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Exposure to benzene and non-Hodgkin lymphoma, an epidemiologic overview and an ongoing case-control study in Shanghai

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Abstract

The interest in the relationship between benzene exposure and non-Hodgkin lymphoma (NHL) appears to have been generated from a 1979 publication, which reported an increased risk of NHL among persons potentially exposed to benzene and/or coal tar fractions. More recently (1997), an increased risk of NHL was reported among 74,828 workers exposed to benzene and other chemicals in a variety of industries in China. On the contrary, no increased risk of NHL was reported in a cohort of 1,165 workers at two rubber hydrochloride plants in Ohio (US), who were exposed to extremely high levels of benzene and were found to have an increased risk of acute myeloid leukemia. In another large cohort of some 7,676 US workers exposed to benzene, no increased risk of NHL was reported. Similarly, no increased risk of NHL was reported in a combined cohort of 308,199 petroleum workers in the US, the UK, Canada, Australia, Italy and Finland, who were exposed to benzene or benzene-containing petroleum products. The lack of an association between benzene exposure and NHL in cohort studies is supported by case-control studies from the US, Canada, Italy and the UK.

To further investigate the relationship between benzene exposure and NHL, we are conducting a hospital-based case-control study in Shanghai, China. Cases are newly diagnosed NHL patients at 29 hospitals in Shanghai. For each case, two matched controls are selected among patients without any lymphatic or hematopoietic diseases at the same hospital. Demographic, employment, medical and lifestyle information is obtained through questionnaires (primary and secondary). Sources for benzene exposure information include a database of 50,000+ benzene measurements maintained by the Shanghai Municipal Institute of Public Health Supervision (IPHS), Shanghai District IPHS, walk-through surveys at factories, additional measurements at factories and reports in Chinese medical journals. Patient enrollment started in 2003 and it is estimated that the study will have 400–450 NHL cases by December 2006. Some of the occupations or industries reported among enrolled study subjects (cases and controls) with potential exposure to benzene include shoe workers, painters, mechanics or machinists, and printers. Some of the unique features of the study are discussed.
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Keywords: Benzene; Occupational exposure; Non-Hodgkin lymphoma; Case-control study; China

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1. Introduction

Lymphoma refers to a group of malignancies in which the cells of lymphoid tissue multiply uncontrollably. Lymphomas with the characteristic Reed-Sternberg cells are called Hodgkin lymphomas, and all others by default are known as non-Hodgkin lymphomas (NHL). As such, NHL represents a heterogeneous group of malignancies whose common link is a characteristic monoclonal expansion of malignant B or T cells, and is the single largest group of neoplasms of the immune system. According to the National Cancer Institute's (NCI) Cancer Surveillance, Epidemiology and End Results (SEER) Program, approximately 45,000 new cases of NHL were diagnosed in 1994 in the US [1]. The average annual age-adjusted incidence rates during 1987–1991 were 17.9/100,000 for men and 11.5/100,000 for women. NHL risk increases rapidly with age. For ages 65 and older, the rates were 81.1/100,000 for men and 60.8/100,000 for women.

Studies have identified a large number of potential risk factors of NHL: inherited immunodeficiency diseases, acquired immunodeficiency diseases, autoimmune diseases, viruses (e.g., Epstein–Barr virus), certain drugs, chemotherapy and radiation therapy, ionizing radiation, chronic infectious diseases, tuberculosis, malaria, diabetes, previous cancer, rheumatoid arthritis, Sjogren syndrome, kidney calculus, duodenal ulcer, pneumonia, scarlet fever, herpes zoster, eczema dermatitis, cysts, family history of cancer, smoking or tobacco consumption, agricultural work, farming or living on a farm, forestry, and employment in the meat industry [2–14].

In this paper, we will present an overview of the epidemiology of benzene exposure and NHL. Further, we will also discuss an ongoing case-control study of NHL in Shanghai, China.

