Environmental Health Perspectives
Vol. 82, pp. 207-213, 1989

A Retrospective Cohort Study of Leukemia and Other Cancers in Benzene Workers

by S.-N. Yin,* G.-L. Li,* F.-D. Tain, Z.-I. Fu,* C. Jin,* Y.-J. Chen,† S.-J. Luo,‡ P.-Z. Ye,§ J.-Z. Zhang,‖ G.-C. Wang,¶ X.-C. Zhang,# H.-N. Wu,** and Q.-C. Zhong††

A retrospective cohort study was carried out in 1982–1983 among 28,460 benzene-exposed workers (15,643 males, 12,817 females) from 233 factories and 28,257 control workers (16,621 males, 12,366 females) from 83 factories in 12 large cities in China. All-cause mortality was significantly higher among the exposed (265.46/100,000 person-years) than among the unexposed (139.06/100,000 person-years), as was mortality from all malignant neoplasms (123.21/100,000 versus 54.7/100,000, respectively). For certain cancers, increased mortality was noted among benzene-exposed males in comparison with that among unexposed males; the standardized mortality ratios (SMR) were elevated for leukemia (SMR = 5.74), lung cancer (SMR = 2.31), primary hepatocarcinoma (SMR = 1.12), and stomach cancer (SMR = 1.22). For females only leukemia occurred in excess among the exposed. Risk of leukemia rose as duration to exposure to benzene increased up to 15 years, and then declined with additional years of exposure. Leukemia occurred among some workers with as little as 6 to 10 ppm average exposure and 50 ppm-years (or possibly less) cumulative lifetime exposure (based on all available measurements for the exposed work units). Among the 30 leukemia cases identified in the exposed cohort, the proportion of subjects with acute lymphocytic leukemia was substantially lower and the proportion with acute nonlymphocytic leukemias was higher than in the general population. During 1972 to 1981, the annual incidence of leukemia ranged from 5.83 to 28.33 per 100,000 with higher rates occurring in the interval 1977 to 1981 than in the earlier years of the study period. Future studies should evaluate more precisely the relationship between exposure levels, job title, and development of leukemia among cases and noncases within the exposed cohort.

Introduction

Clinical reports and epidemiologic studies have repeatedly linked benzene exposure with leukemia, primarily acute myelocytic and other types of acute nonlymphocytic leukemia (*1–3*). A retrospective cohort investigation carried out in the People's Republic of China during 1982 to 1983 among 28,460 benzene-exposed workers (15,643 males, 12,817 females) from 233 factories and 28,257 control workers (16,621 males, 12,336 females) from 83 factories in 12 large cities in China, provided additional evidence supporting the benzene-leukemia association (*4,5*). More detailed information about the relationship of average and cumulative lifetime benzene levels and duration of exposure with development of leukemia is presented. The types of leukemia that occurred among the exposed cohort are compared with the distribution of leukemia types among the general population. All-cause mortality as well as mortality from specific types of malignancies in addition to leukemia is discussed.

Subjects and Methods

Benzene-exposed subjects were identified in work units from 233 factories in 12 cities in China including Shanghai, Tianjin, Chengdu, Chongqing, Harbin, Shenyang, Jinzhou, Zhengzhou, Luoyang, Kaifeng, Guangzhou, and Nanchang. The primary types of factories or manufactur-

*Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, 29 Nan Wei Road, Beijing, China.
†Station for Health and Prevention of Infection of Shanghai, Shanghai, China.
‡Station for Health and Prevention of Infection of Sichuan, Sichuan, China.
§Station for Health and Prevention of Infection of Tianjin, Tianjin, China.
‖Station for Health and Prevention of Infection of Nanchang, Nanchang, China.
¶China Institute for Prevention and Treatment of Occupational Disease of Heilongjing, Heilongjing, China.
#China Institute for Prevention and Treatment of Occupational Disease of Shenyang, Shenyang, China.
**China Institute for Prevention and Treatment of Occupational Disease of Helan, Helan, China.
††China Institute for Prevention and Treatment of Occupational Disease of Guangzhou, Guangzhou, China.
Address reprint requests to S.-N. Yin, Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, 29 Nan Wei Road, Beijing, China.

ing processes involving benzene exposure were spray or brush painting, shoe manufacturing, synthetic rubber production, leather processing, organic chemical, and adhesive production facilities. An exposed subject had to be working in an operation involving benzene exposure for at least 6 months during the period January 1, 1972, through December 31, 1981. There were 28,460 workers (16,621 males, 12,336 females), with 178,556 person-years of follow-up among the exposed.

