Exhibit 243

Occupational Benzene Exposure and Cancer Risk among Chinese Men: A Report from the Shanghai Men's Health Study

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ABSTRACT

Background: Benzene exposure has been associated with increased risk of leukemia and other cancers; however, epidemiologic evidence is inconsistent for the latter, and confounding from smoking and alcohol was rarely adjusted.

Methods: We investigated associations between occupational benzene exposure and risk of leukemia, lymphoma, myeloma, and lung, stomach, liver, and kidney cancers in a population-based cohort of 61,377 men, ages 40 to 74 years. A job-exposure matrix, constructed by industrial hygienists specifically for the study population, was used to derive cumulative benzene exposure from all jobs held. Cox regressions were performed to estimate adjusted HRs (aHR) and 95% confidence intervals (CI) for benzene–cancer risk associations with adjustment for potential confounders.

Results: Over 15 years of follow-up, 1,145 lung cancer, 656 stomach cancer, 445 liver cancer, 243 kidney cancer, 100 leukemia, 124 lymphoma, and 46 myeloma cases were identified. Benzene exposure >550 mg/m^3 was associated with an increased risk of leukemia (aHR = 2.3; 95% CI, 1.1–4.5), lung cancer (aHR = 1.2; 95% CI, 1.0–1.6), and stomach cancer (aHR = 1.4; 95% CI, 1.0–1.9); benzene exposure was associated with early cancer diagnosis age. The benzene–leukemia and benzene–stomach cancer associations followed a linear dose–response pattern (P_{linear} = 0.016 and 0.023), whereas the benzene–lung cancer association was evident at higher exposure levels ($P_{nonlinear}$ = 0.027). Alcohol consumption modified the benzene–leukemia association (aHR = 3.0; 95% CI, 1.1–8.3 for drinkers and aHR = 0.9; 95% CI, 0.4–2.0 for nondrinkers, $P_{interaction}$ = 0.047).

Conclusions: Benzene exposure was associated with an increased risk of leukemia, stomach cancer, and lung cancer. Alcohol consumption may modify the benzene–leukemia association, although estimates are imprecise.

Impact: Our study provides additional evidence that benzene exposure increases cancer risk beyond leukemia, information important for policymakers to develop programs to mitigate cancer risk among benzene-exposed workers.

Introduction

Benzene is one of the most common organic solvents used in industrial settings and has been classified as a group 1 carcinogen by the International Agency for Research on Cancer (IARC; refs. 1, 2). According to the IARC, "there is strong evidence, including in exposed humans, that benzene is metabolically activated to electrophilic metabolites; induces oxidative stress and associated oxidative DNA damage; is genotoxic, inducing DNA damage and chromosomal changes; is immunosuppressive; and causes hematotoxicity" (2). The IARC's conclusion was primarily based on animal bioassay models and mechanistic evidence (1, 2). Supportive evidence from human studies, although not entirely consistent, has shown that benzene exposure was associated with acute myeloid leukemia (AML) in adults and might also be associated with the risk of non–Hodgkin lymphoma (NHL), chronic lymphoid leukemia, chronic myeloid leukemia, and lung cancer (1, 2).

Benzene is introduced in the biological system primarily through inhalation exposure, skin absorption, and ingesting contaminated food and water sources (3). The biological mechanism for benzene relative to cancer onset is twofold and best described by McHale and colleagues (4). First, benzene targets blood cells to generate elevated reactive oxygen species levels and causes cytotoxicity (4, 5). Next, the metabolization of benzene and its metabolites, including benzene oxide, phenol, and hydroquinone, occur primarily in the liver (6) and lungs (7, 8) and benzoquinones via secondary metabolism occurring in the bone marrow (4, 9–12), which may induce carcinogenesis in those tissues (5). Animal carcinogenicity data show that benzene-exposed mice, via inhalation, had increased incidence of leukemia, lymphoma, squamous cell carcinoma of the forestomach, and adenocarcinoma of the lung and increased risk of lymphoma, leukemia, lung cancer (alveolar/bronchiolar and adenoma/carcinoma), liver cancer, and squamous cell carcinoma via gavage or oral injection (2).

Industries such as petroleum, chemical production, and manufacturing are associated with occupational benzene exposures, with higher exposure levels most prevalent in jobs such as shoemaking, painting, printing, and rubber manufacturing (2, 13). Data from a large cohort study of 528,729 Chinese workers showed that 35.4% (n = 17,769) of the 50,255 workplaces in China utilizing benzene as a solvent or chemical intermediate exceeded the maximum allowable concentration of benzene allowed in China during 1980 (40 mg/m^3; ref. 14). Several epidemiologic studies among benzene-exposed workers have shown evidence that benzene exposure is associated with the development of leukemia (15–17), myeloma

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(18), and lymphoma (including NHL; refs. 19–21). A retrospective cohort study by Yin and colleagues (22) among Chinese men (n = 15,643) and women (n = 12,817) exposed to benzene in the workplace showed increased cancer mortality rates (primarily in men) compared with unexposed individuals. The reported standardized mortality ratios among benzene-exposed men were 5.74 for leukemia, 2.31 for lung cancer, 1.12 for hepatocarcinoma, and 1.22 for stomach cancer; among women, leukemia mortality was increased among the exposed (22). These observations may be attributable to the greater likelihood of men to have jobs with higher concentrations of benzene exposure than women or to residual confounding. In an expanded analysis, Linet and colleagues (23) conducted internal comparisons of cancer mortality among benzene-exposed workers in the same study population. The authors found increased mortality from leukemia (RR = 2.8), lymphoma (RR = 4.0), and lung cancer (RR = 1.5) among benzene-exposed workers in China (23). A meta-analysis by Chiavarini and colleagues (24) showed that benzene exposure increased lung cancer risk and mortality. It should be noted that few prior epidemiologic studies assessing benzene risk have collected personal data on potential confounding variables, such as smoking and alcohol, particularly the larger cohort studies (2).