2. An Epidemiologic Overview

In 1979 Vianna and Polan reported the results of an investigation based on the linkage of deaths from lymphosarcoma and reticulosarcoma or Hodgkin disease during 1950–1969 in New York State and the 1960 US census [15]. Fourteen selected occupations were assumed to have exposure to benzene or coal tar fractions. For denominator, Vianna and Polan used the 1960 census data to determine the number of workers in these occupations ("populations at risk"). A total of 242,105 New York residents in these 14 occupations were identified from the 1960 census. The largest groups were farmers (80,366) and woodworkers (47,549). Other occupations with exposure included fishermen, brick and stone workers, and barbers. The numerators were lymphoma deaths (total = 2654) among New York residents in these occupations between 1950 and 1969. Occupations listed on death certificates were used to identify New York residents in these occupations who died from lymphosarcoma or reticulosarcoma. According to Vianna and Polan [15], an increased risk of lymphosarcoma or reticulosarcoma was found in these occupations, and, in particular, the highest risk was reported among fishermen. The Vianna and Polan investigation has been criticized by Enterline [16], Smith and Lickiss [17], and Wong [18]. The major criticism was that information on occupation derived from the US census and from death certificates was not compatible, and the reported mortality excess might simply be an artifact due to the inadequate study design.

Subsequent to the Vianna and Polan record-linkage investigation, several cohort studies addressed the issue of benzene exposure and NHL. Hayes et al. [19] reported a cohort study of 74,828 workers in 12 cities in China, who were exposed to benzene in a wide spectrum of industries with heterogeneous exposures (e.g., food, textile, paper products, agricultural chemicals, pharmaceutical, rubber and plastic, electrical equipment). The comparison group was a cohort of 35,805 Chinese workers who were not exposed to benzene or any other carcinogens. Hayes et al. reported 16 NHL cases among the benzene-exposed workers and three among the non-exposed workers. The risk ratio (RR) was 3.0, with a 95% confidence interval (95% CI) of 0.9–10.5. Analysis by occupation reported the following RRs: "organic, insecticide and benzene production" (RR = 7.8), paint and other coatings (RR = 1.6), and shoe (RR = 1.6). The group "organic, insecticide and benzene production," which had the highest risk, consisted of several heterogeneous industries/occupations with very different exposures. In particular, insecticide workers are exposed to a variety of chemicals not related to benzene, and studies have reported increased risk of NHL among agricultural chemical workers or farmers throughout the world. Thus, the result might have been confounded by chemicals other than ben-

zene. In the Hayes et al. study, individual benzene exposure estimates were developed based on ambient benzene exposure measurements and production/process information at the subjects' factories. Analysis by cumulative benzene exposure reported the following RRs: 1.0, 3.3, 1.1, and 3.5 for non-exposed, <40, 40–99, and 100+ ppm years, respectively. The lack of a clear positive exposure-response relationship further argues against an association between benzene exposure and NHL. Quite appropriately, Hayes et al. did not conclude that the findings established a causal association between benzene exposure and NHL. Instead, they concluded that "the possible links with NHL are all provocative new observations".

Wong reported the mortality experience of a cohort study of 7676 chemical workers in the US [20,21]. Most of these workers were exposed to benzene in the 1940s and 1950s, with some whose first exposure occurred in the 1920s and 1930s. Based on historical exposure measurements and facility histories, exposure estimates were developed for workers' jobs in the study. Some of the jobs entailed relatively high benzene levels in the past (in the range of 50–100 ppm). In the original study, no analysis specific to NHL was reported because of the NHL classification in the past and the grouping of diseases in vital statistics. A subsequent analysis indicated that there were seven deaths from NHL among workers exposed to benzene, compared to 5.12 expected deaths based on the US general population [22]. The corresponding SMR was 1.37 (95% CI 0.55–2.82). Thus, there was no increased risk of NHL in this large cohort of workers exposed to benzene.

