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REVIEW ARTICLE

Occupational exposure to formaldehyde and risk of lung cancer: A systematic review and meta-analysis

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Abstract

Background: Formaldehyde exposure is associated with nasopharyngeal cancer and leukemia. Previously-described links between formaldehyde exposure and lung cancer have been weak and inconsistent. We performed a systematic review and meta-analysis to evaluate quantitatively the association between formaldehyde exposure and lung cancer.

Methods: We searched for articles on occupational formaldehyde exposure and lung cancer in PubMed, EMBASE, Web of Science, and CINAHL databases. In total, 32 articles were selected and 31 studies were included in a meta-analysis. Subgroup analyses and quality assessments were also performed.

Results: The risk of lung cancer among workers exposed to formaldehyde was not significantly increased, with an overall pooled risk estimate of 1.04 (95% confidence interval [CI], 0.97-1.12). The pooled risk estimate of lung cancer was increased when higher exposure studies were considered (1.19; 95% CI, 0.96-1.46). More statistically robust results were obtained when high quality (1.13; 95% CI, 1.08-1.19) and recent (1.13; 95% CI, 1.07-1.19) studies were used in deriving pooled risk estimates.

Conclusions: No significant increase in the risk of lung cancer was evident in the overall pooled risk estimate; even in higher formaldehyde exposure groups. Our findings do not provide strong evidence in favor of formaldehyde as a risk factor for lung cancer. However, since risk estimates were significantly increased for high-quality and recent studies, the possibility that exposure to formaldehyde can increase the risk of lung cancer might still be considered.

KEYWORDS
formaldehyde, lung cancer, meta-analysis, occupational exposure, respiratory cancer

1 | INTRODUCTION

Formaldehyde is a naturally occurring organic compound used in various industries; for instance, in the production of resins and other industrial compounds.[1] It is also used in the textile, leather, rubber, cement, and plastic industries.[2] Pathologists and embalmers tend to be exposed to formaldehyde because it is used as a tissue fixative and embalming agent.

The International Agency for Research on Cancer (IARC) classifies formaldehyde as a group 1 carcinogen based on sufficient evidence that it causes nasopharyngeal cancer and leukemia in humans.[3] However, the association between exposure to formaldehyde and lung cancer is weak and inconsistent. In 1986, a National Cancer Institute (NCI) cohort study by Blair et al[4] showed that the risk of mortality due to lung cancer was significantly increased in those exposed to formaldehyde. The NCI cohort, which is one of the

largest industrial cohorts, has been reanalyzed and updated several times. In a subsequent follow-up analysis of 1990; however, no exposure-response relationship was identified.[5] In 2004, Hauptmann et al[6] reanalyzed the NCI cohort, resuming follow-up where Blair et al left off. The analysis indicated that while lung cancer mortality was slightly increased among workers exposed to formaldehyde, an exposure-response relationship was not observed. In addition to research on the NCI cohort, a 1988 National Institute for Occupational Safety and Health cohort study conducted by Stayner et al[7] showed a slightly increased lung cancer mortality in garment workers exposed to formaldehyde, but the finding was not statistically significant. Acheson et al[8] conducted a cohort study in six British chemical factories that were either using or producing formaldehyde and also found that the risk of mortality for lung cancer was not increased. By contrast, the updated study conducted by Coggon et al,[9] which was followed up to 2000, revealed a significantly increased mortality of lung cancer.

As evinced by the results of the aforementioned epidemiological studies, the association between formaldehyde exposure and lung cancer has not been completely consistent. In 1990, Blair et al[10] performed a meta-analysis on over 30 epidemiologic studies that evaluated cancer risk associated with formaldehyde exposures, which showed a slight significantly increased risk of 1.08 for lung cancer among industrial workers, and none for professional workers. In 1993, Partanen[11] reanalyzed and updated Blair et al's meta-analysis, with similar results; indicating an aggregate risk of 1.11 (95% confidence interval [CI], 1.03-1.19) for lung cancer in industrial workers, 0.34 (95% CI, 0.26-0.44) in relevant medical specialists, and 0.98 (95% CI, 0.89-1.07) in funeral directors and embalmers. In 1997, Collins et al[12] performed a systematic review and meta-analysis of cancer of the respiratory tract, including of the lung. On the basis of the findings of 24 epidemiological studies (14 cohort studies and 10 case-control studies) of lung cancer, the summary risk estimate was 1.0 (95% CI, 0.9-1.0), indicating that formaldehyde exposure did not significantly increase the risk of lung cancer. Since then, several epidemiological studies of the relationship between formaldehyde exposure and cancer mortality or incidence have been performed, and some cohorts involved in prior studies have been followed up; however, there is no up-to-date systematic review. The IARC does not classify formaldehyde as a lung carcinogen due to insufficient evidence.[13] Therefore, an updated systematic review and meta-analysis are needed to clarify the association between formaldehyde and the risk of lung cancer.

We report here on a systematic review and meta-analysis to evaluate quantitatively whether occupational exposure to formaldehyde is associated with lung cancer.

2 | MATERIALS AND METHODS

2.1 | Literature search

The systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[14] We searched the PubMed, EMBASE, Web of Science, and CINAHL databases up to 29 January 2019 using the following keywords: Formaldehyde AND ("lung cancer" OR cancer OR neoplasms OR carcinogen* OR tumor OR tumor OR carcinoma OR bronchus OR thoracic) AND (incidence OR mortality OR risk OR morbidity OR death OR "adverse effect*") AND (case-control OR cohort). Only articles written in English were considered. We excluded duplicate articles, screened the title and abstract of the remaining articles, and read the full text to assess their eligibility according to the inclusion and exclusion criteria listed below. We also reviewed manually the reference lists of the relevant review articles. In some cases, several articles concerned the same cohort study; we included only the latest article if the observation periods overlapped or were duplicated; if not, we combined the results of the articles. The studies conducted by Blair et al[4] and Beane Freeman et al[15] utilized the same cohort but differed in their follow-up periods; Blair et al's follow-up period was 1950-1979 whereas Beane Freeman's was 1980-2004. Hence, we combined the results of two studies by adding the observed and expected numbers of death of each study to calculate the standardized mortality ratio (SMR) and its corresponding 95% CI.

2.2 | Inclusion criteria

The inclusion criteria were studies of workers exposed to formaldehyde which provided risk estimates and CIs for lung cancer or data enabling calculation of the risk estimates and CIs.

2.3 | Exclusion criteria

We excluded studies based on the following criteria: studies in which it was difficult to distinguish exposures to formaldehyde from coexposures to other factors (eg, if the level of coexposures was much higher than level of formaldehyde or if the level of formaldehyde exposure was considerably low in comparison); studies of environmental exposure to formaldehyde; overlapping studies or those with duplicate data; meta-analyses and reviews; nonoriginal research such as commentaries, conference abstracts, and protocols; and studies with insufficient information.

2.4 | Data extraction

From the included studies, we collected the first author, publication year, sex, type of study, study region, type of industry, exposure assessment method, study size, study period, and risk estimates with corresponding 95% CIs for lung cancer. We used the 95% CIs in the articles if provided, and if not, we calculated risk estimates and corresponding 95% CIs from the observed and expected numbers for cohort, proportional mortality ratio (PMR) or proportional incidence ratio (PIR) studies using the *eclpci* command in Stata.[16] If only

stratified risk estimates in a single cohort were given and PMR or PIR study results needed to be integrated, we summed the observed and expected numbers respectively to derive overall observed and expected numbers, from which risk estimates and its corresponding 95% CIs were calculated using the *eclpci* command in the same manner as mentioned above.