Subjects in the control group consisted of 28,257 workers (16,621 males, 12,336 females) employed 6 months or more during the same time interval as the cases, selected from 83 factories in the same cities. Controls were employed in the manufacture of mechanical instruments, textiles, and in clothing production and were not exposed to benzene or any other known occupational carcinogen. The sex and age distribution was similar to those of benzene-exposed workers. For the unexposed group there were 199,201 person-years of follow-up.

Exposed and unexposed workers were followed-up from January 1, 1972, through December 31, 1981, using factory (monthly or annual) salary lists to obtain information about current status including continued employment, retirement, transfer, as well as vital status. Factory and hospital medical records were the source of information about history of benzene poisoning, aplastic anemia, leukemia, and other malignancies. Additional information about history of malignancies, malignant, and nonmalignant causes of death, as well as history of smoking was obtained from a number of possible sources. These included interviews with subjects, their next-of-kin; mailed questionnaires sent to family members of deceased subjects; letters of inquiry sent to families or factories for workers who had transferred jobs; and hospital death certificates or death registration forms kept on file at the subject's local neighborhood police station. For deceased subjects, date and cause of death, date of diagnosis of malignancies, and hospital of diagnosis were abstracted from death certificates and hospital records. Detailed information about histopathology, clinical, and laboratory parameters was obtained for all subjects with leukemia, aplastic anemia, and other hematopoietic and lymphatic malignancies.

Factory records and interviews with factory supervisors and subjects were the source of information about products manufactured, raw materials used, production processes, intermediates, and occupational history of subjects. To determine benzene levels, data were abstracted from factory records about benzene air level measurements, benzene concentration levels in solvents, paint, glue, adhesives, etc., and factories' records about environmental measures and protective devices used to reduce workers' benzene exposure.

All of the factories included in the benzene-exposed group had records detailing benzene concentrations in products used and air level measurements. Control factories were selected from among those with no evidence of benzene, radiation, or other carcinogenic exposures. Among the factories identified as having benzene-exposed work units, the participation rate of these facilities in the study was 99.2%, compared with 98.7% among non-exposed factories.

Criteria used to designate benzene poisoning were based on the "Principles of Diagnosis and Treatment of Benzene Poisoning" published in 1974 by the Ministry of Public Health (*6*). Cases of leukemia and aplastic anemia were diagnosed at hospital departments of internal medicine and hematology and were classified for study purposes as follows: a) grade I, II, bone marrow aspirate and/or biopsy, blood smears, and other histopathologic data used to confirm diagnosis, b) grade III, diagnosis based on clinical evaluation, c) grade IV, diagnosis inferrred after death in the absence of clinical data. Among the accepted leukemia study cases, 96.7% met the criteria for grades I–II, whereas only 3.3% (1 case) were classified as grade III.

Data were collected at all collaborating factories, hospitals, district health stations, etc., using a standardized approach. All forms and data items were checked following abstraction, and missing values and errors were corrected. Inaccurate or incomplete data that could not be corrected were not included in the analyses.

Results

For males and females, age-adjusted all-cause mortality was significantly higher among the benzene-exposed than among control workers (Table 1). For most age groups evaluated, age-specific mortality was higher among exposed workers 25 years of age and older, except for males ages 60 to 69 and females ages 30 to 34 and 55 to 64 as shown in Table 1.

All-cancer mortality was significantly higher among exposed males under age 70 compared with unexposed males (Table 2). For males aged 30 to 45 the cancer death rate was more than twice as high among the exposed than the unexposed, as seen in Table 2. The reverse was noted for females, with cancer mortality actually higher among the unexposed compared with the benzene-exposed group.

