

A Cohort Study of Cancer Among Benzene-Exposed Workers in China: Overall Results

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A large cohort study of 74,828 benzene-exposed and 35,805 unexposed workers employed between 1972 and 1987 in 12 cities in China were followed to determine mortality from all causes and the incidence of lymphohematopoietic malignancies and other hematologic disorders. Benzene-exposed study subjects were employed in a variety of occupations, including painting, printing, and the manufacture of footwear, paint, and other chemicals. All-cause mortality was similar in the benzene-exposed and unexposed comparison group. Statistically significant excess deaths were noted among benzene-exposed subjects for leukemia (RR = 2.3, 95% CI: 1.1-5.0), malignant lymphoma (RR = 4.5, 95% CI: 1.3-28.4), and non-neoplastic diseases of the blood (RR = ∞, 95% CI: 2.5-∞), and a marginally significant excess was noted for lung cancer (RR = 1.4, 95% CI: 1.0-2.0). Risk was significantly elevated for the incidence of all lymphohematopoietic malignancies (RR = 2.6, 95% CI: 1.5-5.0), malignant lymphoma (RR = 3.5, 95% CI: 1.2-14.9), and leukemia (RR = 2.6, 95% CI: 1.3-5.7). Among the leukemia subtypes, only acute myelogenous leukemia (AML) incidence was significantly elevated (RR = 3.1, 95% CI: 1.2-10.7), although nonsignificant excesses were also noted for chronic myelogenous leukemia (CML) (RR = 2.6, 95% CI: 0.7-16.9) and lymphocytic leukemias (RR = 2.8, 95% CI: 0.5-54.5). Significant excesses were found for aplastic anemia (RR = ∞, 95% CI: 2.2-∞) and myelodysplastic syndrome (RR = ∞, 95% CI: 1.7-∞). Employment in benzene-associated occupations in China is associated with a wide spectrum of myelogenous and lymphocytic malignant diseases and related disorders. Investigations continue to assess the nature of these associations.

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INTRODUCTION

Benzene is a solvent widely used in industry and found in cigarette smoke, gasoline, automobile emissions, and other products [Wallace, 1989]. Benzene exposure has been related in numerous occupational studies to increased risk of acute myeloid leukemia (AML) [IARC, 1982] and, in some reports, to other lymphohematopoietic malignancies and solid tumors [Goldstein, 1990; Young, 1989; Mehlman, 1991; Yin et al., 1987a].

In 1981 the Chinese Academy of Preventive Medicine (CAPM) carried out a national occupational survey in which over 500,000 workers exposed to benzene in China were identified [Yin et al., 1987b]. Subsequently, 28,460 of these exposed workers and 28,257 unexposed workers were followed for cancer mortality between 1972 and 1981 [Yin et al., 1987a, 1989]. In that study, 25 leukemia deaths were identified among benzene-exposed workers vs. 4 leukemia deaths among controls, resulting in a mortality ratio of 5.7. Since 1987, the U.S. National Cancer Institute (NCI) has collaborated with the CAPM to expand the mortality study in cohort size, duration, and recency time of follow-up, and to investigate the incidence of hematologic malignancies and related disorders.

The NCI-CAPM collaborative study identified and followed a large cohort of Chinese benzene-exposed workers, determined their exposure histories, and characterized their risk for a variety of diseases potentially related to benzene exposure. Here we report on disease risk in this expanded cohort, providing an overview of all-cause mortality and of the incidence of lymphohematopoietic malignancies and other hematologic disorders.

METHODS

The methods used in this expanded study are described in detail elsewhere [Yin et al., 1994; Dosemeci et al., 1994]. The benzene-exposed group was comprised of workers employed between 1972 and 1987 in 1,427 selected benzene-exposed work units (departments) in 672 factories in 12 cities in China. A variety of industries and occupations using benzene were studied, including painting, printing, and the manufacture of footwear, paint, and other chemicals. An unexposed comparison group was assembled from workers employed between 1972 and 1987 in work units where benzene was not used in 69 of these factories, and in 40 additional factories. Subjects were identified from salary records and other factory written administrative records. We abstracted demographic data, including birth date, and sex, and occupational data, including the dates of employment, by work unit and job title, for all jobs held by subjects in the study factories. Benzene-exposed jobs were determined based upon factory level and job title-specific information on benzene use in seven calendar periods (1949–1959,

1960–1964, 1965–1969, 1970–1974, 1975–1979, 1980–1984, 1985+).

