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Occupational Exposure to Benzene and Risk of Breast Cancer: Systematic Review and Meta-Analysis

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Abstract

Introduction: *Benzene is a recognized carcinogen; however, its association with breast cancer is not well established. Hence, a meta-analysis of cohort and case-control studies was performed to determine the association between occupational benzene exposure and the risk of breast cancer.* **Methods:** *A systematic literature review identified 7573 publications from which 23 cohort and case-control studies were retained and evaluated using meta-analyses (random effects model). PRISMA guidelines were followed. Our protocol was registered in the PROSPERO database (Registration No. CRD42022379720). Study quality was assessed using a modified Newcastle-Ottawa scale (NOS).* **Results:** *The summary relative risk (RR) for ever-benzene exposure was 1.17 (95% CI=1.06-1.28, I2=38.6%,p=0.032, n=23 risk estimates); corresponding RR for cancer incidence and mortality were 1.17 (95% CI=1.05-1.29, I2=56.1%,p=0.003, n=16) and 1.09 (95% CI=0.86-1.38, I2<0.001%,p=0.96, n=10). However, heterogeneity was not detected for publication year (p-het=0.10), study design (p-het=0.78), study quality (p-het=0.06), and industry of employment (p-het=0.86). The RR for a high level of exposure showed a positive association with breast cancer 1.35 (95% CI=1.06-1.72, I2 =<0.001%,p=0.65, n=3) and (P-het=0.87). Publication bias was detected (p=0.03).* **Conclusions:** *The results of our meta-analysis indicate a positive association between occupational benzene exposure and an increased risk of breast cancer, particularly when exposed to higher levels of benzene. However, bias and confounding could not be excluded.*

1. Introduction

According to the 2022 GLOBOCAN database, breast malignancy is a leading cause of cancer incidence and mortality, with an estimated 2.3 million new cases accounting for 11.7% of all cancer cases worldwide. With 666,103 deaths reported in 2022, it serves as the fourth leading cause of cancer mortality globally [1]. The risk of breast cancer is affected by several factors, including aging, family history, reproductive history, genetics, and estrogen levels.

Although there is a firmly established correlation between lifestyle variables such as alcohol

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consumption, there is limited evidence that malignancy of the breast is also associated with exposure to several environmental carcinogens such as 1,3-butadiene, ethylene oxide (EtO), methylene chloride, benzene, and other solvents [2, 3]. The occupational setting is one of the primary sources of benzene exposure. Benzene is an aromatic hydrocarbon that may be found in natural reservoirs, industrial processes, and daily human activities. It is also utilized as a starting or intermediate material in chemical processes and manufacturing in several industries. Occupations reported to have the highest benzene exposure include chemical, manufacturing, steel, paint, shoes, rubber, textile, cleaning, electronics, leather, fur processing, and petroleum and crude-oil extraction and refining [4]. In addition, benzene exposure is observed among workers involved in the transportation of gasoline, service station workers, lab technicians, firefighters, workers in the printing and publishing industry, and other occupations with exposure to exhaust from motor vehicles [5]. At the workplace, the route of exposure to benzene is primarily through inhalation and dermal absorption [6-8].

Benzene has been categorized as a class 1 carcinogen in humans. The International Agency gives this classification for Research on Cancer (IARC) due to sufficient evidence in humans about benzene's association with leukemia, particularly acute myeloid leukemia (AML) [9-14]. Previous studies have shown that benzene exposure is linked to teratogenic effects and may lead to an increased risk of breast cancer due to mutations. Benzene and its byproducts may disrupt the endocrine system, leading to dysplasia and neoplastic transformation in the mammary gland. In its pure form, benzene is a colorless, highly flammable, and volatile liquid that has historically been used as an industrial solvent. Within humans, benzene's primary metabolites include benzene-oxide, hydroquinone, phenol, and catechol, all of which have been evaluated for their carcinogenic activity. The conversion of benzene to these metabolites is the most critical path accounting for benzene toxicity in humans [15-18].

Limited cohort and case-control studies investigating the association of benzene exposure and breast cancer have been published, providing inconsistent findings. It is challenging to isolate benzene exposure from external lifestyle or environmental factors because it usually occurs in conjunction with other chemicals in various occupations [19]. Even still, the health effects of benzene may best be studied in occupational settings where confounding variables may be limited, and dose and duration of exposure may be better measured. In addition, there is a lack of studies evaluating industrial occupations with sufficient dosage and duration of benzene exposure, and studies of female workers tend to be small [19-22].

This meta-analysis seeks to investigate the potential relationship between occupational benzene exposure and the incidence of breast cancer. The study employed a quantitative assessment approach, utilizing cohort and case-control studies.

2. Methods

2.1. Data Sources, Search Strategy

This systematic review and meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [23]. After building a study protocol, it was registered in the Prospective Registry of Systematic Reviews, PROSPERO database (Registration No. CRD42022379720).

The PECOS (Participants; Exposition; Comparators; Outcomes; Study Design) criteria was followed while conducting a comprehensive systematic review. The objective of this study was to include all publications that reported results on occupational exposure to benzene and the associated risk of solid tumors. All relevant publications quoted in the IARC Monograph on benzene exposure published in 2018 were included. In addition, a search of the PubMed, SCOPUS, and EMBASE (Ovid) databases was conducted on the association between occupational exposure to benzene and risk (incidence and mortality) of any solid cancer type by two independent researchers (MSS and MB). The first search was completed in December 2022 and then in April 2024 we updated it. Details of the overall project and results of other than breast cancer reported elsewhere [24, 25, 70].

A string for the search was created by using certain words or phrases (neoplasms * or carcinoma * or cancer * or malignant *) and (benzene * or benzol * or cyclohexa-1* or 3 5 triene * or 5-cyclohexatriene * or 5-cyclohexatriene *) [All Fields]). For this study, these, only studies reporting risk estimates for breast cancer were retained. (The complete search string is reported in Supplementary Table 1).

2.2. Eligibility Criteria

The goal of this study was to include all publications that reported relative risks (RRs) of breast cancer for occupational benzene exposure. For the systematic review, the literature search of titles, abstracts, and full-text publications was independently conducted by two authors (MSS and MB), with the goal of identifying occupational exposure to benzene among workers in a variety of jobs and industries. In order to select a study for this meta-analysis, the following inclusion criteria were established: (i) peer-reviewed industry-based cohort or case-control (including nested case-control within a cohort) studies 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), shoemakers, paint production and painters, chemical industry, rubber industry, printing, laboratory workers; (ii) community-based case-control studies, if they reported results on benzene exposure (not on job/industry of employment). For the studies, the reference population was either an occupational-specific or a general population, not exposed to benzene. The outcome measures were either incident cases or deaths from breast cancer, predominantly among females (with 4 out of the 21 studies also reporting analysis for breast cancers among males). Studies reporting odds ratio (OR), standardized incidence ratio (SIR), standardized mortality ratio (SMR), risk ratio/relative risk (RR), hazard ratio (HR), including their 95% Confidence Intervals (CI), or sufficient data for their computational analysis were included.