Significantly elevated standardized mortality ratios (SMRs) were noted among exposed compared with unexposed males for leukemia (SMR = 5.74) and lung cancer (SMR = 2.31), whereas elevated but nonsignificant SMRs were noted for cancers of the liver, stomach, esophagus, intestine, nasopharynx, and lymphosarcoma, as shown in Figure 1. With the exception of an elevated SMR for leukemia, no major differences were found between exposed and unexposed females (Fig. 1).

The distribution of cancer deaths by site, sex, and rank among benzene-exposed and control workers is shown in Table 3. The rank by cancer site on a national basis is also provided for comparison. For exposed subjects, leukemia is the fourth-ranked site for males and the first-ranked site for females, whereas nationally leukemia is only the seventh most common malignancy. For exposed males, lung cancer is first, and for exposed females second compared with its rank as the fifth most common site nationally.

Table 1. Age-specific mortality from all causes by sex among benzene-exposed and control workers in 12 cities in China, 1972–1981.

	Males						Females					
	Benzene-exposed			Unexposed			Benzene-exposed			Unexposed		
Age group, years	Total no. person-years	No. deaths	Mortality rate (per 100,000 person-years)	Total no. person-years	No. deaths	Mortality rate (per 100,000 person-years)	Total no. person-years	No. deaths	Mortality rate (per 100,000 person-years)	Total no. person-years	No. deaths	Mortality rate (per 100,000 person-years)
15–19	3,328.0	0	0.00	3,360.0	0	0.00	3,301.0	0	0.00	3,357.5	0	0.00
20–24	13,741.0	3	21.83	16,515.5	0	0.00	14,080.0	2	14.20	16,199.0	5	30.87
25–29	14,452.5	5	34.60	20,799.0	8	38.46	14,951.0	2	13.38	16,933.5	1	5.91
30–34	11,307.5	12	106.12	18,474.5	7	37.89	11,748.0	5	37.89	12,693.0	5	39.39
35–39	10,815.5	15	138.69	17,111.5	17	99.35	11,495.5	6	52.19	11,912.0	6	50.37
40–44	13,165.0	30	227.88	16,980.0	18	106.01	11,934.5	12	100.55	10,581.5	6	56.70
45–49	13,772.0	49	355.79	13,467.5	44	326.71	7,750.5	19	245.15	4,922.0	8	162.54
50–54	10,365.0	61	588.52	8,221.0	37	450.07	2,350.5	12	510.53	1,070.0	5	167.29
55–59	6,450.0	93	1,441.86	4,502.5	40	888.40	643.5	6	932.40	228.0	4	1,754.39
60–64	2,128.0	76	3,571.43	1,483.5	35	2,359.29	219.0	8	3,652.97	31.5	1	3,174.60
65–69	406.0	34	8,374.38	290.0	18	6,206.90	41.5	7	16,867.47	4.5	0	0.00
70–74	94.5	16	16,931.22	63.0	12	19,047.62	15.5	1	6,451.61	0.0	0	0.00
Total	100,025.0	394	393.90[a*]	121,268.5	236	194.61[a]	78,531.0	80	101.87[a*]	77,932.5	41	52.61[a]

[a]Age-adjusted according to the indirect method.
*Age-adjusted all-cause mortality is significantly higher among the exposed compared with the unexposed ($p < 0.01$) for both males and females.

Table 2. Age-specific mortality from all cancers by sex among benzene-exposed and control workers in 12 cities in China, 1972–1981.

