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Occupational History and Exposure and the Risk of Adult Leukemia in Shanghai

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PURPOSE: Evaluation of the association of selected occupational exposures with leukemia risk.
METHODS: Population-based case-control study of 486 leukemia subjects and 502 healthy controls residing in Shanghai from 1987 to 1989. Adjusted odds ratios (OR) were calculated for the association between occupational factors and leukemia risk.
RESULTS: Significant increase in leukemia risk was observed in chemical manufacturing industry workers (OR = 3.1, 95% CI = 1.0–9.8). Increased risks for leukemia were observed from self-reported exposures to benzene (OR = 1.7, 95% CI = 1.1–2.6), radioactive materials (OR = 3.7, 95% CI = 1.3–10.2), synthetic fiber dust (OR = 2.0, 95% CI = 1.2–3.5), and toluene (OR = 1.6, 95% CI = 1.0–2.5). Dose–response relations of leukemia risk was observed with the duration of exposure to benzene (OR = 3.3, 95% CI = 1.6–6.9 for $\geqslant$ 15 years exposure; p for trend $<$ 0.01), radioactive materials (OR = 5.2, 95% CI = 1.1–24.7 for $\geqslant$15 years exposure; p for trend = 0.02), paints (OR = 2.3, 95% CI = 1.2–4.7 for $\geqslant$ 15 years exposure; p for trend = 0.09), and toluene (OR = 2.9, 95% CI = 1.3–6.7 for $\geqslant$15 years exposure; p for trend = 0.02).
CONCLUSIONS: Adult leukemia risk may be associated with working in the chemical industry, and exposure to benzene, synthetic fiber dust, radioactive materials, and toluene in the study population.
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KEY WORDS: Leukemia, Occupational Exposures, Risk Factor, Case-control Study.

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INTRODUCTION

Though a number of occupational epidemiologic studies of leukemia have been conducted, there are few established occupational risk factors other than benzene and radiation exposure (1, 2). Most previous studies were small, occupational exposures were not systematically assessed, and were unable to control for potential confounding factors (3–6). Some studies evaluated only a single exposure (e.g. benzene, organic solvents, radiation) (6–8). Moreover, many previous studies did not evaluate exposures by type of leukemia (9). Finally, few studies have been conducted in China.

Shanghai is the largest industrialized city on the east coast of China. The incidence rates for leukemia in Shanghai ranged from 3.5 to 5.0 per 100,000 person-years between 1988 and 1992, which were similar to overall rates in China (10, 11). Since few studies have been conducted in China, a case-control study of leukemia was conducted in Shanghai to evaluate familial, environmental/occupational, medical, and therapy-related risk factors. The industrial diversity in Shanghai provides a unique opportunity to evaluate a number of suspected occupational risk factors for leukemia.

METHODS

Study Participants

The methods for this study have been described in detail in an earlier publication (12). Cases were residents of urban Shanghai diagnosed with leukemia at age 15 or older (ICD-9 codes 204–208 [WHO, 1997]) who were reported to the Shanghai Cancer Registry from June 1, 1987 through

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Selected Abbreviations and Acronyms

CI = confidence interval
OR = odds ratio
ICD-9 = International Classification of Diseases-9
WHO = World Health Organization
SAS = Statistical Analysis Software
ALL = aute lymphocytic leukemia
ANLL = acute non-lymphocytic leukemia
CML = chronic myeloid leukemia
CLL = chronic lymphocytic leukemia
EMF = electromagnetic field
JEM = job-exposure matrix

August 31, 1989. A total of 532 eligible cases were identified. Interviews were completed with 486 (91.4% of the eligible cases). Interviews were obtained directly with 254 cases, while surrogates provided information for 194 cases that were deceased and 38 cases too ill to be interviewed. Forty-eight percent of the surrogates were spouses and 50% other first-degree relatives. Of the eligible cases, 35 (6.5%) could not be located and 11 (2.1%) refused to participate.

Controls were randomly selected from the general urban Shanghai population using the comprehensive, population-based Resident Registry. The Resident Registry maintains a personal registry card for each adult resident (over age 15) in urban Shanghai. The information on each resident includes name, address, date of birth, sex, and other demographic factors. The likely age (5-year intervals) and sex distribution of cases was determined using leukemia incidence data from 1984 to 1985, which was the most recently available information from the Shanghai Cancer Registry at the start of the study. Based on this distribution, 502 potential controls were randomly selected from residents as listed in the Resident Registry. If the first control selected was ineligible or refused to be interviewed, a second control was then chosen using the same method. Only 30 replacement controls (6.0%) were required. These were used because the first controls could not be located (12 out of 30), died prior to being interviewed (8 out of 30), or for other reasons (10 out of 30). The response rate among controls was 94 percent.