Subjects were followed up for history of selected lymphohematopoietic malignancies and other hematologic disorders and for vital status to December 31, 1987 through factory personnel records at study factories and subsequent places of employment, or, as needed, by contacting next of kin, work colleagues, treating physicians, or others. For deceased subjects, cause of death was obtained from employer medical records, other written factory records, or death certificates. Only after extensive search had failed to locate written records listing the cause of death were treating physicians or next of kin contacted.

For cases newly diagnosed with lymphohematopoietic malignancies and other hematologic disorders during follow-up period, pertinent histopathologic material, pathology reports, and medical records were requested. For pathology review, clinical, laboratory, and pathologic data were abstracted onto standardized forms by physician investigators who were not aware of the exposure status or the number of exposed and unexposed cases. All histopathologic and bone marrow aspirate slides and peripheral blood smears were reviewed systematically, by expert hematopathologists affiliated with the Mayo Clinic (C.-Y.L.), NCI (L.B.T.), and Peking Union Hospital (Z.-N.Z. and D.-G.L.) using structured abstract forms to objectively characterize hematopoiesis. Diagnoses were assigned after evaluation of all available clinical, laboratory, and pathologic data, without knowledge of the patient's benzene exposure status. Published criteria were utilized to categorize leukemia and lymphoma cases, and where possible, to classify these cases and those with myelodysplasia (MDS) by subtype [Travis et al., 1994]. For selected analyses, AML and MDS were combined as one disease category because of possible commonalities in the natural history of these conditions and failure in the past to consistently classify MDS as entities distinct from AML.

For the statistical analysis, person-years were accumulated for the benzene-exposed workers from January 1, 1972 or, if hired later, from the first date of employment in a benzene-exposed job. For the unexposed comparison group, person-years were accumulated from January 1, 1972 or, if hired later, from the first date of employment. Initial comparisons for mortality were conducted relative to general population mortality rates (standardized mortality ratio, SMR), derived from a population-based mortality survey in 1973–1975, which included 10 of the 12 study cities (National Cancer Control Office, Ministry of Health, Beijing, People's Republic of China). Further detailed analyses for mortality due to all causes and for incidence of lymphohematopoietic malignancies and other hematologic disorders were made by internal comparison of disease rates in the benzene-exposed group to the rates in the unexposed group, by Poisson regression analysis, yielding rate ratios

TABLE I. Distribution of Benzene-Exposed and Comparison Unexposed Study Subjects in 12 Cities in China, 1972–1987, by Selected Characteristics

	Exposed			Unexposed		
	No.	Person-year	(%)	No.	Person-year	(%)
Total	74,828	782,497	(100)	35,805	419,523	(100)
Male	38,833	414,043	(53)	20,795	250,503	(60)
Female	35,995	368,455	(47)	15,010	169,019	(40)
Employment (1949–1987)						
Age at first employment ^{a,b}						
<20	24,531	248,719	(32)	16,423	191,357	(46)
20–29	32,935	334,320	(43)	15,743	182,015	(43)
≥30	17,362	199,458	(25)	3,639	46,150	(11)
Year at first employment ^{a,b}						
<1960	11,306	168,971	(21)	7,765	121,810	(29)
1960–1972	22,140	326,673	(42)	10,513	166,297	(40)
>1972	41,382	286,853	(37)	17,527	131,415	(31)
Follow-up (1972–1987)						
Age at entry to follow-up						
<20	19,850	158,941	(20)	10,050	90,087	(21)
20–29	31,335	305,874	(39)	14,751	166,771	(40)
≥30	23,643	317,682	(41)	11,004	162,665	(39)
Year at follow-up						
1972–1981		378,517	(48)		222,621	(53)
1982–1987		403,979	(52)		196,902	(47)
Vital status (12/31/87)						
Alive	73,312		(98)	35,117		(98)
Deceased	1,369		(2)	598		(2)
Lost	147		(0.2)	90		(0.2)

^aEntry to employment for exposed at date of first exposed job.^bEntry to employment for unexposed at date of first job.

