

Original Papers

Occupational benzene exposure and skin cancers: a systematic review and meta-analysis

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Background: Exposure to benzene is a widespread occupational hazard that has been associated with haematopoietic neoplasms. The increasing awareness of the health effects that can arise from extended dermal contact with aromatic hydrocarbons, such as benzene, may elevate the risk of skin cancer.

Aims: This study addresses the association between occupational benzene exposure and its incidence and mortality, encompassing non-melanoma skin cancer (NMSC), including basal cell carcinoma and squamous cell carcinoma, as well as cutaneous melanoma (CM).

Methods: After removing duplicates, we screened 5652 articles from four different sources (Embase, Pubmed, Scopus and IARC Monographs), retrieving 29 independent studies on occupational benzene exposure and skin cancer. The meta-analysis used a random-effects model, overall and stratifying by gender, publication year, outcome, geographic region, industry type and study design.

Results: The analysis encompasses 18 risk estimates on CM and 21 on either NMSC or not-specified skin cancer (NM/NS) mostly from Europe and North America and predominantly from oil industry cohorts. There was no association with either CM (relative risk [RR] = 0.99, 95% confidence interval [CI] 0.81; 1.21) or NM/NS (RR = 1.19, 95% CI 0.94; 1.50), except for a positive association between employment in the chemical industry and NM/NS risk. There was no evidence of publication bias for either type of cancer ($P = 0.70$ and $P = 0.08$).

Conclusions: Our meta-analysis found no association between occupational benzene exposure and skin cancer. Further research should aim to describe the association of benzene exposure with skin cancer in less developed countries and among various occupations.

INTRODUCTION

Non-melanoma skin cancer (NMSC), comprising basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), has the highest incidence among all cancers globally [1]. The incidence of cutaneous melanoma (CM) has surged over the past five decades, especially in northern European countries (e.g. Denmark, Norway and Sweden) [2] with the highest rates observed in New Zealand and Australia [1,3].

Ultraviolet radiation (UVR) is considered the most important risk factor for BCC, SCC and CM [4]. Exposure to other occupational skin carcinogenic agents [5], such as coal tar, coal-tar pitch, mineral oils, chimney sweep soot and shale oil is related to high levels of aromatic hydrocarbons (AH), especially for NMSC [6]. Workers exposed to these carcinogens are usually co-exposed by inhalation to significant levels of other known or possible carcinogens, including benzene, a molecule that has causally associated with lymphohematopoietic cancers [7] and that could, in these workers, contaminate the skin and

create a further potential hazard of skin cancer. Therefore, there is a need to investigate the possible association of benzene with skin cancer in occupational cohorts.

The early recognition of AH as human carcinogens, dating back to Sir Percival Pott's 18th-century observations [8], marked a critical milestone in understanding occupational skin cancer. Subsequent experiments in the 1910s solidified the link, particularly in workers exposed to mineral oils, who developed SCCs and premalignant lesions on their hands and forearms [9].

Benzene, a well-known AH, was classified as a human carcinogen in 1982 by IARC [6], linking it to acute myeloid leukaemia and potentially other lymphohematopoietic cancers. Additionally, experimental studies revealed the development of papilloma and carcinoma of the skin and upper aerodigestive tract following local benzene application [10].

Occupational exposure to benzene extends beyond the petroleum industry to other occupations and industries, including oil and gas production, chemical laboratories, being used as

Key learning points

What is already known on this topic:

- Occupational exposure to benzene is prevalent worldwide in various working environments, with the highest level in oil refineries and chemical industries.
- Since the exposure to fumes or particles containing benzene can occur both via inhalation and skin contamination, several studies looked for a possible association among occupational benzene exposure and skin cancer, with heterogeneous results.

What this study adds:

- Our study found no increased risk of either cutaneous melanoma or non-melanoma skin cancer in benzene-exposed workers.
- Although our results are overall reassuring, several characteristics of the available data suggest the need for more detailed research, aiming at a more qualitatively and quantitatively detailed description of the occupational hazards, and for more data from low- and medium-income countries.

