Received: 7 March 2020 | Revised: 15 May 2020 | Accepted: 18 May 2020

DOI: 10.1002/ajim.23142

RESEARCH ARTICLE

AMERICAN JOURNAL OF INDUSTRIAL MEDICINE WILEY

Benzene exposure-response and risk of lymphoid neoplasms in Chinese workers: A multicenter case-cohort study

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Funding information
Intramural Research Program of the National Institutes of Health, National Cancer Institute, and the U.S. Public Health Service of the Department of Health and Human Services

Abstract

Background: While international agreement supports a causal relationship of benzene exposure with acute myeloid leukemia, there is debate about benzene and lymphoid neoplasm risks.

Methods: In a case-cohort study with follow-up of 110 631 Chinese workers during 1972-1999, we evaluated benzene exposure-response for non-Hodgkin lymphoma (NHL), lymphoid leukemias (LL), acute lymphocytic leukemia (ALL), and total lymphoid neoplasms (LN). We estimated benzene exposures using state-of-the-art hierarchical modeling of occupational factors calibrated with historical routine measurements and evaluated cumulative exposure-response using Cox regression.

Results: NHL and other specified LN were increased in exposed vs unexposed workers. However, there was no evidence of exposure-response for NHL or other specified LN. Based on a linear exposure-response, relative risks at 100 parts per million-years (RR at 100 ppm-years) for cumulative benzene exposure using a 2-year lag (exposure at least 2 years before the time at risk) were 1.05 for NHL (95 percent confidence interval (CI) = 0.97, 1.27; 32 cases), 1.11 for LL (95% CI < 0, 1.66; 12 cases), 1.21 for ALL (95% CI < 0, 3.53; 10 cases), and 1.02 for total LN (95% CI < 0, 1.16; 49 cases). No statistically significant exposure-response trends were apparent for these LN for 2 to <10-year or ≥10-year lags. NHL risks were not significantly modified by sex, age, or year at first exposure, attained age, or time since exposure.

Conclusion: Given the study strengths and limitations, we found little evidence of exposure-response for benzene and NHL, LL, ALL, or total LN, although NHL and other specified LN were increased in exposed vs unexposed individuals.

KEYWORDS

benzene, case-cohort study, leukemia, lymphoid, non-Hodgkin lymphoma, occupational exposure

Abbreviations: ALL, acute lymphocytic leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; ERR, excess rate ratio; ICD-9, International Classification of Diseases, 9th revision; LL, lymphoid leukemias; LN, lymphoid neoplasms; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; ppm, parts per million; RR, rate ratio.

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1 | INTRODUCTION

Worldwide, occupational benzene exposures are present in multiple industries including chemical manufacturing, oil refining, petrochemical transport and vehicle repair, affecting an estimated 2 million workers.[1] Notable declines in workplace benzene exposures have been documented in the United States (up to 100-fold reduction since the early 1940s)[2] and in China (13-fold reduction between 1965 and 2000),[3] but low-level occupational exposures persist. In addition, throughout the world, the general population is widely exposed to low-level environmental benzene from tobacco smoke, vehicle exhaust, gasoline stations, and contaminated water and food.[1]

Although there has been international agreement since 1979 that benzene exposure is causally related to acute myeloid leukemia (AML) and likely, albeit more recently, to myelodysplastic syndromes,[4,5] there has been long-standing debate about whether benzene is associated with risk of lymphoid neoplasms (LN). A recent International Agency for Research on Cancer (IARC) Working Group noted that evidence continues to be limited for the relationship of benzene exposure with non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), and multiple myeloma (MM).[1] A meta-analysis of LN concluded that there was support for an association between occupational benzene exposure and risk of ALL, CLL, and MM, but the evidence of an association with NHL was less clear.[6] Mechanistic studies reported by our team have shown an exposure-response relationship with benzene and reduction in CD4+ T cells, a marker of relevance for NHL,[7] and investigators in our group and others have shown that benzene causes immune toxicity and chromosomal aberrations in peripheral lymphocytes, markers also linked with NHL (reviewed in Refs. 1,8).

We previously reported a possible link between benzene and NHL incidence in a large cohort of workers employed and followed up between 1972 and 1987 in 12 cities in China[4] and, more recently, reported extended follow-up of these workers through 1999 for cancer mortality.[9] In the 1972-1999 cohort follow-up, we compared cancer and other causes of mortality and hematopoietic malignancy incidence and mortality risks in benzene-exposed vs unexposed workers. We evaluated risks of these outcomes according to age at first exposure, year of first exposure, industry of employment and demographic factors, but did not consider estimated benzene exposure levels or quantify the dose-response.[9] We sought to add to the limited literature on estimated level of occupational benzene exposure and risk of LN by identification of incident LN through 1999 (up to 28 years of follow-up) in this cohort, including re-evaluation of previously identified cases. To assess efficiently the exposure-response for LN as a function of cumulative exposure, we used the case-cohort study design and applied our state-of-the-art exposure assessment that included a validation component.[10]

2 | MATERIALS AND METHODS

2.1 | Study population and design

The case-cohort population was derived from the large cohort of factory workers employed in 712 factories in multiple industries that were exposed (N = 74 827 workers) and unexposed to benzene (N = 35 804 workers) in 12 cities in China. The case-cohort design was used to enable the collection of more comprehensive exposure data for each worker than would have been possible for each member of the entire large cohort. The cohort, which included workers employed at least 1 month in study factories during 1972-1987, was originally identified retrospectively in 1987-1988 from initial employment, salary, and other factory records. We reviewed factory records to determine exposure status based on information about jobs held, industrial processes, use of benzene-containing materials, and benzene and other occupational exposure measurements. Ascertainment of health outcomes was facilitated by the organization of the health care system, which was integrated with the workplace for employed and retired factory workers in China. Diagnostic and treatment visits took place in health care clinics located in the workplace or in other clinical settings that reported back to the workplace.[11] The entire cohort was initially followed up for cancer and all other mortality outcomes and hematopoietic malignancy incidence and mortality risks during 1972-1987.[4,11] An extended retrospective follow-up of the same cohort for the period 1988-1999 was undertaken during 1999-2000.[9] Additional approaches were needed for the extended follow-up (1988-1999) due to study factory mergers and closings and changes in health care delivery during the 1990s. Among the strategies that were utilized for factories that merged or closed as well as for factories that remained open, we sought and located personnel and health records to provide updated information about current and recent workplace of employment, residences, health information, vital status, and death information for current, retired, and deceased workers. Throughout the initial and extended follow-up periods, we identified referral hospitals and obtained additional information about diagnosis and treatment for suspected LN cases. These strategies were the only feasible methods for ascertainment of LN outcomes in the absence of long-standing, nationwide, comprehensive population-based mortality, and cancer registries to which the cohort members could have been linked.