In a population-based cohort study conducted among women in Shanghai, China, we have reported that occupational benzene exposure was associated with an increased risk of NHL (21). The objective of this study was to assess occupational benzene exposure and its association with the risk of cancers of the lung, liver, kidney, and stomach, as well as myeloma, leukemia, and lymphoma, among Chinese men in a population-based cohort study. These cancers were chosen for study based on the IARC's evaluation of the evidence of their association with benzene exposure, the targeted organ's function in benzene metabolism/excretion (e.g., the liver and kidneys), and a number of specific cancer cases.

Materials and Methods

Study population and design

This study analyzed data collected in the Shanghai Men's Health Study, a population-based cohort study of 61,469 men, ages 40 to 79, enrolled between 2002 and 2006, and followed for cancer incidence and mortality through the end of 2016. A detailed description of the cohort profile and methods is provided elsewhere (25). Briefly, trained interviewers recruited eligible men from eight urban communities in Shanghai, China. In-person interviews with a structured questionnaire were used to collect information on demographics, lifestyle factors, health status, and detailed and complete job history (e.g., type of work, responsibility, nature of the product for all jobs held, etc.). The average number of jobs held by our study participants was 3.16 (range 1–6). New cancer cases, vital status, and causes of death were identified through linkages with the Shanghai Cancer Registry and Shanghai Vital Status Registry. Cancers under study were classified following the International Classification of Diseases (ICD), Ninth Revision: leukemia (204–208), lymphoma (200–202), myeloma (203), lung cancer (162), stomach cancer (151), kidney cancer (189), and liver cancer (155). Histology subtype of lung adenocarcinoma (81403, 81433, 82503, 82513, 82603, and 84803); stomach adenocarcinoma (8140, 8211, 8260, 8262, 8263, and 8480); AML (98403–98413, 98613, 98663, 98713–98743, and 99103); and NHL (95903–95953, 96703–96773, 96803–96883, 96903-06093, 97003–97173, and 98203–98283, excluding lymphoid leukemias ICD-O-2 = 98233) were classified based on the International Classification of Diseases for Oncology, Second Edition (ICD-O-2). Men with preexisting cancers at baseline or nonpermanent residents of Shanghai were not eligible for the study. Ninety-two men were excluded from the current study because of missing information on job codes (n = 87) and loss to follow-up immediately after study enrollment (n = 5), leaving a total of 61,377 participants for analysis.

Exposure assessment

A job–exposure matrix (JEM) is a proxy measure of an individual's occupational exposures of interest based on job codes in population-based studies when direct exposure assessments are limited (26–30). In our study, we applied the JEM for benzene exposure for workers in Shanghai developed by Dosemeci and colleagues (31) which includes both job-specific intensity ratings of benzene exposure and the probability of benzene exposure within an industry. Our study focused on the exposure derived by the job-specific intensity of exposure because it captured individuals' exposure across different jobs held. Specifically, job-specific ratings for exposure intensity were derived based on the maximum allowable concentration (MAC) of occupational benzene exposure in China during 1980 (40 mg/m^3), based on industry hygienists' knowledge of benzene exposure occupations and their knowledge about the local work exposure circumstances, which, among others, included inspection measurement information, although measurement data were not directly incorporated. Scores were assigned in four groups: 0, very low or negligible; 1, low (<10% of the MAC); 2, medium (10%–100% of the MAC); and 3, high (above the MAC). Based on expert consensus, we assigned 0%, 5%, 55%, and 166%, i.e., midpoints of the categories and two thirds of the upper MAC (40 mg/m^3), to each of the four job-specific intensity ratings, multiplied them by the duration of each job participants held, and then summed exposures across all jobs (mg/m^3*years) to estimate the cumulative benzene exposure. The continuous cumulative benzene exposure variable was then categorized as follows: no exposure, 50th percentile, and 80th percentile of the exposure in our study population, corresponding to the following groups: 0 (no exposure), 1 (1–198 mg/m^3*years), 2 (199–550 mg/m^3*years), and 3 (>550 mg/m^3*years). The total cumulative benzene exposure constitutes the exposures of interest in this study. The probability of benzene exposure within industry was not included in the study because of its poor representation of individual exposure.

Statistical analysis

Descriptive statistics were calculated to describe baseline characteristics of the study cohort by cumulative benzene exposure. The Shapiro–Wilk test of normality was used to assess all continuous variables to confirm their underlying distributions. Mann–Whitney U tests and Kruskal–Wallis H tests were used for non-normally distributed data to test differences in the median age of cancer diagnosis for binary and categorical benzene exposures, respectively. χ^2 tests were used to examine differences in binary and categorical variables with occupational benzene exposure. Multivariable Cox proportional-hazards models with age as the timescale were applied to estimate adjusted HRs (aHR) and 95% confidence intervals (CI) for the associations between occupational benzene exposure scores and the risk of myeloma, leukemia, lymphoma, and lung, liver, kidney, and stomach cancers. Cancer-free participants were censored at death or on December 31, 2016, whichever came first. Cases of cancer types not under study were censored at the date of their cancer diagnosis in the study. All models were adjusted for age at

Table 1. Characteristics of the study population by cumulative benzene exposure (n = 61,377).

