with incidence Rates of 20.3 per 100,000 person-years (95% CI: 16.3–24.3) in never smoking men	There was a confirmed positive association of cigarette smoking and lung cancer for both men and women.	III.2

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							(99 carcinomas) and 25.3, 95% CI: 21.3–29.3 in never smoking women (152 carcinomas). Smoking was associated with increased lung carcinoma risk in both men and women with incidence rate of current smokers at 1,259.2 (95%CI: 1,035.0–1,483.3) in men and 1,308.9 (95%CI: 924.2–1,693.6) in women.		
Das et al.	2017	Chennai, India	prospective study	713 patients	1 year; November 2014–October 2015.	Tobacco smoke exposure	495 patients presented with clinic radiologically suspicious findings of lung cancer, exhibiting pathological	The study observed a change of trend in the rise of lung cancer and adenocarcinoma which highly manifested in the never-smokers.	III.2

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							confirmation of cancer.		
Martin et al.	2000	French cohort of electricity and gas industry	Case-Control Survey	310 lung cancer cases	January 1, 1978, to December 31, 1989	Crystalline silica	After adjusting occupational confounding factors, the analysis showed increased lung cancer risks linked to exposure to crystalline silica (highest exposure class: odds ratio = 2.27; 95% confidence interval: 1.10, 4.68) and creosotes (highest exposure level: odds ratio = 2.14; 95% confidence interval: 1.06, 4.31),	There was evidence of positive association of silica chemical agents with increased lung cancer risk.	III.2
Kurahash et al.	2007	Japanese non-smoking women	population-based prospective cohort study	28,414 lifelong non-smoking women	13 years	Passive smoke	Hazard ratio (HR) [95% confidence interval (CI)] for all lung cancer	Study findings confirm that passive smoking is a risk factor for lung cancer.	III.2

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							incidence in women who lived with a smoking husband was 1.34 (95% CI 0.81–2.21). An association was clearly identified for adenocarcinoma (HR 2.03, 95% CI 1.07–3.86), for which dose-response relationships were observed. . Passive smoking at the workplace also increased the risk of lung cancer (HR 1.32, 95% CI 0.85–2.04).		
Lubin et al.	2008	Montana, U.S.A.	cohort study	8,014 workers	10 years (1935-1939, 1985-1990).	Inhaled Inorganic Arsenic in Copper	The association between respiratory cancer and cumulative arsenic exposure was	The study confirmed a direct concentration effect from inhaled	III.2

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							consistent with linearity since the slope increased with increase of arsenic concentration.	inorganic arsenic.	
Gibb et al.	2000	U.S.A	Cohort study	cohort of 2,357 worker	1950–1985; -1992	hexavalent chromium	hexavalent chromium exposure showed a strong dose–response relationship for lung cancer	Findings showed that hexavalent chromium exposure was associated with an increased lung cancer risk; but not trivalent chromium exposure. The association was not confounded by smoking status.	III.2
Mastrangelo et al.	2003	Italian chloride workers cohort.	nested case-referent cohort study	38 lung cancer cases and 224 controls	1987 to 1999	poly(vinyl chloride) (PVC) dust	In cases of high concentration levels of respirable PVC particles, e lung cancer OR increases by 20% for each extra year of work (OR =	Based on the findings, there was an evidence that an increased risk of lung cancer associated with exposure to PVC dust.	III.2

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							1.2003; 95% CI 1.0772 to 1.3469; p = 0.0010), when the influence of age and smoking habits is controlled.		
Hu Chiou et al.	2014	Taiwan	Cohort study	189 lung cancer patients	1993 to 2003	Nickel	high nickel subgroup of patients had an odds ratio (OR) of 3.25 for p53 mutation risk relative to low nickel subgroup. The OR for p53 mutation risk of lifetime non-smokers, in the high-nickel subgroup was greater than that in the low-nickel subgroup.	Based on the study, increased risk of p53 mutation due to defective DNA repair caused by high nickel levels in Lung provides evidence for the mechanism by which nickel exposure contributes to lung cancer development.	III.2
Krewski et al.	2007	U.S.A (North America)	systematic analysis of case-control studies	data set of 4081 cases and 5281 controls	1 year	Residential radon compounds	Estimated odds ratio (OR) of lung cancer increased with	The results provided direct evidence of an association	III.2

