Occupational benzene exposure and lung cancer risk: A pooled analysis of 14 Case-Control Studies

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Potential impact of this study: Previous evidence is limited in linking benzene exposure with lung cancer. In this large, pooled analysis of 14 case-control studies we provided evidence to support the hypothesis based on robust and consistent associations between occupational benzene exposure and increased lung cancer risk.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

Abstract

Rationale: Benzene has been classified as carcinogenic to humans, but there is limited evidence linking benzene exposure to lung cancer.

Objectives: We aimed to examine the relationship between occupational benzene exposure and lung cancer.

Methods: Subjects from 14 case-control studies across Europe and Canada were pooled. We used a quantitative job-exposure matrix to estimate benzene exposure. Logistic regression models assessed lung cancer risk across different exposure indices. We adjusted for smoking and five main occupational lung carcinogens and stratified analyses by smoking status and lung cancer subtypes.

Measurements and Main Results: Analyses included 28048 subjects (12329 cases, 15719 controls). Lung cancer odds ratios ranged from 1.12 (95% CI: 1.03-1.22) to 1.32 (95% CI: 1.18-1.48) (P_{trend}=0.002) for groups with the lowest and highest cumulative occupational exposure, respectively, compared to unexposed subjects. We observed an increasing trend of lung cancer with longer duration of exposure (P_{trend}<0.001) and decreasing trend with longer time since last exposure (P_{trend}=0.02). These effects were seen for all lung cancer subtypes, regardless of smoking status, and were not influenced by specific occupational groups, exposures, or studies.

Conclusion: We found consistent and robust associations between different dimensions of occupational benzene exposure and lung cancer after adjusting for smoking and main occupational lung carcinogens. These associations were observed across different subgroups, including non-smokers. Our findings support the hypothesis that occupational benzene exposure increases the risk of developing lung cancer. Consequently, there is a need to revisit published epidemiological and molecular data on the pulmonary carcinogenicity of benzene.

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1. Introduction

Benzene is a volatile and ubiquitous air pollutant that is mainly produced from anthropogenic sources. It was a common solvent and ingredient in paint, printing inks, and glues, but the benzene content in these products has either been replaced or reduced since the 1980s following regulations and other mitigation measures (1, 2). Nevertheless, it remains a high-production volume chemical and is still widely present in low-/middle income countries (3). Occupational exposure to benzene occurs in various industries including petroleum, chemical, painting, rubber, coke making, and manufacturing. Benzene has been classified as carcinogenic to humans (International Agency for Research on Cancer (IARC) group 1), on the basis of its causal link with acute myeloid leukemia (AML) (4).

Lung cancer is one of the leading causes of death worldwide (5). However, the association between benzene exposure and lung cancer has been less understood as previous studies have reported inconsistent results. For example, some studies indicated an increased risk of lung cancer among exposed subjects (6-11), while other studies showed no evidence of such association (12-19). In 2018, an IARC Monographs working group on benzene concluded that the evidence of carcinogenicity for lung cancer was limited (4). The main concerns were the lack of sufficient adjustments for smoking and exposure to other occupational lung carcinogens (4). Shortly after the publication of the IARC monograph on benzene, a Canadian case-control study (which is also included in the SYNERGY project), including 733 cases and 894 controls, provided support for the association between ever exposure to benzene and lung cancer risk (odds ratio=1.35, 95% CI: 0.99-1.84), after adjusting for both smoking and several lung carcinogens (10). The association, however, was not present among non- and low-level smokers (odds ratio=0.94, 95% CI: 0.49-1.81), possibly due to the limited sample size in this study, leaving the possibility that the observed association was driven by residual confounding. Therefore, studies with larger sample size and stricter control for confounding factors (e.g.,

smoking and co-exposures) are needed to further elucidate the possible association between occupational benzene exposure and lung cancer.

This study aims to examine the association between occupational benzene exposure and lung cancer using a large-scale, pooled case-control study. We investigated lung cancer risk in relation to various benzene exposure metrics (ever/never, cumulative exposure, duration, and time since last exposure), stratified by smoking status and histologic types of lung cancer. Some of the results have been reported in the form of a conference abstract (20).

2. Methods

2.1 Study population

Fourteen population- and hospital-based case-control studies on lung cancer were pooled from 13 European countries and Canada in the SYNERGY project (Table E1). A detailed description of the study population is presented elsewhere (21) and on http://synergy.iarc.fr. Briefly, all studies have provided lifetime occupational and smoking histories (except for MORGEN). In most studies, cases and controls were frequency-matched by sex and age. Most interviews (84%) were conducted face-to-face with the subjects. Lung cancer subtypes were classified based on WHO guidelines (22) after histological or cytological confirmation by the pathologists associated with the participating hospitals. Ethical approvals for the SYNERGY project were obtained following the legislation in each participating country and the IARC institutional review board.

2.2 Exposure assessment

We used a benzene-specific job-exposure matrix (BEN-JEM) to assess occupational exposure based on participants' lifetime occupational histories. One of the authors (R.V.) previously developed BEN-JEM (23) by combining expert assessments of exposure levels and probability factors and incorporating trends from various industries/job titles over time. BEN-JEM

assesses occupational exposure to benzene encoded to the International Classification of Occupations 1988 (ISCO-88): for each ISCO-88 job code, BEN-JEM assigns the proportion of exposed workers (P, also as probability) and the mean level of exposure (L, in parts per million (ppm)) by eight periods (1945-59, 1960-84, 1985-94, 1995-97, 1998-2000, 2001-03, 2004-06, and 2007-09), accounting for the downward trend of workplace exposure in Europe and Northern America (2). Exposure was calculated as a product of the probability and level (P × L). To improve exposure assessment quality, we only included subjects whose job records were within the BEN-JEM assessment period (1945-2009). Details of the exposure assessment are shown in the online supplement.

