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Benzene Exposure Response and Risk of Myeloid Neoplasms in Chinese Workers: A Multicenter Case–Cohort Study

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Abstract

Background: There is international consensus that benzene exposure is causally related to acute myeloid leukemia (AML), and more recent evidence of association with myelodysplastic syndromes (MDS). However, there are uncertainties about the exposure response, particularly risks by time since exposure and age at exposure.
Methods: In a case–cohort study in 110 631 Chinese workers followed up during 1972–1999 we evaluated combined MDS/AML (n = 44) and chronic myeloid leukemia (n = 18). We estimated benzene exposures using hierarchical modeling of occupational factors calibrated with historical routine measurements, and evaluated exposure response for cumulative exposure and average intensity using Cox regression; *P* values were two-sided.
Results: Increased MDS/AML risk with increasing cumulative exposure in our a priori defined time window (2 to <10 years) before the time at risk was suggested (P_{trend} = 08). For first exposure (within the 2 to <10-year window) before age 30 years, the exposure response was stronger (*P* = .004) with rate ratios of 1.12 (95% confidence interval [CI] = 0.27 to 4.29), 5.58 (95% CI = 1.65 to 19.68), and 4.50 (95% CI = 1.22 to 16.68) for cumulative exposures of more than 0 to less than 40, 40 to less than 100, and at least 100 ppm-years, respectively, compared with no exposure. There was little evidence of exposure response after at least 10 years (P_{trend} = .94), regardless of age at first exposure. Average intensity results were generally similar. The risk for chronic myeloid leukemia was increased in exposed vs unexposed workers, but appeared to increase and then decrease with increasing exposure.
Conclusion: For myeloid neoplasms, the strongest effects were apparent for MDS/AML arising within 10 years of benzene exposure and for first exposure in the 2 to less than 10-year window before age 30 years.

More than 2 million workers worldwide are exposed to benzene in the manufacture of chemicals and other products or from oil refining, petrochemical transport, or vehicle repair (1). Occupational benzene exposures have declined notably from an 8-hour time-weighted-average of 100 parts per million (ppm) in 1941 to 0.5 ppm since 1997 in the United States (2), and decreased substantially in China during the past five decades (3). The general population is widely exposed to low-level benzene from tobacco smoke, vehicle exhaust, gasoline stations, and contaminated water and food (1).

Since 1979, an international consensus has developed that benzene exposure is causally related to leukemia, particularly acute myeloid leukemia (AML), which was recently affirmed (4). In Chinese benzene workers followed during 1972–1987, we

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found increasing AML risks with increasing benzene exposure and stronger trends for AML combined with myelodysplastic syndromes (MDS) (5). A meta-analysis focusing on the shape of the exposure response (6) revealed statistically significantly increased risk of total leukemia at low benzene exposure levels, but leukemia subtypes, and temporal and age characteristics, were not evaluated.

To expand the limited data for myeloid neoplasm subtypes at a range of benzene levels, and to investigate modification by age, temporal patterns, demographic, and work history, we studied myeloid neoplasms in Chinese benzene-exposed workers (5,7,8). The case–cohort study design was chosen to efficiently evaluate the exposure response for myeloid neoplasms as a function of cumulative exposure and of average intensity using a new state-of-the-art exposure assessment with a validation component.

Methods

Study Population and Design

We previously compared cancer risks in 74 827 benzene-exposed and 35 804 unexposed workers employed for at least one month in several industries during 1972–1987 in 12 Chinese cities (8). Exposure status was ascertained from factory records (including job information, industrial processes, and measurements) on use of benzene-containing materials. The first (1972–1987) and second (1988–1999) follow-ups of the cohort used salary records and other factory and health records to identify and follow employed and retired workers (9). For employed and retired factory workers, health care was integrated with the workplace, and diagnostic and treatment visits occurred in or were reported back to the workplace (9). In the second follow-up (1988–1999), additional approaches were used due to factory closings and mergers and health-care system changes in the 1990 s. For closed or merged factories, personnel and health records were located to provide the residence, health, vital status, and death information for current, retired, and deceased workers. Additional information was obtained from referral hospitals for suspected myeloid neoplasm cases.

The case–cohort population, identified from the full cohort, included incident and deceased AML, MDS, and CML cases diagnosed 1972–1999 among exposed and unexposed workers and a 1500-worker subcohort (1100 exposed, 400 unexposed) selected by stratified random sampling (by sex, exposure status, and age at start of follow-up) from 110 631 cohort members (Supplementary Table 1, available online). See Supplementary Methods (available online) for additional detail. Future analyses will evaluate lymphoid neoplasms, benzene hematotoxicity, and lung cancer.

Validation of Diagnosis of Myeloid Neoplasms

Physicians, blinded to exposure status, extracted data from all medical records, including pathology, laboratory, and death reports on to standardized forms. We combined MDS (previous nomenclature "refractory anemia") with AML, recognizing MDS as a neoplasm and a frequent precursor of AML (10). Expert hematopathologists reviewed the extracted data to ascertain and confirm diagnoses of myeloid neoplasms as described elsewhere (8,11,12). We coded the myeloid neoplasms using modified code from the *International Classification of Diseases, Ninth Revision* (13) and incorporating elements of the *International Classification of Diseases for Oncology, Third Edition* (14).

