Original Article

Benzene exposure increases the risk of non-Hodgkin's lymphoma: a systematic review and meta-analysis of observational studies

Yang Liu[1], Jingxin Wang[2]

[1]Department of Hematology, The First Hospital of China Medical University, Shenyang, China; [2]Department of Otolaryngology, The First Hospital of China Medical University, Shenyang, China

Contributions: (I) Conception and design: Y Liu; (II) Administrative support: J Wang; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Jingxin Wang. Department of Otolaryngology, The First Hospital of China Medical University, No. 155, Nanjing North Street, Shenyang 110001, China. Email: wjxin870418@163.com.

Background: Although there is sufficient evidence that benzene exposure increases the risk of leukemia, whether benzene exposure increases the risk of non-Hodgkin's lymphoma (NHL) remains controversial. The method of meta-analysis can reduce the uncertainty in evidence-based medicine (EBM) evidence decision-making caused by the bias between studies by systematically searching, evaluating, and combining all relevant literatures.

Methods: PubMed, Embase, ScienceDirect and other databases were searched according to the population exposure comparison outcome principles: whether the general population exposed to benzene has a higher risk of developing NHL than the population without benzene exposure. Two independent researchers extracted the main endpoint indicators from the included literature, including the odds ratio (OR) or relative risk (RR) of benzene exposure to the risk of NHL. Risk of bias was assessed for each study using the Newcastle-Ottawa scale (NOS). Heterogeneity between studies was evaluated using the Cochrane Q test and I^2 statistics, and combined risk estimates were calculated with the random-effects and fixed-effect models. Meanwhile, source of heterogeneity was evaluated by subgroup analysis. Publication bias was evaluated by funnel plot and Egger's test, and the stability of results was evaluated by sensitivity analysis. All results with $P<0.05$ were considered statistically significant.

Results: A total of 14 articles were included in this study for meta-analysis, including 9 cohort studies and 5 case-control studies with NOS scores between 5 and 9. Four of the articles were at low risk of bias, and 10 were at moderate risk of bias. Of 492,719 people with benzene exposure, there were 1,994 cases of NHL. The OR of NHL in the benzene-exposed population compared with nonexposed population was 1.23 ($P=0.03$), with moderate heterogeneity ($I^2=63.47\%$). People with high exposure to benzene showed a higher risk of NHL (OR =1.81) and there was a low degree of heterogeneity ($I^2=27.56\%$). The risk of benzene exposure in China (OR =2.48) was higher than that in Europe (OR =1.19), the United Kingdom (OR =1.07), and the United States (OR =1.24).

Conclusions: Benzene exposure was positively correlated with the incidence of NHL.

Keywords: Benzene; non-Hodgkin's lymphoma (NHL); causality; meta-analysis

Introduction

Non-Hodgkin's lymphoma (NHL), which includes more than 60 subtypes, is a group of malignant hematological tumors originating from lymphoid tissue (1). Due to heterogeneity between the different subtypes, diagnosis and clinical classification of NHL is very challenging, making evaluation of its epidemiological characteristics even more difficult. Although the exact pathogenesis of most NHL subtypes is not clear, many epidemiological studies have shown that the known risk factors of NHL include genetic differences, viral infection [such as human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), human T-lymphotropic virus type I (HTLV-1), hepatitis C virus (HCV), and Kaposi's sarcoma-associated herpesvirus (KSHV)], autoimmune regulatory factors (use of immunosuppressants, congenital immunodeficiency, and acquired immunodeficiency), lifestyle habits (smoking and alcohol use), and exposure to certain occupational and environmental factors (hair dyes, oil refining workers, etc.) (2,3). Benzene is listed as a carcinogen by the International Agency for Research on Cancer (IARC) because it directly leads to an increased risk of acute myeloid leukemia (4). In addition, benzene has developmental, neurological, and hepatocyte toxicity. However, due to its simple aromatic structure and the high activity of its metabolites, benzene plays a vital role in the chemical manufacturing industry. It is indispensable in producing key chemicals used in the synthesis of plastics, resins, and other fibers (5). In addition, the ubiquitous presence of benzene in the industry makes its exposure inevitable, while its important economic status has made the relationship between disease and benzene exposure controversial. Previous observational studies have been controversial as to whether benzene exposure increases the risk of NHL. For example, Schumacher *et al.*, Collins *et al.*, Rinsky *et al.* (6-8) believe that benzene exposure does not increase the risk of NHL, while other studies (9,10) believe that benzene exposure is positively related to the risk of NHL. The method of meta-analysis, by systematically searching, evaluating, and merging all relevant literature, can expand the observed sample size, integrate studies in different regions, and make the research results more general. And the meta-analysis reduces the uncertainty in the decision-making of evidence-based medicine caused by the bias between the studies. Therefore, this study aimed to retrieve observational studies that quantitatively evaluated NHL and benzene exposure in order to provide evidence-based medical data for the prevention of NHL. We present the

following article in accordance with the MOOSE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1434/rc).