For other occupational exposures, we used SYN-JEM to assess the cumulative exposure levels to five main lung carcinogens (asbestos, hexavalent chromium (Cr(VI)), nickel, polycyclic aromatic hydrocarbons (PAHs), and respirable crystalline silica (RCS)), and DEE-JEM to assess exposure to diesel engine exhaust (DEE). Detailed descriptions of SYN-JEM and DEE-JEM can be found in (24) and in (25), respectively, and the positive associations of the individual agents with lung cancer risk within our study population have been previously published where the lung cancer ORs for the ever-exposed ranging from 1.09-1.27 (25-29). In sensitivity analyses, we also accounted for chlorinated, and other types of solvents that may co-occur with benzene using the semi-quantitative ALOHA+ JEM (30, 31).

2.3 Statistical analyses

Unconditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) of lung cancer associated with various indices of occupational benzene exposure. The exposure indices include ever/never exposed, cumulative exposure (>0-1, >1-5, and >5 ppm-year), exposure duration (1-9, 10-19, 20-29, and >29 years), and time since last exposure (<5, 5–9, 10–19, 20–29, 30–39, and >39 years). For all exposure metrics, we examined the associations stratified by main lung cancer subtypes (adenocarcinoma,

squamous cell carcinoma, small cell carcinoma, and large cell carcinoma), and by smoking status (never, former, and current smokers). Smokers were defined as participants who had smoked >1 cigarette per day for >1 year, and former smokers as those who had stopped smoking at least two years before diagnosis/interview. *P* values for linear trend were obtained by treating the exposure metrics (e.g., cumulative exposure, duration) as continuous variables in the logistic regression models for both all subjects and the exposed only.

Assumptions made in the main analyses are shown in a directed acyclic graph (DAG; Figure E1). Based on the DAG, we adjusted for age group (<45, 45-49, 50-54, 55-59, 60-69, 70-74, >74 years), study, sex, pack-years (log [cigarette pack-years +1]) and time-since-quitting smoking (current smokers; quitting 2-7, 8-15, 16-25, >25 years before diagnosis/interview; never smokers), five known lung carcinogens (cumulative exposure to asbestos, PAHs, RCS, Cr(VI) and DEE), and ever-employed in a "List A" job. "List A" is a list of occupations and industries with known excess risk to lung cancer (32, 33), and it is used as an adjustment for other occupational lung carcinogens in this study. We did not adjust for nickel because of its high correlation with Cr(VI) (Pearson r = 0.81, Figure E2).

We evaluated the robustness of associations with the following sensitivity analyses:

1. One-by-one omitting groups of subjects who were ever employed in various specific industries/jobs (e.g., construction, mining, printers, painters, shoemakers) or exposed to known or suspected occupational lung carcinogens (e.g., asbestos, silica, Cr(VI), PAHs, chlorinated solvents) to explore if excluding any specific industry/job/exposure would alter the associations.
2. Restricting the analyses to blue collar workers, to limit possible residual confounding from socioeconomic factors.
3. Applying different exposure lag times (0, 5, 10, 20 years), where the exposure for the specified years before diagnosis/interview was disregarded.

4. Omitting the probability factor *P* in calculating cumulative benzene exposure levels to evaluate the associations based on the concentration (*L*) estimate only.
5. Assessing the association of benzene exposure with the risk of the four major lung cancer subtypes among non-smokers only.
6. Examining the associations without adjusting for the other known lung carcinogens (asbestos, Cr(VI), nickel, PAHs, silica, DEE) and/or list A jobs.

We applied spline analyses (thin-plate regression) to assess the shapes of exposure-response relationships for cumulative benzene exposure and exposure duration. The smoothing function "tp" was used with R package *mgcv* without specifying the smooth term *k*. The spline analyses were also performed for the effect of cumulative exposure on the four lung cancer subtypes.

We evaluated the interaction between smoking and benzene exposure by estimating the RERI (relative excess risks due to interaction) from models based on stratified population according to their status of benzene exposure and smoking (ever/never) (34). The confidence interval of the RERI was estimated based on bootstrapping (35). Meta-analyses were performed using the R package *meta* (36). For the pooled studies, we stratified the analyses based on the sources of controls (hospital vs. population) and imposed both the fixed and random effects on the pooled results.

All statistical analyses were conducted with R, version 4.2.1 (37).

3. Results

From the SYNERGY population, we omitted 1653 subjects (804 cases, 849 controls) due to incomplete covariate data and 335 subjects (145 cases, 191 controls) because of incomplete occupational records. We further excluded 5055 controls and 4427 cases because at least part

of their job history was before 1945. The final study sample included 28048 subjects (12329 cases and 15719 controls).

Table 1 shows the characteristics of the study subjects by lung cancer status. Cases were more frequently current and heavier smokers. The distribution between the exposed and unexposed is comparable for most demographic features and smoking indicators, except for ever employment in List A jobs, where for both cases and controls, more subjects can be found in the exposed than the unexposed group. Around 77% of study subjects were males.

Based on subjects' lifetime occupation records, 47.4% of cases and 39.8% of controls were ever exposed to benzene (Table 2). The prevalence of ever benzene exposure ranged between 29.5-63.6% for cases and 17.1-61.3% for controls among pooled studies (Table E1). The prevalence of six other known lung carcinogens by study was presented in Table E2. Benzene exposure level gradually declined since 1950 to almost none in 2009 among the included population (Figure E3). The job title "Painters and related workers" had the highest average level of exposure (1.11 ppm for 544 ever-employed subjects), followed by "Varnishes and related painters" and "Shoemakers and related workers" (Table E3).