For the current case-cohort study, cases included all incident and deceased NHL, CLL, ALL, MM, and cases with other LN diagnosed during 1972-1999 among exposed and unexposed workers. In 2002 we selected from 106 641 cohort members a subcohort of 1500 workers (including 1100 from exposed workers and 400 from unexposed workers) (Table 1). The rationale for the size of the subcohort, the proportion selected from each exposure group, and the sex and age at the start of follow-up distribution of the subcohort was based on the number of cases and the demographic characteristics of the individuals with one of the three outcomes (hematopoietic malignancies, benzene

TABLE 1 Demographic and work history characteristics of cases and subcohort members in the case-cohort population developing lymphoid neoplasms in benzene-exposed and unexposed workers followed up during 1972-1999[a]

Characteristic	Non-Hodgkin lymphoma Number (%)	Lymphoid leukemias Number (%)	Acute lymphocytic leukemia Number (%)	Total lymphoid neoplasms Number (%)	Subcohort Number (%)
Total	32 (100)	12 (100)	10 (100)	49 (100)	1500 (100)
Stratification variables for case-cohort design					
Exposure status					
Exposed	28 (87.5)	10 (83.3)	8 (80.0)	40 (81.6)	1100 (73.3)
Unexposed	4 (12.5)	2 (16.7)	2 (20.0)	9 (18.4)	400 (26.7)
Sex					
Males	20 (62.5)	7 (58.3)	6 (60.0)	30 (61.2)	837 (55.8)
Females	12 (37.5)	5 (41.7)	4 (40.0)	19 (38.8)	663 (44.2)
Age at entry, y					
14-19	5 (15.6)	3 (25.0)	3 (30.0)	9 (18.4)	226 (15.1)
20-24	3 (9.4)	0 (0.0)	0 (0.0)	3 (6.1)	269 (17.9)
25-34	7 (21.9)	5 (41.7)	5 (50.0)	12 (24.5)	367 (24.5)
35-44	10 (31.3)	3 (25.0)	2 (20.0)	15 (30.6)	307 (20.5)
45-54	5 (15.6)	1 (8.3)	0 (0.0)	8 (16.3)	239 (15.9)
55-64	2 (6.3)	0 (0.0)	0 (0.0)	2(4.1)	92 (6.1)
Age at entry, y (males)					
14-19	1 (5.0)	3 (42.9)	3 (50.0)	5 (16.7)	107 (12.8)
20-24	1 (5.0)	0 (0.0)	0 (0.0)	1 (3.3)	131 (15.7)
25-34	4 (20.0)	2 (28.6)	2 (33.0)	6 (20.0)	158 (18.9)
35-44	7 (35.0)	1 (14.3)	1 (16.9)	9 (30.0)	185 (22.1)
45-54	5 (25.0)	1 (14.3)	0 (0.0)	7 (23.3)	202 (24.1)
55-64	2 (10.0)	0 (0.0)	0 (0.0)	2 (6.7)	54 (6.5)
Age at entry, y (females)					
14-19	4 (33.3)	0 (0.0)	0 (0.0)	4 (21.1)	119 (17.9)
20-24	2 (16.7)	0 (0.0)	0 (0.0)	2 (10.5)	138 (20.8)
25-34	3 (25.0)	3 (60.0)	3 (75.0)	6 (31.6)	209 (31.5)
35-44	3 (25.0)	2 (40.0)	1 (25.0)	6 (31.6)	122 (18.4)
45-54	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	37 (5.6)
55-64	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	38 (5.7)
Other variables					
Birth cohort					
<1920	3 (9.4)	0 (0.0)	0 (0.0)	4 (8.2)	132 (8.8)
1920-1929	7 (21.9)	1 (8.3)	0 (0.0)	9 (18.4)	225 (15.0)
1930-1939	8 (25.0)	3 (25.0)	3 (30.0)	13 (26.5)	292 (19.5)
1940-1949	7 (21.9)	4 (33.3)	3 (30.0)	11 (22.4)	265 (17.7)
1950-1959	4 (12.5)	2 (16.7)	2 (20.0)	6 (12.2)	372 (24.8)
≥1960	3 (9.4)	2 (16.7)	2 (20.0)	6 (12.2)	214 (14.3)
City					
Shanghai	9 (28.1)	1 (8.3)	1 (10.0)	13 (26.5)	281 (18.7)
Tianjin	7 (21 9)	1 (8.3)	1 (10.0)	9 (18.4)	204 (13.6)
Chengdu	1 (3.1)	2 (16.7)	2 (20.0)	4 (8.2)	166 (11.1)
Chongqing	1 (3.1)	3 (25.0)	1 (10.0)	4 (8.2)	180 (12.0)
Harbin	3 (9.4)	0 (0.0)	0 (0.0)	3 (6.1)	169 (11.3)
Shenyang	2 (6.3)	2 (16.7)	2 (20.0)	4 (8.2)	140 (9.3)
Jinzhou	1 (3.1)	0 (0.0)	0 (0.0)	1 (2.0)	62 (4.1)
Zhengzhou	2 (6.3)	0 (0.0)	0 (0.0)	2 (4.1)	70 (4.7)
Luoyang	0 (0.0)	1 (8.3)	1 (10.0)	1 (2.0)	22 (1.5)
Guangzhou	1 (3.1)	0 (0.0)	0 (0.0)	1 (2.0)	57 (3.8)

(Continues)

TABLE 1 (Continued)

Characteristic	Non-Hodgkin lymphoma Number (%)	Lymphoid leukemias Number (%)	Acute lymphocytic leukemia Number (%)	Total lymphoid neoplasms Number (%)	Subcohort Number (%)
Nanchang	5 (15.6)	2 (16.7)	2 (20.0)	7 (14.3)	111 (7.4)
Kaifeng	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	38 (2.5)
Age, y, at first exposure/hire in study factories					
<20	13 (40.6)	5 (41.7)	5 (50.0)	19 (38.8)	362 (24.1)
20-29	7 (21.9)	4 (33.3)	4 (40.0)	13 (26.5)	603 (40.1)
30-39	7 (21.9)	2 (16.7)	1 (10.0)	10 (20.4)	307 (20.5)
≥40	5 (15.6)	1 (8.3)	0 (0.0)	7 (14.3)	228 (15.2)
Year of first exposure/hire in study					
≤1949	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	31 (2.1)
1950-1959	10 (31.3)	4 (33.3)	4 (40.0)	17 (34.7)	304 (20.3)
1960-1971	14 (43.8)	3 (25.0)	3 (30.0)	18 (36.7)	411 (27.4)
1972-1979	4 (12.5)	3 (25.0)	1 (10.0)	7 (14.3)	356 (23.7)
1980-1987	4 (12.5)	2 (16.9)	2 (20.0)	7 (14.3)	398 (26.5)
Industry					
Unexposed	4 (12.5)	2 (16.9)	2 (20.0)	9 (18.4)	400 (26.7)
Exposed					
Coatings	7 (21.9)	5 (41.7)	4 (40.0)	13 (26.5)	542 (36.1)
Rubber	1 (3.1)	0 (0.0)	0 (0.0)	1 (2.0)	54 (3.6)
Chemical	9 (28.1)	2 (16.7)	2 (20.0)	12 (24.5)	145 (9.7)
Shoe	4 (12.5)	2 (16.7)	1 (10.0)	6 (12.2)	133 (8.9)
Other/mixed	7 (21.9)	1 (8.3)	1 (10.0)	8 (16.3)	226 (15.1)
Year of lymphoid neoplasm diagnosis					
1972-1976	5 (15.6)	1 (8.3)	1 (10.0)	6 (12.2)	N/A
1977-1979	3 (9.3)	3 (25.0)	3 (30.0)	7 (14.3)	N/A
1980-1987	16 (50.0)	2 (16.9)	2 (20.0)	20 (40.8)	N/A
1988-1999	8 (25.0)	6 (50.0)	4 (40.0)	16 (32.7)	N/A

Abbreviation: N/A, not applicable.
[a]Refer to text for definition of entities included in each lymphoid neoplasm category.

poisoning [benzene hematotoxicity], and lung cancer). Among the benzene-exposed and unexposed cohort workers, we used random sampling to select the number of workers targeted in each sex and age at cohort entry subgroup to select the subcohort.