Chiazze et al's two case-control studies[17,18] provided only odds ratios (ORs) for exposure categories, so we converted the degree of exposure to ever/never exposure as in other case-control studies and calculated the OR and corresponding 95% CIs using the logit method.[19] However, a study by Checkoway et al[20] provided hazard ratios (HRs) for each exposure category adjusting for smoking, and the smoking-adjusted HR for ever-exposure to formaldehyde could not be calculated using the information provided. Therefore, we used the HR of a group exposed to formaldehyde for ≥10 years as a surrogate of the risk estimate in this study. A nested case-control study by Partanen et al[21] provided 90% CIs, which we converted to 95% CIs using the logit method. Cohort studies by Marsh et al[22] used estimated national and local SMRs as references; we used the local rate for risk estimation because it is less biased than the national rate.[23,24] Beane Freeman et al[15] provided not only RRs for peak exposure, average intensity exposure and cumulative exposure but also SMRs for peak exposure; on the other hand, a study by Blair et al,[4] which was conducted on the same cohort, provided only SMRs. Hence, we decided to combine SMR from each study to ensure better compatibility; for this reason, we used SMRs as the representative risk estimate of Beane Freeman et al's cohort, as in other cohort studies.

If studies provided risk estimates that corrected for smoking and other risk factors for lung cancer, we used those data rather than uncorrected values. Eleven studies reported risk estimates adjusting for smoking and other risk factors. In addition, if a study provided risk estimates for a group with higher formaldehyde exposure based on the cumulative, average, or maximum exposure concentration, we extracted the risk values and 95% CIs for the group separately. Some studies assessed formaldehyde exposures by a job-exposure matrix (JEM) or work history; we extracted the risk values and 95% CIs if they provided separate risk estimates for the higher formaldehyde exposure groups. Eight studies reported separate risk estimates for higher exposure groups classified by quantitative exposure assessment whereas two studies provided risk estimates for higher exposure groups classified by JEM or work history. All data extracted and used for meta-analysis and subgroup analyses are shown in Table 1.

2.5 | Quality assessment

We assessed the risk of bias of each study using the Newcastle-Ottawa Scale (NOS) (see Supporting Information Appendix A).[50] The NOS contains 8-item categories divided into three components of quality: selection, comparability, and outcome (cohort studies) or exposure (case-control study).[51] The NOS score ranges from 0 to 9. The quality of a study was considered to be high if the NOS score was 7 to 9; intermediate if the NOS score was 4 to 6; and low if the NOS score was 0 to 3.[52] We did not evaluate the quality of PMR or PIR studies because they are not appropriate candidates for evaluation by the NOS scoring system as they use only death or disease incidence data.

2.6 | Statistical analysis

We calculated overall pooled risk estimates and the corresponding 95% CIs using fixed- and random-effects models according to the results of a heterogeneity test. We used the I^2 statistic to assess heterogeneity among the studies. I^2 values range from 0% to 100% (I^2 = 0%-25%, no heterogeneity; I^2 = 25%-50%, moderate heterogeneity; I^2 = 50%-75%, large heterogeneity; I^2 = 75%-100%, extreme heterogeneity).[53] We considered an I^2 value of >50% to indicate substantial heterogeneity,[54] and in such cases used random-effects models. We used the funnel plot and Begg's test to evaluate publication bias. Subgroup analyses were performed by type of study, type of comparison, study region, type of industry, exposure assessment method, smoking information, and year of publication to correct for large heterogeneity. For the subgroup analysis based on the type of comparison, the studies reporting SMRs, SIRs, PMRs, and PIRs in respect to the general population were classified as external comparisons, while the studies reporting HRs, RRs, and ORs in respect to other workers from low- or unexposed industries were classified as internal comparisons. For the subgroup analysis based on the year of publication, the year 1996 was chosen as the chronological divisor in creating a subgroup, as the last meta-analysis included studies published until 1995. In the subgroup analyses, the summary risk estimates and corresponding 95% CIs were calculated using a random-effects model irrespective of subgroup heterogeneity to generalize the results.[55] Using the extracted values for the high-formaldehyde exposure group, we calculated summary risk estimates and the corresponding 95% CIs according to smoking information as in the overall meta-analysis. Likewise, studies classified as high quality using the NOS were analyzed separately, and we calculated the summary risk estimates and corresponding 95% CIs according to smoking information. Moreover, we identified the distribution of study quality and exposure assessment method among recent studies, and calculated the summary risk estimates and corresponding 95% CIs according to smoking information in a separate meta-analysis. All analyses were performed using Stata/IC ver. 15.1 software (Stata Corporation, College Station, TX).

3 | RESULTS

3.1 | Characteristics of the selected studies

We identified 1688 articles by searching the PubMed, EMBASE, Web of Science, and CINAHL databases. In addition, we identified a

TABLE 1 Characteristics of included studies

Study[a]	Sex	Type of study[a]	Country[a]	Industry[a]	Exposure assessment[a]	ES[a]	Smoking[a]	Size	Study period	Comments
Jensen et al[25]	Men	Case-control	Denmark	Physician	Ever employed in pathology	RR, 1.0 (0.4-2.4)	No information	77 cases, 225 controls	1943-1977	
Walrath et al[26]	Men	PMR	USA	Embalmer	Time since the first license	PMR, 1.08 (0.84-1.36)	No information	1132 (72 cases)	1925-1980	
Coggon et al[27]	Men	Case-control	UK	Various	JEM (none, low, high)	RR, 1.5 (1.2-1.8)	No information	296 cases, 472 controls	1975-1979	RR, 0.9 (0.6-1.4)[a] for higher exposure
Levine et al[28]	Men	Cohort	Canada	Funeral workers	None	SMR, 0.94 (0.57-1.47)	No information	1477 (19 cases)	1950-1977	
Walrath et al[29]	Men	PMR	USA	Embalmer	Duration of employment	PMR, 0.96 (0.69-1.30)	No information	1007 (41 cases)	1925-1980	PMR, 1.88 (0.61-4.39) for ≥20 y exposure
Pannett et al[30]	Men	Case-control	UK	Various	JEM (none, low, moderate, high)	RR, 1.05 (0.84-1.75)	Adjusted	312 cases, 312 controls	1975-1980	Controls were matched to cases for smoking; RR, 1.47 (0.91-2.37)[a] for moderate exposure and above
Bond et al[31]	Men	Nested case-control	USA	Chemical industry	Exposure profile based on work history (ever/never)	OR, 0.62 (0.29-1.34)	Unadjusted	308 cases, 588 controls	1944-1980	OR, 0.31 (0.11-0.86) with lag period (≥15 y)
Stroup et al[32]	Men	Cohort	USA	Anatomists	Duration	SMR, 0.28 (0.14-0.49)	No information	2317 (12 cases)	1925-1979	SMR, 0.2 (0.0-0.5) for 20-40 y exposure; SMR, 0.2 (0.0-0.5) for ≥20 y exposure
Edling et al[33]	Men	Cohort	Sweden	Abrasive manufacturing	Work history based on exposure measurement	SIR, 0.57 (0.10-2.10)	No information	521	1958-1983	Incidence data
Gérin et al[34]	Men	Case-control	Canada	Various	Exposure profile based on work history (ever, short, long-low, long-medium, long-high)	OR, 0.8 (0.6-1.1)	Adjusted	857 cases, 1523 controls	1979-1985	OR, 1.0 (0.4-2.4)[a] for higher exposure
Bertazzi et al[35]	Men	Cohort	Italy	Resin producing	Duration of employment	SMR, 0.69 (0.25-1.50)	No information	1332 (6 cases)	1959-1986	Mortality data of subcohort definitely exposed to formaldehyde
Hayes et al[36]	Men	PMR	USA	Embalmer, funeral director	None	PMR, 0.95 (0.85-1.06)	No information	4046 (308 cases)	1975-1985	
Partanen et al[21]	Men	Nested case-control	Finland	Wood industry	JEM, work history on factory register, interviews, and questionnaires	OR, 0.89 (0.24-3.36)	Adjusted	136 cases, 408 controls	1957-1980	OR adjusted for vital signs and smoking; Converted 90% CI to 95% CI; OR, 1.19 (0.24-5.90) with induction period (≥10 y)
Hall et al[37]	Both	Cohort	UK	Pathologist	None	SMR, 0.19 (0.09-0.36)	No information	4512 (9 cases)	1974-1987	

