

An Expanded Cohort Study of Cancer Among Benzene-exposed Workers in China

Song-Nian Yin,¹ Richard B. Hayes,² Martha S. Linet,² Gui-Lan Li,¹ Mustafa Dosemeci,² Lois B. Travis,² Zhi-Nan Zhang,¹ De-Gao Li, Wong-Ho Chow,² Sholom Wacholder,² William J. Blot,² and The Benzene Study Group*

¹Chinese Academy of Preventive Medicine, Beijing, China; ²National Cancer Institute, Bethesda, Maryland

An expanded cohort study of 74,828 benzene-exposed and 35,805 unexposed workers were followed during 1972 to 1987, based on a previous study in 12 cities in China. A small increase was observed in total cancer mortality among benzene-exposed compared with unexposed workers (relative risk [RR]=1.2). Statistically significant excesses were noted for leukemia (RR=2.3), malignant lymphoma (RR=4.5), and lung cancer (RR=1.4). When risks were evaluated by leukemia subtype, only acute myelogenous leukemia was significantly elevated (RR=3.1), although nonsignificant excesses were also noted for chronic myelogenous leukemia (RR=2.6) and acute lymphocytic leukemia (RR=2.3). A significant excess was also found for aplastic anemia. — Environ Health Perspect 104(Suppl 6):1339–1341 (1996)

Key words: benzene, leukemia, malignant lymphoma, lung cancer, aplastic anemia

Introduction

Benzene has been widely used in chemical manufacturing and other industries for about a century. A nationwide survey carried out in 1979 to 1981 revealed that 529,000 workers were occupationally exposed to benzene or benzene-containing mixtures in China (1). Similarly, it has been estimated that 233,000 people are occupationally exposed to benzene in petrochemical plants, petroleum refineries, and other operations in the United States (2). In addition to occupational exposures, benzene concentrations varying from 1 to 150 mg/m³ have been described in urban and densely trafficked areas (3). Therefore, benzene is a potentially important

carcinogen not only to workers, but also to the general population (4).

The present study was initiated as a collaboration between the Institute of Occupational Medicine, China, and the U.S. National Cancer Institute (NCI), based on an earlier retrospective cohort study carried out by Chinese investigators among 28,480 benzene-exposed and 28,257 unexposed workers followed up from 1972 to 1981 in China (5). The major reasons for expanding upon the original cohort study were to include substantially more subjects, additional person-years of follow-up, and more leukemia cases, for analyzing in detail the relationship of benzene with subtype of leukemia and other hematolymphoproliferative malignancies. In this paper we summarize the mortality risks for all cancers and the incidence risks for all leukemia and other selected hematolymphoproliferative malignant and nonmalignant disorders (HLD). Further detail is provided in Yin et al. (6).

Methods

Study Population and Data Sources

The methods for this expanded study are described in detail elsewhere (7). Briefly, the study subjects were selected from workers employed in 672 factories in

which benzene was used (exposed factories) compared to unexposed workers at 69 of these factories and at 40 additional factories (unexposed factories) in 12 cities in China (including Shanghai, Tianjin, Chengdu, Chongqing, Harbin, Shenyang, Jinzhou, Zhengzhou, Luoyang, Guangzhou, Nanchang, Kaifeng) in China. Using monthly salary records, field center staff in each city identified all workers employed for any length of time in the eligible work units or factories during 1972 to 1987. If salary records were not available or incomplete for the eligible work units or factories during the study period, other data sources used in a standardized hierarchical approach included job registers (completed upon initiation of employment at a factory), health examination forms, and hazardous work compensation registries.

Data Collection and Follow-up Procedures

For each eligible study subject, data abstracted included the worker's name, birthdate, sex, job history in study factories, vital status on December 31, 1987, date last known alive if lost to follow up, cause(s) of death and date of death for deceased workers, history and date of diagnosis of leukemia or other HLD, and history and date of diagnosis of benzene poisoning.

