Exhibit 270

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A retrospective cohort study of cause-specific mortality and incidence of hematopoietic malignancies in Chinese benzene-exposed workers

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Benzene exposure has been causally linked with acute myeloid leukemia (AML), but inconsistently associated with other hematopoietic, lymphoproliferative and related disorders (HLD) or solid tumors in humans. Many neoplasms have been described in experimental animals exposed to benzene. We used Poisson regression to estimate adjusted relative risks (RR) and the likelihood ratio statistic to derive confidence intervals for cause-specific mortality and HLD incidence in 73,789 benzene-exposed compared with 34,504 unexposed workers in a retrospective cohort study in 12 cities in China. Follow-up and outcome assessment was based on factory, medical and other records. Benzene-exposed workers experienced increased risks for all-cause mortality (RR = 1.1, 95% CI = 1.1, 1.2) due to excesses of all neoplasms (RR = 1.3, 95% CI = 1.2, 1.4), respiratory diseases (RR = 1.7, 95% CI = 1.2, 2.3) and diseases of blood forming organs (RR = ∞, 95% CI = 3.4, ∞). Lung cancer mortality was significantly elevated (RR = 1.5, 95% CI = 1.2, 1.9) with similar RRs for males and females, based on three-fold more cases than in our previous follow-up. Significantly elevated incidence of all myeloid disorders reflected excesses of myelodysplastic syndrome/acute myeloid leukemia (RR = 2.7, 95% CI = 1.2, 6.6) and chronic myeloid leukemia (RR = 2.5, 95% CI = 0.8, 11), and increases of all lymphoid disorders included excesses of non-Hodgkin lymphoma (RR = 3.9, 95%CI = 1.5, 13) and all lymphoid leukemia (RR = 5.4, 95%CI = 1.0, 99). The 28-year follow-up of Chinese benzene-exposed workers demonstrated increased risks of a broad range of myeloid and lymphoid neoplasms, lung cancer, and respiratory diseases and suggested possible associations with other malignant and non-malignant disorders.

Epidemiology

Workers and the general population have been exposed to benzene for more than a century.[1] Historically, benzene has been a key chemical component in the manufacturing of shoes, leather, and rubber goods, paint, dyes, inks, lubricants, detergents, pesticides, and pharmaceuticals, and more recently in the production of styrene, polymers, latexes, hydroquinone, benzene hexachloride, plastics and insecticides.[1] Jobs in crude oil refining and in sea and land transport of crude oil and gasoline also involve exposure to benzene. Surveys have identified more than 2.1 million benzene-exposed manufacturing workers in the European Union,[2] the United States,[3] and China,[4] although exposure

Key words: benzene, leukemia, lymphoma, lung cancer, mortality

Abbreviations: ALL: acute lymphocytic leukemia; AML: acute myeloid leukemia; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; CI: confidence intervals; HLD: hematopoietic, lymphoproliferative and related disorders; ICD: international classification of diseases; MDS: myelodysplastic syndrome; NHL: non-Hodgkin lymphom; RR: relative risk

Additional Supporting Information may be found in the online version of this article.

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What's new?

More than two million workers worldwide are exposed to benzene each year. In this long-term study of Chinese workers, the authors found that chronic benzene exposure was associated with a substantial increase in the risk of myeloid and lymphoid neoplasms, lung cancer, and respiratory diseases. The results also suggest possible associations with other malignant and non-malignant disorders.

levels were generally higher in China than in western countries at the time of these surveys due to long-standing regulations in western countries. Possible sources of benzene exposure to the general population include gasoline filling stations, motor vehicle exhaust, tobacco smoke, contaminated water and foods, and leaking underground gasoline storage tanks.[1]

The International Agency for Research on Cancer (IARC) concluded in 1982 that there was sufficient evidence linking benzene with leukemia, particularly acute myeloid leukemia (AML), and numerous investigations have confirmed that benzene increases risk of AML.[1] Acquired aplastic anemia has long been associated with benzene exposure based on small numbers of heavily exposed cases.[5–7] More limited evidence[8,9] has implicated benzene in myelodysplastic syndrome (MDS), a heterogeneous group of clonal stem cell disorders characterized by low peripheral blood counts, dysplasia of one or more myeloid cell lineages, and ineffective hematopoiesis that may progress to AML.[10]

On the basis of several studies, meta-analyses,[11,12] and reviews,[1] benzene has been inconsistently associated with several types of lymphoid neoplasms.[8,13–17] The inconsistencies may reflect small case numbers and evolving disease classifications. Four investigations have described relationships of benzene with risk of lung cancer.[13,18–20] A few studies have linked benzene with other solid tumors, but findings have been inconsistent.[1,21]

Since 1987, the International Agency for Research on Cancer has determined that there is sufficient evidence documenting the carcinogenicity of benzene in experimental animals. Inhalation of benzene increases incidence of lymphoid and myeloid neoplasms in male and female mice; Zymbal gland carcinomas, squamous cell carcinomas of the preputial gland and lung adenomas in male mice; and Zymbal gland carcinomas, liver adenomas, and forestomach and oral cavity carcinomas in female rats. Oral administration of benzene increased the incidence of Zymbal gland carcinomas, oral cavity papillomas and carcinomas, and forestomach acanthomas in rats of both sexes; carcinomas of the tongue, papillomas and carcinomas of the skin, lip, and palate in male rats; forestomach carcinomas in female rats; Zymbal gland carcinomas, forestomach papillomas and carcinomas in mice of both sexes; and lung adenomas and liver carcinomas, adrenal gland pheochromocytomas, harderian gland adenomas and preputial gland squamous cell carcinomas in male mice.[1]

In China, benzene has been used for decades to manufacture paint, shoes and other leather products, sports equipment, machinery, and electronics.[22,23] After an initial report of mortality in a cohort of Chinese benzene-exposed workers followed-up during 1972–1981,[4] we expanded the cohort and reported on all-cause mortality and incidence of hematopoietic, lymphoproliferative and related disorders (hereafter abbreviated HLD) risks during 1972–1987.[6,7,18] The aim of the present study was to provide information on long-term health effects in one of the first benzene-exposed, non-western cohorts to be studied through an additional 12 years (1988–1999) of follow-up. Other novel features of this population include the large size, the diversity of industries represented in hundreds of factories in 12 cities in China, and a substantial fraction of female benzene-exposed workers.

Material and Methods

Study population

The present collaborative project, conducted by the National Institute of Occupational Health and Poison Control in the Chinese Center for Disease Control and Prevention (previously the Institute of Occupational Medicine in the Chinese Academy of Preventive Medicine (CAPM)) and the Division of Cancer Epidemiology and Genetics in the U.S. National Cancer Institute (NCI), assessed all-cause mortality and HLD incidence in a 28-year retrospective cohort follow-up (1972–1999) of Chinese benzene-exposed ($N = 74{,}827$) and unexposed ($N = 35{,}804$) workers carried out during 1999–2000. A detailed description of the methods used to identify and follow-up the cohort during 1972–1987 is provided elsewhere.[6,7,18] Briefly, benzene-exposed workers in the spray and brush painting (coatings), rubber, chemical (including pharmaceutical manufacturing), shoe-making and other (including printing and insulation) industries were identified from those employed any length of time during 1972–1987 in 1,427 work units (departments) in 672 factories in 12 Chinese cities (see Table 1). Unexposed workers were assembled from those employed during 1972–1987 in 69 work units in which benzene was not used in the same 672 factories (mixed factories) and from 40 additional factories in which benzene exposure was not present. All workers were identified from initial employment, salary and other factory records. Factory- and job title-specific information on use of benzene-containing materials formed the basis for determining whether workers held benzene-exposed or unexposed jobs. The study obtained initial and annual renewal of ethics approval from the Chinese Center for Disease Control and Prevention (formerly the Chinese Academy of Preventive

