Progress of Epidemiological and Molecular Epidemiological Studies on Benzene in China

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ABSTRACT: Benzene is an organic solvent that has been used in industry for about 100 years throughout the world. Since 1973, a series of toxicological and molecular epidemiological studies on benzene were conducted by researchers at the Chinese Academy of Preventive Medicine (CAPM) (1973–1986) and subsequently by a collaboration between the CAPM and the National Cancer Institute (NCI) in the United States that began in 1986, which was joined by investigators from the University of California at Berkeley, the University of North Carolina at Chapel Hill, and New York University. The findings demonstrated that the risk of leukemia and lymphoma among benzene-exposed workers was significantly increased, with elevated risks for leukemia present not only at higher exposure but also among workers exposed to under 10 ppm. Therefore, the benzene permissible level was decreased to 1.8 ppm (6 mg/m^3) and benzene-induced leukemia is treated as an occupational cancer in China. The benzene permissible level is 1.0 in the United States and in several other developed countries and it has been suggested to be decreased to 0.5 ppm (ACGIH). A number of potential biomarkers are related to benzene exposure and poisoning. Some of these are benzene oxide–protein adducts, chromosome aberration of lymphocytes, and GPA mutations in erythrocytes, a decrease in B cell and CD4$^-$T cell counts in peripheral blood, and altered expression of CXCL16, ZNF331, JUN, and PF4 in lymphocytes. Variation in multiple benzene metabolizing genes may be associated with risk of benzene hematotoxicity, including CYP2E1, MPO, NQO1, and GSTT1.

KEYWORDS: benzene; epidemiology; poisoning; hematotoxicity; genomics; molecular aspects; individual susceptibility; adducts

INTRODUCTION

Benzene is an organic solvent and has been used in industry for about 100 years throughout the world. High benzene exposure has been controlled in

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developed countries, but low benzene exposure, including industrial and environmental contamination and its risk, still exists in developed and developing countries.

There were reports of some individual occupational health investigations and of BP in some factories in China in the 1950s–1970s. Since 1978, when the reform and open policy was issued in China, the progress of epidemiological and molecular epidemiological study of workers exposed to benzene in China can be probably divided into three phases.

RESULTS

First Phase

To understand the risk of BP and prevention, the Ministry of Health of China organized a nationwide investigation of workers exposed to benzene and four other chemicals. We found that 500,000 workers were exposed to benzene and benzene mixtures. The geometric average benzene concentration was 18.3 mg/m^3 (5.5 ppm) in 19,969 factories, and the prevalence of chronic BP was 0.5%. In addition, nine cases of aplastic anemia and nine cases of leukemia were found in benzene-exposed workers.[1]

Based on these results, a retrospective cohort study of benzene and leukemia was conducted by the Chinese Academy of Preventive Medicine (CAPM) and cooperating institutions in 12 cities. The period of follow-up was 1972–1981. The mortality of leukemia was 14 of 105 among 28,460 benzene-exposed workers and 2/10^5 among 28,257 non-benzene-exposed workers (Standard Mortality Rate [SMR] = 5.47). Lymphosarcoma, lung cancer, and liver cancer were significantly higher in the benzene cohort than in the control cohort. This was the first report that benzene might be a multiple carcinogen in humans.[2] Based on these findings, prevention measures were enhanced, and the health standard of benzene was decreased to 40 mg/m^3. Benzene-related leukemia was treated as an occupational cancer in China.[3] These findings were cited in a 1987 IARC monograph[4] and by IPCS, WHO in 1993.[5] The mechanism of the action of benzene on blood and hematopoietic function includes benzene–DNA and protein adducts; benzene metabolism patterns of workers exposed to benzene, toluene, and benzene mixtures; diagnostic criteria for BP and use of Chinese herb extracts "XUEZASISHEN" for the treatment of chronic BP were reported at Annual Meeting of the Council of Fellows, Collegium Ramazzini in 1989.[6]