(RR) for exposed versus unexposed workers [Breslow and Day, 1987]. Both external (SMR) and internal (RR) analyses were controlled for age and, where appropriate, for sex. Confidence intervals (CI, 95%) for the SMR were based on asymptotic methods [Breslow and Day, 1987] and, for the RR, were obtained from the profile likelihood [Preston et al., 1993; Moolgavkar and Venzon, 1987]. Confidence intervals that exclude 1.0 are considered statistically significant.

RESULTS

The study group consisted of 74,828 benzene-exposed and 35,805 unexposed workers (Table I). On average, benzene-exposed subjects were followed for 10.5 years, while unexposed subjects were followed for 11.7 years. Women contributed 47% of the person-years in the benzene-exposed study group and 40% in the unexposed group. Person-year distributions for the benzene-exposed and unexposed

groups are also shown in Table I, with respect to age and year at first employment, age at entry to study, and year at risk. Overall, the study groups were young, with about 60% of the total person-years at risk being contributed by subjects less than 30 years of age at study entry. In this young study population, about 2% died during the follow-up period (1,369 benzene-exposed and 598 unexposed). Only 147 exposed and 90 unexposed workers were lost to follow-up.

Mortality in Benzene-Exposed Workers

In initial analyses compared to Chinese population mortality rates, the all-cause standardized mortality ratios (SMRs) were 0.5 (95% CI: 0.4–0.5) and 0.4 (95% CI: 0.4–0.5) for the benzene-exposed and unexposed study groups, respectively. The respective SMRs were 0.6 (95% CI: 0.5–0.6) and 0.5 (95% CI: 0.4–0.5) for men, and 0.3 (95% CI: 0.3–0.4) and 0.3 (95% CI: 0.3–0.4) for women. Analysis by specific causes of death also indicated substantial defi-

TABLE II. Mortality Among Benzene-Exposed Compared With Unexposed Workers, China, 1972–1987

Cause of death (ICD 9th revision)	Women			Men			Total	
	Obs ^a	RR ^b	(95% CI) ^c	Obs	RR	(95% CI)	RR ^d	(95% CI)
All causes	272	1.0	0.8–1.2	1097	1.1	1.0–1.3	1.1	1.0–1.2
Infectious, parasitic (001–139)	12	1.7	0.5–7.3	35	0.9	0.5–1.6	1.0	0.6–1.7
Tuberculosis (010–018)	7	0.9	0.3–4.3	21	0.9	0.4–1.8	0.9	0.5–1.7
Malignant neoplasms (140–208)	99	0.9	0.6–1.3	425	1.2	1.0–1.5	1.2	1.0–1.4
Metabolic disorders (240–279)	5	0.8	0.2–5.5	7	0.8	0.2–3.1	0.8	0.3–2.3
Blood and blood production (280–289)	2	∞	0.3–∞	8	∞	2.0–∞	∞	2.5–∞
Circulatory system (390–459)	88	0.8	0.6–1.2	388	1.0	0.9–1.3	1.0	0.9–1.2
Respiratory system (460–519)	7	1.1	0.3–7.2	47	1.7	1.0–3.4	1.6	0.9–3.1
Digestive system (520–579)	8	1.6	0.4–10.9	65	0.7	0.5–1.0	0.7	0.5–1.1
Cirrhosis (571)	5	∞	0.9–∞	53	0.8	0.5–1.2	0.9	0.6–1.3
Urinary tract (580–629)	12	0.7	0.3–2.0	15	0.9	0.4–2.1	0.8	0.4–1.6
Pregnancy and puerperium (630–676)	2	1.0	0.1–21.6					
Occupational injury, poisoning	0	und		14	2.2	0.8–7.7	2.2	0.8–7.7
Accident, non-occupational (800–999)	14	1.3	0.5–4.0	50	1.1	0.7–1.8	1.1	0.7–1.8
Suicide (E950–E959)	16	1.8	0.6–6.2	11	0.8	0.3–2.1	1.2	0.6–2.4
Other known causes	6	0.9	0.2–4.2	15	1.6	0.6–4.9	1.3	0.6–3.2
Diagnosis not clear	1	0.4	0.0–10.8	17	2.9	1.0–12.3	2.2	0.8–7.8