(Continues)

TABLE 1 (Continued)

Study[a]	Sex	Type of study[a]	Country[a]	Industry[a]	Exposure assessment[a]	ES[a]	Smoking[a]	Size	Study period	Comments
Chiazze et al[17]	ND	Case-control	USA	Fiberglass manufacturing	Quantitative assessment including cumulative exposure (0, 0.25-99.99, 100-999, >1000 ppm)	OR, 0.98 (0.58-1.66)	Unadjusted	162 cases, 363 controls		Unadjusted OR calculated by converting exposure stage to dichotomous (never/ever); adjusted OR, 0.872 (0.19-4.09)[a] for higher exposure (>1000 ppm)
Brownson et al[38]	Women	Case-control	USA	Various	Telephone and in-person interview (ever/never)	OR, 0.9 (0.2-3.3)	Adjusted	429 cases, 1021 controls	1986-1991	OR adjusted for age, history of lung disease, and smoking
Hansen et al[39]	Men	PIR	Denmark	Various	On the basis of job titles according to low (white-collar) and above baseline (blue-collar)	SPIR, 0.95 (0.86-1.05)	No information	216 347 (410 cases)	1970-1984	
Andjelkovich et al[40]	Men	Cohort	USA	Iron foundry	Quantitative assessment including cumulative exposure (none, low, medium, high)	SMR, 1.20 (0.89-1.58)	Unadjusted	3929 (51 cases)	1960-1989	RR, 0.59 (0.28-1.20)[a] for higher exposure (Q3, Q4)
Chiazze et al[18]	Men	Nested case-control	USA	Fiberglass manufacturing	Quantitative assessment including cumulative exposure (0, 0.25-99.99, 100-999, >1000 ppm)	OR, 1.15 (0.49-2.70)	Adjusted	45 cases, 121 controls	1951-1991	Restriction to smokers only; converted exposure stage to dichotomous (ever/never); OR, 2.07 (0.17-25.5)[a] for higher exposure (>1000 ppm)
Stellman et al[41]	Men	Cohort	USA	Wood-related industry	Self-reported	RR, 0.93 (0.73-1.18)	Adjusted	45 399 (104 cases)	1982-1988	RR adjusted for age and smoking
Marsh et al[22]	Men	Cohort	USA	Fiberglass manufacturing	Quantitative assessment including cumulative and average exposure	SMR, 1.07 (1.00-1.14)	Unadjusted	32 110 (838 cases)	1945-1992	Based on local county rates. SMR with national rates 1.17 (1.09-1.25)
Kjærheim et al[42]	Men	Nested case-control	Denmark, Norway, Sweden, Germany	Rock and slag wool production	Quantitative assessment including cumulative exposure and expert panels	OR, 1.33 (0.76-2.34)	Adjusted	132 cases, 509 controls	1971-1996	OR adjusted for smoking; OR, 1.25 (0.70-2.22)[a] for higher exposure (cumulative exposure 0.76-33 ppm)
De Stefani et al[43]	Men	Case-control	Uruguay	Various	Self-reported	OR, 1.7 (1.1-2.8)	Adjusted	32 cases, 65 controls	1994-2000	Cases of lung adenocarcinoma; OR adjusted for age, residence, education, smoking
Ambroise et al[44]	Men	Cohort	France	Pest control	JEM	SMR, 0.39 (0.01-2.19)	No information	181 (1 case)	1979-2000	

(Continues)

TABLE 1 (Continued)

Study[a]	Sex	Type of study[a]	Country[a]	Industry[a]	Exposure assessment[a]	ES[a]	Smoking[a]	Size	Study period	Comments
Checkoway et al[20]	Women	Case-cohort	China	Textile	JEM	HR, 2.10 (0.40-11.00)	Adjusted	628 cases, 3179 controls	1989-1998	≥10-y exposure to formaldehyde; HR adjusted for age, smoking
Siew et al[45]	Men	Cohort	Finland	Various	JEM	RR, 1.18 (1.12-1.25)	Adjusted	1 200 000 (1831 cases)	1971-1995	20-y latency period was assumed; RR adjusted for socioeconomic status, age, F/U period, and smoking
Meyers et al[46]	Both	Cohort	USA	Garment industry	Exposure estimation based on personal sampling among 549 employees; duration of exposure	SMR, 1.04 (0.92-1.17)	No information	11 043 (267 cases)	1960-2008	SMR, 0.71 (0.53-0.91) for ≥10-y exposure
Blair et al[4] and Beane Freeman et al[15]	Both	Cohort	USA	Various	Quantitative assessment including cumulative, average, and highest peak exposure	SMR, 1.13 (1.07-1.19)	Unadjusted	25 619 (1350 cases)	1950-2004	F/U period of Blair et al was 1950-1979; Beane Freeman et al was 1980-2004; SMR for cumulative exposure was used for the meta-analysis; SMR, 1.11 (0.85-1.43)[a] for higher exposure (cumulative exposure of 5.5 ppm-y) in White men
Mahboubi et al[47]	Both	Case-control	Canada	Various	Quantitative assessment including cumulative exposure, duration of exposure, maximum concentration, and age at first exposure	OR, 1.06 (0.89-1.27)	Adjusted	2060 cases, 2046 controls	1979-1986, 1996-2002	OR for cumulative exposure was used for the meta-analysis; OR adjusted for age, sex, and smoking; OR, 1.22 (0.80-1.84)[a] for medium and higher exposure (maximum concentration)
Coggon et al[48]	Men	Cohort	UK	Chemical industry	Quantitative assessment (background, low, moderate, high)	SMR, 1.26 (1.17-1.35)	No information	14 008 (813 cases)	1941-2012	SMR, 1.59 (1.42-1.77)[a] for higher exposure (time-weighted concentration >2.0 ppm)
Pira et al[49]	Both	Cohort	Italy	Laminated plastic	Duration	SMR, 0.97 (0.72-1.27)	No information	2750 (51 cases)	1947-2011	

Abbreviations: CI, confidence interval; HR, hazard ratio; JEM, job-exposure matrix; OR, odds ratio; PIR, proportional incidence ratio; PMR, proportional mortality ratio; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPIR, standardized proportional incidence ratio.

[a]The extracted information used in the meta-analysis and subgroup analyses.

