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Review article

Occupational benzene exposure and risk of head and neck cancer: A systematic review and meta-analysis

Alessandro Godono [a], Andrea Dito [a], Giorgio Martini [a], Maria Vittoria Picciaiola [a], Antonio Di Lorenzo [b], Catalina Ciocan [a], Paolo Boffetta [b,c,d,*], Monireh Sadat Seyyedsalehi [b,e]

[a] Department of Public Health and Pediatrics, University of Torino, Turin, Italy
[b] Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[c] Stony Brook Cancer Center, Stony Brooke University, Stony Brook, NY, USA
[d] Department of Family, Population and Preventive Medicine, Renaissance School of Medicine, Stony Brook University, Stony Brook, NY, USA
[e] Cancer Research Center, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Introduction: Benzene, an aromatic hydrocarbon, is a well-known leukemogen. To date, the link between benzene exposure and solid cancers is under examination. Our objective is to perform a systematic review and meta-analysis to evaluate if the occupational exposure to benzene is associated with the incidence and mortality of head and neck cancers (HNCs).

Methods: We systematically reviewed the literature for pertinent cohort studies mentioned in the most recent IARC Monograph on benzene working exposure and other cohorts and case-controls identified via a literature search performed in PubMed, Scopus, and Embase, from their inception to March 2024. Stratified multilevel meta-analyses according to study design, cancer type, industrial sector, quality score of the articles, geographic region and risk of exposure bias were conducted.

Results: A total of 29 independent studies were included in our review and multilevel meta-analysis. The findings revealed a bordeline association between exposure to occupational benzene and incidence of HNCs RR = 1.27, 95% CI = 1.00–1.64, I^2 level2 = 0%, I^2level3 = 43.30%, P < 0.05). In addition, we found a significant increased overall risk of HNCs in females (RR = 1.68, 95% CI = 1.07–2.61; I^2level2 = 0%, I^2level3 = 0%, P = 0.433). Stratification analysis according to cancer sites showed a significant increase in risk of nose & sinuses cancers (RR = 3.72, 95% CI = 2.07–6.68; I^2level2 = 34.13%, I^2level3 = 0%, P = 0.17). European cohorts (RR = 1.31, 95% CI = 1.08–1.59, p < 0.01) and lower quality studies (RR = 1.39, 95% CI = 1.00–1.91; I^2level2 = 0%, I^2level3 = 45.94%, P < 0.001). No evidence of publication bias was found (Egger test P = 0.103).

Conclusions: In conclusion, this systematic review and meta-analysis provide evidence that workers with occupational exposure to benzene might be at increased risk of HNCs, in particular for nose & sinuses cancer. However, it is essential to consider the limitations of the studies, particularly residual confounding, and the areas that need further study to improve our understanding of the subject.

1. Introduction

Benzene is the smallest aromatic hydrocarbon, with chemical formula C_6H_6. It is produced via either catalytic reforming, cracking or toluene hydrodealkylation in large amounts worldwide, and it has been listed by the Organisation for Economic Co-operation and Development as a high production volume chemical (OECD, 2009). It is naturally present in petroleum products such as gasoline and has had a variety of uses over time (Williams et al., 2008). Nowadays, the usage of benzene has decreased significantly due to the knowledge of its carcinogenic properties, and it is mainly used for the synthesis of other aromatic compounds and the octane-enhancement of unleaded gasoline(Sharon Wilbur et al., 2007). With regard to its toxicodynamics, benzene enters the body mostly through inhalation and it produces toxic metabolites,

Abbreviations: IARC, International Agency for Research on Cancer; HNCs, Head and neck cancers; HR, Hazard ratio; OR, Odds ratio; RR, Risk ratio, rate ratio; SMR, Standardized mortality ratio; SIR, Standardized incidence ratio.

* Corresponding author. Department of Medical and Surgical Sciences, University of Bologna, Via Massarenti 9, 40138, Bologna, Italy.
E-mail address: paolo.boffetta@unibo.it (P. Boffetta).

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primarily in lungs and the liver, and is finally excreted in the urine. Metabolites can negatively impact other organs through several mechanisms such as the formation of reactive oxygen species (ROS) that can lead to genetic mutations, altering cellular function and compromising organ health, through DNA, lipids and proteins damage. Metabolites also affect the process of kinases and signal transduction pathways that regulate various cellular processes, including cell proliferation, growth and apoptosis; metabolites can finally impact on inflammation (Falzone et al., 2016; Lian, 2022; Rappaport et al., 2010; Snyder and Hedli, 1996; Tsao et al., 2017).

Previous research reported that benzene exposure can result in both short-term and long-term health effects. Short-term exposure has been linked to effects on the nervous system (drowsiness, dizziness, tremors, headaches, confusion, and unconsciousness), digestive complications, irritation of the skin, eyes, and throat; while among the long-term complications anemia, and some chronic disease like cancer were mentioned (Smith, 2010). Benzene was classified by the International Agency for Research on Cancer (IARC) as a human carcinogen, specifically linking it to the development of leukemia, particularly acute myeloid leukemia (AML). However, despite the numerous findings reported on this topic, the association between benzene exposure and solid tumors is still not entirely clear and requires further investigation (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2018).

Head and Neck Cancer (HNC) is the collective definition for a heterogeneous group of tumors of the head and neck region; most of them are squamous-cell carcinomas of mucous membranes, although other organs such as the thyroid might be involved (Chow, 2020). The oral and sinonasal cavities, the pharynx and the larynx are the primary regions affected. Collectively, HNCs were the seventh most common cancer worldwide in 2018, with around 890.000 new cases and 450.000 deaths (Bray et al., 2018).

The main risk factors for HNCs are the use of alcohol and tobacco (both smoking and smokeless), betel nuts chewing for Asian countries (Cohen et al., 2018; Gormley et al., 2022), and Human Papillomavirus infection (Gormley et al., 2022). In terms of occupational exposure, a relationship has been suggested between HNCs and asbestos (Clin et al., 2022), flour dust (Carton et al., 2018), hardwood dust(Mayr et al., 2010), pesticides (Brasil et al., 2018), and leather dust (Radoï et al., 2019), as well as formaldehyde, nickel and chromium compounds and other chemicals used in the textile industry and in construction works (Binazzi et al., 2015). However,the evidence for benzene exposure remains unclear.

Therefore, we aimed to conduct a systematic review and meta-analysis to explore the association between occupational benzene exposure and the incidence and mortality ofHNCs.

2. Methods

2.1. Data sources and search strategy

The review protocol was registered on the international prospective register of systematic reviews (PROSPERO; Registration NO CRD42022379720). The systematic review and meta-analysis were conducted and reported in accordance with the Conducting Systematic Reviews and Meta-Analysis for Observational Studies of Etiology (COSMOS-E) guide (Dekkers et al., 2019) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-statement (Page al., 2021). All studies mentioned in the most recent IARC Monograph on benzene exposure (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2018) were included. Other relevant peer-reviewed articles were identified via literature search performed in online databases MEDLINE (PubMed), SCOPUS, and EMBASE (Ovid) from their inception to March 2024. Moreover, we search for grey literature by analyzing the references of included articles. The databases searches were completed on the April 30, 2024.

The search strategy focused on investigateing the association between benzene exposure and the risk of any solid cancerlIt was conducted on PubMed first and then adapted for all databases (the complete search string is reported in Supplementary Table 1). For this report, we included all cohort and case-control studies examining occupational exposure to benzene and its association with the risk of any type of HNCs (oral and sinonasal cavities, the pharynx and the larynx), with respect to both mortality and incidence.