Workers who left study factories before December 31, 1987, were followed up and traced to determine vital status, cause of death, and occurrence of leukemia and other HLD. For deceased subjects, cause of death was obtained from medical records, other written factory records, or death certificates at local police stations. The subject's physician or the next of kin was contacted only if written records listing cause of death could not be obtained. For all subjects whose cause of death was suspected to be cancer or HLD, hospital and other medical records were sought to verify the diagnosis. The specific histopathology, date of diagnosis, date of death, hospital/place of death, source of medical information, and other important diagnosis-related information were abstracted on a standard diagnostic validation form and reviewed by the field center director and the investigators. For cases of HLD, medical records and all available pathology and peripheral blood smear slides were reviewed by hematopathologists from the Beijing Union Medical College Hospital, the NCI, and the Mayo Clinic in Rochester, Minnesota.

This paper was presented at Benzene '95: An International Conference on the Toxicity, Carcinogenesis, and Epidemiology of Benzene held 17–20 June 1995 in Piscataway, New Jersey. Manuscript received 16 January 1996; manuscript accepted 14 June 1996.

*The Benzene Study Group includes Y.Z. Wang, Z.L. Jiang, T.R. Dai, W.Y. Zhang, X.Y. Chao, P.Z. Ye, Q.R. Kou, X.C. Chang, X.F. Lin, J.F. Meng, C.Y. Ding, and J.S. Zhu.

Address correspondence to Dr. S. Yin, Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, 29 Nan Wei Road, Beijing 100950, China. Telephone: (86-10) 6301-4187. Fax: (86-10) 6301-4187. E-mail: yinsn@public3.bta.net.cn

Abbreviations used: NCI, National Cancer Institute; HLD, hematolymphoproliferative disorders; RR, relative risk.

Table 1. Distribution of benzene-exposed and nonexposed subjects.

	Exposed			Nonexposed		
	No.	Person-years	%	No.	Person-years	%
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

The exposure assessment methods used to determine time period-specific quantitative estimates of benzene exposure by job title within work units are described elsewhere (8). For the statistical analysis, relative risks (RR) were derived as the ratio of age- and sex-adjusted rates in the exposed and unexposed groups.

Results

The expanded cohort consisted of 74,828 exposed and 35,805 unexposed persons in 781 factories and 12 cities (Table 1). They were followed up for an average of 10.5 and 11.7 years, respectively. Approximately 1.8% of exposed and 1.7% of unexposed workers were deceased, and 0.2% of exposed and 0.3% of unexposed workers were lost to follow-up (Table 2).

There were 1369 deceased in the exposed cohort and 598 deceased in the unexposed cohort.

Age-adjusted RR for cancer mortality for the exposed compared with the unexposed groups are shown in Table 3. The RR ranged from 0.4 to 2.8 for women and from 0.9 to 3.3 for men. RR for leukemia was 2.8 for women and 2.1 for men. RR for lung cancer was 1.5 for men and 1.0 for women.

Incidence risks for HLD were analyzed using the internal comparison to assess the difference between exposed and unexposed workers. Table 4 presents RR for the specific HLD. HLD, including leukemia, myelodysplastic syndromes, and lymphoma, were significantly elevated, with RR ranging from 2.5 to 3.1. The observed number of aplastic anemia and agranulocytosis cases were nine and two, respectively, in exposed workers, but there were no cases in unexposed workers.

Discussion

There have been several reports describing risks of leukemia, lymphoma, and other cancers in relation to occupational benzene exposure in several countries (9-17). Most of the studies have reported mortality excesses for all hematopoietic and lymphatic cancers. However, most of the investigations yielded small numbers in the

Table 3. Cancer mortality among benzene-exposed compared to nonexposed workers by sex.