Exposure Assessment

Factory records were the primary source for historical benzene, toluene, and xylene air measurements and associated data, production processes, and complete job histories. See details described elsewhere (15) and in Supplementary Methods (available online). Questionnaires administered to subjects or next of kin were used to identify jobs held outside the cohort factories.

To estimate individual monthly benzene exposures, a Bayesian hierarchical model was built from the historic monitoring data. This model allowed for clustering of measurements by factory, workshop, job, and date (15). The exposure assessors were blinded to exposure status. A study-specific job-exposure matrix was used to develop monthly indicators for other exposures linked with myeloid neoplasms (eg, formaldehyde, butadiene, and chlorinated solvents). Questionnaire-reported "outside the cohort" jobs were linked to the exposure prediction model by imputing exposures from similar job titles from cohort factories in particular cities. A 2004–2005 survey of a sample of study factories revealed moderate correlation of the statistical model with full-shift personal measurements, albeit with potential underestimation of benzene exposures less than 3 ppm (15).

Statistical Analysis

Cox proportional hazards regression (16), with age at risk of myeloid neoplasms (attained age) as the timescale, was used to estimate hazard rate ratios (RR), using the Epicure program (17). Analyses were stratified on sex and adjusted for calendar year (1988–1999 vs 1972–1987); the latter adjustment was motivated by lower rates for myeloid neoplasms in 1988–1999 than during 1972–1987 due to factory closings, increasing retirements, and medical care changes that made case ascertainment more difficult. Analyses of MDS/AML were also adjusted for time since start of employment because risk declined sharply with this variable ($P < .001$), with little effect on the benzene exposure response. To verify the proportional hazards assumption, we allowed the calendar year and follow-up time variables to depend on attained age (timescale) with little evidence of such dependency. We estimated RR by exposure categories, but tests for trend with exposure were based on a model in which the RR is 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, and β is the ERR expressed per unit of exposure (18). Hypothesis tests and confidence intervals were based on likelihood ratio tests and direct evaluation of the profile likelihood. Two-sided *P* values are considered statistically significant if less than .05. To address effect modification, we estimated the ERR per unit of exposure (β) by categories of variables (such as birth year and attained age) but consider the test of trend with these variables to be the main test of effect modification. The test for trend of the ERR with attained age can be regarded as a test of the proportionality assumption for this variable. The analysis was adapted for the case–cohort design using methods described in (19) (see Supplementary Methods, available online).

Based on a comprehensive review of epidemiologic studies of myeloid neoplasms and occupational benzene exposure (1,20), radiation exposure in the atomic bomb survivors (21), and

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Table 1. Summary of occupational benzene exposure data according to year first worked among Chinese benzene-exposed workers diagnosed with myelodysplastic syndromes/acute myeloid leukemia (MDS/AML) or chronic myeloid leukemia (CML), and an exposed subcohort followed up during 1972–1999

	No. of exposed workers			Mean total years worked*			Mean cumulative benzene exposure level, ppm-years, no lag		
Year first worked	MDS/AML	CML	Subcohort	MDS/AML	CML	Subcohort	MDS/AML	CML	Subcohort
Total	37	15	1100	12.5	18.9	17.4	264.7	199.1	252.5
1949 or before	0	0	7	NA	NA	34.9	NA	NA	1288.9
1950–1959	4	2	143	23.8	41.5	27.2	356.6	260.5	737.7
1960–1971	18	8	328	14.5	19.8	21.1	409.8	281.8	348.7
1972–1979	11	5	289	8.1	8.6	14.7	84.6	42.2	113.3
1980–1987	4	0	333	4.3	NA	11.6	14.7	NA	48.3

*Based on number of years with exposure estimates. NA = not applicable; ppm = parts per million.

selected chemotherapy exposures (22), our a priori analysis plan emphasized exposure accumulated between 2 and 10 years (2 to <10-year window) before the age at risk (age at myeloid neoplasm diagnosis for cases). We also evaluate cumulative exposure in the exposure windows of at least 10 years and at least 2 years; the latter is similar to our earlier analysis (5). Other windows were explored (Supplementary Materials, available online). We evaluated both cumulative exposure and average intensity, calculated by dividing the cumulative exposure by the number of exposed years within a given window. We used the subcohort to evaluate the correlation coefficient of cumulative exposure and average intensity with weighting by person-years.

Ethics

Prior to data collection, the investigators obtained approval from the Chinese Center for Disease Control and Prevention Ethics Review Committee and the National Cancer Institute's Special Studies Institutional Review Board. Written informed consent was obtained before interviews.

