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ORIGINAL ARTICLE

Occupational Benzene Exposure and Lung Cancer Risk
A Pooled Analysis of 14 Case-Control Studies

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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 28,048 subjects (12,329 cases, 15,719 control subjects). Lung cancer odds ratios ranged from 1.12 (95% confidence interval, 1.03–1.22) to 1.32 (95% confidence interval, 1.18–1.48) ($P_{trend} = 0.002$) for groups with the lowest and highest cumulative occupational exposures, respectively, compared with unexposed subjects. We observed an increasing trend of lung cancer with longer duration of exposure ($P_{trend} < 0.001$) and a 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.

Conclusions: 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 nonsmokers. 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.

Keywords: lung cancer; benzene; occupational exposure

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At a Glance Commentary

Scientific Knowledge on the Subject: Benzene has been classified as carcinogenic to humans, but there is limited evidence linking benzene exposure to lung cancer.

What This Study Adds to the Field: In this large, pooled analysis of 14 case-control studies, we provide evidence to support the hypothesis based on robust and consistent associations between occupational benzene exposure and increased lung cancer risk.

Benzene is a volatile and ubiquitous air pollutant that is produced mainly from anthropogenic sources. It was a common solvent and ingredient in paint, printing inks, and glues, but the benzene content in these products has been either replaced or reduced since the 1980s after regulations and other mitigation measures (1, 2). Nevertheless, it remains a high-production-volume chemical and is still widely present in low- and 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 (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 because previous studies have reported inconsistent results. For example, some studies indicated an increased risk of lung cancer among exposed subjects (6–11), whereas 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 control subjects, provided support for the association between ever exposure to benzene and lung cancer risk (odds ratio [OR], 1.35; 95% confidence interval [CI], 0.99–1.84) after adjusting for both smoking and several lung carcinogens (10). The association, however, was not present among nonsmokers and low-level smokers (OR, 0.94; 95% CI, 0.49–1.81), possibly because of the limited sample size in this study, leaving the possibility that the observed association was driven by residual confounding. Therefore, studies with larger

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sample sizes and stricter control for confounding factors (e.g., smoking and coexposures) are needed to further elucidate the possible association between occupational benzene exposure and lung cancer.

This study aimed 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).

Methods

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 (*see* Table E1 in the online supplement). A detailed description of the study population is presented elsewhere (21) and online (http://synergy.iarc.fr). Briefly, all studies have provided lifetime occupational and smoking histories (except for MORGEN [Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands]). In most studies, cases and control subjects were frequency matched by sex and age. Most interviews (84%) were conducted face-to-face with the subjects. Lung cancer subtypes were classified on the basis of World Health Organization guidelines (22) after histological or cytological confirmation by the pathologists associated with the participating hospitals. Ethical approvals for the SYNERGY project were obtained according to the legislation in each participating country and the IARC institutional review board.

Exposure Assessment

We used a benzene-specific job-exposure matrix (BEN-JEM) to assess occupational exposure on the basis of 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 (1945–1959, 1960–1984, 1985–1994, 1995–1997, 1998–2000, 2001–2003, 2004–2006, and 2007–2009), accounting for the downward trend of workplace exposure in Europe and North America (2). Exposure was calculated as a product of the probability and level ($P \times L$). To improve exposure assessment quality, we included only 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 diesel engine exhaust (DEE)-JEM to assess exposure to 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 the SYNERGY study were previously published (lung cancer ORs for the ever-exposed ranged from 1.09 to 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 semiquantitative ALOHA + JEM (30, 31).