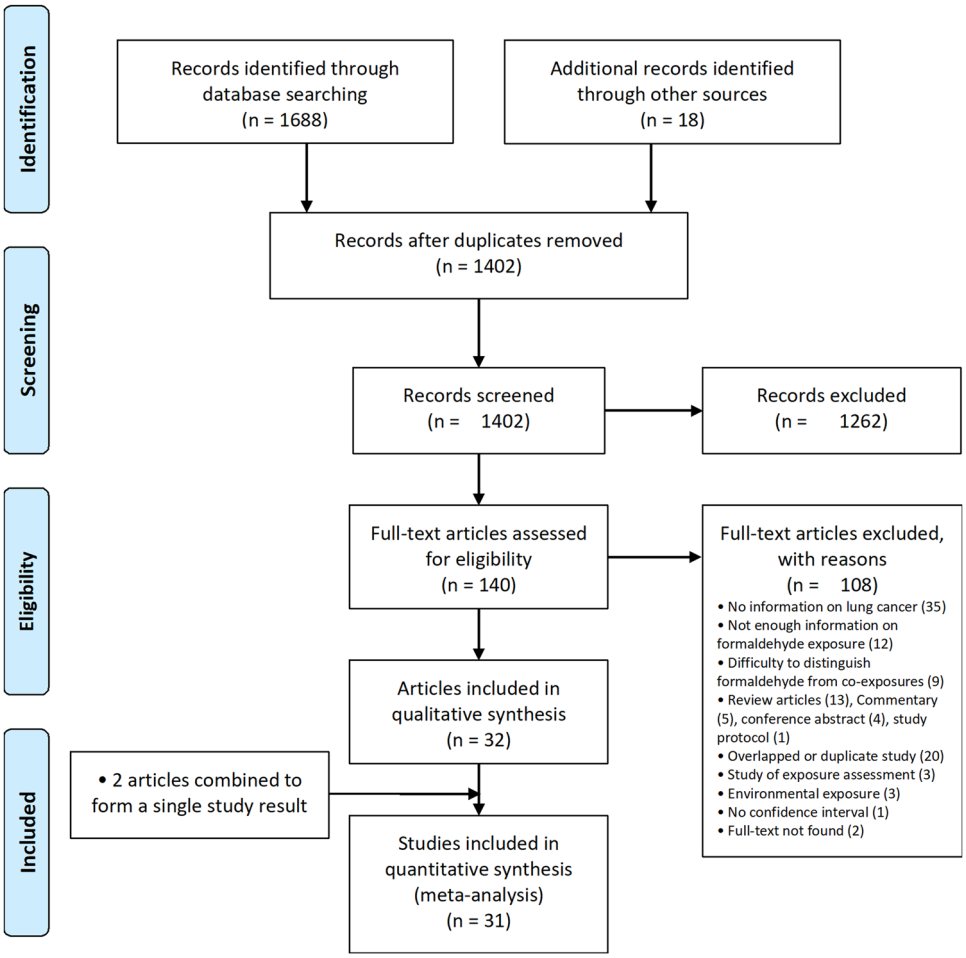

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of selection of studies for the systematic review [Color figure can be viewed at wileyonlinelibrary.com]

further 18 articles by reviewing the reference lists of relevant review articles. After removing duplicate articles, we excluded 1262 articles based on their title and abstract and performed a full-text assessment of 140 articles. Thirty-five articles were included in the meta-analysis following the application of the inclusion and exclusion criteria. Among them, the articles by Blair et al[4] and Beane Freeman et al[15] were combined because they involved the same cohort but different follow-up periods (Figure 1).

The studies included in the meta-analysis were conducted in Europe, the United States, Canada, Uruguay, and China between 1982 and 2014. We included all types of epidemiological studies, including 14 cohort studies, 13 case-control studies (including nested case-control studies or case-cohort studies), and 4 PMR or PIR studies. Five studies involved both males and females, 23 involved only males, and 2 studies involved only females. The sex of the subjects was not provided in one article. Four studies focused on the chemical industry (including the plastic or resin industry), four on funeral directors and embalmers, three on medical professionals (such as physicians, pathologists, and anatomists), three on fiberglass manufacturing, two on the wood industry, and two on the textile and garment industry. The other studies focused on the abrasive manufacturing, iron foundry, rock- and slag wool-production, and pest control industries. Nine studies did not target a specific industry but involved formaldehyde-exposed workers in several industries. Sixteen studies provided information on smoking, 11 of which corrected for smoking by performing a multivariate analysis or restricting the analysis to only smokers. Fifteen studies did not provide information on smoking (Table 1).

3.2 | Overall meta-analysis

There was large heterogeneity among the studies (I^2 = 72.0%; P < .001), so we used the random-effects model in the meta-analysis. The overall risk estimate of lung cancer was slightly increased to 1.04, but it was not significant (95% CI, 0.97-1.12) (Figure 2).

3.3 | Subgroup analysis of study characteristics

The risk of lung cancer was slightly increased in the subgroup analysis that addressed different types of study, but none were

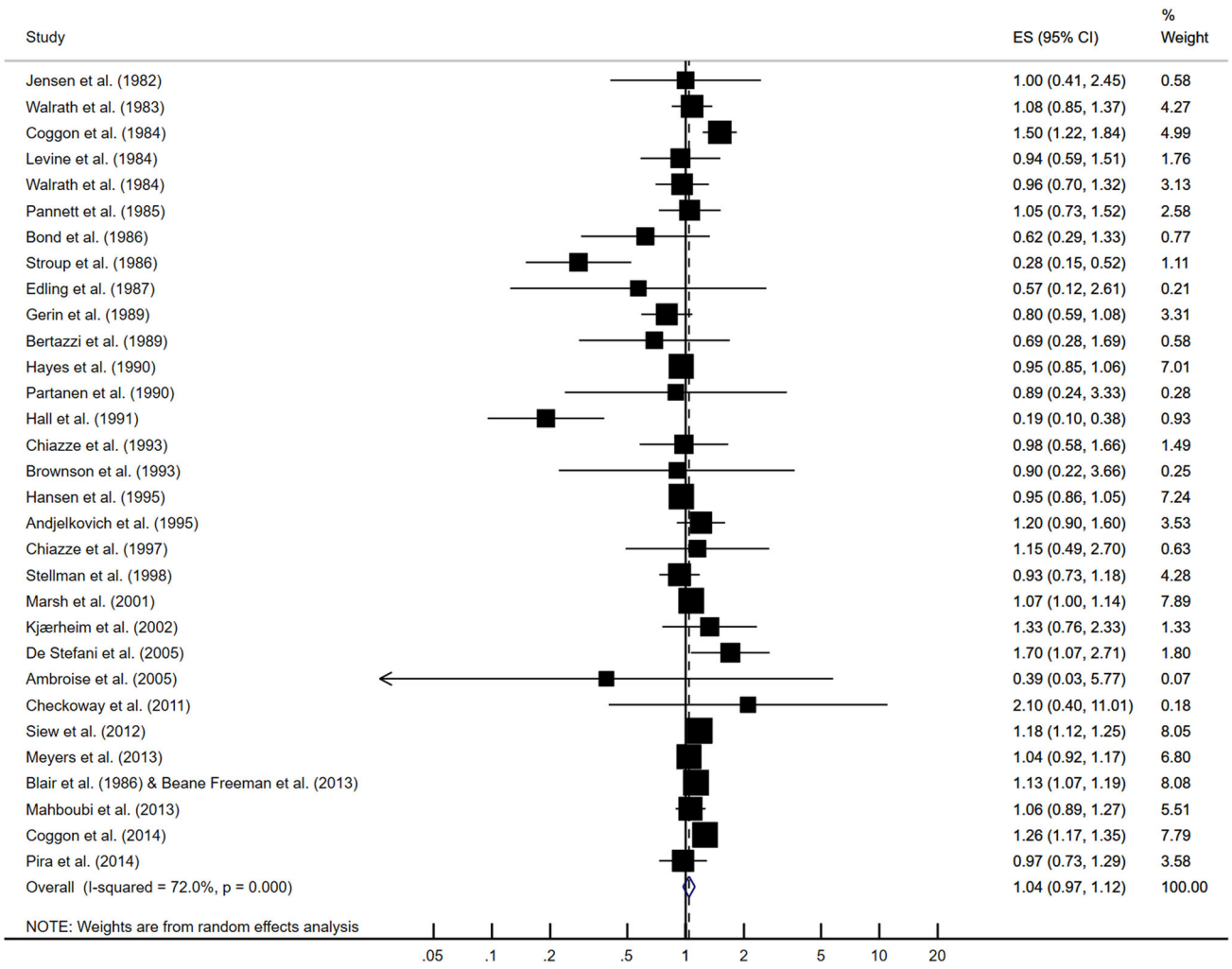

FIGURE 2 Forest plot of studies included in the meta-analysis of exposure to formaldehyde and the risk of lung cancer