	Males						Females					
	Benzene-exposed			Unexposed			Benzene-exposed			Unexposed		
Age group, years	Total no. person-years	No. deaths	Mortality rate (per 100,000 person-years)	Total no. person-years	No. deaths	Mortality rate (per 100,000 person-years)	Total no. person-years	No. deaths	Mortality rate (per 100,000 person-years)	Total no. person-years	No. deaths	Mortality rate (per 100,000 person-years)
15–19	3,328.0	0	0.00	3,360.0	0	0.00	3,301.0	0	0.00	3,357.5	0	0.00
20–24	13,741.0	2	14.55	16,515.5	0	0.00	14,080.0	0	0.00	16,199.0	2	12.35
25–29	14,452.5	4	27.68	20,799.0	1	4.81	14,951.0	1	6.69	16,933.5	1	5.91
30–34	11,307.5	8	70.75	18,474.5	4	21.65	11,748.0	0	0.00	12,693.0	1	7.88
35–39	10,815.5	11	101.71	17,111.5	9	52.60	11,495.5	3	26.10	11,912.0	4	33.58
40–44	13,165.0	14	106.34	16,980.0	7	41.22	11,934.5	4	33.52	10,581.5	3	28.35
45–49	13,772.0	18	130.70	13,467.5	16	118.80	7,750.5	14	180.63	4,922.0	3	60.95
50–54	10,365.0	34	328.02	8,221.0	11	133.80	2,350.5	1	42.54	1,070.0	2	186.91
55–59	6,450.0	48	744.19	4,502.5	21	466.41	643.5	4	621.60	228.0	2	877.19
60–64	2,128.0	31	1,456.77	1,483.5	11	741.49	219.0	3	1,369.86	31.5	0	0.00
65–69	406.0	13	3,201.97	290.0	7	2,413.70	41.5	1	2,409.64	4.5	0	0.00
70–74	94.5	4	4,232.80	63.0	4	6,349.21	15.5	2	12,903.23	0.0	0	0.00
Total	100,025.0	187	186.95[a*]	121,268.5	91	75.04[a*]	78,531.0	33	42.02[a]	77,932.5	18	23.10[a]

[a]Age-adjusted according to the indirect method.
*Age-adjusted all-cancer mortality is significantly higher ($p < 0.01$) among exposed compared with unexposed.

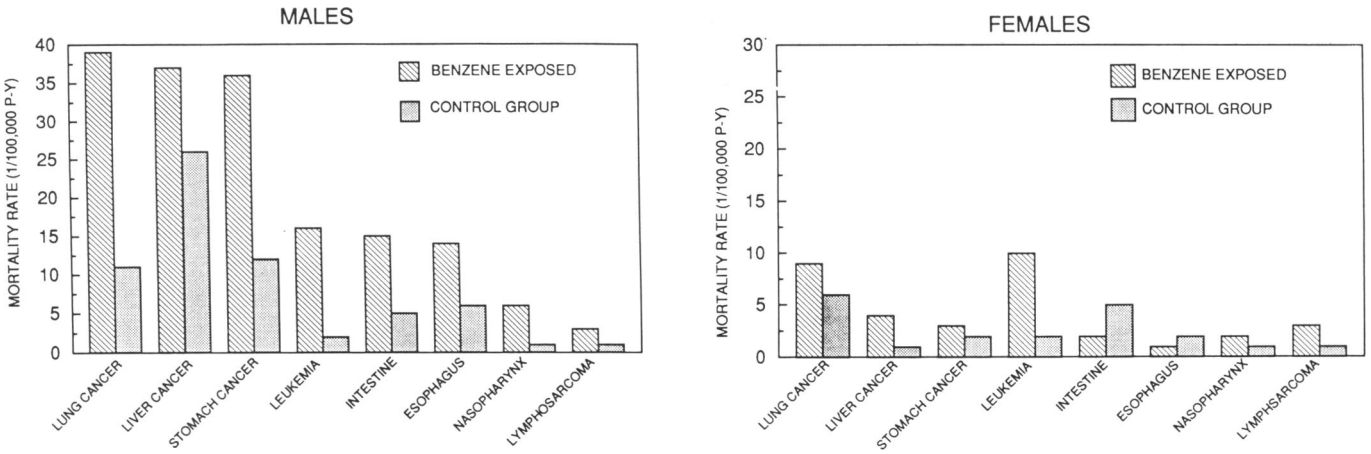

FIGURE 1. Cancer mortality rates by site and sex among benzene exposed and control workers in 12 cities in China, 1972–1981.

Table 3. The distribution of cancer deaths by site, sex, and rank among benzene-exposed and control workers in 12 cities in China, 1972–1981.