How this study might affect research, practice or policy:

- The effects of aromatic hydrocarbons, including benzene, on the human health and on the environment, are subject to great attention by the scientific community.
- This study could help direct the focus for further research on occupational settings entailing benzene exposure other than the oil industry, on less developed countries and on other solid cancers that have not been clearly associated to benzene exposure.

solvent and reagent [11], manufacturing of rubber, plastic, dyes and detergents. Smokers face chronic inhalation exposure to benzene from tobacco smoke, and environmental sources including gasoline vapours and automobile exhaust further contribute to such exposures.

This study describes a systematic review and meta-analysis of results of occupational cohort and case-control studies, to evaluate the association between occupational benzene exposure and skin cancer incidence and mortality.

METHODS

Our study protocol was registered in the PROSPERO database (Registration No. CRD42022379720); we followed the COSMOS-E and PRISMA-statement to conduct and report this systematic review and meta-analysis [12,13].

Figure 1 shows the flow diagram of the literature search and study selection process. First, we included all studies that were mentioned in the IARC Monograph [14] on benzene exposure published in 2018. Next, we conducted a search in the MEDLINE (PubMed), SCOPUS and EMBASE (Ovid) database for studies reported after that publication. Two researchers performed independently the search in online databases. Searches were undertaken in March 2024 for English, French, Italian, German and Spanish

language cohort and case-control peer-reviewed publications published on the association of occupational exposure to benzene and risk (incidence and mortality) of any type of solid cancer.

The search strategy was designed using MeSH terms like ((‘neoplasms’[Title/Abstract] OR ‘carcinoma’[Title/Abstract] OR ‘cancer’[Title/Abstract] OR ‘malignant’[Title/Abstract]) AND ((‘benzene’[All Fields] OR ‘benzol’[All Fields] OR ((‘cyclohexa-1’[All Fields] OR ‘3 5 triene’[All Fields])) OR ‘5-cyclohexatriene’[All Fields])) OR ‘cyclohexatriene’[All Fields]).

Two reviewers independently reviewed the list of titles, abstracts and full text of paper. If multiple reports were based on the same database, we included only the most informative report, typically based on the most recent update. We included cohort studies, nested case-control analyses, of workers employed in industries and occupations in which benzene represents a major source of exposure. These include petroleum industry (all phases: extraction, refining, distribution and gas station), shoemakers, paint production and painters, chemical industry, rubber industry, printing and laboratory workers. We excluded studies of workers mainly exposed to other carcinogens: PAH (incl. diesel exhausts, coke oven, aluminium production and firefighting), UV radiation (road builders, truck and boat drivers and agricultural machine technicians), silica, butadiene, etc. Community-based case-control studies were included if they reported results on benzene (not on job/industry of employment). Studies involving animals, blood, tissue, genetic evaluation and studies without full text were excluded. Also, we excluded study types other than cohort and case-control designs, such as letters, ecological and case reports. Studies on non-solid tumours including leukaemia, lymphoma or myeloma were excluded. This strategy led to the identification of 74 independent cohort ($n = 46$) and case-control ($n = 28$) studies (Figure 1). Details of the other solid cancers are reported elsewhere [15]. The data extraction file was completed based on the full text of potentially relevant articles. It contained the author’s name, the year of publication, the title, the type of study, the country, the sample size, job title, period of employment, outcome, the type of controls, the type of cancer (including topography and histology), the effect size measures, including the relative risks (HRs/RRs/SMRs) for the cohort studies and the odds ratios for the case-control studies and their 95% confidence interval (CI). Also, we extracted the results for subgroups by gender, different doses and duration of exposure if available. If RR or CI were not reported, we calculated them from the raw data if possible.

The quality and susceptibility to bias of each included study were evaluated using a modified version of Newcastle-Ottawa Scale for case-control (9 items) and cohort studies (10 items) by MSS [16] and reported in Table 1 (available as Supplementary data at *Occupational Medicine* online). Studies that scored <8 corresponded to low quality and those that scored ≥8 were considered of high quality. During the process of all steps, if there were any major discrepancies, P.B. intervened.