2.2 | Exposure assessment

Factory records were the primary source for historical benzene, toluene, and xylene air measurements and associated data, production processes, and job histories, as described elsewhere[10] and in Supporting Information Methods. Questionnaires administered to subjects or next of kin were used to identify jobs held outside the cohort study factories. For the case-cohort study, information was compiled on a complete list of jobs held by each worker. Local exposure assessment experts filled out a standardized questionnaire for each workshop to collect information on potential exposure determinants associated with jobs held by the workers. This questionnaire included questions on source of materials used, tasks performed, and the presence and efficiency of industrial hygiene measures for nine different time periods.

To estimate individual monthly benzene, toluene, and xylene exposures, a Bayesian hierarchical model was built from the historic monitoring and other workplace data. This model allowed for clustering of measurements by factory, workshop, job, and date (month).[10] The exposure assessors were blinded to individual study participant case-subcohort status and their individual work histories. For jobs held outside of study cohort factories, two members of the exposure assessment team coded the jobs. The jobs were linked to the exposure prediction model by imputing exposures from similar job titles within cohort factories in the same city. We previously estimated that only 2.4% of benzene occupational exposures of cohort members were received from jobs held outside the cohort factories.[12] A study-specific job-exposure matrix was also developed that included monthly indicators for other exposures linked with LN (eg, chlorinated solvents, formaldehyde, butadiene, and asbestos). A 2004-2005 survey of a sample of study factories (N = 51 and including 98 jobs) revealed moderate correlation of the statistical model with full-shift personal

measurements, albeit with potential underestimation and limited validity of the predictive model for benzene exposure estimates in the range below 3 ppm.[10] See Supporting Information Methods for additional detail.

2.3 | Case definition and validation of LN

Physicians, blinded to exposure status, extracted data from all medical records, including pathology (with review of pathology slides, if available), laboratory, and death reports, on to standardized forms. Expert hematopathologists reviewed the extracted data to ascertain and confirm diagnoses of LN, as described elsewhere.[9,13,14] We coded the LN using a modified ICD-9 (nternational Classification of Diseases, 9th revision) code.[15] We evaluated four outcome categories: NHL (N = 32), lymphoid leukemia ([LL] comprised of ALL and CLL; N = 12), ALL (N = 10), and total LN (N = 49). There were too few cases of CLL (N = 2, both exposed), MM (N = 1, exposed; N = 3, unexposed), or Hodgkin lymphoma (N = 1, exposed; N = 1, unexposed) for separate analysis. We also considered disease categories as defined by the World Health Organization, for example, including CLL within the category of NHL. We evaluated NHL (with and without CLL) and LL (CLL and ALL) as separate groups to allow comparison with prior studies.

2.4 | Statistical analysis

Cox proportional hazards regression,[16] with age at risk of LN (attained age) as the time-scale, was used to estimate hazard rate ratios (RRs), using Epicure,[17] adapted to the case-cohort design by weighting the likelihood function by the inverses of the sampling fractions. For subcohort members, the follow-up period began at the beginning of 1972 or 1 month following the first exposure date (hire date for unexposed workers), whichever occurred later, and ended on the date of LN diagnosis, date of death, date lost to follow-up, or the end of 1999, whichever occurred earliest. For cases that were not part of the subcohort, workers entered into the analyses just before their LN diagnoses. Analyses were adjusted for sex through stratification and for calendar year by including the RR for 1988-1999 compared to 1972-1987 as a parameter; the calendar-year adjustment was motivated by lower rates for LN in 1988-1999 than during 1972-1987 for the reasons indicated above.[9] We estimated the RR for each of several exposure categories. Test for trend was based on a model in which exposure was treated as a continuous variable and in which the RR was expressed as a linear function of exposure, $RR = 1 + \beta z$, where βz is the excess rate ratio (ERR = RR−1) at exposure z, z is a continuous measure of exposure (cumulative exposure in ppm-years or average intensity in ppm) and β is the ERR expressed per unit of exposure.[18] Because readers may be more familiar with RR than ERR, we frequently express cumulative exposure results as the RR at 100 ppm-years, which is obtained as $1 + 100\beta$ when β is expressed per ppm-year. With the linear relative risk model ($RR = 1 + \beta z$), negative β can be problematic since β must be greater than $-1/(\text{maximum exposure})$ to avoid negative relative risks.[18] For this reason, lower confidence limits and a few estimates of β are reported simply as "<0"; in these cases, the corresponding values for the relative risk at 100 ppm-years are reported as "<1". Unless stated otherwise, all analyses reported in this paper are based on the case-cohort population.

Hypothesis tests and confidence intervals (CIs) for the ERR estimates were based on likelihood ratio tests and direct evaluation of the profile likelihood. CIs for the categorical RR were based on the Wald method. To address effect modification, we estimated the ERR per unit of exposure (β) by categories of covariates (such as birth year and attained age) and consider the test of trend with these variables to be the main test of effect modification. The analysis was adapted for the case-cohort design using methods described in Langholz and Jiao.[19] See Supporting Information Methods for additional detail.

Based on a comprehensive review of epidemiologic studies of LN and occupational benzene exposure[1,8] and our previous study,[4] our a priori analysis plan for all outcomes emphasized exposure accumulated following a lag of 2 years (*eg*, exposure received at least 2 years before the age at risk or, in other words, excluding the exposure in the 2 years before the age at risk), of 2 to <10 years and, particularly for NHL, of ≥10 years.

2.5 | Ethics review and approval

We obtained approval from the ethics review committees of the collaborating institutions before data collection. Before interviewing any subjects or next of kin, we obtained written informed consent from each individual providing information.

3 | RESULTS

There were 49 total LN (40 exposed and 9 unexposed) with subtypes and exposure status shown in Table 1 and described according to disease categories specified in Section 2.3. The distributions by sex, age at entry, age at first exposure, year of birth, year of first exposure, and industry are shown for total LN and LN subtypes and for the subcohort (Table 1). For the case-cohort population, the mean cumulative benzene exposure generally declined with calendar period first worked for NHL, LL, ALL, LN, and the subcohort (Table 2). In case-cohort comparisons of exposed vs unexposed workers, we found elevated risks for NHL (RR = 3.57, 95% CI = 1.40, 12.06), LL (RR = 2.53, 95% CI = 0.66, 16.48), ALL (RR = 2.10, 95% CI = 0.52, 13.91), and LN (RR = 2.28, 95% CI = 1.16, 5.01) (Table 3). We compared risk estimates for exposed vs unexposed workers in the case-cohort population with those from the entire cohort to determine whether the case-cohort population mirrored the entire cohort population. The entire cohort estimates for NHL (RR = 3.9, 95% CI = 1.5, 13.2) and LN (RR = 2.4, 95% CI = 1.2, 5.2) among exposed vs

TABLE 2 Summary of occupational exposure data among Chinese benzene-exposed workers diagnosed with lymphoid neoplasms and the benzene-exposed subcohort members in the case-cohort population according to year first worked[a,b]