Statistical Analyses

Unconditional logistic regression models were used to calculate ORs and 95% 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-yr), exposure duration (1–9, 10–19, 20–29, and >29 yr), and time since last exposure (<5, 5–9, 10–19, 20–29, 30–39, and >39 yr). Different histological types of lung cancer have different morphological features, molecular characterization, and etiology (32). To examine the possibly heterogeneous associations, we stratified the analyses by main lung cancer subtypes (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma). We also stratified the analyses by smoking status (never, former, and current smokers), in which smokers were defined as participants who had smoked more than one cigarette per day for >1 year and former smokers were defined as those who had stopped smoking at least 2 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 (Figure E1). On the basis of the directed acyclic graph, we adjusted for age group (<45, 45–49, 50–54, 55–59, 60–69, 70–74, >74 yr), study, sex, pack-years (log [cigarette pack-years + 1]) and time since quitting smoking (current smokers; quitting 2–7, 8–15, 16–25, >25 yr 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 (33, 34), 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 yr), in which 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 on the basis of the concentration (*L*) estimate only.
5. Assessing the association of benzene exposure with the risk of the four major lung cancer subtypes among nonsmokers 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 relative excess risks due to interaction (RERI) from models on the basis of stratified population according to their status of benzene exposure and smoking (ever/never) (35). The CI of the RERI was estimated on the basis of bootstrapping (36). Meta-analyses were performed using the R package *meta* (37). For the pooled studies, we stratified the analyses on the basis of sources of control subjects (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 (38).

Results

From the SYNERGY population, we omitted 1,653 subjects (804 cases, 849 control subjects) because of incomplete covariate data and 335 subjects (145 cases, 191 control subjects) because of incomplete occupational records. We further excluded 5,055 control subjects and 4,427 cases because at least part of their job history was before 1945. The final study sample included 28,048 subjects (12,329 cases and 15,719 control subjects).

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, in which, for both cases and control subjects, more subjects can be found in the exposed than the unexposed group. Around 77% of study subjects were males.

On the basis of subjects' lifetime occupation records, 47.4% of cases and 39.8% of control subjects were ever exposed to benzene (Table 2). The prevalence of ever benzene exposure ranged between 29.5% and 63.6% for cases and between 17.1% and 61.3% for control subjects among pooled studies (Table E1). The prevalence of the six known lung carcinogens by study is presented in Table E2. Benzene exposure level gradually declined from 1950 to almost none in 2009 among the included population (Figure E3). The job title "painters and

Table 1. Descriptive Characteristics of Study Participants, Stratified by Occupational Benzene Exposure Status

	Control Subjects ($n = 15,719$)		Cases ($n = 12,329$)	
Characteristics	**Exposed ($n = 6,253$)**	**Unexposed ($n = 9,466$)**	**Exposed ($n = 5,838$)**	**Unexposed ($n = 6,491$)**
Sex				
Female	910 (14.6%)	2,801 (29.6%)	797 (13.7%)	1,791 (27.6%)
Male	5,343 (85.4%)	6,665 (70.4%)	5,041 (86.3%)	4,700 (72.4%)
Age group, yr				
<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%)	1,209 (12.8%)	897 (15.4%)	901 (13.9%)
55–59	1,340 (21.4%)	1,724 (18.2%)	1,380 (23.6%)	1,246 (19.2%)
60–64	1,259 (20.1%)	1,812 (19.1%)	1,205 (20.6%)	1,315 (20.3%)
65–69	1,052 (16.8%)	1,697 (17.9%)	913 (15.6%)	1,111 (17.1%)
70–74	590 (9.4%)	1,160 (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	5,478 (87.6%)	9,324 (98.5%)	4,770 (81.7%)	6,310 (97.2%)
Ever	775 (12.4%)	142 (1.5%)	1,068 (18.3%)	181 (2.8%)
Smoking status				
Never smoker	1,860 (29.7%)	3,655 (38.6%)	321 (5.5%)	663 (10.2%)
Former smoker	2,437 (39.0%)	3,345 (35.3%)	1,651 (28.3%)	1,861 (28.7%)
Current smoker	1,956 (31.3%)	2,466 (26.1%)	3,866 (66.2%)	3,967 (61.1%)
Pack-years				
>0–10	1,052 (16.8%)	1,604 (16.9%)	275 (4.7%)	377 (5.8%)
>10–19	795 (12.7%)	1,072 (11.3%)	516 (8.8%)	517 (8.0%)
>19	2,546 (40.7%)	3,135 (33.1%)	4,726 (81.0%)	4,934 (76.0%)
Time since quitting smoking, yr				
>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%)	2,254 (38.6%)	2,163 (33.3%)
Small cell lung cancer	0 (0%)	0 (0%)	975 (16.7%)	1,034 (15.9%)
Adenocarcinoma	0 (0%)	0 (0%)	1,604 (27.5%)	2,117 (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 Odds Ratios and 95% Confidence Intervals Based on Various Indices of Occupational Benzene Exposure