Methods

Literature search

This study used medical subject headings (MeSH) search words in English databases such as PubMed, Embase, Sciencedirect and other Chinese databases such as Wanfang Database and China National Knowledge Infrastructure (CNKI) for literature retrieval. The included articles were published before 2022. The search keywords were: ("benzene" [MeSH Terms] OR "benzidine" [tiab] OR "petrochemical") AND ("lymphoma, non-Hodgkin" [MeSH Terms] OR "Chronic lymphocytic leukemia").

Literature screening

The literature inclusion criteria were: (I) peer-reviewed cohort studies and case-control studies that reported the relative risk (RR) or odds ratio (OR) of benzene exposure to the risk of NHL; (II) The study population was benzene exposed population, and the control population was non-benzene exposed population (III) literature that directly provided the mean and standard deviation or 95% confidence interval (CI) of the risk estimate or could be calculated; (IV) bias and confounding were adjusted and controlled by a multifactor model, and the results had good reliability; and (V) studies with benzene exposure duration, cumulative exposure concentration, or maximum exposure concentration as observation factors.

The literature exclusion criteria were: (I) study populations limited to a particular group, such as a specific occupation or patient group; (II) studies that did not distinguish NHL from other tumor disease types in reported risk estimates; (III) overlapping observation populations between studies, studies with high risk of bias, and studies published previously; and (IV) reviews, academic conferences, and case reports. A total of 14 studies were ultimately included for meta-analysis.

Document data sorting and evaluation

Two researchers independently screened and extracted the following data from the included literature: study design type (cohort, case-control), country or region where the study population was located, number of included

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observers, measurement method and level of exposure, the estimated value of risk [OR, RR or hazard ratio (HR)], and statistical methods for adjusting confounding or bias. NOS was used to evaluate the methodological quality of the included literature. Literature with a score of less than 5 was considered to be at high risk of bias, 5–8 was considered to be at moderate risk of bias, and literature with a score of 8 or more was considered to be at low risk of bias. If there was disagreement between the 2 researchers, discussion was held with a third researcher to reach a consensus (11).

Statistical methods

STATA 17.0 (Texas, USA) was used in this study for statistical analysis of the data. Since the main clinical indicators observed in this study were continuous variables, they are expressed in the form of mean ± standard deviation. A random-effects model can combine interstudy variance into a total variance estimation and CI to avoid a reduction of the CI caused by a fixed-effect model. However, the random-effects model also has the disadvantage of giving a larger proportion of consolidation to studies with a smaller sample size, and thus the combined estimation is too conservative (12-14). Therefore, we integrated all studies using both random-effects and fixed-effects models, and then pooled risk estimates OR from case-control studies and RR from cohort studies separately (subgroup analysis by study type). Heterogeneity between studies was evaluated using Cochran's Q test (15,16). If there was significant heterogeneity between studies ($I^2 > 50\%$), the random-effects model was used. Otherwise, the fixed-effect model was used. Publication bias was evaluated by funnel plot and Egger's and Begg's tests (17). Hypothesis tests in this study were all two-sided tests. P<0.05 was considered statistically significant.

Results

Search results and literature characteristics

Through a systematic electronic database search, 224 relevant studies were retrieved, of which 14 met the criteria for inclusion in the meta-analysis. A PRISMA flow chart of the literature screening process is shown in *Figure 1*. The characteristics of the included literature were shown in *Table 1*. The included literature comprised observational studies, including 9 cohort studies and 5 case-control studies. A total of 1,994 cases of NHL were observed

in the 14 studies, which included 492,719 participants. The observation population of 5 studies was considered to have high exposure to benzene (annual average exposure concentration ≥25 ppm or cumulative exposure concentration ≥720 ppm). The other 9 studies involved low to severe exposure levels. In addition, the observation populations came mainly from the United States (n=6), Britain (n=3), China (n=2), Norway (n=1), and Italy (n=2). The NOS scores of the 14 included studies ranged from 5 to 9, of which 4 had low risk of bias and 10 had moderate risk of bias.

Combined effect of benzene exposure on the risk of NHL

All 14 studies quantified the increased risk of observed outcomes in people exposed to benzene relative to people without benzene exposure, using NHL as the endpoint. The risk estimates in 14 studies were meta-analyzed using the random-effects model and fixed-effect model. Both statistical models showed that benzene exposure increased the risk of NHL. As shown in *Figures 2,3*, the random-effects model demonstrated that the risk of NHL in the exposed population was 1.23 times higher than that in the nonexposed population (OR =1.23, 95% CI: 1.01, 1.51, P=0.03). The combined risk estimate of the random-effects model was higher than that of the fixed-effect model, which found that the risk of lymphoma in the exposed population increased by only 41% compared with the nonexposed population (RR =1.41, 95% CI: 1.31, 1.52, P=0.00). Both models showed some heterogeneity between the included studies, with $I^2 = 63.47\%$ in the random-effects model and $I^2 = 71.12\%$ in the fixed-effect model, although the difference was not statistically significant. As a result, we conducted subgroup analysis to explore the possible sources of heterogeneity to provide further basis for the inclusion of more homogeneous literature in the future.