	Mean total years worked[c] (number of exposed workers)					Mean cumulative benzene exposure level, ppm-years, no lag				
Year first worked	Non-Hodgkin lymphoma	Lymphoid leukemias	Acute lymphocytic leukemia	Total lymphoid neoplasms	Subcohort	Non-Hodgkin lymphoma	Lymphoid leukemias	Acute lymphocytic leukemia	Total lymphoid neoplasms	Sub-cohort
Total	15.6 (28)	14.5 (10)	16.1 (8)	14.9 (40)	17.4 (1100)	308.4	234.1	263.6	277.0	252.5
≤1949	(0)	(0)	(0)	(0)	34.9 (7)	(0)	(0)	(0)	(0)	1288.9
1950-1959	23.1 (8)	25.3 (3)	25.3 (3)	23.7 (11)	27.2 (143)	468.2	616.9	616.9	508.7	737.7
1960-1971	15.3 (8)	10.3 (3)	10.3 (3)	13.9 (10)	21.1 (328)	337.8	68.5	68.5	278.1	348.7
1972-1979	7.0 (2)	7.0 (3)	5.0 (1)	7.0 (5)	14.7 (289)	67.5	77.9	1.0	73.8	113.3
1980-1987	6.3 (4)	17.0 (1)	17.0 (1)	8.5 (6)	11.6 (333)	6.6	51.4	51.4	18.1	48.3

Abbreviation: ppm, parts per million.
[a]Refer to text for definition of entities included in each lymphoid neoplasm category.
[b]The subcohort is followed to end of study and the cases are censored at diagnosis thereby probably underestimating the greater cumulative exposure at any point in time among cases.
[c]Based on number of years with exposure estimates.

unexposed workers were similar to those of the case-cohort study, but cohort study risk estimates were higher for LL (RR = 5.4, 95% CI = 1.0, 99) and ALL (RR = 4.5, 95% CI = 0.8, 84) due to exclusion of one of two unexposed ALL cases in workers employed less than 6 months in the cohort study.[9]

Table 3 shows the categorical exposure-responses for cumulative benzene exposure for the case-cohort population. Elevated risks were observed in benzene-exposed individuals for nearly all exposure categories compared to the unexposed group for all four endpoints, NHL, LL, ALL, LN; for NHL and LN, some risk estimates were significantly elevated. Table 4 shows linear regression coefficients (ERR per 100 ppm-years) for three time-windows (≥2 years, 2 to <10 years, ≥10 years), and also shows relative risks at 100 ppm-year (=1 + ERR per 100 ppm-years) which were 1.05 for NHL (95% CI = 0.97, 1.27), 1.11 for LL (95% CI < 0, 1.66), 1.21 for ALL (95% CI < 0, 3.53), and 1.02 for LN (95% CI < 0, 1.16) for the ≥2-year lag. The analyses shown in Table 4 provide little indication that risk increased with increasing exposure (*P*-trend ≥ .30 for all but one of the 12 endpoint/time-windows combinations).

Because the majority of cases were NHL, we undertook a more detailed analysis of this LN to describe the exposure-response relationships for cumulative and for average intensity exposure metrics by individual exposure categories and by trend tests with exposures treated as a continuous variable within three time-windows (Table 5). In the case-cohort population there was little evidence of continuous exposure-response trends for either cumulative or average intensity estimated exposures within any of the time-windows evaluated, although elevated risks were apparent for many individual categories of cumulative and average intensity exposures. We investigated whether there was any improvement in the fit of the model by fitting separate estimates for the 2 to <10-year and ≥10-year windows compared with a single estimate for the ≥2-year window and found no evidence of such a difference (*P* > .5). Although not shown in Table 5, the combined grouping of NHL + CLL (N = 34) yielded results that were similar to those for NHL using a ≥2-year lag (ERR per 100 ppm-years= 0.039 [95%CI ≤ 0, 0.25; *P*-trend = .46]).

There was little evidence of modification of the benzene exposure-response by sex, age at first exposure, attained age, year of first exposure or time since first exposure based on overall trends with these variables (Table 6). The exposure-response was borderline statistically significant (*P* = .049) among those who were first exposed before age 19, but this finding should be interpreted cautiously in the absence of an overall trend with age and given that many statistical tests were performed. Industry appeared to modify the overall benzene exposure-response (*P* = .023) for NHL with a significantly positive exposure-response for chemical workers (*P* = .010). However, the benzene exposure-response among chemical workers was no longer close to statistical significance (*P* > .5) when adjusted for either duration of exposure to chlorinated solvents or to formaldehyde (data not shown). Neither benzene nor formaldehyde were associated with NHL (*P* > .5) after adjustment for duration of exposure to chlorinated solvents (data not shown). The overall benzene exposure-response for NHL was little modified when adjusted

TABLE 3 RR for total and specific groupings of lymphoid neoplasms for exposed vs unexposed and categories of cumulative benzene exposure based on ≥2-y lag, case-cohort population, 1972-1999[a]

		Non-Hodgkin lymphoma		Lymphoid leukemias		Acute lymphocytic leukemia		Total lymphoid neoplasms	
Risk assessment method for cumulative exposure, ppm-years	**Mean exposure, ppm-years**	**Number of cases[b]**	**RR (95% CI)**	**Number of cases[b]**	**RR (95% CI)**	**Number of cases[b]**	**RR (95% CI)**	**Number of cases[b]**	**RR (95% CI)**
All workers	182	32		12		10		49	
RR benzene-exposed vs unexposed workers ≥2-y lag									
RR, exposed vs unexposed (95% CI); *P*-value		28/4[b]	3.57 (1.40, 12.06) *P* = .0059	10/2[b]	2.53 (0.66, 16.48) *P* = .19	8/2[b]	2.10 (0.52, 13.91) *P* = .32	40/9[b]	2.28 (1.16, 5.01) *P* = .016
RR according to benzene exposure categories in ppm-years, ≥2-y lag									
Exposure category, ppm-years									
0	0.0	5	1.0	2	1.0	2	1.0	10	1.0
>0 to <5	2.3	3	4.21 (0.97, 18.17)	1		1		4	2.56 (0.78, 8.41)
5 to <40	19.0	7	3.43 (1.08, 10.92)	1	2.46 (0.58, 10.42)	1	2.03 (0.45, 9.19)	9	2.12 (0.85, 5.26)
40 to <100	66.1	6	3.33 (1.01, 11.02)	4		3		11	3.19 (1.35, 7.58)
100 to <300	174.8	4	1.47 (0.28, 7.66)	1	2.19 (0.45, 10.65)	0	1.87 (0.34, 10.21)	5	0.95 (0.29, 3.05)
≥300	901.5	7	3.10 (0.99, 9.75)	3		3		10	2.24 (0.93, 5.40)
P-trend[c]			0.40		>0.5		0.37		>0.5

Abbreviations: CI, confidence interval; ppm, parts per million; RR, rate ratio (relative risk).

[a]Refer to text for definition of entities included in each lymphoid neoplasm category.

[b]Exposed/unexposed.

[c]*P*-trend is based on benzene exposure treated as a continuous linear variable.