^aObs: observed benzene-exposed cases.^bRR: relative risk, compared with nonexposed workers, adjusted for age.^cCI: confidence interval.^dRR: relative risk, compared with nonexposed workers, adjusted for age and sex.

cits in mortality in the benzene-exposed group relative to the general (10 city) population rates, except for lung cancer (125 deaths, SMR = 1.0, 95% CI: 0.8–1.2), leukemia (38 deaths, SMR = 1.5, 95% CI = 1.1–2.1), and lymphoma (17 deaths, SMR = 1.2, 95% CI = 0.7–2.0).

Because of the large differences between the external population mortality rates and the mortality experience in the study populations, further analyses consider only disease occurrence in the benzene-exposed group compared with the unexposed group. As shown in Table II, all-cause mortality in the benzene-exposed group was similar to mortality in the unexposed comparison group (RR = 1.1), for both women (RR = 1.0) and men (RR = 1.1). Mortality due to diseases of the circulatory (RR = 1.0) and digestive systems (RR = 0.7), and the urinary tract (RR = 0.8), was not in excess in the exposed group, while statistically nonsignificant excesses were noted for occupational injuries (RR = 2.2), nonmalignant diseases of the respiratory system (RR = 1.6), largely due to an excess among men (RR = 1.7), and for deaths due to uncertain causes (RR = 2.2). Benzene-exposed subjects had a small but statistically significant increased mortality due to malignant neoplasms (RR = 1.2). Mortality due to nonmalignant diseases of blood and blood production were significantly elevated (RR = ∞, 95% CI: 2.5–∞), based on 10 cases among the exposed and 0 among the unexposed.

Site-specific cancer mortality results are shown in Table III. An excess of lung cancer was found among benzene-exposed workers (RR = 1.4), due to a significantly elevated risk among men (RR = 1.5), but not among women (RR = 1.0, based on 16 cases). Fourteen cases of nasopharyngeal cancer were identified (RR = 2.4). Esophageal cancer also showed a nonsignificant excess (RR = 1.8). Significant excesses of mortality due to leukemia (RR = 2.3) and lymphoma (RR = 4.5) were found in benzene-exposed workers, with similar excesses for men and women. No deaths were noted from multiple myeloma (MM).

Incidence of Lymphohematopoietic Malignancies and Other Hematologic Disorders in Benzene-Exposed Workers

Eighty-one incident cases of lymphohematopoietic malignancies (n = 63) and other hematologic disorders (n = 18) were documented among benzene-exposed workers, with 13 lymphohematopoietic malignancies and no other hematologic disorders identified among the unexposed comparison group [Travis et al., 1994]. Of nine ANLL with sufficient information to classify by French-American-British (FAB) subtype, three cases were M2, four cases were M3, one case was M2 or M4, and one case was M4 or M5 (the latter two cases could not be further specified). One addi-

TABLE III. Cancer Mortality Among Benzene-Exposed Compared With Unexposed Workers, China, 1972–1987

Cause of death (ICD 9th revision)	Women			Men			Total	
	Obs ^a	RR ^b	(95% CI) ^c	Obs	RR	(95% CI)	RR ^d	(95% CI)
Malignant neoplasms (140–208)	99	0.9	0.6–1.3	425	1.2	1.0–1.5	1.2	1.0–1.4
Nasopharynx (147)	2	∞	0.3–∞	12	2.1	0.7–9.3	2.4	0.8–10.5
Esophagus (150)	2	0.8	0.1–16.7	25	2.0	0.9–5.4	1.8	0.8–4.5
Stomach (151)	14	1.0	0.4–2.8	71	0.9	0.6–1.4	0.9	0.7–1.4
Colon, rectum (153,154)	10	0.7	0.3–2.0	24	1.1	0.5–2.3	0.9	0.5–1.7
Liver and gall bladder (155,156)	8	0.4	0.2–1.3	101	1.3	0.9–1.9	1.2	0.8–1.6
Trachea, bronchus and lung (162)	16	1.0	0.4–2.9	109	1.5	1.0–2.2	1.4	1.0–2.0
Breast (174)	8	0.9	0.3–3.2					
Cervix uteri (179–180)	1	0.2	0.0–2.0					
Bladder (188)	2	∞	0.2–∞	4	0.6	0.1–3.3	0.9	0.2–4.3
Brain tumor ^e (191,225)	6	∞	1.1–∞	7	0.8	0.2–2.6	1.3	0.5–4.1
Malignant lymphoma and related disorders (200–202)	5	∞	1.0–∞	12	3.3	0.9–21.6	4.5	1.3–28.4
Multiple myeloma (203)	0	und	und	0	und	0.0–3.2	und	0.0–3.2
Leukemia (204–208)	13	2.8	0.8–17.6	25	2.1	1.0–5.3	2.3	1.1–5.0
Other malignant neoplasms ^f	16	0.6	0.3–1.3	42	0.8	0.5–1.4	0.8	0.5–1.2