Study population characteristic	Cumulative benzene exposure (mg/m³*years)				
	No exposure (n = 48,336)	1–198 mg/m³*years (n = 6,600)	199–550 mg/m³*years (n = 3,970)	>550 mg/m³*years (n = 2,471)	
	n (%)	n (%)	n (%)	n (%)	P value
Age at enrollment (years)					
≤49	16,541 (34.2)	3,454 (52.3)	2,080 (42.4)	817 (33.1)	**<0.001**[a]
50–59	15,248 (31.6)	1,826 (27.7)	1,360 (34.3)	738 (29.9)	
60–69	10,492 (21.7)	907 (13.7)	327 (8.2)	483 (19.6)	
≥70	6,055 (12.5)	413 (6.3)	203 (5.1)	433 (17.5)	
BMI (kg/m²)					
Underweight (<18.5)	1,990 (4.1)	296 (4.5)	189 (4.8)	126 (5.1)	**0.001**[a]
Healthy weight (≥18.5 and <25.0)	30,191 (62.5)	4,144 (62.8)	2,566 (64.6)	1,571 (63.6)	
Overweight (≥25.0 and <30.0)	14,880 (30.8)	2,006 (30.4)	1,131 (28.5)	710 (28.7)	
Obesity (≥30.0)	1,275 (2.6)	154 (2.3)	84 (2.1)	64 (2.6)	
Education					
<Junior high school	18,842 (39.0)	2,966 (44.9)	1,623 (40.9)	1,277 (51.7)	**<0.001**[a]
High school	16,354 (33.8)	2,861 (43.4)	1,830 (46.1)	978 (39.6)	
≥College/professional	13,140 (27.2)	773 (11.7)	517 (13.0)	216 (8.7)	
Income (yuan)					
<500	5,747 (11.9)	969 (14.7)	636 (16.0)	321 (13.0)	**<0.001**[a]
500–999	20,173 (41.7)	2,893 (43.8)	1,815 (45.7)	1,342 (54.3)	
1,000–1,999	17,266 (35.7)	2,280 (34.6)	1,290 (32.5)	692 (28.0)	
≥2,000	5,150 (10.7)	458 (6.9)	229 (5.8)	116 (4.7)	
Ever smoked					
No	15,498 (32.1)	1,559 (23.6)	867 (21.8)	723 (29.3)	**<0.001**[a]
Yes	32,838 (67.9)	5,041 (76.4)	3,103 (78.2)	1,748 (70.7)	
Packs per year of smoking					
None	15,498 (32.1)	1,559 (23.6)	867 (21.8)	723 (29.3)	**<0.001**[a]
≤16 packs	11,301 (23.4)	1,708 (25.9)	1,129 (28.4)	609 (24.7)	
>16 and ≤30 packs	11,676 (24.2)	2,064 (31.3)	1,163 (29.3)	594 (24.0)	
>30 packs	9,861 (20.4)	1,269 (19.2)	811 (20.4)	545 (22.1)	
Family history of cancer					
No	34,491 (71.4)	4,813 (72.9)	2,879 (72.5)	1,795 (72.6)	**0.019**[a]
Yes	13,845 (28.6)	1,787 (27.1)	1,091 (27.5)	676 (27.4)	
Drinks of alcohol per week					
None	32,392 (67.0)	4,154 (62.9)	2,544 (64.1)	1,589 (64.3)	**<0.001**[a]
<7 drinks	2,985 (6.2)	420 (6.4)	200 (5.0)	166 (6.7)	
≥7 drinks	10,831 (22.4)	1,732 (26.2)	1,049 (26.4)	587 (23.8)	
Former drinkers	2,128 (4.4)	294 (4.5)	177 (4.5)	129 (5.2)	
Chronic gastritis					
No	40,896 (84.6)	5,642 (85.5)	3,415 (86.0)	2,123 (85.9)	**0.014**[a]
Yes	7,440 (15.4)	958 (14.5)	555 (14.0)	348 (14.1)	
Hepatitis					
No	47,128 (97.5)	6,443 (97.6)	3,864 (97.3)	2,402 (97.2)	0.867[a]
Yes	1,208 (2.5)	157 (2.4)	106 (2.7)	69 (2.8)	

Bold text indicates statistical significance.
[a]χ^2.

study entry, education, body mass index (BMI, kg/m²), income, alcohol consumption, pack-years of smoking, and family history of cancer. Pesticide exposure at jobs was adjusted for all cancers under study, except for lung and kidney cancer analyses, as there was no evidence of confounding. Occupational exposures to asbestos and silica were evaluated but showed no evidence of confounding based on a 10% change in point estimates; therefore, they were not included in the multivariable models. Multivariable Cox models for liver cancer and stomach cancer included additional adjustment for hepatitis and chronic gastritis, respectively. Covariates were categorized in the analysis, including age (≤49, 50–59, 60–69, and ≥70); BMI (<18.5, ≥18.5–<25.0, ≥25.0–<30.0, and ≥30.0); pack-years smoked (none, ≤16 packs, >16–≤30 packs, and >30 packs); and alcohol consumption per week (none, <7 drinks, ≥7 drinks, and former drinker). Alcohol consumption was not included in the adjustment for leukemia analysis because of its interaction with benzene. We examined the patterns of dose–response association between cumulative benzene exposure and cancer risks using restricted cubic spline regression with three knots placed at 5%, 50%, and 95% of exposures, corresponding to 20, 200, and 1,328 mg/m³*years cumulative benzene exposure, respectively. We applied Wald statistics to test linear and nonlinear relationships using the R package "rms." Multiplicative interactions between cumulative benzene exposure and alcohol consumption (never- or former-drinkers vs.