found statistically significant. In the subgroup analysis by type of comparison used, the effect size was greater in the studies using internal comparisons (risk estimate, 1.11; 95% CI, 0.995-1.248), but neither were statistically significant. By study region, the risk of lung cancer was significantly increased in locations other than Europe and North America (risk estimate, 1.73; 95% CI, 1.10-2.71), with no heterogeneity ($I^2 = 0.0\%$; $P = .803$). By type of industry, workers in the fiberglass industry (risk estimate, 1.07; 95% CI, 1.00-1.14) had significantly increased risks of lung cancer, with no heterogeneity ($I^2 = 0.0\%$; $P = .935$). The studies that did not target specific industries also showed a significantly increased risk of lung cancer (risk estimate, 1.12; 95% CI, 1.02-1.23), with large heterogeneity ($I^2 = 73.5\%$; $P < .001$). In contrast, occupational groups that use formalin solutions containing formaldehyde (such as anatomists, pathologists, and funeral workers) had a significantly lower risk of lung cancer (risk estimate, 0.72; 95% CI, 0.52-0.99), with extreme heterogeneity ($I^2 = 83.3\%$; $P < .001$). By exposure assessment method, quantitative assessments including area measurements or individual sampling (risk estimate, 1.13; 95% CI, 1.06-1.19) and JEMs (risk estimate, 1.24; 95% CI, 1.08-1.43) yielded significantly higher risks of lung cancer, and both exhibited moderate heterogeneity (quantitative assessment: $I^2 = 45.4\%$; $P = .075$; JEM: $I^2 = 26.6\%$; $P = .235$). Among the studies that provided information on smoking, those that did not adjust for smoking showed a significantly increased risk of lung cancer (risk estimate, 1.10; 95% CI, 1.05-1.16), with no heterogeneity ($I^2 = 7.3\%$; $P = .365$), while studies that adjusted for smoking did not. Finally, studies published post-1996 (risk estimate, 1.13; 95% CI, 1.07-1.19), but not those published pre-1996, had a significantly increased risk of lung cancer, with moderate heterogeneity ($I^2 = 49.7\%$; $P = .021$) (Table 2).

3.4 | Risk of lung cancer of higher formaldehyde exposure

Ten studies included separate risk estimates for higher formaldehyde exposure. The summary risk estimate for higher formaldehyde exposure in the random-effects meta-analysis was increased to 1.19, with large heterogeneity ($I^2 = 53.4\%$; $P = .023$). The effect was larger than that in the overall meta-analysis, but it was not significant (95% CI, 0.96-1.46). Also, the risk of lung

TABLE 2 Pooled risk estimates by subgroup analysis

	No. of studies	Pooled risk estimates	Heterogeneity	
			I^2 (%)	*P* value
Type of study				
Cohort study	14	1.03 (0.94-1.14)	80.6	<.001
Case-control study (including case-control study within a cohort)	13	1.12 (0.95-1.32)	39.4	.071
PMR/PIR study	4	1.08 (0.89-1.30)	0.0	.803
Type of comparison				
Internal comparison	15	1.11 (0.995-1.248)	40.4	.053
External comparison	16	0.99 (0.90-1.09)	80.9	<.001
Study region				
North America (USA and Canada)	16	1.01 (0.94-1.09)	56.7	.003
Europe	13	1.06 (0.92-1.22)	79.4	<.001
Other	2	1.73 (1.10-2.71)	0.0	.810
Type of Industry				
Professionals (medical technician, embalmer, funeral director)	7	0.72 (0.52-0.99)	83.3	<.001
Chemicals (including plastic or resin producing)	4	1.02 (0.76-1.35)	61.6	.050
Fiberglass	3	1.07 (1.00-1.14)	0.0	.935
Wood	2	0.93 (0.73-1.18)	0.0	.949
Textile & garment	2	1.04 (0.93-1.18)	0.0	.407
Miscellaneous	4	1.19 (0.93-1.53)	0.0	.635
Various	9	1.12 (1.02-1.23)	73.5	<.001
Exposure assessment				
Quantitative assessment	9	1.13 (1.06-1.19)	45.4	.075
JEM	6	1.24 (1.08-1.43)	26.6	.235
Duration of employment	5	0.80 (0.57-1.13)	75.2	.003
Based on work history	5	0.93 (0.85-1.02)	0.0	.623
Interview or self-reported	3	1.17 (0.72-1.89)	60.9	.078
None	3	0.60 (0.28-1.26)	90.1	<.001
Smoking				
Adjusted	11	1.09 (0.97-1.22)	29.2	.168
Unadjusted	5	1.10 (1.05-1.16)	7.3	.365
No information	15	0.94 (0.81-1.09)	83.6	<.001
Year of publication				
Early (1982-1995)	18	0.90 (0.77-1.04)	72.3	<.001
Late (1997-2014)	13	1.13 (1.07-1.19)	49.7	.021

Abbreviations: JEM, job-exposure matrix; PIR, proportional incidence ratio; PMR, proportional mortality ratio.

cancer was not significantly increased in the studies that adjusted for smoking (risk estimate, 1.19; 95% CI, 0.99-1.43) (Figure 3).

3.5 | Quality assessment and meta-analysis of the high-quality studies

The quality of the included case-control and cohort studies is shown in Tables S1 and S2 (see Supporting Information Appendix B). The 13 studies classified as high quality (NOS score ≥ 7) were subjected to a separate meta-analysis. The summary risk estimate for high-quality studies in the random-effects meta-analysis was significantly increased to 1.13 (95% CI, 1.08-1.19), with moderate heterogeneity (I^2 = 40.2%; *P* = .066). Also, the risk of lung cancer was significantly increased in the studies that adjusted for smoking (risk estimate, 1.17; 95% CI, 1.11-1.23), with no heterogeneity (I^2 = 0.0%; *P* = .784). The effect size was greater than that of the studies that did not adjust for smoking (Figure 4).

3.6 | Meta-analysis of recent studies

In the subgroup analysis, post-1996 studies had larger effect sizes of the risk of lung cancer. Therefore, we analyzed the distribution of study quality and exposure assessment methods according to the year of publication. Only two pre-1996 studies performed a quantitative exposure assessment, compared with seven of those published post-1996. In addition, few pre-1996 studies were rated as high quality, compared with eight of the post-1996 (Table 3). Therefore, a larger proportion of the post-1996 than the pre-1996 studies involved a quantitative assessment of formaldehyde exposure and were of high quality. Moreover, the risk of lung cancer was significantly increased in the post-1996 studies that adjusted for smoking (risk estimate, 1.14; 95% CI, 1.02-1.26), and the effect size was similar to that in the studies that did not adjust for smoking (Figure 5).