TABLE 4 ERR per 100 ppm-years and relative risks at 100 ppm-years for continuous cumulative benzene exposure for total and specific groupings of lymphoid neoplasms for ≥2-y, 2 to <10-y, and ≥10-y lags, respectively, case-cohort population, 1972-1999[a]

	Non-Hodgkin lymphoma (n = 32)			Lymphoid leukemias (n = 12)			Acute lymphocytic leukemia[a] (n = 10)			Total lymphoid neoplasms (n = 49)		
Lag	ERR per 100 ppm-years (95% CI)[b]	RR at 100 ppm-years[c] (95% CI)[b]	*P*-trend	ERR per 100 ppm-years (95% CI)[b]	RR at 100 ppm-years[c] (95% CI)[b]	*P*-trend	ERR per 100 ppm-years (95% CI)[b]	RR at 100 ppm-years[c] (95% CI)[b]	*P*-trend	ERR per 100 ppm-years (95% CI)[b]	RR at 100 ppm-years[c] (95% CI)[b]	*P*-trend
≥2-y	0.047 (<0, 0.27)	1.05 (0.97, 1.27)	.40	0.11 (<0, 1.66)	1.11 (<1, 1.66)	>.5	0.21 (<0, 2.53)	1.21 (<1, 3.53)	.37	0.018 (<0, 0.16)	1.02 (<1, 1.16)	>.5
2 to <10-y	0.15 (<0, 0.88)	1.15 (<1, 1.88)	.44	1.14 (<0, 9.09)	2.14 (<1, 10.09)	.18	0.69 (<0, 6.85)	1.69 (<1, 7.85)	.31	0.19 (<0, 0.88)	1.19 (<1, 1.88)	.30
≥10-y	0.060 (<0, 0.37)	1.06 (<1, 1.37)	.41	0.028 (<0, 1.14)	1.03 (<1, 2.14)	>.5	0.19 (<0, 2.43)	1.19 (<1, 3.43)	.49	0.010 (<0, 0.18)	1.01 (<1, 1.18)	>.5

Abbreviations: CI, confidence interval; ERR, excess rate ratios (excess relative risks); ppm, parts per million; RR, rate ratios (relative risks).

[a]Refer to text for definition of entities included in each lymphoid neoplasm category.

[b]With the linear relative risk model (RR = 1 + βz), negative β can be problematic since β must be greater than −1/(maximum exposure) to avoid negative relative risks.[18] For this reason, lower confidence limits and a few estimates of β are reported simply as "<0"; in these cases, the corresponding values for the relative risk at 100 ppm-years are reported as "<1".

[c]RR at 100 ppm-years = 1 + ERR per 100 ppm-years.

for cumulative (ppm-years) toluene or xylene exposure or for duration of chlorinated solvents (data not shown). When we evaluated benzene-associated risks for NHL with a ≥2-year lag after excluding workers in the chemical industry, we found excess risk comparing exposed to unexposed (RR = 2.76, 95% CI = 1.03, 9.55) and an ERR of 0.0063 per 100 ppm-years (95% CI < 0, 0.23; *P*-trend > .5), both slightly lower than the estimates with chemical industry workers included (Supporting Information Table S1).

Our analyses were adjusted for calendar year by including the RR for 1988-1999 compared to 1972-1987 as a parameter. With a ≥2-year lag, this RR for calendar period was estimated to be 0.22 (0.09-0.50) for NHL and 0.32 (0.17-0.60) for LN, confirming likely under-ascertainment in the 1988-1999 period. Because of the low ascertainment of NHL in the 1988-1999 period, we repeated the analyses shown in Table 3 with restriction to the follow-up period when ascertainment was more complete, for example, 1972-1987 in the case-cohort population (Supporting Information Table S2). The analyses for the case-cohort population are based on the same follow-up period evaluated in our previous analyses in the entire cohort population[4] but differ from the earlier cohort analyses in case composition, analytic approach and the use of the most recent exposure estimates based on hierarchical modeling. Overall, the case-cohort findings restricted to the initial follow-up period were similar to those for the entire (1972-1999) period although the excess relative risk per 100 ppm-years for NHL was slightly higher for the initial follow-up period (ERR = 0.087, 95% CI < 0, 0.43; *P*-trend = .22) than that for the combined period (ERR = 0.047, 95% CI < 0, 0.27; *P*-trend = .40).

4 | DISCUSSION

We found little evidence of exposure-response for NHL, ALL, LL, and LN for the follow-up period 1972-1999 using a state-of-the-art exposure assessment despite increased risks in benzene-exposed compared with unexposed workers in the same population. Using statistical models that evaluated NHL (or the other specified LN groups) risks as a linear function of cumulative exposure, there was no evidence of exposure-response for these neoplasms for ≥2-year, 2 to <10 years, or ≥10 years lag periods. NHL risks were not modified by sex, age at first exposure, attained age, year of first exposure, or time since exposure. Among the subset of workers in the chemical industry, there was a statistically significant benzene exposure-response for NHL, although adjustment for duration of exposure to chlorinated solvents attenuated the benzene exposure-response relationship with NHL. The RR at 100 ppm estimates based on the entire follow-up period (1972-1999) were generally similar to those based on only the initial follow-up period (1972-1987) when overall ascertainment was more complete.

Most of the limited number of previous cohort studies found no association of occupational benzene exposure with LN (Supporting Information Table S3). Risks were not statistically significantly increased for NHL, MM, CLL, or groupings of these LN in chemical industry and in petroleum refining or distribution workers in the United States,[20-24] US Pliofilm manufacturing workers,[25,26] Canadian

TABLE 5 RR and ERR per unit of exposure for non-Hodgkin lymphoma by categories of cumulative exposure and average intensity exposure and for continuous exposure per unit of exposure for benzene accumulated for ≥2, 2 to <10, and ≥10 y lags, case-cohort population, 1972-1999

	≥ 2-y before the time at risk				2 to <10-y before time at risk				≥10-y before the time at risk			
Cumulative exposure category (ppm-years)	Mean exposure (ppm-years)	Person-years in cohort $\times 10^{-3}$	Number of cases	RR (95% CI)	Mean exposure (ppm-years)	Person-years in cohort $\times 10^{-3}$	Number of cases	RR (95% CI)	Mean exposure (ppm-years)	Person-years in cohort $\times 10^{-3}$	Number of cases	RR (95% CI)
Total	182	2368	32		37.7	2368	32		98.4	2368	32	
0	0.0	852	5	1.0	0.0	1023	9	1.0	0.0	1314	9	1.0
>0 to <5	2.3	197	3	4.2 (1.0, 18)	2.1	306	7	3.2 (1.2, 8.7)	2.1	152	4	5.3 (1.3, 21)
5 to <40	19.0	455	7	3.4 (1.1, 11)	18.1	576	6	1.2 (0.4, 3.4)	19.1	292	5	2.9 (0.9, 9.3)
40 to <100	66.1	305	6	3.3 (1.0, 22)	63.1	243	3	1.1 (0.3, 4.3)	66.1	206	5	3.3 (1.0, 11)
100 to <300	174.8	291	4	1.4 (0.3, 6.0)	167.6	156	5	1.9 (0.6, 6.4	176.1	201	5	2.9 (0.9, 9.5)
≥300	901.5	269	7	3.1 (1.0, 90.7)	584.6	63	2	1.9 (0.4, 9.4)	885.1		4	2.6 (0.8, 8.7)
P-trend				0.40				0.44				0.41
ERR per 100 ppm-years				0.047 (<0, 0.27)				0.15 (<0, 0.89)				0.060 (<0, 0.37)
Average intensity (ppm)	**Mean exposure (ppm)**	**Person-years in cohort $\times 10^{-3}$**	**Number of cases**	**RR (95% CI)**	**Mean exposure (ppm)**	**Person-years in cohort $\times 10^{-3}$**	**Number of cases**	**RR (95% CI)**	**Mean exposure (ppm)**	**Person-years in cohort $\times 10^{-3}$**	**Number of cases**	**RR (95% CI)**
Total	11.5	2368	32		6.1	2368	32		8.2	2368	32	
0	0	852	5	1.0	0	1023	9	1.0	0.0	1314	9	1.0
>0 to <5	1.5	680	14	4.5 (1.6, 12.6)	1.9	751	12	2.1 (0.9, 4.9)	2.1	398	10	4.7 (1.7, 12.9)
5 to <9	4.8	249	1	1.8 (0.6, 5.7)	6.8	208	1	1.0 (0.3, 3.2)	6.9	174	1	2.7 (0.9, 7.6)
9 to <25	9.5	336	5		14.7	242	4		15.3	252	7	
≥25	34.7	251	7	2.8 (0.8, 9.2)	55.6	144	6	2.5 (0.8, 7.7)	58.8	231	5	2.3 (0.7, 7.5)
P-trend				>0.50				>0.50				0.27
ERR per 10 ppm				0.067 (<0, 0.45)				0.05 (<0, 0.52)				0.11 (<0, 0.56)