After excluding the studies that are not reporting results on skin cancer, we retained 29 articles, from which we abstracted effect size measurements and the corresponding 95% CIs for incidence or mortality from skin cancer. All analyses were completed using the STATA version 14.0 (Stata, College Station, TX, USA). Due to variation in study design features among

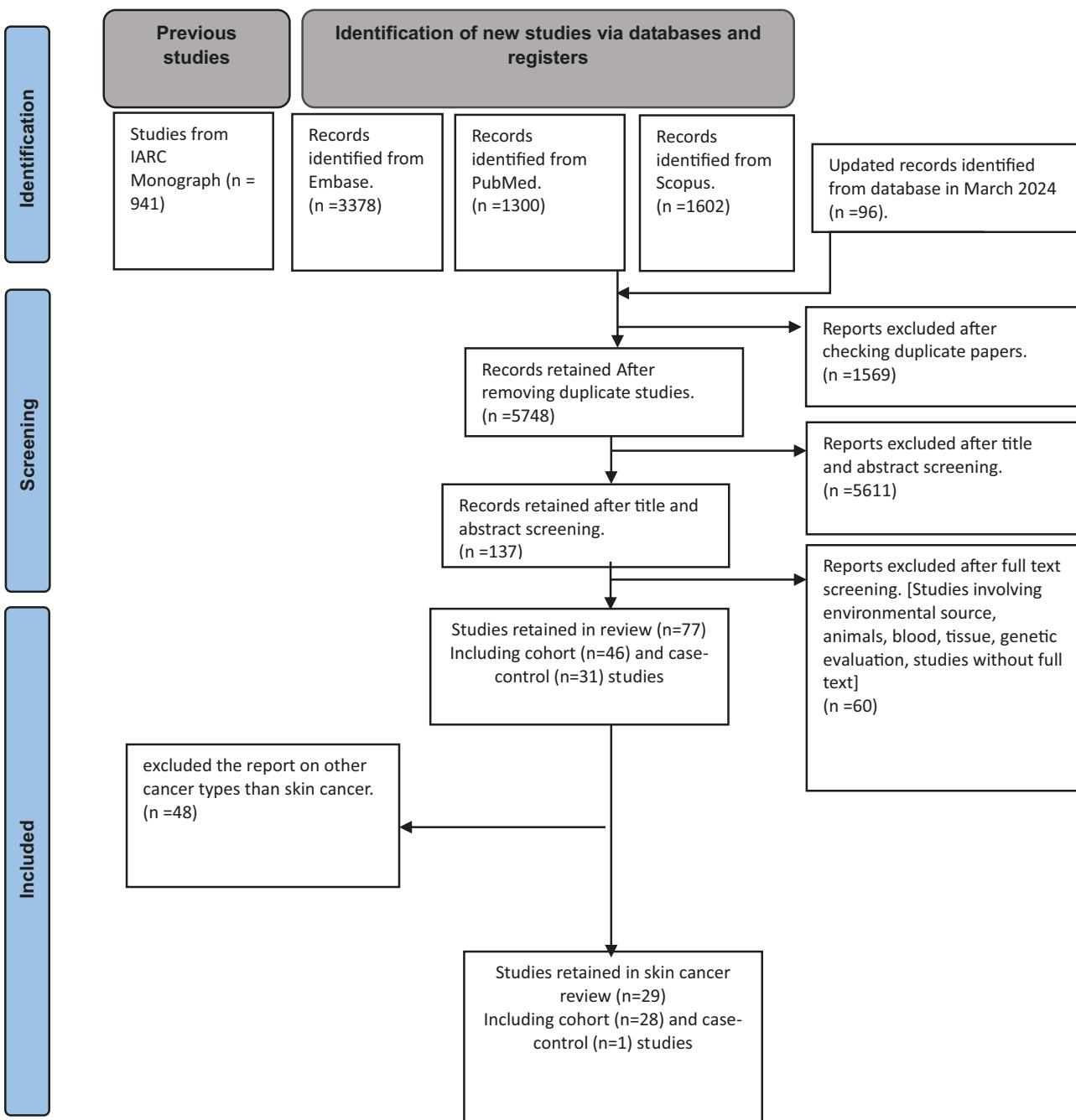


Figure 1. Selection of studies for inclusion in the review and meta-analysis.