In the US there is another often-cited cohort study of workers exposed to benzene, consisting of 1165 white men at two rubber hydrochloride plants in Ohio, where benzene exposures were reported to be very high (up to several hundred ppm) [23]. Individual benzene exposure estimates were developed for the workers in the study. A significant increase of leukemia mortality was reported in the study. In particular, a remarkable risk of acute myeloid leukemia (AML) was found and a positive exposure-response relationship between cumulative exposure to benzene and AML was also reported [24]. In terms of NHL, however, based on the latest update, Rinsky et al. reported 5 NHL deaths, comparable to 5.01 expected (SMR = 1.00, 95% CI 0.32–2.33) [25]. Thus, there was no elevated risk of NHL in this cohort of workers who were exposed to extremely high levels of benzene and who were found to have experienced an elevated risk of AML.

Petroleum workers are exposed to benzene or benzene-containing petroleum products, such as gasoline, which typically contains 2–3% of benzene by volume. A comprehensive review of airborne concentrations of benzene in the petroleum industry can be found in an International Agency for Research on Cancer (IARC) Monograph [26]. Studies of petroleum workers, therefore, provide an opportunity for investigating the relationship between benzene and NHL. Wong and Raabe reviewed and summarized the results of 26 cohorts of petroleum workers in the US, the UK, Canada, Australia, Italy, and Finland [27]. Data from these studies were reviewed individually as well as combined in a pooled analysis (meta-analysis). The combined multinational cohort consisted of 308,199 petroleum workers (6.6 million person-years), and the observation period covered an interval of 60 years from 1937 to 1996. A total of 506 NHL deaths were observed, compared to 561.68 expected. The SMR was 0.90 and the 95% CI was 0.82–0.98. Stratified analyses were performed by type of facility or industrial process. Stratum-specific SMRs (95% CIs) were 0.96 (0.86–1.07) for US refinery workers, 1.12 (0.90–1.37) for non-US refinery workers, 0.64 (0.50–0.82) for product (gasoline) distribution workers, and 0.68 (0.47–0.95) for crude oil workers. When individual cohorts were stratified by length of observation, no pattern was detected. In general, occupational exposure levels prior to 1950 were much higher than thereafter. However, analysis of workers by hire date (<1950, ≥1950) revealed no difference in NHL mortality. Furthermore, none of the individual studies showed significant exposure-response relationship. In summary, results from individual studies as well as from the pooled analysis indicated that petroleum workers were not at an increased risk of NHL as a result of their exposure to benzene or other benzene-containing petroleum products in their work environment.

Table 1 summarizes the findings of NHL from the above cohort studies. Only the study of Chinese workers reported an increased risk (RR = 3.0, 95% CI 0.9–10.5). However, there was no clear exposure-response relation when the data were analyzed by cumulative benzene exposure. The potential confounding due to other chemicals (such as insecticides) further weakened the finding. Other cohort studies of work-

Table 1
Cohort studies of benzene exposure and non-Hodgkin lymphoma

Authors (reference)	Location	Cohort	No. of NHL	Findings
Hayes et al. [19]	12 cities in China	74,828 workers in a variety of industries exposed to benzene and other chemicals	16	RR = 3.0 (95% CI 0.9–10.5)
				Analysis by cumulative exposure: No exposure: RR = 1.0 <40 ppm year: RR = 3.3 40–99 ppm years: RR = 1.1 100+ ppm years: RR = 3.5
Wong [20,21,22]	US (7 plants)	7676 chemical workers exposed to benzene	7	SMR = 1.37 (95% CI 0.55–2.82)
Rinsky et al. [25]	Ohio, US	1165 chemical workers exposed to benzene	5	SMR = 1.00 (95% CI 0.32–2.33)
Wong and Raabe [27]	US, UK, Canada, Australia, Italy and Finland	308,199 workers exposed to benzene and benzene-containing products in the petroleum industry (refinery, distribution and crude oil)	506	SMR = 0.90 (95% CI 0.82–0.98)
				Analysis by industrial division: Refinery: SMR = 0.99 (95% CI 0.90–1.09) Distribution: SMR = 0.64 (95% CI 0.50–0.82) Crude oil: SMR = 0.68 (0.47–0.95)

RR, risk ratio; SMR, standardized mortality ratio; 95% CI = 95% confidence interval, ppm = parts per million.

ers exposed to benzene or benzene-containing products consistently demonstrated no increased risk of NHL.