TABLE 6 ERR for non-Hodgkin lymphoma for benzene accumulated in the period ≥2 y before the time at risk according to demographic and occupational characteristics of the case-cohort population, 1972-1999

Modifying variable	Number of cases	ERR % per ppm-year	*P*-trend for exposure within category
Total	32	0.047	
By sex			
Male	20	0.0039	>.5
Female	12	0.21	.17
P-difference		.28	
By age at first exposure, y			
<19	10	0.37	.049
19-29	10	−0.015	>.5
≥30	12	0.027	>.5
P-trend		.40	
By attained age, y			
<37	10	0.12	>.5
37-54	12	0.12	.24
≥55	10	−0.014	>.5
P-trend		.46	
By year of first exposure			
<1965	14	0.033	>.5
1965-1974	11	0.13	.26
1975-1987	7	<0	.17
P-trend		>.5	
By time since first exposure, y			
<2	1	NC[a]	
2 to <11	9	−0.045	>.5
11 to <24	12	0.057	.47
≥24	10	0.0442	>.5
P-trend		>.50	
By industry			
Unexposed[a]	4		
Coatings	7	<0	.25
Chemical	9	0.74	.010
Other exposed	12	0.060	.47
P-heterogeneity[b]		.023	

[a]Unexposed workers are included in the analyses of each of the three exposed groups.
[b]Calculated using log-linear model.

petroleum workers,[27] United Kingdom petroleum workers,[28] or French gas and utility workers.[29] However, we previously reported that risk of NHL was significantly elevated and an exposure-response relationship was observed in the Shanghai women's general population cohort that utilized a job-exposure matrix with tens of thousands of benzene measurements.[30] MM risk was borderline significantly increased but no increase in risk or exposure-response was seen for B-cell NHL, diffuse large B-cell lymphoma, follicular lymphoma, or CLL among Norwegian offshore oil industry workers.[31] Interpretation of the mostly null findings of most of the cohort studies is difficult due to small numbers of the specified outcomes (Supporting Information Table S3). To address some of these limitations, Vlaanderen et al[6] conducted a meta-analysis of cohort studies that incorporated three study quality dimensions (*eg*, stratification based on the start of follow-up, the significance level for AML, and the exposure assessment quality). The investigators concluded that with quantitative exposure estimates there was suggestive evidence for the association of benzene exposure with CLL (based on 43 benzene-exposed cases), MM (28 benzene-exposed cases), and ALL (5 benzene-exposed cases) but the evidence for NHL (50 benzene-exposed cases) was less clear although potentially complicated by etiologic heterogeneity of NHL subtypes. There was no evidence for an association of benzene with HL (6 benzene-exposed cases). Vlaanderen et al[6] noted that most analyses were based on data sets of limited size. Few cohort studies included state-of-the-art exposure assessments and thus measurement error may have affected the results, particularly given the relatively small numbers of LN in these studies.

Overall, the findings from case-control studies have been inconsistent (data not shown). Early case-control studies of benzene and LN, despite including much larger numbers of LN cases than cohort studies, were characterized by limited retrospective exposure assessment that was based on self-report and/or indication of job title. Often the earlier studies reported risks for all NHL combined.[32-34] Among the small number of case-control studies that employed higher-quality job exposure matrices or detailed review by expert industrial hygienists and evaluated risks for specific NHL subtypes, some found elevated or borderline elevated risks for specific LN including CLL,[35,36] diffuse large B-cell lymphoma,[37-39] follicular lymphoma,[40] and MM.[36,41] Interpretation, however, is complicated because of older LN classification schemes during an era of limited diagnostics, variation in the benzene-containing agents among studies, exposure assessment limitations and potential associated errors, and variation in findings in risk of different LN subtypes. More recent case-control studies have increasingly included notable improvements in benzene exposure assessment and emphasized more recent understanding of modern classification of LN. The cumulative body of literature to date does not clearly identify consistent associations for LN overall or by subtype, although few reported cohort or case-control studies to date have conducted or reported rigorous assessment of exposure-response and centralized review of the LN by expert hematopathologists.

Our earlier analyses of NHL in China, 1972-1987,[4] produced several provocative findings that helped motivate the current study. Risk for NHL was elevated overall and particularly among chemical workers. In our earlier report, we also noted increased benzene-associated risks for NHL in relation to exposures that occurred greater than 10 years before diagnosis[4] in contrast to the shorter-term effects that we found for myeloid malignancies in our earlier analysis[4] and more recent extended follow-up assessment.[12] In the current analysis, we found no evidence of exposure-response for LN, and while NHL and other specified LN were increased in exposed vs unexposed individuals, none of our current analyses support dose-response associations including analyses based on exposure occurring 10 or more years before time at risk. As noted above, the

association of NHL and benzene exposure in the chemical industry may have been accounted for by co-exposure to chlorinated solvents.

The difference in estimates between the current analysis and that of Hayes et al[4] for the calendar-year period 1972-1987 could reflect differences in case composition, statistical models, measures used for the trend tests, and the exposure assessment (see Supporting Information Methods and Supporting Information Table S4). With improved case ascertainment and detailed case review in the current investigation, we identified 23 NHL that occurred during the period 1972-1987, compared to 19 NHL cases that we had identified in our initial study.[4]

Our current investigation is one of a limited number of cohort studies assessing occupational benzene exposure and LN. We identified the second largest number of benzene-exposed NHL cases in any cohort study reported to date and our data were based on a broader range of occupational exposures compared with other cohort studies (Supporting Information Table S3), although statistical power remains limited. The study also employed a state-of-the-art exposure assessment including benzene and other exposures. We have previously shown that the exposure models used in the current study predicted independent 8-hour weighted average benzene exposure levels fairly well.[10] Using the same exposure assessment as this study, we have shown positive exposure-response associations between cumulative exposure and risk of AML in this case-cohort population.[12] Lastly, this was one of few cohort studies that investigated potential modifying effects of age, latency, occupational characteristics, and other workplace exposures on benzene exposure-response relationships. The association of NHL with chlorinated solvent exposure that we observed is supported by other studies.[42,43]