Exposures

Trained interviewers used standardized Chinese questionnaires to obtain information on demographic factors, occupational exposures, lifestyle, occupational history, family history, dietary habits, tobacco smoking, education, diagnostic X-ray procedures, specific medications and medically related topics. Each subject was asked to provide the information for each job he/she held for at least 3 years during his/her lifetime. Self-reported information was also sought on exposure to benzene, gasoline, pesticides, synthetic fiber dust, toluene, radioactive materials (exposure to X-rays and diagnostic radiation), electromagnetic fields (EMF), asbestos, paints, and other organic solvents. Excessive risks for leukemia have been associated with some of these exposures by others (13–16). Subjects who reported having these exposures were questioned further for information on the frequency and duration of exposure. The job titles were classified using industrial and occupational headings defined for the 1982 Chinese population census (17). The census code grouped industries and occupations according to three levels of increasing detail. The major headings reflected general industry or occupation groupings, whereas the second and third levels provided finer, more specific classifications of each industry or occupation (17).

A job-exposure matrix (JEM), along with lifetime job history, was used to indicate the probability of exposure to benzene, other organic solvents, pesticides, and EMF. The JEM was developed by Mustafa Dosemeci at the US National Cancer Institute for occupations commonly held by Chinese in Shanghai. It assigned an overall probability of exposure of none (0), low (1), medium (2), or high (3) to each job using an algorithm based on a combination of the three-digit job title and three-digit industry codes.

Odds ratios for specific jobs were calculated by comparing “ever” vs. “never” holding a specific job for at least 3 years during his/her lifetime. Only job titles with at least 15 cases and controls combined were analyzed. One-, two-, and three-digit job title codes were analyzed, but numbers for three-digit job codes were too small for presentation. For self-report of exposures, analyses were by “ever exposed” vs. “never exposed” and by the total number of years spent on jobs with exposure, i.e. <15 years, and $\geqslant 15$ years. Finally, the JEM-based exposure assessment was combined with the self-reported exposures and categorized into “ever” vs. “never”. For each exposure, the “never” group was those with “no” job probability of exposure on the JEM and who also reported “no” on self-report. The “ever” group was made up of any one with “yes” on self-report or who had a “low”, “medium”, or “high” probability of job-exposure on the JEM.

We evaluated the relationship between occupational exposures in jobs held 3 years or more and total leukemia, as well as with subtypes (acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), and chronic myeloid leukemia (CML)). Odds ratios (OR) are used in our analyses to approximate relative risk (RR) because of the rarity of leukemia. ORs and 95% confidence intervals (CI) were calculated using multivariate logistic regression (18) for all types of leukemia combined. Analyses by subtypes of leukemia were conducted using polychotomous logistic regression where the subtypes of leukemia are treated as discrete variables as there was more than one case group compared with the same control referent group. The associations between leukemia and occupational exposures were evaluated by gender and interview type, i.e., direct vs. surrogate. All odds ratios were adjusted for age, gender and income. Age was entered as a continuous variable and income was categorized into tertiles. All analyses done were performed using Statistical Analysis Software (SAS).

RESULTS

Cases and controls were well matched for age and gender. The mean age for cases was 51.1 years and 50.8 years for controls. The leukemia cases were similar to controls in years of education, but had a slightly lower household income (Table 1). There was some variation in demographic factors among the different leukemia subtypes. The male-to-female ratio ranged from 1.0 for AML to 1.6 for CLL. The ALL cases tended to be younger than AML, CLL, and CML participants. The CLL participants were mostly over age 65. Because of the small number of the CLL subtype group (N = 21), findings on CLL from the analysis are not shown in the tables, but are summarized briefly in the text.

The odds ratios for the risk of leukemia by lifetime occupations are shown in Table 2. The risk for leukemia was increased significantly among those who worked in the chemical manufacturing industry (OR = 3.1, 95% CI = 1.0–9.8). Borderline significant excesses for leukemia were seen in government officials, leaders and managers (OR = 1.7, 95% CI = 0.9–3.2), and textile workers (OR = 1.4, 95% CI = 0.9–2.3). Non-significant increases in risk for leukemia were also seen among medical and public health professionals (OR = 1.4, 95% CI = 0.6–3.2), primary metal workers (OR = 1.5, 95% CI = 0.6–3.7), and construction workers (OR = 1.8, 95% CI = 0.7–4.5). The risk for all leukemias was significantly reduced among participants who worked as metal machine operators (OR = 0.4, 95% CI = 0.2–0.9). The small numbers for all these job titles, however, prevented analyses by subtypes of leukemia.