Subgroup analysis and sensitivity analysis

Subgroup analysis was carried out for different study regions, study design types, and exposure levels of benzene. The forest maps are shown in *Figures 4-6*. Overall, subgroup analysis showed that the exposure level of benzene (Q=11.40, P≤0.001) and the region of the study population (Q=5.58, P=0.13) were the main sources of heterogeneity, while no significant difference was found for study design type (Q=2.28, P=0.13). The Meta-OR of the case-control
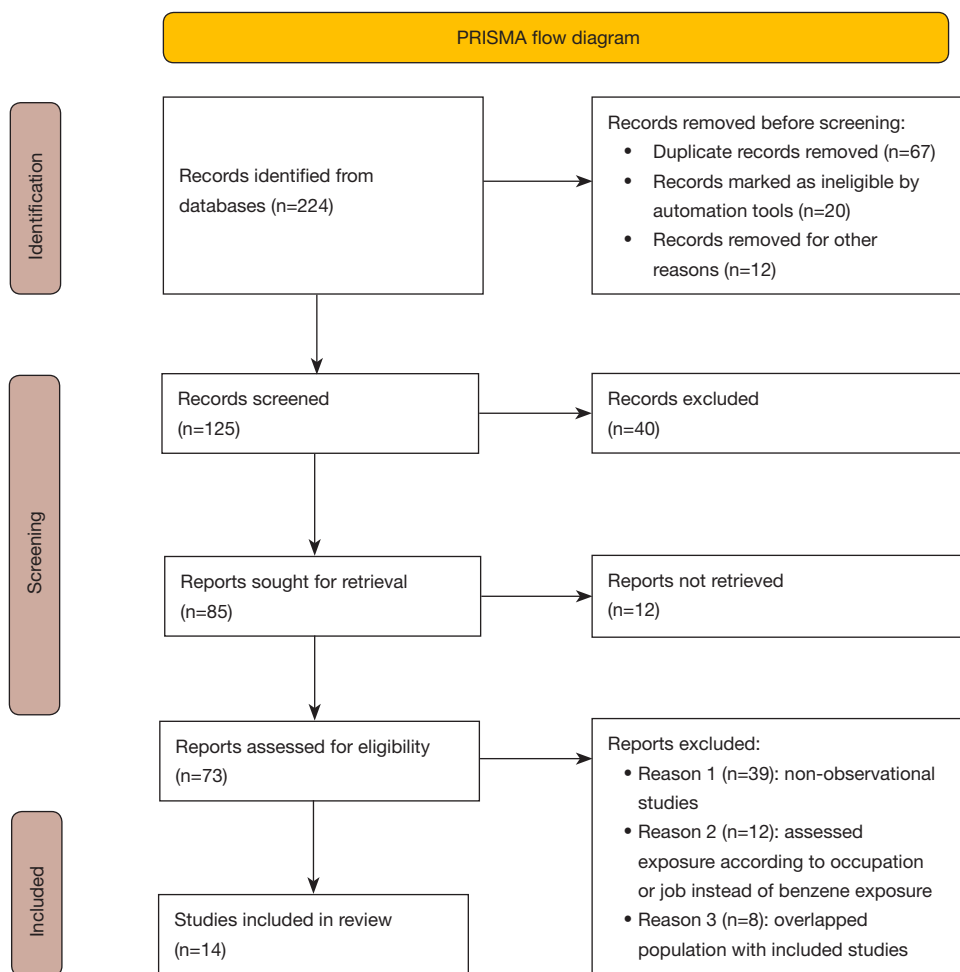
Figure 1 PRISMA flow chart of literature screening process.

study subgroup: 1.06 (95% CI: 0.84, 1.32), and the Meta-RR of the cohort study subgroup: 1.39 (95% CI: 1.06, 1.81). Subgroup analysis of exposure levels showed that the risk of NHL increased by 0.81 times in people with high benzene exposure compared with those without exposure (OR =1.81, 95% CI: 1.34, 2.43), and the heterogeneity was very low (I^2=27.56%). The risk estimates of the low and medium exposure groups were closer to the total combined estimates (OR =1.03, 95%: 0.90, 1.18, I^2=7.89%). Risk estimates from studies based on the Chinese population (OR =2.48, 95% CI: 1.24, 4.94) were greater than those based on the populations of Europe (OR =1.19, 95% CI: 0.89, 1.59), the United Kingdom (OR =1.07, 95% CI: 0.92, 1.26), and the United States (OR =1.24, 95% CI: 0.80, 1.92). Regional differences may be due to the stricter control of occupational benzene exposure in developed countries (the United States has an average of 1 ppm every 8 hours,

while China had 12 ppm in 1979–2002 and has had 2 ppm since 2002) (27).