							radon concentration and the OR trend was consistent with linearity (p = .10).	between residential radon and lung cancer risk.	
Lane et al.	2019	Czech, French, and Canadian cohorts of uranium miners	Joint cohort analysis	394,236 persons	1953–1999, 1956–1999, and 1965–1999	Low radon exposure	Excess relative risk per working-level month was 0.022 (95% confidence intervals: 0.013–0.034), based on 408 lung cancer deaths and 394,236 person-years of risk.	The cohort analysis provides strong evidence for increased risk of lung cancer mortality from low radon exposures.	III.2

Table 1. Summary of characteristics of Included Studies

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Discussion & Conclusion

This systematic review with data from 24 different publications to 2021 explored the relationship between environmental factors and lung cancer. The results from the included studies showed a significantly increased risk of lung cancer mortality and morbidity.

Only five of the 24 included studies mentioned chemical exposures, which were explained in different exposures for each study. TCDD or tetrachlorodibenzo dioxin was characterized by the regulatory role on the microRNAs, which possibly altered their expression to regulate toxicity. Consistent with the above, a study by Moffat et al.[35] noted that in vivo TCDD treatment caused changes in the microRNA levels in mice or rats, which were of substantial magnitude. The other pesticide chemical carcinogens with the potential of propagating lung cancer incidence as per the findings are pendimethalin, dieldrin, and parathion. In relation to the findings, previous studies by Alavanja et al.[36] found that dieldrin is positively associated with increased lung cancer risks, especially when the exposure is high.

Another three of the included studies explored indoor and outdoor air pollution's carcinogenicity and found a positive association between air pollution and lung cancer. Smoking is considered one of the main sources of indoor air pollution. Passive smokers are usually exposed to sidestream smoke and exhaled mainstream smoke, and the side stream is believed to emit more than 17 higher-level carcinogens. In this relation, Stading et al.[37] also observed that passive smoking contributed to increased polycyclic aromatic hydrocarbon (PAHs) and benzoapyrene diol epoxide related to lung cancer. The findings also discussed solid fuels like coal, specifically solid fuels used for heating and cooking. The above findings were consistent with the prior results that observed that individuals who burned solid fuel like coal, wood, and honeycomb for cooking throughout their life had four times increased risk of lung cancer than fellows who used clean energy. Other factors related to varied toxicities include benzene and formaldehyde volatility levels found in the incomplete gas phase of incomplete combustion. Several studies reported a positive association of passive smoking with lung cancer incidence,[38] including a dose-dependent relationship between lung cancer incidence and childhood exposure to environmental smoke.

Three other studies exploring the association of metal compounds found a positive relationship between metal compounds and lung cancer risk. Arsenic compounds were the dominant compound previously classified as both occupational and environmental lung cancer carcinogen that exists as an arsenate. A scholarly explanation for the impact of arsenic compound exposure associated with respiratory lung cancer is understood through the concentration-dependent ability of the cells to detoxify and methylate the arsenic compounds. Consistent with the findings, epidemiologic studies suggested that the toxic effects of arsenic compounds in drinking water were more remarkable for individuals exposed to higher concentrations. The former is further supported by toxicological studies that show that methylated arsenic, especially MMA(iii), exhibit higher affinity than the nonmethylated arsenic for protein binding to the trithiol, monothiol, and dithiol sites; thereby potentially disrupting some processes, including gene transcription, DNA methylation, glutathione synthesis, generation of reactive oxygen species, DNA repair, cell division, and signal transduction pathways within cells. The findings also provided a positive association between nickel and the risk of p53 mutation. This observation was consistent with the findings by Huang et al. that the incidence of squamous cell carcinoma and lung adenocarcinoma had a positive correlation with levels of soil nickel.[39]

Regarding asbestos, the findings of two of the included studies provided evidence for the association between asbestos and lung cancer development. Constant exposure to asbestos is understood to induce malignant mesothelioma. Asbestos increases the mutagenicity of tobacco carcinogens and thereby acts independently on damaged tissues causing fibrosis, a condition referred to as asbestosis.