Conversely, the exclusion criteria utilized for the systematic literature search included: (i) conference abstracts, letters, book chapters, descriptive, ecological, and cross-sectional studies, as well as systematic reviews or meta-analyses that did not mention or include analysis on benzene exposure; (ii) studies on non-solid tumors including leukemia, lymphoma or myeloma; (iii) studies on solid tumors and benzene not reporting OR, SIR, SMR, RR, HR or sufficient data to compute them. In instances where multiple publications referenced the same study population, the publication with the highest number of cases, or the one considered the most comprehensive, was included. To minimize the effects of confounding variables such as exposure to other chemicals or toxins, workers with occupational benzene exposure were only included if the study explicitly isolated benzene as the primary carcinogen. A flow diagram of the literature search and study selection process has been provided in Supplementary Figure 1.

Two sets of independent reviewers (MSS and MB) carefully examined the abstracts, titles, and full texts of the remaining studies. They then meticulously analyzed each study to extract pertinent data to advance the study's goals. Given the aforementioned inclusion and exclusion criteria, the two independent sets of researchers were in concordance with the studies selected for this meta-analysis.

2.3. Data Extraction

Utilizing a standardized template form, data was recorded independently by five authors (MSS, MB, DS, VD, and VS) on (i) author details, (ii) publication year, (iii) publication title, (iv) country/geographical location, (v) type of study design, (vi) period of employment, (vii) study's overall sample size, (viii) occupation and industry-type (with mixed industry defined as a combination of occupations with benzene exposure at work), (ix) type of cancer (including topography and histology), (x) workers' sex, (xi) ICD code associated with breast cancer, (xii) outcomes (incidence and mortality), (xiii) duration of benzene exposure (based on years of employment), (xiv) effects size measures including the relative risks (HRs/RRs/SMRs) for the cohort studies and the odds ratios (ORs) for the case-control studies and their corresponding 95% CI, (xv) number of outcome cases, (xvi) factors adjusted, such as but not limited to body mass index (BMI), smoking status, alcohol consumption, family history of breast cancer,

age at menarche/menopause, and exposure to other occupational solvents.

2.4. Quality Assessment

The study's quality metric was assessed by utilizing the original version of the Newcastle-Ottawa Scale (NOS) [26]. For a total score of 9 (for case-control studies) and 10 (for cohort studies), the NOS study checklist utilized for this study included eight questions. The mean of the scores assigned independently by four reviewers (MSS, DS, VD, and VS) was used to calculate this meta-analysis's final NOS QA score. Summary statistics were performed on the NOS scores that were obtained. Subgroup analysis was then conducted for studies < or ≥ median NOS score. NOS quality assessment questions and the corresponding assigned scores for each paper are provided in Supplementary Tables 2 and 3. A fifth author (PB) resolved any significant discrepancies throughout the study inclusion, data collection, and the quality assessment process.

2.5. Meta-Analysis

Both breast cancer incidence and mortality data were combined to begin the analysis. Our overall analysis included only mortality for the studies where incidence and mortality were reported. However, each respective metric was incorporated for pertinent cohort analysis. Subgroup analyses were performed based on outcomes (incidence and mortality), study type (cohort, case-control), study region (North America, Europe, Eastern Hemisphere), participants' sex (female, male), industry type (oil industry, chemical industry, miscellaneous (rubber, shoe, and printing industries) and mixed industries), publication year (<2003 and ≥2003), NOS quality score (< median, and ≥ median), and different level of exposure [low, medium, high (Supplementary Table 4)].

Based on the random-effects model, meta-analyses of non-overlapping studies were conducted, and RRs and 95% CIs were estimated [27]. Statistical heterogeneity was calculated by utilizing Cochran's Q test and I2 statistic.

Egger's test and a visual examination of the funnel plot [28] evaluated publication bias. This study's statistical analyses were computed in STATA, version 17.0 BE (Stata Corp., College Station, TX, US).

3. Results

A total of 7,573 studies were obtained from IARC monograph, PubMed, EMBASE, and SCOPUS. In the literature search of recent studies, after a review of the title and abstract, 1,669 publications from the list were excluded while accounting for duplicates. Further, 5,750 manuscripts were excluded upon abstract screening. Out of 154 reports retained with risk estimates for solid cancers, 74 were excluded upon full-text evaluation. Of those 80 studies remaining, 23 were included that reported risk estimates for breast cancer in males and females. The flow chart displaying the selection of the research studies is included in Supplementary Figure 1.

This meta-analysis included 23 studies from various geographical regions: 4 in North America (3 in the United States, 1 in Canada) and 15 in Europe (1 in the United Kingdom, 3 in Italy, 2 in Finland, 1 in Sweden, 1 in Denmark, 2 in Poland, 1 in France, 1 in Russia, 1 in Norway, and 2 mixed), 4 in Eastern Hemisphere Countries (1 in Australia, 2 in China, and 1 in Taiwan). These included 16 studies based on incidence and ten studies based on mortality. The median NOS score was 8 (range: 5.5-10.0). Characteristics of the included studies are reported in Table 1.

Utilizing a random-effects analysis model, the overall RR was 1.17 (95% CI=1.06-1.28, I2=38.6%,p=0.03, n=23 risk estimates, Figure 1). After stratification by the outcome, the summary RR was 1.17 (95% CI=1.05-1.29. I2 =56.1%, p=0.003, n=16, Figure 2) for studies based on incidence and 1.09 (95% CI=0.88-1.37, I2<0.001%, p=0.96, n=10, Figure 3) for studies based on mortality. Exclusion of one study at a time did not provide evidence for results being strongly dependent on a single study (Supplementary Figure. 3).

The results of the stratified analyses are reported in Table 2. Using a random effects model, heterogeneity was demonstrated in the sub-group analysis of

Table 1. Main characteristics of the studies included in the meta-analysis.

First author, year	Country	Study period	Study Design	Type of study	Type of workers	Exposure assement method	Overall Study Sample size	Sex, male, female (%)	Outcome	Variables adjusted for in the analysis other than gender, age and calendar period	NOS score
(Paci et al. 1989) [29]	Italy	1950-84	Cohort	Industry-based	Shoe workers	Documents (plant and inspection records, and information from the glue suppliers)	M 1,008 F 1,005	M 50.1% F 49.9%	Mortality	-	8
(Szeszenia-Dabrowska et al. 1991) [30]	Poland	1945-85	Cohort	Industry-based	Rubber Workers	Job title	M 6978	M 100%	Mortality	-	6
(Lagorio et al. 1994) [31]	Italy	1981-92	Cohort	Industry-based	Service (gas) station attendants	Available employment documents	M 2,308 F 357	M 86.6% F 13.4%	Mortality	-	7
(Satin et al. 1996) [32]	USA	1937-87	Cohort	Industry-based	Oil refinery workers	Job title and available employment documents	M 15,855 F 1,989	M 88.9% F 11.1%	Mortality	-	7
(Collingwood et al. 1996) [33]	USA	1946-87	Cohort	Industry-based	Petroleum refinery	Job title and available employment documents	M 4,433 F 422	M 91.3% F 8.7%	Mortality	-	8
(Lynge et al. 1997) [34]	European Nordic countries: Denmark, Norway, Sweden, Finland	1970-87	Cohort	Community-based	Service station workers	Job title and available employment documents (skin exposure and inhalation)	M 16,524 F 2,445	M 87.1% F 12.9%	Incidence	Smoking status, and alcohol consumption rates considered but not completely adjusted for	7
(Pukkala 1998) [35]	Finland	1971-94	Cohort	Industry-based	Oil refinery	Job title	M 7,512 F 1,942	M 79.4% F 20.6%	Incidence	-	7
(Petralia et al. 1998) [36]	China	1980-84	Cohort	Industry-based	Various jobs with benzene exposure	Job title (questionnaire)	2623	F 100%	Incidence		5.5