Table 1. Industry/factory characteristics and description of Chinese benzene-exposed and unexposed workers followed-up during 1972–1999.[1]

Characteristics	Exposed no. (%)	Unexposed no. (%)	Total no. (%)
Total	73,789 (100.0)	35,504 (100.0)	109,293 (100.0)
Factory/industry city			
Shanghai	11,199 (15.2)	7,633 (21.5)	18,832 (17.2)
Tianjin	9,463 (12.8)	2,794 (7.9)	12,257 (11.2)
Chengdu	7,889 (10.7)	3,436 (9.7)	11,325 (10.4)
ChongQing	10,277 (13.9)	3,589 (10.1)	13,866 (12.7)
Harbin	8,026 (10.9)	4,220 (11.9)	12,246 (11.2)
Shenyang	6,831 (9.3)	3,638 (10.2)	10,469 (9.6)
Jinzhou	2,960 (4.0)	2,983 (8.4)	5,943 (5.4)
Zhengzhou	3,644 (4.9)	2,145 (6.0)	5,789 (5.3)
Luoyang	1,792 (2.4)	969 (2.7)	2,761 (2.4)
Guangzhou	3,276 (4.5)	715 (2.0)	3,991 (3.7)
Nanchang	6,433 (8.7)	2,648 (7.5)	9,081 (8.3)
Kaifeng	1,999 (2.7)	734 (2.1)	2,733 (2.5)
Sex			
Male	38,329 (51.9)	20,628 (58.1)	58,957 (53.9)
Female	35,460 (48.1)	14,876 (41.9)	50,336 (46.1)
Age at first exposure/hire (yrs)			
<20	24,115 (32.7)	16,227 (45.7)	40,342 (36.9)
20–29	32,513 (44.1)	15,653 (44.1)	48,166 (44.1)
30–39	11,665 (15.8)	2,769 (7.8)	14,434 (13.2)
≥40	5,496 (7.4)	855 (2.4)	6,351 (5.8)
Year of first exposure/hire			
≤1949	178 (0.2)	508 (1.3)	686 (0.6)
1950–54	1,509 (2.0)	1,775 (5.0)	3,284 (3.0)
1955–59	5,141 (7.0)	5,471 (15.4)	10,612 (9.7)
1960–64	5,479 (7.4)	2,670 (7.5)	8,149 (7.5)
1965–71	13,991 (19.0)	6,889 (19.4)	20,880 (19.1)
1972–79	22,745 (30.8)	9,656 (27.2)	32,401 (29.6)
1980–87	24,746 (33.5)	8,535 (24.1)	33,281 (30.5)
Time since first exposure/hire (yrs)			
0–1	79 (0.1)	20 (0.1)	99 (0.1)
2–9	206 (0.3)	103 (0.3)	309 (0.3)
10–14	7,425 (10.1)	2,564 (7.2)	9,989 (9.1)
15–24	36,194 (49.1)	14,297 (40.3)	50,491 (46.2)
25–34	19,170 (26.0)	8,998 (25.3)	28,168 (25.8)
≥35	10,715 (14.5)	9,522 (26.8)	20,237 (18.5)
Age at end of follow-up (yrs)			
<40	17,618 (23.9)	7,806 (22.0)	25,424 (23.3)
40–49	24,983 (33.9)	12,004 (33.8)	36,987 (33.8)
50–59	14,420 (19.5)	7,341 (20.7)	21,761 (19.9)
60–69	11,311 (15.3)	6,109 (17.2)	17,420 (15.4)
≥70	5,457 (7.4)	2,244 (6.3)	7,701 (7.1)
Industry			

Table 1. Industry/factory characteristics and description of Chinese benzene-exposed and unexposed workers followed-up during 1972–1999. (Continued)

Characteristics	Exposed no. (%)	Unexposed no. (%)	Total no. (%)
Unexposed		35,504 (100.0)	35,504 (32.5)
Exposed	73,789 (100.0)		73,789 (67.5)
Coatings	37,422 (50.7)		37,422 (34.2)
Rubber	3,244 (4.4)		3,244 (3.0)
Chemical	9,836 (13.3)		9,836 (9.0)
Shoe	7,515 (10.2)		7,515 (6.9)
Other/mixed	15,772 (21.4)		15,772 (14.4)

[1]Excludes subjects exposed or employed (unexposed) <0.5 years (1,012 exposed; 284 unexposed) and subjects under age 12 at start of exposure or employment (unexposed) (26 exposed; 16 unexposed).

Medicine) Ethics Review Committee and the NCI Special Studies Institutional Review Board.

Follow-up of the population

Using salary, personnel, and medical records from factories along with hospital records and death certificates, we collected data retrospectively for the initial follow-up during 1972–1987. Subsequently, follow-up was extended through 1999 to assess vital status and cause of death and incidence of HLD.

Ascertainment and validation of HLD and lung cancer diagnoses

Suspected incident cases of HLD were identified based on health care information reported in factory records and medical records for working and retired subjects in the cohort. Deaths from HLD, lung cancer, and other causes were identified from factory records, medical records and death certificates. For all exposed and unexposed workers with suspected diagnoses of HLD and lung cancer, we sought medical records for pathology reports, laboratory studies, diagnostic procedures, radiologic imaging and other relevant reports, treatment records, and death certificates. Information was abstracted onto standardized forms by physician-investigators blinded to benzene exposure status of the patients. For suspected diagnoses of HLD, all abstracted forms, medical records, and available hematopathologic laboratory data and slides were reviewed systematically by expert Chinese and US hematopathologists.[24] HLD cases were coded using the ninth edition of the International Classification of Diseases (ICD-9) for mortality[25] and a modification of ICD-9 that reflected key elements of the third edition of the ICD for Oncology.[26] For all exposed and unexposed workers with lung cancer as the underlying or contributory cause of death, the diagnostic materials were evaluated systematically by expert oncologists and pathologists. Lung cancer cases were coded using ICD-9.

Statistical analysis

In the extended 28-year follow-up, statistical analyses excluded workers exposed to benzene for <6 months (1,012 workers) and unexposed workers who were employed for <6 months (284 workers) to reduce the potential for including serious health outcomes unlikely to be due to benzene exposure. Also excluded were workers who were <12 years of age at the time of first exposure or hire (26 exposed and 16 unexposed), since employment at such young ages seemed implausible. Person-years were accumulated beginning at the date that the 6 month requirement was met or January 1, 1972, whichever occurred later, and ending at the date of death (or date of diagnosis for HLD incidence analyses), date lost to follow-up, or December 31, 1999, whichever occurred earliest. There were no missing data for any of the variables used in the analyses. Those with unknown cause of death were treated as a separate cause of death category, but only 0.4% of the deaths had unknown cause. To allow for a possible latent period, we excluded the first 2 years for HLD or 10 years for all other endpoints following the date of first exposure or hire. Analyses of mortality and HLD incidence compared disease rates in the benzene-exposed to rates in the unexposed by calculating relative risks (RR) using Poisson regression with adjustment through stratification on sex, attained age (*e.g.,* age at observation in 5-year intervals), and attained calendar year (*e.g.,* calendar year of observation for the periods 1972–1977, 1978–1982, 1983–1987, 1988–1991, 1992–1995, 1996–1999). For deaths and HLD cases, attained age/calendar year is the age/calendar year at death or diagnosis. To investigate the potential influence of data from any one city on the overall results, we conducted analyses that excluded data from one city at a time and found no substantive differences. Parameter estimates were computed using maximum likelihood methods. Confidence intervals and two-sided p values were based on the likelihood ratio statistic. Tests for heterogeneity and trend among the RR for different subgroups were based on the likelihood ratio tests and direct evaluation of the likelihood ratio profile. Analyses were implemented using the AMFIT module of the software package Epicure.[27] Additional detail on statistical methods is provided in Supporting Information I.