The study adhered to the general approach outlined in the preregistered PROSPERO protocol, with some modifications to make it adaptable to this case, including study quality evaluation and risk of biass assessment, strength of evidence appraisal, and statistical methods. These modifications are explained in detail in the following paragraphs.

2.2. Eligibility criteria

Two reviewers (MSS, AD) independently reviewed the list of titles, abstracts, and full text of paper. The process included the following steps: 1) scanning of title and abstract of articles identified during the initial database search; 2) review of the full texts of articles included after step 1; 3) review of the references of articles included after step 2. Inclusion criteria of the studies for the meta-analysis were.

(1) Design: cohort studies, nested case-control studies and occupational case-control studies;
(2) Benzene exposure: studies considering occupations where benzene is a significant/predominant source of exposure (workers of petroleum industry, shoemakers, paint production and painters, rubber industry, chemical industry, printing, laboratory workers.)
(3) Outcome: studies reporting measures of risk of HNCs (including oral cavity & oro-/hypo-pharynx, nasopharynx, larynx, nose & sinuses) such as odds ratio (OR), standardized mortality ratio (SMR), standardized incidence ratio (SIR), risk ratio/relative risk (RR), hazard ratio (HR), with 95% confidence intervals (CI), or sufficient data for their computational analysis.

Exclusion criteria consisted in.

(1) Design: every study design other than cohort or case-control.
(2) Type of exposure: studies of workers mainly exposed to other carcinogenic agents such as PAH (e.g., diesel exhaust, coke oven, aluminum production, firefighting), silica, and butadiene.
(3) Type of tumor: studies on non-solid tumors (e.g., lymphoma, leukemia, myeloma)
(4) Language: studies written in languages other than English, French, Italian, German or Spanish.

A summary of the inclusion and exclusion criteria following the PECOS is available in Supplementary Table 2.

2.3. Data extraction

Following duplicate removal and eligibility assessment, four reviewers (MSS, AD, ADL, GM) independently extracted relevant data from selected papers, and any disagreement was solved with a fifth reviewer (PB).

The data extraction file was calculated using Microsoft Excel® e subsequently checked by four other reviewers (AG, AD, GM, MVP). For each paper, the relative risks (SMRs/SIRs) for cohort studies or the ORs for case-control studies, as well as their respective 95% Confidence Intervals (95CI), were extracted as outcome measures. When articles provided the number of observed and expected cases of HNCs but no SIRs or SMRs, these values and their respective 95% CIs were calculated. If 90% CIs were reported, they were converted to 95% CIs through the following formula:

$$[L95; U95] = \frac{L90}{90} 2 \pm z95 \frac{U90 - L90}{2 \cdot z^{\wedge}}$$

where $L90$ and $U90$ are respectively the lower and upper bound of the 90% CI; $z95 = 1.96$ and $z90 = 1.645$.

Relevant study characteristics were also extracted, such as: author's name, publication year, study design, country, cohort size (or number of cases and controls), industry of employment (ISIC code -(Department of Economic and Social Affairs. Statistics Division, 2008)), occupations (ISCO-08 code - International Labour Office, 2012), period of employment, period of follow-up, the type of cancer, gender, dose and duration of exposure, outcome (incidence or mortality),outcome measures and information on conflict of interest.

2.4. Statistical analysis

We conducted a multilevel meta-analysis of the RR of HNCs, to account for the dependencies between the study specific effect sizes. Maintaining the independence of effect sizes within the dataset is a critical requirement in meta-analytic methods and failing to do so can result in a loss of information and reduced statistical power. (Assink and Wibbelink, 2016). Multilevel approaches can address three different sources of variance: the sampling variance of extracted effect sizes at level 1 (i.e., between participants); the variance among effect sizes from the same study at level 2 (i.e., between outcomes measured in the same participants); and the variance between different studies at level 3. Moreover, unlike other methods used to account for effect size correlations, the multilevel approach does not require knowledge of the correlations between outcomes, which are rarely reported in primary studies. Therefore, a multilevel meta-analysis was conducted using the rma.mv function in the metafor package, which can be executed in the R statistical software environment.

We carried out our analysis both combining the results for incidence and mortality and separating them. When both estimates were available for the same cohort, we utilized the SIR for the combined pooled estimate.

Cochran's Q test and the I-square test were used to calculate statistical heterogeneity (Higgins and Thompson, 2002).

Subgroup meta-analyses were conducted, if three or more independent studies were available, categorized by study design (cohort vs. case-control studies), geographic region (Europe, North America, Eastern Hemisphere Countries), cancer type (oral cavity & oro-/hypo-pharynx, nasopharynx, larynx, nose & sinuses), study quality (high vs low quality), and risk of bias for exposure assessment (high vs low risk of bias). Additionally, we performed subgroup meta-analysis by industrial sector (manufacture of refined petroleum products), whenever the ISIC code could be unambiguously identified. We decided not to include stratification by dose and duration of benzene exposure because available data were too sparse.

Regarding the publication bias and small study effects investigation, while considering effect size dependencies, none of the already existing methods for multilevel meta-analyses are completely suitable (Fernández-Castilla et al., 2021). Aware of these limitations, we employed a multifaceted approach. This included visual inspection of Doi plots and the Luis Furuya-Kanamori Index (LFK index) (L. Furuya-Kanamori et al., 2018) to assess small study effects, and an adaptation of the Egger Test for multilevel context, considering the inverse of the standard error as a moderator.

We also performed a series of meta-regressions to investigate the association between quality of studies, first year of employment and first year of follow-up with respect to association between benzene exposure and risk of HNCs. All analyses were completed using STATA SE/17 (StataCorp LLC, College Station, TX, USA) and RStudio (version 024.04.2 + 764).

2.5. Quality assessment

Methodological quality was assessed via a modified version of the Newcastle-Ottawa Scale (NOS) (Stang, 2010)

Each study was given a score ranging either from 0 to 9, for case-control studies, or from 0 to 10 for cohort studies (0 = no criteria met by the study; 9/10 = all criteria met by the study). The mean of the scores assigned independently was used to calculate the final NOS QA score for this meta-analysis. No articles were excluded based on the QA score. Since there are no predefined cut-offs in the NOS score, the Authors considered the studies with NOS score $\geq$8 of high quality, studies with score 6–7 of moderate quality and <6 of low quality.

Quality assessment was performed by two independent reviewers (MSS, ADL), and results were discussed with a third reviewer (PB) until reaching consensus. NOS quality assessment questions are provided in Supplementary Table 3.

2.6. Risk of bias assessment

The risk of bias was assessed through the Navigation Guide tool (Woodruff and Sutton, 2014) on the individual study level and across the body of evidence for each domain. The nine risk of bias domains explored were: (i) source population representation; (ii) blinding; (iii) exposure assessment; (iv) outcome assessment; (v) confounding; (vi) incomplete outcome data; (vii) selective outcome reporting; (viii) conflict of interest; and (ix) other sources of bias. All risk of bias assessors collaboratively tested the application of the risk of bias criteria until they had aligned their understanding and application of these criteria. AG, AD and GM independently evaluated the risk of bias for each study by outcome. When there were discrepancies among individual assessments, MVP resolved them.