(*Continued*)

First author, year	Country	Study period	Study Design	Type of study	Type of workers	Exposure assement method	Overall Study Sample size	Sex, male, female (%)	Outcome	Variables adjusted for in the analysis other than gender, age and calendar period	NOS score
(Bulbulyan et al. 1999) [37]	Russia	1979-93	Cohort	Industry-based	Bookbinders printing industry	Air sampling data	3,473	F 100%	Mortality	-	8
(Petralia et al. 1999) [38]	USA	1986-91	Case control	Hospital-based	Various jobs with benzene exposure	Job exposure matrix	301 cases / 316 controls	F 100%	Incidence		7
(Kauppinen et al. 2003) [39]	Finland	1979-88	Cohort	Industry-based	Chemical laboratory	Job title and employment documents (skin exposure and inhalation)	M 1,037 F 3,673	M 22% F 78%	Incidence	-	8
(Lewis et al. 2003) [40]	Canada	1964-94	Cohort	Industry-based	Petroleum workers	Job title and available employment documents (skin exposure and inhalation)	M 17,230 F 8,062	M 68.1% F 31.9%	Incidence, Mortality	Time since hire	8
(Sorahan et al. 2005) [41]	UK	I: 1971-2001 M: 1968-2002	Cohort	Industry-based	Various jobs with benzene exposure	Job title and available employment documents (skin exposure and inhalation)	M 5,130 F 384	M 93.1% F 6.9%	Incidence, Mortality	-	8
(Costantini et al. 2009) [42]	Italy	1950-2003	Cohort	Industry-based	Shoe factory workers	Industry based job exposure matrix.	F 797	F 100%	Incidence, Mortality	-	7
(Peplonska et al. 2010) [43]	Poland	2000-2003	Case control	Population-based	Various jobs with benzene exposure	Job title (questionnaire)	2,383 cases / 2,502 controls	F 100%	Incidence	Study site, education, body mass index, age at menarche, menopausal status, age at menopause, number of full-term births, age at first full-term birth, breastfeeding, family history of breast cancer and previous screening mammography.	8

(Bonneterre et al. 2012) [44]	France	1979-2002	Cohort	Industry-based	Chlorochemical plant workers	Job title (questionnaire)	M 2,742	M 100%	Incidence	Date of hire	7.5
(Linet et al. 2015) [45]	China	1972-1999	Cohort	Industry-based	Various jobs with benzene exposure	Job title and other details (Available documents and self report)	73,789 benzene-exposed and 34,504 unexposed workers	F 100%	Mortality	-	8
(Glass et al. 2015) [46]	Australia	2009-2011	Case control	Population-based	Various jobs with benzene exposure	Job title (questionnaire)	1,205 cases / 1,789controls	F 100%	Incidence	Exposure to other solvents	8
(Gustavsson et al. 2017) [47]	Sweden	1950-89	Cohort	Industry-based	Chemical laboratory workers	Job title and other details (documents and self report)	F 2,245	F 100%	Incidence	-	8
(Laouali et al. 2018) [48]	European countries (Denmark, France, Germany, Italy, Latvia, Portugal, Spain, and Sweden)	1995-97	Case control	Population-based	Various jobs with benzene exposure	Job title (questionnaire)	104 cases / 1,901 controls	M 100%	Incidence	Country, education, body mass index, alcohol consumption, all solvents	8.5
(Pedersen et al. 2020) [49]	Denmark	1964-2016	Case control	Population-based	Various jobs with benzene exposure (1-9y)	Job title (questionnaire)	F 38,375	F 100%	Incidence	Parity, age at first live birth, heavy physical activity at work, reproductive factors, socioeconomic status	8
(Liu et al. 2022) [50]	Norway	1965-98	Cohort	Industry-based	Petroleum workers	Job title and other details (documents and self report)	F 600 (86 cases and 514 non-cases)	F 100%	Incidence	Education	10
(Westra S et al., 2023) [51]	Canada	2008-11	Case control	Population-based	Various jobs with benzene exposure	Job title (questionnaire)	1246 (661 case and 587 cntrol)	F 100%	Incidence	-	5.5

HR: hazard ratio, SMR: standardized mortality ratio, SIR: standardized incidence ratio, RR: relative risk, ICD: International Classification of Diseases. Standardized: as per standard SMR calculation, all studies were adjusted for age, calendar period, and sex.