Further supporting evidence that there is no association between benzene exposure and NHL comes from case-control studies, which have been summarized by Wong [22,27]. In a case-control study consisting of 501 NHL patients in North Carolina, Schumacher and Delzell reported 66 cases exposed to benzene [28]. The risk ratios for benzene exposure were 0.77 (95% CI 0.56–1.07) in whites and 0.94 (95% CI 0.47–1.87) in blacks. Ott et al. [29] conducted a detailed case-control study of lymphatic and hematopoietic tissue cancers among 29,139 Union Carbide employees in West Virginia. Based on 52 cases, the NHL risk ratio for exposure to benzene was reported as 1.0. In a case-control study consisting of 303 NHL cases in Boston, the risk ratio for benzene exposure was 1.2 (95% CI 0.5–2.6) [10]. In a case-control study conducted by the US National Cancer Institute, the exposure histories of 622 NHL cases in Iowa and Minnesota were compared to those of 1245 controls [13]. A total of 153 cases were reported to have been exposed to benzene. The risk ratio for benzene exposure was 1.1 (95% CI 0.9–1.4), indicating no increased risk.

Case-control studies from other countries also support the results of no association reported in the American studies. In a case-control study consisting of 215 NHL patients in Montreal, 26 cases reported exposure to benzene [30]. The relative risks were 0.7 for any exposure to benzene and 0.8 for substantial exposure to benzene. In another report based on the same data, Siemiatycki et al. [31] reported the following relative risks for a variety of petroleum-derived fuels or solvents: 0.8 for automotive gasoline, 0.4 for aviation gasoline, 0.8 for mineral spirits, 0.4 for kerosene, 0.7 for jet fuel, 1.1 for diesel fuel, and 0.7 for heating oil. In an Italian case-control study of 208 NHL cases, the risk ratio for exposure to benzene and solvents was reported as 1.14, with a 95% CI of 0.57–2.28 [3]. In a case-control study of NHL conducted in the UK, the employment and medical histories of 158 cases were compared to those of their matched controls [6,32]. The risk ratio for benzene exposure was 0.49, with a 95% CI of 0.21–2.00.

The risk ratios reported in these case-control studies of NHL and benzene or benzene-containing solvents ranged from 0.49 to 1.2 (Table 2). Although exposure classification in some of these case-control studies

Table 2
Case-control studies of benzene exposure and non-Hodgkin lymphoma

Authors (reference)	Location	No. of cases	Exposure as stated	Odds ratios (95% CI)
Schumacher and Delzell [28]	North Carolina, US	501	Benzene	0.77 (0.56–1.07) for whites 0.94 (0.47–1.87) for blacks
Ott et al. [29]	West Virginia, US	52	Benzene	1.0 (95% CI not stated)
Scherr et al. [10]	Boston, US	303	Benzene	1.2 (0.5–2.6)
Blair et al. [13]	Iowa & Minnesota, US	622	Benzene	1.1 (0.9–1.4)
Siemiatycki et al. [30,31]	Montreal, Canada	215	Benzene	0.7 (0.5–1.0) for any exposure 0.8 (0.4–1.7) for substantial exposure
Franceschi et al. [3]	Northeastern Italy	208	Benzene and solvents	1.14 (0.57–2.28)
Cartwright et al. [6] Bernard et al. [32]	Yorkshire, UK	158	Benzene	0.49 (0.21–2.00)

95% CI = 95% confidence interval.

might lack specificity, these investigations have consistently demonstrated that no association was found between exposure to benzene and NHL. Thus, these case-control studies confirm the results of cohort studies of workers exposed to benzene or benzene-containing petroleum products.

3. An Ongoing case-control study of NHL in Shanghai

To further investigate the relationship between NHL and exposure to benzene or other substances, we are currently conducting a case-control study of NHL in Shanghai. The study is one of the research projects of the Shanghai Health Study sponsored by the Benzene Health Research Consortium. The Shanghai Health Study is a collaborative research program between the USA and China. Participants in the Shanghai Health Study include the following US and Chinese organizations:

- Applied Health Sciences;
- University of Colorado;
- ExxonMobil Biomedical Sciences;
- Fudan University School of Public Health, Shanghai;
- Shanghai Municipal Institute of Public Health Supervision;
- Shanghai District Institutes of Public Health Supervision;
- Shanghai Center for Disease Prevention and Control;
- Twenty-nine hospitals in Shanghai.