Results

The mean cumulative benzene exposure declined with calendar period first worked for MDS/AML cases, CML cases, and the subcohort (Table 1) (15). In case–cohort comparisons of exposed vs unexposed workers we found elevated risks for MDS/AML (RR = 2.20, 95% confidence interval [CI] = 1.02 to 5.49; 37 exposed cases and 7 unexposed cases) and CML (RR = 2.64, 95% CI = 0.76 to 11.41; 15 exposed cases and 3 unexposed cases) (data not shown), similar to full cohort estimates (MDS/AML: RR = 2.7, 95% CI = 1.2 to 6.6; CML: RR = 2.5, 95% CI = 0.8 to 11) (8).

Table 2 shows the MDS/AML exposure responses for cumulative exposure and average intensity in the time windows of 2 to less than 10 years and at least 10 years. Because these exposure metrics are highly correlated (correlation coefficient = 0.94 for the 2- to <10-year window) and patterns were similar, we focus on the cumulative exposure results. For the window of 2 to less than 10 years, risk of MDS/AML increased with increasing cumulative exposure with an estimated ERR per 100 ppm-years of 0.30 (95% CI = −0.02 to 1.09; P_{trend} = .08) corresponding to a rate ratio of 1.30 at 100 ppm-years (RR = 1 + ERR = 1 + .30 × 100). There was no evidence of nonlinearity based on comparisons with linear-quadratic (P = .70), linear-exponential (P = .64), and log-linear functions (P = .65) or with the categorical analyses (P = .24) (data not shown). For AML (n = 36), the ERR per 100 ppm-years was 0.19 (95% CI = <0 to 0.97); for MDS (n = 8) it was 1.28 (95% CI = <0 to 18.12) (Table 2). Restricting the results to nonzero exposures, the ERR per 100 ppm-years was 0.24 (P_{trend} = .15) for MDS/AML, 0.17 (P_{trend} = .29) for AML, and 0.66 (P_{trend} = .21) for MDS. There was little evidence of exposure response for the time window of 10 years or more. A model with separate ERR for the windows of 2 to less than 10 years and 10 years or more fitted the data somewhat better (P = .10) than a model with only the total exposure in the window of at least 2 years. Additional detail on the distribution of cases is shown in Supplementary Table 2 (available online).

For addressing potential modification of the MDS/AML (44 cases) cumulative exposure response in the 2-year to less than 10-year window (Supplementary Table 3, available online), age and year of first exposure were defined by the date of first exposure within that window. The ERR per 100 ppm-years in the time window of 2 to fewer than 10 years decreased statistically significantly with increasing age at first exposure (P_{trend} = .01). The ERR also declined with attained age (P_{trend} = .02) and was higher for exposures before age 35 years than for exposure received at older ages (P = .004). Results for the time window of at least 2 years were similar, although the trend with age at first exposure was not statistically significant (P_{trend} = .21). The exposure response for MDS/AML was not statistically significantly modified by sex (based on 13 female vs 31 male MDS/AML cases), time since first exposure, year of first exposure, or attained calendar year. Results for the 1972–1987 follow-up period were similar to those for the full 1972–1999 period with little evidence of exposure response for the 1988–1999 period.

For ages at first exposure under 30 years within the window of 2 to less than 10 years, MDS/AML risk rose with increasing cumulative exposure (P_{trend} = .004), with an ERR per 100 ppm-years of 1.45 (95% CI = 0.21 to 5.70) (Table 3). Rate ratios were 1.12 (95% CI = 0.27 to 4.29), 5.58 (95% CI = 1.65 to 19.68), and 4.50 (95% CI = 1.22 to 16.68) for cumulative exposure categories of more than 0 to less than 40, 40 to less than 100, and at least 100 ppm-years, respectively, compared with no exposure. The exposure response remained statistically significant when restricted to nonzero exposures (P_{trend} = .01) (data not shown). Average intensity results were generally similar (data not shown). The strong exposure response among younger workers persisted using the window of at least 2 years (Supplementary Table 4, available online), because younger workers were mostly exposed in the 2 to less than 10 year window.

For CML (18 cases), RRs were increased in several benzene exposure categories, although the increases were not statistically significant (Table 4). Nevertheless, negative log-linear risk coefficients indicated an overall decrease with decreasing exposure resulting from a paucity of cases at higher exposures.

Table 2. Rate ratios and excess rate ratios per unit of exposure for myelodysplastic syndromes/acute myeloid leukemia (MDS/AML) by categories of cumulative exposure and average exposure based on exposure 2 to fewer than 10 years before time at risk and in the period at least 10 years before time at risk*