Table 2. Association between occupational benzene exposure and cumulative benzene exposure and risk of leukemia, lymphoma, myeloma, lung cancer, stomach cancer, kidney cancer, and liver cancer (n = 61,377).

	Leukemia[a]		Lymphoma[a]		Myeloma[a]		Lung cancer		Stomach cancer[a]		Kidney cancer		Liver cancer[a]	
Benzene exposure	**Cases**	**aHR (95% CI)**	**Cases**	**aHR (95% CI)**	**Cases**	**aHR (95% CI)**	**Cases**	**aHR (95% CI)**	**Cases**	**aHR (95% CI)**	**Cases**	**aHR (95% CI)**	**Cases**	**aHR (95% CI)**
Occupational benzene exposure														
Unexposed	82	Ref.	99	Ref.	38	Ref.	924	Ref.	515	Ref.	194	Ref.	355	Ref.
Exposed	18	1.3 (0.7–2.4)	25	1.6 (0.9–2.6)	8	1.3 (0.5–3.2)	221	1.0 (0.9–1.2)	141	**1.4 (1.1–1.7)**	49	1.1 (0.8–1.5)	90	0.7 (0.5–1.0)
Cumulative benzene exposure (mg/m^3*years)														
No exposure	82	Ref.	99	Ref.	38	Ref.	924	Ref.	515	Ref.	194	Ref.	355	Ref.
1–198 mg/m^3*years	6	0.8 (0.2–2.6)	10	1.8 (0.7–4.3)	6	**3.7 (1.2–11.7)**	109	1.0 (0.8–1.3)	59	1.1 (0.7–1.7)	29	1.3 (0.9–2.0)	44	0.5 (0.3–0.9)
199–550 mg/m^3*years	2	0.4 (0.1–1.8)	7	1.4 (0.6–3.0)	1	0.6 (0.1–4.2)	44	0.8 (0.6–1.0)	42	**1.4 (1.0–2.0)**	15	1.2 (0.7–2.0)	26	0.7 (0.4–1.1)
>550 mg/m^3*years	10	**2.3 (1.1–4.5)**	8	1.6 (0.8–3.4)	1	0.6 (0.1–4.4)	68	**1.2 (1.0–1.6)**	40	**1.4 (1.0–1.9)**	5	0.5 (0.2–1.3)	20	0.8 (0.5–1.3)
Test for trend (all subjects), P value		0.054		0.407		0.765		0.085		**0.027**		0.469		0.364
Test for trend (exposed only), P value		0.157		0.919		0.829		**0.040**		0.926		0.118		0.796

Cancer-free participants and other cancer cases are censored; multivariable analysis using Cox regression; adjusted for age at study entry, education, BMI, income, alcohol consumption, pack-years of smoking, and family history of cancer. Alcohol was not adjusted in leukemia models because of the observed interaction. Liver cancer was adjusted for all covariates listed + hepatitis; stomach cancer was adjusted for all variables listed + chronic gastritis.

Bold text indicates statistical significance.

[a]Cancer models further adjusted for pesticide exposure. Continuous measures applied for trend tests.

Ninetieth percentile (>863.2 mg/m^3*years) lung cancer [aHR = 1.5, (95% CI, 1.1–2.0), N = 39].

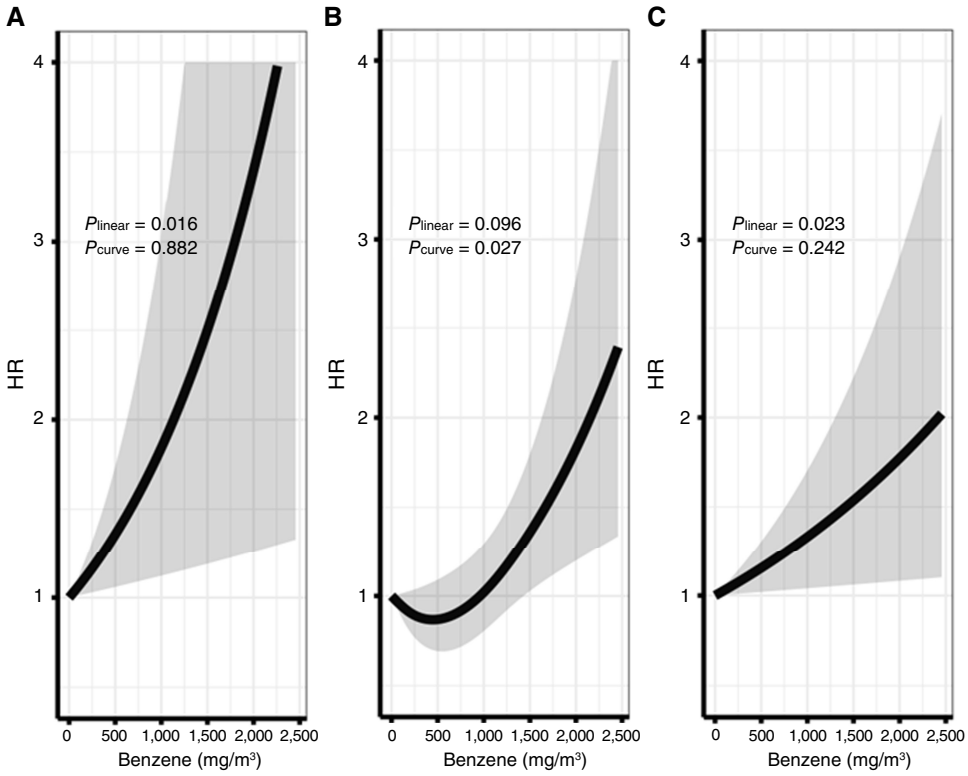

Figure 1.