A comprehensive ongoing state-of-the-art hierarchical statistical model for reconstructing exposure levels was initiated after the extended cohort follow-up and restricted to a subset

of 2,898 subjects using a case-cohort design for efficiency. Because updated work histories and detailed occupational exposure information were only available for a small group of subjects and selected disease endpoints (*i.e.,* HLD, lung cancer and benzene poisoning), we did not examine quantitative metrics of exposure. Instead we evaluated the limited work-related metrics available for the entire population (*e.g.,* age at first exposure, year of first exposure, time since first exposure, and industry of employment).

Results

Population characteristics

By the end of the 1972–1999 follow-up, similar proportions of exposed and unexposed workers were known to be alive (exposed 92.0%; unexposed 92.5%) and deceased (exposed 6.2%; unexposed 5.6%). The loss to follow-up for the period 1972–1987 was 0.14%, while the loss to follow-up for the period 1988–1999 was 1.7%. For both periods, the loss to follow-up was similar for exposed and unexposed workers. Although there is indeed greater loss to follow-up in the later period, a loss <2% is generally considered very good. Exposed workers included 51.9% males, 32.7% under age 20 at hire, 64.3% hired in 1972 or later, and 9.0% hired before 1960. Unexposed workers included 58.1% males, 45.7% under age 20 at hire, 51.3% hired in 1972 or later, and 20.4% hired before 1960 (Table 1). Approximately half (50.7%) of the exposed workers were in the coatings industry. By the end of follow-up in 1999, only 13% of workers were still employed in study factories. More than half of the exposed (57.8%) and unexposed (55.8%) workers were <50-years old at the end of follow-up, consistent with the typical retirement ages of 50 years for males and 45 years for females in China during the study period.

Mortality

Benzene-exposed workers experienced a 13% excess risk for all causes of death, due primarily to a 28% increase in all malignant neoplasms, a 70% increase in respiratory diseases, and an increase in diseases of blood-forming organs (Table 2). For solid tumors, benzene-exposed workers demonstrated a significant 50% excess of lung cancer ($p < 0.001$), and borderline significant increases ($p < 0.1$) of cancers of the nasopharynx ($p = 0.076$), esophagus ($p = 0.056$), colon/rectum ($p = 0.062$), pancreas ($p = 0.075$) and uterus ($p = 0.092$). HLD increases observed in benzene-exposed workers included elevated mortality from lymphoma (RR = 4.0, 95% CI = 1.6, 13.4), leukemia (RR = 2.8, 95% CI = 1.6, 5.5) and MDS (RR = ∞, 95% CI = 1.5, ∞).

Elevated risk was also observed for non-malignant diseases of blood-forming organs (RR = ∞, 95% CI = 3.4, ∞). For other non-malignant disorders, there was a significant excess for respiratory diseases (RR = 1.7, 95% CI = 1.2, 2.3) (Table 2) due primarily to significant increases in risk for the combined category of bronchitis/emphysema and asthma (RR = 1.5, 95% CI = 1.03, 2.2; $p = 0.034$) and a nearly significant increase in risk for other and unspecified respiratory diseases (RR = 1.6, 95% CI = 0.97, 2.9; $p = 0.065$). We found no evidence of excess mortality for circulatory, digestive (including cirrhosis of the liver), or urinary tract diseases. A non-significant increase for occupational diseases included one death from unspecified toxic effects of benzene.

More detailed analyses of mortality from lung cancer and respiratory diseases are shown in Table 3. Lung cancer RRs were nearly identical for males and females, although the 50% excess mortality was statistically significant only for males. For both sexes combined, there were no significant trends in risk of lung cancer according to age or year of first exposure/hire, time since first exposure/hire, or attained age, but there was heterogeneity in the RR by industry ($p = 0.049$), with the highest RR for workers in the rubber and coatings industries. RRs for lung cancer were significantly elevated and of the same magnitude in the original (1972–1987) and extended (1988–99) follow-up periods. Results based on males alone were very similar to those for both sexes combined (Table 3). Data on females were sparse, but no significant trends or differences were found.

RRs for respiratory diseases were significantly higher for males than females ($p = 0.02$), and were elevated only in males (RR = 1.9, 95%CI 1.4, 2.7). For both sexes combined, the RR of respiratory diseases decreased with increasing age at first exposure/hire ($p = 0.005$) and year of first exposure/hire ($p = 0.038$), and tended to increase with increasing time since first exposure/hire ($p = 0.073$). There were no significant differences by age at death, calendar year period of death, or industry. When analyses were restricted to males, the trend results were similar to those for both sexes combined although the trend with time since first exposure/hire was stronger ($p = 0.042$) and the trend with year of first exposure/hire was weaker ($p = 0.075$). For males, heterogeneity by industry was suggested ($p = 0.077$) with the highest risks in the coatings (RR = 2.4, 95%CI = 1.7, 3.5) and chemical (RR = 2.0 (95%CI = 1.1, 3.3) industries. Approximately 80% of the deaths from respiratory diseases deaths occurred in workers first exposed at age 30 years or older compared to 62% of the lung cancer deaths.

Leukemia mortality RRs were similarly elevated in benzene-exposed males and females (Table 4). RRs declined with increasing age at first exposure/hire ($p = 0.054$) and attained age $p = 0.036$), and were especially high for those under age 20 years at first exposure/hire or at attained age younger than 40 years. Although RRs were highest 2–9 years following first exposure, leukemia mortality was not related to year of first exposure/hire, and the trend with time since first exposure/hire was not significant. RRs were significantly elevated in benzene-exposed workers during both the original and the more recent follow-up periods. There was little evidence of heterogeneity by industry.

HLD incidence

HLD incidence results are shown in Tables 5–7. Overall, RRs were elevated significantly for lymphoma, non-Hodgkin lymphoma (NHL), all lymphoid leukemia, all myeloid leukemia,

Epidemiology

Table 2. Relative risk of mortality among Chinese benzene-exposed versus unexposed workers followed-up during 1972–1999 by (or according to) cause of death.[1]

Causes of death (ICD-9 codes)	No. deaths exposed	No. deaths unexposed	RR (95%CI) (1972–1999)
All causes (000-989)	4,287	1,908	1.13 (1.07, 1.22)
Infectious diseases (000-136)	15	6	1.4 (0.6, 4.0)
Neoplasms, all (140–239)[2]	1,347	562	1.28 (1.16, 1.41)
Buccal/pharynx excluding nasopharynx (140–146, 148, 149)	10	6	0.9 (0.3, 2.7)
Nasopharynx (147)	29	9	1.9 (0.9, 4.3)
Esophagus (150)	70	24	1.6 (1.0, 2.5)
Stomach (151)	211	108	1.0 (0.8, 1.3)
Colon/rectum (153,154)	79	28	1.5 (1.0, 2.3)
Liver (155,156)	286	141	1.2 (0.9, 1.4)
Pancreas (157)	45	15	1.7 (1.0, 3.1)
Lung (162)	351	119	1.5 (1.2, 1.9)
Female breast (174)	32	12	1.2 (0.6, 2.5)
Uterus (182)	19	3	2.6 (0.9, 10.9)
Bladder (188)	18	9	0.9 (0.4, 2.2)
Brain (includes benign tumors) (191, 225)	18	13	0.8 (0.4, 1.6)
Lymphoma (200, 202)	31	4	4.0 (1.6, 13.4)
Multiple myeloma (203)	1	3	0.1 (0.01, 1.0)
Leukemia (204–208)	61	12	2.8 (1.6, 5.5)
Myelodysplastic syndrome (238)	7	0	∞ (1.5, ∞)
Diseases of blood-forming organs (280–283,284,285,288, 289)	14	0	∞ (3.4, ∞)
Cardiovascular diseases (390–458)	1,785	835	1.0 (0.9, 1.1)
Respiratory diseases (460–519)	189	53	1.7 (1.2, 2.3)
Digestive diseases (520–569)	155	83	1.0 (0.8, 1.4)
Cirrhosis of the liver (571)	104	53	1.1 (0.8, 1.6)
Urinary tract diseases (580–629)	63	31	1.0 (0.7, 1.6)
Toxic effects of workplace chemicals (980,982)	8	2	3.2 (0.8, 21.5)
Symptoms, signs, and other ill-defined conditions (992)	242	111	1.0 (0.8, 1.2)
Unknown	21	6	1.9 (0.8, 5.3)