	2 to <10 y before time at risk				≥10 y before time at risk			
Exposure metric	Mean exposure†	Person-years in cohort × 10^{-3}	No. of cases	RR (95% CI)	Mean exposure†	Person-years in cohort × 10^{-3}	No. of cases	RR (95% CI)
Cumulative exposure category, ppm-years								
Total	37.7	2368	44	—	98.4	2368	44	—
0	0.0	1023	13	1.00 (reference)	0.0	1314	22	1.00 (reference)
>0-<5	2.1	306	6	1.47 (0.50 to 3.88)	2.1	152	2	0.54 (0.03 to 2.74)
5-<40	18.1	576	6	0.74 (0.25 to 1.93)	19.1	297	7	1.56 (0.59 to 3.71)
40-<100	63.1	243	9	2.52 (1.04 to 6.02)	66.1	198	2	0.60 (0.09 to 2.16)
100-<300	167.6	156	6	1.44 (0.45 to 4.06)	176.1	206	5	1.69 (0.58 to 4.38)
≥300	584.6	63	4	2.82 (0.76 to 8.56)	885.1	201	6	1.75 (0.57 to 4.90)
ERR per unit of continuous exposure, per 100 ppm-years (95% CI)				0.30‡ (−0.02 to 1.09)				0.008§ (<0 to 0.32)
P_{trend}				.08				.92
Average intensity, ppm								
Total	6.1	2368	44	—	8.2	2368	44	—
0	0	1023	13	1.00 (reference)	0.0	1314	22	1.00 (reference)
>0-<5	1.9	751	8	0.80 (0.31 to 1.97)	2.1	398	4	0.63‖ (0.20 to 1.66)
5-<9	6.8	208	7	2.29 (0.84 to 5.79)	6.9	174	1	
9-<25	14.7	242	7	1.68 (0.64 to 4.21)	15.3	252	12	2.79 (1.24 to 6.16)
≥25	55.6	144	9	2.59 (0.97 to 6.57)	58.8	231	5	1.05 (0.33 to 2.81)
ERR per unit of continuous exposure, per 10 ppm-years (95% CI)				0.22¶ (−0.004 to 0.78)				0.072# (<0 to 0.43)
P_{trend}				.06				.42

*Cox regression and linear relative risk models were used to estimate rate ratios (RR), excess rate ratios (ERR) per unit of exposure, and 95% confidence intervals (CI). Two-sided P_{trend} tests were based on continuous linear variables and likelihood ratio methods. Analyses were adjusted for age, sex, calendar period, and time since first employed in a study factory.

†Mean exposures weighted by person-years in cohort.

‡For AML (36 cases) the ERR per 100 ppm-years was 0.19 (95% CI = <0 to 0.97; P_{trend} = .24). For MDS (8 cases) the ERR per 100 ppm-years was 1.28 (95% CI = <0 to 18.12; P_{trend} = .09).

§For AML (36 cases) the ERR per 100 ppm-years was −0.05 (95% CI = <−0.05 to 0.24; P_{trend} = .43). For MDS (8 cases) the ERR per 100 ppm-years was 0.16 (95% CI = <0 to 2.38; P_{trend} = .38).

‖This RR is for the combined >0 to <5 and 5 to <9 ppm-year exposure groups.

¶For AML the ERR per 10 ppm was 0.18 (95% CI = <0 to 0.77; P_{trend} = .13). For MDS the ERR per 10 ppm was 0.58 (95% CI = <0 to 7.26; P_{trend} = .18).

#For AML the ERR per 10 ppm was 0.024 (95% CI = <0 to 0.41; P_{trend} = .81). For MDS the ERR per 10 ppm was 0.30 (95% CI = <0 to 5.11; P_{trend} = .24).

However, linear-quadratic log-linear models suggested a nonmonotonic exposure-response relationship that increased up to about 126 ppm-years and then decreased (overall P_{trend} = .02). There was little evidence of effect modification for CML (data not shown). Negative log-linear risk coefficients were observed for both men (13 cases) and women (5 cases), and for both age-at-first-exposure groups shown in Table 3.

The benzene exposure responses for MDS/AML and CML were modified little when adjusted for toluene or xylene exposure or for duration of formaldehyde, butadiene, or chlorinated solvents exposures; none of these exposures modified the benzene exposure response (data not shown). Sensitivity analyses yielded results similar to those described above. These included analyses restricted to those who first worked in 1960 or later (38 MDS/AML and 14 CML cases) to address lack of information on myeloid neoplasms before the start of follow-up in 1972 (Supplementary Table 5, available online); analyses restricted to 1972–1987 to address the likely under-ascertainment in 1988–1999 (Supplementary Table 6, available online); analyses restricted to factories that remained open until 2000; analyses that omitted adjustment for time since first employment (Supplementary Table 7, available online); and analyses that excluded exposure received outside of the cohort factories (2.4% of the total). Because measurement error rather than incomplete ascertainment might explain the lower baseline rates in the 1988–1999 period, we also conducted analyses for the full period (1972–1999) without calendar year adjustment. Because this analysis allowed the lower dose/lower risk data from 1988–1999 to be included in the referent group for the 1972–1987 period, the evidence for exposure response for MDS/AML became stronger (Supplementary Table 8, available online).