Dose–response relationship between cumulative benzene exposure and the risk of leukemia (n = 18) adjusted for age at study entry, education, BMI, income, pack-years of smoking, family history of cancer, and pesticide exposure (**A**), lung cancer (n = 221) adjusted for age at study entry, education, BMI, income, alcohol consumption, pack-years of smoking, and family history of cancer (**B**), and stomach cancer (n = 141) adjusted for age at study entry, education, BMI, income, alcohol consumption, pack-years of smoking, family history of cancer, chronic gastritis, and pesticide exposure (**C**).

current-drinkers) or smoking status (ever- vs. never-smokers) were evaluated. Lastly, we evaluated a ≥5-year lag for time since enrollment for all cancers under study relative to their exposure status and cumulative benzene exposure. Tests for linear trend were done for both non–time lag and time lag analyses for continuous measures of cumulative benzene exposure among all participants and separately for benzene-exposed men. All statistical tests were based on two-tailed probability and a significance level set at α <0.05.

Ethics statement

The study was approved by the institutional review boards of Vanderbilt University and the Shanghai Cancer Institute, and written consent was obtained from all study participants.

Data availability

Data used in the article will be available (https://swhs-smhs.app.vumc.org/swhs_index.php) upon request, pending approval of data use agreement and proper payment for the related data and documentation preparation cost.

Results

Table 1 shows the characteristics of the study population by categories of cumulative benzene exposure. Among all participants, 21.2% (n = 13,041) had some level of benzene exposure. Age, BMI, education, income, ever smoked, pack-years of smoking, family history of cancer, alcohol consumption, and chronic gastritis differed significantly across benzene exposure levels. Compared with those with no benzene exposure, individuals with the highest exposure were more likely to be <50 years old, have less than a junior high school education, have a lower income, and have smoked and consumed alcohol (**Table 1**).

Table 2 shows the associations between benzene exposure levels and the risk of lung, liver, kidney, and stomach cancers, as well as myeloma, leukemia, and lymphoma. Men who had cumulative benzene exposure greater than 550 mg/m^3*years (e.g., 80th percentile) had a 2.3-fold risk of leukemia (aHR = 2.3; 95% CI, 1.1–4.5), a 20% increased risk of lung cancer (aHR = 1.2; 95% CI, 1.0–1.6), and a 40% increased risk of stomach cancer (aHR = 1.4; 95% CI, 1.0–1.9) compared with nonexposed men. Lung cancer risk further increased up to 1.5-fold (95% CI, 1.1–2.0) for cumulative exposure above the 90th percentile [>863.2 mg/m^3*years, (aHR = 1.5; 95% CI, 1.1–2.0)]. Stomach cancer risk was also significantly increased among those with exposures of 199 to 550 mg/m^3*years (aHR = 1.4; 95% CI, 1.0–2.0). Myeloma risk was significantly increased among men exposed to 1 to 198 mg/m^3*years (aHR = 3.7; 95% CI, 1.2–11.7) but not among those with a higher cumulative exposure compared with nonexposed men, although the latter was based on only one case. We did not observe any significant association between benzene exposure and the risk of lymphoma, liver cancer, or kidney cancer.

Restricted cubic spline regression analyses showed that the benzene–leukemia and benzene–stomach cancer associations were linear across all levels of exposure (P_{linear} = 0.016 and p_{linear} = 0.023, respectively), whereas the benzene–lung cancer association, only observed at high levels of exposure, was curved ($P_{nonlinear}$ = 0.027; **Fig. 1**).

Additional analyses were performed by histologic subtypes of leukemia, lymphoma, and lung and stomach cancers when sample size permitted. The results are presented in Supplementary Table S1. Due to the small sample size, most of the associations failed to reach statistical significance with few exceptions. The aHR for adenocarcinoma of the lung was 1.3 (95% CI, 0.8–2.1) when cumulative benzene exposure was >550 mg/m^3*year and 2.0 (95% CI, 1.2–3.4) when cumulative exposure

Table 3. Lag analysis for occupational benzene exposure, cumulative benzene exposure, and risk of lymphoma, leukemia, myeloma, lung cancer, stomach cancer, kidney cancer, and liver cancer (n = 61,377).

