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REVIEW

Occupational benzene exposure and risk of lung cancer: a systematic review and meta-analysis

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Abstract
Lung cancer is a major global health issue, especially among men. While smoking and occupational or environmental exposures are known risks, the role of benzene remains under investigation. We aimed to conduct a systematic review and meta-analysis to evaluate the association between occupational benzene exposure and lung cancer incidence and mortality. We included cohort and case–control studies mentioned in the 2018 IARC Monograph on benzene and performed a systematic literature review to identify studies published up to 2024 by using PubMed, SCOPUS, and EMBASE databases. We constructed forest plots of relative risk (RR) to visualize and analyze the data. A random-effects model was used to address heterogeneity between studies. Stratified analyses were conducted to explore effect modification. We included 44 independent studies in our meta-analysis. The findings didn't reveal an association between total occupational benzene exposure and lung cancer overall (RR = 1.00, 95% CI 0.93–1.07, p-het ≤ 0.001, 45 risk estimates) or in major industries. Stratified analyses suggested an association in case controls studies (RR = 1.16, 95% CI 1.10–1.22: 7 risk estimates, p-het = 0.001), and in studies with results adjusted for smoking (RR = 1.17, 95% CI 1.11–1.24: 6 risk estimates, p-het = 0.001). There was also an association between high-level benzene exposure and lung cancer (p-trend = 0.03). Publication bias was excluded ($p = 0.16$). The increased risk after adjustment for smoking and the suggestion of a dose-response, are consistent with the hypothesis of an association between benzene exposure and lung cancer risk.

Keywords Lung cancer · Occupational exposure · Benzene · Meta-analysis

Abbreviations

ASR	Age-standardized incidence rate
AML	Acute myeloid leukemia
CI	Confidence interval
IARC	International Agency for Research on Cancer
OR	Odds ratio
RR	Risk ratio, rate ratio
ROS	Reactive oxygen species
SMR	Standardized mortality ratio
SIR	Standardized incidence ratio

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Introduction

Lung cancer is a major global health burden and the leading cause of cancer incidence and death, with an estimated 2.5 million new cases and 1.8 million deaths worldwide in 2022. It is the most common cancer in men (ASR 32.1 per 100,000) and the second most common in women (ASR 16.2 per 100,000), associated by various risk factors [1, 2]. In many populations, tobacco smoking is the main risk factor, followed by indoor radon. Secondhand tobacco smoke, family history [3, 4], and some occupational and environmental agents such as asbestos, arsenic, cadmium, silica, and diesel exhaust and other mixtures of polycyclic aromatic hydrocarbons (PAH) are also known risk factors [5, 6].

Benzene is an aromatic hydrocarbon produced in various natural processes such as volcanic activity and forest fires

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[7]. It is also a component of crude oil and gasoline and other oil-based products. Human activities, including cigarette smoking and certain industrial processes involved in the production of plastics, resins, nylon and synthetic fibers, lubricants, rubbers, dyes, detergents, drugs, and pesticides [7], can entail benzene exposure and its release into the environment. The International Agency for Research on Cancer (IARC) has classified benzene as a human carcinogen, specifically linking it to the development of acute myeloid leukemia (AML) [8]. However, the association between benzene exposure and solid tumors, including lung cancer, is still not entirely clear and requires further investigation [9]. When benzene is inhaled, respiratory organs, including the lungs, are the first sites affected by this compound. Metabolism of benzene occurs in the liver, but the lung is involved in this process as well [10–12]. So, the presence of benzene in the lung raises concerns about its potential role in lung carcinogenesis.

Raising awareness about occupational exposure to benzene and implementing measures to reduce it can have a significant impact on public health [13]. The paucity of good-quality comprehensive reviews on the association between benzene and lung cancer was the rationale to conduct a systematic review and meta-analysis of occupational cohort and case–control studies to evaluate the association between exposure to benzene and lung cancer incidence and mortality.

Methods

Data sources, search strategy

The Prospective Registry of Systematic Reviews PROSPERO registered the study protocol under the number (CRD42022379720) and we followed the COSMOS-E and PRISMA-statement (Supplementary Table 4) to conduct and report this systematic review and meta-analysis [14, 15].

First, we included all studies which were mentioned in the most recent IARC Monograph on benzene published in 2018. Then relevant peer-reviewed articles were retrieved by scanning databases, including MEDLINE (PubMed), SCOPUS, and EMBASE (Ovid). Two authors (MSS and MB) independently performed the search in online databases. The final search was completed in April 2024.

We developed the search strategy according to the Patients, Exposure, Comparator, Outcomes, Study design (PECOS) framework [16], with the following structure:

Population (P): workers in multiple industrial settings,
Exposure I: occupational benzene exposure,
Comparator (C): individuals not exposed to benzene,
Outcome (O): incidence and mortality of solid cancers,
Study design (S): cohort or case–control.

We used the following MeSH terms in our search process across three databases: ((neoplasms * or carcinoma * or cancer * or malignant *) and (benzene * or benzol * or cyclohexa-1* or 3 5 triene * or 5-cyclohexatriene *) [All Fields])) (The complete search string is reported in Supplementary Table 3).

Eligibility criteria

Four reviewers (MSS, MB, DS, VS, and VD) independently reviewed the list of titles, abstracts, and full texts of papers. We conducted an eligibility assessment for this systematic review and meta-analysis and included:

(i) Cohort studies and nested case–control analyses, of workers employed in industries and occupations in which benzene represents a major source of exposure such as, petroleum industry (all phases: extraction, refining, distribution, gas station), shoemaking, paint production and painters, chemical industry, rubber industry, printing, laboratory workers.
(ii) community-based case–control studies if they reported results on benzene exposure assessed across multiple industries or occupations (e.g., via job-exposure matrix or expert evaluation).

Papers from all countries were included, written in English, French, Italian, German, and Spanish -language.

We excluded following types of studies:

(i) Animal-, other experimental-, blood-, tissue-, or other biomarker-based studies,
(ii) Studies without full text,
(iii) Studies of workers primarily exposed to other carcinogens, such as PAHs (e.g., diesel exhaust, coke ovens, aluminum production, firefighting), silica, butadiene. substances.
(iv) Studies with design other than cohort and case control, such as ecological studies and case reports.
(v) Studies on non-solid tumors including leukemia, lymphoma or myeloma.

If multiple reports were based on the same database, we included the most informative report, typically based on the most recent update. Figure 1 shows the flow diagram of the literature search and study selection process.