National mortality ranking by site	Cancer site	Males						Females					
		Benzene-exposed			Unexposed			Benzene-exposed			Unexposed		
		No. deaths	%	Rank	No. deaths	%	Rank	No. deaths	%	Rank	No. deaths	%	Rank
1	Stomach	37	19.8	3	15	16.5	2	2	6.0	5	1	5.6	4
2	Esophagus	15	8.0	6	8	8.8	4	0	0		1	5.6	5
3	Liver	38	20.3	2	32	35.2	1	3	9.0	4	0	0	
4	Cervix and uterus	—	—	—	—	—	—	1	3.0	7	1	5.6	7
5	Lung	39	20.9	1	13	14.3	3	7	21.2	2	5	27.8	1
6	Intestine	16	8.6	5	6	6.6	5	1	3.0	8	4	22.2	2
7	Leukemia	17	9.1	4	3	3.3	6	8	24.2	1	1	5.6	8
8	Nasopharynx	7	3.7	7	0	0		1	3.0	9	0	0	
9	Breast	—	—	—	—	—		5	15.2	3	3	16.7	3
10	Brain	0	0		3	3.3	7	0	0		1	5.6	9
11	Lymphosarcoma	3	1.6	8	0	0		2	6.0	6	0	0	
12	Bladder	1	0.5	9	2	2.2	8	1	3.0	10	0	0	
13	Other	14	7.5	10	8	8.8	9	2	6.0	11	2	11.1	10
Total		187	100.00		91	100.00		33	100.00		18	100.00	

Though not shown, leukemia mortality among male benzene-exposed smokers (91.1 per 100,000, unadjusted by age) was not higher than leukemia mortality among male exposed nonsmokers (128.2 per 100,000, unadjusted). However, lung cancer mortality in males was significantly higher among smokers in the benzene-exposed group than among smokers in this cohort as shown in Table 4. It is surprising to note that non-smokers in the benzene-exposed group had substantially higher lung cancer mortality than nonsmokers in the control group, as well as smokers (Table 4), though not statistically significant.

The relative risk of leukemia increased with longer duration of benzene exposure up to 15 years and then declined with additional years of exposure. Figure 2 represents an orthogonal polynomial curve graphed using the function of $y = 15.024 + 3.67x - 0.117\,x^2$, where y is the risk of leukemia (mortality of leukemia in the benzene exposed group/mortality of leukemia in the control group) and x is the duration of benzene exposure in years.

For each of the 30 benzene-exposed leukemia cases, average and cumulative lifetime levels of exposure were estimated using all available measurements (Table 5). The minimum average exposure was 6.5 mg/m^3 and the lowest cumulative lifetime exposure was estimated to be 33.2 mg/m^3 years, as shown in Table 5. It is also interesting to note that three cases had a lifetime cumulative exposure of less than 50 mg/m^3 year.

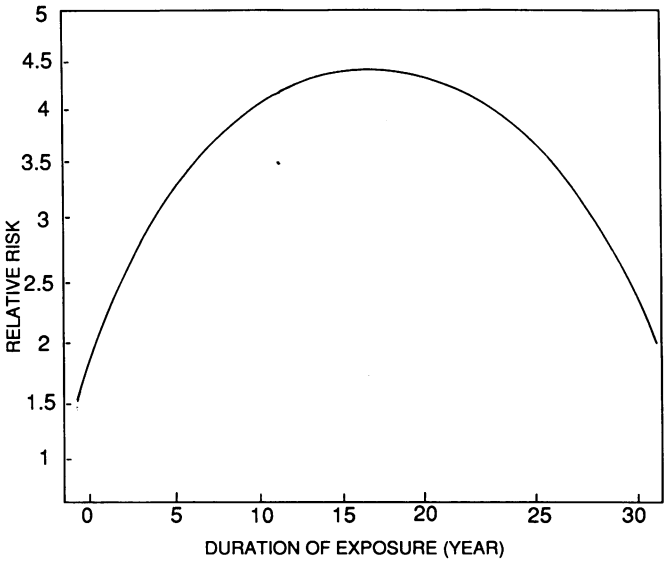

FIGURE 2. Association of the relative risk of leukemia with the duration of exposure to benzene among the benzene-exposed cohort from 12 cities in China, 1972–1981.

The distribution of exposed and unexposed cases by type of leukemia is shown in Tables 6 and 7. As noted in Table 7, 66.6% of the exposed cases had a variant of acute

Table 4. Risk of lung cancer for smokers and nonsmokers among male benzene-exposed and control workers from 12 cities in China, 1972–1981.