	Leukemia[a]		Lymphoma[a]		Myeloma[a]		Lung cancer		Stomach cancer[a]		Kidney cancer		Liver cancer[a]	
Benzene exposure	**Cases**	**aHR (95% CI)**	**Cases**	**aHR (95% CI)**	**Cases**	**aHR (95% CI)**	**Cases**	**aHR (95% CI)**	**Cases**	**aHR (95% CI)**	**Cases**	**aHR (95% CI)**	**Cases**	**aHR (95% CI)**
<5 years lag period occupational benzene exposure														
Unexposed	28	Ref.	35	Ref.	12	Ref.	318	Ref.	180	Ref.	76	Ref.	159	Ref.
Exposed	7	1.3 (0.4–3.7)	9	1.6 (0.7–3.9)	2	0.8 (0.1–6.5)	64	0.9 (0.7–1.1)	48	1.1 (0.7–1.8)	13	0.8 (0.4–1.5)	31	0.5 (0.3–1.0)
<5 years lag period (cumulative benzene exposure)														
No exposure	28	Ref.	35	Ref.	12	Ref.	318	Ref.	180	Ref.	76	Ref.	159	Ref.
1–198 mg/m^3*years	2	0.7 (0.1–5.3)	3	1.5 (0.3–7.6)	2	3.1 (0.4–24.9)	29	0.9 (0.6–1.2)	20	0.8 (0.4–1.8)	8	1.0 (0.5–2.1)	13	0.3 (0.1–0.8)
199–550 mg/m^3*years	1	0.5 (0.1–4.6)	3	1.8 (0.5–6.4)	0	—	10	0.5 (0.3–1.0)	15	1.3 (0.7–2.4)	3	0.7 (0.2–2.2)	13	0.8 (0.4–1.6)
>550 mg/m^3*years	4	2.0 (0.6–6.3)	3	1.5 (0.4–5.2)	0	—	25	1.2 (0.8–1.8)	13	1.1 (0.6–2.0)	2	0.5 (0.1–2.2)	5	0.4 (0.2–1.0)
Test for trend (all subjects), P value		0.303		0.975		0.473		0.291		0.322		0.325		0.123
Test for trend (exposed only), P value		0.374		0.334		0.296		**0.043**		0.737		0.260		0.634
≥5 years lag period occupational benzene exposure														
Unexposed	54	Ref.	64	Ref.	26	Ref.	606	Ref.	335	Ref.	118	Ref.	196	Ref.
Exposed	11	1.2 (0.6–2.7)	16	1.5 (0.8–2.8)	6	1.4 (0.5–4.1)	157	1.1 (0.9–1.3)	93	**1.5 (1.1–2.0)**	36	1.3 (0.9–1.9)	59	0.8 (0.5–1.3)
≥5 years lag period (cumulative benzene exposure)														
No exposure	54	Ref.	64	Ref.	26	Ref.	606	Ref.	335	Ref.	118	Ref.	196	Ref.
1–198 mg/m^3*years	4	0.9 (0.2–4.3)	7	2.1 (0.7–6.1)	4	**3.9 (1.0–15.7)**	80	1.1 (0.9–1.4)	39	1.3 (0.8–2.1)	21	1.5 (0.9–2.4)	31	0.6 (0.3–1.3)
199–550 mg/m^3*years	1	0.4 (0.0–2.7)	4	1.2 (0.4–3.2)	1	0.8 (0.1–5.7)	34	0.8 (0.6–1.2)	27	**1.5 (1.0–2.3)**	12	1.5 (0.8–2.7)	13	0.6 (0.3–1.2)
>550 mg/m^3*years	6	2.1 (0.9–5.1)	5	1.6 (0.6–3.9)	1	0.9 (0.1–6.6)	43	1.3 (0.9–1.7)	27	**1.6 (1.1–2.4)**	3	0.5 (0.2–1.7)	15	1.2 (0.6–2.1)
Test for trend (all subjects), P value		0.182		0.590		0.369		0.171		**0.036**		0.892		0.811
Test for trend (exposed only), P value		0.334		0.941		0.174		0.225		0.944		0.281		0.500

Cancer-free participants and other cancer cases are censored; multivariable analysis using Cox regression; adjusted for age at study entry, education, BMI, income, alcohol consumption, pack-years of smoking, and family history of cancer. Alcohol was not adjusted in leukemia models. Liver cancer was adjusted for all covariates listed + hepatitis; stomach cancer was adjusted for all variables listed + chronic gastritis.
Bold text indicates statistical significance.
[a]Cancer models further adjusted for pesticide exposure. Lag analysis defined at time since enrollment. Continuous measures applied for trend tests.
Ninetieth percentile (>863.2 mg/m^3*years) lung cancer ≥5 years lag period [aHR = 1.5, (95% CI, 1.0–2.3), N = 25].

reached 863.2 mg/m^3*years (90th percentile). A significant association between benzene exposure and adenocarcinoma of the stomach was observed among those ever exposed to benzene (aHR = 1.3; 95% CI, 1.0–1.7) but not for cumulative benzene exposure >550 mg/m^3*year (aHR = 1.4; 95% CI, 0.9–2.1). Positive but not significant associations were observed between cumulative benzene exposure and AML and NHL (see Supplementary Table S1).

Table 3 shows the results of analyses stratified by a 5-year time lag since cohort enrollment. Among men exposed to benzene, stomach cancer risk increased by 50% after 5 or more years since study enrollment (aHR = 1.5; 95% CI, 1.1–2.0). Additionally, cumulative benzene exposure between 199 and 550 mg/m^3*years and >500 mg/m^3*years was associated with an increased risk of stomach cancer during the ≥5-year lag period (aHR = 1.5; 95% CI, 1.0–2.3 and aHR = 1.6; 95% CI, 1.1–2.4, respectively). Lastly, cumulative benzene levels between 1 and 198 mg/m^3*years were associated with increased risk of myeloma (aHR = 3.9; 95% CI, 1.0–15.7) with a ≥5-year lag period. The benzene–lung cancer association increased during the ≥5-year lag period when the cumulative exposure reached >863.2 mg/m^3*years (aHR = 1.5; 95% CI, 1.0–2.3). No significant association was observed with a <5-year lag period for all cancers under study.

Table 4 shows the median age at diagnosis for all cancers under study by benzene exposure. Men exposed to benzene were more likely to be diagnosed with leukemia (7 years), lymphoma (6 years), myeloma (4 years), lung cancer (3 years), stomach cancer (3 years), kidney cancer (3 years), and liver cancer (5 years) at a younger age compared with men who had no benzene exposure. No significant difference in age at diagnosis was observed for myeloma and kidney cancer across all benzene measurements.

Table 5 shows the results of multiplicative interaction assessments between benzene exposure (yes/no) and alcohol consumption (current vs. noncurrent drinker) and ever-smoking status on the risk of leukemia, lymphoma, and lung and stomach cancers. No significant interactions were observed with the exception of alcohol consumption and leukemia risk. Men with benzene exposure who were current alcohol drinkers had a threefold risk of leukemia (aHR = 3.0; 95% CI, 1.1–8.3), whereas a null association was found among nondrinkers ($P_{interaction}$ = 0.047). No significant interaction was observed between ever-drinking and benzene on leukemia risk.