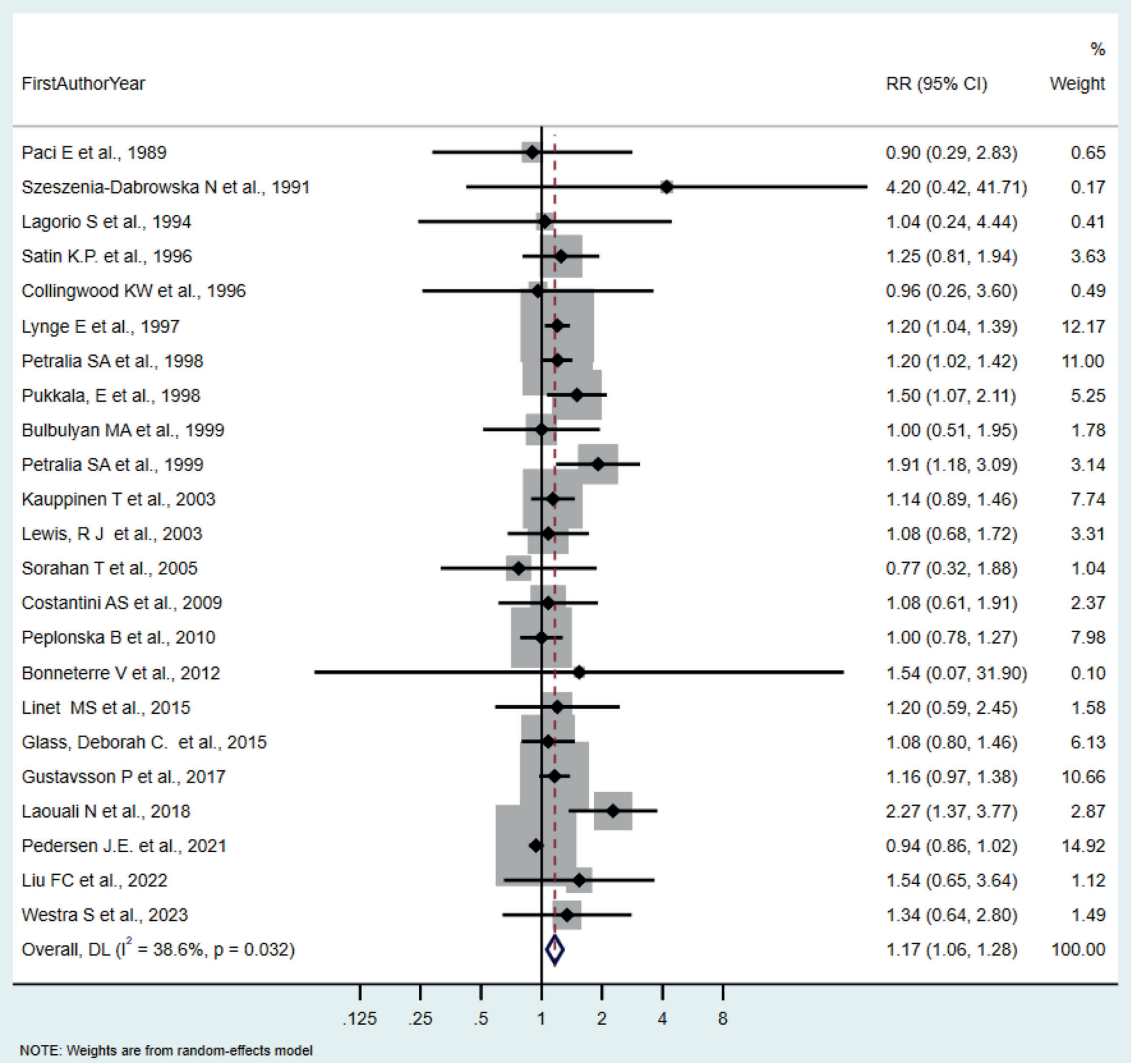

Figure 1. Forest plot with results of the overall meta-analysis of studis on occupational exposure to benzene and breast cancer.

studies. Based on sub-analyses by sex, heterogeneity was detected between sexes (p-het=0.004), and female subjects were observed to have a summary RR of 1.13 (95% CI=1.04-1.22, I2=23.8%,p=0.16, n=21) driven by incidence with an RR of 1.13 (95% CI=1.03-1.24, I2=45.7%, p= 0.03, n=12). Summary RR for males was reported to be 2.33 (95% CI=1.42-3.83, I2<0.001%,p=61, n=2).

No heterogeneity was detected in the subgroup analysis based on quality score (p-het=0.06), years of publication (p-het=0.10), study design (p-het=0.78), geographical region (p-het=0.10), industry of employment type (p-het=0.86), and level of exposure (low, high; p-het=0.87), although the RR for high level of exposure showed positive association with breast cancer 1.35 (95% CI=1.06-1.72, I2 =<0.001%,p=0.65, n=3).

Egger's test was performed to detect publication bias in the included studies; evidence of such bias was found (p=0.03). In addition, qualitatively, asymmetry in the contour-enhanced funnel plot was evident (Supplementary Figure 2).

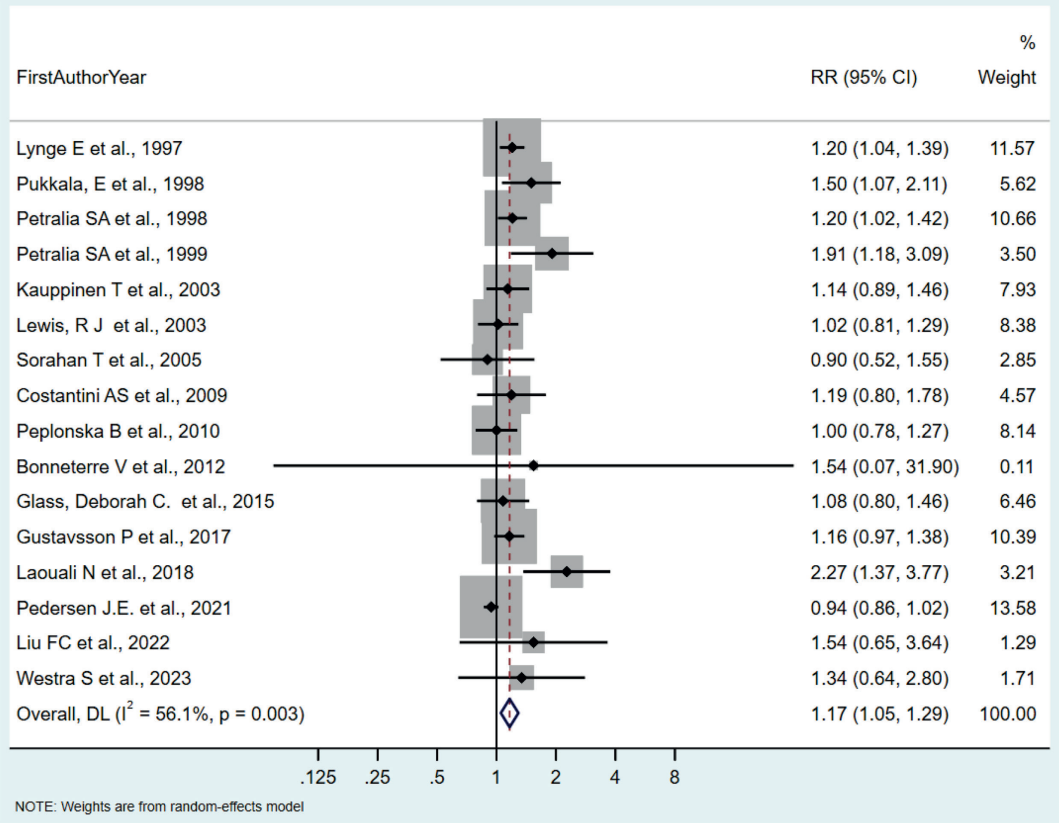

Figure 2. Forest plot with results of the overall meta-analysis of studies on occupational exposure to benzene and incidence of breast cancer.