The study design is that of a hospital-based case-control study. Cases are defined as patients who are aged 18 or older and newly diagnosed with NHL at one of the 29 participating hospitals in Shanghai between August 2003 and December 2006. The hospital diagnosis is verified or confirmed by a newly completed clinical laboratory at Fudan University, which has been built specifically for the Shanghai Health Study. The World Health Organization (WHO) definition of NHL is used for diagnosis [33]. For each case, two individually matched controls are randomly selected from patients at the same hospitals, but free from any malignant or non-malignant diseases of the lymphatic or hematopoietic system. However, patients diagnosed with cancers other than lymphatic and hematopoietic malignancies are eligible for control selection. Matching criteria included: gender, age (within 5 years), and admission date.

To obtain relevant information from study participants, face-to-face interviews at the hospitals are conducted by trained interviewers from Fudan University School of Public Health. The case/control status is not made known to the interviewers. A 17-page primary questionnaire is used to obtain the following information:

- Demographics;
- Medical history;
- Family history;
- Medication history (both Western and Chinese traditional medicines);
- Employment and exposure history (factories, departments, job titles, job duties, chemicals used, frequencies and dates);

- Non-occupational exposures (e.g., tobacco, alcohol, hobbies and farming).

Certain occupations of interest will trigger secondary questionnaires that are more detailed and industry- or occupation-specific. Some examples of these occupations are shoe worker, farmer, mechanic, machinist, electrician, assembly worker, health care worker, textile worker, laborer, manager and supervisor. The secondary questionnaires range from four to nine pages. A typical secondary questionnaire asks for the following information:

- Industry and occupational title;
- Description of tasks;
- Substances handled;
- Frequency and duration of exposure;
- Workplace environment;
- Use of personal protection equipment.

The employment histories are reviewed by the "Exposure Assessment" Committee at Fudan University, whose members are blinded to the case/control status. Jobs held by study subjects are assessed for exposure to benzene, with considerations of several relevant parameters. These parameters include industry, factory, work location, job title, tasks, and time. Primary sources of benzene exposure information include the following:

- Shanghai Municipal Institute of Public Health Supervision (IPHS) database (computerized);
- Records of exposure measurements at Shanghai District IPHS;
- Previous monitoring data maintained at the factories;
- Facility histories (e.g., raw materials, engineering changes, work practice changes) maintained at the factories;
- Walk-through surveys and exposure measurements at the factories;
- Exposure data in the Chinese medical journals.

The Shanghai Municipal IPHS database consists of more than 50,000 benzene measurements taken at factories in Shanghai since the 1950s. Each measurement record includes the following items: date of sampling, industry code, occupational code, hazard (chemical) code, name and address code of the factory, sampling location at the factory, and individual and average values of benzene measurements. The names and the addresses of the factories from the questionnaires provide the necessary linkage between benzene measurements in the database and individual study subjects. Table 3 shows an example of a measurement record in the Shanghai Municipal IPHS database.

Table 3
An exposure record in the Shanghai Municipal Institute of Public Health Supervision database of benzene measurements taken at factories in Shanghai

Date of sampling	26-12-1986
Industry code	341 (rubber products, including tires, hoses, shoes, and bags)
Occupational code	741c (glue application workers)
Hazard code	0715 (benzene)
Name of the factory	XYZ Athletic Shoe factory[a]
Address code of the factory	310115
Sampling location	Breathing zone of glue application workers
Benzene measurements (mg/m^3)	391.28, 391.28, 330.39, 330.39 (average = 360.84)

[a] To protect confidentiality, the real name of the shoe factory is not revealed in this table.

The Shanghai Municipal IPHS database is based on benzene measurements reported by Shanghai District IPHS. Unfortunately, the reporting may not be always complete, and it is sometimes necessary to search records maintained at Shanghai District IPHS for records of factories where the study subjects worked.