In Table 2, subjects ever exposed to benzene showed higher lung cancer risk compared to the unexposed (OR=1.17, 95% CI: 1.10-1.24). Increased ORs were found for subjects with higher cumulative benzene exposure (e.g., >5 ppm-year, OR=1.32 (95% CI: 1.18-1.48)), longer duration (e.g., >29 years, OR=1.34 (95% CI: 1.21-1.48)), and more recent exposure, where the highest lung cancer risk was observed (<5 years since last exposure, OR=1.43 (95% CI: 1.20-1.70)). Analyses based on continuous exposure metrics showed evidence for linear increasing trends of cumulative benzene exposure ($P_{trend,\ all\ subjects}$=0.002) and exposure duration (P_{trend}-<0.001), and declining trend in time since last exposure ($P_{trend,\ exposed}$=0.02). These trends in cumulative exposure categories were similar in men and women (Table E4).

Table 3 shows ORs associated with cumulative benzene exposure by major lung cancer subtypes. Increased risks for all four subtypes were associated with ever benzene exposure (ORs ranged from 1.13-1.26). The three cumulative exposure groups had mostly positive associations with all subtypes: ORs of the four subtypes ranged from 1.04-1.19 to 1.15-1.55, among the lowest (>0-1 ppm-year) and highest (>5 ppm-year) benzene exposure groups, respectively. For exposure duration, we found evidence for the increasing trends in ORs among all lung cancer subtypes (all P_{trend}<0.05). For time since last exposure, we observed the decreasing trend in the risk of squamous cell carcinoma (P_{trend}=0.01).

Non-parametric spline analyses showed a monotonic increase in lung cancer risks with higher cumulative benzene exposure and longer exposure duration (Figure 1). We also observed similar exposure-response relationships for most lung cancer subtypes (except for large-cell carcinoma where non-linear relationship was observed) (Figure E4).

We found associations between occupational benzene exposure and lung cancer risk regardless of smoking status (Table 4). For non-smokers, we observed increased ORs with both ever benzene exposure (OR=1.18, 95% CI: 1.00-1.38) and cumulative benzene exposure (P_{trend}-=0.005 for both exposed and all subjects). The OR for non-smokers in the highest exposure group was 1.80 (95% CI: 1.26-2.53), versus an OR of 1.09 (95% CI: 0.89-1.32) in the lowest exposure group. Benzene exposure among non-smokers that lasted for 20-29 years and occurred most recently (<5 years) was associated with higher lung cancer risk (ORs were 1.46 (95% CI: 1.07-1.98) and 1.79 (95% CI: 1.10-2.88), respectively). For both former and current smokers, higher lung cancer ORs were found in subjects ever exposed to benzene and with longer exposure duration. Time since last exposure showed no clear trends among the three smoking strata (P_{trend}>0.1). Interaction analysis suggested the joint effect of ever-benzene exposure and ever-smoking was on an additive scale (RERI = 2.66 (95% CI: 1.89-3.23)).

After omitting subjects in each of the benzene-related jobs and industries, and the subjects ever exposed to known lung carcinogens and other solvents, increased ORs remained for the various benzene exposure metrics and lung cancer risk (Table 5). The meta-analysis, stratified by control types, showed consistent ORs (for ever benzene exposure) across most studies (heterogeneity statistic I^2=19%). No obvious difference was observed in the pooled ORs between hospital- and population-based studies (Figure 2). We also showed stable associations after setting different lag years (Table E5), omitting the probability factor from the cumulative exposure calculation (Table E6-8) and excluding ever-smokers (Table E9). Similar exposure-response relationships were found for analyses where the probability factor was omitted (Figure E5). Applying models without adjusting for the five main occupational lung carcinogens resulted in higher risk estimates for benzene and lung cancer risk (Table E10).

4. Discussion

We comprehensively investigated the association between occupational benzene exposure and lung cancer within a large, pooled international case-control study. Our main analyses suggested that increased lung cancer risk was associated with higher cumulative benzene exposure, longer exposure duration, and time since exposure cessation. Positive associations were present for the main lung cancer subtypes and among all smoking sub-groups, including non-smokers.

Previous studies have reported heterogeneous risk estimates regarding the effect of benzene on lung cancer. In some studies, positive associations were reported between benzene exposures and lung cancer risk (6-11), while other studies showed no such association (13-19). Based on the available studies, it appears that the evidence for the association is stronger in case-control studies than in cohort studies. Specifically, in case-control studies (6, 10, 11, 16, 18), the

relative risk estimates for ever-benzene exposure ranged from 1.10 to 1.84, while in cohort studies (7-9, 13-15, 17, 19), the estimates ranged from 0.22 to 1.50. However, restricting the evidence base on benzene and lung cancer to the cohort studies that reported a positive association for the known causal benzene-AML association (7-9), as previously shown to be informative in the systematic evaluation of the risk of benzene on lymphoma (4, 38, 39), showed that of the remaining three cohort studies all of them reported a positive association for ever benzene exposure and lung cancer risk. It would appear that the more informative cohort studies are more in line with the case-control evidence, lending together support for a possible association between benzene exposure and lung cancer.

Smoking is the main contributor to lung cancer risk, as shown also from previous analysis in SYNERGY study that lung cancer OR was as high as 23.6 (95% CI: 20.4–27.2) for current smokers (40). Confounding from smoking has been the main concern in occupational epidemiologic analyses involving benzene and lung cancer and was also highlighted by the IARC Monographs Working Group as one of the main factors for calling the evidence on benzene related lung cancer limited in 2018 (4). In our analyses, we not only controlled for pack-years and time since quit smoking, but also performed various stratified analyses by smoking status. We observed clear exposure-response relationships for benzene-related lung cancer risk among non-smokers, strongly suggesting that confounding by smoking is not the explanation for the observed associations in this study.