2.7. Quality of evidence assessment

A GRADE (Grading of Recommendations Assessment, Development and Evaluation) (Xie and Machado, 2021) framework was used to assess the overall certainty of evidence across studies for each outcome. GRADE provides a framework for the classification of the quality of a body of evidence in a systematic review into four categories: "high", "moderate" "low" and "very low". We began the rating process at moderate certainty due to the risk of unmeasured confounding in observational studies. The certainty of evidence was then downgraded or upgraded based on the following GRADE domains. Downgrading reasons included: 1. Limitations in studies; 2. Indirectness; 3. Inconsistency; 4. Imprecision; 5. Publication bias. Upgrading reasons included: 1. Large magnitude of effect size; 2. All plausible confounding decreases observed RR; 3. Concentration-response gradient. The assessments for the GRADE domains were primarily based on the results of the Risk of Bias assessment, heterogeneity measures and publication bias analyses. Imprecision was assessed by examining the confidence intervals, with downgrading applied when the interval limits indicated opposing effects. Large magnitude of effect size was upgraded when the RR (RR > 1.25 or <0.75), adopting the criterion used in various WHO Systematic Reviews on Work-related Burden of Diseases and Injury (Van Kempen et al., 2018; Loomis et al., 2022). Quality of evidence assessment was performed by two independent reviewers (MVP, AD) and results were discussed with a third reviewer (AG) to reach consensus.

3. Results

The search of the Medline, Scopus, and Embase databases, combined with all studies mentioned by the most recent IARC monograph, yielded a total of 7317 articles. After duplicates removal (n = 1569), 5748 articles remained. After the revision of articles by titles and abstracts, 137 were considered relevant for inclusion. The complete full text of these articles was examined and assessed against the inclusion and exclusion

criteria; 60 articles did not meet the inclusion criteria as described. After excluding all non-HNCs studies and previous updates of included cohorts (n = 47), a total of 29 publications (Barul et al., 2018; Bonneterre et al., 2012; Budroni et al., 2010; Carton et al., 2017; Collingwood et al., 1996; Collins et al., 2015; Consonni et al., 1999; Fu et al., 1996; Greenland et al., 1994; Guberan and Raymond, 1985; Gun et al., 2006; Gustavsson et al., 2017; Honda et al., 1995; Järvholm et al., 1997; Kauppinen et al., 2003; Koh et al., 2011, 2014; Lagorio et al., 1994; Lewis et al., 2003; Linet et al., 2015; Lynge et al., 1997; Pukkala, 1998; Rushton and Alderson, 1980; Satin et al., 1996; Sorahan et al., 2005; Swaen et al., 2005; Szeszenia-Dabrowska et al., 1991; Tsai et al., 1983; Walker et al., 1993) including independent cohort (n = 27) and case-control (n = 3) studies containing, and 105 different risk estimates (by considering different gender, type of cancer, and outcome) were included in our review and meta-analysis (Fig. 1).

These articles reported on a total of 30 cohorts of workers with occupational benzene exposure. The screening process is summarized in Fig. 1. Included articles were published from 1980 (Rushton and Alderson, 1980) to 2018 (Barul et al., 2018). Among the 30 cohorts, 15 comprised only men, 2 only women and 13 provided data for both men and women. Most of the cohorts was assessed in Europe (n = 18: 4 in Italy, 3 in France, 3 in UK, 2 in Finland, 2 in Sweden, 1 in Switzerland, 1 in Poland, 1 in the Netherlands, 1 in Northern European countries), followed by North America (n = 8: 7 in USA, 1 in Canada) and Asian and Pacific Countries (n = 4: 2 in Korea, 1 in China, 1 in Australia). Details of these studies are provided in Table 1. A comprehensive list of the RRs considered, their location in the original article, and any possible transformation applied are represented in Supplementary Table 4.

3.1. Meta-analysis

Utilizing a multilevel random-effects model, the overall RR of HNCs for benzene exposure was 1.20 (95% CI = 0.99–1.46; $I^2level_2 = 24.92\%$, $I^2level_3 = 30.61\%$, $P < 0.001$). Figs. 2 and 3 present the forest plots of pooled results for mortality and incidence, after stratification by the outcome. The summary RR was 1.24 (95% CI = 0.89–1.72; $I^2level_2 = 23.12\%$, $I^2level^3 = 34.02\%$ $p < 0.01$) for studies reporting mortality (Collingwood et al., 1996; Collins et al., 2015; Consonni et al., 1999; Fu et al., 1996; Greenland et al., 1994; Guberan and Raymond, 1985; Gun et al., 2006; Honda et al., Koh et al., 2011, 1995; Lagorio et al., 1994; Lewis et al., 2003; Linet et al., 2015; Rushton and Alderson, 1980; Satin et al., 1996; Sorahan et al., 2005; Szeszenia-Dabrowska et al., 1991; Swaen et al., 2005; Tsai et al., 1983; Walker et al., 1993) and 1.27 (95% CI = 1.00–1.64, $I^2level_2 = 0\%$, $I^2level_3 = 47.30\%$, $P < 0.01$)) for studies reporting incidence (Barul et al., 2018; Bonneterre et al., 2012; Budroni et al., 2010; Carton et al., 2017; Guberan and Raymond, 1985; Gun et al., 2006; Gustavsson et al., 2017; Järvholm et al., 1997; Kauppinen et al., 2003; Koh et al., 2014; Lewis et al., 2003; Lynge et al., 1997; Pukkala, 1998; Sorahan et al., 2005; Szeszenia-Dabrowska et al., 1991). After stratifying the results by sex, we found that female workers (Carton et al., 2017; Gustavsson et al., 2017; Lynge et al., 1997; Lewis et al., 2003; Satin et al., 1996; Walker et al., 1993) exposed to benzene had significantly higher HNCs risk (RR = 1.68, 95% CI = 1.07–2.61; $I^2level_2 = 0\%$, $I^2level_3 = 0\%$, $P = 0.433$), whereas no significant association (RR = 1.24, 95% CI = 0.94–1.64; $I^2level_2 = 38.91\%$, $I^2level_3 = 30.97\%$, $P < 0.001$) was observed for male workers (Barul et al., 2018; Bonneterre et al., 2012; Budroni et al., 2010; Consonni et al., 1999; Fu et al., 1996; Greenland et al., 1994; Guberan and Raymond, 1985; Gun et al., 2006; Honda et al., 1995; Koh et al., 2011, 2014; Lagorio et al., 1994; Lewis et al., 2003; Lynge et al., 1997; Rushton and Alderson, 1980; Satin et al.,

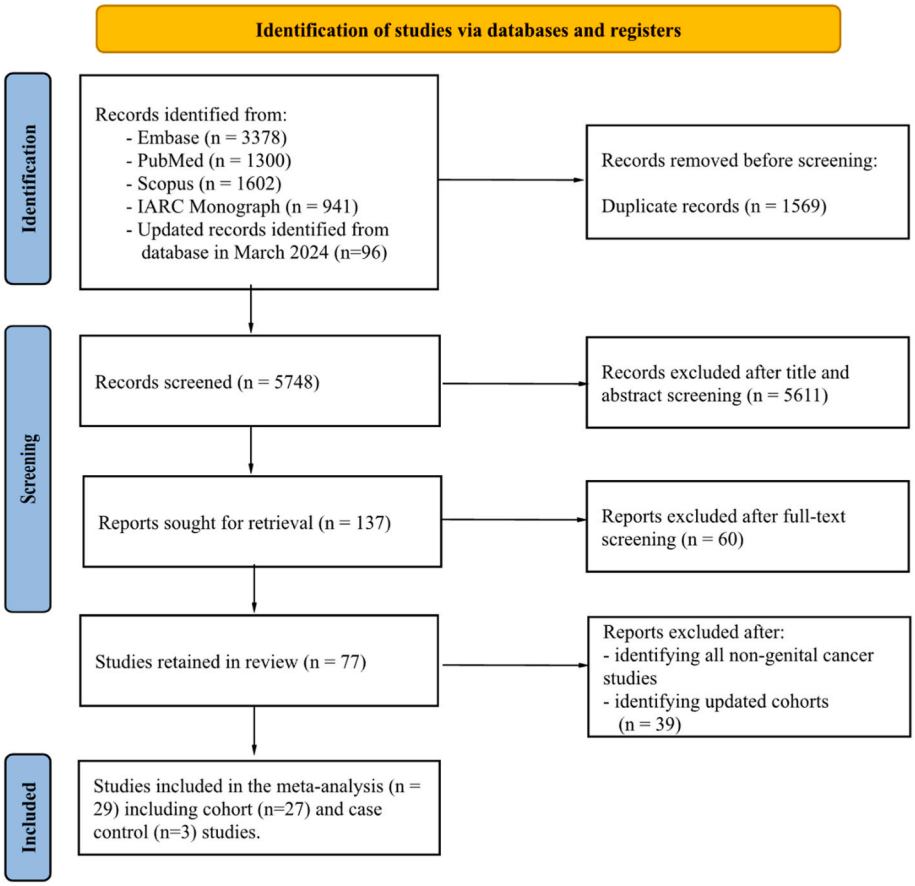

Fig. 1. Selection of studies for inclusion in the review and meta-analysis.