Second Phase

To verify the dose–response relationship between benzene exposure and leukemia and to carry out molecular epidemiology studies to further understand benzene's mechanism of action, CAPM collaborated with National Cancer Institute (NCI) and the NIH in the United States to do an expanded cohort study

among exposed and unexposed workers between 1972 and 1987. A total of 75,000 benzene-exposed workers and 35,000 unexposed workers were investigated in the same 12 cities.[7] Historical benzene measurements were collected and benzene exposure estimates were made for job title, work units, and factories from 1950 through 1987. The benzene exposure level was 25–33 ppm in 1950–1974, 11–15 ppm in 1975–1984, and 8 ppm in 1985–1988.[8] There were 38 cases of leukemia in the benzene cohort and 9 cases of leukemia in the nonbenzene cohort. Relative risk (RR) was 2.5. Acute nonlymphocytic leukemia (ANLL) and acute nonlymphocytic leukemia/myelodysplastic syndrome (ANLL/MDS) each showed patterns of increasing risk with increasing average exposure. Risk for non-Hodgkin's lymphoma (NHL) increased with increasing duration (RR = 3.3) among those exposed for 5–9 years and 4.2 for those exposed for 10 or more years.[9–12] This study provided evidence that benzene may cause hematological neoplasm and related disorders at average exposures of less than 10 ppm and cumulative exposure of less than 40 ppm-years.[13]

After the completion of the expanded cohort study, we continued our collaboration of doing molecular epidemiology studies among benzene-exposed workers and BP in Shanghai and Tianjin, working with investigators at NCI and several universities in the United States including University of California (UC) at Berkeley, University of North Carolina (UNC) at Chapel Hill, and New York University (NYU). The main results follow.

1. **Validation of benzene metabolites as a biomarker**

   It is well known that benzene metabolites include phenol, hydroquinone, tt-muconic acid, and S-PMA. They are all related to benzene exposure in the middle or higher level, but are not good markers for lower-level exposure. Qu *et al.*[14] reported that urine tt-MA and S-PMA are sensitive biomarkers for exposure levels of 0.1–1.0 ppm in shoe makers in Tianjin. Waidyanatha *et al.*[15] determined urine benzene and metabolites of benzene-exposed workers with gas chromatography mass spectroscopy (GC-MS) and found that urine benzene is a specific biomarker for exposure of less than 1.0 ppm.
2. **Benzene DNA, Alb adducts**

   Benzene DNA adducts[16] have been found in animals exposed to benzene 10 years ago. Recently Yeowell-O'Connell *et al.*[17] reported that benzene oxide–albumin adduct (BO-Alb) and 1.4-benzoquinone albumin adducts (BQ-Alb) are 2.4 times higher in benzene-exposed workers ($n = 160$) than non-benzene-exposed workers ($n = 102$). This relationship is linear at lower benzene exposures but not at high exposures.
3. **Chromosome aberrations in lymphocytes and glycoprotein A (GPA) mutation of erythrocytes in peripheral blood**

   Since the metaphase preparation method was established, many epidemiological studies focused on benzene exposure and chromosomal

aberrations. In most studies using the nonbanding staining method, elevated chromosome aberration levels in peripheral lymphocytes were detected in BP patients and also in nondiseased workers exposed to benzene. Our studies using G-banding indicated that aberrations on the long arms of chromosomes 5 and 7 were increased in BP patients, and structural aberrations were most common on the long arms of chromosome 2 and 10 in nondiseased workers exposed to benzene.[18]

In 1992, in collaboration with the NCI, UC Berkeley, and UNC, we conducted a molecular epidemiological study in Shanghai, China. Forty-three workers exposed to benzene (median = 31 ppm, 8-h time-weighted average) and 44 matched controls were sampled. Specific chromosome aberrations were detected using FISH. The results showed:

1. Benzene exposure was associated with increases in the rates of monosomy 5 and 7 but not monosomy 1 and with increases in trisomy and tetrasomy frequencies of all three chromosomes. Long-arm deletion of chromosomes 5 and 7 was increased in a dose-dependent fashion up to 3.5-fold in the exposed workers.[19]
2. High benzene exposure (>31 ppm, $n = 22$) increased the hyperdiploid frequency of chromosome 9; trisomy 9 was the major form of benzene-induced hyperdiploidy. The level of hyperploidy 9 in exposed workers correlated with their urinary phenol level, a measure of internal benzene dose.[20]
3. Benzene exposure was associated with significant increases in hyperdiploidy of chromosomes 8 and 21. Translocations between chromosomes 8 and 21 were increased up to 15-fold in highly exposed workers. In one highly exposed individual, these translocations were reciprocal and were detectable by reverse transcriptase-polymerase chain reaction (PCR).[21]

   Loss and long (q)-arm deletion of chromosomes 5 and 7 are two of the most common cytogenetic changes in therapy- and chemical-related leukemia. Numerical and structural aberrations in chromosomes 8 and 21 are commonly observed in AML. These data indicate a potential role for aberrations in chromosomes 5, 7, 8, and 21 in benzene-induced leukemogenesis, and these chromosome aberrations may be useful biomarkers of early biological effect for benzene exposure.

   In 2000–2001, in collaboration with the NCI, UC Berkeley, and UNC, we conducted another molecular epidemiological study in Tianjin, China. To determine if selective effects of benzene can occur Zhang *et al*.[22] employed three-color painting on an 8-square slide to screen numerical changes in all 24 human chromosomes (Octo-Chrome FISH) in a pilot study of 11 subjects (6 exposed to >5 ppm benzene and 5 age- and sex-matched controls). Selective effects were observed on monosomy of chromosomes 5, 6, 7, and 10, and were also observed on trisomy

induction with chromosomes 8, 9, 17, 21, and 22. These results suggest that benzene has the capability of producing selective effects on certain chromosomes.[22] These selective effects are under further study in a larger population. Effects of low-level benzene exposure on chromosome aberrations and the dose–response relationship are also in process.

Rothman *et al*.[23] used the GPA gene loss mutation assay to evaluate 24 workers exposed to benzene and 23 matched control workers in Shanghai. The GPA assay identifies stem cell or precursor erythroid cell mutations expressed in peripheral erythrocytes of MN-heterozygous subjects, distinguishing the NN and *N*ϕ mutation variants. A significant increase in NN GPA variant cell frequency (Vf) was found in benzene-exposed workers as compared with unexposed control workers (Vf 13.9/7.4 per 10^6 cells). In contrast, no significant difference existed between these two groups for the *N*ϕ. The lifetime cumulative occupational exposure to benzene was also associated with NN Vf ($P < 0.01$) but not with *N*ϕ Vf ($P < 0.31$). These findings suggested that NN mutations occur in long-lived bone marrow stem cells, and variants result from loss of the GPA M allele and duplication of the N allele.

4. **Genetic polymorphism and susceptibility to benzene hematotoxicity:**

To evaluate the impact of interindividual variation in activating enzymes (CYP2E1) and detoxifying enzymes (NQOI) of benzene, in 1997 Rothman *et al*.[24] reported the BP cases ($n = 50$) and control ($n = 50$) study in Shanghai. Subjects with both a rapid fe6-OH and two copies of the NQOI^{609}C→T mutation had a 7.6-fold increased risk of BP compared to subjects with a low fe6-OH who carried one or two wild-type NQOI allele, but the CYP2E1 Rsal/Pst1 polymorphism did not influence BP risk.