individual studies, we decided to use a random-effects model to address heterogeneity across different studies, which is the recommended appropriate approach in this situation. We conducted a series of meta-analyses of non-overlapping studies for CM, NMSC or non-specified skin cancers and benzene exposure based on random-effects model and tested for heterogeneity among studies using the *Q* statistics and the *I*-square test based on the variation across studies rather than within studies [17]. The division among the subtypes of skin cancer was quite heterogeneous among the studies, with some of them reporting results for any skin cancer (without distinguishing CM and NMSC), we decided to create a group called non-melanoma or

not-specified skin cancer (NM/NS). This decision was made for two main reasons: first, to avoid excessive fragmentation of the limited available data; second, since epidemiologically the majority of skin cancers are NMSC, the category of non-specified cancers would include mostly NMSC. Further aspects of the classification of skin cancers in this paper are addressed in the discussion.

In addition, we conducted stratified analyses by geographic region (Europe, North America, others including Asia and Australia), study design (cohort and case control), quality score (low and high quality), outcome (incidence and mortality), years of publication (<2000 and ≥2000), gender (male, female

and both). Finally, we assessed publication bias by the visual inspection of the funnel plot and the Egger test [18].

RESULTS

We selected 29 independent studies reporting data on incidence and/or mortality for skin cancer in occupationally benzene-exposed populations. The analysis was first performed on all subtypes of skin cancer combined, then stratified between CM and NM/NS.

As shown in **Table 1** (available as *Supplementary data* at *Occupational Medicine* online), reporting the main characteristics of the studies included in our meta-analysis, 28 out of the 29 studies were of cohort design, and most of them were performed in Europe (n. 16) or North America (n. 9). Furthermore, 15 studies reported data referring to a male population only, 2 to a female population and 12 to both genders, of which just 3 reported events separately for males and females. Eleven studies included skin cancer not specified, 10 studies reported separate results for CM and NM/NS and 8 studies only for CM, yielding a total of 18 risk estimates for CM and 21 for NM/NS. A total of 17 studies were performed in the oil industry, 4 on chemical industries and 8 in various other industries.

The overall RR for all types of skin cancer and every benzene exposure was 1.09 (95% CI 0.93; 1.27).

The summary RR for CM in workers exposed to benzene was 0.99 (95% CI 0.81; 1.21, 15 risk estimates), with no significant difference when considering males, females and both genders ($p_{het} = 0.190$), whose RR were respectively 1.18 (95% CI 0.82; 1.69), 1.05 (95% CI 0.65; 1.69.) and 0.82 (95% CI 0.67; 1.01) (**Table 1**).

Similarly, results after stratifications by year of publication ($p_{het} = 0.650$), outcome ($p_{het} = 0.561$), geographic region ($p_{het} = 0.773$) and type of industry ($p_{het} = 0.311$) did not reveal any significant heterogeneity. Due to the scarcity of data, the results stratified study type are reported only in **Table 1**. No data were available for analyses of CM risk stratified for duration of benzene exposure.

No evidence of publication bias was identified according to the funnel plot asymmetry ($P = 0.70$) (**Figure 2a**).

We did not find a statistically significant association for benzene exposure and NM/NS, where the RR was 1.19 (95% CI 0.94; 1.50, 18 risk estimates), as shown in **Figure 3**.

The analysis stratified by gender ($p_{het} = 0.744$), year of publication ($p_{het} = 0.375$), outcome ($p_{het} = 0.650$), geographic region ($p_{het} = 0.848$) did not reveal any significant heterogeneity (**Table 1**). Four studies reported results by duration of exposure, which are summarized in **Table 2** (available as *Supplementary data* at *Occupational Medicine* online). There was no suggestion of an increased risk of NM/NS with increasing duration of exposure. The meta-analysis of studies of chemical industries showed an association with NM/NS, with RR = 1.56 (95% CI: 1.17; 2.06, $p_{het} = 0.519$), while RR for the mineral oil industry and other industries were respectively 1.01 (95% CI 0.79; 1.30, $p_{het} = 0.061$) and 1.45 (95% CI 0.61; 3.44, $p_{het} = 0.226$). We did not stratify the analysis by study type due to insufficient data.