The odds ratios for the associations between ever exposed to selected self-reported occupational exposures, duration of exposure, and the risk of all leukemias and leukemia subtypes were obtained by polychotomous logistic regression and are presented in Table 3. The OR among those ever exposed to benzene was 1.7 (95% CI = 1.1–2.6) for total leukemia. The risk was increased with the duration of exposure to benzene (p for trend < 0.01) to an OR of 3.3 (95% CI = 1.6–6.9) among those with 15 years or over of exposure. The ever exposed category had a significantly increased risk for CML (OR = 2.5, 95% CI = 1.3–4.9) and a non-significant increase for ALL (OR = 1.5, 95% CI = 0.7–3.3) and AML (OR = 1.4, 95% CI = 0.8–2.3). However, elevated risk associated with long-term benzene exposure ($\geqslant$15 years) was observed for all leukemia subtypes.

Among those ever exposed to radioactive materials, the ORs for all leukemias combined, ALL and CML were statistically significant, but not significant for AML. Long-term exposure of 15 or more years to radioactive materials was significantly associated with an increased risk for all leukemias. The duration of exposure to radioactive materials increased the risk to all leukemias (p for trend = 0.02). Significant increases in risk for ALL and CML were also noted among subjects with long-term exposure to radioactive materials. However, numbers were small for some duration and leukemia subtypes categories.

TABLE 1. Percentage distribution of controls and adult leukemia participants by subtypes according to selected demographic factors

		Leukemia cases				
Characteristics	Controls (n = 502)	Total (n = 486)	ALL (n = 81)	CLL (n = 21)	AML (n = 236)	CML (n = 79)
Sex						
Male	52.8	52.7	54.3	61.9	48.7	58.2
Female	47.2	47.3	45.7	38.1	51.3	41.8
Age group (yrs)						
<35	25.1	24.3	34.6	9.5	24.2	20.3
35–54	24.7	23.9	27.2	4.8	23.3	34.2
55–64	23.1	24.9	22.2	9.5	25.4	20.3
65+	27.1	27.0	16.1	76.2	27.1	25.3
Education (yrs)						
<6	31.7	31.3	23.8	47.6	30.5	29.5
6–11	46.0	44.5	55.0	33.3	44.9	42.3
12+	22.3	24.2	21.3	19.1	24.6	28.2
Income tertile						
T_1 (low)	34.3	47.1	46.9	57.1	50.0	41.8
T_2	36.1	33.1	39.5	19.1	30.5	39.2
T_3	29.7	19.8	13.6	23.8	19.5	19.0

TABLE 2. Odds ratios of leukemia by lifetime occupation

Code[a]	Lifetime occupation[b]	No. of exposed case/control[c]	OR[d]	CI[e]
I.	Professional and technical workers, scientists, and research workers	79/76	1.2	0.8–1.7
01	Scientific research workers	22/19	1.2	0.6–2.3
02	Medical and Public Health	15/11	1.4	0.6–3.2
03	Financial and related workers	17/21	0.9	0.5–1.8
04	Teachers	20/22	1.1	0.6–2.1
II.	Leaders of government agencies, branches, parties, mass organizations and Businesses	46/44	1.3	0.8–2.0
06	Officials, leaders and managers	27/21	1.7	0.9–3.2
07	Clerical and related workers	19/23	0.9	0.5–1.7
III.	Commercial workers (sales workers)	30/39	0.8	0.5–1.4
08	Salesman	21/32	0.7	0.4–1.3
09	Buyers	9/7	1.4	0.5–3.9
IV.	Service workers	32/43	0.7	0.4–1.1
14	Other service workers	15/19	0.7	0.3–1.4
15	Cooks	9/13	0.7	0.3–1.6
V.	Agricultural workers, foresters, animal husbandry workers, fishermen, and hunters	12/15	0.8	0.4–1.7
16	Farmers	12/15	0.8	0.4–1.7
VII.	Production, transportation, and related workers (manufacturing)	194/193	1.1	0.8–1.4
18	Primary metal workers	11/8	1.5	0.6–3.7
19	Chemical processors/related workers	13/4	3.1	1.0–9.8
20	Rubber and plastics product makers	10/8	1.3	0.5–3.3
21	Textile workers	42/33	1.4	0.9–2.3
22	Apparel	14/12	1.2	0.5–2.7
28	Tool makers	15/11	1.3	0.6–3.0
29	Metal machine operators	10/23	0.4	0.2–0.9
30	Machine assembler	17/21	0.8	0.4–1.6
31	Electrician	10/13	0.7	0.3–1.7
32	Welders and sheet metal	9/7	1.3	0.5–3.6
34	Production inspector	9/11	0.9	0.4–2.2
35	Package and warehouse	16/16	1.1	0.5–2.3
VIII.	Construction	27/17	1.5	0.8–2.9
38	Construction	13/7	1.8	0.7–4.5
IX.	Utility and transport	27/41	0.7	0.4–1.1
40	Water and rail transportation	11/23	0.5	0.2–1.1
41	Auto and truck drivers	8/10	0.8	0.3–2.0
X.	Housewives	22/20	1.0	0.5–1.9