A major shortcoming of the study was the relatively small number of total LN (*eg*, 49) and very tiny numbers of some specific subtypes (*eg*, 2 CLL, both exposed; 4 MM, including 3 exposed and 1 unexposed; and 2 Hodgkin lymphoma, including 1 exposed and 1 unexposed), precluding separate analysis of CLL, MM, and Hodgkin lymphoma. The limited statistical power, wide CIs (which include the possibility of increased risks), possible misclassification of LN, limited number of benzene exposure measurements particularly before 1960, and measurement error could mitigate exposure-response estimates and also affect the ability to draw strong conclusions. Follow-up was more complete in the initial phase (1972-1987) than in the extended phase (1988-1999) as demonstrated by similar risk estimates for the initial follow-up to those for the entire follow-up period. Reasons for incomplete ascertainment during 1988-1999 were closure or merger of study factories in the 1990s, relatively young age at Chinese worker retirement, and frequent return of retired workers to rural villages or towns of origin to join their extended families. We were able to follow-up workers whose factories shut down or merged through identification of almost all personnel records of the merged or closed factories. However, follow-up of retired workers who returned to their rural villages or towns of origin proved to be difficult since we had not captured lifetime residential history during our interviews with workers or their next of kin. The incomplete follow-up was unlikely to lead to bias since there was no evidence that under-ascertainment differed by benzene exposure level or between exposed and unexposed workers. However, the loss of statistical power from under-ascertainment could have resulted in failure to detect a true increase in LN risk with increasing exposure level. We addressed the differential follow-up in initial compared with extended follow-up by stratification in our analyses for calendar year, *eg*, including the relative risks for 1988-1999 compared to 1972-1987 as a parameter. To quantify the level of under-ascertainment of all incident LN in the multicenter Chinese benzene workers cohort, it would have been necessary to link the individuals in the cohort to long-standing, nationwide, high-quality population-based cancer and mortality registries. China (and many other countries) lacks a nationwide population-based cancer registry and also lacks a nationwide mortality registry.

The findings of excess relative risks ranging from 2.1- to 3.6-fold in benzene-exposed vs unexposed workers in the absence of exposure-response trends were puzzling. Possible explanations include small numbers of LN cases; imperfect assessment of benzene exposure and other occupational exposures, particularly in the unexposed work units; and failure to identify LN cases, particularly more indolent LN cases in unexposed individuals as we have previously noted,[9] although the analyses in the current study did not reveal evidence of differential (by benzene exposure level) case ascertainment. The limited ability to trace retired workers was particularly problematic for ascertainment of certain LN (eg, CLL and MM) because of the generally older age-at-onset characterizing these entities in the general population.

Outcome characterization was hampered by the limited clinical, pathology (including pathology slides), and laboratory data available for review and rare information on molecular and cytogenetic testing due to lack of availability of this testing during much of the era in which the retrospective follow-up was undertaken (1972-1999). The paucity of available clinical and pathology data, and notable changes worldwide in classification of LN during the follow-up period may have resulted in increased misclassification of LN, although we attempted to address this, in part, by assessing LN overall and in certain specific categories. The absence of medical records for some LN cases during the long period of follow-up (1972-1999) necessitated reliance on death certificates. Limitations of the exposure assessment were primarily due to limited and missing measurements related to some job titles in several workshops. These methodologic challenges would generally result in underestimation of risks, particularly if true associations of benzene that are limited to specific NHL subtypes were weak in nature. Lastly, it is important to also consider the wide CIs and the role of chance when interpreting our findings.

In conclusion, this extended follow-up study in Chinese workers found an increased risk of NHL and other specified LN among benzene-exposed compared with unexposed workers but little evidence of a benzene exposure-response. Overall, the findings from this Chinese worker study, together with those of other published studies do not currently support the hypothesis that occupational exposure to benzene is associated with increased risk of LN but this

conclusion must be considered in relation to the methodological shortcomings of this investigation and many other studies. The data from some epidemiologic studies linking benzene exposure with specific lymphoma subtypes, the mechanistic data supporting biological plausibility (studies reviewed in Refs 1,8 and the methodological shortcomings of most studies support the need for further investigation. Vlaanderen et al[6] have taken a first step in addressing the limitations of individual studies with the report of their findings from a meta-analysis. Due to the rarity of LN and shortcomings of the current and previous studies of benzene and LN, the next step would be to pool data from the current study with those from other previously and future reported occupational cohorts with a range of benzene exposures, high-quality exposure assessment, long-term follow-up and detailed histopathological characterization of LN. It is unclear whether this approach would provide sufficiently precise estimates of risk due to limited numbers of outcomes. Therefore, to complement completed and ongoing cohort studies, large case-control studies of specific LN subtypes are needed. Those currently underway and future case-control studies should be distinguished by high-quality study design components including appropriate control selection, state-of-the-art exposure assessment and expert hematopathologist review of all LN cases. Such studies should also be designed in a way that facilitates pooling of results.

ACKNOWLEDGMENTS

The authors are indebted to members of the Chinese Center for Disease Control and Prevention—U.S. National Cancer Institute Benzene Study Group for high-quality data collection over many years. Our colleague, Dr Sholom Wacholder, provided key input on study design and the analysis plan before his untimely death in 2015. We are grateful for advice and guidance since 2002 from the members of the Organic Solvents (Benzene) and Cancer Working Group including Drs Ellen Eisen (Chair), David Christiani, Lawrence Fine, Katherine Hammond, Richard Hornung, Judith Karp, Noah Seixias, Jack Siemiatycki, and Jennifer West. We also thank Tom Helde of IMS Inc for programming support; Michelle Brotzman, MPH of Westat Inc for project coordination; and Ka Lai Lou for technical assistance in manuscript preparation. This study was supported solely by funding from the Intramural Research Program of the National Institutes of Health, National Cancer Institute, and the U.S. Public Health Service of the Department of Health and Human Services.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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

Study design (MSL RV, S-NY, RBH, QL, G-LL, NR); data collection (MSL, RV, S-NY, B-TJ, QL, G-LL, NR); exposure assessment (RV, LP, MSL, S-NY, B-TJ, G-LL, NR); outcome validation (GMD, MSL, S-NY, B-TJ, QL, NR); developed data analysis plan (ESG, MSL, RV, NR); data analysis (ESG, MSL, RV, LP, RBH, QL, NR); data interpretation (MSL, NR, ESG, RBH, GMD, S-NY, QL, G-LL); writing manuscript (MSL, ESG, RV, NR, QL); manuscript review and comments (GMD, S-NY, LP, RBH, B-TJ, G-LL).

ETHICS APPROVAL AND INFORMED CONSENT

We obtained approval from the Chinese Center for Disease Control and Prevention Ethics Review Committee and the NCI Special Studies Institutional Review Board before data collection. Before interviewing any subjects or next of kin, we obtained written informed consent from each individual providing information.