Cause of death (ICD9)	Women			Men		
	Observed	RR	95% CI	Observed	RR	95% CI
Malignant neoplasms (140-208)	99	0.9	0.6-1.3	425	1.2	1.0-1.5
Nasopharynx (147)	2	∞	0.3-∞	12	2.1	0.7-9.3
Esophagus (150)	2	0.8	0.1-16.7	25	2.0	0.9-5.4
Stomach (151)	14	1.0	0.4-2.8	71	0.9	0.6-1.4
Colon, rectum (153,154)	10	0.7	0.3-2.0	24	1.1	0.5-2.3
Liver and gall bladder (155,156)	8	0.4	0.2-1.3	101	1.3	0.9-1.9
Lung, trachea, and bronchus (162)	16	1.0	0.4-2.9	109	1.5	1.0-2.2
Malignant lymphoma (200-202)	5	∞	1.0-∞	12	3.3	0.9-21.6
Leukemia (204-208)	13	2.8	0.8-17.6	25	2.1	1.0-5.3

Abbreviations: ICD, International Classification of Diseases; RR, relative risk; CI, confidence interval.

Table 4. Incidence of hematolymphoproliferative disorders among benzene-exposed compared to nonexposed workers (1972-1987).

Diagnosis	Exposed workers	Nonexposed workers	RR	95% CI
All hematolymphoproliferative 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
Acute myelogenous leukemia	23	4	3.1	1.2-10.7
Chronic myelogenous leukemia	9	2	2.6	0.7-16.9
Acute lymphocytic leukemia	5	1	2.8	0.5-54.5
Myelodysplastic syndrome	7	0	∞	1.7-∞
Aplastic anemia	9	0	∞	2.2-∞
Agranulocytosis	2	0	∞	0.3-∞
Total	81	13	3.4	1.9-5.2

cohorts studied and few leukemia cases. While a few cohort studies evaluated more than 10,000 workers in rubber factories or oil companies, the findings were not significantly elevated for leukemia. Most of the studies usually compared the study population with the general population; few used an internal comparison cohort.

This study was designed specifically to avoid the disadvantage of earlier investigations (18). To date, this study is the largest cohort mortality investigation, comprising 81 cases and 13 cases of HLD observed in exposed and unexposed groups, respectively. The distribution by sex, age, and calendar-year at first entry were similar for exposed and unexposed groups. Such an internal comparison group makes it possible to minimize the healthy worker effect.

Table 2. Vital status of benzene-exposed and nonexposed subjects (1972-1987).

	Exposed		Nonexposed	
	No.	%	No.	%
Alive	73,312	98	35,117	98
Deceased	1,369	2	598	2
Lost to follow up	147	0.2	90	0.3

Table 5. Comparison of this study with the previous study in China (5).

Follow-up	1972-1981	1972-1987
Subjects		
Exposed	26,460	74,828
Unexposed	23,257	35,805
Leukemia		
Exposed	25	49
Unexposed	4	9
Exposure data	For leukemia cases only	For all subjects
Nested case-control	No	94 cases, 376 controls

Comparison of this cohort study with the previous cohort study in China (Table 5) reveals that this study has a longer duration of follow-up, a larger population, more leukemia cases, and an in-depth

examination of information. It will be important to continue to follow these workers, since substantial numbers, particularly those first employed after 1980, will only have experienced low exposure levels of benzene since start of employment.

The risk was significantly increased for the combined grouping of acute myelogenous leukemia and myelodysplastic

syndromes, since the latter may precede overt leukemia. Risk was also increased for chronic myelogenous leukemia and acute lymphocytic leukemia, but not statistically significant. Risk was significantly increased for malignant lymphoma and for non-Hodgkin's lymphoma, but not for multiple myeloma. Mortality from lung cancer was significantly increased due to a significant

excess among males, consistent with the results from a previous study in China.

Based on analysis of the incidence in the largest cohort, it was confirmed that benzene is a leukemogen, especially for myelogenous leukemia in humans, and benzene is possibly also associated with excess risk of non-Hodgkin's lymphoma and lung cancer among humans.