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

First author and year of publication	Country	Study design	Follow-up period	Industrial sector (ISIC-4 code)	Occupation (ISCO-08 code)	Gender	Number of subjects (total or case/control)	Outcome studied	Cancer type	Quality assessment
Rushton L, 1980	UK	cohort	1950–1975	1920	2145/2146/3117/3134	male	34781	mortality	nose & sinuses	7
Tsai SP, 1983	USA	cohort	1973–1982	1920	3117/3134/9333	male	454	mortality	oral cavity & oro-hypo- pharynx	7
Guberan E, 1985	Swiss	cohort	1942–1980 1970–1980	2023	2113/8131	male	1168	mortality incidence	oral cavity & oro-hypo- pharynx/ larynx	8
Szeszenia Dabrowska N, 1991	Poland	cohort	1945–1985	1520	not specified	male	6978	mortality	oral cavity & oro-hypo- pharynx/ larynx	6
Walker JT, 1993	USA	cohort	1940–1982	1520	8156	male female	2529 5285	mortality	oral cavity & oro-hypo- pharynx/ larynx	9
Greenland S, 1994	USA	case-control	1969–1984	2710	8212	male	512/1202	mortality	oral cavity & oro-hypo- pharynx/ larynx	6
Lagorio S, 1994	Italy	cohort	1981–1992	4730	5245	male female	2308 357	mortality	oral cavity & oro-hypo- pharynx/ larynx	7
Honda Y, 1995	USA	cohort	1940–1989	1920	not specified	male	9796	mortality	oral cavity & oro-hypo- pharynx/ larynx	8
Collingwood KW, 1996	USA	cohort	1947–1987	1920	not specified	both	4855	mortality	oral cavity & oro-hypo- pharynx/ larynx	8
Fu H, 1996	Italy	cohort	1950–1990	1520	8156	both	2008	mortality	nose & sinuses/ larynx	8
Fu H, 1996	UK	cohort	1939–1991	1520	8156	male	4215	mortality	nose & sinuses/ larynx	8
Satin KP, 1996	USA	cohort	1937–1987	1920	3134	male female	15855 1989	mortality	oral cavity & oro-hypo- pharynx	7
Järvholm B, 1997	Sweden	cohort	1958–1991	mixed	3134/7232/8332/9333	male	4128	incidence	nasopharynx	8
Lynge E, 1997	Europe	cohort	1970–1991	4730	5245	male female	16524 2445	incidence	oral cavity & oro-hypo- pharynx/ nose & sinuses/ larynx	7
Pukkala E (1998)	Finland	cohort	1971–1994	1920	2145/3116/3134/3133	both	9454	incidence	larynx	7
Consonni D, 1999	Italy	cohort	1949–1991	1920	3134	male	1583	mortality	larynx	8
Kauppinen T, 2003	Finland	cohort	1980–1999	7120	3111	both	4722	incidence	oral cavity & oro-hypo- pharynx/ nose & sinuses/ larynx	8
Lewis RJ, 2003	Canada	cohort	1964–1994 1969–1994	mixed	2113/3134/8342/8131	male female male female	17230 8062 17230 8062	mortality incidence	nose & sinuses	8
Sorahan T, 2005	UK	cohort	1968–2002 1971–2001	mixed	not specified	both	5514	mortality incidence	oral cavity & oro-hypo- pharynx/ nose & sinuses/ larynx	8
Swaen GMH, 2005	Netherlands	cohort	1951–2001	2029	not specified	male	311	mortality	oral cavity & oro-hypo- pharynx/ larynx	8
Gun RT, 2006	Australia	cohort	1980–2001 1980–2000	1920	not specified	male	16547	mortality incidence	oral cavity & oro-hypo- pharynx/ larynx	8.5
Budroni M, 2010	Italy	cohort	1990–2006	1920	not specified	male	5350	incidence	larynx	6
Koh DH, 2011	Korea	cohort	1992–2007 1997–2005	1920	not specified	male	8866	mortality incidence	oral cavity & oro-hypo- pharynx/ nasopharynx oral cavity & oro-hypo- pharynx/ nasopharynx/ larynx	7,5
Bonneterre V, 2012	France	cohort	1979–2002	2011/2021/2029	not specified	male	2742	incidence	oral cavity & oro-hypo- pharynx/ nose & sinuses/ larynx	7.5

(*continued on next page*)

Table 1 (*continued*)

First author and year of publication	Country	Study design	Follow-up period	Industrial sector (ISIC-4 code)	Occupation (ISCO-08 code)	Gender	Number of subjects (total or case/control)	Outcome studied	Cancer type	Quality assessment
Koh DH, 2014	Korea	cohort	2002–2007 2002–2005	1920	7212/7126/ 7124/8122	male	14698	mortality incidence	oral cavity & oro-hypo- pharynx/ nasopharynx/ larynx	6
Collins JJ, 2015	USA	cohort	1940–2009	2011	3111/3116/ 3133/8131	both	2266	mortality	oral cavity & oro-hypo- pharynx	8
Linet S, 2015	China	cohort	1972–1999	1520/1622/ 1811/2119	not specified	both	73789	mortality	oral cavity & oro-hypo- pharynx/ nasopharynx	8
Carton M, 2017	France	case-control	2001–2007	1920/2011	not specified	female	278/759	incidence	oral cavity & oro-hypo- pharynx/ larynx	8
Gustavsson P, 2017	Sweden	cohort	1958–2012	7120/7210	not specified	female	2245	incidence	oral cavity & oro-hypo- pharynx	8
Barul C, 2018	France	case-control	2001–2007	1920/2011	not specified	male	762/2672	incidence	oral cavity & oro-hypo- pharynx/ larynx	8