[a]Occupational codes based on 1982 Chinese population census (19).
[b]Lifetime job.
[c]Based on ten or more total cases and controls employed in the occupation.
[d]All OR (odds ratio) adjusted for age, sex and income.
[e]95% confidence interval.

Those ever exposed to toluene had a significant 60% elevation in risk for all leukemias, but non-significant excesses for ALL, AML, and CML. Duration of exposure to toluene was also associated with increasing risk for leukemia (p for trend = 0.02) with 15 or more years of exposure.

A borderline significant excess was observed among ever exposed compared with never exposed to paints for CML. Long-term exposure to paints was associated with significant elevations for all leukemias, ALL, and CML, while a non-significant elevation was observed for AML. The trend for duration of exposure to paints and association with leukemia and the subtypes were not significant.

Exposure to other organic solvents increased the risk for CML, but not for ALL or AML. Long-term exposure to organic solvents was associated with non-significant risks for ALL and CML. Trends by duration of exposure were generally unimpressive for organic solvents exposure and other exposures.

Information on duration of exposure was not available for exposure to synthetic fiber dust, or asbestos. Significant excesses for all leukemias, AML, and ALL, but borderline for CML, were observed among subjects ever exposed to synthetic fiber dust. On further analyses, we observed that the association of synthetic fiber dust with an increased risk

TABLE 3. Odds ratios of leukemia by selected occupational exposures on lifetime job from self-report among all participants