Occupational Benzene Exposure	Cases, *n* (%)	Control Subjects, *n* (%)	OR*	95% CI
Never	6,491 (52.6)	9,466 (60.2)	1	Referent
Ever exposure	5,838 (47.4)	6,253 (39.8)	1.17	1.10–1.24
Cumulative exposure, ppm-yr†				
>0–1	2,190 (17.8)	2,549 (16.2)	1.12	1.03–1.21
>1–5	2,553 (20.7)	2,698 (17.2)	1.17	1.08–1.27
>5	1,095 (8.9)	1,006 (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, yr				
1–9	2,128 (17.3)	2,414 (15.4)	1.10	1.02–1.19
10–19	1,181 (9.6)	1,401 (8.9)	1.10	1.00–1.22
20–29	1,022 (8.3)	1,017 (6.5)	1.23	1.10–1.37
>29	1,507 (12.2)	1,421 (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‡, yr				
<5	1,165 (9.4)	1,083 (6.9)	1.43	1.20–1.70
5–9	738 (6.0)	783 (5.0)	1.12	0.94–1.33
10–19	1,485 (12.0)	1,571 (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)	1,081 (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	

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
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).
*OR adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking), list A jobs, cumulative exposures of asbestos, hexavalent chromium, polycyclic aromatic hydrocarbons, silica, and diesel engine exhaust.
†Cumulative exposure was calculated by taking the product of intensity (L) and probability (P).
‡OR in time since last exposure is additionally adjusted for duration (continuous) of benzene exposure.

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 than 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-yr; OR, 1.32; 95% CI, 1.18–1.48), longer duration (e.g., >29 yr; OR, 1.34; 95% CI, 1.21–1.48), and more recent exposure, in which the highest lung cancer risk was observed (<5 yr 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 ($P_{trend} = 0.002$ for all subjects) and exposure duration ($P_{trend} < 0.001$) and a declining trend in time since last exposure ($P_{trend} = 0.02$). 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 to 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-yr) and highest (>5 ppm-yr) 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 ($P_{trend} = 0.01$).

Nonparametric 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, for which a nonlinear relationship was observed) (Figure E4).

We found associations between occupational benzene exposure and lung cancer risk, regardless of smoking status (Table 4). For nonsmokers, 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 nonsmokers 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 nonsmokers that lasted for 20–29 years and occurred most recently (<5 yr) was associated with higher lung cancer risk (ORs, 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

Table 3. Odds Ratios 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		
	Cases, *n* (%)	OR	95% CI	Cases, *n* (%)	OR	95% CI	Cases, *n* (%)	OR	95% CI	Cases, *n* (%)	OR	95% CI
Unexposed	2,117 (56.9)	1	Referent	2,163 (49.0)	1	Referent	1,034 (51.5)	1	Referent	317 (51.9)	1	Referent
Ever exposed	1,604 (43.1)	1.13	1.04–1.23	2,254 (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, ppm-yr												
>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	1,055 (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, yr												
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*, yr												
<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	

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, hexavalent chromium, polycyclic aromatic hydrocarbons, silica, and diesel engine exhaust.