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Consistent with this finding, Hashim and his colleague observed that lung cancer can develop in nonsmoker groups exposed to asbestos. However, induced passive or active smoking could further magnify the risk.[40] Velasco-Garcia et al.[41] also echoed through their study that about 0.8975: 0.8029 for autopsy samples and 0.9592 for biopsy samples cases of lung cancer had more than 5000 asbestos particles per gram of dry lung cancer. In another similar study of textile workers, heavy exposure to various types of asbestos-like crocidolite showed that the RR of lung cancer risk significantly increased in periods after employment with a standardized mortality ratio of 302, 363, and 278, respectively.

The study findings on two of the 24 included studies also correlated with the significant association of polyvinyl chloride and vinyl chloride dust exposure with lung cancer development. Polyvinyl chloride is among the majorly used plastic materials globally produced by polymerizing the vinyl chloride monomer. In this respect, other studies found that the polyvinyl bagging was used as a surrogate of exposure to the polyvinyl dust particles for the cohort of vinyl chloride workers. The lung cancer risk was 0.95 (95% CI 0.84 to 1.07) in the whole cohort and 1.24 (95% CI 0.84 to 1.77) in PVC baggers.[28] The evidence evaluating the relationship between lung cancer risks and styrene exposure was also strengthened by cohort studies' findings in the reinforced plastic industries.[42,43].

Nevertheless, three other included studies also discussed the carcinogenic relationship of various ionizing radiation compounds and lung cancer risks. After tobaccos smoke, residual radon exposure is echoed as the second leading risk factor for lung development for the never-smokers. In accordance, a case-control study by Darby et al.[44] in the European cohort also found a linear relationship between residual radon exposure and lung cancer morbidity risks. Furthermore, a systematic review by Torres-Duran et al.[30] also suggested a possible association between radon exposure and risk incidence of lung cancer on a dose-response pattern for the never-smokers.

Cumulative findings from four other included studies found that tobacco smoke or second-hand smoke poised environmental carcinogens affirming their association with increased lung cancer risk. Consistent with the findings, the study by Malik et al. of 434 pathologically confirmed lung cancer cohort, squamous cell carcinoma was found to be the most common subtype,[45] however, a further review revealed adenocarcinoma as the most common histology, which attributed to the crucial role played by molecular pathology towards a diagnosis of lung cancer. Two more included studies identified red meat consumption and bisphenol A (BPA) exposure as other environmental carcinogens associated with lung cancer development. Studies have hypothesized that mutagenic meat by-products like HCAs and PAHs from cooking meat significantly contributed to lung carcinogenesis. For instance, the study by Tasevska and colleagues demonstrated that consumption of well-done meat was associated with increased risks of lung cancer.[46] Concerning the above finding, another study by Cross and colleagues found that heme iron was also shown to induce the formation of N-nitroso compounds (NOCs).[47]

The review has several strengths and weaknesses. The first strength was that the study deployed a procedural method of a criteria in searching and assessing the articles possible for inclusion to maximize identification of suitable published sources for inclusion. The other main strength was the large sample size of the included studies, which poised a relatively high quality for assessing the association of various environmental factors to lung cancer carcinogenicity. The review used most cohorts and case-control studies for the limitations, implying the possibility of existing recall bias. The fact that most of the surveying or data collection techniques were standardized meant that observations were biased to the objectives of various case-control studies. There later could also signify the possibility of selection bias for the cohorts used in various case-control studies.

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Conclusion

The present systematic review collected and synthesized data available and revealed a positive association between various environmental carcinogens and lung cancer mortality and morbidity risks. In summary, other than tobacco smoking is heavily hyped to cause lung cancer carcinogenesis, included articles provided substantial evidence of association on chemical compounds exposure, outdoor and indoor air pollutants like coal and styrene, second-hand smoke exposure, metal compounds from copper, lead, and gold dust, asbestos, crystalline silica, vinyl chloride, and polymers compounds, ionizing radiation by-products like radon, red meat mutagen, and BPA.

Declarations

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