Group	No. persons	No. deaths	Mortality (1/100,000)[a]	RR	U	p
Benzene-exposed smokers	10.957	31	282.92	1.20[b]	0.53	> 0.05
Benzene-exposed nonsmokers	4.680	11	235.00	2.31[c]	2.61	< 0.01
Control group smokers	10.617	13	122.44	1.92[d]	1.62	<0.05
Control group nonsmokers	6.004	0	0.00			

[a]Crude rates.
[b]RR = 282.92/235.00.
[c]RR = 282.92/122.44.
[d]RR = 235.00/122.44.

nonlymphocytic leukemia compared with 50.1% of the leukemia cases from the general population. Only 10% of the cases among the exposed group had acute lymphocytic leukemia compared with 23.5% in the general population.

Although the data are shown, the incidence of leukemia was higher in the later 5 years of the study period (19.79/100,000) than in the earlier years (10.79/100,000). However, the number of cases is too small to provide stable annual estimates.

Discussion

The substantially elevated risks for leukemia observed for both males and females in the benzene-exposed cohort confirm findings from earlier clinical reports and epidemiologic studies. In 1928, Delore and Borgomano first reported cases of benzene-caused leukemia in Italy (*1*). Vigliani and Saita later estimated a 20-fold higher risk of acute leukemia among printing shop workers and shoemakers in Milan and Pavia who were exposed to benzene (*7*). Among atomic bomb survivors in Hiroshima and Nagasaki, risk of leukemia was about 2.5-fold higher in those with a past history of exposure to benzene and medical X-rays than in those without such exposures (*8*). Aksoy et al. identified 34 leukemia cases diagnosed during 1967 to 1975 among 28,500 shoemakers in Istanbul, Turkey, estimating an incidence of 13 per 100,000 compared with approximately 6 per 100,000 in the general population (*9*). An SMR of 5.6 for leukemia was noted in a retrospective cohort study of Pliofilm workers employed in factories in Akron, Ohio (*10,11*); for workers exposed to benzene more than 5 years, the SMR for leukemia was 21.

Although there have been case reports of other malignancies associated with benzene exposure (*1*), the current investigation is one of the first analytic studies demonstrating a significant excess of lung cancer and suggesting possible increases of stomach, liver, esophagus, intestine, and nasopharyngeal cancer, as well as lymphosarcoma. The excess risk of leukemia among female workers exposed to benzene has also not previously been reported.

This retrospective cohort study was also one of the first to evaluate the effect of smoking on cancer outcomes among benzene-exposed and unexposed workers. No effect was found for smoking on leukemia mortality. Risk of lung cancer was slightly higher among smokers than among nonsmokers in the benzene-exposed group. However, nonsmokers among the benzene-exposed had a significantly higher mortality than nonsmokers in the control group, suggesting that lung cancer was more strongly related to benzene exposure than to smoking. These surprising results require additional evaluation.

Table 5. Description of leukemia cases among benzene-exposed workers by duration and years of benzene exposure, average estimated exposure level, and lifetime cumulative exposure.

Case identification no.	Duration of exposure (——>) and benzene measurements, mg/m³						Average estimated exposure level, mg/m³	Cumulative exposure, mg/m³ year
	1950–1959	1960–1964	1965–1969	1970–1974	1975–1979	1980–1982		
1						136.2	136.2	1498.2
2					253.9		253.9	1015.6
3	129	67		47.9			47.9	287.4
4	129	67		47.9			57.5	1150.0
5 (1925)		93.7	412.7	37.8	9.7		181.4	8888.6
6			67	91.7	3.75		54.2	975.6
7						15.5	15.5	310.0
8				15			15.0	90.0
9				346.9	37.7		37.7	37.7
10	225		141	50.7	36.5	9.1	113.3	5438.4
11					9.2	54.1	9.2	110.4
12					474.2		474.2	3319.4
13						81.8	81.8	1390.6
14					282.1		282.1	1410.5
15				6.5			6.5	52.0
16				11.5	15.0		13.3	93.1
17					149.1	385.5	149.1	2087.4
18					13.3		13.3	39.9
19					173.2	57.2	173.2	2251.6
20					44.9	732.6	44.9	853.1
21					301		301.0	5418.0
22				206.4		31.3	206.4	1651.2
23					487	101.7	487.0	7792.0
24					42.0	0.8	42.0	798.0
25					54.7	138.8	96.8	1548.8
26					96.3		96.3	96.3
27			10	6.5			8.3	33.2
28			86.2		9	16	86.2	16359.0
29				105.3	80.1		92.5	555.0
30					65	346	65.0	1170.0

Table 6. Description of leukemia cases by sex, age, duration of exposure, and type of leukemia among benzene-exposed and control workers from 12 cities in China, 1972–1981.