To evaluate the impact of each included study on meta-analysis, we conducted sensitivity analysis and excluded 12 studies one at a time, with the results remaining consistent. As shown in *Figure 7*, the overall range of OR values of sensitivity analysis was 1.15–1.30. The upper and lower limits were the risk estimates after excluding the studies of Switchenko *et al.* (10) and Schumacher *et al.* (6) Overall, robust sensitivity analysis showed that our results were reliable.

Publication bias

The funnel chart (*Figure 8*) describing the overall symmetrical distribution of each study was in the shape of an inverted funnel. Within the 95% CI, Egger's test (*t*=1.55,

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Table 1 Characteristics of the included literature

Author [year]	RR/OR (95% CI)	Study location	Cases of non-Hodgkin's lymphoma	Study design	Exposure level	NOS	Exposure level
Hayes et al. [1996] (18)	4.7 (1.2–18.1)	China	7/19	Cohort	Higher than 25 ppm/year for average intensity	7	High
Stenehjem et al. [2015] (19)	1.55 (0.83–2.88)	Norway	20/85	Cohort	0.013–0.04 ppm for average intensity	8	Low to moderate
Sorahan et al. [2005] (20)	1.0 (0.64–1.49)	UK	24/75	Cohort	Ever	6	Low to moderate
Collins et al. [2015] (7)	0.53 (0.12–1.69)	Michigan, USA	3/15	Cohort	Cumulative ≥25 ppm per year	7	Low to moderate
Bassig et al. [2015] (9)	2.04 (1.08–3.86)	Shanghai, China	12/102	Cohort	Cumulative >102.4 mg/m^3 per year (10-year lag)	8	High
Cartwright et al. [1988] (21)	1.2 (0.9–1.5)	Yorkshire, UK	103/153	Case-control	Ever	6	Low to moderate
Franceschi et al. [1989] (22)	1.14 (0.57–2.28)	Italy	15/28	Case-control	Ever	8	Low to moderate
Blair et al. [1993] (23)	1.5 (0.7–3.1)	Iowa, Minnesota, USA	12/622	Case-control	High intensity	6	High
Ott et al. [1989] (24)	1.0 (0.83–1.33)	UK	5/29	Cohort	Low intensity	7	Low to moderate
Schumacher [1988] (6)	0.77 (0.56–1.07)	North Carolina, USA	56/522	Case-control	Ever	7	Low to moderate
Wong [1987] (25)	4.12 (1.11–10.55)	USA	4/15	Cohort	Cumulative ≥720 ppm (adjusted)	8	High
Rinsky et al. [2002] (8)	0.96 (0.31–2.25)	Ohio, USA	5/16	Cohort	Ever	5	Low to moderate
Fritschi et al. [2005] (26)	1.09 (0.75–1.59)	Italy	347/744	Case-control	Ever	7	Low to moderate
Switchenko et al. [2016] (10)	1.56 (1.44–1.68)	USA	9/257	Cohort	Ever	6	High

RR, relative risk; OR, odds ratio; CI, confidence interval; NOS, Newcastle-Ottawa Scale.

P=0.121) illustrated no significant publication bias in this meta-analysis.

Discussion

This meta-analysis provided new evidence-based medical data that benzene exposure increases the risk of NHL to some extent. Although there was no significant difference between the random-effects model and the fixed-effect model, the results of subgroup analysis and sensitivity analysis showed that there was still an epidemiological causal.