The second reservation expressed by the IARC working group was the potential confounding by other occupational exposures (4). We adjusted for five main lung carcinogens in the regression models, where four were from SYN-JEM, a JEM that was developed specifically for the SYNERGY population. SYN-JEM estimates time-, job-, and region-specific exposure levels from statistical modeling based on large amounts of personal measurement data (24). This quantitative assessment of exposure to the major lung carcinogens, in addition to the

adjustment of list-A jobs in regression models, enabled us to further reduce residual confounding by other occupational exposures. By performing various sensitivity analyses to study the potential effect of confounding by other exposures, we showed robust associations for all exposure metrics (increased ORs for ever exposure, highest cumulative level, longest duration group, and most recent exposure) after excluding subjects ever employed in various occupations, indicating that the effect was not limited to a certain industry or occupation. Additionally, we excluded subjects ever exposed to any of the six known lung carcinogens that had shown effects with lung cancer in previous analyses in the SYNERGY study (asbestos (26), silica (27), nickel (28), Cr(VI) (28), PAHs (29), and diesel engine exhaust (25)). These analyses clearly showed that the observed associations between benzene and lung cancer were not driven by any co-exposure. Additionally, we accounted for exposure to other solvents (e.g., chlorinated solvents) which have weaker evidence for an association with lung cancer (41). Additionally excluding these exposed subjects from the analyses did not lead to an obvious change in results. Altogether these analyses suggest that confounding by known or suspected occupational lung carcinogens, or jobs with known excess risk to lung cancer, is unlikely to explain the observed results.

The observed benzene-lung cancer association is further strengthened by the coherent associations observed between increased lung cancer risk with longer exposure duration and the decrease in risk after exposure cessation (Table 2) and the strong mechanistic evidence showing that benzene exhibits seven out of the ten key characteristics of carcinogens (42), including: is metabolically activated to electrophilic metabolites; induces oxidative stress; is genotoxic; is immunosuppressive; alters DNA repair and causes genomic instability (4). Additionally, benzene is mainly absorbed in humans by inhalation, making lungs the first organ to be involved in benzene's metabolism (43), and thus a potential target for its carcinogenic effects.

The observed risk patterns for all lung cancer combined were largely reflected in the analyses per lung cancer sub-type with positive associations for all four major lung cancer subtypes. The effect of ever exposure to benzene was stronger for large cell carcinoma, followed by squamous cell carcinoma and small cell carcinoma. Evidence to support an exposure-response relationship for each subtype was weaker than that for all lung cancer combined, possibly due to the limited statistical power in individual subtype analyses.

There are several potential limitations of this study. Given that the individual benzene exposure was assigned by a JEM based on job titles, exposure may be misclassified due to the exposure variability within a job title (44). However, such misclassification is unlikely to be differential for cases and controls as job coding and exposure assignments were done blinded for case-control status. Moreover, misclassification of group-based exposure assessment (e.g., using a JEM), usually has a Berkson-like error structure, where obtained risk estimates are (in most scenarios) unbiased but with less precision (45). Unlike many other JEMs, the high time-resolved temporal variation of benzene exposure was incorporated in BEN-JEM, and we only included subjects whose job history fell within the assessment timespan (1945-2009) to reduce uncertainties in exposure assessment.

We acknowledge that detailed harmonised data on socioeconomic status (SES) were not available in the SYNERGY project. The effect of unmeasured confounding from SES could be reflected by the attenuated effect estimates when limiting the analyses to blue-collar workers only. Nevertheless, by restricting the analyses to blue-collar workers, to minimize confounding by SES (but at the expense of losing some informative exposure contrast), we still observed an increased risk of lung cancer (Table 5), further supporting the consistent effect of benzene on lung cancer. From the sensitivity analyses using different co-variate adjustments, we also observed lower risk estimates when List-A job and/or other lung carcinogens were included in the models compared with the models without (Table E10). Although we rigorously adjusted

for main lung carcinogens and performed analyses where subjects working in certain industries or exposures to lung carcinogens were excluded, residual confounding from other unmeasured co-exposures cannot be fully excluded.

We also acknowledge the limited statistical power to examine the exposure-response relationship in females. The analyses nevertheless demonstrated clear evidence of increased lung cancer risk among females with ever benzene exposure and low cumulative exposure (Table E4).

Benzene has been extensively regulated over the past decades and, as a result, occupational exposure to benzene has declined to <1 ppm among most occupational groups in North America and Europe (2). However, benzene exposure at unregulated workplaces and in low- and middle-income countries remain of great concern because higher exposure levels are still often observed (46, 47). In addition to its occupational occurrence, benzene is widely present in the general environment via the emission of motor vehicle exhaust, burning of coal and oil, and fuel evaporation (4, 48), leading to a far greater population being potentially exposed to benzene.

In conclusion, we found consistent and robust associations between different dimensions of occupational benzene exposure and lung cancer after adjusting for smoking and main occupational lung carcinogens. These associations are coherent over different strata of the study population including non-smokers. Our findings support the hypothesis of an effect of occupational benzene exposure on lung cancer risk and warrant to revisit the published epidemiological and molecular data addressing the pulmonary carcinogenicity of benzene.

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Figure Legends

Fig 1:

ORs adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking), list A jobs, and cumulative exposures of asbestos, Cr(VI), PAHs, silica, and diesel engine exhaust. Note the histograms above two plots only included exposed subjects to better reflect the distribution of exposure metrics, and the x axis range of cumulative exposure (0-22 ppm-year) covered the exposure level of 99% included population.