Abbreviations: ICD-9 = ninth edition of the International Classification of Diseases; RR = relative risk.
[1]Analyses of lymphoma, multiple myeloma, leukemia, and diseases of the blood-forming organs are undertaken excluding the first 2 years of follow-up and are based on 1,517,350 person-years for benzene-exposed and 782,911 person-years for unexposed workers. Analyses of all other causes of mortality exclude the first 10 years of follow-up and are based on 1,046,190 person-years for benzene-exposed and 588,952 for unexposed workers.
[2]The "neoplasms, all" category includes benign neoplasms (ICD-9 codes 225–229), unspecified neoplasms (ICD-9 code 239), and malignant neoplasms (detailed in the table).

myelodysplastic syndrome, and diseases of blood forming organs (Table 5). For the myeloid malignancies (Table 6), overall RRs were elevated and about the same magnitude for the combined category of MDS/AML, chronic myeloid leukemia (CML), and all myeloid malignancies (MDS/AML and CML), with little variation in risk by either sex or industry ($p > 0.5$), and a lower but not significantly different RR for MDS/AML in 1988–1999 compared with the RR in 1972–1987. For the lymphoid malignancies (Table 7), overall RRs were increased, with no significant differences by gender or attained calendar year. However, heterogeneity by industry was suggested ($p = 0.084$ for NHL; $p = 0.049$ for all lymphoid malignancies), with especially high RRs for chemical industry workers. After excluding chemical workers, risks were lower, albeit still increased for NHL (RR = 3.1, 95% CI = 1.2, 10.5), lymphoid leukemia (RR = 4.4, 95%CI = 0.8, 82.3) and all lymphoid malignancies (RR = 1.8, 95%CI = 0.9, 4.2).

Comparison of current findings (1972–1999) with those from the earlier CAPM-NCI analyses (1972–1987)

We compared results from our current follow-up to findings from our previous reports of mortality and incidence of

Table 3. Relative risk of lung cancer and respiratory diseases mortality among Chinese benzene-exposed versus unexposed workers followed up during 1972–1999 by occupational and other characteristics

	Lung cancer[1] (both sexes)		Lung cancer[1] (males)		Respiratory diseases[1] (both sexes)		Respiratory diseases[1] (males)	
Characteristics	No. exposed/ unexposed	RR[2] (95%CI)	No. exposed/ unexposed	RR[2] (95%CI)	No. exposed/ unexposed	RR[2] (95%CI)	No. exposed/ unexposed	RR[b] (95%CI)
Total	351/119	1.5 (1.2, 1.9)			189/53	1.7 (1.2, 2.3)		
Sex								
Male	279/99	1.5 (1.2, 1.9)			167/42	1.9 (1.4, 2.7)		
Female	72/20	1.5 (0.9, 2.5)			22/11	0.7 (0.4, 1.6)		
P-difference		>0.5				0.020		
Age at first exposure/hire (yrs)								
<20	39/24	2.2 (1.3, 3.7)	25/18	2.2 (1.2, 4.2)	4/0	3.3 (1.8, 6.2)	3/0	3.5 (1.8, 7.4)
20–29	94/47	1.8 (1.3, 2.6)	66/37	1.8 (1.2, 2.7)	36/14		28/11	
30–39	102/40	1.0 (0.7, 1.5)	84/38	1.0 (0.7, 1.5)	71/28	1.2 (0.8, 1.9)	66/21	1.6 (1.0, 2.7)
≥40	116/8	2.6 (1.4, 5.9)	104/6	3.2 (1.5, 8.3)	78/11	1.3 (0.7, 2.7)	70/10	1.4 (0.7, 2.8)
P trend		>0.5		>0.50		0.005		0.007
Year of first exposure/hire								
<1955	37/39	1.4 (0.9, 2.2)	30/37	1.3 (0.8, 2.1)	15/14	1.6 (0.8, 3.4)	12/14	1.4 (0.6, 2.9)
1955–59	96/49	1.7 (1.2, 2.5)	75/41	1.6 (1.1, 2.4)	53/17	2.3 (1.4, 4.1)	49/11	3.4 (1.9, 7.0)
1960–71	160/26	1.6 (1.1, 2.5)	130/18	1.8 (1.1, 3.1)	98/21	1.0 (0.7, 1.7)	92/17	1.2 (0.7, 2.0)
1972–87	58/6	2.3 (1.0, 6.6)	44/3	2.9 (1.0, 11.8)	23/1		14/0	
P-trend		>0.5		0.42		0.038 (neg)		0.075 (neg)
Time since first exposure/hire (yrs)								
10–14	36/6	1.2 (0.5, 3.2)	31/3	2.1 (0.7, 8.7)	9/1	2.2 (1.0, 5.2)	5/0	2.4 (1.0, 7.0)
15–24	106/13	2.5 (1.5, 4.7)	87/11	2.4 (1.3, 4.7)	54/6		45/5	
25–34	137/45	1.6 (1.1, 2.3)	103/38	1.5 (1.0, 2.1)	74/26	1.0 (0.7, 1.7)	70/22	1.2 (0.8, 2.0)
≥35	72/55	1.5 (1.0, 2.1)	58/47	1.5 (1.0, 2.2)	52/20	2.6 (1.6, 4.4)	47/15	3.3 (1.9, 6.2)
P trend		>0.5		0.43		0.073		0.042 (pos)
Attained age[3] (yrs)								
<60	150/52	1.7 (1.2, 2.3)	105/37	1.8 (1.3, 2.7)	34/9	2.3 (1.1, 5.1)	27/7	2.5 (1.1, 6.2)
60–69	125/47	1.4 (1.0, 1.9)	112/43	1.3 (0.9, 1.9)	81/24	1.7 (1.1, 2.7)	73/19	1.9 (1.2, 3.3)
≥70	72/20	1.4 (0.9, 2.4)	62/19	1.4 (0.8, 2.4)	74/20	1.5 (0.9, 2.4)	67/16	1.7 (1.0, 3.1)
P trend		0.39		0.21		0.30		0.50
Attained calendar year[4]								
1972–1987	113/40	1.5 (1.0, 2.1)	99/34	1.5 (1.1, 2.3)	48//14	1.6 (0.9, 3.0)	49/1	1.7 (0.9, 3.4)
1988–1999	238/79	1.5 (1.2, 2.0)	180/65	1.5 (1.1, 2.0)	141/39	1.7 (1.2, 2.4)	124/30	2.0 (1.4, 3.1)
P difference		>0.5		>0.5		>0.5		>0.5
Industry								
Unexposed	119	1.0	99	1.0	53	1.0	42	1.0
Coatings	189	1.7 (1.4, 2.2)	144	1.8 (1.4, 2.3)	104	2.0 (1.4, 2.8)	91	2.4 (1.7, 3.5)
Rubber	20	1.8 (1.1, 2.9)	15	2.0 (1.1, 3.3)	5	1.1 (0.4, 2.4)	4	1.2 (1.1, 3.0)
Chemical	34	1.3 (0.9, 1.9)	30	1.4 (0.9, 2.0)	20	1.6 (0.9, 2.7)	20	2.0 (0.4, 3.3)
Shoe	52	1.3 (0.9, 1.8)	49	1.3 (0.9, 1.9)	32	1.4 (0.9, 2.1)	29	1.5 (0.9, 2.4)
Other/mixed	56	1.2 (0.9, 1.7)	41	1.1 (0.8, 1.6)	28	1.4 (0.9, 2.2)	23	1.5 (0.9, 2.5)
P homogeneity		0.049		0.049		0.18		0.077

[1]Lung cancer includes ICD, ninth edition (ICD-9) code 162 and respiratory diseases include ICD-9 codes 460–519.
[2]All analyses are stratified on sex, attained age, and attained calendar year. Analyses of age at hire, year of hire, and time since hire include main effects for these variables. Analyses exclude the first 10 years of follow-up and are based on 1,046,190 person-years for benzene-exposed and 588,952 among unexposed workers.
[3]This is age at death for subjects dying of the cause of interest.
[4]This is calendar year of death for subjects dying of the cause of interest. Abbreviations: CI = confidence intervals; RR = relative risk; ICD = international classification of diseases.