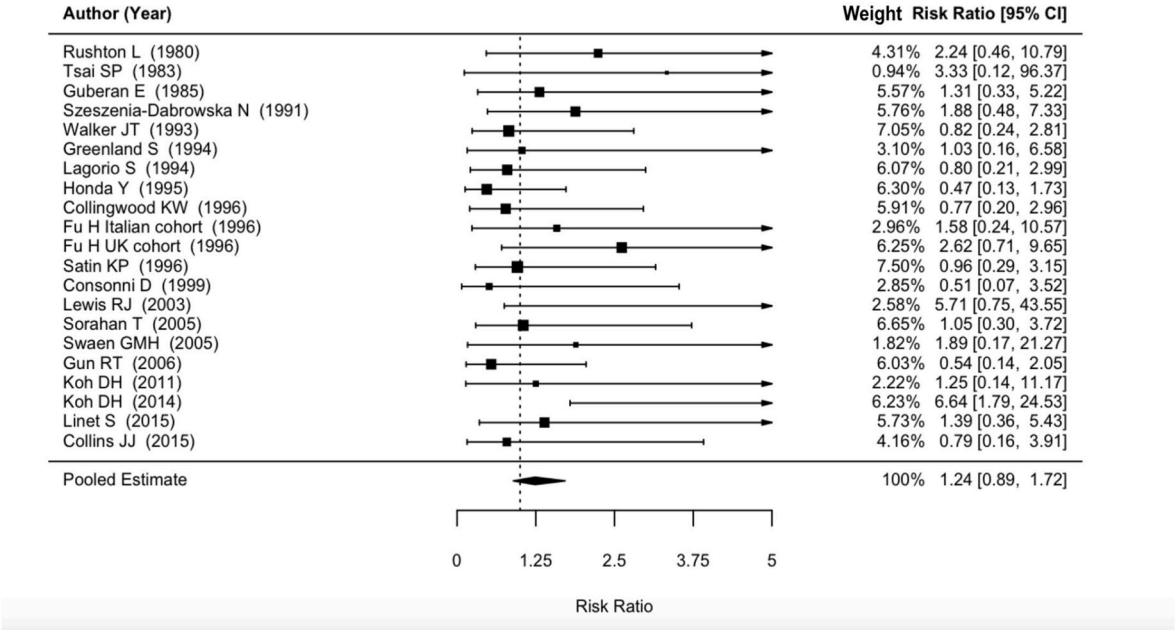

Fig. 2. Forest plot with results of multilevel meta-analysis on the studies on occupational exposure to benzene and mortality of HNC.

1996; Swaen et al., 2005; Szeszenia-Dabrowska et al., 1991; Tsai et al., 1983; Walker et al., 1993). This data, however, presented high heterogeneity.

Subgroup analysis by geographic region indicated an increased risk among European cohorts of workers (RR 1.31; 95% CI = 1.08,1.59; $I^2level_2 = 46.87\%$, $I^2level_3 = 0.1\%$ $p < 0.01$) (Barul et al., 2018; Bonneterre et al., 2012; Budroni et al., 2010; Carton et al., 2017; Consonni et al., 1999; Fu et al., 1996; Guberan and Raymond, 1985; Gustavsson et al., 2017; Järvholm et al., 1997; Kauppinen et al., 2003; Lagorio et al., 1994; Lynge et al., 1997; Pukkala, 1998; Rushton and Alderson, 1980 Sorahan et al., 2005; Swaen et al., 2005; Szeszenia-Dabrowska et al., 1991). Results of the cancer type sub-group analysis demonstrated a significant increase in the risk of nasal & sinuses cancer (RR = 3.72, 95% CI = 2.07–6.68; $I^2level_2 = 34.13\%$, $I^2level_3 = 0\%$, P = 0.171) (Bonneterre et al., 2012; Lynge et al., 1997; Lewis et al., 2003; Fu et al., 1996; Rushton and Alderson, 1980; Sorahan et al., 2005). However, no significant association was found related to larynx cancer (RR = 1.04, 95% CI = 0.87–1.24; $I^2level_2 = 0\%$, $I^2level_3 = 6.84\%$, P = 0.729) (Barul et al., 2018; Bonneterre et al., 2012; Budroni et al., 2010; Carton et al., 2017; Collingwood et al., 1996; Collins et al., 2015; Consonni et al., 1999; Fu et al., 1996; Guberan and Raymond, 1985; Gun et al., 2006; Honda et al., 1995; Kauppinen et al., 2003; Koh et al., 2011, 2014; Lagorio et al., 1994; Lynge et al., 1997; Pukkala, 1998; Sorahan et al., 2005; Swaen et al., 2005; Szeszenia-Dabrowska et al., 1991; Walker et al., 1993), nasopharyngeal cancer (RR = 2.70, 95% CI = 0.51–14.46; $I^2level_2 = 22.97\%$, $I^2level_3 = 22.97\%$, P = 0.145) (Järvholm et al., 1997; Koh et al., 2011, 2014; Linet et al., 2015) and oral cavity (RR = 1.00, 95% CI = 0.81–1.22; $I^2level_2 = 0\%$, $I^2level_3 = 32.84\%$, P = 0.139) (Barul et al., 2018; Bonneterre et al., 2012; Carton et al., 2017; Collingwood et al., 1996; Collins et al., 2015; Guberan and Raymond, 1985). When considering the distinction with regard to study quality according to the NOS scale, we found that moderate quality studies (Bonneterre et al., 2012; Budroni et al., 2010; Greenland et al., 1994; Koh et al., 2011, 2014 Koh et al., 2014; Lagorio et al., 1994; Lynge et al., 1997; Pukkala, 1998; Rushton and Alderson, 1980; Satin et al., 1996; Szeszenia-Dabrowska et al., 1991; Tsai et al., 1983) showed a higher risk of HNC (RR = 1.39, 95% CI = 1.00–1.91; $I^2level_2 = 0\%$, $I^2level_3 = 45.94\%$, P < 0.01) compared to high quality studies (RR = 1.06, 95% CI = 0.84–1.35;

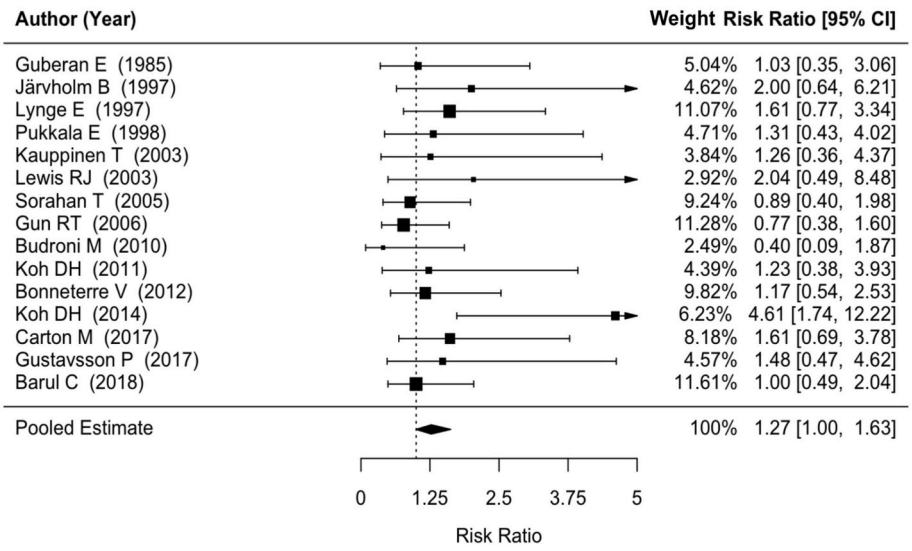

Fig. 3. Forest plot with results of multilevel meta-analysis on the studies on occupational exposure to benzene and incidence of HNC.

$I^2level_2 = 52.32\%$, $I^2level3 = 7.04\%$, $P < 0.001$) (Barul et al., 2018; Carton et al., 2010, 2017; Collingwood et al., 1996; Collins et al., 2015; Consonni et al., 1999; Fu et al., 1996; Guberan and Raymond, 1985; Gun et al., 2006; Gustavsson et al., 2017; Honda et al., 1995; Järvholm et al., 1997; Kauppinen et al., 2003; Lewis et al., 2003; Linet et al., 2015; Sorahan et al., 2005; Swaen et al., 2005; Walker et al., 1993). Finally, no significant result was observed after stratification by study design, risk of bias, and industrial sector. Results of the stratified analyses are reported in Table 2.