Fig 2:

Comparisons were made between ever exposed to occupational benzene vs. never exposure. ORs are adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking), list A jobs, and cumulative exposures of asbestos, Cr(VI), PAHs, silica, and diesel engine exhaust.

For LUCA and LUCAS, ORs were not adjusted for sex because they only included male participants.

Controls from TORONTO and INCO_Poland were from both population and hospitals; We consider the controls to be hospital-based here for the meta-analyses.

Table Footnote

Table 2:

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

*OR adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking), list A jobs, cumulative exposures of asbestos, Cr(VI), PAHs, silica, and diesel engine exhaust.

† Cumulative exposure was calculated by taking the product of intensity (L) and probability (P), see Equation (1).

‡ OR in “time since last exposure” is additionally adjusted for duration (continuous) of benzene exposure.

P values for trend test were obtained by taking the continuous variables (e.g., duration of exposure in years) in the logistic regression models (same for all subsequent analyses).

Table 3:

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

OR adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking), list A jobs, and cumulative exposures of asbestos, Cr(VI), PAHs, silica, and diesel engine exhaust.

† OR in “time since last exposure” is additionally adjusted for duration (continuous) of benzene exposure.

Table 4:

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

* ORs are adjusted for study, age group, sex, list A jobs, and cumulative exposures of asbestos, Cr(VI), PAHs, silica, and diesel engine exhaust.

† ORs are adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking), list A jobs , and cumulative exposures of asbestos, Cr(VI), PAHs, silica, and diesel engine exhaust.

¶ ORs are adjusted for study, age group, sex, smoking (pack-years), list A jobs and , and cumulative exposures of asbestos, Cr(VI), PAHs, silica, and diesel engine exhaust.

‡ OR in “time since last exposure” is additionally adjusted for duration (continuous) of benzene exposure.

Table 5:

Definition of abbreviations: CI = confidence interval; OR = odds ratio; Cr(VI): hexavalent chromium.

OR1 represents the comparisons on ever exposed to benzene vs. the never exposed; OR2 exposed to high benzene exposure group (cumulative exposure > 5 ppm-year) vs. the never exposed; OR3 exposed to longest duration group (duration >29 years) vs. the never exposed; and OR4 exposed within 5 years before enrolment (time since last exposure < 5 years) vs. the never exposed. Note that all OR4 are additionally adjusted for benzene exposure duration (continuous).

*For specific industries and jobs, all ORs (OR1-OR4) were adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking), list A, cumulative exposures of asbestos, Cr(VI), PAHs, silica, and diesel engine exhaust.

†Printers were classified based on the corresponding ISCO-68 codes 92XXX.

‡Painters were classified based on the corresponding ISCO-68 codes 93XXX.

§For specific exposures, all ORs (OR1-OR4) were adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking), and list A. Exposure were assessed with SYN-JEM and ALOHA+ JEM

Tables and Figures

Table 1 Descriptive characteristics of the study participants stratified by occupational benzene exposure status

Characteristics	Control (N=15719)		Case (N=12329)	
	Exposed (N=6253)	Unexposed (N=9466)	Exposed (N=5838)	Unexposed (N=6491)
Sex				
Female	910 (14.6%)	2801 (29.6%)	797 (13.7%)	1791 (27.6%)
Male	5343 (85.4%)	6665 (70.4%)	5041 (86.3%)	4700 (72.4%)
Age group (in years)				
<45	484 (7.7%)	870 (9.2%)	330 (5.7%)	376 (5.8%)
45-49	547 (8.7%)	760 (8.0%)	529 (9.1%)	534 (8.2%)
50-54	909 (14.5%)	1209 (12.8%)	897 (15.4%)	901 (13.9%)
55-59	1340 (21.4%)	1724 (18.2%)	1380 (23.6%)	1246 (19.2%)
60-64	1259 (20.1%)	1812 (19.1%)	1205 (20.6%)	1315 (20.3%)
65-69	1052 (16.8%)	1697 (17.9%)	913 (15.6%)	1111 (17.1%)
70-74	590 (9.4%)	1160 (12.3%)	504 (8.6%)	810 (12.5%)
>75	72 (1.2%)	234 (2.5%)	80 (1.4%)	198 (3.1%)
List A jobs				
never	5478 (87.6%)	9324 (98.5%)	4770 (81.7%)	6310 (97.2%)
ever	775 (12.4%)	142 (1.5%)	1068 (18.3%)	181 (2.8%)
Smoking status				
never smoker	1860 (29.7%)	3655 (38.6%)	321 (5.5%)	663 (10.2%)
former smoker	2437 (39.0%)	3345 (35.3%)	1651 (28.3%)	1861 (28.7%)
current smoker	1956 (31.3%)	2466 (26.1%)	3866 (66.2%)	3967 (61.1%)
Pack-year				
>0-10	1052 (16.8%)	1604 (16.9%)	275 (4.7%)	377 (5.8%)
>10-19	795 (12.7%)	1072 (11.3%)	516 (8.8%)	517 (8.0%)
>19	2546 (40.7%)	3135 (33.1%)	4726 (81.0%)	4934 (76.0%)
Time since quit smoking (in years)				
>0-7	428 (6.8%)	661 (7.0%)	661 (11.3%)	757 (11.7%)
8-15	599 (9.6%)	758 (8.0%)	457 (7.8%)	521 (8.0%)
16-25	695 (11.1%)	996 (10.5%)	356 (6.1%)	374 (5.8%)
>25	715 (11.4%)	930 (9.8%)	177 (3.0%)	209 (3.2%)
Histological type				
Squamous cell carcinoma	0 (0%)	0 (0%)	2254 (38.6%)	2163 (33.3%)
Small cell lung cancer	0 (0%)	0 (0%)	975 (16.7%)	1034 (15.9%)
Adenocarcinoma	0 (0%)	0 (0%)	1604 (27.5%)	2117 (32.6%)
Large cell lung carcinoma	0 (0%)	0 (0%)	294 (5.0%)	317 (4.9%)
Unavailable	0 (0%)	0 (0%)	29 (0.5%)	30 (0.5%)
Others/unspecified	0 (0%)	0 (0%)	682 (11.7%)	830 (12.8%)