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

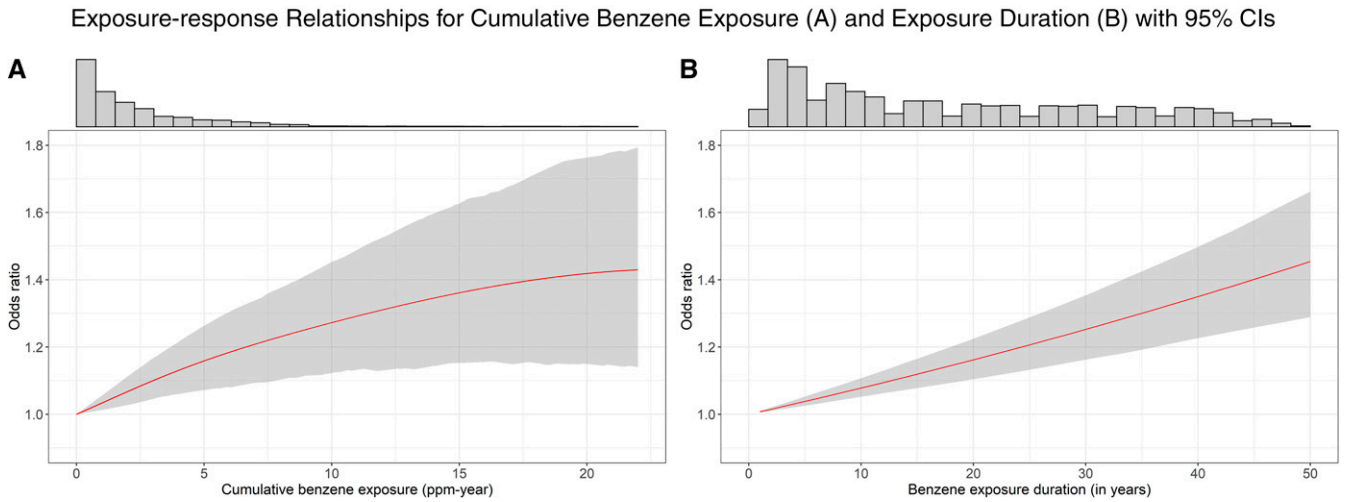

Figure 1. Odds ratios adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking), list A jobs, and cumulative exposures of asbestos, hexavalent chromium, polycyclic aromatic hydrocarbons, silica, and diesel engine exhaust. Note the histograms above two plots only included exposed 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.

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 (Tables E6–E8) and excluding ever-smokers (Table E9). Similar exposure–response relationships were found for analyses in which 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).

Discussion

We 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 subgroups, including nonsmokers.

Previous studies have reported mixed results regarding the effect of benzene on lung cancer (6–11, 13–19). On the basis of available studies, it appears 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, whereas 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–acute myeloid leukemia association (7–9), as previously shown to be informative in the systematic evaluation of the risk of benzene on lymphoma (4, 39, 40), showed that of the remaining three cohort studies, all reported a positive association for ever benzene exposure and lung cancer risk. The more informative cohort studies are more in line with the case-control evidence, together lending support for a possible association between benzene exposure and lung cancer.

Smoking is the main contributor to lung cancer risk, as shown also in previous analysis in SYNERGY (OR for lung cancer, 23.6 [95% CI, 20.4–27.2] for current smokers) (41). Confounding from smoking is thus the main concern in occupational epidemiologic analyses involving lung cancer and was also highlighted by the IARC monographs as one of the main factors for calling the evidence on benzene-related lung cancer limited (4). In our analyses, we not only controlled for pack-years and time since quitting smoking but also performed various stratified analyses by smoking status. We observed clear exposure–response relationships for benzene-related lung cancer risk among nonsmokers, 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, in which 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. In addition, 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

Table 4. Lung Cancer Odds Ratios Associated with Different Degrees of Benzene Exposure, by Smoking Status