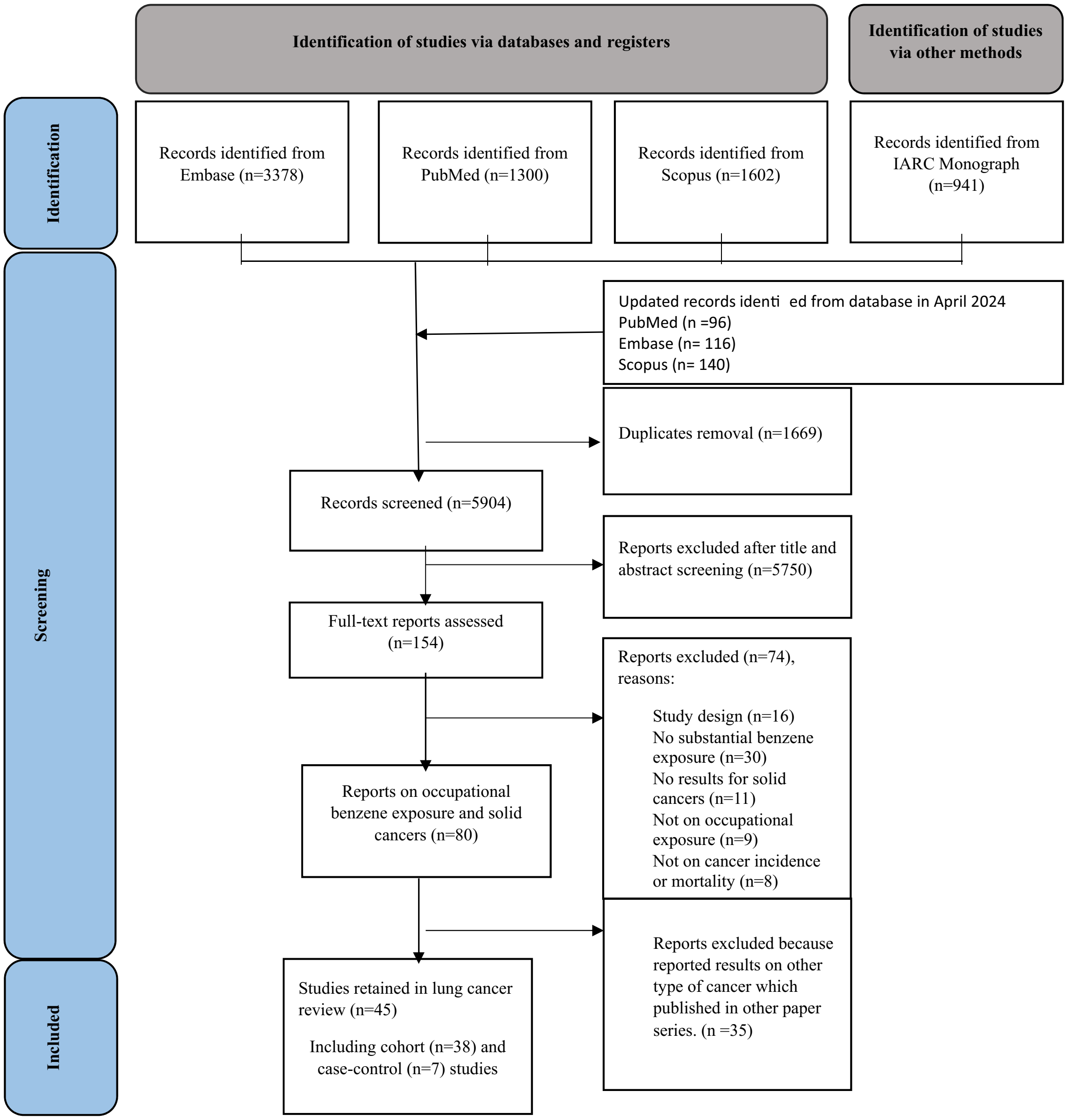

Fig. 1 Selection of studies for inclusion in the review and meta-analysis

Data extraction

After removing duplicates, and selecting the relevant publications, five reviewers (MSS, MB, DS, VS and VD) completed the data extraction based on the available full text publications, independently. It contained reference, type of study, studies by region, sample size, job title, period of employment, outcome, the type of controls, the type of cancer (including topography and histology), the effect measures, including the relative risks (RRs) [hazard ratios (HRs), standardized mortality ratios (SMRs), standardized incidence ratios (SIRs)] for cohort studies and the odds ratios (ORs) for case-control studies and their 95% Confidence interval (CI). We also recorded the number of studies whose analyses were adjusted for tobacco use. Different effect measures were considered equivalent to RRs [17].

If available, we extracted the results by gender, industry, morphology, as well as different doses, and durations of exposure.

Quality assessment

Five independent reviewers (MSS, MB, DS, VS, and VD) used a modified version of Newcastle-Ottawa Scale (NOS) to evaluate the quality of each study [18]. The NOS uses design-specific criteria (e.g., adequacy of follow-up), therefore, the maximum attainable score differs for cohort and case–control studies. Each reviewed study was scored, with a possible range of 0–9 for case–control and 0–10 for cohort studies (0 if no criteria were met and 9 or 10 if all criteria were met). Studies with quality score below < 7.5 were considered of low quality and those which scored 7.5 or above were considered of high quality. During the process of all steps if there were any major discrepancies, a sixth author (PB) intervened. Supplementary Tables 1 and 2 includes details on the quality assessment questions and assigned scores.

Definition of exposure categories

For the primary pooled analysis, we combined all eligible occupational studies into a single category representing benzene exposure across all industrial settings. This category included all workers with documented occupational benzene exposure, regardless of specific industry or job type. In stratified analyses, industrial sectors were classified into predefined categories (petroleum refining, chemical manufacturing, shoe and rubber industries, and other specific industries). In addition, we identified a separate group of studies in which benzene exposure was assessed across multiple occupational sectors, typically through job-exposure matrices or expert exposure ratings. These were classified as cross-industry benzene exposure studies. This distinction allowed comparison of risk estimates from industry-specific cohorts with those from studies covering broader and more heterogeneous occupational settings.

Meta-analysis

For the purpose of this analysis on the association between occupational benzene exposure and lung cancer, we retained 44 publications which reported effect measurements and the corresponding 95% CIs of incidence or mortality for cancer of the lung, including bronchus and trachea, for 45 non-overlapping study populations (see Table 1 for details). Results for other solid cancers were reported elsewhere [19–27].

We conducted a series of meta-analyses based on random effects models and tested for heterogeneity among studies using the Q statistics and the I-square test [72]. Furthermore, we stratified the meta-analysis according to study design (cohort, and case control), quality score (low, and high quality), outcome (incidence, and mortality), geographic region (Europe, North America, other countries including Asia, Latin America, and Australia), adjustment for tobacco smoking (yes, no), year of publication (< 2000 and ≥ 2000), industry/job of employment according to the definition of exposure categories, gender (men, women, both).

Results on exposure level were available from a few studies, and were classified as low, medium or high level; we also calculated the p value of test for linear trend. Finally, we assessed publication bias by the visual inspection of funnel plot and the Egger test [73]. All analyses were completed using the STATA version 14.0 (Stata, College Station, TX, USA).