Leukemia cases identified	Sex	Age	Duration of benzene exposure, years	Type of leukemia
Benzene-exposed workers				
1	M	35	11	Acute myelomonocytic
2	M	25	4	Acute monocytic
3	M	37	6	Acute monocytic
4	M	61	20	Acute monocytic
5	M	62	49	Lymphosarcomatous
6	M	32	18	Acute promyelocytic
7	M	46	20	Acute myelocytic
8	F	60	6	Acute myelocytic
9	M	30	1	Chronic myelocytic
10	M	61	48	Acute myelocytic
11	M	31	12	Acute myelocytic
12	M	25	7	Acute lymphocytic
13	F	47	17	Chronic myelocytic
14	M	23	5	Acute myelocytic
15	F	53	8	Chronic myelocytic
16	F	36	7	Acute myelocytic
17	F	37	14	Acute myelocytic
18	M	57	3	Acute myelomonocytic
19	M	36	13	Chronic myelocytic
20	M	41	19	Acute myelocytic
21	F	47	18	Acute unspecified
22	M	24	8	Acute myelocytic
23	F	45	16	Acute erythromyelocytic
24	F	57	19	Chronic myelocytic
25	M	41	16	Acute myelocytic
26	M	47	1	Acute monomyelocytic
27	M	40	4	Acute myelocytic
28	M	42	19	Acute lymphocytic
29	F	25	6	Acute myelocytic
30	M	41	18	Lymphocytoid
Control workers				
1	F	36	22	Chronic myelocytic
2	M	34	12.5	Acute myeloblastic
3	M	72	30	Chronic myelocytic
4	M	54	22	Leukemia unspecified

The findings of leukemia risk subsequent to relatively low estimated average and cumulative lifetime benzene exposure supports a recent report by Rinsky et al. (*12*). However, these findings must be interpreted cautiously because the estimated average and cumulative lifetime benzene exposure levels are based on relatively few measurements. In addition, it would be useful to evaluate differences in average and cumulative benzene exposure between leukemia cases and non-cases randomly selected from the exposed cohort in order to more completely evaluate the relationship of benzene exposure with development of leukemia.

This investigation is one of a few to evaluate the types of leukemia occurring among benzene-exposed and compare this distribution to that observed in a general population. The results support findings from other studies of an excess of acute nonlymphocytic leukemia among benzene-exposed subjects (*1,7–11*).

Table 7. The distribution of 30 leukemia cases by type among benzene-exposed workers from 12 cities in China (1972–1981) compared with the distribution of 23,048 leukemia cases identified from the general population of China.

Type of leukemia	Distribution of 30 leukemia cases from the benzene-exposed population by leukemia type, %	Distribution of 23,048 leukemia cases from the general population by leukemia type, %[a]
Acute lymphocytic	10.0	23.5
Acute myelocytic	43.3	40.0
Acute monocytic	10.0	10.1
Acute myelomonocytic	10.0	–
Acute erythromyelocytic	3.3	–
Chronic myelocytic	16.7	18.1
Chronic lymphocytic	–	1.1
Chronic lymphosarcomatous	3.3	–
Leukemia, not otherwise specified	3.3	–

[a]From Chu (*13*).

One of the somewhat surprising findings in this retrospective cohort study was the increase in all-cause mortality. Further evaluation is underway to identify the specific diseases primarily responsible for the excess, as well as possible reasons for a relative deficit of these conditions among the unexposed. Other reasons that might explain the excess of deaths due to all causes and all malignancies will also be examined in an expansion of the present study conducted in collaboration with the U.S. National Cancer Institute.