Table 4. Relative risk of leukemia mortality among Chinese benzene-exposed versus unexposed workers followed-up during 1972–1999 by occupational and other characteristics.[1]

Characteristics	No. exposed/ unexposed	RR[2] (95%CI)
Total	61/12	2.8 (1.6, 5.5)
Sex		
Male	41/9	2.8 (1.4, 6.1)
Female	20/3	2.8 (1.0, 12)
P difference		>0.5
Age at first exposure/hire (yrs)		
<20	15/3	5.0 (1.6, 21)
20–29	22/6	2.2 (0.9, 6.0)
≥30	24/3	1.9 (0.7, 7.9)
P trend		0.054
Year of first exposure/hire		
<1960	9/6	1.7 (0.6, 5.2)
1960–71	30/2	6.3 (1.9, 39)
≥1972	22/4	1.6 (0.6, 5.5)
P trend		0.48
Time since first exposure/hire (yrs)		
2–9	20/1	6.7 (1.4, 121)
10–24	31/7	2.1 (1.0, 5.2)
25+	10/4	2.2 (0.7, 8.0)
P trend		0.40
Attained age (yrs)[3]		
<40	19/2	5.7 (1.3, 24)
40–49	25/5	2.7 (1.0, 7.2)
≥50	17/5	1.7 (0.6, 4.6)
P trend		0.036
Attained calendar year[4]		
1972–1987	38/9	2.4 (1.2, 5.2)
1988–1999	23/3	4.0 (1.4, 17.2)
P difference		0.44
Industry		
Unexposed	12	1.0
Coatings	28	2.6 (1.4, 5.3)
Rubber	1	1.0 (0.1, 5.0)
Chemical	11	4.0 (1.8, 9.2)
Shoe	6	2.6 (0.9, 7.0)
Other/mixed	15	2.9 (1.4, 6.3)
P homogeneity		>0.5

[1]Leukemia disease category includes International Classification of Diseases, ninth edition (ICD-9) codes 204–208.
[2]All analyses are stratified on sex, attained age, and attained calendar year. Analyses of age at hire, year of hire, and time since hire include main effects for these variables. Mortality analyses exclude the first 2 years of follow-up and are based on 1,517,350 person-years for benzene-exposed and 782,911 person-years for unexposed workers.
[3]This is age at death for subjects dying of the cause of interest.
[4]This is calendar year of death for subjects dying of the cause of interest.

HLD. For comparability with the previous report, exclusions of the first 10 or 2 years of follow-up were not incorporated and the same definitions were used to evaluate and compare the specific outcomes for the two calendar year periods.[6,7] With the extended follow-up, the number of total cancer deaths nearly tripled whereas the number of HLD cases increased by about 50%. Mortality results for neoplasms and respiratory diseases and for incidence of HLD was similar in both calendar year periods, but more precisely estimated in our current 28-year follow-up (see Supporting Information Tables 1-SII and 2-SII in Supporting Information II).

Discussion

Overall, results from the 28-year follow-up of Chinese benzene-exposed workers, which included nearly triple the number of deaths from our initial follow-up, revealed similar or stronger associations compared to our earlier observations for a broad range of HLD and for lung cancer in workers of both sexes. Particularly noteworthy was the occurrence of 11 new cases of NHL, 4 new cases of acute lymphocytic leukemia (ALL), and two new cases of chronic lymphocytic leukemia (CLL). There was also persistence of the significantly elevated RRs for lung cancer and respiratory diseases that we had identified in our first follow-up. New cases of MDS/AML and CML were also diagnosed in the extended follow-up, although there was a non-significant decline in RR of MDS/AML in the more recent compared with the earlier period.

Inhalation is the major route by which workers are exposed to benzene. Our earlier investigation with 16 years of follow-up[18] found an increased risk of lung cancer associated with benzene exposure that persisted with 12 additional years of follow-up. A recent IARC review found no consistent evidence of such an association,[1] although three studies in addition to our earlier study have also linked benzene with lung cancer.[13,19,20] Among 4,417 US chemical manufacturing workers initially exposed to benzene during 1940–1977 and followed up through 1997, 60% excesses of lung cancer were apparent, but there was no clear exposure-response relationship in either group.[13] A multi-country Nordic study reported a 30% elevated risk of lung cancer in 19,000 gasoline service station workers identified from the 1970 censuses and linked with nationwide cancer registries during a 20-year follow-up.[19] Among 5,514 workers exposed to benzene in 233 factories in the United Kingdom during 1966/1967 or earlier and followed-up for mortality during 1968–2002, there was a 20% significant increase in lung cancer mortality and no clear evidence of heterogeneity by type of industry, despite exposure of some of these workers to other carcinogens such as asbestos and polycyclic aromatic amines.[20] Our study demonstrated heterogeneity in risk of lung cancer by industry, with highest risks seen in workers in the coatings and rubber industries. Elevated incidence and mortality from lung cancer has been consistently observed in painters, with a 35% increase from a meta-analysis of 47 epidemiologic studies.[28] IARC has designated occupational exposure as a painter as carcinogenic since

Table 5. Relative risks for incidence of hematopoietic and lymphoproliferative and other related disorders (HLD) among Chinese benzene exposed *versus* unexposed workers followed up during 1972–1999

Incident HLD cases (ICD-9 codes)	No. incident cases exposed	No. incident cases unexposed	RR[1] (95%CI) (1972–1999)
Lymphoma (200–202)	31	5	3.2 (1.4, 9.4)
Non-Hodgkin lymphoma (200, 202)	30	4	3.9 (1.5, 13.2)
Multiple myeloma (203)	1	3	0.12 (0.01, 0.96)
Leukemia (204-208)	60	13	2.5 (1.4, 4.9)
All lymphoid leukemia (204)	10	1	5.4 (1.0, 99.3)
>Acute lymphocytic leukemia (204.0)	8	1	4.5 (0.8, 83.9)
>Chronic lymphocytic leukemia (204.1, 204.2)	2	0	∞ (0.3, ∞)
All myeloid leukemia (205, 206)	39	10	2.2 (1.1, 4.6)
>Acute myeloid leukemia (205.0, 206.0, 207.0, 207.1, 207.2)	26	7	2.1 (0.9, 5.2)
>Chronic myeloid leukemia (205.1, 205.2)	13	3	2.5 (0.8, 10.7)
Leukemia, acute, NOS (208.0)	6	1	3.5 (0.6, 66.1)
Leukemia, NOS (208.8, 208.9)	5	1	2.4 (0.4, 44.4)
Myelodysplastic syndrome (238)	8	0	∞ (1.9, ∞)
Diseases of blood-forming organs (280–289)	17	0	∞ (4.1, ∞)
Aplastic anemia (284)	10	0	∞ (2.5, ∞)
Other diseases of blood forming organs (280–283, 285–289)	7	0	∞ (1.4, ∞)

[1]All analyses are stratified on sex, attained age, and attained calendar year. Analyses of incidence excluding first 2 years of follow-up are based on 1,516,970 person-years for benzene-exposed and 782,836 person-years for unexposed workers.
Abbreviations: NOS = not otherwise specified.