Results

Based on our search of the literature and selection procedure, we included a total of 45 independent studies, including 38 cohort studies [28–37, 40–46, 48–57, 60–64, 67, 69, 71, 74, 75] and 7 case-control studies [38, 47, 58, 65, 66, 68, 70] (one publication included two separate cohorts). Details of these studies are provided in Table 1.

These studies included a total of 56 risk estimates by considering different genders, industries, and outcomes. The primary meta-analysis (Fig. 2) across all industrial settings combined showed no association between occupational benzene exposure and lung cancer (RR = 1.00, 95% CI 0.93–1.07; I2 = 84.9%, p-het ≤ 0.001, 45 risk estimates). Publication bias was suggested based on the funnel plot examination (Fig. 3); however, the Egger test was not statistically significant (p = 0.16).

Stratified analyses by industry category revealed a statistically significant association in studies evaluating cross-industry benzene exposure, typically based on job-exposure matrices or expert exposure assessment (RR = 1.17, 95% CI 1.11–1.24; 13 risk estimates, p-het = 0.003). An increased risk was also observed among women workers (RR = 1.18, 95% CI 1.05–1.53; 6 risk estimates, p-het = 0.02). Analyses by study design indicated an association in case–control studies (RR = 1.16, 95% CI 1.10–1.22; 7 risk estimates), but not in cohort studies (RR = 0.98, 95% CI 0.90–1.08), with a statistically significant difference between the two groups (p = 0.001).Similarly studies that adjusted for smoking showed an association between benzene exposure and lung cancer (RR = 1.17, 95% CI 1.11–1.24: 6 risk estimates), which was not present in studies that did not adjust for it (p < 0.001). No heterogeneity was detected according to outcome (p = 0.88), region (p = 0.88), publication year (p = 0.64), or quality score (p = 0.87) (Table 2).

Eight studies reported lung cancer risk by level of benzene exposure (Table 3). Overall, relative risks tended to increase with higher exposure level. In the meta-analysis (Table 4), pooled relative risks rose from 1.14 (95% CI 1.06–1.22) at low exposure to 1.35 (95% CI 1.21–1.50) at high exposure (p-trend = 0.03). When stratified by outcome, mortality studies showed a more pronounced increase in risk with exposure, with RR ranging from 1.14 to 1.49 across low to high categories, whereas incidence studies showed smaller and less consistent increases (RR = 1.14–1.25).

Table 1 Selected characteristics of the studies included in the review and meta-analysis

References number	First author	Year of publication	Country	Gender	Outcome‡	Study type	Industry/occupation	Quality score	Adjustment for smoking
[28]	Rushton L*	1980	UK	Men	Mortality	Cohort	Oil industry	7	No
[29]	Decouflé P	1983	USA	Men	Mortality	Cohort	Multiple industries	7.5	No
[30]	Tsai SP	1983	USA	Men	Mortality	Cohort	Refinery area	7	No
[31]	Guberan E	1985	Switzerland	Men	Incidence, mortality	Cohort	Perfumery and flavour industry	8	No
[32]	Bond GG	1986	USA	Both	Mortality	Cohort	Multiple industries	7	No
[33]	Wong O	1987	USA	Men	Mortality	Cohort	Chemical industry	8	No
[34]	Wongsrichanalai C.	1989	USA	Men	Incidence	Cohort	Petroleum refinery	8	No
[35]	Szeszenia-Dabrowska N	1991	Poland	Men	Mortality	Cohort	Rubber industry	6	No
[36]	Walker JT	1993	USA	Both	Mortality	Cohort	Shoe manufacture	9	No
[37]	Lagorio S	1994	Italy	Men	Mortality	Cohort	Service station workers	7	No
[38]	Greenland S	1994	USA	Men	Mortality	NCC	Transformer-assembly facility	6	No
[39]	Honda Y	1995	USA	Men	Mortality	Cohort	Petroleum refinery	8	No
[40]	Satin K.P.	1996	USA	Both	Mortality	Cohort	Petroleum refinery	7	No
[41]	Yin SN	1996	China	Both	Mortality	Cohort		7	No
[42]	Collingwood KW	1996	USA	Both	Mortality	Cohort	Multiple industries	8	No
[43]	Fu H†	1996	UK	Men	Mortality	Cohort	Shoe manufacture	8	No
[44]	Järvholm B	1997	Sweden	Men	Incidence	Cohort	Petroleum refinery	8	No
[45]	Ireland B	1997	USA	Men	Mortality	Cohort	Multiple industries	8	No
[46]	Lynge E	1997	European Countries	Both	Incidence	Cohort	Service station workers	7	No
[47]	Martin JC	1998	France	Both	Incidence	NCC	Electricity and gas industry	7	No
[48]	Pukkala, E	1998	Finland	Both	Incidence	Cohort	Petroleum refinery	7	No
[49]	Bulbulyan MA	1999	Russia	Women	Mortality	Cohort	Printing industry	8	No
[50]	Consonni D.	1999	Italy	Men	Mortality	Cohort	Petroleum refinery	8	No
[51]	Kauppinen T	2003	Finland	Both	Incidence	Cohort	Chemical laboratory	8	No
[52]	Lewis, R J	2003	Canada	Both	Incidence, mortality	Cohort	Petroleum workers	8	No
[53]	Collins J.	2003	USA	Both	Mortality	Cohort	Multiple industries	7.5	No
[54]	Sorahan T	2005	UK	Both	Incidence, mortality	Cohort	Multiple industries	8	No
[55]	Swaen G.	2005	Netherlands	Men	Mortality	Cohort	Caprolactam manufacture	8	No
[56]	Hoshuyama T.	2006	China	Men	Mortality	Cohort	Iron and steel foundry	8	No
[57]	Gun RT	2006	Australia	Men	Incidence, mortality	Cohort	Petroleum refinery	8.5	No
[58]	Baccarelli A	2006	Russia	Both	Incidence	CC	Mixed	6.5	Yes
[59]	McHugh MK	2010	USA	Both	Incidence	CC	Mixed	7.5	Yes
[60]	Budroni M	2010	Italy	Both	Incidence	Cohort	Petrochemical industry	6	No
[61]	Koh DH	2011	South Korea	Men	Incidence, mortality	Cohort	Petrochemical industry	7.5	No
[62]	Bonneterre V	2012	France	Both	Incidence	Cohort	Chlorochemical industry	7.5	No
[63]	Koh DH	2014	South Korea	Men	Incidence, mortality	Cohort	Petrochemical industry	6	No
[64]	Collins J.	2015	USA	Men	Mortality	Cohort	Multiple industries	8	No
[65]	Linet M.	2015	China	Men	Mortality	Cohort	Multiple industries	8	No
[66]	Mattei F	2016	France	Men	Incidence	CC	Mixed	8	Yes
[67]	Gustavsson P	2017	Sweden	Both	Incidence	Cohort	Chemical laboratory	8	No
[68]	Warden, H	2018	Canada	Both	Incidence	CC	Mixed	8	Yes
[69]	Bonzini M	2019	Italy	Men	Mortality	Cohort	Petroleum refinery	8	No