Discussion

Employing a state-of-the-art exposure assessment and statistical models that expressed myeloid neoplasm risk as linear functions of cumulative exposure during different time windows

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Table 3. Rate ratios (RR) and excess rate ratios (ERR) per unit of exposure for myelodysplastic syndromes/acute myeloid leukemia (MDS/AML) by categories of cumulative exposure and average exposure based on exposure in the period 2 to <10 years prior to the time at risk, according to age at first exposure within the 2 to <10-year window*

	All ages		Age of first exposure in 2 to <10 window <30 years		Age of first exposure in 2 to <10 window ≥30 years	
Exposure metric	No. of MDS/AML cases	RR (95% CI)	No. of MDS/AML cases	RR (95% CI)	No. of MDS/AML cases	RR (95% CI)
Cumulative exposure, ppm-years						
0	13	1.00 (reference)	4	1.00 (reference)	9	1.00 (reference)
>0 to <5	6	1.48 (0.50 to 3.91)	3	1.12† (0.27 to 4.29)	3	1.02 (0.22 to 3.51)
5 to <40	6	0.74 (0.25 to 1.94)	1		5	0.78 (0.23 to 2.34)
40 to <100	9	2.52 (1.02 to 6.08)	6	5.58 (1.65 to 19.68)	3	1.22 (0.32 to 3.95)
≥100	10	1.84 (0.60 to 5.01)	6	4.50 (1.22 to 16.68)	4	0.87 (0.22 to 2.87)
ERR per unit of continuous exposure, per 100 ppm-years (95% CI)		0.30‡ (−0.02 to 1.09)		1.45||§ (0.21 to 5.70)		−0.080|| (<0 to 0.44)
P_{trend}		.08		.004		.55
Average intensity, ppm						
0	13	1.00 (reference)	4	1.00 (reference)	9	1.00 (reference)
>0 to <5	8	0.80 (0.31 to 1.97)	2	0.68 (0.10 to 3.18)	6	0.78 (0.25 to 2.24)
5 to <9	7	2.29 (0.84 to 5.79)	4	4.18 (1.03 to 15.95)	3	1.32 (0.28 to 4.59)
9 to <25	7	1.68 (0.64 to 4.21)	4	3.44 (0.84 to 13.12)	3	0.94 (0.24 to 3.03)
≥25	9	2.59 (0.97 to 6.57)	6	6.58 (1.80 to 24.15)	3	1.06 (0.22 to 3.82)
ERR per unit of continuous exposure, per 10 ppm (95% CI)		0.22¶ (−0.004 to 0.78)		1.09# (0.19 to 4.14)		−0.024** (<0 to 0.33)
P_{trend}		.06		.002		.82

*Cox regression and linear relative risk models were used to estimate RR and ERR per unit of exposure, and 95% confidence intervals (CI). Two-sided P_{trend} tests were based on continuous linear variables and likelihood ratio methods. Analyses were adjusted for age, sex, calendar period, and time since first employed in a study factory.

†This RR is for the combined >0 to <5 and 5 to <40 ppm-year exposure groups.

‡For AML (36 cases) the ERR per 100 ppm-years was 0.19 (95% CI = <0 to 0.97; P_{trend} = .24). For MDS (8 cases) the ERR per 100 ppm-years was 1.28 (95% C = <0 to 18.12; P_{trend} = .09).

§For AML (18 cases) the ERR per 100 ppm-years was 1.16 (95% CI = 0.07 to 5.0; P_{trend} = .02). For MDS (2 cases) the ERR per 100 ppm-years was 0.35 (95% CI = 0.13 to ∞; P_{trend} = .03).

||For AML (18 cases) the ERR per 100 ppm-years was −0.14 (95% CI = <−0.14 to 0.24; P trend = .36). For MDS (6 cases) the ERR per 100 ppm-years was 0.35 (95% CI = <0 to 19.69; P_{trend} = .55).

¶For AML (36 cases) the ERR per 10 ppm was 0.18 (95% CI = <0 to 0.77; P_{trend} = .13). For MDS (8 cases) the ERR per 10 ppm was 0.58 (95% CI = <0 to 7.26; P_{trend} = .18).

#For AML (18 cases) the ERR per 10 ppm was 0.93 (95% CI = 0.11 to 3.78; P_{trend} = .007). For MDS (2 cases) the ERR per 10 ppm was infinite (95% CI = 0.016 to ∞; P_{trend} = .05).

**For AML (18 cases) the ERR per 10 ppm was 1.16 (95% CI = 0.07 to 5.0; P_{trend} = .02). For MDS (2 cases) the ERR per 10 ppm was infinite (95% CI = 0.13 to ∞; P_{trend} = .03).

and ages, we found an increase in risk of MDS/AML with increasing age of first exposure within the 2 to less than 10-year window with a particularly strong exposure response for age at first exposure under age 30 years. We found no evidence of exposure response in the time window of at least 10 years or at older ages. Although CML risks were elevated among workers in exposed factories, risk appeared to increase and then decrease with increasing exposure.

To our knowledge, ours is the first study to identify a strong dependence of the MDS/AML exposure response on age. For the window of 2 to less than 10 years specified in our analysis plan, age at first exposure within this window and the related variables of attained age and age at exposure all statistically significantly modified the exposure-response relationship with a stronger MDS/AML exposure-response at younger ages. This may indicate that younger workers are more susceptible to benzene. More complete ascertainment at younger ages is possible although bias is unlikely unless ascertainment varied by exposure level. Furthermore, the trend with age at first exposure in the 2 to less than 10-year window persisted for attained ages under 50 years (P_{trend} = .04) before retirement was likely. Declines in therapy-related AML risk with increasing age at chemotherapy treatment have been reported following several first cancers (23). Although Richardson (24) reported higher total leukemia (15 cases) risks for benzene exposures accrued at ages of at least 45 years than at younger ages in the U.S. pliofilm workers, the ERRs per ppm-year for this same older age category in the Chinese workers were negative for both MDS/AML and total leukemia in the exposure windows of 2 to less than 10 years and two or more years. Few other studies provide the opportunity to assess potential effect modification by age with adequate power.