The leave-one-out sensitivity analysis revealed that the exclusion of certain individual studies (Bonneterre et al., 2012; Budroni et al., 2010; Carton et al., 2017; Collingwood et al., 1996; Collins et al., 2015; Consonni et al., 1999; Greenland et al., 1994; Guberan and Raymond, 1985; Gun et al., 2006; Honda et al., 1995; Kauppinen et al., 2003; Koh et al., 2011; Lagorio et al., 1994; Pukkala, 1998; Satin et al., 1996; Sorahan et al., 2005; Tsai et al., 1983; Walker et al., 1993) significantly altered the pooled effect estimates for the overall risk of HNC, rendering the results statistically significant. This finding is consistent with the fact that the pooled effect confidence interval was already near the threshold of significance. No substantial changes were observed in the risk estimates for HNC incidence and mortality.

No evidence of publication bias was found in the main results of our multilevel meta-analysis from the visual inspection of the Doi plot and Funnel plot (Figs. 4 and 5), and the computation of Egger's test ($p = 0.103$).

As the quality score of the articles increased multilevel meta-regressions showed that there appeared to be a significantly lower risk of HNCs ($p = 0.029$; Supplementary Fig. 1), while no significant association was found with first year of follow-up ($p = 0.353$, Supplementary Fig. 2) and first year of employment ($p = 0.457$, Supplementary Fig. 3).

The results of Quality Assessment evaluated with the modified NOS are presented in Supplementary Table 5. A total of 17 articles yielded high quality ratings, while 12 ended up with moderate quality ratings.

The risk of bias rating for each domain for all 30 included cohorts is represented in Table 3. The descriptive justification for each rating in each domain is presented in Supplementary Table 6.

- Selection bias: we assessed risk of bias in this domain through the evaluation of the risk that the study groups were not representative of source populations in a manner that could have introduced selection bias. For five studies the risk of bias was rated to be low, 20 studies gave a probably low risk and 5 probably high risk.

Table 2
Results of the meta-analysis by outcome, gender, Country, cancer type, study design, ISIC-code, Risk of Bias, Newcastle - Ottawa quality assessment scale.

Three-levels meta-analysis model	ES	Studies	Pooled RR	Lower CI	Upper CI	p-value	I2 level 3	I2 level 2	p-het
Total	79	30	1.20	0.99	1.46	<0.0001	30.61%	24.92%	
Mortality	47	21	1.24	0.89	1.72	<0.0001	34.02%	34.12%	0.063
Incidence	48	15	1.27	1.00	1.64	0.011	47.30%	0%	
Males	48	21	1.24	0.94	1.64	<0.0001	30.97%	38.91%	0.082
Females	10	6	1.68	1.07	2.61	0.4339	0%	0%	
Europe	52	18	1.31	1.08	1.59	0.007*	0.1%	46.87%	0.069
Asia	10	4	1.55	0.64	3.78	0.379	79.50%	0%	
USA	17	8	0.80	0.64	1.01	0.4823	5.44%	0%	
Nose & sinuses	9	7	3.72	2.07	6.68	0.1730	0%	34.13%	<0.0001
Larynx	23	21	1.04	0.87	1.24	0.7291	6.84%	0%	
Oral cavity	43	21	1.00	0.81	1.22	0.1387	32.84%	0%	
Nasopharynx	3	3	2.70	0.51	14.46	0.1451	22.97%	22.97%	
Case Control	7	3	1.19	0.73	1.85	0.6671	21.61%	0%	0.169
Cohort	72	27	1.20	0.96	1.50	<0.0001	27.18%	29.20%	
Low RoB	14	7	1.11	0.82	1.52	0.8065	10.75%	0%	0.163
High RoB	65	24	1.20	0.95	1.50	<0.0001	27.98%	33.32%	
NOS ≥ 8	41	18	1.06	0.84	1.35	<0.0001	7.04	52.32%	0.043
NOS < 8	38	12	1.39	1.00	1.91	<0.001	45.94%	0%	
ISIC - 1920	19	10	1.02	0.60	1.72	<0.001	0%	78.66%	

ES, number of effect sizes included in the analysis; Studies, number of studies included in the meta-analysis; Pooled RR, meta-relative risk, based on multilevel model; CI, confidence interval; p-het, p-value of test for heterogeneity of strata-specific RR.

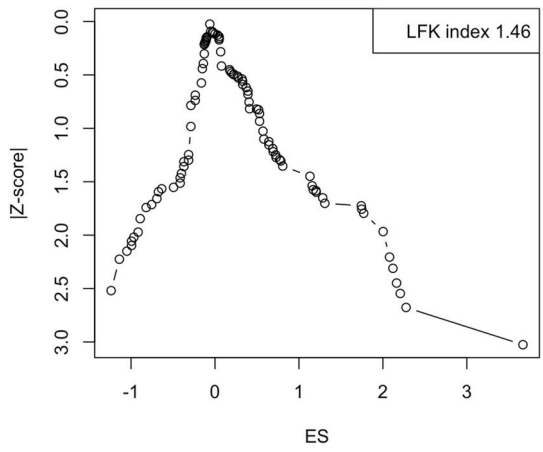

Fig. 4. Doi plot showing the risk of publication bias in the multilevel meta-analysis on the association between benzene exposure and HNCs (LFK: Luis Furuya-Kanamori Index).

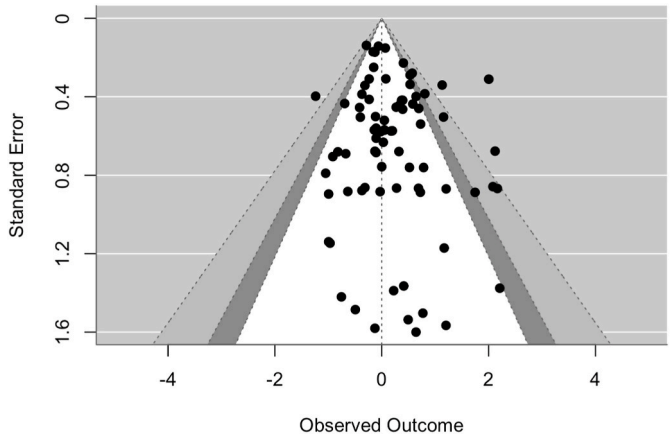

Fig. 5. Funnel plot showing the risk of publication bias in the multilevel meta-analysis on the association between benzene exposure and HNCs.

- Performance bias: for cohort studies (n = 27) we do not consider blinding as an element of study design capable of introducing risk of bias in the study. For case-control studies, the risk of performance bias was rated as low for two studies and probably low for one study.
- Detection bias (exposure assessment): robust data on exposure assessment were often missing or incomplete. In most cases, this information was retrieved from reported industries and occupations. Only one study satisfied the requirements for low risk of bias, 5 resulted in a probably low risk, 19 probably high, and 5 high yielded a risk of bias.
- Detection bias (outcome assessment): for 22 studies outcomes were assessed and defined consistently across all study participants, using valid and reliable measures, while 8 studies provided a probably low risk.
- Confounding: in 16 studies, the Authors did not account for or evaluate multiple important confounders (Tier I), and in 10 studies some but not all the important confounders (Tier I), and some but not all of the other potentially important confounders relevant (Tier II) were evaluated. Only 4 studies yielded low or probably low risk of bias.
- Selection bias (incomplete outcome data): in most cases (n = 27) participants were followed long enough to obtain outcome measurements and the reason for missing outcome data was unlikely. Only 3 studies ended with a probably high risk of selection bias.
- Reporting bias: in all 30 studies a pre-published protocol was not available, but the pre-specified outcomes were outlined in the published manuscript's methods, abstract, and/or introduction section. For these reasons reporting bias was evaluated probably low (n = 30)
- Conflict of interest: in 4 studies there was indirect evidence which suggested that the study was not free of support from entities having a financial interest in the outcome of the study. The other articles yielded probably low (n = 9) or low (n = 17) risk with regard to conflict of interest.
- Other risk of bias: for all 30 studies included there was insufficient information to permit a judgment of low risk of bias, but there was indirect evidence which suggests the study was free of other threats to validity.