To further investigate the role of the polymorphisms of benzene-metabolizing enzymes in human susceptibility to BP, Chen *et al*.[25] analyzed BP cases ($n = 100$) and matched control workers ($n = 90$) with the same job title. PCR and PCR-RFLP were used for genotyping. The results showed that single gene mutation of NQO1^{609}C→T(T/T) was increased 2.82-fold in BP compared with those carrying heterozygons (C/T) and wild type (C/C). The subjects with GSTTI null genotype had a 1.91-fold increased risk of BP compared with those carrying GSTT1 non-null genotype. There was evidence that individual with genetic variants in several genes (NQO1, GSTT1, and GSTM1) had a substantially increased risk of BP.

Third Phase: To Identify the Risk of Low Benzene Exposure and Molecular Mechanism of Carcinogenesis

In early reports, benzene exposure was about 100–1000 ppm before 1940 in Europe and America. After WWII, benzene exposure was gradually decreased

to 65–259 ppm in 1946; 22–96 ppm in 1949–1957; 18–69 ppm in 1964–1969; and 3–52 ppm after 1970 in a rubber manufacture factory in the United States.[26] In recent years, the benzene health standard has decreased to about 1 ppm in many developed countries. Further studies are needed to determine the safety or risk in low benzene exposure in China, the United States, and other countries.

1. The retrospective and prospective cohort study on the original cohort of 110,000 workers

   We followed up subjects in our cohort study through 1999 and then designed a "case–cohort control study" of hematopoietic malignancies and related disorders (HLD) and lung cancer (LC) in benzene-exposed workers, with a subcohort from the cohort identified to be used as a comparison group. Historical benzene measurements have been collected and are being used to estimate benzene exposure for the study subjects. The main goal is to study the relationship between benzene exposure and the incidence of HLD and mortality from LC. The study is ongoing.
2. Molecular mechanism of benzene toxicity and carcinogenesis.

   Benzene's effects on the blood and bone marrow include leukopenia, pancytopenia, aplastic anemia, and myelodysplastic syndrome (MDS), and leukemia, as established by many animal and epidemiological studies. However, the mechanism of benzene-induced hematotoxicity and leukemogenesis is still unclear. In order to identify the risk and mechanism at the molecular level among workers with low benzene exposure, we performed studies on benzene-exposed and unexposed workers in Tianjin.

   A. The first report from the project was a detailed exposure assessment for each shoe making factory [27.]

      The result showed benzene concentration <1.0 ppm for 109 workers, <10 ppm for 110 workers, >10 ppm for only 31 workers in the exposed group, and <0.04 ppm in the unexposed group of 140 workers.

   B. We then reported on the hematotoxicity in workers exposed to low-level of benzene in *Science* (Dec. 2004).

      Workers were categorized based upon exposure in the month prior to phlebotomy. The result showed benzene concentration <1.0 ppm for 109 workers, <10 ppm for 110 workers, and >10 ppm for 31 workers in the exposed group; the benzene concentration was <0.04 ppm in unexposed group of 140 workers.[28]

      Lan *et al*.[28] found that all types of WBC and platelets were significantly decreased in 109 workers exposed to <1 ppm benzene compared to controls; further, lymphocyte subset analysis showed that $CD4^+$ T cells, the $CD4^+/CD8^+$ ratio, and B cells were also significantly decreased. Tests for the linear trend using benzene air

level as a continuous variable were significant for platelets and each WBC type measured except monocytes and $CD8^+$ T cells. Because benzene affected nearly all blood cell types, toxicity to hematopoietic progenitor cells was suspected. We used peripheral blood from 29 benzene-exposed subjects and 24 matched controls to culture CFU-GM (granulocyte-macrophage), CFU-E (erythroid), and CFU-GEMM (granulocyte erythroid macrophage, megakaryocyte) colonies. Highly significant dose-dependent decreases in colony formation for these progenitor cells were observed.[28] Also, the progenitor cells are more sensitive than mature cells to the hematotoxic effect of benzene.