Discussion

This analysis applied a population-specific JEM to estimate cumulative benzene exposure from jobs to evaluate its associations with cancer risk in a large population-based cohort of men in Shanghai, China. We found that men with a history of working in occupations with high benzene exposure (e.g., 80th percentile) were at an increased risk of leukemia and lung and stomach cancers, as well as having their cancer diagnosed at a younger age, compared with those working at jobs with no benzene exposure. Additionally, for risk of leukemia, we observed a multiplicative interaction between benzene exposure and alcohol consumption, although the association estimates were imprecise with wide CIs.

Several of the most recent and informative studies on benzene exposure and cancer risk with large cohort sizes, longer follow-up times, higher occupational benzene exposures, or more robust exposure assessments did not control for potential confounders, such as smoking, among benzene-exposed persons (2). This limitation was emphasized by the IARC in their most recent monograph on benzene exposure and the risk of lung cancer (2). The Shanghai Men's Health Study is a large cohort study (n = 61,469) with a long follow-up time and applied robust occupational benzene exposure assessment methodologies. The extensive baseline survey data enabled comprehensive adjustment for various potential confounders, including pack-years of smoking. This allowed for an assessment of multiplicative interactions between occupational benzene exposure and alcohol consumption and smoking status.

Epidemiologic studies of benzene-exposed workers showed increased risks of leukemia (15–17), myeloma (18), and lymphoma (including NHL; refs. 19–21), and associations with lung (22–24), stomach (22), and liver cancers were also reported (22). The findings from our study are, in general, consistent with previous studies, particularly the results of Yin and colleagues' study (22), which found increased risks of leukemia and lung and stomach cancers among benzene-exposed workers in China, as well as the findings on NHL from the Shanghai Women's Health Study, a large population-based cohort study conducted in the same region (21). The findings from our study on the association of benzene with leukemia are also consistent with the conclusions of the IARC and more recent reports (1, 2, 13). In our study, we found that the association of cumulative benzene exposure with leukemia and

Table 4. Median age of cancer diagnosis by occupational and cumulative benzene exposures (n = 61,377).

Benzene exposure	Leukemia		Lymphoma		Myeloma		Lung cancer		Stomach cancer		Kidney cancer		Liver cancer	
	MA	*P*	MA	*P*	MA	*P*	MA	*P*	MA	*P*	MA	*P*	MA	*P*
Occupational benzene exposure														
Unexposed	70.3	0.304	69.9	0.065	67.2	0.426	69.7	<0.000	70.4	0.035	65.3	0.532	65.2	0.018
Exposed	63.6		63.5		63.6		66.3		67.5		61.9		60.4	
Cumulative benzene exposure (mg/m^3*years)														
No exposure	70.3	0.228	69.9	0.172	67.2	0.446	69.7	<0.000	70.4	0.033	65.3	0.232	65.2	0.003
1–198 mg/m^3*years	57.1		59.1		63.6		65.2		66.0		62.8		59.4	
199–550 mg/m^3*years	55.1		64.0		53.2		62.9		65.8		58.9		59.2	
>550 mg/m^3*years	71.0		68.9		72.7		69.6		71.9		71.2		70.0	

NOTE: Kruskal–Wallis H tests and Mann–Whitney U tests were used for assessing categorical and binary median relationships, respectively.
Abbreviations: MA, median age; *P*, *P* value.

Table 5. Association of occupational benzene exposure with leukemia, lymphoma, and lung and stomach cancers by alcohol consumption and smoking status.

Cumulative benzene exposure (mg/m^3*years)	Alcohol consumption					Ever smoked				
	Yes		No			Yes		No		
	Cases	aHR (95% CI)	Cases	aHR (95% CI)	$P_{interaction}$	Cases	aHR (95% CI)	Cases	aHR (95% CI)	$P_{interaction}$
Leukemia[a]										
N = 100										
Benzene exposure										
No	15	Ref.	67	Ref.	**0.047**	52	Ref.	30	Ref.	0.208
Yes	8	**3.0 (1.1–8.3)**	10	0.9 (0.4–2.0)		10	0.8 (0.3–2.1)	8	2.1 (0.9–5.1)	
Lymphoma[a]										
N = 124										
Benzene exposure										
No	20	Ref.	62	Ref.	0.890	62	Ref.	37	Ref.	0.195
Yes	6	1.3 (0.4–4.3)	14	1.6 (0.9–2.9)		14	1.2 (0.6–2.4)	11	**2.3 (1.1–4.9)**	
Lung cancer										
N = 1,145										
Benzene exposure										
No	325	Ref.	599	Ref.	0.347	778	Ref.	146	Ref.	0.894
Yes	95	1.1 (0.9–1.4)	126	1.0 (0.8–1.2)		195	1.0 (0.9–1.2)	26	1.0 (0.7–1.6)	
Stomach cancer[a]										
N = 656										
Benzene exposure										
No	171	Ref.	344	Ref.	0.526	348	Ref.	167	Ref.	0.717
Yes	57	1.2 (0.7–1.8)	84	**1.5 (1.1–2.0)**		102	**1.3 (1.0–1.7)**	39	**1.6 (1.0–2.4)**	

NOTE: Cancer-free participants and other cancer cases are censored; multivariable analysis using Cox regression; adjusted for age at study entry, education, BMI, income, alcohol consumption (smoking-only model), pack-years of smoking (alcohol-only models), and family history of cancer. Stomach cancer was further adjusted for chronic gastritis.