Our results affirm our earlier important finding that exposures within 10 years of diagnosis were more strongly associated with MDS/AML risks than more distant exposures (5). Similarly, risks were highest within 10 years of first exposure for

Table 4. Rate ratios and log-linear risk coefficients per unit of exposure for chronic myeloid leukemia (CML) by categories of cumulative exposure and average exposure based on exposure 2- to less than 10 years before time at risk and at least 10 years before time at risk*

	2 to <10 y before time at risk				≥10 y before time at risk			
Exposure metric	Mean exposure†	Person-years in cohort × 10^{-3}	No. of cases	RR* (95% CI)	Mean exposure†	Person-years in cohort × 10^{-3}	No. of cases	RR* (95% CI)
Cumulative exposure category, ppm-years								
Total	38	2368	18		98.4	2368	18	
0	0.0	1025	6	1.00 (reference)	0.0	1315	6	1.00 (reference)
>0 to <5	2.1	306	2	1.08‡ (0.30 to 3.71)	2.1	152	2	2.10§ (0.68 to 6.70)
5 to <40	18.0	576	3		19.1	297	4	
40 to <100	63.1	244	6	2.26||¶ (0.71 to 7.66)	66.1	198	1	
100 to <300	169.8	156	1		176.1	205	2	1.85# (0.49 to 6.84)
≥300	587.2	63	0		884.9	201	3	
Log-linear* risk coefficient per unit of continuous exposure, per 100 ppm-years (95% CI)				−0.24**†† (−1.22 to 0.17)				−0.005†† (−0.20 to 0.082)
P_{trend}*				.39				.94
Average intensity, ppm								
Total	6.1	2368	18		18.2	2368	18	
0	0	1025	6	1.00 (reference)	0.0	1315	6	1.00 (reference)
>0 to <5	1.9	751	4	1.36‡‡ (0.44 to 4.36)	2.1	397	4	2.07‡‡ (0.62 to 6.94)
5 to <9	6.8	209	3		6.9	171	2	
9 to <25	14.7	242	5	1.88§§|||| (0.51 to 5.77)	15.3	254	4	1.94§§|||| (0.58 to 6.53)
≥25	55.6	143	0		58.8	231	2	
Log-linear* risk coefficient per unit of continuous exposure, per 10 ppm (95% CI)				−0.14¶¶ (−0.76 to 0.13)				−0.067## (−0.43 to 0.10)
P_{trend}*				.44				.57

*Cox regression models were used to estimate rate ratios (RR), log-linear risk coefficients, and 95% confidence intervals (CI). Two-sided P_{trend} tests were based on continuous log-linear variables and likelihood ratio methods. Log-linear models were used due to poor asymptotic properties of the linear excess rate ratio (ERR) model with small numbers and negative excess risks as discussed in Supplementary Methods (available online). Analyses adjusted for age, sex, and calendar period.

†Mean exposures weighted by person-years in the cohort.

‡This RR is for the combined >0 to <5 and 5 to <40 ppm-year exposure groups.

§This RR is for the combined >0 to <5, 5 to <40, and 40 to <100 ppm-year exposure groups.

||This RR is for the combined 40 to <100, 100 to <300 and ≥300 ppm-year exposure groups.

¶If the ≥40 ppm-year category is subdivided, the RR for 40 to <60 ppm-year subcategory (4 cases) is 6.00 (1.48 to 22.43) whereas that for the ≥60 ppm-year subcategory (3 cases) is 1.19 (0.24 to 4.88).

#This RR is for the combined 100 to <300 and ≥300 ppm-year exposure groups.

**Log-linear-quadratic model: linear coefficient = 4.42 per 100 ppm-year; quadratic coefficient = −3.54; P_{trend} = .02.

††Log-linear-quadratic model: linear coefficient = 0.42 per 100 ppm-year; quadratic coefficient = −.04; P_{trend} = .28.

‡‡This RR is for the combined >0 to <5 and 5 to <9 ppm exposure groups.

§§This RR is for the combined 9 to <25 and ≥25 ppm exposure groups.

||||If the ≥9-ppm category is subdivided, the RR for 9- to <12-ppm subcategory (3 cases) is 6.1 (1.5 to 25) whereas that for the ≥12-ppm subcategory (2 cases) is 0.9 (0.2 to 4.8).

¶¶Log-linear-quadratic model: linear coefficient = 2.66 per 10 ppm; quadratic coefficient = −1.34; P_{trend} = .02.