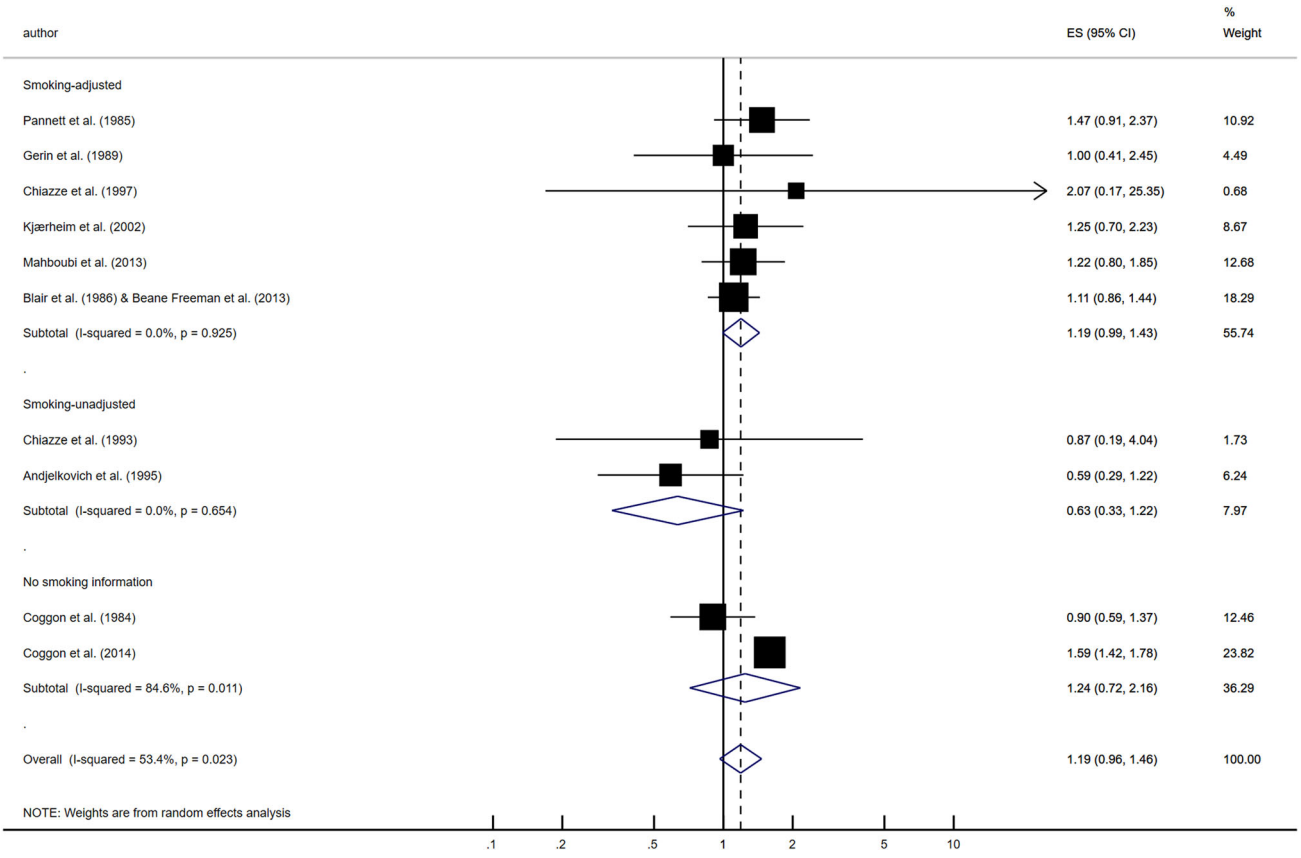

FIGURE 3 Forest plot of studies reporting effect sizes for higher exposure to formaldehyde, grouped by smoking information

3.7 | Publication bias

Begg's funnel plot was approximately symmetrical (Figure 6), but Egger's regression asymmetry test was significant (*P* value for bias = .031) while the result of Begg's test for publication bias was not significant (*P* value for bias = .905). This meant that while there was a slight bias in the negative direction in some small size studies, a critical bias was not present. Thus, we concluded that there was no evidence of publication bias in the selected studies.

4 | DISCUSSION

We performed a systematic review and meta-analysis of the association between occupational formaldehyde exposure and the risk of lung cancer. Workers ever exposed to formaldehyde had a slightly increased risk of lung cancer than never-exposed groups, with an overall pooled risk estimate of 1.04, which was not significant. This result was consistent with that of previous meta-analyses.

Summary risk estimates for workers highly exposed to formaldehyde were larger than the initial overall risk estimate, but also lacked statistical significance, which implies that the risk of lung cancer did not increase even at higher levels of formaldehyde exposure. However, high-quality studies and post-1996 studies demonstrated a significantly increased effect size for the risk of lung cancer which persisted after adjusting for smoking. Likewise, results incorporating only high-quality studies showed a similar increased risk estimate also unchanged after adjusting for smoking. In summary, the association between formaldehyde exposure and the risk of lung cancer was increased in well-designed, high-quality, and recent studies, although the effect sizes were small.

Most cohort studies that are included in this review reported SMRs calculated by external comparisons. Further, PMR or PIR studies also made comparisons with external references. In total, about half of the studies provided risk estimates that were calculated through external comparisons. Among studies included in this review, the effect size of the risk for lung cancer was larger in studies employing internal comparisons than those using external comparisons. Since external comparisons are conducted with respect to the general population, the risk of lung cancer could be underestimated due to healthy worker effects.[56] However, as mentioned before, even in the studies employing internal comparison, the increase in risk for lung cancer was not found to be statistically significant.

Most studies included in our analysis were conducted in Europe and North America. In our study, lung cancer risk was not significantly increased in Europe and North America in the subgroup analysis, whereas lung cancer risk was significantly increased in regions other than Europe and North America. This discrepancy may