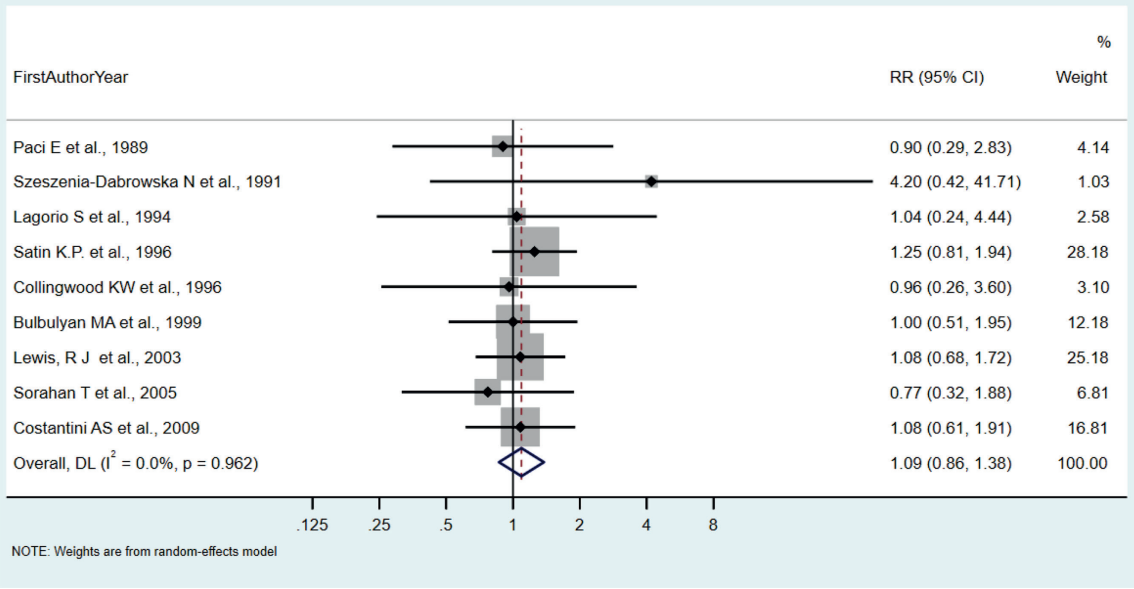

Figure 3. Forest plot with results of the overall meta-analysis of studies on occupational exposure to benzene and mortality of breast cancer.

Table 2. Results of the meta-analysis on the association between occupational exposure to benzene and breast cancer.

Outcome	Stratum	n of risk estimates	RR	95% CI	I^2 (95%CI), p-value	p-het
Incidence and mortality (Overall)	**Overall**	23	1.17	1.06-1.28	38.6% (0.0%-66.4%), 0.03	-
	Sex					0.004
	Female	21	1.13	1.04-1.22	23.8% (0.0%-56.9), 0.16	
	Male	2	2.33	1.42-3.83	<0.001% (0.0%-24.5 %), 0.61	
	Publication year					0.10
	Prior to 2003	10	1.24	1.13-1.37	<0.001% (0.0%-52.7), 0.68	
	2003 or after	13	1.10	0.98-1.23	34.2% (0.0%-64.8) , 0.11	
	Region					0.56
	North America	5	1.34	1.05-1.71	<0.001% (0.0%-64.1%), 0.51	
	Europe	15	1.15	1.02-1.31	52.5% (0.0%-72.7%), 0.01	
	Eastern Hemisphere Countries	4	1.17	1.01-1.34	<0.001% (0.0%-67.9), 0.89	
	Industry Type					0.86
	Petroleum Industry	7	1.23	1.09-1.39	<0.001% (0.0%-40.9%), 0.90	
	Chemical Industry	3	1.15	1.00-1.33	<0.001%(0.0%-0.0%) , 0.98	
	Miscellaneous (shoe, rubber, printing industries.)	4	1.07	0.72-1.60	<0.001% (0.0%-47.0%), 0.68	
	Mixed Industries	9	1.18	0.99-1.41	67.5% (0.0%-88.1%), 0.002	
	Quality score					0.06
	< median	10	1.25	1.13-1.38	<0.001%(0.0%-39.0), 0.74	
	≥ median	13	1.08	0.97-1.21	31.9% (0.0%-67.2), 0.13	
	level of exposure (Dose category)					0.87
	Low	3	1.27	0.66-2.45	72.3% (0.0%-92.7%), 0.03	
	High	3	1.35	1.06-1.72	<0.001% (0.0%-44.7 %), 0.65	
	Study Type					0.78
	Case-control	6	1.24	0.96-1.58	74.8% (0.0%-91.9), <0.001	
	Cohort	17	1.19	1.10-1.29	<0.001% (0.0%-26.9%), 0.99	
Incidence	**Overall**	16	1.17	1.05-1.29	56.1% (0.0%-78.7%), 0.003	-
	Sex					0.008
	Female	15	1.13	1.03-1.24	45.7% (0.0%-73.1%), 0.03	
	Male	1	2.27	1.37-3.77	<0.001% (N/A) , N/A	
	Publication year					0.07
	Prior to 2003	4	1.29	1.12-1.48	34.8% (0.0%-79.7%), 0.20	
	Post-2003	12	1.09	0.98-1.22	40% (0.0%-72.0), 0.07	
	Region					0.84
	North America	3	1.32	0.86-2.04	63.3% (0.0%-90.5%), 0.07	
	Europe	11	1.16	1.02-1.32	61.7% (0.0%-84.0%), 0.004	
	Eastern Hemisphere Countries	2	1.17	1.01-1.36	<0.001% (0.0%-46.4%), 0.54	
	NOS score					0.08
	< median	6	1.25	1.13-1.39	<0.001% (0.0%-58.4%), 0.46	

Outcome	Stratum	n of risk estimates	RR	95% CI	I^2 (95%CI), p-value	p-het
	≥ median	10	1.08	0.96-1.23	53.2% (0.0%-80.7%), 0.03	
Mortality	**Overall**	10	1.09	0.86-1.38	<0.001% (0.0%-18.0), 0.96	-
	Sex					0.25
	Female	9	1.08	0.85-1.36	<0.001% (0.0%-15.3%), 0.99	
	Male	1	4.20	0.42-41.71	<0.001% (N/A), N/A	
	Publication year					0.64
	Prior to 2003	6	1.15	0.83-1.60	<0.001% (0.0%-37.6%), 0.88	
	2003 or after	4	1.03	0.74-1.44	<0.001% (0.0%-26.4%), 0.89	
	Region					0.86
	North America	3	1.15	0.85-1.57	<0.001% (0.0%-37.1%) , 0.87	
	Europe	5	1.02	0.67-1.55	<0.001% (0.0%-38.0%), 0.75	
	Eastern Hemisphere Countries	2	1.00	0.51-1.95	<0.001% (N/A), NA	
	NOS score					0.41
	< median	4	1.21	0.86-1.69	<0.001% (0.0%-52.2%), 0.72	
	≥ median	6	0.99	0.72-1.37	<0.001% (0.0%-17.3%), 0.98	

RR: relative risk, CI: confidence interval, nc: not computable, na: not applicable.

4. Discussion

To our knowledge, this is the first meta-analysis investigating the association between occupational exposure to benzene and breast cancer, providing for an improved characterization of this agent's carcinogenicity. An association between occupational exposure to benzene and breast cancer was elucidated overall, predominantly driven by incidence and particularly when exposed to higher levels of benzene.