Occupational Benzene Exposure	Never Smokers			Former Smokers			Current Smokers		
	Cases, *n* (%)/ Control Subjects, *n* (%)	OR*	95% CI	Cases, *n* (%)/ Control Subjects, *n* (%)	OR†	95% CI	Cases, *n* (%)/ Control Subjects, *n* (%)	OR‡	95% CI
Unexposed	663 (67.4)/3,655 (66.3)	1	Referent	1,861 (53.0)/3,345 (57.9)	1	Referent	3,967 (50.6)/2,466 (55.8)	1	Referent
Ever exposed	321 (32.6)/1,860 (33.7)	1.18	1.00–1.38	1,651 (47.0)/2,437 (42.1)	1.20	1.08–1.33	3,866 (49.4)/1,956 (44.2)	1.14	1.04–1.24
Cumulative benzene exposure, ppm-yr									
>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	1,525 (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)/1,132 (19.6)	1.21	1.06–1.37	1,671 (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, yr									
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	1,445 (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§, yr									
<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	

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, hexavalent chromium, polycyclic aromatic hydrocarbons, 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, hexavalent chromium, polycyclic aromatic hydrocarbons, 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, hexavalent chromium, polycyclic aromatic hydrocarbons, silica, and diesel engine exhaust.

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

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

Definition of abbreviations: CI = confidence interval; Cr(VI) = hexavalent chromium; OR = odds ratio; PAH = polycyclic aromatic hydrocarbon. OR1 represents the comparisons of ever exposed to benzene versus never exposed; OR2 represents the comparisons of exposed to high benzene exposure group (cumulative exposure > 5 ppm-yr) versus never exposed; OR3 represents the comparisons of exposed to longest duration group (duration >29 yr) versus never exposed; and OR4 represents the comparisons of exposed within 5 years before enrollment (time since last exposure <5 yr) versus 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 on the basis of corresponding ISCO-68 codes 92XXX.
‡Painters were classified on the basis of 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. Exposures were assessed with SYN-job-exposure matrix (JEM) and ALOHA (arial locations of hazards atmosphere) + JEM.

analyses clearly showed that the observed associations between benzene and lung cancer were not driven by any coexposure. In addition, we accounted for exposure to other solvents (e.g., chlorinated solvents) that have weaker evidence for an association with lung cancer (42). Also excluding these exposed subjects 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 7 of the 10 key characteristics of carcinogens (43), including being metabolically activated to electrophilic metabolites, inducing oxidative stress, being genotoxic, being immunosuppressive, altering DNA repair, and causing genomic instability (4). In addition, benzene is absorbed in humans mainly by inhalation, making the lungs the first organ to be involved in benzene's metabolism (44) and thus a potential target for its carcinogenic effects.

The observed risk patterns for all lung cancer combined were largely reflected by the positive associations found for 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 because of the limited statistical power in individual subtype analyses.

Limitations

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 because of the exposure variability within a job title (45). However, such misclassification is unlikely to be differential for cases and control subjects because 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, in which obtained risk estimates are (in most scenarios) unbiased but with less precision (46). Unlike many other JEMs, the high time-resolved temporal variation of benzene exposure was