The quality of evidence rating according to the GRADE system is presented in Table 4. A descriptive justification for each rating is available in the Supplementary Table 7.

For the pooled result of risk of overall HNC we started our assessment at "moderate quality of evidence" because the body of evidence comprised only observational studies. We downgraded by one level (−1) for risk of bias and arrived at a final rating of "low quality of evidence": further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. For the morality outcome we started our assessment at "moderate quality of evidence" and downgraded by one level (−1) for risk of bias and one level (−1) for inconsistency, arriving at a final rating of "very low quality of evidence": we are very uncertain of the evidence. For the incidence outcome, starting our assessment at "moderate quality of evidence" we downgraded by one level (−1) for risk of bias and upgraded by one level for large magnitude of effect and arrived at a final rating of "moderate quality of evidence": the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. The same rating was assigned to the pooled results for the risk of Nose and Sinuses cancer, the risk of HNCs in females, European cohorts and low-quality studies.

4. Discussion

This systematic review and meta-analysis synthesized evidence on the incidence and mortality of HNCs among workers with occupational benzene exposure. To date, few other systematic reviews and meta-analyses have investigated the relationship between benzene exposure and solid cancers, suggesting a positive association with colorectal cancer, and lung cancer (Chiavarini et al., 2024; Sassano et al., 2024). To the best of our knowledge, this is the first systematic review and meta-analysis to summarize the relationships between benzene exposure and HNCs.

We found a borderline statistical association between occupational benzene exposure and the overall risk for HNCs. However, after stratification by outcome, the tendency on an increase incidence of HNCs in workers exposed to benzene was confirmed, while no statistically significant association with mortality was found.

Regarding cancer site subgroup analysis, we found a strong increase of the overall risk of nose and sinuses cancers, suggesting that our borderline statistically significant results for HNCs were mainly driven by the positive association with this specific cancer site and, to a lesser extent, with larynx, oral cavity and hypo-nasopharynx cancers. Among the organs considered, the nasal cavity tissue has the highest metabolic activity, including high sulfoconjugating activity and significant amount of cytochrome P-450 monooxygenase activity (Low et al., 1995). These properties are consistent with the nasal mucosa being the first tissue to encounter xenobiotics and its capability of bio-transform benzene into potentially reactive intermediates, providing a possible mechanism for the susceptibility of this tissue to benzene induced tumorigenicity.

Despite the limited number of studies, an association was also observed between benzene exposure and HNCs cancer among female

Table 3
Summary of risk of bias.

	1. Are the study groups at risk of not representing their source populations in a manner that might introduce selection bias?	2. Was knowledge of the group assignments inadequately prevented (i.e. blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?	3. Were exposure assessment methods lacking accuracy?	4. Were outcome assessment methods lacking accuracy?	5. Was potential confounding inadequately incorporated?	6. Were incomplete outcome data inadequately addressed?	7. Does the study report appear to have selective outcome reporting?	8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?	9. Did the study appear to have other problems that could put it at a risk of bias?
Rushton L, 1980	Probably Low	Not Applicable	Probably High	Low	Probably High	Probably High	Probably Low	Low	Probably Low
Tsai SP, 1983	Low	Not Applicable	Probably Low	Low	Probably High	Low	Probably Low	Probably High	Probably Low
Guberan E, 1985	Low	Not Applicable	Probably High	Probably Low	High	Low	Probably Low	Low	Probably Low
Szeszenia-Dabrowska N, 1991	Probably Low	Not Applicable	Probably High	Probably Low	High	Low	Probably Low	Low	Probably Low
Walker JT, 1993	Low	Not Applicable	High	Low	High	Low	Probably Low	Low	Probably Low
Greenland S, 1994	Probably High	Low	Probably High	Low	High	Low	Probably Low	Probably High	Probably Low
Lagorio S, 1994	Probably High	Not Applicable	Probably Low	Low	Probably High	Probably High	Probably Low	Low	Probably Low
Honda Y, 1995	Low	Not Applicable	Probably High	Low	High	Low	Probably Low	Probably High	Probably Low
Collingwood KW, 1996	Probably Low	Not Applicable	Probably High	Low	Probably High	Low	Probably Low	Probably High	Probably Low
Fu H, 1996 (Italian cohort)	Probably Low	Not Applicable	Probably High	Low	Probably High	Low	Probably Low	Low	Probably Low
Fu H, 1996 (UK cohort)	Probably Low	Not Applicable	Probably High	Low	Probably High	Low	Probably Low	Low	Probably Low
Satin KP, 1996	Probably Low	Not Applicable	Probably High	Low	Probably Low	Low	Probably Low	Probably Low	Probably Low
Järvholm B, 1997	Probably Low	Not Applicable	Probably High	Probably Low	High	Low	Probably Low	Probably Low	Probably Low
Lynge E, 1997	Probably Low	Not Applicable	Probably High	Probably Low	Probably High	Probably Low	Probably Low	Probably Low	Probably Low
Pukkala E, 1998	Probably Low	Not Applicable	Probably High	Low	High	Low	Probably Low	Probably Low	Probably Low
Consonni D, 1999	Probably Low	Not Applicable	High	Low	High	Low	Probably Low	Probably Low	Probably Low
Kauppinen T, 2003	Probably Low	Not Applicable	Probably High	Probably Low	Probably High	Probably Low	Probably Low	Probably Low	Probably Low
Lewis RJ, 2003	Probably Low	Not Applicable	Low	Low	Probably Low	Low	Probably Low	Probably Low	Probably Low
Sorahan T, 2005	Probably High	Not Applicable	Probably High	Low	High	Low	Probably Low	Low	Probably Low
Swaen GMH, 2005	Probably Low	Not Applicable	Probably High	Probably Low	High	Low	Probably Low	Probably Low	Probably Low
Gun RT, 2006	Probably High	Not Applicable	Probably High	Probably Low	Probably High	Probably Low	Probably Low	Low	Probably Low
Budroni M, 2010	Probably High	Not Applicable	Probably High	Low	High	Low	Probably Low	Low	Probably Low
Koh DH, 2011	Probably Low	Not Applicable	High	Low	High	Probably Low	Probably Low	Low	Probably Low
Bonneterre V, 2012	Probably Low	Not Applicable	Probably High	Low	Probably High	Probably Low	Probably Low	Probably Low	Probably Low
Koh DH, 2014	Probably Low	Not Applicable	High	Probably Low	High	Probably High	Probably Low	Low	Probably Low
Collins JJ, 2015	Low	Not Applicable	Probably Low	Low	High	Low	Probably Low	Low	Probably Low
Linet S, 2015	Probably Low	Not Applicable	High	Low	High	Low	Probably Low	Low	Probably Low
Carton M, 2017	Probably Low	Low	Probably Low	Low	Low	Low	Probably Low	Low	Probably Low
Gustavsson P, 2017	Probably Low	Not Applicable	Probably High	Low	High	Low	Probably Low	Low	Probably Low
Barul C, 2018	Probably Low	Probably Low	Probably Low	Low	Low	Low	Probably Low	Low	Probably Low

Table 4
GRADE summary of findings.