This study included 492,719 cases of observation, among which there were 1,994 cases of NHL. The incidence of NHL in this group was significantly higher than that in the general population reported by the literature. In a previous study, the incidence rate of NHL was 7.8 males/10,000 and 5.6 females/10,000 (28). The results of this study demonstrated a causal relationship between benzene exposure and the increased risk of NHL and was in line
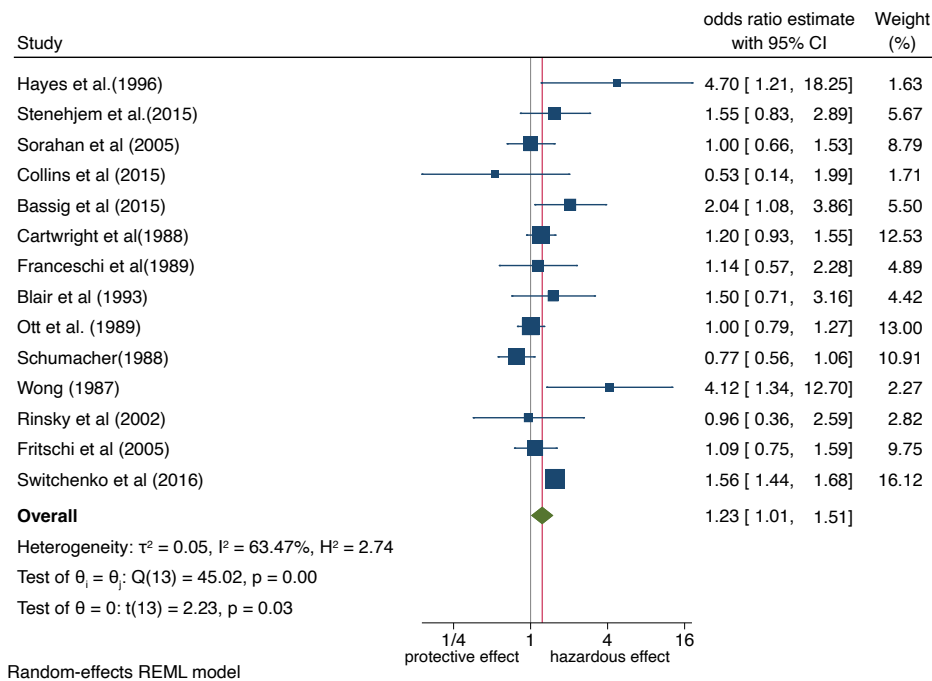
Figure 2 Random-effects model of risk estimate. CI, confidence interval; REML, restricted maximum likelihood.
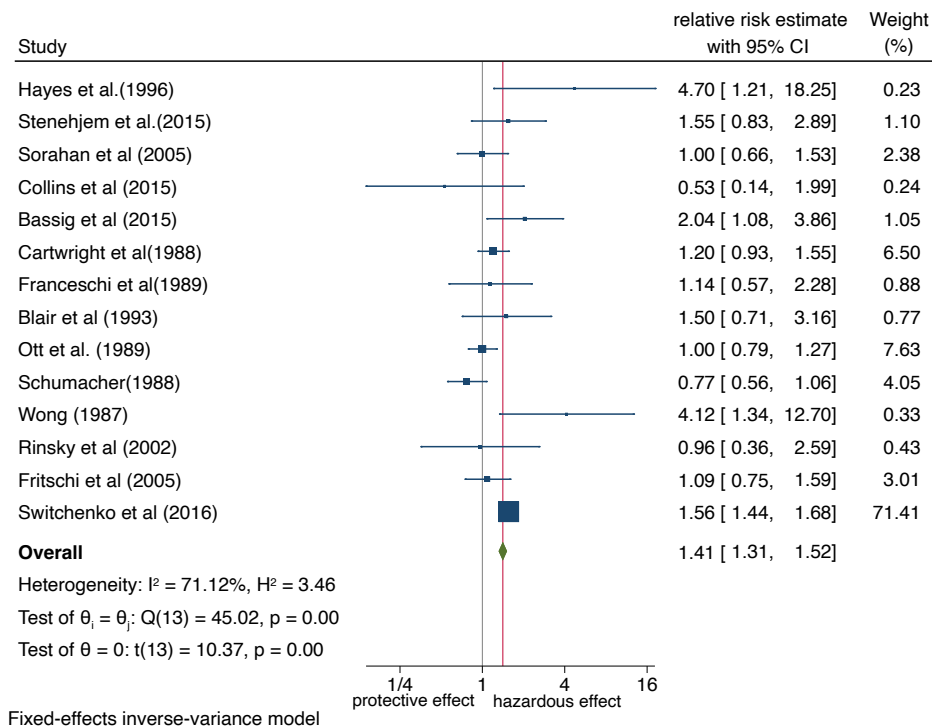