Table 1 (continued)

References number	First author	Year of publication	Country	Gender	Outcome‡	Study type	Industry/occupation	Quality score	Adjustment for smoking
[70]	Wan W	2023	North American and European countries	Both	Incidence	CC	Mixed	7.5	Yes
[71]	Babigumira R	2024	Norway	Men	Incidence	Cohort	Offshore Petroleum Workers	11.5	Yes

CC Case–control, *NCC* nested case–control

*Includes also pleural neoplasm

†Includes two separate cohorts

‡For studies with multiple outcomes, results on incidence were used in thr main meta-analysis

Discussion

Our systematic review and meta-analysis found no association between overall occupational benzene exposure and risk of lung cancer, but we found an association in studies which adjusted for tobacco smoking and for high level of benzene exposure. In subgroup analyses we also found an association in studies of women workers.

Also, an important finding of our study is the discrepancy between results from analyses including all industrial settings combined and those limited to studies assessing cross-industry benzene exposure. The former yielded no association, whereas the latter consistently resulted in an increased lung cancer risk. This difference likely reflects underlying methodological contrasts. Sector-specific cohort studies especially in the petroleum industry, often lack individual smoking information and tend to involve relatively uniform workplace environments with generally declining benzene exposures. In contrast, cross-industry case–control studies depend on expert or JEM-based exposure assessment, cover a broader range of occupations, and more frequently adjust for major confounders such as smoking. These methodological differences may explain why the cross-industry studies identified a positive association while the pooled estimate across all industrial sectors did not. The fact that the positive signal appears precisely in the studies with the strongest control for smoking supports the hypothesis that negative confounding by smoking may have obscured a modest benzene effect in the large industry-based cohorts.

Chiavarini et al. [76] recently published a meta-analysis on benzene exposure and lung cancer, which included 21 studies and found a significant increase in lung incidence and mortality. The low number of studies reviewed by these authors compared to our review (21 vs. 45) is probably explained by the fact that these authors included in their search strategy terms for lung cancer, therefore missing relevant publications which reported results on lung cancer risk in the text or the tables, but not in the title or the abstract. This is not an uncommon limitation in meta-analysis of occupational risk factors [75] and likely leads to publication bias because the restricted search strategy is more likely to identify positive findings. In addition, the authors of the previous meta-analysis combined occupational and environmental exposure and included studies based on biological markers. Furthermore, the important case–control study by Wan et al. [70] was excluded from their report. For these reasons, we believe our review provides a more thorough and valid estimate of the association between occupational benzene exposure and risk of lung cancer.

After benzene enters the body mostly through inhalation, it produces toxic metabolites, primarily in the liver and lung, which can negatively impact other organs by various mechanisms including: (i) formation of reactive oxygen species (ROS) which can damage DNA, and other macromolecules leading to genetic mutation, and disruption of cellular organ function. (ii) effects on kinases and signal transduction pathways that regulate various cellular processes, including cell proliferation and apoptosis. (iii) impact on inflammation [77–79]. The possibility that benzene contributes to lung cancer development has been suggested in mechanistic studies and noted in the literature [77], but no comprehensive systematic review has previously evaluated this hypothesis using epidemiologic evidence.The incidence of lung cancer is influenced by several risk factors. Smoking tobacco, including secondhand smoke exposure, exposure to indoor and outdoor air pollution and radon, family history [78], and exposure to occupational carcinogens such as asbestos, radon, arsenic, chromium, nickel, and diesel exhaust, can increase the risk of developing lung cancer [80, 81].

Among them, tobacco smoking is the main risk factor for lung cancer and can be associated with exposure to benzene, and tobacco smoke is itself an important source of benzene; adjustment for its potential confounding effect is therefore critical. However, in most studies included in our meta-analysis, particularly industry-based studies based on mortality data, data on smoking were not available, thus potentially leading to biased results.