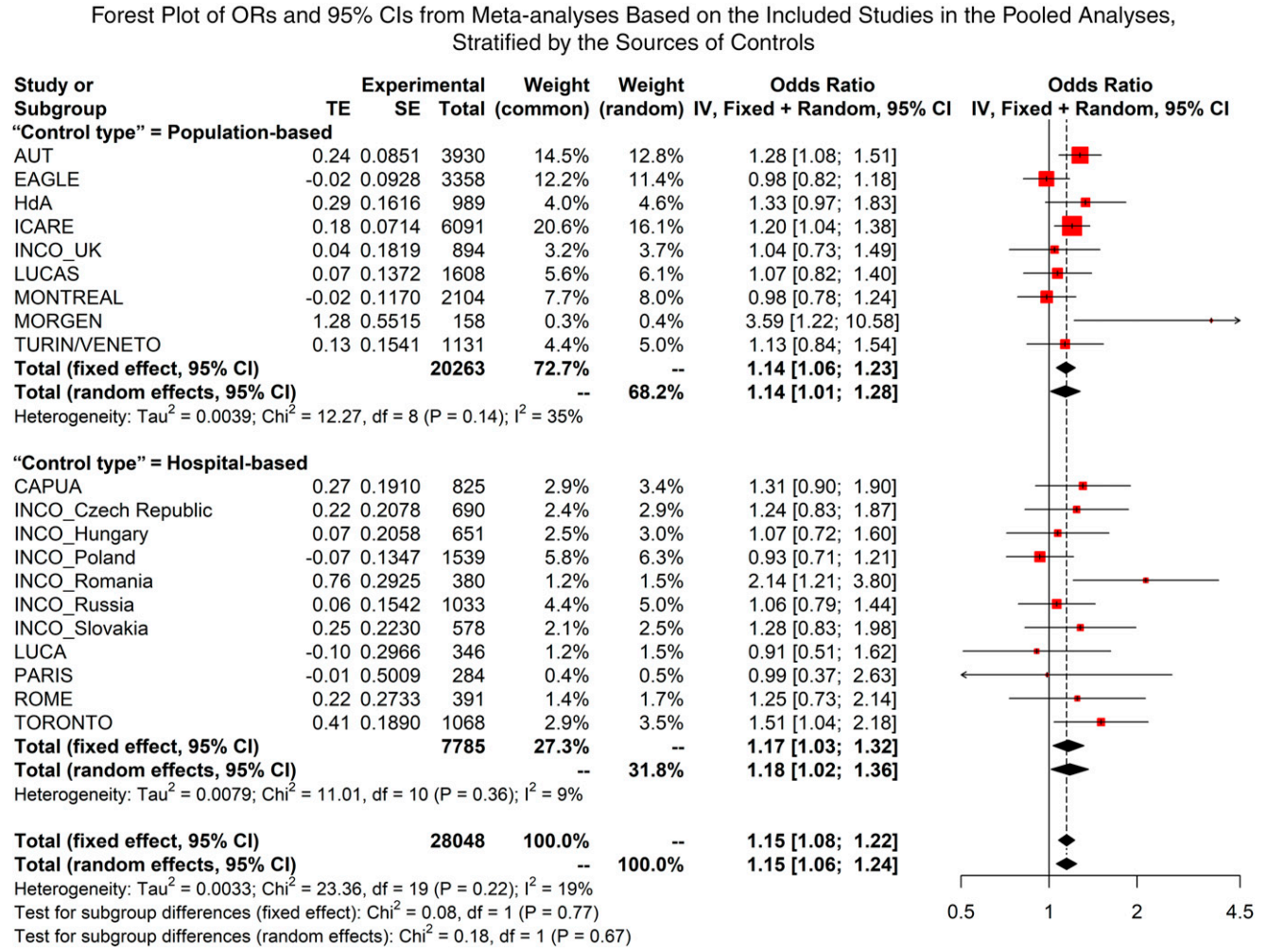

Figure 2. Comparisons were made between ever exposed to occupational benzene versus never exposure. Odds ratios are adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking), list A jobs, and cumulative exposures of asbestos, hexavalent chromium, polycyclic aromatic hydrocarbons, silica, and diesel engine exhaust. For LUCA and LUCAS, odds ratios 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 control subjects to be hospital based here for the meta-analyses. CI = confidence interval; IV = inverse-variance weighting; SE = standard error; TE = treatment effect (log-transformed).

incorporated in BEN-JEM, and we included only subjects whose job history fell within the assessment timespan (1945–2009) to reduce uncertainties in exposure assessment.

We acknowledge that detailed harmonized 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 covariate 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 in which subjects working in certain industries or exposures to lung carcinogens were excluded, residual confounding from other unmeasured coexposures 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).

Conclusions

Benzene has been regulated extensively over the past several 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 remains of great concern because higher exposure levels are still often observed (47, 48). 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, 49), leading to a far greater population being potentially exposed.

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 nonsmokers. Our findings support the hypothesis of an effect of occupational benzene exposure on lung cancer risk and warrant revisiting the published epidemiological and molecular data addressing the pulmonary carcinogenicity of benzene. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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