Figure 3 Fixed-effect model of risk estimate. CI, confidence interval.
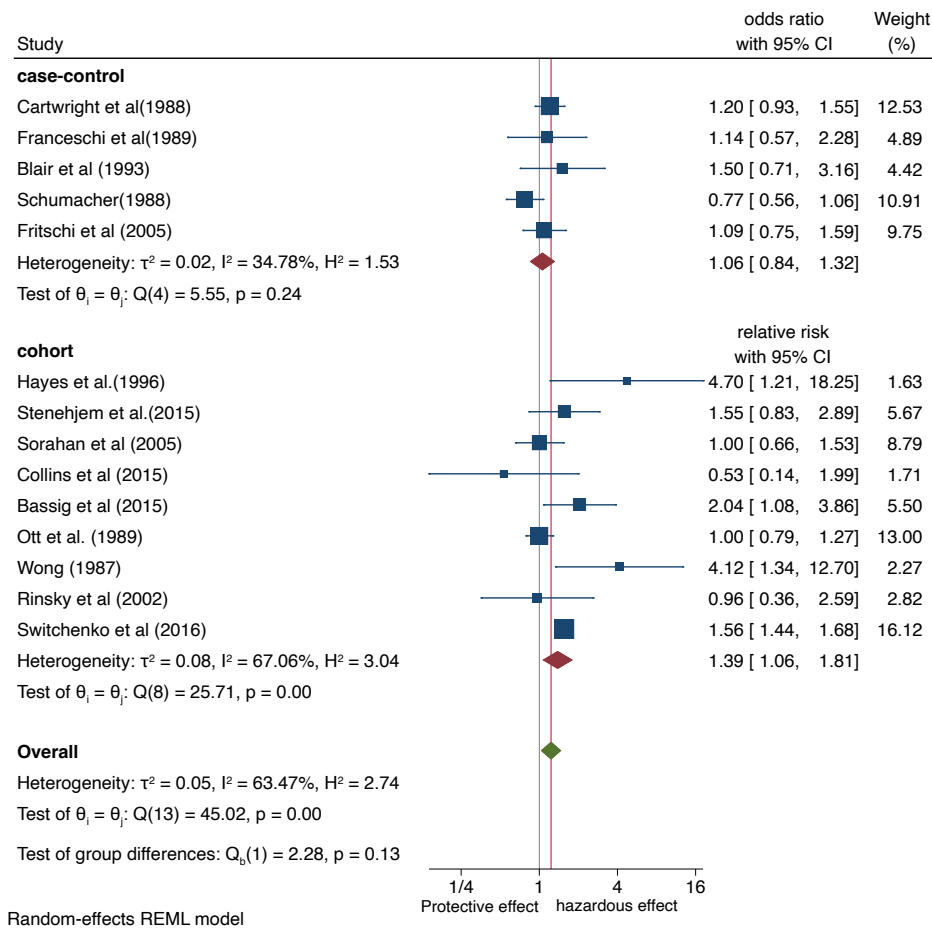
Figure 4 Subgroup analysis: case-control study/cohort study. CI, confidence interval; REML, restricted maximum likelihood.

with Bradford Hill criteria for establishing causal inference, to a certain extent (29). First, the fixed-effect model of meta-analysis showed that benzene exposure increased the risk of NHL by 10% (OR =1.41, 95% CI: 1.31, 1.52, P=0.00), while the random-effects model, with lower heterogeneity, revealed a value of 23% (OR =1.23, 95% CI: 1.01, 1.51, P=0.031). Second, correlation results showed consistency among cohort studies, case-control studies, different exposure levels, and different study regions. Third, in subgroup analysis, we found that the risk of NHL in people exposed to high-dose benzene was significantly higher than that in people exposed to low and medium-dose benzene (OR =1.81, 95% CI: 1.34, 2.43). Most of the included studies (n=9) were prospective cohort studies and showed that benzene exposure was related to the risk of NHL over time, and the results were statistically significant. A previous animal experiment also showed that benzene

exposure is associated with the risk of NHL (30). Fourth, the causal relationship between exposure and disease was exclusive and did not include other malignant hematological tumors such as Hodgkin's lymphoma.

The pathogenic mechanism of NHL is mainly related to immunosuppression and the presence of autoimmune disease. Many epidemiological and experimental studies have shown that chronic inhalation of benzene damages the human immune system by reducing the level of circulating B lymphocytes, blood immunoglobulin, T lymphocytes, and interleukin-2 (3,6,31). In addition, benzene mediates oxidative damage of related DNA and chromosomes by inducing oxidative responses such as reducing the level of serum glutathione, increasing lipid peroxide, reactive oxygen species, and oxidative protein damage, and decreasing the ability of antioxidants (32). In addition, studies have shown that benzene is genotoxic and can induce DNA damage
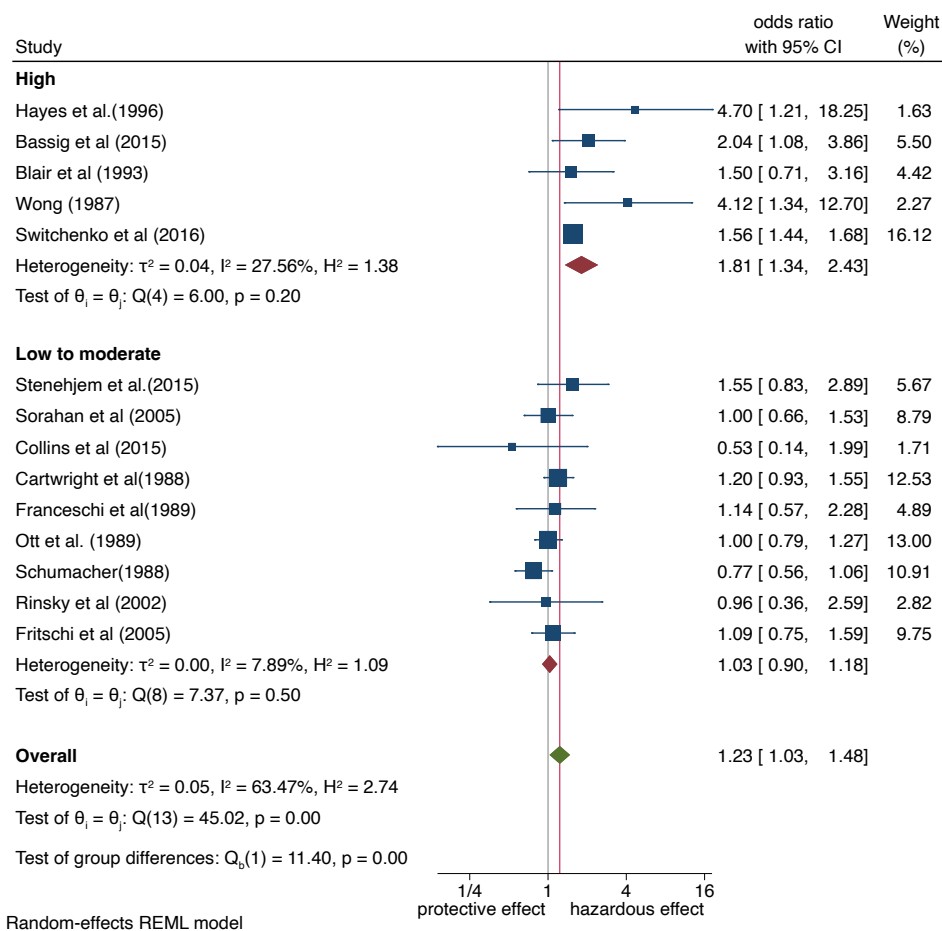
Figure 5 Subgroup analysis: exposure level: low to medium exposure/high exposure. CI, confidence interval; REML, restricted maximum likelihood.