Regarding pathogenesis, benzene is detoxified in the liver via the CYP2E1 cytochrome P450 system, producing harmful benzene-oxide metabolites. Toxic effects of benzene oxide-oxepin have been confirmed in vivo, whereby this metabolite blocks one-electron oxidation by cytochrome P450 monooxygenase, resulting in the (E, Z)-muconaldehyde. Benzene-oxide may induce significant genotoxicity and thus yield malignancy [15, 18]. Additionally, the lung may metabolize benzene, whereby the CYP2F1 and CYP2A13 enzymes produce the toxic benzene-oxide metabolites. *In vivo*, benzene-oxide is in equilibrium with its tautomer, oxepin, which may spontaneously form phenol, and excess metabolite may be hydrolyzed to produce catechol and 1,2-benzoquinone. These metabolites are then further catalyzed to produce S-phenylmercapturic acid. Benzene and its metabolic byproducts have demonstrated the potential to induce hematotoxicity, chromosomal aberrations, and selective chromosomal aneuploidy. Such genotoxic alterations may present with variations in microRNA expression [52].

These toxic metabolites may have teratogenic effects, as evidenced by maternal benzene exposure with subsequent alterations in the developmental and functional properties of hematopoietic stem cells in fetuses and children [53]. Of relevance, *in vivo*, experimentation has demonstrated a correlation between benzene exposure and breast cancer risk, specifically frequent p53 and H-ras mutations inducing mammary gland carcinomas [54-57]. In addition to the genotoxic effects, benzene and its toxic byproducts may exhibit endocrine-disrupting properties [58-60]. For example, such compounds may bind to the estrogen receptors of the breast, interfere with the normal function of estrogen-mediated pathways, and alter gene expression [61]. As a result, the

mammary gland is at risk of dysplasia and neoplastic transformation [62, 63].

Studies published before 2003 demonstrated an association, while those published in the year 2003 or after did not. This may be validated by a 1997 alignment of North American and European regulatory standards, which limit benzene exposure to 1.63-3.25 mg/m3 (0.5-1 ppm) [64]. One may speculate that this finding is due to improved occupational benzene safety over time; however, this finding requires further inquiry. Despite not discovering any noteworthy disparity between low and high levels of exposure, it is worth noting that a higher level of exposure exhibited a stronger correlation. Furthermore, these findings were particularly pronounced in workplaces related to petroleum and chemistry.

The evaluation of sub-groups based on study design showed varied results. A correlation was observed in cohort studies, possibly due to the higher number of cohort studies (n=17) compared to case-control studies (n=6) in this analysis. However, it is crucial to acknowledge that cohort studies may lack adjustments in their modeling to account for confounding variables, including cigarette smoke, secondhand tobacco smoke, alcohol consumption, genetic mutations such as BRCA, family history, and exposure to other environmental toxins [65-69].

Our study has several strengths. First, this is the only systematic review and meta-analysis regarding the risk of breast cancer in workers with occupational exposure to benzene. To ensure a comprehensive analysis, we extensively screened and reviewed the literature, including all relevant recent studies. Data analysis was performed with a validated methodology for meta-analysis. Five authors (MSS, MB, DS, VD, and VS) independently verified all aspects of data extraction and quality assessment, thereby optimizing accuracy and comprehensiveness of the overall analysis. Additionally, this association was depicted from various perspectives by computing several stratified calculations. Overall heterogeneity was tested and was observed to be I2<50% for all the studies.

Our study has limitations. We found evidence of publication bias, which could be interpreted because of some variation in the study design of different studies and included subjects' features, for example, hormone-related breast cancer or menopause situation and so on. Only 8 of the 23 studies evaluated adjusted for at least one confounding variable other than age and period calendar, and therefore, insufficiently accounted for possible confounding effects or bias. Due to limited control over confounding variables, we were unable to address the impact of individual participants' characteristics in each study, such as reproductive histories compared to referent populations (e.g., individuals with children being more likely to leave the workforce) or low socioeconomic status. These factors may have led to over- or under-estimate of the results. Also, we couldn't fully evaluate the impact of different durations of benzene exposure and time since cessation of exposure due to limited studies and risk estimates. Furthermore, with studies that collected exposure through questionnaires or self-reports, there could be a possibility of interview or memory bias, which may lead to differential misclassification. In addition, our results cannot be generalized to male breast cancer cases as there was an insufficient sample size of male breast cancer studies to run any meaningful statistics or draw remarkable conclusions.

5. Conclusion

In conclusion, our meta-analysis has found a correlation between occupational benzene exposure and the incidence of breast cancer, although bias and confounding prevent any conclusion in terms of causality. Nonetheless, it is recommended that workers take necessary safety precautions to avoid the potential adverse health consequences associated with such exposure. To fully understand the relationship between occupational benzene exposure and the risk of breast cancer, future studies should be well-designed. They should consider factors such as varying duration of exposure, clinical and hormonal characteristics of breast tumors, and other important confounders. These studies will help in complying with the newer occupational benzene exposure regulations.

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Declaration on the use of AI: None.

Supplementary Materials:
Supplementary Table 1: Detailed search strategy used on the different databases.
Supplementary Figure 1. Flow diagram of the study selection process.
Supplementary Figure 2. Contour-enhanced funnel plot to study publication bias in breast cancer studies with incidence and mortality combined.
Supplementary Figure 3: Leave-one-out meta-analysis for the association between occupational benzene exposure and breast cancer incidence and mortality combined.
Supplementary Table 2. Modified version of the Newcastle-Ottawa Scale (NOS) for case-control studies adopted for quality assessment.
Supplementary Table 3. Modified version of the Newcastle-Ottawa Scale (NOS) for cohort studies adopted for quality assessment.
Supplementary Table 4. Details of results on level-response relationship