##Log-linear-quadratic model: linear coefficient = 1.05 per 10 ppm; quadratic coefficient = −0.27; P_{trend} = .10.

Table 5. Selected epidemiological studies of benzene-exposed workers based on exposure category with no lag or 2-year lag

Studies according to exposure category	Reference	Population	Follow-up time period	Lag time, y
Low-to-high occupational benzene exposures				
Chinese benzene workers*	Current study	106 641	1972–1999	2
US pliofilm workers	Rinsky et al., 2002 (27)	1845	1950–1996	0
Italian shoe factory workers	Seniori Costantini et al., 2003 (28)	1687	1950–1999	0
Low-to-medium occupational benzene exposures				
US chemical industry workers	Wong et al., 1987 (31)	7676†	1946–1977	0
Netherlands caprolactam (for nylon) workers	Swaen et al., 2005 (30)	311	1951–2001	0
US chemical workers	Collins et al., 2015 (29)	2266	1940–2009	0
Low occupational benzene exposures				
US chemical industry workers	Collins et al., 2003 (32)	4417	1940–1977	0
Australia, UK, Canada petroleum workers	Schnatter et al., 2012 (20)	48 469‡	—	—
Australia		16 910	1981–2006	0
UK		23 300	1950–2005	0
Canada		6672	1964–1994	0

*Data are from the current case–cohort study.
†Among the total population, 4602 individuals were exposed.
‡The study population also included 1587 controls.

leukemia mortality in the US pliofilm cohort (24,25), for AML in a hospital-based case–control study in Shanghai (26), and for AML within 5–7 years following use of alkylating agents (22). However, this pattern differs from that in the atomic bomb survivors (21) whose AML risks were highest in initial years but remained elevated many years after the bombing.

Our earlier analyses (5) demonstrating a statistically significant exposure response for MDS/AML based on all cumulative exposure received at least 1.5 years before the time at risk contrast with our current study showing little evidence of overall exposure-response for the similar window of two or more years (Supplementary Table 3, available online, all ages). This difference is primarily due to a different metric for the trend tests (see Supplementary Methods and Supplementary Table 9, available online) and perhaps other methodological differences. Additional follow-up from 1988–1999 did not greatly modify our findings, probably because low exposures in the 2- to less than 10-year window resulted in little increase in statistical power.

Our MDS/AML findings in the 2 to less than 10 year window are difficult to compare with other studies because most of them included all leukemias and all exposures except those within a short lag period ($\leq$2 years). Only the US pliofilm cohort (24,25) reported on temporal and age effects. Tables 5 and 6 show all leukemia and AML results from the literature using a short lag for high-level (27,28), mid-level (29–31), and low-level benzene exposures (20,32). Overall, the studies showed a positive exposure response for all leukemias or AML, with risks highest for the highest exposure levels. Results at cumulative exposures under 400 ppm-years were generally compatible across the studies given the wide CIs reflecting the small number of leukemia cases in most studies (20,32). Among those with exposures that exceed 400 ppm-years, risks in pliofilm workers are larger than in our study, likely reflecting higher exposures within this category.

For CML, a meta-analysis showed higher RRs for studies starting follow-up in 1970 or later (33) and the Australian/Canadian/UK study suggested an excess 2–20 years before diagnosis (34). We found no evidence of an increase over the full exposure range based on a single continuous exposure variable (as specified in our analysis plan), but exploration of nonmonotonic models suggested a positive response at lower exposures. Despite more CML cases than in most other studies, our investigation had limited statistical power.

Strengths of our study included a relatively large number of MDS/AML cases, evaluation of myeloid neoplasm subtypes, long-term follow-up, use of continuous variables for modeling the exposure response, inclusion of workers from different industries, a state-of-the-art exposure assessment (15), and an extensive outcome validation effort (8). We had reasonable power to investigate the modifying effects of age, latency, and occupational characteristics on exposure-response relationships compared with other studies of benzene workers.

Study limitations included potential under-ascertainment of MDS/AML, especially in 1988–1999 due to the young retirement age in China and a small proportion of workers returning to their rural villages where follow-up is difficult. We adjusted for calendar year for handling the less complete 1988–1999 follow-up, but this reduced statistical power and could have underestimated risk. Like most retrospective occupational cohort studies, MDS/AML cases diagnosed before follow-up commenced (in 1972) would have been missed. Despite more myeloid neoplasms than in most previous investigations, the small numbers in subtype categories and in the referent group limit precision in estimating risks. Exposure estimates were calibrated with limited measurements and are less certain at low exposure levels (15). Missing measurements are another potential limitation, but unlikely differential by exposure or by case-comparison status. Misclassification of cases is possible because of limited histopathology or medical records, and reliance on death certificates. These methodologic issues would likely lead to underestimation of risks (35). Finally, chance may explain some findings given the many variables and subgroups evaluated.

Overall, our study adds new insights into age and temporal effects associated with benzene exposure, and provides support for the recent IARC working group review (4). Our results point to the importance of careful assessment of age and temporal characteristics and use of comprehensive exposure measurements in future studies to facilitate greater understanding of the pathogenesis and susceptibility for benzene-induced myeloid neoplasms.