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REFERENCES

1. IARC. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Chemicals and Industrial Processes Associated with Cancer in Humans, Vol. 1 to 20, Benzene*. Lyon: IARC Press; 2018.
2. Galbraith D, Gross SA, Paustenbach D. Benzene and human health: a historical review and appraisal of associations with various diseases. *Crit Rev Toxicol*. 2010;40(Suppl 2):1-46.
3. Friesen MC, Coble JB, Lu W, et al. Combining a job-exposure matrix with exposure measurements to assess occupational exposure to benzene in a population cohort in Shanghai, China. *Ann Occup Hyg*. 2012;56(1):80-91.
4. Hayes RB, Dosemeci M, Wacholder S, et al. Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine—National Cancer Institute Benzene Study Group. *J Natl Cancer Inst*. 1997;89(14):1065-1071.
5. Schnatter AR, Glass DC, Tang G, Irons RD, Rushton L. Myelodysplastic syndrome and benzene exposure among petroleum workers: an international pooled analysis. *J Natl Cancer Inst*. 2012;104(22):1724-1737.
6. Vlaanderen J, Lan Q, Kromhout H, Rothman N, Vermeulen R. Occupational benzene exposure and the risk of lymphoma subtypes: a meta-analysis of cohort studies incorporating three study quality dimensions. *Environ Health Perspect*. 2011;119(2):159-167.
7. Lan Q, Zhang L, Li G, et al. Hematotoxicity in workers exposed to low levels of benzene. *Science*. 2004;306(5702):1774-1776.
8. IARC. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Chemical Agents and Related Occupations, A review of Human Carcinogens, Vol. 100F, Benzene*. Lyon: IARC Press; 2012.
9. Linet MS, Yin SN, Gilbert ES, et al. A retrospective cohort study of cause-specific mortality and incidence of hematopoietic malignancies in Chinese benzene-exposed workers. *Int J Cancer*. 2015;137(9):2184-2197.
10. Portengen L, Linet MS, Li GL, et al. Retrospective benzene exposure assessment for a multi-center case-cohort study of benzene-exposed workers in China. *J Expo Sci Environ Epidemiol*. 2016;26(3):334-340.
11. Yin SN, Linet MS, Hayes RB, et al. Cohort study among workers exposed to benzene in China: I. General methods and resources. *Am J Ind Med*. 1994;26(3):383-400.
12. Linet MS, Gilbert ES, Vermeulen R, et al. Benzene exposure response and risk of myeloid neoplasms in Chinese workers: a multicenter case-cohort study. *J Natl Cancer Inst*. 2019;111(5):465-474.
13. Linet MS, Yin SN, Travis LB, et al. Clinical features of hematopoietic malignancies and related disorders among benzene-exposed workers in China. Benzene Study Group. *Environ Health Perspect*. 1996;104(Suppl 6):1353-1364.
14. Travis LB, Li CY, Zhang ZN, et al. Hematopoietic malignancies and related disorders among benzene-exposed workers in China. *Leuk Lymphoma*. 1994;14(1-2):91-102.
15. WHO. *International Statistical Classification of Diseases and Related Health Problems*. Geneva, Switzerland: World Health Organization; 1992.
16. Cox DR. Regression models and life-tables (with discussion). *J Roy Statist Soc B*. 1972;34(2):187-220.
17. The EPICURE Regression Programs. *EPICURE User Manual and Command Summary*. http://epicurehelp.risksciences.com/index.html#!Documents/theepicureregressionprograms.htm. Accessed 13 December 2017.
18. Prentice RL, Mason MW. On the application of linear relative risk regression models. *Biometrics*. 1986;42(1):109-120.
19. Langholz BL, Jiao J. Computational methods for case-cohort studies. *Comput Stat Data Anal*. 2007;51:3737-3748.
20. Collins JJ, Anteau SE, Swaen GM, Bodner KM, Bodnar CM. Lymphatic and hematopoietic cancers among benzene-exposed workers. *J Occup Environ Med*. 2015;57(2):159-163.
21. Collins JJ, Ireland B, Buckley CF, Shepperly D. Lymphohaematopoeitic cancer mortality among workers with benzene exposure. *Occup Environ Med*. 2003;60(9):676-679.
22. Ireland B, Collins JJ, Buckley CF, Riordan SG. Cancer mortality among workers with benzene exposure. *Epidemiology*. 1997;8(3):318-320.
23. Wong O. An industry wide mortality study of chemical workers occupationally exposed to benzene. II. Dose response analyses. *Br J Ind Med*. 1987;44(6):382-395.
24. Wong O, Harris F, Smith TJ. Health effects of gasoline exposure. II. Mortality patterns of distribution workers in the United States. *Environ Health Perspect*. 1993;100:63-76.
25. Rinsky RA, Hornung RW, Silver SR, Tseng CY. Benzene exposure and hematopoietic mortality: a long-term epidemiologic risk assessment. *Am J Ind Med*. 2002;42(6):474-480.
26. Wong O. Risk of acute myleoid leukaemi and multiple myeloma in workers exposed to benzene. *Occup Environ Med*. 1995;52(6):380-384.
27. Schnatter AR, Armstrong TW, Nicolich MJ, et al. Lymphohaematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers. *Occup Environ Med*. 1996;53(11):773-781.
28. Rushton L, Romaniuk H. A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. *Occup Environ Med*. 1997;54(3):152-166.
29. Guenel P, Imbernon E, Chevalier A, Crinquand-Calastreng A, Goldberg M. Leukemia in relation to occupational exposures to benzene and other agents: a case-control study nested in a cohort of gas and electric utility workers. *Am J Ind Med*. 2002;42(2):87-97.
30. Bassig BA, Friesen MC, Vermeulen R, et al. Occupational exposure to benzene and non-Hodgkin lymphoma in a population-based cohort: the Shanghai Women's Health Study. *Environ Health Perspect*. 2015;123(10):971-977.
31. Stenehjem JS, Kjærheim K, Bråtveit M, et al. Benzene exposure and risk of lymphohaematopoietic cancers in 25 000 offshore oil industry workers. *Br J Cancer*. 2015;112(9):1603-1612.
32. Blair A, Linos A, Stewart PA, et al. Evaluation of risks for non-Hodgkin's lymphoma by occupation and industry exposures from a case-control study. *Am J Ind Med*. 1993;23(2):301-312.
33. Fritschi L, Benke G, Hughes AM, et al. Risk of non-Hodgkin lymphoma associated with occupational exposure to solvents, metals, organic dusts and PCBs (Australia). *Cancer Causes Control*. 2005;16(5):599-607.
34. Gerin M, Siemiatycki J, Desy M, Krewski D. Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene: results of a case-control study in Montreal. *Am J Ind Med*. 1998;34(2):144-156.
35. Cocco P, t'Mannetje A, Fadda D, et al. Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case-control study. *Occup Environ Med*. 2010;67(5):341-347.
36. Costantini AS, Benvenuti A, Vineis P, et al. Risk of leukemia and multiple myeloma associated with exposure to benzene and other organic solvents: evidence from the Italian multicenter case-control study. *Am J Ind Med*. 2008;51(11):803-811.
37. Miligi L, Costantini AS, Benvenuti A, et al. Occupational exposure to solvents and the risk of lymphomas. *Epidemiology*. 2006;17(5):552-561.

38. Orsi L, Monnereau A, Dananche B, et al. Occupational exposure to organic solvents and lymphoid neoplasms in men: results of a French case-control study. *Occup Environ Med*. 2010;67(10):664-672.
39. Wang R, Zhang Y, Lan Q, et al. Occupational exposure to solvents and risk of non-Hodgkin lymphoma in Connecticut women. *Am J Epidemiol*. 2009;169(2):176-185.
40. Wong O, Harris F, Armstrong TW, Hua F. A hospital-based case-control study of non-Hodgkin lymphoid neoplasms in Shanghai: analysis of environmental and occupational risk factors by subtypes of the WHO classification. *Chem Biol Interact*. 2010;184(1-2):129-146.
41. De Roos AJ, Spinelli J, Brown EB, et al. Pooled study of occupational exposure to aromatic hydrocarbon solvents and risk of multiple myeloma. *Occup Environ Med*. 2018;75(11):798-806.
42. Karami S, Bassig B, Stewart PA, et al. Occupational trichloroethylene exposure and risk of lymphatic and haematopoietic cancers: a meta-analysis. *Occup Environ Med*. 2013;70(8):591-599.
43. Rieutort D, Moyne O, Cocco P, de Gaudemaris R, Bicout DJ. Ranking occupational contexts associated with risk of non-Hodgkin lymphoma. *Am J Ind Med*. 2016;59(7):561-574.

SUPPORTING INFORMATION

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

How to cite this article: Linet MS, Gilbert ES, Vermeulen R, et al. Benzene exposure-response and risk of lymphoid neoplasms in Chinese workers: A multicenter case-cohort study. *Am J Ind Med*. 2020;63:741–754. https://doi.org/10.1002/ajim.23142