		All leukemias (n = 486)			ALL (n = 81)			AML (n = 236)			CML (n = 79)		
Exposures[a]	Controls (n = 502)	Cases	OR[b]	CI[c]	Cases	OR[b]	CI[c]	Cases	OR[b]	CI[c]	Cases	OR[b]	CI[c]
Benzene													
Never	462	424	1.0	—	72	1.0	—	212	1.0	—	65	1.0	—
Ever	40	62	1.7	1.1–2.6	9	1.5	0.7–3.3	24	1.4	0.8–2.3	14	2.5	1.3–4.9
<15 yrs	30	34	1.2	0.7–2.1	4	0.8	0.3–2.4	12	0.8	0.4–1.7	7	1.7	0.7–4.0
≥15 yrs	10	28	3.3	1.6–6.9	5	3.9	1.3–11.8	12	2.9	1.2–7.0	7	5.0	1.8–13.9
Trend test		p < 0.01			p = 0.12			p = 0.01			p < 0.01		
Other organic solvents													
Never	413	396	1.0	—	69	1.0	—	192	1.0	—	58	1.0	—
Ever	89	90	1.1	0.8–1.5	12	0.7	0.4–1.4	44	1.1	0.8–1.7	21	1.7	1.0–3.0
<15 yrs	57	54	1.0	0.7–1.5	3	0.2	0.1–0.8	29	1.1	0.7–1.9	13	1.7	0.8–3.4
≥15+ yrs	32	36	1.2	0.8–2.1	9	2.0	0.9–4.4	15	1.1	0.6–2.1	7	1.8	0.8–4.1
Trend test		p = 0.62			p = 0.82			p = 0.86			p = 0.08		
EMF													
Never	358	361	1.0	—	55	1.0	—	182	1.0	—	49	1.0	—
Ever	144	125	0.9	0.7–1.2	26	1.1	0.7–1.8	54	0.8	0.5–1.1	30	1.6	0.9–2.6
<15 yrs	93	64	0.7	0.5–1.0	13	0.8	0.4–1.5	31	0.7	0.4–1.1	13	1.0	0.5–2.0
≥15 yrs	51	61	1.2	0.8–1.8	13	1.8	0.9–3.6	23	0.9	0.6–1.6	17	2.4	1.3–4.5
Trend test		p = 0.91			p = 0.28			p = 0.23			p = 0.02		
Pesticides[a]													
Never	479	464	1.0	—	79	1.0	—	225	1.0	—	74	1.0	—
Ever	23	22	0.9	0.5–1.7	2	0.4	0.1–1.8	11	1.0	0.5–2.0	5	1.3	0.5–3.7
<10 yrs	18	15	0.8	0.4–1.7	1	0.3	0.1–1.9	7	0.8	0.3–1.9	13	1.0	0.5–2.0
≥10 yrs	5	7	1.4	0.4–4.3	1	0.9	0.1–8.4	4	1.6	0.4–6.1	1	1.2	0.1–10.5
Trend test		p = 0.81			p = 0.55			p = 0.73			p = 0.56		
Gasoline													
Never	379	379	1.0	—	66	1.0	—	187	1.0	—	56	1.0	—
Ever	123	107	0.9	0.6–1.2	15	0.6	0.3–1.1	49	0.8	0.5–1.2	23	1.2	0.7–2.1
<15 yrs	68	55	0.8	0.5–1.2	9	0.6	0.3–1.2	28	0.8	0.5–1.3	10	0.9	0.4–2.0
≥15 yrs	55	53	1.0	0.6–1.4	6	0.6	0.3–1.5	22	0.8	0.5–1.4	13	1.5	0.8–3.0
Trend test		p = 0.58			p = 0.20			p = 0.33			p = 0.25		
Radioactive materials													
Never	497	471	1.0	—	78	1.0	—	230	1.0	—	75	1.0	—
Ever	5	15	3.7	1.3–10.2	3	4.4	1.0–19.2	6	3.2	0.9–10.5	4	5.7	1.5–22.0
<15 yrs	3	7	2.7	0.7–10.5	0	0.0	—	3	2.5	0.5–12.5	2	4.3	0.7–26.5
≥15 yrs	2	8	5.2	1.1–24.7	3	14.1	2.2–89.9	3	4.2	0.7–25.8	2	7.9	1.1–58.5
Trend test		p = 0.02			p = 0.01			p = 0.10			p < 0.01		
Paints													
Never	452	429	1.0	—	71	1.0	—	216	1.0	—	66	1.0	—
Ever	50	57	1.2	0.8–1.7	10	1.1	0.5–2.4	20	0.8	0.5–1.4	13	1.7	0.9–3.2
<15 yrs	38	30	0.8	0.5–1.3	4	0.5	0.2–1.6	10	0.5	0.2–1.1	6	1.0	0.4–2.5
≥15 yrs	12	27	2.3	1.2–4.7	6	3.4	1.2–9.5	10	1.8	0.7–4.2	7	3.7	1.4–9.9
Trend test		p = 0.09			p = 0.15			p = 0.92			p = 0.02		
Toluene													
Never	468	437	1.0	—	74	1.0	—	215	1.0	—	69	1.0	—
Ever	34	49	1.6	1.0–2.5	7	1.3	0.6–3.1	21	1.4	0.8–2.4	10	2.0	0.9–4.2
<15 yrs	26	28	1.1	0.7–2.0	3	0.6	0.2–2.2	12	1.0	0.5–2.0	6	1.5	0.6–3.9
≥15 yrs	8	21	2.9	1.3–6.7	4	3.7	1.1–12.9	9	2.6	1.0–6.9	4	3.4	1.0–11.7
Trend test		p = 0.02			p = 0.22			p = 0.14			p = 0.03		
Synthetic fiber dust[d]													
Never	479	444	1.0	—	73	1.0	—	213	1.0	—	72	1.0	—
Ever	23	42	2.0	1.2–3.5	8	2.5	1.0–5.9	23	2.2	1.2–4.1	7	2.3	0.9–5.6
Asbestos[d]													
Never	491	475	1.0	—	78	1.0	—	231	1.0	—	76	1.0	—
Ever	11	11	1.1	0.5–2.6	3	1.6	0.4–6.0	5	1.1	0.4–3.2	3	1.7	0.5–6.2

[a]Duration of exposure categories different because of small numbers.
[b]All OR (odds ratio) adjusted for age, sex, and income.
[c]95% confidence interval.
[d]No duration of exposure information collected for synthetic fiber use and asbestos.

for all leukemia was higher among non-textile workers compared with textile workers. Exposure to asbestos showed non-significant increases in risk for ALL and CML. A few other non-significant excesses were also observed for CML from exposure to EMF, pesticides, and gasoline.