In some situations it is helpful to conduct walk-through surveys at the factories where the study subjects worked or, if the factories no longer exist, at similar factories. Such walk-through surveys are arranged by the Shanghai Municipal IPHS and accompanied by its personnel. Some factories may have maintained historical benzene measurements. If appropriate or necessary, new benzene air samples are collected. Other relevant records kept at the factories such as changes in work practice and ventilation are also reviewed.

In utilizing these data in exposure assessment, priority is given to actual historical measurements taken at the subjects' factories maintained in the Shanghai Municipal IPHS database, at the District IPHS offices or at the subjects' factories, if such measurements exist. If no actual measurements at the factories are available, measurements taken at similar factories in the same industry maintained in the Shanghai Municipal IPHS database are considered. Additional supplemental data are derived from reports of benzene exposure in sim-

Table 4
Benzene measurements (mg/m^3) at a refining unit inside a Chinese coal tar plant by work area and year

Work area	1973	1973	1983	1995
Distillation	18.1	31.1	9.33	1.80
Washing	104.2	157.2	17.75	5.20
Finished products	156.0	531.1	26.96	2.90
Chemical analysis	233.0	316.4	15.44	1.95

Note: Major renovations (primarily ventilation) since 1980.

ilar occupations or industries in the Chinese medical literature.

Generally speaking, two types of articles in the Chinese literature provide benzene exposure data: industrial hygiene surveys and benzene poisoning case reports. Even though the facilities described in these articles are not the actual factories where the study subjects worked, the exposure data are useful in providing possible range of exposure for similar jobs, factories or industries.

Table 4 provides an example of data reported in an industrial hygiene survey [34]. The air samples were collected at a refining unit inside a coal tar plant in China. The authors stated that major renovations had been taking place at the plant since 1980, which was reflected in much lower exposure measurements reported in 1983 and 1995 (Table 4). To put the values in Table 4 in perspective, it should be noted that the occupational exposure limit for benzene in China before 2002 was 40 mg/m^3.

The Chinese occupational medical journals are replete with reports of cases of benzene poisoning and leukemia in workers exposed to benzene. The majority of cases occurred among shoe workers, bag workers and painters. Some of these workers were exposed to extremely high levels of benzene, particularly at small workshops. For example, Zhao et al. [35] reported a cluster of benzene poisoning cases among workers at small township-owned leather bag workshops in a small town in Hebei Province. In a survey of 6482 leather bag workers (4906 females and 1576 males) conducted in 2001 and 2002, 33 benzene poisoning cases (27 females and 6 males) were reported, including 23 aplastic anemia, 5 pancytopenia, 2 myelodysplastic syndrome, and 1 acute myeloid leukemia. Duration of exposure ranged from 3 to 23 months (average = 10.8). Subsequently, 9 patients died. The interval between diagnosis and death ranged from 1 to 8 months (average = 3.1). The ages of the workers ranged from 16 to 22 (average = 17). The workshops were converted rooms inside residential houses, ranging from 30 to 80 m^2 and with inadequate or no ventilation. Of the some 20 adhesives used at the workshops, the benzene content in seven exceeded 30%. Working hours were usually exceedingly long, 12 to 17 h. Benzene measurements as high as 2040 mg/m^3 were reported. Furthermore, high measurements of toluene (up to 949 mg/m^3) and *n*-hexane (up to 85,800 mg/m^3) were also reported at the workshops (Table 5).

Table 5
Benzene poisoning cases and benzene levels among leather bag workers in China

Diagnosis	33 cases of benzene poisoning cases reported in leather bag workers in a small town in Hebei Province
Age of workers	16–22 (average = 17)
Gender of workers	27 females and 6 males
Workshops	Converted rooms in residential homes, 30–80 m^2, inadequate ventilation
Adhesives	Benzene content of 7 of the 20 adhesives used exceeded 30%
Working hours	12–17 h a day
Benzene levels	Up to 2040 mg/m^3
Toluene levels	Up to 949 mg/m^3
n-Hexane levels	Up to 85,800 mg/m^3