Table 2 Lung cancer ORs and 95% CIs based on various indices of occupational benzene exposure

Occupational benzene exposure	N Cases (%)	N controls (%)	OR*	95% CI
Never	6491 (52.6%)	9466 (60.2%)	1	Referent
Ever exposure	5838 (47.4%)	6253 (39.8%)	1.17	1.10-1.24
Cumulative exposure, ppm-years †				
>0-1	2190 (17.8%)	2549 (16.2%)	1.12	1.03-1.21
>1-5	2553 (20.7%)	2698 (17.2%)	1.17	1.08-1.27
>5	1095 (8.9%)	1006 (6.4%)	1.32	1.18-1.48
Test for trend (exposed only), *p* value			0.05	
Test for trend (all subjects), *p* value			0.002	
Duration, years				
1-9	2128 (17.3%)	2414 (15.4%)	1.10	1.02-1.19
10-19	1181 (9.6%)	1401 (8.9%)	1.10	1.00-1.22
20-29	1022 (8.3%)	1017 (6.5%)	1.23	1.10-1.37
>29	1507 (12.2%)	1421 (9.0%)	1.34	1.21-1.48
Test for trend (exposed only), *p* value			<0.001	
Test for trend (all subjects), *p* value			<0.001	
Time since last exposure ‡, years				
<5	1165 (9.4%)	1083 (6.9%)	1.43	1.20-1.70
5-9	738 (6.0%)	783 (5.0%)	1.12	0.94-1.33
10-19	1485 (12.0%)	1571 (10.0%)	1.17	1.02-1.34
20-29	858 (7.0%)	983 (6.3%)	1.06	0.94-1.21
30-39	953 (7.7%)	1081 (6.9%)	1.07	0.95-1.20
>39	639 (5.2%)	752 (4.8%)	1.02	0.89-1.16
Test for trend (exposed only), *p* value			0.020	

Table 3 ORs of different lung cancer subtypes associated with various occupational benzene exposure indices

Occupational benzene exposure	Adenocarcinoma			Squamous Cell Carcinoma			Small Cell Carcinoma			Large Cell Carcinoma		
	N Cases (%)	OR	95% CI	N Cases (%)	OR	95% CI	N Cases (%)	OR	95% CI	N Cases (%)	OR	95% CI
Unexposed	2117 (56.9%)	1	Referent	2163 (49.0%)	1	Referent	1034 (51.5%)	1	Referent	317 (51.9%)	1	Referent
Ever exposed	1604 (43.1%)	1.13	1.04-1.23	2254 (51.0%)	1.20	1.10-1.30	975 (48.5%)	1.18	1.05-1.32	294 (48.1%)	1.26	1.04-1.51
Cumulative Exposure (in ppm-years)												
>0-1	691 (18.6%)	1.10	0.98-1.22	751 (17.0%)	1.19	1.07-1.33	355 (17.7%)	1.11	0.96-1.28	107 (17.5%)	1.04	0.81-1.32
>1-5	633 (17.0%)	1.11	0.99-1.25	1055 (23.9%)	1.18	1.06-1.32	452 (22.5%)	1.27	1.09-1.46	137 (22.4%)	1.48	1.16-1.88
>5	280 (7.5%)	1.31	1.10-1.55	448 (10.1%)	1.26	1.08-1.46	168 (8.4%)	1.15	0.93-1.42	50 (8.2%)	1.55	1.08-2.20
Test for trend (exposed only), *p* value		0.08			0.36			0.97			0.08	
Test for trend (all subjects), *p* value		0.03			0.06			0.35			0.08	
Duration of benzene exposure (in years)												
1-9	643 (17.3%)	1.12	1.00-1.25	760 (17.2%)	1.11	0.99-1.24	354 (17.6%)	1.09	0.94-1.27	109 (17.8%)	1.13	0.88-1.43
10-19	319 (8.6%)	1.01	0.87-1.17	466 (10.6%)	1.18	1.03-1.36	204 (10.2%)	1.12	0.93-1.35	57 (9.3%)	1.04	0.76-1.41
20-29	271 (7.3%)	1.15	0.98-1.35	406 (9.2%)	1.31	1.13-1.52	173 (8.6%)	1.25	1.02-1.53	65 (10.6%)	1.74	1.27-2.36
>29	371 (10.0%)	1.29	1.11-1.50	622 (14.1%)	1.31	1.15-1.50	244 (12.1%)	1.38	1.14-1.66	63 (10.3%)	1.52	1.10-2.09
Test for trend (exposed only), *p* value		0.05			0.002			0.007			0.002	
Test for trend (all subjects), *p* value		0.003			<0.001			<0.001			0.001	
Time since last exposure†, years												
<5	226 (6.1%)	1.21	0.93-1.57	504 (11.4%)	1.53	1.21-1.95	238 (11.8%)	1.45	1.06-1.98	70 (11.5%)	1.55	0.94-2.54
5-9	210 (5.6%)	1.09	0.85-1.40	271 (6.1%)	1.18	0.92-1.51	120 (6.0%)	1.16	0.84-1.59	23 (3.8%)	0.83	0.46-1.44
10-19	430 (11.6%)	1.00	0.82-1.22	560 (12.7%)	1.36	1.12-1.65	225 (11.2%)	1.17	0.91-1.51	85 (13.9%)	1.26	0.84-1.87
20-29	261 (7.0%)	1.08	0.90-1.29	302 (6.8%)	1.07	0.89-1.28	150 (7.5%)	1.06	0.84-1.34	48 (7.9%)	1.10	0.75-1.58
30-39	278 (7.5%)	1.12	0.95-1.32	373 (8.4%)	1.10	0.94-1.28	154 (7.7%)	1.06	0.86-1.32	38 (6.2%)	0.91	0.62-1.31
>39	199 (5.3%)	1.02	0.85-1.23	244 (5.5%)	1.05	0.87-1.25	88 (4.4%)	1.00	0.77-1.29	30 (4.9%)	1.10	0.71-1.64
Test for trend (exposed only), *p* value		0.80			0.01			0.18			0.57	