1989[29] and reconfirmed this designation recently.[30] In addition to benzene, painters may be exposed to solvents, pigments, extenders, binders, additives, asbestos and crystalline silica. Benzene-exposed chemical industry, insulation, and rubber workers may also be exposed to asbestos.[31]

Smoking has been estimated to account for 90 percent of the lung cancer burden in high income countries.[32] Neither our extended cohort follow-up study nor most of the aforementioned studies[13,18–20] had the data needed to take account of potential confounders such as smoking. Thus, smoking differences between exposed and unexposed workers may have contributed to the elevated lung cancer risks that we observed, as well as those for respiratory and other smoking-related diseases. It is of interest that the RR for lung cancer in benzene-exposed female Chinese workers, who were unlikely to have smoked during the study period,[33] was of the same magnitude as in males although the RR of 1.5 for females had a wider confidence interval (95% CI 0.9, 2.4). By contrast, the association of occupational benzene exposure with respiratory diseases was apparent only in men, a pattern that suggests confounding by smoking. Trends in risk with age at first exposure/hire, year of first exposure/hire, and time since first exposure/hire also differed for respiratory diseases and lung cancer. The differences between these two outcomes may suggest differences in inherent susceptibility to these diseases, fatality rates, types or levels of exposure, or etiology.

Our findings of borderline excess risks for nasopharyngeal, esophageal, pancreatic, colorectal and uterine cancers should be regarded cautiously since of these, only nasopharyngeal cancer has been linked with benzene exposure in other studies.[34] Assessment of solid tumors may have been limited in other studies by the small cohort sizes, low-dose benzene exposures, short length of follow-up, the rarity of these outcomes, and the relatively small associated risks. The mechanisms by which benzene may cause lung cancer, other solid tumors or respiratory diseases are unclear.

Exposure-related increases in risk of AML have been observed in benzene-exposed chemical manufacturing, petroleum refining, marketing and distribution workers[13,15,35] and in our previous investigation in China.[8] Some studies, including our previous investigation, linked benzene with CML, but none have shown an exposure-response relationship.[1] Absence of cases of aplastic anemia among unexposed workers may reflect lack of screening of blood counts, as was done in the benzene-exposed workers, to identify benzene-related hematotoxicity. Compared with population-based incidence rates of aplastic anemia in Asian populations,[36,37] rates of aplastic anemia were about 1.6-fold higher in the Chinese benzene-exposed workers for the period of the extended follow-up, compared to no cases (3.2 cases expected) in the unexposed workers. Case-control studies[5] have found associations of benzene with aplastic anemia, but most aplastic anemia cases have no identified cause. Evidence linking benzene exposure with MDS has increased in conjunction with recognition of misclassification of MDS as AML in earlier years.[6,9] The limited Chinese population-

based incidence data along with underascertainment and changing classification of MDS preclude comparison of rates in the Chinese benzene-exposed workers with those in the general Chinese population and calculation of expected numbers in the unexposed workers.

Our previous cohort study was the first to find an increase in risk of NHL with increasing benzene level.[8] Other cohort investigations, with follow-up of 2,266,[38] 4,417[13] and 34,597 chemical manufacturing workers[21] that identified 10, 21, and 8 NHL cases, respectively, found no clear evidence of a statistically significant relationship of benzene and NHL. A meta-analysis of cohort studies incorporating quality dimensions demonstrated support for associations of occupational benzene exposure with CLL, ALL, and multiple myeloma, but noted that the evidence was less clear for a relation of benzene with NHL.[39] Excess risk of CLL has been associated with benzene in historical retrospective cohort studies of rubber and styrene manufacturing workers, in newer cohorts of chemical manufacturing, oil refinery, and petrochemical distribution workers, and in population-based case-control studies (reviewed in Ref. [1), but data linking benzene with ALL are more limited.[40,41] Other investigations have found exposure-response relationships for benzene and multiple myeloma among chemical manufacturing,[13] upstream petroleum[42] and US Pliofilm workers,[15,16] but our study showed lower risk of multiple myeloma among the exposed than among unexposed workers based on small numbers. Multiple myeloma is a rare hematopoietic malignancy, occurs primarily at older ages,[43] requires a high level of suspicion and a combination of clinical, laboratory and histopathologic assessment for diagnosis,[44] and the incidence is substantially lower in Asian than in western populations.[45,46] Given the very small numbers and the likely underascertainment of this malignancy in the Chinese benzene workers, our data are of limited value in evaluating multiple myeloma risks and our results should not be interpreted as contradicting previous findings.

Our earlier exposure assessment for the period 1949–1987[47] and that of others for the period from the mid-1950s through 2000[22,48] have revealed that average occupational benzene measurement levels in China have declined substantially. However, for a given period, there has been notable variation in air level measurements among benzene-exposed workers in different occupations and across industries,[47] and among painting and paint manufacturing workers.[48] Between 1972–1987 and 1988–1999, the exposure effect for MDS/AML and all myeloid neoplasms decreased somewhat, albeit not significantly and based on small numbers (Table 6), but there was no decrease for lymphoid disorders or lung cancer. The heterogeneity in risks across industries for lung cancer is consistent with results from our earlier follow-up.[47] The small numbers of lymphoid malignancies arising among workers in the different industries preclude firm conclusions, particularly in the absence of individual measurements. However, manufacture of industrial solvents and exposure to phenoxyacetic acid and certain other herbicides and insecticides have been linked with increased risk of non-Hodgkin lymphoma,[49] supporting the elevated risks we observed for this endpoint in chemical workers within the cohort.

The mechanisms by which benzene exposure causes MDS/AML are not completely understood, but have been widely thought to be similar to therapy-related MDS/AML since benzene, cytotoxic therapy, and radiation all may cause chromosomal translocations.[50] More recently, some data have shown that the pattern of clonal cytogenetic abnormalities may be more consistent with *de novo* AML than t-AML.[51,52] Benzene-induced leukemia may begin as a mutagenic event in a stem cell or progenitor cell with subsequent genomic instability that allows for sufficient mutations to be acquired in a relatively short time.[53] The benzene metabolite hydroquinone induces genomic instability in the bone marrow of susceptible mice.[54] Molecular data provide evidence of genotoxicity of benzene metabolites on pluripotent bone marrow progenitor cells.[55] Animal studies, including an investigation in *Tp53*-deficient mice,[56] demonstrate that benzene may cause lymphomas, while decades of experimental research provide strong evidence that benzene is associated with a broad array of different types of neoplasms. Postulated mechanisms for benzene-related lymphomagenesis include induction of chromosome rearrangements[57] and immunosuppression.[1,55]

The large size of the cohort, the long follow-up, and the small numbers of subjects lost to follow-up represent important strengths of this investigation. Another unique aspect of this study is that workers were employed in several different industries. The larger numbers of deaths and HLD cases with the extended follow-up have led to more precise estimates and increased the reliability of the results. The most important limitation of our study was absence of individual exposure estimates; exposure assessment was limited to classification as ever versus never exposed. Another limitation was the possible underascertainment of indolent malignancies (such as chronic lymphocytic leukemia, MDS, and certain types of lymphomas) and HLD that occur rarely among Asian populations (*e.g.,* multiple myeloma), misclassification of diagnoses (due to the limited availability of histologic, molecular, and genetic studies for many HLD, and paucity of tumor tissue and advanced imaging studies for lung cancer, and reliance on death certificates for some cases with no other source of diagnostic validation. Findings for CLL and multiple myeloma must be interpreted cautiously due to small numbers of cases in young and middle-aged workers; these HLD more typically arise in the elderly.[58,59] Other limitations included the relatively small numbers of workers with specific types of myeloid and lymphoid malignancies and solid tumors, particularly among unexposed workers, and the relatively small numbers of female workers. We lacked cohort data on smoking and other known confounders including other occupational carcinogens, a limitation characterizing many occupational cohort studies. Finally, there is the potential for chance as an explanation of some of the findings due to assessment of multiple outcomes.