REFERENCES

1. Yin SN, Li GL, Yin Y, Tain F, Du C, Jin C. Occupational exposure to benzene in China. *Br J Ind Med* 44:124-128 (1987).
2. Mehlman M. Benzene health effects: unanswered questions still not addressed. *Am J Ind Med* 20:707-711 (1991).
3. Wolff SP. Correlation between car ownership and leukemia: Is non-occupational exposure to benzene from petrol and motor vehicle exhaust a causative factor in leukemia and lymphocytic: *Experientia* 48. Basel, Switzerland: Birkhauser Verlag, CH-4010.
4. Wallace LA. Major sources of benzene exposure. *Environ Health Perspect* 82:165-169 (1989).
5. Yin SN, Li GL, Tain FD, Fu ZI, Jin C. Leukemia in benzene workers: a retrospective cohort study. *Br J Ind Med* 44:124-28 (1987).
6. Yin SN, Hayes RB, Linet MS, Li GL, Dosemeci M, Wang YZ, A cohort study of benzene exposed workers in China. *Am J Ind Med* (in press, 1996).
7. Yin SN, Linet MS, Hayes RB, Li GL, Dosemeci M, Wang YZ, Chow WH, Jiang ZL, Wacholder S, Zhang WU et al. Cohort study among workers exposed to benzene in China: I General Methods and Resources. *Am J Ind Med* 26:383-400 (1994).
8. Dosemeci M, Li GL, Hayes RB, Yin SN, Linet MS, Chow WH, Wang YZ, Jiang ZL, Dai TR, Zhang WU et al. Cohort study among workers exposed to benzene in China. II: Exposure assessment. *Am J Ind Med* 26:401-411 (1994).
9. Thorpe JJ. Epidemiologic survey of leukemia in persons potentially exposed to benzene. *J Occup Med* 16:375-382 (1974).
10. Infante PF, Rinsky RA, Wagoner JK. Leukemia in benzene workers. *Lancet* 2:76-78 (1977).
11. Rinsky RA, Young JL, Smith AB. Leukemia in benzene workers. *Am J Ind Med* 2:217-245 (1981).
12. Rinsky RA, Alexander BS, Hornung R, Filloon TG, Young RL, Okum AH, Landrigan PJ. Benzene and leukemia-an epidemiologic risk assessment. *N Engl J Med* 316:1044-1059 (1987).
13. Ott MG, Townsend JC, Fishbeck WA et al. Mortality among individuals occupational exposed to benzene. *Arch Environ Health* 33:3-16 (1987).
14. Bond CG, McLaren EA, Baldwin CL, Cook RR. An update of mortality among chemical workers exposed to benzene. *Br J Ind Med* 43:685-691 (1986).
15. Tsai SP, Wen CP, Weiss NS, Gibson RL, McClellan WA. Retrospective mortality and medical surveillance studies of workers in benzene areas of refineries. *J Occup Med* 26(5):635-692 (1983).
16. Wong O. An industry wide mortality study of chemical workers occupational exposed to benzene. I: General results. *Br J Ind Med* 44:365-381 (1987).
17. Paci E, Buiatti E, Costantini AS, Miligi L, Pucci N, Scarpelli A, Petrioli G, Semonate L, Winkelmann R, Kalder JM. Aplastic anemia, leukemia and other cancer mortality in cohort of shoe workers exposed to benzene. *Scand J Work Environ Health* 15:313-318 (1989).
18. Paganini-Hill A, Glazer E, Henderson RE et al. Cause-specific mortality among newspaper web pressman. *J Occup Med* 22:542-554 (1980).
19. Yin SN, Li GL, Tain FD, Fu ZI, Jin C et al. A retrospective cohort study of leukemia and other cancers in benzene workers. *Environ Health Perspect* 82:207-213 (1989).