When the analysis was restricted to directly interviewed subjects only (data not shown in tables) the ORs typically increased slightly compared with those that also included information from surrogate respondents. For example, the ORs for all leukemia for "ever" exposed to benzene increased from 1.7 to 2.3 (both significant) and for ALL increased from 1.5 to 2.0 (both non-significant). Since direct ORs were in general similar to the overall ORs, we have chosen to present the overall ORs (i.e., both direct and proxy interviews).

The results of gender-specific analyses for selected occupational exposures are shown in Table 4. Among the men, statistically significantly elevated risks occurred for leukemia among those ever exposed compared with those never exposed to radioactive materials (OR = 7.5, 95% CI = 1.6–34.1) and synthetic fiber dust (OR = 3.2, 95% CI = 1.0–10.2), and the OR associated with toluene OR = 1.6, 95% CI = 0.9–1.9) was of borderline significance. Risk for leukemia among men reporting exposure to benzene was elevated, not significantly. For women, significantly elevated risks were observed for benzene exposure (OR = 2.3, 95% CI = 1.2–4.6) and synthetic fiber dust exposure (OR = 1.8, 95% CI = 1.0–3.3) and there was a borderline significant risk for paints. Risks among women reporting exposure to pesticides and toluene were elevated, but not significant. We have not reported the results of gender-specific analyses for leukemia subtypes due to small numbers.

To refine the exposure classification, we incorporated information from both the JEM and self-reports in defining exposure status. The results are presented in Table 5. Individuals in the unexposed category in both exposure systems, i.e., the No/No group, served as the reference. Ever exposed included those classified as exposed by either the self-report or the JEM. The results from this analysis were very similar to those presented in Table 3 based on self-reported exposure information alone.

TABLE 4. Gender-specific odds ratios of leukemia by selected occupational exposures on lifetime job from self-report for all leukemias among all participants

	Men (n = 521)				Women (n = 467)			
Exposures	Controls	Cases	OR[a]	CI[b]	Controls	Cases	OR[a]	CI[b]
Benzene								
Never	238	222	1.0	—	224	202	1.0	—
Ever	27	34	1.5	0.8–2.5	13	28	2.3	1.2–4.6
Other organic solvents								
Never	214	207	1.0	—	199	189	1.0	—
Ever	51	49	1.0	0.7–1.6	38	41	1.2	0.7–2.0
EMF								
Never	179	186	1.0	—	179	175	1.0	—
Ever	86	70	0.8	0.5–1.2	58	55	1.0	0.7–1.6
Pesticides								
Never	248	246	1.0	—	231	218	1.0	—
Ever	17	10	0.6	0.3–1.3	6	12	1.9	0.7–5.3
Gasoline								
Never	178	187	1.0	—	201	192	1.0	—
Ever	87	69	0.7	0.5–1.1	36	38	1.2	0.7–1.9
Radioactive materials								
Never	263	244	1.0	—	234	227	1.0	—
Ever	2	12	7.5	1.6–34.1	3	3	1.2	0.2–5.9
Synthetic fiber dust								
Never	261	245	1.0	—	218	199	1.0	—
Ever	4	11	3.2	1.0–10.2	19	31	1.8	1.0–3.3
Asbestos								
Never	257	248	1.0	—	234	227	1.0	—
Ever	8	8	1.1	0.4–2.9	3	3	1.2	0.2–6.0
Paints								
Never	230	224	1.0	—	205	205	1.0	—
Ever	35	32	0.9	0.5–1.5	15	25	1.7	0.9–3.4
Toluene								
Never	244	227	1.0	—	224	210	1.0	—
Ever	21	29	1.6	0.9–2.9	13	20	1.5	0.7–3.2

[a]All OR (odds ratio) adjusted for age and income.
[b]95% confidence interval.