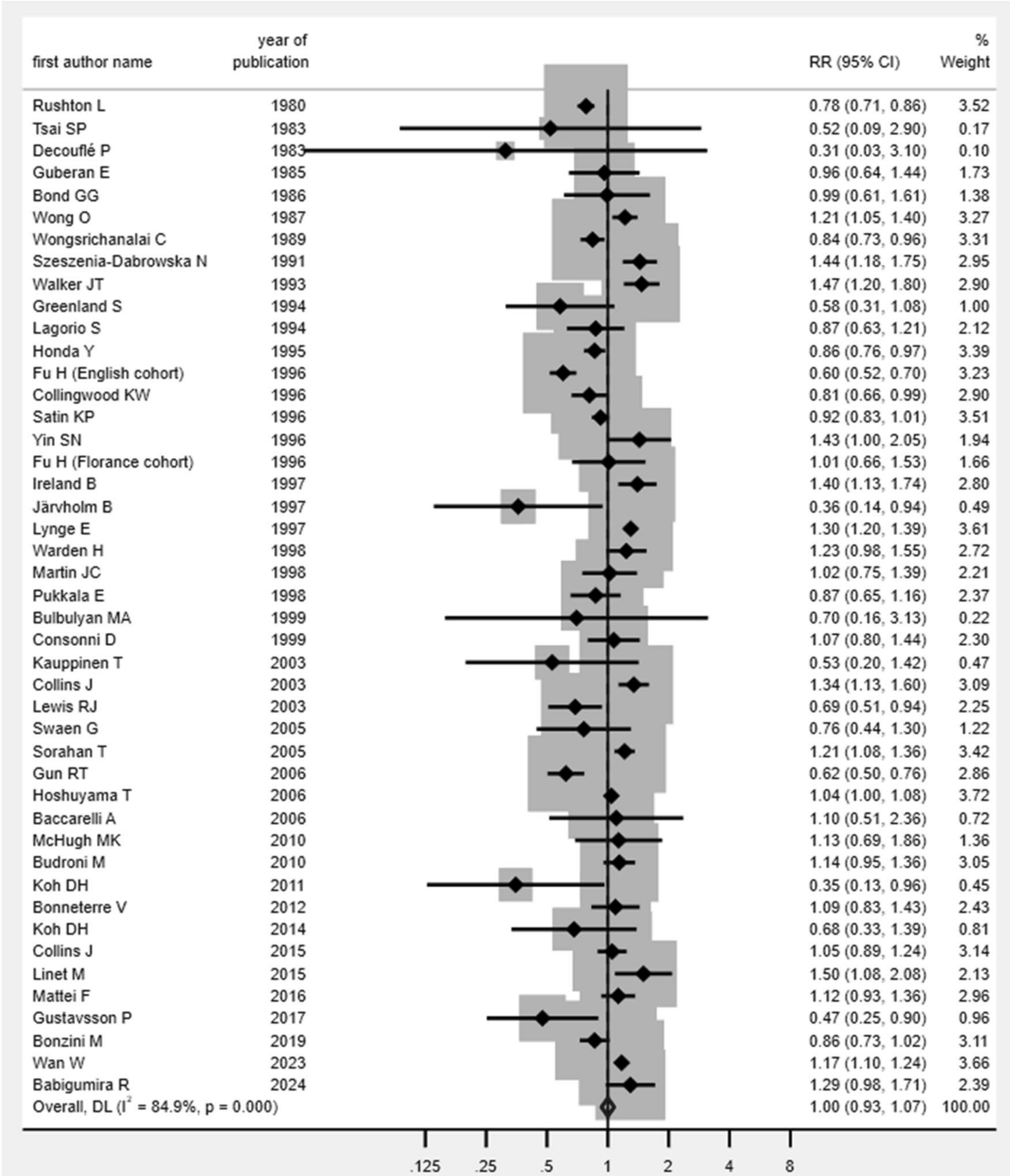

Fig. 2 Forest plot (random-effects model) of results on the association between benzene exposure and lung cancer

We used the approach proposed by Axelson and Steenland [82] for estimating the potential confounding by tobacco smoking in studies which did not adjust for it. Specifically, we used the age-adjusted smoking prevalence rates in a large US refinery and petrochemical plant and in the general US population for three time periods (1978, 1986, and 1995) reported by Tsai et al. [83], which showed a lower smoking prevalence among refinery workers. Results on lung cancer risk in this population have been included in the meta-analysis, based on a separate publication [30]. We used the RR for current smokers = 9.0 and former smokers = 3.9 reported by Gandini et al. [84] and calculated a confounding RR by smoking of 0.93 based on 1978 data, 0.91 based on 1986 data and 0.88 based on 1995 data. These results are close to our summary RR for benzene exposure, particularly when we limited the meta-analysis to studies of US refinery workers (RR = 0.88; 95% CI 0.82–0.94, 5 studies). Therefore, negative confounding by tobacco smoking is a plausible explanation of the reduced occurrence of lung cancer in industry-based studies and might obfuscate a

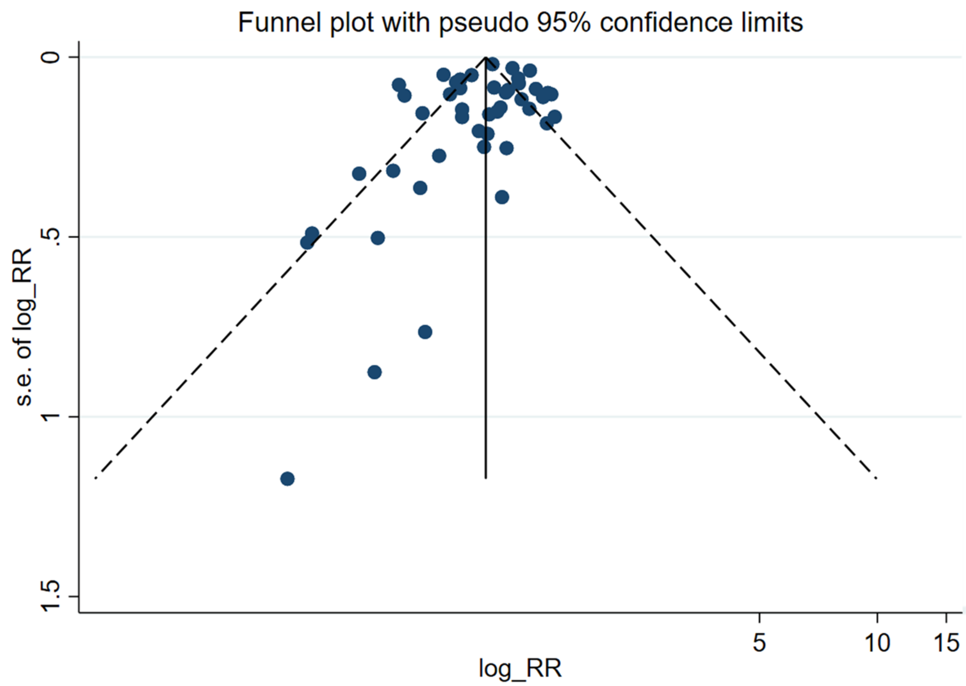

Fig. 3 Funnel plot of results on the association between benzene exposure and lung cancer

relatively small effect of benzene exposure. Such potential negative confounding underscores the complexity involved in clarifying the association between benzene exposure and lung cancer.

Although the number of studies examining sex-specific associations is limited, our analysis suggests a stronger association between benzene exposure and lung cancer in women compared to men. One possible explanation is the lower prevalence of tobacco smoking among women in many of the included studies, which could reduce negative confounding and make the effect of benzene more apparent. Quantitatively, among studies that provided sex-specific results, the relative risk estimates for women varied between 0.64 and 1.3 (6 studies), whereas for men, the estimates ranged from 0.36 to 1.77 (28 studies).This pattern suggests that benzene exposure may have a more consistent association with lung cancer risk in women, potentially reflecting an independent effect of benzene beyond other risk factors.

Notably, the results from case-control studies and cohort studies in this review show some differences. Case-control studies often reported stronger associations between benzene exposure and lung cancer, whereas cohort studies generally showed more modest effects or non-significant associations. These differences may be explained by study design factors: case-control studies are more susceptible to recall and selection bias, which can inflate observed associations, while cohort studies benefit from prospective exposure assessment and generally lower bias but may have limited power if the number of exposed cases is small. Differences in exposure measurement, population characteristics, and confounding adjustment may also contribute. Future research should consider these methodological differences when interpreting the evidence and synthesizing results across study designs.

Our systematic review and meta-analysis have several strengths including an up-to-date review of the available literature, stratification for potential confounders and effect modifiers, and particularly tobacco smoking, and a focus on results on dose-response.

On the other hand, there are some limitations to consider. We couldn't stratify our analysis by histologic types of lung cancer, which are known to have distinct morphological and molecular characteristics [85]. The small number of available studies on women workers and of studies conducted outside North America and Europe can impact the generalizability of the findings. It is important to design future studies that integrate occupational and non-occupational sources of benzene exposure, address clinical characteristics of lung cancer, such as stage at diagnosis and histology, and control for potential confounding variables.

Although we did not detect an association between occupational benzene exposure and lung cancer in the overall analysis, such association was present in studies which adjusted for tobacco smoking, which might be explained by negative confounding of tobacco smoking. Also, high-level occupational exposure to benzene was associated with an increased risk of lung cancer. These results are supported by experimental and mechanistic evidence. Overall, the available evidence supports the hypothesis of an association between benzene exposure and lung cancer risk.