Outcome	Included studies	GRADE	RR [95% CI]
Overall risk of HNC	30	**LOW** *due to risk of bias*	1.20 [0.99; 1.46]
Mortality of HNC	21	**VERY LOW** *due to risk of bias imprecision and inconsistency*	1.24 [0.89; 1.72]
Incidence of HNC	15	**MODERATE** *due to risk of bias and magnitude of effect size*	1.27 [1.00, 1.64]
Risk of Nose and Sinuses Cancer	7	**MODERATE** *due to risk of bias and large magnitude of effect size*	3.72 [2.07, 6.68]
Risk of HNC in females	6	**MODERATE** *due to risk of bias and large magnitude of effect size*	1.68 [1.07; 2.61]
Risk of HNC among european cohorts	18	**MODERATE** *due to risk of bias and large magnitude of effect size*	1.31 [1.08; 1.59]
Risk of HNC in moderate quality studies	12	**MODERATE** *due to risk of bias and large magnitude of effect size*	1.39 [1.00; 1.91]

workers. Women may have a greater susceptibility to the toxic effects of benzene due to biological, hormonal and genetic differences, affecting the formation of carcinogenic metabolites (Kim et al., 2006). Additionally, differences in health-related behaviors, such as smoking, alcohol, diet and other environmental exposures between man and women may influence the risk of developing HNCs cancer. In this view, this finding can be explained by the lower prevalence of tobacco smoking among women, potentially minimizing the negative confounding effect, in comparison with men.

To date in fact, it is well known that the incidence and mortality of HNCs are influenced by several risk factors both in the occupational and non-occupational setting. Alcohol drinking and smoking habits (including smokeless tobacco and second-hand smoke) are the two most important risk factors of HNCs, mainly for cancers of the oral cavity, hypo-pharynx, and larynx. People who use both tobacco and alcohol face a higher risk of developing these cancers compared to individuals who use either tobacco or alcohol alone (Jethwa and Khariwala, 2017; Kawakita and Matsuo, 2017). Infection with high-risk human papillomavirus (HPV), especially HPV types 16 and 18, is a risk factor for oropharyngeal cancer that involves the tonsil and the base of the tongue (Tumban, 2019). Other known risk factors for specific cancers of the head and neck include: paan (betel quid) chewing, a common habit in South and Southeast Asia, associated with the occurrence of oral cavity cancer (Chen et al., 2008); local radiation exposure for salivary glands' cancers(Mayne et al., 2006); Epstein-Barr virus infection, a known risk factor for cancer of the salivary glands and nasopharyngeal cancer (Prabhu and Wilson, 2016); Chinese ancestry, for nasopharyngeal cancer (Yu and Yuan, 2002). Moreover, genetic disorders like Fanconi anaemia, can elevate the risk of developing precancerous lesions and HNCs at an early age (Chihanga et al., 2022). In occupational settings, exposure to wood dust is identified as a risk factor for sinonasal cancer (Blot et al., 1997), while certain industrial exposures, including asbestos, have been linked to cancer of the larynx, although the extent of the risk remains controversial (Olshan, 2006). Higher risks of larynx cancer have been found in individuals working in specific sectors such as construction, metal, textile, ceramic, logging, and food industries (Boffetta et al., 2003). Furthermore, industrial exposure to nickel dust or formaldehyde is established as a risk factor for cancers of the paranasal sinuses and nasal cavity (Littman and Vaughan, 2006; Luce et al., 1993). Some of these risk factors, especially alcohol intake and smoking habits, may exert a confounding effect on the association with benzene exposure and the adjustment for their potential confounding effect is therefore critical. However, in most studies included in our meta-analysis, data on smoking and alcohol were not available, thus potentially leading to biased results.

According to geographic region, the association between HNCs and benzene exposure differed, with positive results among European cohorts of workers. Although various factors might explain regional or ethnic differences in the effect of benzene on human health, including differences in exposure levels across countries, background incidence of the disease, and genetic factors (Jephcote and Mah, 2019) this finding might also be due to chance.

Subgroup analyses by quality score revealed articles with moderate methodological quality reported an increased risk of HNCs in comparison with high quality studies. This result was confirmed by the multilevel meta-regression according to the quality assessment of the studies. To this end, this finding underscores the importance of obtaining reliable data, as biases or design flaws in the primary studies could raise questions about the overall validity of results.

Our findings underline the need to emphasize compliance with safety regulations for workers exposed to benzene. The main steps involved are summarized in the principles of primary prevention: hazard communication and training of the personnel; engineering controls for preventing benzene exposure through substitution of the hazardous substance, whenever possible, ventilation and isolation; use of personal protective equipment (PPE) such as respiratory protection, protective clothing, eye protection; air monitoring of working places, biological monitoring and defining exposure limits; work practices such as minimizing the exposure, good hygiene, proper storage, the establishment of emergency procedures, spill response, first aid and evacuation plans; record-keeping and compliance with relevant regulations; labeling and signage of dangerous substances. By following these procedures, employers can significantly reduce the risk of benzene exposure and protect the health and safety of workers. Regular review and updating of safety protocols in response to new information or incidents are also essential.

If the substitution of the hazardous substance is not applicable and all the principles of primary prevention are applied, secondary prevention rules, specifically workers' health surveillance, must be enforced to diagnose the onset of a neoplasm at an early stage. In this view, disease recognition for HNCs in workers exposed to benzene results in a complex task involving several steps to identify and confirm the occupational nature of the disease.

4.1. Strengths and limitations

To our knowledge, this is the first systematic review and meta-analysis on the association between occupational benzene exposure and HNC. Our analysis includes large numbers of high-quality cohort and case control studies, based on a broad search strategy and rigorous literature screening process. Moreover, validated methodologies for meta-analyses were adopted to perform data analyses.

Our systematic review and meta-analysis also suffer from some limitations. While no consistent publication bias was found, the level of heterogeneity was high. Dataon duration or level of exposure were scarce, thus pre-empting stratified analyses which would have been informative. Additionally, we couldn't run our analysis for cancer of subsites of head and neck organs, such as tongue, gum, cheek and palate. There was also a small number of women exposed to benzene in the available studies, and most populations were from North America and Europe. Future studies need to take into account factors such as clinical characteristics of HNC, such as stage at diagnosis, female gender, regions other than North America and Europe with less attention to prevention guidelines, and control for other confounding factors and risk factors, particularly smoking and alcohol drinking.

5. Conclusion

In conclusion, our findings suggest that occupations entailing

benzene exposure may be associated with HNCs, with a statistically significant increase int the overall risk of nose and sinuses cancer. This study brings new evidence on a potentially important topic, even if it suffers from some limitations. It is important to stress the need for primary and secondary prevention in the workplace by minimizing exposure to benzene and emphasizing adherence to regulatory provisions.

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CRediT authorship contribution statement

Alessandro Godono: Writing – original draft, Validation, Supervision, Methodology, Data curation. **Andrea Dito:** Writing – original draft, Data curation. **Giorgio Martini:** Writing – original draft, Validation, Data curation. **Maria Vittoria Picciaiola:** Methodology, Formal analysis. **Antonio Di Lorenzo:** Writing – original draft, Validation, Data curation. **Catalina Ciocan:** Writing – original draft, Validation, Data curation. **Paolo Boffetta:** Writing – review & editing, Validation, Supervision, Methodology, Data curation, Conceptualization. **Monireh Sadat Seyyedsalehi:** Writing – review & editing, Validation, Supervision, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Paolo Boffetta acted as an expert witness in litigation involving benzene exposure and head and neck cancer, unrelated to the present work. Other authors declare no conflict of interest. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.120033.

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