and chromosome changes. Specific cytogenetic changes, including aneuploidy, chromosome translocation, and various other structural chromosome changes, have also been observed in people exposed to benzene (33-35).

All meta-analyses inevitably have limitations. This study did not review the incidence risk of benzene exposure in various subtypes of NHL. Further, this study did not include all literature that classified NHL. However, the diagnostic and typing criteria of NHL were revised in 2008. More importantly, bias in observational studies may mask causality between disease subtypes and benzene exposure. Most of the observational studies included in this study were published between 1987 and 2015. The World Health Organization revised the definition of lymphoma classification in 2008 and further divided lymphoma into T-cell and B-cell lymphoma by integrating clinical,

molecular, biological, and morphological evidence in 2014. These changes in the diagnostic criteria of NHL may have led to the misclassification of nondifferential observations, thus affecting the results of our meta-analysis. In addition, given the variability of chronic lymphoid leukemia, which is highly similar to lymphoma in clinical diagnosis, observational studies may underestimate the real risk estimate by minimizing the actual number of patients with NHL. There were 4 case-control studies included in this study. In such studies, exposure estimates are usually based on participant recall, with recall bias possibly leading to misclassification of exposure. However, the combined value of risk in subgroup analysis of cohort studies and case-control studies was comparable, which to some extent showed that study design was not a primary source of offset.