Table 6. Relative risks for incidence of myeloid malignancies among Chinese benzene-exposed *versus* unexposed workers followed-up during 1972–1999 by sex and industry

	MDS/AML		CML		All myeloid[1]	
Characteristics	No. exposed/ unexposed	RR[2] (95%CI)	No. exposed/ unexposed	RR[2] (95%CI)	No. exposed/ unexposed	RR[2] (95%CI)
Total	34/7	2.7 (1.2, 6.6)	13/3	2.5 (0.8, 11)	47/10	2.6 (1.4, 5.5)
Sex						
Male	23/5	2.8 (1.2, 8.5)	10/2	3.0 (0.8, 20)	33/7	2.9 (1.4, 7.2)
Female	11/2	2.3 (0.6, 14)	3/1	1.4 (0.2, 28)	14/3	2.0 (0.6, 8.5)
P difference		>0.5		>0.5		>0.5
Attained calendar year[3]						
1972–1987	26/4	3.7 (1.5, 12.8)	7/2	2.2 (0.5, 14)	33/6	3.2 (1.4, 8.5)
1988–1999	8/3	1.3 (0.4, 5.9)	6/1	3.0 (0.5, 58)	14/4	1.7 (0.6, 6.1)
P difference		0.23		>0.5		0.40
Industry						
Unexposed	7	1.0	3	1.0	10	1.0
Total exposed	34		13		47	
Coatings	15	2.3 (1.0, 6.1)	5	2.0 (0.5, 9.8)	20	2.2 (1.1, 5.0)
Rubber	2	3.6 (0.5, 15)	0	0.0 (0.0, ∞)	2	2.5 (0.4, 9.4)
Chemical	6	3.8 (1.2, 12)	2	3.0 (0.4, 18)	8	3.6 (1.4, 9.1)
Shoe	2	1.4 (0.2, 6.0)	2	3.0 (0.4, 20)	4	1.9 (0.5, 5.9)
Other/mixed	9	3.1 (1.2, 8.8)	4	3.2 (0.7, 17)	13	3.2 (1.4, 7.4)
P homogeneity		>0.5		>0.5		>0.5

[1]"All myeloid" disease category includes MDS, AML, and CML.
[2]All analyses are stratified on sex, attained age, and attained calendar year. Analyses of incidence excluding first 2 years of follow-up are based on 1,516,970 person-years for benzene-exposed and 782,836 person-years for unexposed workers.
[3]This is calendar year of diagnosis for subjects with the disease of interest.
Abbreviations: MDS = myelodysplastic syndrome; AML = acute myeloid leukemia; CML = chronic myeloid leukemia.

Epidemiology

Subsequent to completing the 1972–1999 follow-up of the cohort, further follow-up was not pursued due to closure, moving or merger or many of the study factories, the high proportion of workers (87%) who had retired and the large fraction of retirees who moved back to rural areas and small villages, thereby making it difficult to contact the workers in a cost-efficient manner.

This 28-year follow-up of Chinese benzene-exposed workers provides important evidence that strengthens our earlier observations of elevated risks of a broad range of myeloid and lymphoid neoplasms. Increased risks of lung cancer were observed in workers of both sexes and were highest for workers in the coatings and rubber industries. Evaluation of exposure-response along with detailed consideration of potential confounders is needed to assess the likelihood of causality of the lung cancer findings. The borderline increases of nasopharyngeal, esophageal, colorectal, pancreatic and uterine cancers in the benzene-exposed workers require further evaluation in large well-designed cohort studies in Asian, western and other racial or ethnic populations of benzene-exposed workers with long-term follow-up. Pooling of data on these HLD and other cancer outcomes from multiple cohorts with a broad range of historical benzene exposure levels could also further elucidate risks. Case-control studies of the HLD or the other associated cancer outcomes in populations with substantial occupational exposure to benzene, with potential for linkage with measurement data, and with assessment of confounders may also contribute useful information. The ubiquitous exposure of the general population to low levels of benzene from motor vehicle exhaust, tobacco smoke, contaminated water and foods, and at gasoline filling stations provides important impetus to increasing our knowledge about associated serious health risks. Findings from this study and future investigations with individual worker exposure estimates, could inform risk protection measures for workers and the general population.

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Table 7. Relative risks for incidence of lymphoid malignancies among Chinese benzene-exposed versus unexposed workers followed-up during 1972–1999 by sex and industry

	NHL		Lymphoid leukemia[1]		All lymphoid[1]	
Characteristics	No. exposed/ unexposed	RR[2] (95%CI)	No. exposed/ unexposed	RR[2] (95%CI)	No. exposed/ unexposed	RR[2] (95%CI)
Total	30/4	3.9 (1.5, 13)	10/1	5.4 (1.0, 99)	42/9	2.4 (1.2, 5.2)
Sex						
Male	19/3	3.6 (1.2, 15)	6/0	∞ (1.7, ∞)	26/6	2.4 (1.1, 6.6)
Female	11/1	4.6 (0.9, 86.5)	4/1	1.7 (0.2, 33)	16/3	2.2 (0.7, 9.5)
P difference		>0.5		0.14		>0.5
Attained calendar year[3]						
1972–1987	19/3	3.5 (1.2, 15)	5/1	3.0 (0.5, 58)	25/6	2.3 (1.0, 6.1)
1988–1999	11/1	5.1 (1.0, 96)	5/0	∞ (1.0, ∞)	17/3	2.6 (0.9, 11)
P difference		>0.5		0.30		>0.5
Industry						
Unexposed	4	1.0	1	1.0	9	1.0
Coatings	9	2.4 (0.8, 8.9)	5	5.4 (0.9, 104)	15	1.7 (0.8, 4.1)
Rubber	1	2.6 (0.1, 18)	0	0.0 (0.0, 667)	1	1.2 (0.1, 6.3)
Chemical	9	9.7 (3.1, 36)	2	8.9 (0.8, 192)	12	5.7 (2.4, 14)
Shoe	4	3.9 (0.9, 17)	2	13.7 (1.2, 305)	6	2.7 (0.9, 7.6)
Other/mixed	7	4.2 (1.3, 16)	1	2.2 (0.1, 55)	8	2.1 (0.8, 5.4)
P homogeneity		0.084		0.45		0.049

[1]"Lymphoid leukemia" disease category includes chronic lymphocytic leukemia (CLL) and acute lymphocytic leukemia (ALL). The "all lymphoid" category includes NHL, Hodgkin lymphoma, CLL, ALL, and multiple myeloma.
[2]All analyses are stratified on sex, attained age, and attained calendar year. Analyses of incidence excluding first 2 years of follow-up are based on 1,516,970 person-years for benzene-exposed and 782,836 person-years for unexposed workers.
[3]This is calendar year of diagnosis for subjects with the disease of interest.
Abbreviations: NHL = non-Hodgkin lymphoma.

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Supplement I. Detailed description of the methods for the statistical analysis.

Separate person-year files were used for mortality and HLD incidence analyses. Person-years, deaths, and incident cases were categorized by exposure status (benzene-exposed versus unexposed), sex, attained age (5-year intervals), and attained calendar year (1972-1977, 1978-1982, 1983-1987, 1988-1991, 1992-1995, 1996-1999), and also by year of first exposure, age at first exposure, time since first exposure, and industry using the categories shown in Table 1. Hire date is substituted for date of first exposure in determining these values for unexposed workers. Based on substantial data indicating a minimum latency between first exposure and cancer onset, we allowed for a 2-year latency for HLD and a 10-year latency for all other endpoints [60]. This was accomplished by excluding the first 2 or 10 years following the date of first exposure or hire.