No evidence of publication bias was identified according to the funnel plot asymmetry ($P = 0.078$) (**Figure 2b**).

DISCUSSION

Our meta-analysis provided evidence for the lack of an association between benzene exposure and both CM and NM/NS skin cancer.

The data available in the literature were mostly related to oil industries, male gender and to working populations from Europe and North America. These regions include high-income countries, which are likely to have a stricter control of occupational benzene exposure due to technical development, higher standards of health policies and lower threshold limit values established by law. Due to limited data from South America, Asia and Africa, we were not able to make a comparison between geographical areas in which both exposure circumstances and biological susceptibility might be different.

Few studies reported information on level, duration of exposure, duration of employment or according to a stratification by job tasks. Unfortunately, the four studies including information on the duration of benzene exposure (**Table 2**, available as *Supplementary data* at *Occupational Medicine* online), provided insufficient data for a stratified meta-analysis, also because of the heterogeneity of the time intervals used for the comparison. However, the results on duration of employment or exposure did not suggest a trend with the risk of NM/NS. For these reasons, we concluded that, given the presence of a single statistically significant result in the subgroup analysis of chemical industry and NM/NS skin cancer, which might result from multiple comparisons, the evidence is too weak to assume a relation among the exposure and the outcome considered, and should be further investigated in studies on occupational cohorts with exposure to chemical compounds containing benzene.

Benzene is usually found in combination with other AH, especially solvents, so it is difficult to associate an excess of a given cancer with a specific molecule.

Furthermore, the studies included in our review were mostly based on petroleum, oil and chemical industry cohorts, while relevant benzene exposure is present in many other sectors as well, like metalworking, rubber, automobile repair, shoe production and other jobs involving the use and production of petroleum derivates [19]. A factor influencing the level of occupational exposure to benzene is the time period. National and international guidelines decreased the permissible exposure levels, which are now about a hundred times lower than the ones established in 1946 [20]. Although exposure in the past was likely to be much higher, we did not find a significant difference according to year of publication for both types of skin cancers, which we used as a proxy for a period of employment of the working cohort.

One limitation to our meta-analysis is the possible misclassification between different histological types of skin cancer. In fact, some studies reporting results for non-specified cancer were included in the NM/NS category, as they probably include mostly NMSC as well as some cases of CM. Therefore, although we found no evidence of publication bias, some asymmetry was evident in the funnel plot of this category. Very few studies reported subclassification for the various histological types of NMSC. The classification of NMSC itself is a complex feature because it may include some rare forms of cancer of specific cell populations of the skin, including Merkel cell carcinoma and sebaceous gland carcinoma, which have different

Table 1. Results of the metanalyses stratified by region, outcome, study design, year of publication, gender, industry and quality score for CM and NM/NS