Table 4 Lung cancer ORs associated with different levels of benzene exposure by smoking status

Occupational benzene exposure	Never-smoker			Former smokers			Current smokers		
	N Cases (%) / N Controls (%)	OR*	95% CI	N Cases (%) / N Controls (%)	OR†	95% CI	N Cases (%) / N Controls (%)	OR¶	95% CI
Unexposed	663 (67.4%) / 3655 (66.3%)	1	referent	1861 (53.0%) / 3345 (57.9%)	1	referent	3967 (50.6%) / 2466 (55.8%)	1	referent
Ever exposed	321 (32.6%) / 1860 (33.7%)	1.18	1.00-1.38	1651 (47.0%) / 2437 (42.1%)	1.20	1.08-1.33	3866 (49.4%) / 1956 (44.2%)	1.14	1.04-1.24
Cumulative benzene exposure (in ppm-years)									
>0-1	159 (16.2%) / 862 (15.6%)	1.09	0.89-1.32	506 (14.4%) / 875 (15.1%)	1.09	0.95-1.25	1525 (19.5%) / 812 (18.4%)	1.12	1.00-1.25
>1-5	107 (10.9%) / 749 (13.6%)	1.17	0.92-1.50	775 (22.1%) / 1132 (19.6%)	1.21	1.06-1.37	1671 (21.3%) / 817 (18.5%)	1.15	1.03-1.29
>5	55 (5.6%) / 249 (4.5%)	1.80	1.26-2.53	370 (10.5%) / 430 (7.4%)	1.46	1.22-1.75	670 (8.6%) / 327 (7.4%)	1.15	0.98-1.36
Test for trend (exposed only), *p* value		0.005			0.94			0.07	
Test for trend (all subjects), *p* value		0.005			0.36			0.02	
Duration of benzene exposure (in years)									
1-9	121 (12.3%) / 742 (13.5%)	1.05	0.84-1.31	562 (16.0%) / 914 (15.8%)	1.14	0.99-1.30	1445 (18.4%) / 758 (17.1%)	1.07	0.96-1.20
10-19	81 (8.2%) / 427 (7.7%)	1.20	0.91-1.56	328 (9.3%) / 533 (9.2%)	1.12	0.94-1.32	772 (9.9%) / 441 (10.0%)	1.04	0.91-1.20
20-29	60 (6.1%) / 299 (5.4%)	1.46	1.07-1.98	273 (7.8%) / 394 (6.8%)	1.15	0.95-1.38	689 (8.8%) / 324 (7.3%)	1.22	1.05-1.43
>29	59 (6.0%) / 392 (7.1%)	1.25	0.90-1.71	488 (13.9%) / 596 (10.3%)	1.43	1.22-1.68	960 (12.3%) / 433 (9.8%)	1.32	1.15-1.53
Test for trend (exposed only), *p* value		0.15			0.006			0.001	
Test for trend (all subjects), *p* value		0.02			<0.001			<0.001	
Time since last exposure ‡, years									
<5	64 (6.5%) / 295 (5.3%)	1.79	1.10-2.88	228 (6.5%) / 375 (6.5%)	1.32	0.95-1.82	873 (11.1%) / 413 (9.3%)	1.38	1.09-1.75
5-9	40 (4.1%) / 221 (4.0%)	1.28	0.77-2.08	171 (4.9%) / 273 (4.7%)	1.11	0.80-1.53	527 (6.7%) / 289 (6.5%)	1.07	0.85-1.35
10-19	84 (8.5%) / 514 (9.3%)	1.15	0.79-1.65	495 (14.1%) / 608 (10.5%)	1.23	0.96-1.58	906 (11.6%) / 449 (10.2%)	1.08	0.90-1.31
20-29	42 (4.3%) / 288 (5.2%)	0.97	0.66-1.41	235 (6.7%) / 364 (6.3%)	1.17	0.94-1.47	581 (7.4%) / 331 (7.5%)	0.98	0.82-1.16
30-39	49 (5.0%) / 316 (5.7%)	0.99	0.70-1.38	264 (7.5%) / 459 (7.9%)	1.00	0.83-1.22	640 (8.2%) / 306 (6.9%)	1.11	0.95-1.31
>39	42 (4.3%) / 226 (4.1%)	1.22	0.84-1.73	258 (7.3%) / 358 (6.2%)	1.07	0.88-1.29	339 (4.3%) / 168 (3.8%)	0.93	0.75-1.14
Test for trend (exposed only), *p* value		0.71			0.11			0.21	

Table 5 Sensitivity analyses for overall lung cancer risk with various occupational benzene exposure indices, by various subgroups