^aObs: observed benzene-exposed cases.^bRR: relative risk, compared with nonexposed workers, adjusted for age.^cCI: confidence interval.^dRR: relative risk, compared with nonexposed workers, adjusted for age and sex.^eIncludes malignant (2 women, 0 men) and other and unspecified CNS tumors (4 women, 7 men).^fIncludes oral (2), larynx (3), other respiratory (1), bone (6), melanoma (3), uterine (2), ovarian (4), other urogenital (3), thyroid (2), and unspecified (14). und. = undetermined.

tional benzene-exposed subject, previously described on histopathologic review as exhibiting morphologic changes indicative of some type of “toxic effect” [Travis et al., 1994], is not considered here, since classification was not possible.

The relative risks in benzene-exposed workers for lymphohematopoietic malignancies and other hematologic disorders are shown in Table IV. Risk was significantly elevated for all lymphohematopoietic malignancies combined (RR = 2.6), malignant lymphoma (RR = 3.5), and leukemia (RR = 2.6). Among the leukemia subtypes, only AML was significantly elevated (RR = 3.1), although nonsignificant excesses were also noted for CML (RR = 2.6) and lymphocytic leukemia (RR = 2.8), the latter attributable to five cases of acute lymphocytic leukemia.

Although point estimates of risk for the other nonmalignant hematologic disorders could not be established (because no cases were identified in unexposed workers), the lower bound of the confidence intervals indicates the statistical lower range for these estimates (Table IV). Significant excess risks are shown for all nonmalignant hematopoietic disorders combined (95% CI_{lower}: 4.8), aplastic anemia (95% CI_{lower}: 2.2), and myelodysplastic syndrome (95% CI_{lower}: 1.7). The relative risk for the rubric of acute myeloid leukemia plus MDS was RR = 4.1 (95% CI: 1.6–

13.8, 30 exposed cases). The relative risk for all lymphohematopoietic malignancies and other hematologic disorders combined was 3.4.

For all lymphocytic and histiocytic malignancies combined, the RR = 2.7 (95% CI: 1.1–8.1, 26 exposed cases) and for non-Hodgkin's lymphoma, the RR = 3.0. The RRs for nodal and extranodal non-Hodgkin's lymphoma were 4.0 (95% CI: 1.1–25.7, 15 exposed cases) and 1.0 (95% CI: 0.1–22.3, 2 exposed cases), respectively. No cases of Hodgkin's disease were identified.

DISCUSSION

This large cohort study identified excess mortality and incidence of lymphohematopoietic malignancies and related disorders among benzene-exposed workers. Risk was increased for AML, consistent with U.S. cohort studies of benzene-exposed pliofilm [Infante et al., 1977; Rinsky et al., 1987] and chemical manufacturing workers [Ott et al., 1978; Bond et al., 1986]. In an earlier report, we described similar excesses among men and women, within broad occupational categories [Li et al., 1994]. Of the nine ANLL cases classified in our study by FAB subtype, three (or possibly four) were M2 and four were M3. One previous study of ANLL subtypes suggested an increased risk for

TABLE IV. Incidence of Lymphohematopoietic Malignancies and Other Hematologic Disorders Among Benzene-Exposed and Unexposed Workers, China, 1972–1987