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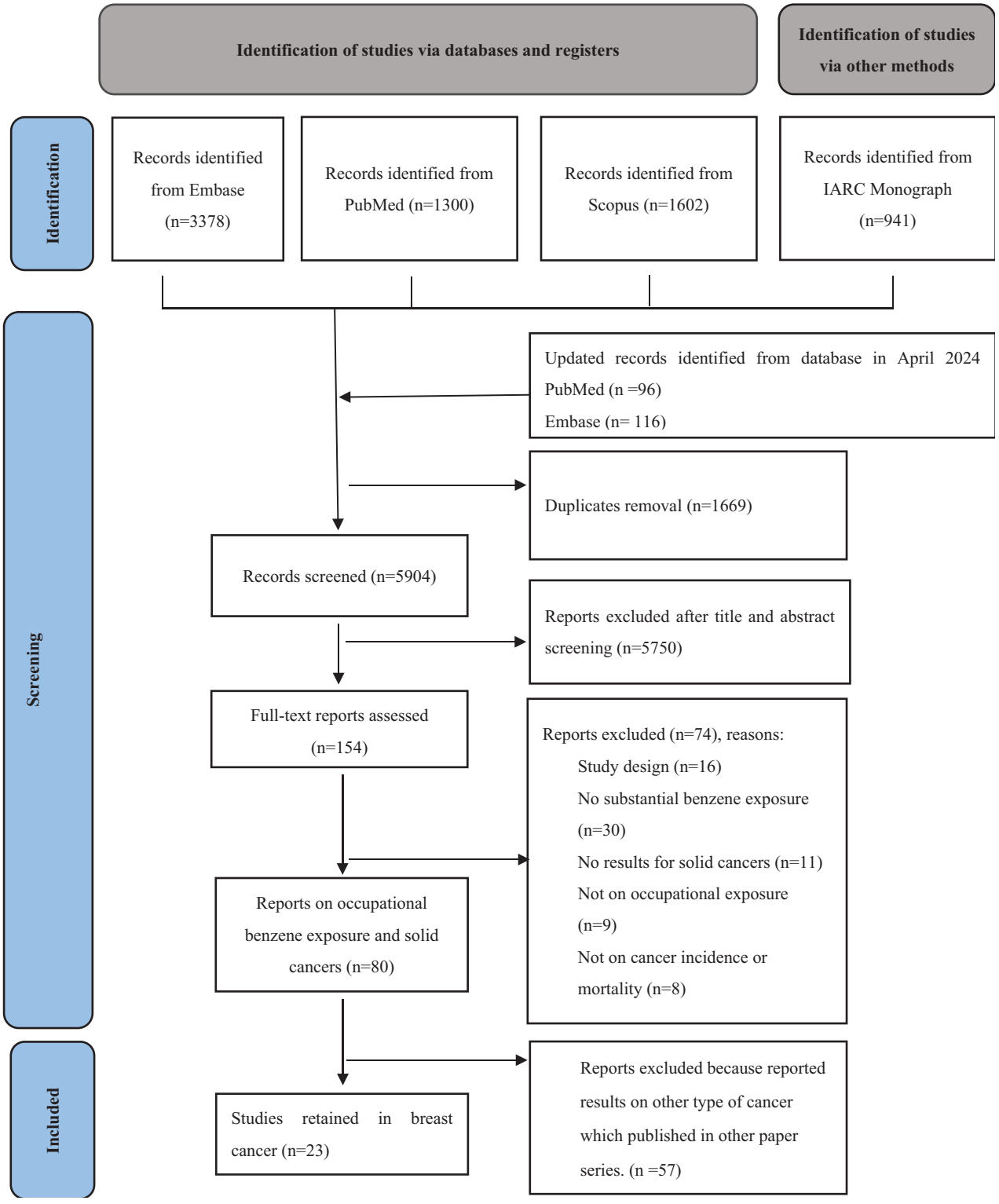
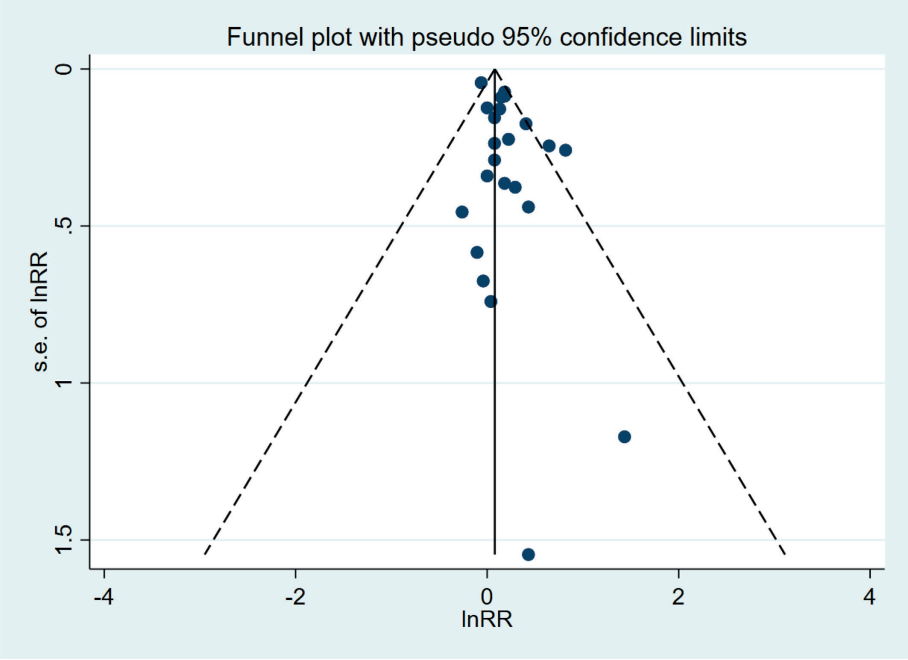
Supplementary Material

Supplementary Table 1. Detailed search strategy used on the different databases.

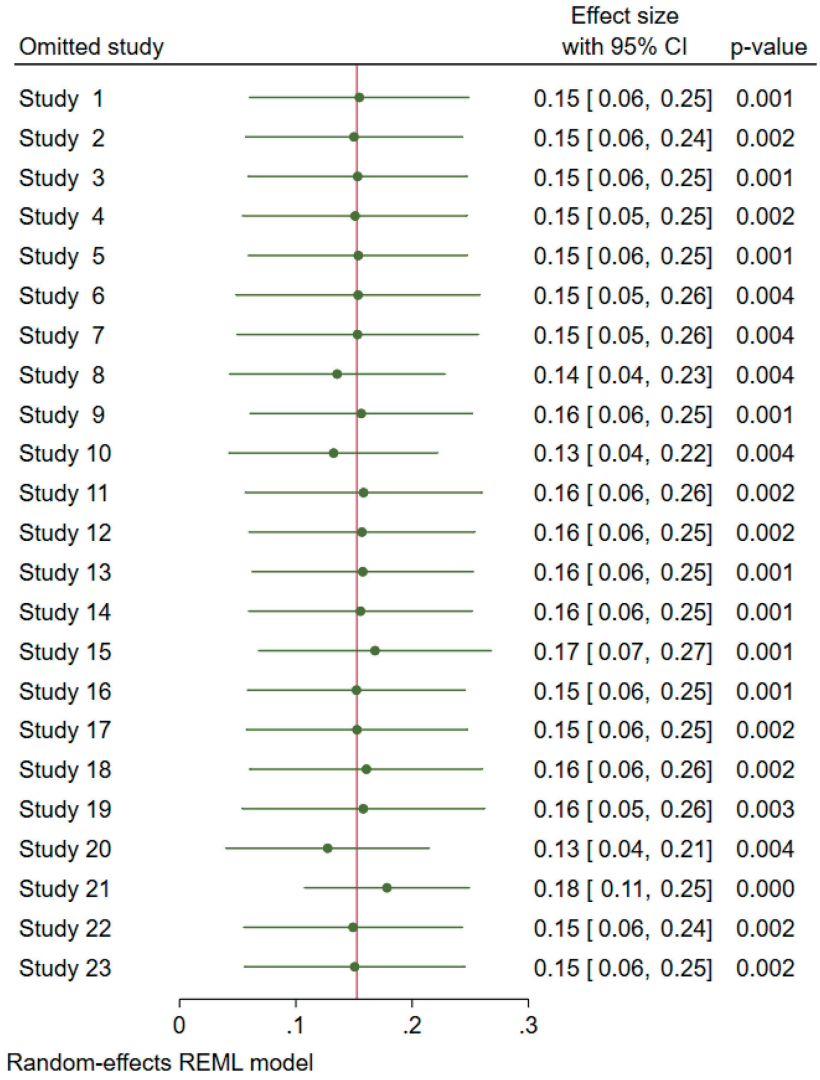
Database	Search string
PubMed	(("neoplasms"[Title/Abstract] OR "carcinoma"[Title/Abstract] OR "cancer"[Title/Abstract] OR "malignant"[Title/Abstract]) AND ("benzene"[Title/Abstract] OR "benzol"[Title/Abstract] OR ("cyclohexa-1"[All Fields] AND "3 5 triene"[Title/Abstract]) OR (("1"[All Fields] AND "3"[All Fields]) AND "5-cyclohexatriene"[Title/Abstract]) OR "cyclohexatriene"[Title/Abstract])) AND ((humans[Filter]) AND (english[Filter] OR french[Filter] OR german[Filter] OR italian[Filter] OR spanish[Filter]))
Embase (Ovid)	("benzene" or "benzol" or "cyclohexa-1,3,5-triene" or "1,3,5-cyclohexatriene" or "cyclohexatriene").tw. and ("neoplasms" or "carcinoma" or "cancer" or "malignant").tw. limit to ((behavioral & social sciences or clinical medicine or health professions or life sciences or medical humanities or nursing or patient education or public health or science) and original articles)
Scopus	((TITLE-ABS-KEY (benzene) OR TITLE-ABS-KEY (benzol) OR TITLE-ABS-KEY (cyclohexa-1,3,5-triene) OR TITLE-ABS-KEY (1,3,5-cyclohexatriene) OR TITLE-ABS-KEY (cyclohexatriene))) AND ((TITLE-ABS-KEY (neoplasms) OR TITLE-ABS-KEY (carcinoma) OR TITLE-ABS-KEY (cancer) OR TITLE-ABS-KEY (malignant))) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re")) AND (LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "ENVI")) AND (LIMIT-TO (LANGUAGE , "English") OR LIMIT-TO (LANGUAGE , "German") OR LIMIT-TO (LANGUAGE , "Italian") OR LIMIT-TO (LANGUAGE , "French") OR LIMIT-TO (LANGUAGE , "Spanish")) AND (LIMIT-TO (SRCTYPE , "j")) AND (EXCLUDE (SUBJAREA , "BIOC") OR EXCLUDE (SUBJAREA , "EART") OR EXCLUDE (SUBJAREA , "ENGI") OR EXCLUDE (SUBJAREA , "CENG")) AND (EXCLUDE (SUBJAREA , "COMP") OR EXCLUDE (SUBJAREA , "MATH")) AND (EXCLUDE (LANGUAGE , "Portuguese") OR EXCLUDE (LANGUAGE , "Turkish"))