Table 6. Exposure-response rate ratios (RR) for cumulative benzene exposure (ppm-years) and risk of total leukemia, acute myeloid leukemia (AML), acute non-lymphocytic leukemia (ANLL), and myelodysplastic syndromes (MDS) in selected epidemiologic studies of benzene-exposed workers based on exposure category with no lag or 2-year lag

	Reference category		Lowest category		Medium category		Medium-to-high category		Highest category	
Study population and outcome(s)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)
Low-to-high occupational benzene exposures										
Chinese benzene workers (this study)										
Occupational benzene exposure levels, ppm-years		Workers with no exposure in ≤2- year window		>0–<40		40–199		200 to <400		≥400
All leukemias (n = 78)	18	1.00 (Ref)	13	0.81 (0.38 to 1.68)	25	2.02 (1.09 to 3.82)	10	2.37 (1.03 to 5.19)	12	2.23 (1.01 to 4.78)
AML (n = 36)	9	1.00 (Ref)	8	0.94 (0.34 to 2.53)	12	1.90 (0.79 to 4.77)	5	2.41 (0.71 to 7.34)	2	0.80 (0.12 to 3.29)
US pliofilm workers (27)										
Occupational benzene exposure levels, ppm-years		External US population		<40		40–199		200 to <400		≥400
All leukemias (n = 15)	—	1.00 (Ref)	6	1.5 (0.5 to 3.3)	4	3.2 (0.9 to 8.9)	2	5.6 (0.6 to 24)	3	24.0 (4.8 to 78.5)
AML (n = 8)	—	1.00 (Ref)	0	0 (0.0 to 2.1)	3	5.2 (1.1 to 15.3)	1	3.9 (0.1 to 21.9)	4	34.8 (9.5 to 89.1)
Italian shoe factory workers (28)										
Occupational benzene exposure levels, ppm-years		External national and regional Italian population		<40		40–99		100–199		≥200
All leukemias (n = 11)	—	1.00 (Ref)	3	1.3 (0.3 to 3.7)	2	4.1 (0.5 to 14.7)	2	2.5 (0.3 to 9.1)	4	5.1 (1.4 to 13.0)
Low-to-medium occupational benzene exposures										
US chemical industry workers (31)										
Occupational benzene exposure levels, ppm-yrs		Chemical workers from same plants with no benzene exposure		<15		15–60				>60
All leukemias* (n = 6)	3704	RR undefined, P_{trend} = .01	2	0.97 (0.12 to 3.49)	1	0.78 (0.02 to 4.34)			3	2.76 (0.57 to 8.06)
Netherlands Caprolactam (for nylon) workers (30)										
Occupational benzene exposure levels, ppm-yrs†	—	External national Dutch male population		Lowest tertile: mean = 3.4		Middle tertile: mean = 68.8		—		Highest tertile: mean = 401.5
All leukemias (n = 1)	—	1.00 (Ref)	0	NA	1	3.13 (0.04 to 15.8)				Not provided
US chemical workers (29)										
Occupational benzene exposure levels, ppm-yrs	—	Age-, race-, sex-, year-, cause-specific US mortality rates		0–3.9		4.0–24.9		—		≥25
All leukemias (n = 14)		1.00 (Ref)	3	0.60 (0.12 to 1.76)	7	1.23 (0.49 to 2.53)		—	4	1.72 (0.86 to 3173)
ANLL (AML) (n = 5)		1.00 (Ref)	0	0.0 (0.00 to 2.38)	3	1.77 (0.37 to 5.18)		—	2	1.30 (0.16 to 4.69)

(continued)

Table 6. (continued)

Study population and outcome(s)	Reference category		Lowest category		Medium category		Medium-to-high category		Highest category	
	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)
Low occupational benzene exposures										
US chemical industry workers (32)										
Occupational benzene exposure levels, ppm-yrs	—	External Illinois state population		<1		1–6				>6
All leukemias (n = 16)	—	1.00 (Ref)	2	0.7 (0.1 to 2.5)	4	1.4 (0.4 to 3.6)	—		10	1.7 (0.6 to 3.8)
ANLL (AML) (n = 5)	—	1.00 (Ref)	1	1.4 (0.1 to 5.1)	2	2.7 (0.3 to 9.9)	—		2	2.2 (0.3 to 8.1)
Australia, UK, Canada petroleum workers (20)										
Occupational benzene exposure levels, ppm-yrs		≤0.348‡				>0.348–2.93		—		>2.93
AML§ (n = 60)	20	1.00 (Ref)		—‡	19	1.04 (0.50 to 2.19)		—	21	1.39 (0.68 to 2.85)
MDS (n = 29)	6	1.00 (Ref)		—‡	8	1.73 (0.55 to 5.47)		—	15	4.33 (1.31 to 14.3)

*There were no leukemias in the unexposed group.
†Mean exposure; exposure ranges were not provided.
‡The analysis compared medium exposure and high exposure to the low-exposure group.
§Sixty cases of AML from 139 total leukemias; the latter were not reported.

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