Occupational safety measures, such as proper ventilation, personal protective equipment, and workplace monitoring,

Table 2 Results of the meta-analyses stratified by region, study design, quality score, outcome, gender, industry of employment, year of publication, and adjustment for tobacco smoking

Characteristic	*N* risk estimates	RR (95% CI)	*p* heterogeneity
Region			
North America	16	1.02 (0.90–1.14)	0.88
Europe	20	0.98 (0.87–1.10)	
Other regions	9	0.97 (0.75–1.24)	
Study design			
Case control	7	1.16 (1.10–1.22)	0.001
Cohort	38	0.98 (0.90–1.08)	
Quality score			
Low quality (<7.5)	13	1.01 (0.86–1.18)	0.87
High quality (>=7.5)	32	0.98 (0.91–1.08)	
Publication year			
<2000	26	0.99 (0.88–1.11)	0.64
>=2000	19	1.02 (0.93–1.11)	
Outcome			0.88
Incidence	21	0.98 (0.89–1.10)	
Mortality	30	0.97 (0.89–1.07)	
Gender			
Men	28	0.98 (0.89–1.07)	0.02
Women	6	1.18 (1.05–1.53)	
Both	20	1.10 (1.00-1.20)	
Industry of employment			
Petroleum refinery	17	0.88 (0.77-1.00)	0.003
Chemical industry	4	0.92 (0.65–1.30)	
Other industries	11	0.99 (0.80–1.22)	
Benzene exposure across multiple industries	13	1.17 (1.07–1.27)	
Adjustment for tobacco smoking			0.001
No	43	0.97 (0.89–1.05)	
Yes	6	1.17 (1.11–1.24)	

Table 4 Meta-analysis of results on level of benzene exposure

Characteristic	Dose category	RR (95% CI)	*p* trend
Overall (8 studies)	Low	1.14 (1.06–1.22)	0.03
	Medium	1.19 (1.10–1.27)	
	High	1.35 (1.21–1.50)	
Incidence (4 studies)	Low	1.14 (1.05–1.23)	0.56
	Medium	1.17 (1.09–1.27)	
	High	1.25 (1.06–1.48)	
Mortality (4 studies)	Low	1.14 (0.90–1.44)	0.06
	Medium	1.29 (1.02–1.63)	
	High	1.49 (1.28–1.73)	

should be implemented to minimize exposure and protect workers in industries containing benzene.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10654-026-01400-7.

Table 3 Relative risk of lung cancer by level of benzene exposure

First author, year	Outcome	Exposure level	Dose detail	RR (95% CI)
Wong O (1987)	Mortality	Low	<25 ppm_m	1.27 (0.50–1.66)
		Medium	25–100 ppm_m	1.45 (0.28–6.26)
		High	>100 ppm_m	1.19 (0.48-1.00)
Hayes RB (1996)	Mortality	Low	>40 ppm-y	1.08 (0.73–1.60)
		Medium	40–99 ppm-y	1.40 (0.89–2.19)
		High	<100 ppm-y	1.55 (1.25–1.92)
Ireland B (1997)	Mortality	Low	<12 ppm_m	1.30 (0.60–2.20)
		Medium	12–72 ppm_m	0.80 (0.30–1.80)
		High	>72 ppm_m	1.40 (0.60–2.30)
Martin JC (1998)	Incidence	Low	N/A	1.21 (0.76–1.94)
		Medium	N/A	1.25 (0.90–1.74)
		High	N/A	1.62 (1.03–2.53)
Collins J (2003)	Mortality	Low	<1 ppm-y	1.10 (0.69–1.50)
		Medium	1–6 ppm-y	1.30 (1.00-1.80)
		High	>6 ppm-y	1.60 (1.20–2.09)
Mattei F (2016)	Incidence	Low	N/A	1.29 (0.92–1.80)
		Medium	N/A	1.14 (0.80–1.60)
		High	N/A	0.97 (0.70–1.35)
Wan W (2023)	Incidence	Low	<1 ppm-y	1.12 (1.03–1.21)
		Medium	1–5 ppm-y	1.17 (1.08–1.27)
		High	>5 ppm-y	1.32 (1.18–1.48)
Babigumira R (2024)	Incidence	Low	<0.019 ppm-y	1.47 (0.9–2.4)
		Medium	0.019–<0.071 ppm-y	1.30 (0.75–2.26)
		High	>0.175 ppm-y	1.16 (0.75–1.08)

y year, *m* months

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Data availability The data supporting this study's findings are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Paolo Boffetta acted as expert witness on benzene-related litigation, unrelated to the present work. Other authors declare no conflict of interest.