Analyses of mortality and HLD incidence were based on comparison of the disease rates in the benzene-exposed to the rates in the unexposed using Poisson regression, in which it is assumed that the number of deaths or incident HLD cases follows a Poisson distribution with expectation given by the product of the person-years and the cause-specific mortality rate (or HLD incidence rate). All analyses were adjusted for sex, attained age, and attained calendar year by stratifying on these variables using the categories noted above. In the simplest model, the expected value of $O_{s,a,c,y}$, denoted by $E(O_{s,a,c,y})$, is as follows:

$$E(O_{s,a,c,y}) = \lambda_{s,a,c}\, P_{s,a,c,y}\, \exp(\beta y),$$

where *s* indicates sex, *a* indexes 5-year categories of attained age, *c* indexes categories of attained calendar year as defined above, y = 1 for benzene-exposed workers and 0 for unexposed workers, $O_{s,a,c,y}$ is the number of observed deaths (or incident cases) in the category defined by s, a, c, and y, $P_{s,a,c,y}$ is the number of person-years in this category, $\lambda_{s,a,c}$ is the baseline (unexposed) rate for this category, and exp(β) is the relative risk for exposed versus unexposed. In addition to estimating relative risks for all exposed workers, we also estimated separate risks for individual industries involving benzene exposure.

In equation 1, the relative risk is assumed to be constant for all subjects. For selected disease categories, we investigated departures from this assumption by estimating relative risks separately for categories defined by sex, attained age, age at hire, year of hire, time since hire. If k indexes the categories of interest,

$$E(O_{s,a,c,y,k}) = \lambda_{s,a,c}\, P_{s,a,c,y,k}\, \exp(\theta_k + \beta_k y),$$

where the parameter θ_k is needed only for variables that are not a part of the baseline, (age at first exposure, year of first exposure, and time since first exposure). For continuous variables, tests for trend were conducted based on

$$E(O_{s,a,c,y,x}) = \lambda_{s,a,c} P_{s,a,c} \exp(\theta x + \beta xy),$$

where x is a continuous variable (such as age at first exposure) and is obtained as the mean value for each cell in the person-year table. The parameter θ is needed only for variables that are not a part of the baseline.

Parameter estimates were computed using maximum likelihood methods. Confidence intervals and two-sided p-values were based on the likelihood ratio statistic. Analyses were implemented using the AMFIT module of the software package Epicure [27].

Supplement II. Comparison of findings from current follow-up (1972-1999) with previous follow-up (1972-1987)

For comparability with our previous reports of mortality and incidence of HLD, exclusions of the first 10 or two years of follow-up, respectively, were not incorporated and the same definitions were used to evaluate and compare the specific outcomes for the two calendar years periods assessed. Compared to the previous 1972-1987 follow-up, data from the extended follow-up demonstrated that elevated mortality risks were still apparent for nasopharyngeal and esophageal cancers, while there was a new small increase for colorectal cancer (Table 1-SII). For the comparison of HLD incidence risks, the additional 12 years of follow-up generally revealed sustained increases and/or strengthened results. Significant increases were apparent in both follow-up periods for all HLD, malignant lymphoma, NHL, all leukemia, myeloid leukemia, AML, aplastic anemia, and MDS (Table 9). An increase in CML, apparent in our earlier follow-up, was sustained in the extended follow-up as was the elevated risk for lymphoid leukemia. Previously, lymphoid leukemia consisted solely of acute lymphocytic leukemia, while the current analysis included two new cases of CLL (Table 2-SII)

Table 1-SII. Relative risks for mortality from selected causes of death among Chinese benzene-exposed versus unexposed workers followed up during 1972-1987 compared with risks for same workers followed up during 1972-1999

Cause of Death (ICD-9 codes)	Follow-up period 1972-1987[a, b]		Follow-up period 1972-1999[a]	
	No. Exposed/ Unexposed	RR (95%CI)	No. Exposed/ Unexposed	RR (95%CI)
Neoplasms, all (140-239)	524 (527/219)	1.2 (1.0, 1.4)	1450/586	1.2 (1.l, 1.4)
Nasopharynx (147)	14 (14/3)	2.4 (0.8, 10.5)	33/9	2.0 (0.9, 4.2)
Esophagus (150)	27 (28/8)	1.8 (0.8, 4.5)	75/25	1.5 (1.0, 2.4)
Colon/rectum (153, 154)	34 (35/17)	0.9 (0.5, 1.7)	86/33	1.3 (0.9, 1.9)
Lung (162)	125(125/40)	1.4 (1.0, 2.0)	367/120	1.5 (1.2, 1.8)
Respiratory diseases (460-519)				
Total	53 (54/14)	1.6 (0.9, 3.1)	197/53	1.7 (1.2, 2.3)
Males only	47 (47/12)	1.7 (1.0, 3.4)	173/42	1.9 (1.4, 2.3)

Abbreviations: ICD-9=ninth edition of the International Classification of Diseases.
[a]Analyses include all years of follow-up with no exclusions for comparability of the current analysis of mortality with our previous report.
[b]Based on data from Yin et al, 1996a; 1996b[6, 7].

Table 2-SII. Relative risks for incident hematopoietic and lymphoproliferative and other related disorders (HLD) among Chinese benzene-exposed versus unexposed workers followed up during 1972-1987 compared with risks for same workers followed-up during 1972-1999

Diagnosis (ICD-9 codes)	**Follow-up period 1972-1987[a,b]**		**Follow-up period 1972-1999[a]**	
	No. Exposed/ Unexposed	**RR (95%CI)**	**No. Exposed/ Unexposed**	**RR (95%CI)**
All HLD[c] (200-208)	63/13	2.6 (1.5, 5.0)	97/21	2.4 (1.5, 4.0)
Malignant lymphoma (200-202)	20/3	3.5 (1.2, 14.9)	32/5	3.2 (1.4, 9.5)
NHL (ICD 200)[d]	17/3	3.0 (1.0, 13.0)	24/4	3.1 (1.2, 10.5)
Multiple myeloma (203)	1/1	0.4 (0.0, 10.7)	1/3	0.1 (0.01, 0.95)
All leukemia (204-208)	42/9	2.6 (1.3, 5.7)	64/13	2.7 (1.5, 5.1)
All leukemia, excluding CLL (204.0, 205.0-205.9, 206.0, 207.0, 207.2, 207.8, 208.0)	42/9	2.6 (1.3, 5.7)	62/13	2.6 (1.5, 5.0)
Myeloid leukemia[e] (205.0-205.9, 206.0)	32/6	3.0 (1.3, 7.9)	43/10	2.4 (1.2, 4.8)
Acute myeloid leukemia (204.0, 205.0, 206.0, 207.0, 207.2)	23/4	3.1 (1.2, 10.7)	29/7	2.3 (1.1, 5.7)
Chronic myeloid leukemia (205.1)	9/2	2.6 (0.7, 16.9)	14/3	2.6 (0.9, 11)
Lymphoid leukemia 204.0-204.9)	5/1	2.8 (0.5, 54.5)	10/1	5.0 (1.0, 98)
Acute lymphoid leukemia (204.0)	5/1	2.8 (0.5, 54.5)	8/1	4.3 0.8, 82)
Aplastic anemia (284)	9/0	∞ (2.2, ∞)	14/0	∞ (3.7, ∞)
Myelodysplastic syndrome	7/0	∞ (1.7, ∞)	8/0	∞ (1.9, ∞)

Abbreviations: CLL=chronic lymphocytic leukemia; ICD-9=ninth edition of the International Classification of Diseases; HLD=hematopoietic, lymphoproliferative and related disorders; NHL=non-Hodgkin lymphoma.

[a]Analyses included all years of follow-up with no exclusions for comparability of the current analysis of incidence with our previous report.

[b]Based on data from Yin et al, 1996a; 1996b[6, 7].

[c]Myelodysplastic syndrome and aplastic anemia were not included in the publication by Yin et al, 1996a; Yin et al, 1996b[6, 7]

[d]Includes ICD-9 code 200 to be comparable with Yin et al, 1996a; 1996b[6, 7].

[e]This category does not include myelodysplastic syndrome, similar to Yin et al, 1996a; 1996b[6, 7].