Supplementary Figure 1. Flow diagram representing selection of studies for inclusion in the review and meta-analysis.



Supplementary Figure 2. Contour-enhanced funnel plot to study publication bias in breast cancer studies with incidence and mortality combined.



Supplementary Figure 3. Leave-one-out meta-analysis for the association between occupational benzene exposure and breast cancer incidence and mortality combined.

Supplementary Table 2.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES (maximum score: 9)
Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1. **Is the case definition adequate?**
   a. yes, with independent validation **(1)**
   b. yes, eg record linkage **(1)** or based on self-reports **(0.5)**
   c. no description **(0)**
2. **Representativeness of the cases**
   a. consecutive or obviously representative series of cases **(1)**
   b. potential for selection biases or not stated **(0)**
3. **Selection of Controls**
   a. community controls **(1)**
   b. hospital controls **(0.5)**
   c. no description **(0)**
4. **Definition of Controls**
   a. no history of disease (endpoint) **(1)**
   b. no description of source **(0)**

Comparability

1. **Comparability of cases and controls on the basis of the design or analysis**
   a. study controls for age, gender, province **(0)**
   b. study controls for age, gender, province +smoking **(1)**
   c. study controls for age, gender, province +smoking + other additional factors **(2)**

Exposure

1. **Ascertainment of exposure**
   a. secure record (eg surgical records) **(1)**
   b. structured interview where blind to case/control status **(1)**
   c. interview not blinded to case/control status **(0.5)**
   d. written self-report or medical record only **(0.5)**
   e. no description **(0)**
2. **Same method of ascertainment for cases and controls**
   a. yes **(1)**
   b. no **(0)**
3. **Non-Response rate**
   a. one or both groups over 90% **(1)**
   b. one or both groups between 60- 90% **(0.5)**
   c. one or both groups under 60% **(0)**
   d. no statement **(0)**

Supplementary Table 3.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES (maximum score: 10)
Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1. **Representativeness of the exposed cohort**
   a. truly representative of the average _____ (describe) in the community **(2)**
   b. somewhat representative of the average _____ in the community **(1)**
   c. selected group of users eg nurses, volunteers **(0.5)**
   d. no description of the derivation of the cohort **(0)**
2. **Selection of the non-exposed cohort**
   a. drawn from the same community as the exposed cohort **(1)**
   b. drawn from a different source **(0.5)**
   c. no description of the derivation of the non-exposed cohort **(0)**
3. **Ascertainment of exposure**
   a. secure record (eg surgical records) **(1)**
   b. structured interview **(1)**
   c. written self-report **(0.5)**
   d. no description **(0)**
4. **Demonstration that the outcome of interest was not present at the start of the study**
   a. yes **(1)**
   b. no **(0)**

Comparability

1. **Comparability of cohorts based on the design or analysis**
   a. study controls for age, gender, province **(0)**
   b. study controls for age, gender, province +smoking **(1)**
   c. study controls for age, gender, province +smoking + other additional factors **(2)**

Outcome

1. **Assessment of outcome**
   a. independent blind assessment **(1)**
   b. record linkage **(1)**
   c. self-report **(0.5)**
   d. no description **(0)**
2. **Was follow-up long enough for outcomes to occur**
   a. yes (select an adequate follow-up period for the outcome of interest) **(1) (average 15 years)**
   b. no **(0)**
3. **Adequacy of follow-up of cohorts**
   a. complete follow-up - all subjects accounted for over 90% **(1)**
   b. subjects lost to follow-up unlikely to introduce bias - small number lost - > ____ % (select an
   c. adequate %) follow up, or description provided of those lost) between 60- 90% **(0.5)**
   d. follow-up rate < ____% (select an adequate %) and no description of those lost under 60% **(0)**
   e. no statement **(0)**

Supplementary Table 4. Details of results on level-response relationship

first author name	Dose details	Dose category	Outcome	RR (95%CI)
Petralia SA,1998	N/A	High	incidence	1.3 (1-1.7)
	N/A	Low		0.9 (0.6-1.3)
Costantini AS, 2009	>40ppm-y	High	mortality	1.31 (0.54-3.14)
	<=40 ppm-y	Low		0.96 (0.45-2.01)
Laouali N, 2018	>=0.87ppm_y	High	incidence	1.9 (0.9-4.1)
	>0<0.87 ppm_y	Low		2.6 (1.3-5.1)