Bold text indicates statistical significance.

[a]Cancer models further adjusted for pesticide exposure.

stomach cancer followed a linear dose–response trend. It is noteworthy that in a meta-analysis of 15 studies (9 presenting cumulative exposure), Khalade and colleagues (17) reported that the high–benzene exposure category, i.e., >100 ppm*year (equivalent to >325 mg/m^3*year), was associated with a 2.6-fold risk of leukemia, whereas in our study, we observed a 2.3-fold risk of leukemia being associated with a higher cumulative benzene exposure, i.e., >550 mg/m^3*years. It should be noted that most of the studies included in Khalade and colleagues' (17) meta-analysis were case–control studies and did not control for major confounders (e.g., smoking) or assess potential interactions with alcohol consumption. We found that the benzene–lung cancer association seemed to be nonlinear, with an increased risk starting at a higher cumulative exposure level. In the present study, higher cumulative benzene exposure (>863.2 mg/m^3*years) was associated with adenocarcinoma of the lung. This finding partially agrees with a study by Wan and colleagues (32) in which they also found that benzene exposure was associated with an increased risk of adenocarcinoma of the lung, with a linear dose–response trend, in contrast to our findings of a nonlinear relationship. It should be noted that our histologic subtype analyses were limited by a small sample size. The potential confounding from smoking, which was associated with increased risk of lung (33), stomach, (34) and liver cancers (35), as well as leukemia (36), was often not controlled for in previous studies and could have also contributed to observed inconsistencies. Lacking information on cumulative exposure dose from some of the previous studies also prevented an in-depth evaluation of the reasons for inconsistent results across studies.

We also found that the median age at diagnosis of lung, stomach, and liver cancers was statistically lower among men with benzene exposure compared with those without such exposure. We did not observe asignificant age onset association for liver cancer. Aggregately, these data support the creditability of the positive associations found in our study.

Nakajima and colleagues' (37) study in rats showed that the metabolic process of benzene is accelerated through ethanol consumption. We found that alcohol consumption modified the association of benzene exposure with leukemia, with benzene exposure being linked to a threefold risk among alcohol consumers, although the risk estimate is imprecise. In contrast, no association was observed among nondrinkers. Given that benzene metabolites are potentially more toxic to human health (38), research directly evaluating the biological efforts of benzene's metabolites, incorporating alcohol consumption, is warranted. Additionally, Kim and colleagues (39) found that smokers had higher levels of hydroquinone and catechol (metabolites of benzene) than nonsmokers. However, we found no evidence of interaction between benzene and smoking in the current study.

Our study has several strengths, including assessing occupational benzene exposure and cancer risk in a large population-based cohort with a complete job history, a high response rate, and a high follow-up rate. Extensive information on lifestyle factors, disease history, and other covariates allowed for careful control of confounders. Cancer ascertainment is likely to be complete because outmigration from Shanghai was extremely low for this cohort and cancer and death registrations are legally mandated in Shanghai and cross-checked.

Additionally, the JEM we used had incorporated temporal changes that likely improved the accuracy of benzene exposure across jobs. However, there are also limitations to consider. First, similar to most of the previous cohort studies, our study did not measure occupational benzene exposure directly. The JEMs used in our study were developed by industrial hygienists who assigned benzene exposure based on participants' job codes and China's MAC for benzene, established in 1980. Thus, exposure misclassification cannot be ruled out. Nevertheless, these misclassifications are likely to bias point estimates toward the null, though we are not able to determine the magnitude. This study was also limited by a lack of occupational benzene exposure updates after enrollment. The median age at cohort enrollment in our study is 53.2 years. Because the retirement age for male manufacturing workers was 55 years in Shanghai, exposure misclassification due to a lack of exposure updates should not be a big concern. However, it is possible that survival bias may be present as workers with benzene exposure might have died of cancer before reaching the study eligibility age (40 years). This bias could lead to an underestimation of the benzene–cancer association. Although we have adjusted for a wide range of covariates in the analysis, there is a possibility that residual confounding, particularly from unmeasured confounding variables, remains. This includes environmental exposures, such as particulate matter and heavy metals; ref. 40) and polycyclic aromatic hydrocarbons (41), for certain cancers under study. However, we have assessed occupational exposures to pesticides, silica, and asbestos and found that only pesticide exposure was a potential confounder for cancers under study, with the exception of lung and liver cancers. Accordingly, occupational pesticide exposure was not adjusted in the analyses of lung and liver cancers. Lastly, because multiple cancers were assessed in this study, an *a priori* decision was made to include all known or suspected risk factors as covariates in our analysis. We acknowledge that adjustment for nonconfounders (e.g., family history of cancer) may have reduced the statistical power of the study.

In conclusion, we observed an elevated risk of leukemia, lung cancer, and stomach cancer among Chinese men who were employed in jobs with high benzene exposure, and the risk increased with cumulative exposure. Our findings on the association of benzene with an increased risk of lung cancer and leukemia are consistent with the proposed mechanisms detailed by McHale and colleagues (4). We found that alcohol consumption modified the benzene–leukemia risk association. Our study adds additional evidence on the carcinogenic potential of occupational benzene exposure.

Authors' Disclosures

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Authors' Contributions

D. DeMoulin: Conceptualization, formal analysis, validation, methodology, writing–original draft. **H. Cai:** Formal analysis, visualization, writing–review and editing. **R. Vermeulen:** Methodology, writing–original draft. **W. Zheng:** Resources, data curation, funding acquisition, writing–review and editing. **L. Lipworth:** Writing–review and editing. **X.-O. Shu:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, methodology, project administration, writing–review and editing.

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Note

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