TABLE 5. Odds ratios of leukemia by lifetime job occupational exposure by self-report combined with job-exposure matrix assessment among all participants

Self-report/JEM	Controls (n = 502)	All leukemias (n = 486) Cases	OR[a]	CI[b]	ALL (n = 81) Cases	OR[a]	CI[b]	AML (n = 236) Cases	OR[a]	CI[b]	CML (n = 79) Cases	OR[a]	CI[b]
Benzene													
Never[c]	457	420	1.0	—	72	1.0	—	210	1.0	—	64	1.0	—
Ever[d]	45	65	1.6	1.1–2.4	9	1.3	0.6–2.9	26	1.3	0.8–2.2	15	2.4	1.3–4.7
Other organic solvents													
Never[c]	410	392	1.0	—	69	1.0	—	190	1.0	—	57	1.0	—
Ever[d]	92	93	1.1	0.8–1.5	12	0.7	0.4–1.4	46	1.1	0.8–1.7	22	1.8	1.0–3.1
EMF													
Never[c]	355	356	1.0	—	55	1.0	—	179	1.0	—	48	1.0	—
Ever[d]	147	129	0.9	0.7–1.2	26	1.1	0.6–1.8	57	0.8	0.6–1.2	31	1.6	1.0–2.7
Pesticides													
Never[c]	474	460	1.0	—	79	1.0	—	223	1.0	—	73	1.0	—
Ever[d]	28	25	0.9	0.5–1.6	2	0.3	0.1–1.5	13	0.9	0.5–1.9	6	1.4	0.5–3.5

[a]All OR (odds ratio) adjusted for age, sex, and income.
[b]95% confidence interval.
[c]No on both the self-report and the JEM.
[d]Yes on either self-report or JEM or both.

DISCUSSION

This population-based case-control study assessed the possible association of the risk of adult leukemia with occupational history and several occupational exposures using self-reported and JEM assessments among a population in Shanghai. It has a relatively large number of cases thus providing the opportunity to examine the relationship between occupational exposures to leukemia by its subtypes. Although the literature suggests that smoking may be a risk factor for leukemia (14), cigarette smoking was not associated with leukemia risk in this population and was not adjusted for in our data analyses.

The risk for leukemia was increased significantly among those who worked in the chemical manufacturing industry (OR = 3.1, 95% CI = 1.0–9.8), consistent with findings from some (19–21) but not all previous studies (22, 23). We noted borderline significant increases for risk of leukemia among textile workers and officials, leaders and managers. This is similar to the study by Costantini et al. (2) who reported a doubling in relative risk for leukemia among managers. Miligi et al. (24) had previously noted an increase in risk for leukemia among textile workers, as well as among housewives, teachers and hairdressers. We did not see any increase in risk among housewives and teachers. Several studies had earlier reported an increased risk of leukemia among nursing and healthcare workers (25–27). We found an increased risk for leukemia among medical and public health workers, but it was not significant. The increase in risk for leukemia that we observed in primary metal workers, though non-significant, is consistent with what has been reported in an earlier study (27). The increase in risk for leukemia among construction workers that we observed has also been previously reported (28). However, our own finding was not significant.

In analyses by specific substances, exposure to benzene, radioactive materials, synthetic fiber dust, and toluene all were associated with an elevated risk of leukemia. We also found that potential exposure to paints was associated with an increased risk for leukemias, but not significantly. Exposure to radioactive materials was more strongly associated with ALL, AML, and CML than exposure to benzene. Synthetic fiber dust was associated with more than two-fold risks for ALL, AML, and CML. A review of the literature revealed that very little has been reported about synthetic fiber dust as an independent risk factor for leukemia. In general, longer durations of exposure to benzene, radioactive materials, and toluene resulted in larger relative risks to all leukemias, ALL, AML, and CML than shorter durations. Wang et al. (7) had previously reported an increased risk to leukemia associated with increased duration of exposure to radioactive materials among Chinese workers. The risk of all leukemias combined following occupational exposure to toluene, and of CML following exposure to EMF, paints, and toluene also increased with increasing years of exposure. Seventy-eight percent of the subjects who reported exposure to toluene and 52% of the subjects that reported occupational exposure to paints also reported exposure to benzene. Industrial and environmental benzene is present as a contaminant or constituent of many industrial solvents (29, 30). Therefore, the risk related to occupational exposure to toluene and to paints may actually be due to the co-existence of benzene.

The combination of self-reports of exposure with assessments from the JEM, slightly increased the number of

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cases exposed to the various substances and yielded a statistically significant elevated risk for leukemia for benzene exposure. This combined exposure assessment also revealed significantly elevated risks for CML for benzene, other organic solvents, and EMF. These results were consistent with those from the self-report analysis. It has generally been accepted that benzene exposure in human populations is causally related to the development of ANLL (or AML) (31, 32). We observed a significant association between benzene exposure and CML. We noted a 60% excess risk for CML among subjects ever exposed to EMF by combined self-reported and JEM assessment, but results in the literature are mixed. A recent mortality study in the UK of electricity generation and transmission workers did not show an association between occupational exposure to EMF and the risk of leukemia (33), but a recent study by Minder and Pfluger (34) did.