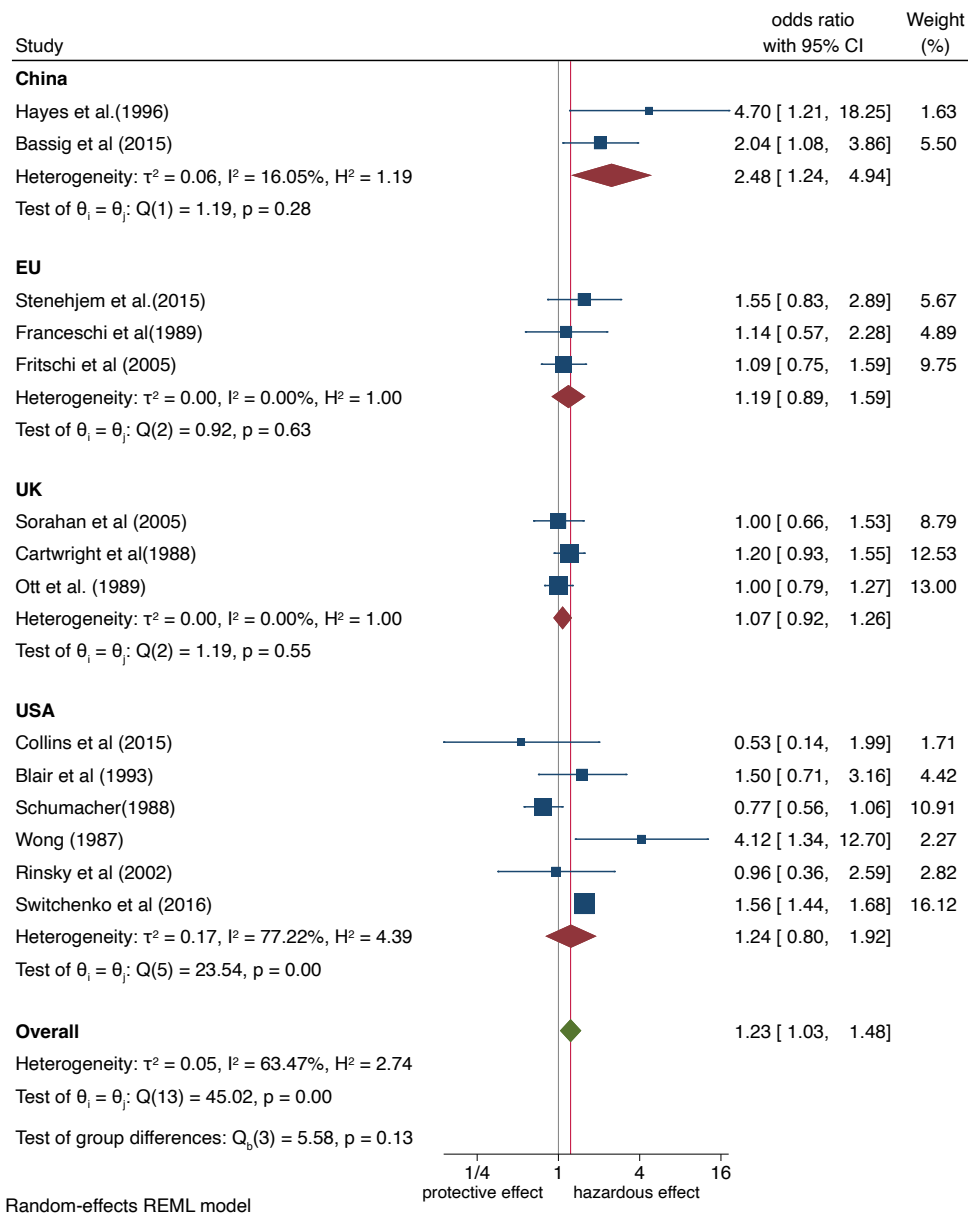In conclusion, the results of our study suggested that

Figure 6 Subgroup analysis for the regions of regions of the observed population: China, Europe, UK, and the United States. CI, confidence interval; REML, restricted maximum likelihood.
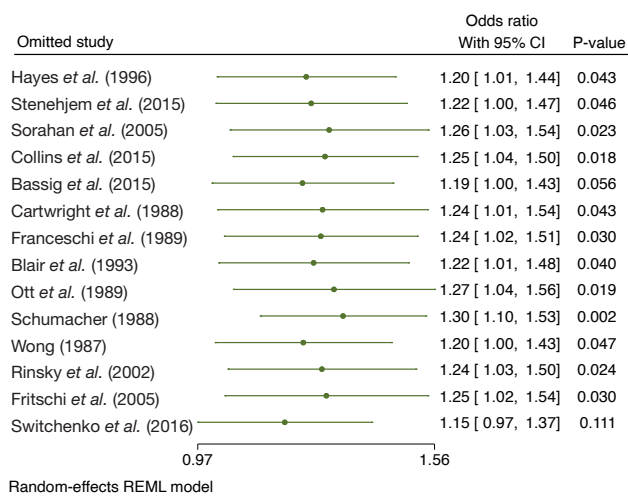
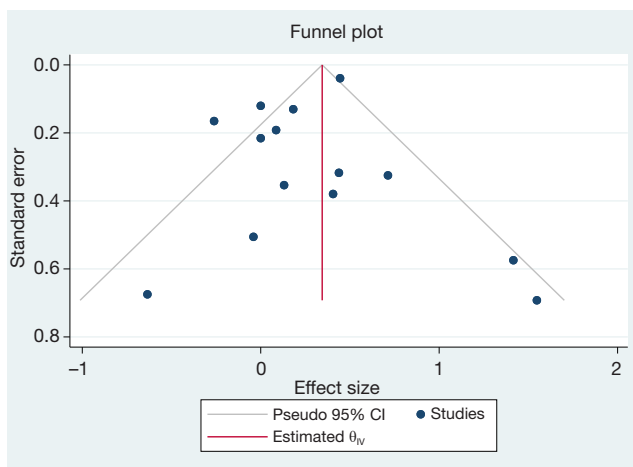**Figure 7** Sensitivity analysis. CI, confidence interval; REML, restricted maximum likelihood.

Figure 8 Funnel diagram of meta-analysis of the correlation between benzene exposure and non-Hodgkin's lymphoma. CI, confidence interval.

benzene exposure increased the risk of NHL. The results were statistically and biologically feasible and met most of the Bradford Hill criteria for causal inference.

Acknowledgments

Footnote

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