References

1. Mahabadi N, Goizueta AA, Bordoni B, Anatomy. Thorax, Lung Pleura And Mediastinum [Updated 2022 Oct 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519048/.
2. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F. (2024). Global Cancer Observatory: Cancer Today (version 1.1). Lyon: International Agency for Research on Cancer. https://gco.iarc.who.int/today. Accessed 28 Mar 2024.
3. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med. 2011;32:605–44.
4. Thandra KC, Barsouk A, Saginala K, et al. Epidemiology of lung cancer. Contemp Oncol (Pozn). 2021;25:45–52.
5. Spyratos D, Zarogoulidis P, Porpodis K, et al. Occupational exposure and lung cancer. J Thorac Dis. 2013;5(Suppl 4):S440–5.
6. Armstrong B, Hutchinson E, Unwin J, et al. Lung cancer risk after exposure to polycyclic aromatic hydrocarbons: a review and meta-analysis. Environ Health Perspect. 2004;112:970–8.
7. Spatari G, Allegra A, Carrieri M, et al. Epigenetic Effects of Benzene in Hematologic Neoplasms: The Altered Gene Expression. Cancers (Basel). 2021;13:2392.
8. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Benzene. Lyon: International Agency for Research on Cancer; 2018.
9. Beach J, Burstyn I. Cancer risk in benzene exposed workers. Occup Environ Med. 2006;63:71–2.
10. Sammett D, Lee EW, Kocsis JJ. Partial hepatectomy reduces both metabolism and toxicity of benzene. J Toxicol Environ Health. 1979;5:785–92.
11. Snyder R, Hedli CC. An overview of benzene metabolism. Environ Health Perspect. 1996;104(Suppl 6):1165–71.
12. Powley MW, Carlson GP. Benzene metabolism by the isolated perfused lung. Inhal Toxicol. 2002;14:569–84.
13. Schulte PA, Pandalai S, Wulsin V, et al. Interaction of occupational and personal risk factors in workforce health and safety. Am J Public Health. 2012;102:434–48.
14. Moher D, Liberati A, Tetzlaff J, et al. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Ann Intern Med. 2009;151:264–69.
15. Dekkers OM, Vandenbroucke JP, Cevallos M, et al. COSMOS-E: guidance on conducting systematic reviews and meta-analyses of observational studies of etiology. PLoS Med. 2019;16:e1002742.
16. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environ Int. 2018;121(Pt 1):1027–31.
17. Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev. 1987;9:1–30.
18. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–5.
19. Shah V, Shah D, DeStefano V, Bonetti M, Boffetta P, Seyyedsalehi MS. Occupational-related exposure to benzene and risk of cervical, ovarian, and endometrial cancers: Systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2025;34(11):1877–87. https://doi.org/10.1158/1055-9965.EPI-25-0018.
20. Sassano M, Seyyedsalehi MS, Boffetta P. Occupational benzene exposure and hepatobiliary and pancreatic cancers: A systematic review and meta-analysis. Saf Health Work. 2026;17(1):1–11. https://doi.org/10.1016/j.shaw.2025.10.002.
21. Godono A, Quattrocolo A, Caradonna R, Picciaiola MV, Boffetta P, Seyyedsalehi MS. Occupational Benzene Exposure and Risk of Male Genital Cancers: A Systematic Review and Meta-Analysis. Am J Ind Med. 2025;68(8):666–78. https://doi.org/10.1002/ajim.23740.
22. Angelini M, Seyyedsalehi MS, Boffetta P. Occupational benzene exposure and skin cancers: a systematic review and meta-analysis. Occup Med (Lond). 2025;75(3):163–70. https://doi.org/10.1093/occmed/kqae112.
23. Mangiaterra S, Boffetta P, Seyyedsalehi MS. Occupational benzene exposure and risk of nervous system cancers: A systematic review and meta-analysis. Cancer Epidemiol. 2025;95:102779. https://doi.org/10.1016/j.canep.2025.102779.
24. Seyyedsalehi MS, Destefano V, Shah D, Shah V, Bonetti M, Boffetta P. Occupational exposure to benzene and risk of breast cancer: Systematic review and meta-analysis. Med Lav. 2024;115(5):e2024034. https://doi.org/10.23749/mdl.v115i5.16306
25. Seyyedsalehi MS, Bonetti M, Shah D, DeStefano V, Boffetta P. Occupational benzene exposure and risk of kidney and bladder cancers: a systematic review and meta-analysis. Eur J Cancer Prev. 2025;34(3):205–13. https://doi.org/10.1097/CEJ.0000000000000911.
26. Godono A, Dito A, Martini G, Picciaiola MV, Di Lorenzo A, Ciocan C, Boffetta P, Seyyedsalehi MS. Occupational benzene exposure and risk of head and neck cancer: A systematic review and meta-analysis. Environ Res. 2024;263(Pt 1):120033. https://doi.org/10.1016/j.envres.2024.120033
27. Sassano M, Seyyedsalehi MS, Boffetta P. Occupational benzene exposure and colorectal cancer: A systematic review and meta-analysis. Environ Res. 2024;257:119213. https://doi.org/10.1016/j.envres.2024.119213.
28. Rushton L, Alderson M. The influence of occupation on healt—-some results from a study in the UK oil industry. Carcinogenesis. 1980;1:739–43.
29. Decouflé P, Blattner WA, Blair A. Mortality among chemical workers exposed to benzene and other agents. Environ Res. 1983;30:16–25.
30. Tsai SP, Wen CP, Weiss NS, et al. Retrospective mortality and medical surveillance studies of workers in benzene areas of refineries. J Occup Med. 1983;25:685–92.
31. Guberan E, Raymond L. Mortality and cancer incidence in the perfumery and flavour industry of Geneva. Br J Ind Med. 1985;42:240–5.
32. Bond GG, McLaren EA, Baldwin CL, et al. An update of mortality among chemical workers exposed to benzene. Br J Ind Med. 1986;43:685–91.
33. Wong O. An industry wide mortality study of chemical workers occupationally exposed to benzene. II. Dose response analyses. Br J Ind Med. 1987;44:382–95.