Characteristic	N risk estimates	RR, 95% CI	P heterogeneity
CM			
Region			
North America	4	0.92 (0.67–1.27)	0.77
Europe	13	1.07 (0.77–1.50)	
Other	2	0.91 (0.56–1.47)	
Study design			
Case control	1	0.60 (0.30–1.20)	0.16
Cohort	17	1.02 (0.83–1.25)	
Quality score			
Low quality (<8)	8	1.10 (0.80–1.53)	0.29
High quality (≥ 8)	10	0.88 (0.66–1.15)	
Outcome			
Incidence	9	1.05 (0.83–1.33)	
Mortality	9	1.17 (0.89–1.52)	
Years of publication			
<2000	10	1.04 (0.74–1.46)	0.65
≥ 2000	8	0.94 (0.71–1.26)	
Gender			
Male	8	1.18 (0.82–1.69)	0.19
Female	2	1.05 (0.65–1.69)	
Both	7	0.82 (0.67–1.01)	
Industry			
Oil industry	11	1.06 (0.82–1.36)	0.31
Chemical industry	3	0.82 (0.31–2.17)	
Other industries	4	0.66 (0.37–1.67)	
NM/NS			
Region			
North America	5	1.39 (0.97–1.98)	0.85
Europe	14	1.10 (0.83–1.45)	
Other	4	1.18 (0.14–10.05)	
Study design			
Case control	1	1.14 (0.71–1.84)	0.85
Cohort	22	1.20 (0.93–1.56)	
Quality score			
Low quality (<8)	8	1.31 (0.90–1.91)	0.61
High quality (≥ 8)	15	1.16 (0.91–1.48)	
Outcome			
Incidence	11	1.11 (0.85–1.45)	0.65
Mortality	12	1.24 (0.84–1.84)	
Years of publication			
<2000	12	1.30 (0.96–1.76)	0.37
≥ 2000	11	1.04 (0.70–1.54)	
Gender			
Men	14	1.06 (0.82–1.37)	0.74
Female	3	1.05 (0.56–1.95)	
Both	8	1.30 (0.81–2.08)	
Industry			
Oil industry	12	1.01 (0.79–1.30)	0.073
Chemical industry	4	1.56 (1.17–2.06)	
Other industries	7	1.45 (0.61–3.44)	