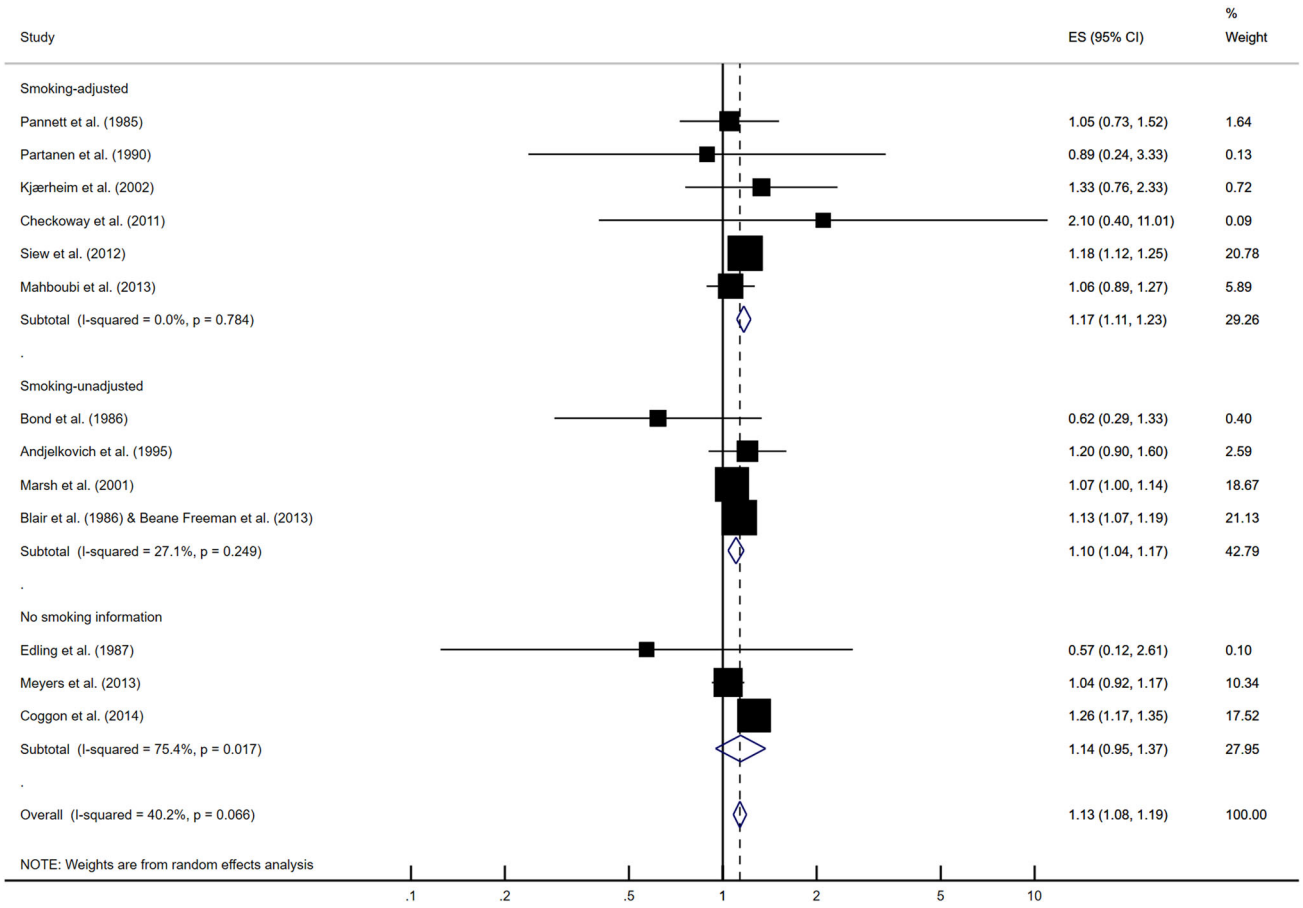

FIGURE 4 Forest plot of studies classified as high quality, grouped by smoking information

be attributable to potentially lower exposure levels of hazardous agents including formaldehyde that workers face in Europe and North America owing to their developed economic status and more rigorous industrial health regulations. However, as only two studies conducted outside Europe and North America were included for analysis, it is difficult to generalize this finding.

TABLE 3 Frequency of study quality and exposure assessment methods according to the publication year

	Study quality			
Publication year	**High**	**Intermediate**	**NA**	**Total**
1982-1995	**5**	**9**	**4**	**18**
Quantitative assessment	1	1		2
JEM	2	1		3
Duration of employment		2	2	4
Based on work history	2	2	1	5
Interview or self-reported		1		1
None		2	1	3
1997-2014	**8**	**5**		**13**
Quantitative assessment	6	1		7
JEM	2	1		3
Duration of employment		1		1
Interview or self-reported		2		2
Total	**13**	**14**	**4**	**31**

Abbreviations: JEM, job exposure matrix; NA, not applicable.

The risk of lung cancer was significantly higher in the fiberglass industry. Professionals such as pathologists, anatomists, embalmers and funeral directors and workers in the wood industry had lower risks of lung cancer. Fiberglass manufacturing workers were found to have a low level of exposure to formaldehyde.[57] In our study lung cancer risk increased for the fiberglass industry, but the effect size was so small that we could only conclude that a weak association was present. Furthermore, we predict that even this weak association is likely due in part to other coexposures such as respirable fibers, silica, and fumes that are present in the fiberglass production process. Levels of exposure to formaldehyde have been found to be high in wood-product[58] and furniture manufacturing.[59] Levels of short-term exposure to formaldehyde were also high in embalmers[60] and pathologists.[61,62] Thus, the results of prior exposure assessments are inconsistent with the risks of lung cancer found in this review. However, embalmers, funeral directors, anatomists, and pathologists are of high socioeconomic status,[63] and most of the articles involving these occupations were PMR or SMR studies that performed comparisons with the general population, with the exception of one case-control study. It is possible that the different socioeconomic status of embalmers, funeral directors, anatomists, and pathologists compared with the general population resulted in an underestimation of the risk of lung cancer. This may explain the inconsistency between the risk of lung cancer of such professionals in

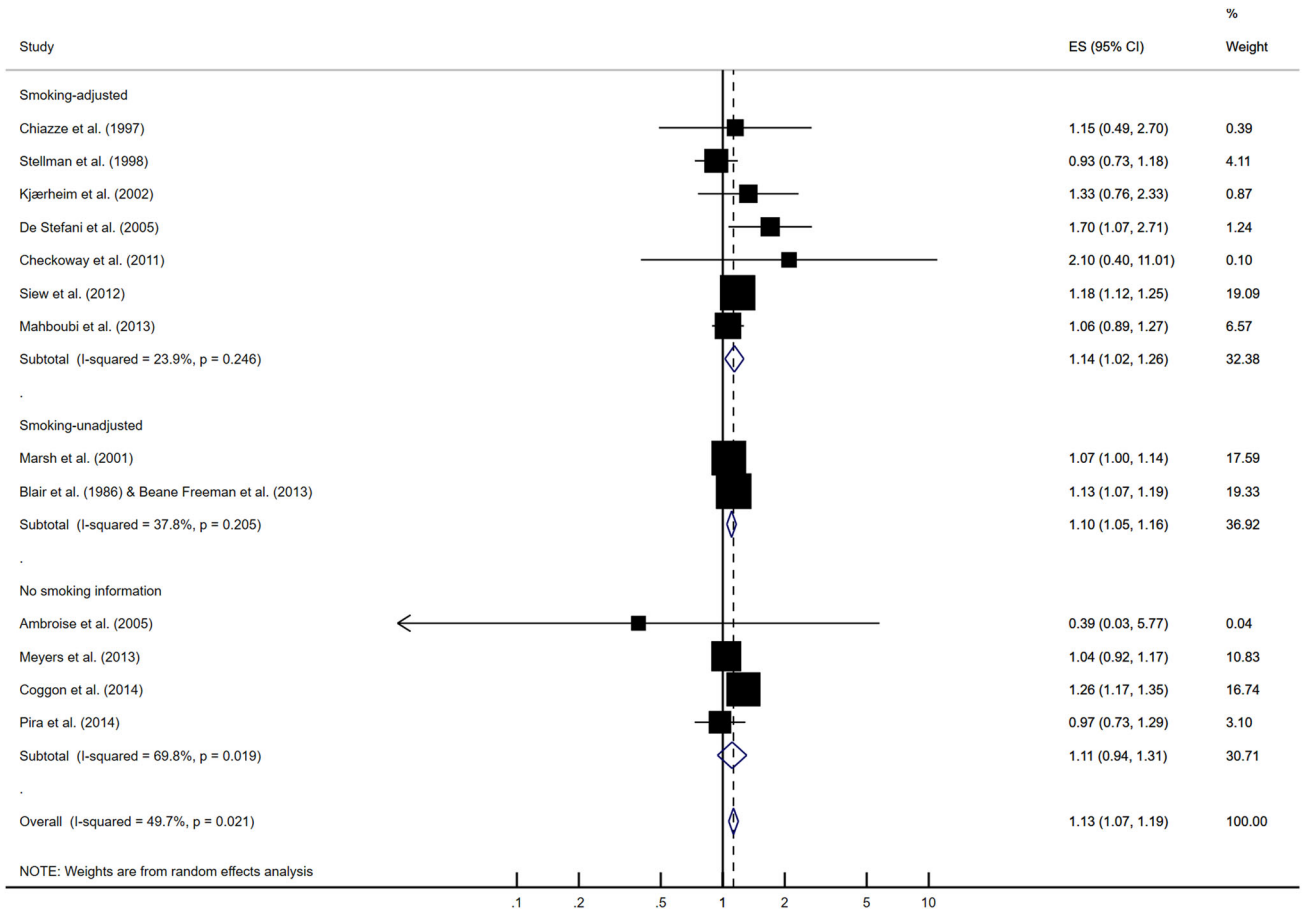

FIGURE 5 Forest plot of studies published post-1996, grouped by smoking information