A total of four single nucleotide polymorphisms (SNPs) in the CYP2E1, MPO, and NQO1 genes were examined for their effects on benzene-induced WBC toxicity. Two genotypes significantly influenced WBC counts in benzene-exposed workers, MPO 463 GG (rs2333227) ($P = 0.04$) and NQO1-465 CT (rs4986998) ($P = 0.014$). In exposed subjects who carry either one ($n = 191$) or both of the "at risk" genotypes ($n = 11$), there was a strong gene-dosage effect (P trend $= 0.004$), which was also present among those exposed to <1 ppm benzene ($P = 0.003$).[28]

C. We hypothesized that genetic variation in cytokines and cellular adhesion molecule genes may modify the relationship between benzene exposure and hematotoxicity. One or more SNPs in each of 18 candidate genes were studied for their association with hematotoxicity in 250 workers exposed to benzene and the 140 unexposed controls that were studied. Lan *et al*. showed that SNPs in several genes (e.g., ILA, IL-10, CSF3, VCAM1) were associated with a highly significant decrease in WBC counts and with several specific WBC subtypes.[29]

D. Microarray analysis of gene expression in benzene-exposed workers.

The new "Omic" technologies include genomics, transcriptomics (gene expression profiling), proteomics, and metabolomics, which can be used to develop novel biomarkers of exposure, susceptibility, expression, and response to benzene. We have applied microarrays to the study of global gene expression in the peripheral blood mononuclear cells of benzene workers ($n = 6$) and matched controls ($n = 6$). Three recently developed software programs—LIMMA, EASE, and HOPACH—were used to analyze the array data.

The expression of 19 known cytokine genes was significantly different between the exposed and control subjects. Six genes were selected for conformation by real-time PCR and of those CXCL16 (chemokine), ZNF331 (zinc finger protein), JUN (oncogene), and PF4 (platelet factor 4) were most significantly affected by benzene exposure. Thus, microarray analysis along with real-time

PCR conformation showed that altered expression of CXCL16, ZNF331, JUN, and PF4 are potential biomarkers of benzene exposure.[30]

CONCLUSION

Since 1973, the Benzene Research Group in the Chinese Academy of Medical Science (1973–1982) and the Chinese Academy of Preventive Medicine (1983–2002), which was renamed the China CDC in 2002, have conducted a series studies on benzene toxicity and occupational epidemiology, then collaborated with NCI (1986–2006) to do the expanded retrospective cohort, prospective cohort study, and molecular epidemiology studies on benzene and leukemia and other cancers, along with investigators from UC Berkeley, UNC, and NYU. It is the largest and longest international collaboration to study the benzene toxicity and carcinogenicity in the world.

The findings are of benefit to the occupational benzene-exposed workers in China, the United States, and other countries. The benzene permissible level had been decreased to 1.8 ppm (6 mg/m^3) from 12 ppm (40 mg/m^3), and leukemia among benzene-exposed workers was treated as occupational cancer in China. The benzene permissible exposure level has been considered and a decrease to 0.5 ppm has been suggested in the United States. Many developed countries have also decreased the benzene permissible exposure level to about 1.0 ppm. A number of biomarkers were found as potential biomarkers related with benzene exposure and poisoning including benzene–oxide protein adducts, chromosome aberrations of lymphocyte, GPA mutations in erythrocytes in peripheral blood, and altered expression of CXCL16, ZNF331, JUN, and PF4. Also, variation in multiple genes involved in benzene metabolism and in the control of hematopoiesis may be important risk factors for BP. Ongoing work will continue to study risk of adverse health effects at lower levels of occupational exposure to benzene and ultimately at environmental exposure levels. Also, it is anticipated that molecular epidemiology studies will continue to produce new insights into the genetic susceptibility and mechanism of benzene-induced BP and malignancies.

In China, benzene exposure levels have gradually decreased as we have shown in the benzene cohort study.[31] However, benzene exposure is still higher in some new private factories established after the 1980s. Therefore, we need to do more to control benzene exposure in accordance with the law for occupational disease prevention and control in China.

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