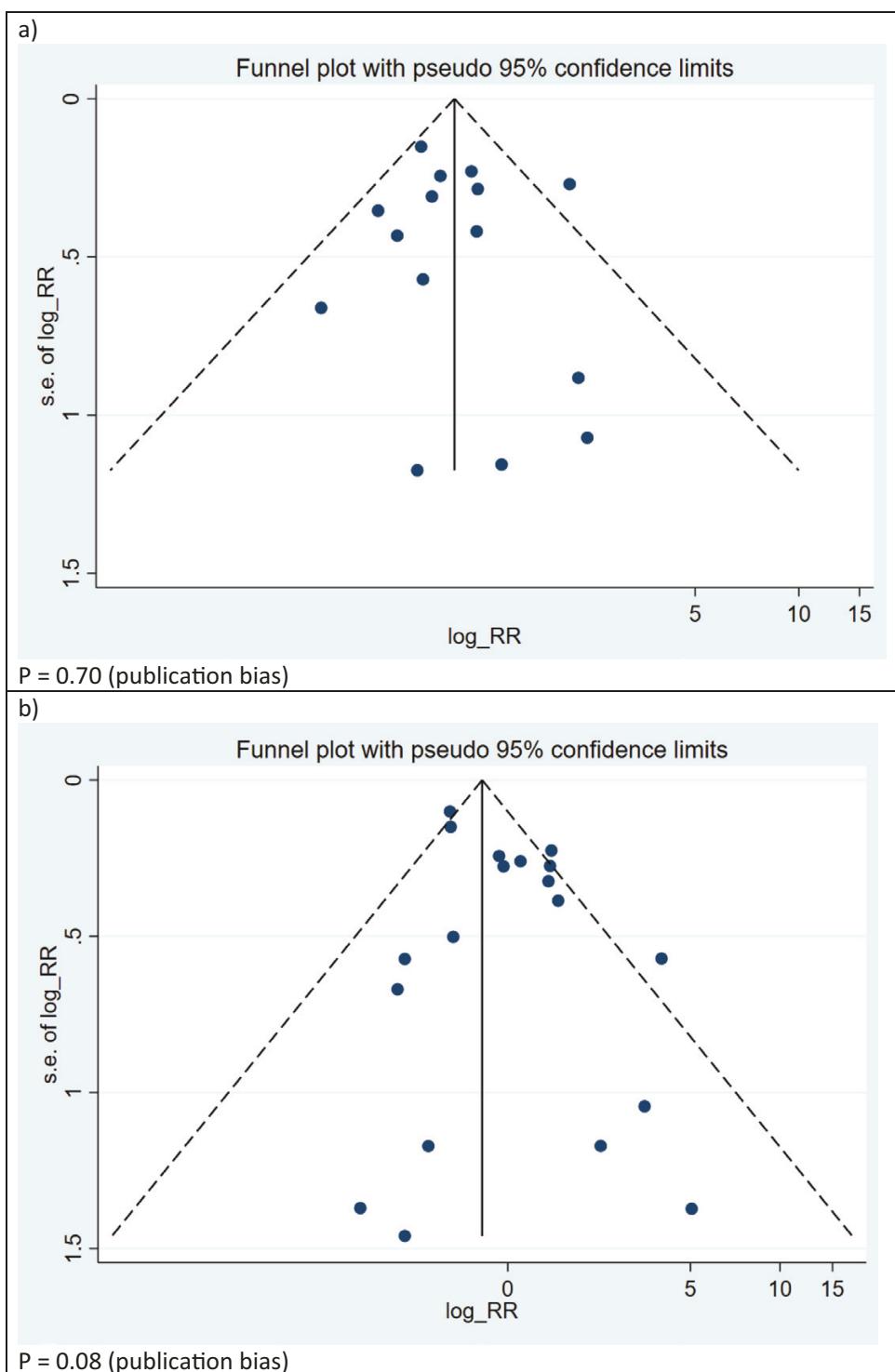
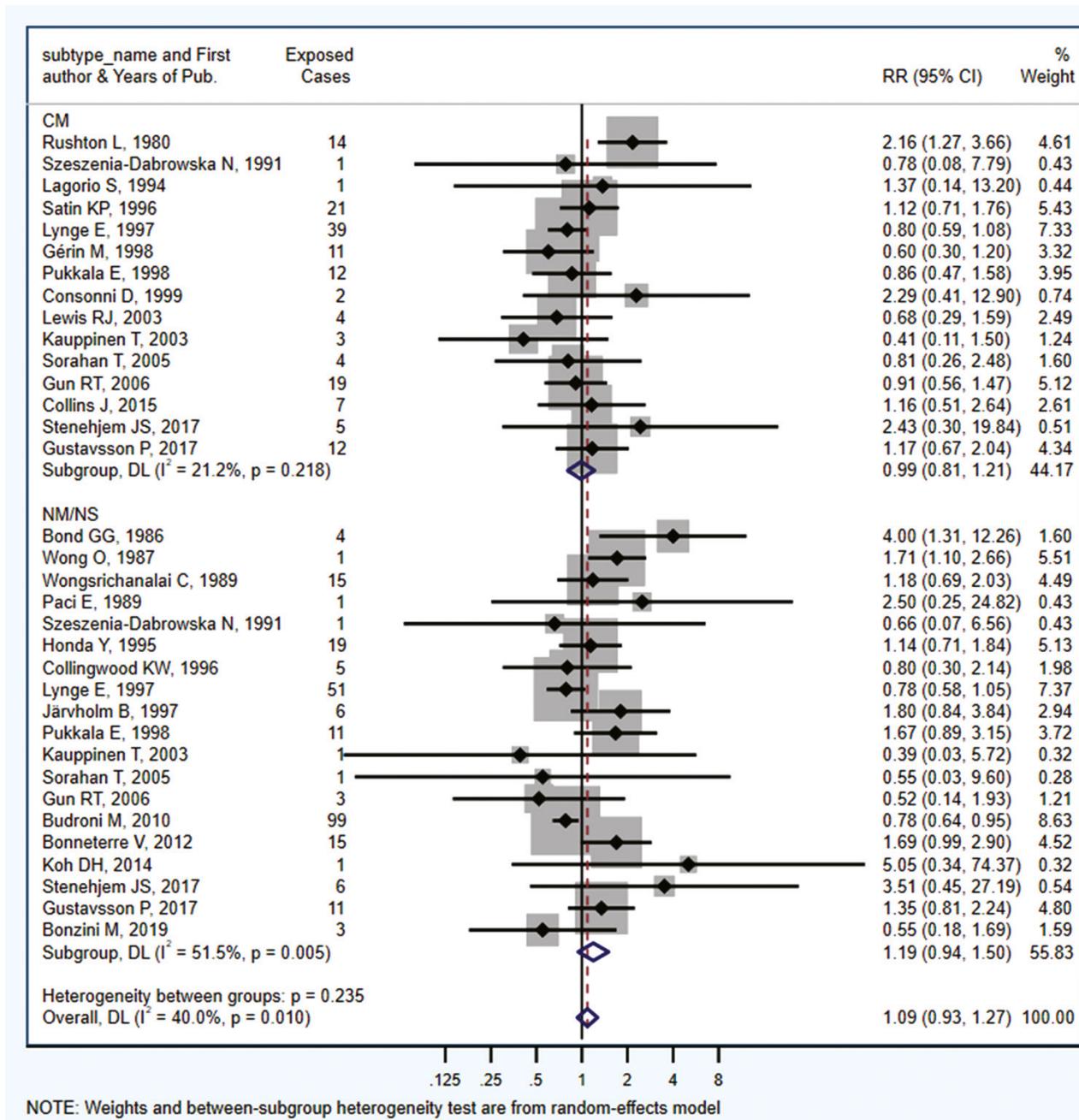