epidemiological studies and their actual level of exposure to formaldehyde. In addition, according to the US National Health Interview survey that studied smoking prevalence by different industries and occupations, the estimated smoking prevalence of professionals was 13.2%, much lower than that of manufacturing workers.[64] Such lower smoking prevalence may also have an impact on lowering lung cancer risk in professionals.

Formaldehyde is highly soluble in water, and during nasal respiration it is taken up in the nasopharynx and upper respiratory tract, causing irritation. In animal studies, formaldehyde affected cells and induced toxic effects mainly in the upper respiratory tract. DNA-protein cross-linking, which is used to monitor formaldehyde exposure,[65] is induced in several regions of the upper respiratory tract of animals exposed to formaldehyde.[66,67] Formaldehyde inhalation reportedly induces nasal squamous cell carcinoma in rats[68–70] in a concentration-dependent manner.[71] However, DNA-protein cross-linking was not induced in the lung in animal studies.[66,67] These studies indicate that the lower respiratory tract may not be affected by formaldehyde exposure. In addition, there were no animal studies showing that lung cancer was caused by exposure to formaldehyde alone.

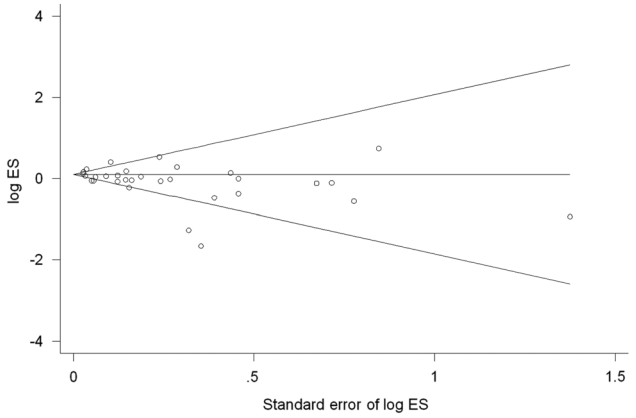

FIGURE 6 Begg's funnel plot with pseudo 95% confidence limits

With respect to possible associations between formaldehyde and lung cancer, another potential mechanism is that formaldehyde acts in combination with other compounds to increase the risk of lung cancer. The incidence of lung cancer was higher in rats treated with benzo[a]pyrene and formaldehyde than in those treated with benzo[a]pyrene or formaldehyde alone.[2] With some exceptions, almost all workers exposed to formaldehyde simultaneously come into contact with other compounds. In addition, although not for lung cancer, PMR studies have shown greater mortality excess due to nasal cancer in workers who were coexposed with formaldehyde and wood dust.[2] An animal study showed the presence of synergistic effects in inducing

Alzheimer-like changes in mouse brain when mice were coexposed to particulate matter 2.5 and formaldehyde.[72] Therefore, we could suggest a possibility that concurrent exposure to formaldehyde and other chemicals and particles may increase the risk of lung cancer synergistically. However, synergistic effects owing to similar coexposures in different industries are unlikely to occur.

This study has several limitations. First, there was a large heterogeneity among the studies. We used a random-effects model to calculate summary overall estimates and performed a subgroup analysis to correct for the large heterogeneity. However, such large heterogeneity implies inconsistent results, which limits their generalizability.[53] Second, only around one-third of the studies evaluated the risk of lung cancer after adjustment for smoking. Also, the effects of other hazardous agents such as chromium, nickel, and polyaromatic hydrocarbons cannot be ruled out. Third, the NOS tool we used to assess the quality of studies is difficult to apply to exposure assessment. The options for exposure assessment in the NOS tool differed from the method of exposure assessment in the select studies from this review. Therefore, there may have been misclassification in the rating of quality for exposure assessment and bias in the result of the subgroup analysis based on quality assessment. However, subgroup analysis of recent studies may complement this limitation of quality assessment to some extent.

This study also has several strengths. First, we quantitatively evaluated the association between occupational exposure to formaldehyde and lung cancer by performing a systematic review and meta-analysis. The preceding meta-analysis was conducted in 1997 and has not been updated. We reviewed and summarized relevant articles, and our results add to the understanding of the relationship between exposure to formaldehyde and the risk of lung cancer. Next, we performed subgroup analyses according to study characteristics to adjust for the large heterogeneity and to identify factors that affected the association of exposure to formaldehyde with the risk of lung cancer. In particular, we evaluated and adjusted for smoking, which is the most important risk factor for lung cancer, using the smoking information of the selected articles. In addition, we performed a separate meta-analysis of the studies that estimated the association with the risk of lung cancer of higher levels of exposure to formaldehyde instead of depending on an exposure-response analysis. Moreover, we conducted a meta-analysis of high-quality studies of the relationship between exposure to formaldehyde and the risk of lung cancer.

5 | CONCLUSION

In this review, the effect size of the overall risk estimate for lung cancer among workers exposed to formaldehyde was small and not statistically significant. Furthermore, the risk of lung cancer was not significantly increased even in the higher formaldehyde exposure groups.

However, the risk of lung cancer was increased in high-quality studies and those published post-1996, and for these studies, the significance of the association was maintained after adjusting for smoking. In particular, the finding that risk estimates in high quality, well-designed and recent studies were statistically significant is the most important finding of this review. Although there are limitations on inferring the association between formaldehyde and lung cancer from the overall outcome, the results of subanalyses suggest a possibility that exposure to formaldehyde could be associated with an increased risk of lung cancer.

Although there were some statistically significant findings from subgroup analyses, cautious interpretation is warranted in generalizing these results since the effect size was not much larger than the background risk. Furthermore, animal experiments that have been published so far, though not included in this meta-analysis, have yet to confirm that formaldehyde exposure increases the risk of lung cancer. On whole, our review does not provide sufficient evidence in demonstrating that formaldehyde exposure is related to lung cancer. However, since risk estimates were found significantly increased when high quality and recent studies were accounted for, the possibility that exposures to formaldehyde can increase the risk of lung cancer should not be totally excluded.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DISCLOSURE BY AJIM EDITOR OF RECORD

John D. Meyer declares that he has no conflict of interest in the review and publication decision regarding this article.

AUTHOR CONTRIBUTIONS

DP and J-TP conceived and designed the concept of the systematic review. KK searched and selected the articles, extracted data, and drafted the manuscript. All authors contributed to conduct statistical analyses and interpret the results. All authors reviewed the manuscript and approved the version to be submitted for publication. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or

integrity of any part of the work are appropriately investigated and resolved.

ETHICS APPROVAL AND INFORMED CONSENT

Ethics review/approval and informed consent were not required for a systematic review/meta-analysis.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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