We saw no clear gender differences for the risk for all leukemias combined for several occupational exposures, but some variation existed for others. The association between leukemia and pesticide exposure showed a deficit among men and an excess among women. On the other hand, the significant excess risk for leukemias following exposure to radioactive materials was only among men, but few women reported exposure to radioactive materials. The reason for this is unclear and it could be a chance finding, or gender-related differences in exposure pattern (e.g., frequency, intensity, duration and mode of exposure) and host factors that affect chemical absorption and metabolism.

This study has several strengths. It is relatively large and allowed analyses by histologic type. It was conducted in the People's Republic of China, which has several advantages, including fewer jobs held per subject, and fewer exposures per subject (35). By holding fewer jobs, Chinese workers generally have fewer types of occupational exposures than workers in western industrialized countries; thus the potential for confounding by other hazardous substances is reduced. Studies in China also present an unusual opportunity to evaluate cancer risks from occupational exposures among women because they are typically employed in production jobs with exposures similar to those experienced by men. Evaluation of occupational risks among women can, thus, be done more effectively than in western countries, which is something desperately needed (36).

Since this study was an interview-based case-control study, there are several possible limitations. Recall bias is a concern because cases may have had a tendency to recall more factors that had been discussed with them in the past during their clinical management process than controls. The possible over-report of exposure or more accurate recalls by cases will bias the ORs away from the null. Nondifferential exposure misclassification is also a potential problem because of the high proportion of interviews obtained from the next-of-kin of cases (48%). This would tend to bias the ORs towards the null. It is difficult to validate self-reported data on *long-term* exposure. However, we found in our study that results were similar between directly interviewed subjects and surrogate interview subjects and that self-reported assessment of occupational exposure appeared to be in a good agreement with JEM assessment in this population. For example, the ORs for all leukemia for "ever" exposed to benzene increased from 1.7 among all subjects to 2.3 among directly interviewed subjects only, both statistically significant, and for ALL increased from 1.5 among all subjects to 2.0 among directly interviewed subjects only, both non-significant. In addition, although the literature is not entirely consistent, some methodological studies have shown that self-reported occupational exposure could be useful in epidemiological studies especially when objective information on occupational exposure is not available (37–42).

In addition, although the JEM used is specifically developed for occupations commonly held by the Chinese in Shanghai, it may not reflect the true occupational exposures. As with most observational epidemiologic studies of rare diseases, such as leukemia, the exposure assessment in this study was based on self-reported data. We recently compared self-reported data with those derived from a job-exposure matrix in this study population and found they are highly correlated. Agreement between self-reported exposures and JEM assessment was good (kappa coefficients [κ]:0.48–0.84) (43). With JEM as the "gold standard", the sensitivities for the self-reported exposures ranged from 0.75 to 0.98. However, that for pesticide exposure was 0.44 in subjects $>$ 51 years of age. The self-reported exposures specificities ranged from 0.87 to 0.99 (43). We were unable to compare the JEM with actual environmental or biological measurements, as we did not have this information. It should be noted that despite the large size of this study, some of the results by subtype of leukemia were based on small numbers that may render the association estimates imprecise. Chance findings are sometimes unavoidable in epidemiologic studies when multiple exposures are evaluated, however, most of the associations reported in this manuscript are biologically plausible and consistent with results from in vitro, animal experiments, and limited epidemiologic studies conducted in other populations. Furthermore, the internal consistency of our findings, including the dose–response relationships, also argues against the possibility of chance findings for most of the associations we have reported.

In summary, we found an association between risk of adult leukemia and working in the chemical industry. Analyses of specific exposures revealed increased risks for all leukemias from occupational exposure to benzene, synthetic fiber dust, radioactive materials, and toluene. Radioactive materials and synthetic fiber dust were identified as possible risk factors for ALL, AML, and CML specifically. Likewise, benzene, other organic solvents, EMF, and toluene were identified as possible risk factors for CML. The risk of all leukemias combined increased with duration of exposure to benzene, radioactive materials, and toluene, the risk of ALL rose with duration of exposure to radioactive materials, AML with duration of exposure to benzene, and CML with duration of exposure to benzene, EMF, radioactive materials, paints, and toluene. This implies that continuous long-term exposure rather than short-term exposure to these occupational factors increases the risk of workers developing leukemia.

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