Preliminary findings suggest a risk of leukemia, primarily acute nonlymphocytic in type, from relatively low average and cumulative benzene exposure. Risk of leukemia is elevated in females exposed to benzene, as well as males, although the former do not seem to develop other types of malignancies in excess following this exposure. In summary, the present study has suggested that other cancers, as well as some nonmalignant conditions, may be associated with benzene exposure. Future studies should evaluate more precisely and, in relation to nonleukemia cases, the relationship between levels of exposure and development of leukemia. In addition, it would be useful to determine which industries, occupations, and particular job titles are linked with higher risks. Finally, possible modifying factors affecting occurrence of leukemia (such as radiaton, medications, other occupational exposures, etc.) should be evaluated in nested case-control leukemia studies, undertaken within large benzene-exposed cohorts.

This investigation was supported and organized by the Ministry of Public Health of the Government of China. We are grateful to M. Linet, R. Hayes, M. Dosemeci, and W. Blot, National Cancer Institute, Bethesda, MD, for their critical review of the manuscript. We thank S.-Y. Yand, Y.-Z. Wang, D.-Y. Ding, W.-Y. Zhang, R.-R. Dai, X.-J. Chao, F.-Y. Jie, Y.-H. Huan, Z.-L. Jian, C.-Q. Wu, J.-F. Mun, and A.-M. Wang for participating in this study.

REFERENCES

1. IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 29. International Agency for Research on Cancer, Lyon, France, 1982, pp. 148–293.
2. Infante, P. F., and White, M. C. Projection of leukemia risk associated with occupaitonal exposure to benzene. Am. J. Ind. Med. 7: 403–413 (1985).
3. Slooff, W., Ed. Integrated Criteria Document: Benzene. National Institute of Public Health and Environmental Hygiene, Bilthoven, The Netherlands, 1988.
4. Yin, S.-N, Li, G.-L., Tain, F.-D., Fu, Z.-I., Jin, C., Chen, Y.-J., Luo, S.-J., Ye, P.-Z., Zhang, X.-C., Wu, H.-N., Zhong, Q.-C., Zhang, J.-Z., and Wang, G.- C. Leukemia in benzene workers: a retrospective cohort study. Br. J. Ind. Med. 44: 124–128 (1987).
5. Yin, S.-N., Li, G.-L., Tain, F.-D., Fu, Z.-I., Jin, C., Chen, Y.-J., Luo, S.-J., Ye, P.-Z., Zhang, J.-Z., Wang, G.-C., Zhan, X.-C., Wu, H.-N., and Zhong, Q.-C. Epidemiological study on relationship between benzene and leukemia and other cancers (abstract). Chin. J. Ind. Hyg. Occup. Dis. 4: 11–13: (1986) (in Chinese).
6. Principles of Diagnosis and Treatment of Benzene Poisoning. Ministry of Public Health, China, 1974.
7. Vigniani, E. C., and Saita, G. Benzene and leukemia. N. Engl. J. Med. 271: 876–882 (1964).
8. Ishimaru, T., Okada, H., Tomayasu, T., Tsuchimoto, T., Hoshino, T., and Tchimaru, M. Occupational factors in the epidemiology of leukemia in Hiroshima and Nagasaki. Am. J. Epidemiol. 93: 157–165 (1971).
9. Aksoy, M. Different types of malignancies due to occupational exposure to benzene. A review of recent observations in Turkey. Environ. Res. 23: 181–190 (1980).
10. Infante, P. F., Rinsky, P. A., Wagoner, J. K., and Young, R. J. Leukemia in benzene workers. Lancet ii: 76–78 (1977).
11. Rinsky, R. A., Young, R. J., and Smith, A. B. Leukemia in benzene workers. Am. J. Ind. Med. 2: 217–245 (1981).
12. Rinsky, R. A., Smith, A. B., Hornung, R., Filloon, T. G., Young, T. G., Young, R. J., Okun, A. H., and Landrigan, P. J. Benzene and leukemia—an epidemiologic risk assessment. N. Engl. J. Med. 316: 1044–1050 (1987).
13. Chu, J. X. Epidemiology of leukemia in China (a review). Tianjin Med. J. 10: 323–326 (1982) (in Chinese).