Occupational benzene exposure	OR1	95% CI	OR2	95% CI	OR3	95% CI	OR4	95% CI
All subjects	1.17	1.10-1.24	1.32	1.18-1.48	1.34	1.21-1.48	1.43	1.20-1.70
Blue collar worker only	1.08	1.00-1.16	1.24	1.09-1.40	1.26	1.13-1.41	1.32	1.09-1.59
Omit specific industries/jobs *								
Construction	1.14	1.06-1.22	1.33	1.15-1.53	1.28	1.13-1.44	1.44	1.17-1.78
Mining	1.16	1.09-1.23	1.32	1.18-1.49	1.35	1.22-1.50	1.41	1.18-1.68
Metal-related industry	1.17	1.10-1.24	1.31	1.16-1.48	1.37	1.24-1.52	1.40	1.17-1.67
Transport	1.20	1.12-1.28	1.37	1.21-1.55	1.39	1.25-1.54	1.44	1.20-1.74
Farmer	1.18	1.11-1.26	1.36	1.21-1.54	1.36	1.22-1.50	1.51	1.26-1.82
Vehicle mechanic	1.17	1.10-1.25	1.33	1.18-1.50	1.34	1.21-1.49	1.40	1.17-1.68
Shoemakers and related workers	1.16	1.09-1.23	1.31	1.16-1.47	1.33	1.21-1.48	1.42	1.19-1.69
Printers and related workers†	1.17	1.10-1.24	1.31	1.16-1.49	1.35	1.22-1.50	1.47	1.23-1.75
Painter and related workers‡	1.17	1.10-1.24	1.34	1.18-1.51	1.32	1.19-1.46	1.46	1.22-1.75
Omit subjects with specific exposures§								
Asbestos	1.16	1.07-1.26	1.29	1.09-1.52	1.32	1.14-1.53	1.43	1.10-1.86
PAHs	1.21	1.13-1.30	1.39	1.21-1.60	1.43	1.27-1.61	1.41	1.13-1.75
Nickel	1.17	1.10-1.25	1.29	1.13-1.48	1.39	1.23-1.56	1.39	1.14-1.70
Cr(VI)	1.17	1.09-1.25	1.29	1.13-1.48	1.38	1.23-1.56	1.35	1.10-1.67
Silica	1.16	1.09-1.25	1.39	1.23-1.58	1.36	1.22-1.52	1.41	1.15-1.73
Diesel engine exhaust	1.18	1.09-1.28	1.38	1.18-1.60	1.37	1.21-1.56	1.32	1.03-1.67
Chlorinated solvents	1.19	1.08-1.30	1.83	1.29-2.59	1.43	1.17-1.77	1.38	1.01-1.89
Other types of solvents	1.17	1.05-1.31	1.58	1.10-2.27	1.49	1.17-1.90	1.68	1.17-2.41

Figure 1 Exposure-response relationships for cumulative benzene exposure (A) and exposure duration (B) with 95% CIs

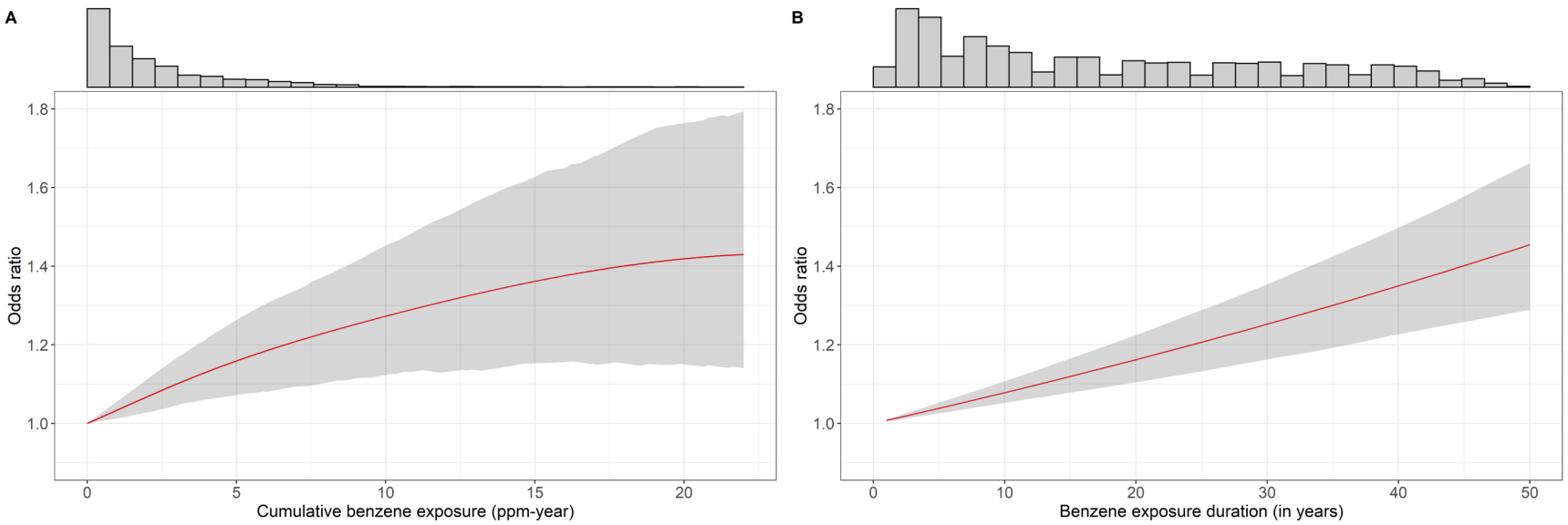

Figure 2 Forest plot of ORs and 95% CIs from meta-analyses based on the included studies in the pooled analyses, stratified by the sources of controls