Diagnosis	Exposed workers	Unexposed workers	RR ^a	95% CI ^b
Lymphohematopoietic malignancies	63	13	2.6	1.5–5.0
Malignant lymphoma	20	3	3.5	1.2–14.9
Non-Hodgkin's lymphoma	17	3	3.0	1.0–13.0
Multiple myeloma	1	1	0.4	0.0–10.7
All leukemia	42	9	2.6	1.3–5.7
Myeloid leukemia	32	6	3.0	1.3–7.9
Acute myelogenous leukemia	23	4	3.1	1.2–10.7
Chronic myelogenous leukemia	9	2	2.6	0.7–16.9
Lymphocytic leukemia	5	1	2.8	0.5–54.5
Acute lymphocytic leukemia	5	1	2.8	0.5–54.5
Other NOS ^c	5	2	1.3	0.3–9.2
Other hematologic disorders	18	0	∞	4.8–∞
Agranulocytosis	2	0	∞	0.3–∞
Aplastic anemia	9	0	∞	2.2–∞
Myelodysplastic syndrome	7	0	∞	1.7–∞
Total	81	13	3.4	1.9–6.3

^aRR: relative risk, compared with nonexposed workers, adjusted for age and sex.^bCI: confidence interval.^cNOS = not otherwise specified.

FAB M4 associated with benzene exposure [Crane et al., 1992]. In another study, two benzene-exposed ANLL cases were classified as M2 and M3, respectively [Vineis et al., 1990]. Others have shown an increased risk for FAB M2 associated with tobacco use [Sandler et al., 1993].

We found an increased risk for MDS in benzene-exposed workers, and the risk associated with benzene exposure was greater for the combined rubric of AML plus MDS (RR = 4.1) than it was for AML alone (RR = 3.1). The recognition of this syndrome is relatively recent and has not routinely been considered in evaluations of risk associated with benzene exposure. Early case studies among benzene-exposed populations noted abnormalities in bone marrow and peripheral blood consistent with MDS in some pancytopenic patients prior to the development of acute leukemia [Goguel et al., 1967a; Aksoy and Erdem, 1978; Van den Berghe et al., 1979]. More recently, cases of MDS exposed to solvents [Vineis et al., 1990] and to benzene [Ciccone et al., 1993] have been described, and a case-control study in Great Britain [Farrow et al., 1989] showed an association of MDS with a history of exposure to gasoline and diesel fumes or liquids. It is noteworthy that a myelodysplastic phase precedes overt leukemia in the majority of AML related to treatment with alkylating agents [Michels et al., 1985; Pedersen-Bjergaard and Philip, 1987], suggesting that a similar pathogenesis could occur with benzene. The etiology and natural history of MDS requires further study.

In terms of other myelogenous leukemias, we found a

suggestive increase in CML, which has been reported in varying frequencies among earlier series of benzene-exposed cases [Browning, 1965; Vigliani and Forni, 1976; Goguel et al., 1967b; Aksoy, 1985]. Risk estimates, however, have generally not been available, except for the earlier report of findings on a subset of the present study [Yin et al., 1989]. Our study showed a significant excess of aplastic anemia, which has been linked to benzene exposure in numerous other reports [Aksoy, 1989; IARC, 1982; Paci et al., 1989].

Considering malignancies of lymphoid origin, we found a significant excess of malignant lymphoma and related disorders, based on a relatively large number (20 cases) of cases among benzene-exposed workers, and we also identified five cases of ALL, but the excess risk for this condition was not statistically significant. In the United States, ALL occurs most commonly among children and older adults. The exposed study subjects with ALL ranged in age from 22 to 41 years. The one unexposed case was age 49 at diagnosis. Only one case of multiple myeloma, one lymphoproliferative disorder, and none of CLL or Hodgkin's disease were identified in the exposed group. Our cross-sectional study of benzene-exposed workers [Rothman et al., 1995] showed that exposure to benzene can affect the level of all the major blood elements, but particularly lymphocytes. Although there are other reports of a possible link between benzene exposure and malignancies of lymphoid origin [Young, 1989], including lymphocytic

leukemia [Aksoy, 1980; Goguel et al., 1967b; Vigliani and Forni, 1976], non-Hodgkin's lymphoma [Wong, 1987; Blair et al., 1993], and multiple myeloma [Rinsky et al., 1987; La Vecchia et al., 1989; Goldstein, 1990], a specific relationship has not consistently been established. One report [Aksoy et al., 1974] also suggested an association with Hodgkin's disease, but we observed no cases in our study.