As stated earlier, case and control enrollment in our case-control study in Shanghai started in August 2003. A preliminary estimate projects that by December 2006, we will have approximately 400–450 NHL cases and twice as many controls. In terms of statistical power, assuming an exposure frequency of 5%, the sample size will be able to detect a relative risk of approximately two-fold ($\alpha = 0.05$, $\beta = 0.20$). Some of the occupations or industries reported among accrued study subjects (cases and controls) with potential exposure to benzene include shoe workers, painters, mechanics or machinists, and printers. The earliest exposure was in 1941, and the occupations with the highest exposure were brush painters and spray painters. The highest exposures exceeded 1000 mg/m^3. The most frequent occupations or industries of study subjects (cases and controls) exposed to other substances are farmers, textile workers, engineers, drivers, cooks or chefs, and military personnel.

4. Discussion and concluding remarks

The epidemiologic overview presented earlier shows that there is little epidemiologic evidence supporting an association between benzene exposure and NHL. The record-linkage investigation reported by Vianna and Polan [15] was a classic example of misleading results derived from linking health data to administrative databases that were not set up for research purposes [16,18]. Another investigation suggesting an increased risk of NHL among benzene-exposed workers was based on a cohort of Chinese workers in a variety of industries involving exposures to not only benzene but also other chemicals [19]. The group reported to have the highest risk was "organic, insecticide and benzene production," consisting of several heterogeneous industries/occupations with very different exposures. In particular, insecticide workers are exposed to a variety of chemicals not related to benzene, and studies have reported increased risk of NHL among agricultural chemical workers or farmers throughout the world.

No other cohort studies of benzene-exposed workers have reported an association between benzene exposure and NHL. In particular, the study of workers at rubber hydrochloride plants in Ohio did not report any increased risk of NHL, even though benzene exposure levels were extremely high [23,25]. In fact, a remarkable increase of AML was found among the same workers. For example, Wong reported an SMR of 98-fold among workers with a cumulative exposure of 400+ ppm years in the study [24]. For NHL, however, there was no suggestion for any increase in the cohort. Based on the latest update, Rinsky et al. [25] reported five NHL deaths with an SMR of 1.00. Similarly, as discussed earlier, other cohort studies and case-control studies provide ample evidence supporting the finding of Rinsky et al., that is, no increased risk of NHL in benzene-exposed workers.

Nevertheless, to further investigate the possible role of benzene in the etiology of NHL, we are conducting a hospital-based case-control study in Shanghai. The study has a number of advantages. First, Shanghai is the largest city in China and its large population (17 million) will allow a prospective accrual of NHL patients in a relatively short period of time. The prospective case accrual and the newly created clinical laboratory will ensure the quality and specificity of diagnosis. The WHO definition is used and NHL cases are classified by subtypes, which will reduce the heterogeneity of the disease and allow analysis by subtype. Although the study design is, strictly speaking, a hospital-based case-control study, because of the large number of hospitals ($n = 29$) participating in the study, we are confident that case ascertainment is virtually complete. Employment histories are obtained through face-to-face interviews, using a two-tier approach. This two-tier approach utilizes secondary questionnaires for certain occupations or industries, which are more detailed and more exposure-specific. Sources for benzene exposure include the Shanghai Municipal IPHS database, which consists of more than 50,000 benzene measurements taken at factories in Shanghai since the 1950s. The Shanghai Municipal IPHS database is supplemented by additional data maintained at Shanghai District IPHS or at factories, walk-through surveys at factories, and benzene levels reported for similar occupations/industries in the Chinese medial journals. Furthermore, our Exposure Assessment team includes local experts who are familiar with the industries and factories in Shanghai. One team member is a retired Shanghai Municipal IPHS employee, who had personally visited hundreds of factories in Shanghai during his long career of several decades before retirement.

All these valuable resources in our Shanghai study are quite unique, and they are seldom, if not rarely, available to community- or hospital-based case-control studies. We estimate that case ascertainment will be completed by December 2006 and that the project (including analysis and report) by 2007. We hope that the results of the study will provide some additional insights into the relationship between benzene exposure and NHL.

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