34. Wongsrichanalai C, Delzell E, Cole P. Mortality from leukemia and other diseases among workers at a petroleum refinery. J Occup Med. 1989;31:106–11.
35. Szeszenia-Dabrowska N, Wilczyńska U, Kaczmarek T, Szymczak W. Cancer mortality among male workers in the Polish rubber industry. Pol J Occup Med Environ Health. 1991;4:149–57.
36. Walker JT, Bloom TF, Stern FB, et al. Mortality of workers employed in shoe manufacturing. Scand J Work Environ Health. 1993;19:89–95.
37. Lagorio S, Forastiere F, Iavarone I, et al. Mortality of filling station attendants. Scand J Work Environ Health. 1994;20:331–8.
38. Greenland S, Salvan A, Wegman DH, et al. A case-control study of cancer mortality at a transformer-assembly facility. Int Arch Occup Environ Health. 1994;66:49–54.
39. Honda Y, Delzell E, Cole P. An updated study of mortality among workers at a petroleum manufacturing plant. J Occup Environ Med. 1995;37:194–200.
40. Satin KP, Wong O, Yuan LA, et al. A 50-year mortality follow-up of a large cohort of oil refinery workers in Texas. J Occup Environ Med. 1996;38:492–506.
41. Yin SN, Hayes RB, Linet MS, et al. An expanded cohort study of cancer among benzene-exposed workers in China. Benzene Study Group. Environ Health Perspect. 1996;104(Suppl 6):1339–41.
42. Collingwood KW, Raabe GK, Wong O. An updated cohort mortality study of workers at a northeastern United States petroleum refinery. Int Arch Occup Environ Health. 1996;68:277–88.
43. Fu H, Demers PA, Costantini AS, et al. Cancer mortality among shoe manufacturing workers: an analysis of two cohorts. Occup Environ Med. 1996;53:394–8.
44. Järvholm B, Mellblom B, Norrman R, et al. Cancer incidence of workers in the Swedish petroleum industry. Occup Environ Med. 1997;54:686–91.
45. Ireland B, Collins JJ, Buckley CF, et al. Cancer mortality among workers with benzene exposure. Epidemiology. 1997;8:318–20.
46. Lynge E, Andersen A, Nilsson R, et al. Risk of cancer and exposure to gasoline vapors. Am J Epidemiol. 1997;145:449–58.
47. Martin JC, Imbernon E, Goldberg M, et al. Occupational risk factors for lung cancer in the French electricity and gas industry: a case-control survey nested in a cohort of active employees. Am J Epidemiol. 2000;151:902–12.
48. Pukkala E. Cancer incidence among Finnish oil refinery workers, 1971–1994. J Occup Environ Med. 1998;40:675–9.
49. Bulbulyan MA, Ilychova SA, Zahm SH, et al. Cancer mortality among women in the Russian printing industry. Am J Ind Med. 1999;36:166–71.
50. Consonni D, Pesatori AC, Tironi A, et al. Mortality study in an Italian oil refinery: extension of the follow-up. Am J Ind Med. 1999;35:287–94.
51. Kauppinen T, Pukkala E, Saalo A, et al. Exposure to chemical carcinogens and risk of cancer among Finnish laboratory workers. Am J Ind Med. 2003;44:343–50.
52. Lewis RJ, Schnatter AR, Drummond I, et al. Mortality and cancer morbidity in a cohort of Canadian petroleum workers. Occup Environ Med. 2003;60:918–28.
53. Collins JJ, Ireland B, Buckley CF, et al. Lymphohaematopoeitic cancer mortality among workers with benzene exposure. Occup Environ Med. 2003;60:676–9.
54. Sorahan T, Kinlen LJ, Doll R. Cancer risks in a historical UK cohort of benzene exposed workers. Occup Environ Med. 2005;62:231–6.
55. Swaen GM, Scheffers T, de Cock J, et al. Leukemia risk in caprolactam workers exposed to benzene. Ann Epidemiol. 2005;15(1):21–8.
56. Hoshuyama T, Pan G, Tanaka C, et al. Mortality of iron-steel workers in Anshan, China: a retrospective cohort study. Int J Occup Environ Health. 2006;12:193–202.
57. Gun RT, Pratt N, Ryan P. Update of mortality and cancer incidence in the Australian petroleum industry cohort. Occup Environ Med. 2006;63:476–81.
58. Baccarelli A, Tretiakova M, Gorbanev S, et al. Risk of lung cancer and exposure to industrial acids, solvents, and metals in leningrad province, Russia. J Occup Environ Med. 2006;48(1):48–55.
59. McHugh MK, Kachroo S, Liu M, et al. Assessing environmental and occupational risk factors for lung cancer in Mexican-Americans. Cancer Causes Control. 2010;21:2157–64.
60. Budroni M, Sechi O, Cesaraccio R, et al. Incidenza di patologie neoplastiche nei lavoratori del complesso petrolchimico di Porto Torres, 1990–2006 [Cancer incidence among petrochemical workers in the Porto Torres industrial area, 1990–2006]. Med Lav. 2010;101(3):189–98 **(in Italian)**.
61. Koh DH, Kim TW, Yoon YH, et al. Lymphohematopoietic cancer mortality and morbidity of workers in a refinery/petrochemical complex in Korea. Saf Health Work. 2011;2:26–33.
62. Bonneterre V, Mathern G, Pelen O, et al. Cancer incidence in a chlorochemical plant in Isère, France: an occupational cohort study, 1979–2002. Am J Ind Med. 2012;55:756–67.
63. Koh DH, Chung EK, Jang JK, et al. Cancer incidence and mortality among temporary maintenance workers in a refinery/petrochemical complex in Korea. Int J Occup Environ Health. 2014;20:141–5.
64. Collins JJ, Anteau SE, Swaen GM, et al. Lymphatic and hematopoietic cancers among benzene-exposed workers. J Occup Environ Med. 2015;57:159–63.
65. Linet MS, Yin SN, Gilbert ES, Chinese Center for Disease Control and Prevention-U.S. National Cancer Institute Benzene Study Group, et al. A retrospective cohort study of cause-specific mortality and incidence of hematopoietic malignancies in Chinese benzene-exposed workers. Int J Cancer. 2015;137:2184–97.
66. Mattei F, Liverani S, Guida F, ICARE Study Group, et al. Multidimensional analysis of the effect of occupational exposure to organic solvents on lung cancer risk: the ICARE study. Occup Environ Med. 2016;73:368–77.
67. Gustavsson P, Andersson T, Gustavsson A, et al. Cancer incidence in female laboratory employees: extended follow-up of a Swedish cohort study. Occup Environ Med. 2017;74:823–6.
68. Warden H, Richardson H, Richardson L, et al. Associations between occupational exposure to benzene, toluene and xylene and risk of lung cancer in Montréal. Occup Environ Med. 2018;75:696–702.
69. Bonzini M, Grillo P, Consonni D, et al. Cancer risk in oil refinery workers: a pooled mortality study in Italy. Med Lav. 2019;110:3–10.
70. Wan W, Peters S, Portengen L, et al. Occupational benzene exposure and lung cancer risk: a pooled analysis of 14 case-control studies. Am J Respir Crit Care Med. 2023;209(2):185–96.
71. Babigumira R, Veierød MB, Hosgood HD, et al. Benzene exposure and risk of lung cancer in the Norwegian Offshore Petroleum Worker cohort: a prospective case-cohort study. Occup Environ Med. 2023;81(1):e109139.
72. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58.
73. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.
74. Hayes RB, Yin SN, Dosemeci M, et al. Mortality among benzene-exposed workers in China. Environ Health Perspect. 1996;104(Suppl 6):1349–52.
75. Greco T, Zangrillo A, Biondi-Zoccai G, Landoni G. Meta-analysis: pitfalls and hints. Heart Lung Vessel. 2013;5(4):219–25.
76. Chiavarini M, Rosignoli P, Sorbara B, et al. Benzene exposure and lung cancer risk: a systematic review and meta-analysis of human studies. Int J Environ Res Public Health. 2024;21:205.

77. Falzone L, Marconi A, Loreto C, et al. Occupational exposure to carcinogens: Benzene, pesticides and fibers (Review). Mol Med Rep. 2016;14:4467–74.
78. Snyder R, Hedli CC. An overview of benzene metabolism. Environ Health Perspect. 1996;104(Suppl 6):1165–71.
79. Rappaport SM, Kim S, Lan Q, et al. Human benzene metabolism following occupational and environmental exposures. Chem Biol Interact. 2010;184:189–95.
80. Spyratos D, Zarogoulidis P, Porpodis K, et al. Occupational exposure and lung cancer. J Thorac Dis. 2013;5(Suppl 4):S440–5.
81. Gustavsson P, Jakobsson R, Nyberg F, Pershagen G, Järup L, Schéele P. Occupational exposure and lung cancer risk: a population-based case-referent study in Sweden. Am J Epidemiol. 2000;152(1):32–40.
82. Axelson O, Steenland K. Indirect methods of assessing the effects of tobacco use in occupational studies. Am J Ind Med. 1988;13:105–18.
83. Tsai SP, Wendt JK, Hunter RB. Trends in cigarette smoking among refinery and petrochemical plant employees with a discussion of the potential impact on lung cancer. Int Arch Occup Environ Health. 2001;74:477–82.
84. Gandini S, Botteri E, Iodice S, et al. Tobacco smoking and cancer: a meta-analysis. Int J Cancer Int J Cancer. 2008;122:155–64.
85. Petersen I. The morphological and molecular diagnosis of lung cancer. Dtsch Arztebl Int. 2011;108(31–32):525–31.
86. Thandra KC, Barsouk A, Saginala K, et al. Epidemiology of lung cancer. Contemp Oncol (Pozn). 2021;25:45–52.