In contrast to the mortality and incidence analyses for lymphohematopoietic malignancies and related disorders, only mortality data were collected for other diseases. Of the solid tumors, a marginally significant excess was seen for lung cancer, due to increased deaths among men. In assessing this finding, it is noteworthy that tobacco use is frequent among Chinese men, but not among women. We, however, did not have information on tobacco use among the lung cancer cases. Nonsignificant excesses were also noted for nasopharyngeal and esophageal cancer mortality. Except for earlier findings on a subset of our study population [Yin et al., 1989], excesses of lung cancer have not been reported from cohort studies of benzene-exposed workers. Benzene is a multipotent carcinogen in experimental studies [Maltoni et al., 1989; National Toxicology Program, 1986], suggesting that excesses of hematological and nonhematological tumors in humans could be causally related to exposure. Further investigations of benzene exposure and risk for solid tumors are planned.

This study had several important characteristics. The cohort was large, including 74,828 benzene-exposed workers. Extensive information was collected concerning occupational history and exposure to benzene, which will be the subject of further reports. The principal results of this study were based upon disease occurrence in the benzene-exposed group vs. an "internal" unexposed group of industrial workers, thereby providing a more appropriate comparison group than the general Chinese population.

Our initial analyses of mortality in the benzene-exposed group utilized "external" population mortality rates, but these rates were not available for all 12 cities, were restricted to the years 1973–1975, and employed diagnostic criteria that may have differed from those used in our follow-up. Thus the low SMRs with that external standard may be unreliable. In contrast, the all-cause mortality and deaths due to major disease groups were similar between the benzene-exposed and unexposed cohorts, suggesting that the "internal" comparison was more appropriate. In our assessment of the incidence of lymphohematopoietic malignancies and other hematologic disorders, diagnoses were confirmed by review by hematopathologists of pathology reports, medical records, and/or histopathologic material. Comparisons of diagnoses based only on reports or records vs. those based on tissue examination revealed good concordance, providing confidence in the adequacy of the diagnoses [Travis et al., 1994]. Completeness of ascertainment was thought to be high, with the low occupational

mobility in China facilitating follow-up of study subjects for disease outcome. Also, the results were likely not due to increased detection of incident cases in the benzene-exposed group, as excesses were also found for deaths due to lymphohematopoietic disease.

In comparing this with other studies of cancer among benzene-exposed workers that have taken place in the United States and Europe, it should be noted that the occurrence of several of the lymphohematopoietic malignancies is less frequently diagnosed in China, particularly CLL and multiple myeloma, and that nasopharyngeal cancer is considerably more common [Parkin et al., 1992; Groves et al., 1995]. The differences in disease occurrence affect the power to assess risks, as reflected by the relative risk confidence intervals, but may also indicate ethnic differences in susceptibility to these diseases.

The benzene-exposed subjects in this study were employed in a variety of occupations, including painting, printing, and the manufacture of footwear, paint, and other chemicals. Aksoy [1989] has suggested that different types of benzene-induced lymphohematopoietic conditions may be related to the intensity, per unit time, and the total extent of benzene exposure. Our recent investigation of hematotoxicity among currently exposed workers [Rothman et al., 1995] and experimental studies [Henderson et al., 1992] suggests that the kinetics of benzene metabolism may also be influenced by the intensity of exposure. For some work settings, confounding exposures may also contribute to the observed benzene-associated risk [Checkoway et al., 1984]. Analyses are underway to assess exposure-specific disease risk among occupational subgroups with varying intensity and temporal exposure to benzene, and with potential differences in confounding exposures.

In summary, this study of benzene-exposed workers in China provides further support for the association of benzene exposure with an increased risk for myelogenous leukemia. The risk was strongest for AML, but an excess of CML was also noted. Risks were also markedly increased for AA and MDS, and for ALL and NHL, but not for multiple myeloma or Hodgkin's disease. Employment in benzene-associated occupations in China is associated with a wide spectrum of myelogenous and lymphoid malignant diseases, and related disorders. Investigations are continuing to assess the nature of these associations in relationship to various aspects of benzene exposure.

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