Figure 2. Funnel plot of results on the association between benzene exposure and CM (a) and NM/NS (b) skin cancers.

risk factors and epidemiological behaviour compared to the most common BCC and SCC. More than that, it is known that epidemiologic data on skin cancers, especially in NMSC, suffer low sensitivity in the mortality data because of the high incidence on the population, which makes them probably one of the most underreported cancers. Two additional causes might have contributed to this phenomenon: first not all skin biopsies are routinely sent for pathological examination and second,

because many cancer registries do not always record NMSC as BCC or SCC, causing underreporting due to the recurrent behaviour of these malignancies [21].

As known, the challenge of diagnosing cutaneous cancers is also due to their latency and low morbidity. Pre-neoplastic lesions typically progress slowly to BCC/SCC, which is why regular dermatologic check-ups are recommended in high-risk populations.



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Figure 3. Forest plot (random-effects model) of results on the association between benzene exposure and CM and NM/NS skin cancer.

A further limitation comes from the inability to discriminate the anatomical site of onset of the cases in almost all studies included in our review. The exposure to airborne pollutants typically involves the skin of head, neck, hands and forearms, sparing the parts covered by clothes or personal protective equipment (PPE). As it happens for other conditions caused by exposure to airborne pollutants (e.g. chloracne after exposure to halogenated aromatic compounds), it would be reasonable to expect a similar behaviour if there was an association between benzene exposure and skin cancer. Unfortunately, in our meta-analysis only one study [22] reported information on the localization of the skin cancer cases, making it a crucial factor to focus on for further studies on the topic. Our analysis did not find an overall increase

of skin cancer in benzene-exposed workers, suggesting no effect from an exposure through the clothing or via contamination between PPE-protected areas and other areas. As in the historical example of chimney sweeps [8] prolonged contact with the carcinogen could locally increase the incidence of a malignancy in non-directly exposed body parts.

Even having the topographic information of the cancer cases, the skin parts most affected by airborne pollution (head, neck, hands and forearms) are among the ones most often affected by exposure to UVR and other airborne pollution, such as PAH, that are the two main confounders in our study. While the first is unlikely to be significantly increased in benzene-exposed workers compared to the general population, because most of the job

tasks in the studies included in the review were performed in closed environments such as oil refineries and chemical plants, PAHs are probably present as air pollutant along with benzene in some occupational settings under investigation, in particular the oil industry. Both UVR and PAH are known skin carcinogens [6] and might have caused residual confounding in our results. Some authors suggested that, given the lipophilic profile of benzene's molecule, this agent can be absorbed through the skin and to accumulate in other fat-rich organs [23], where it may exert its cancerogenic potential. This hypothesis could explain the absence of an association between benzene exposure and skin cancers in general in our review.

In conclusion, no association between occupational benzene exposure and skin cancer has been found in the present meta-analysis, but several characteristics of the available data suggest the need for more detailed research, aiming to a more qualitatively and quantitatively detailed description of the occupational hazards, and for more data from low- and medium-income countries.

COMPETING INTERESTS

P.B. acted as an expert witness for the plaintiff and defense in benzene-related litigation, unrelated to the present work. Other authors declare no competing interests.

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