Clinical Features of Hematopoietic Malignancies and Related Disorders among Benzene-exposed Workers in China

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Abstract

Previous occupational cohort studies of benzene-exposed workers have for the most part used only death certificates to validate diagnoses of workers developing leukemia and other hematopoietic and lymphoproliferative malignancies and related disorders (HLD). In a follow-up study of 74,828 benzene-exposed workers and a comparison group of 35,805 nonexposed workers from 12 cities in China, we sought to characterize clinicopathologically and to confirm diagnoses of all cases of HLD. Using medical records, laboratory hematology results, and histopathology, U.S. and Chinese expert hematopathologists, blinded to exposure status, carried out a detailed review using standardized evaluation forms. Key among the findings were a notable diversity of malignant and nonneoplastic hematopoietic and lymphoproliferative disorders, documentation of excess myelodysplastic syndromes among benzene workers, and widespread dyspoiesis involving all hematopoietic cell lines. As sophisticated clinicopathologic characterization and corresponding classification schemes for HLD become increasingly widespread, it is recommended that future epidemiologic investigations of benzene workers incorporate similarly detailed morphologic evaluation. In extending follow-up of this cohort of young workers, we will continue to use all available clinical, laboratory hematology, and pathology data as well as cytogenetic and biochemical markers to characterize various HLD outcomes. These careful surveillance mechanisms should also provide additional insight into carcinogenic mechanisms of benzene and allow comparison of the molecular pathogenesis of HLD induced by benzene versus chemotherapy, radiation, or other exposure. -- Environ Health Perspect 104(Suppl 6): 1353-1364 (1996)

Key words: hematopoietic malignancies, benzene, leukemia, acute myeloid leukemia, chronic myeloid leukemia, nonHodgkin's lymphoma, aplastic anemia, myelodysplastic syndromes, dyspoiesis

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Abbreviations used: AML, acute myeloid leukemia; CAPM, Chinese Academy of Preventive Medicine; HLD, hematolymphoproliferative disorders; NCI, National Cancer Institute; NOS, not otherwise specified.

Introduction

Benzene, a ubiquitous constituent of cigarette smoke, industrial solvents, automobile emissions, and a broad variety of other products, (1) is widely recognized to be etiologically linked with acute myeloid leukemia (2). Other hematopoietic and lymphoproliferative malignant and related disorders (HLD) associated with benzene exposure include aplastic anemia (3,4) and possibly non-Hodgkin's lymphoma (5), chronic myeloid leukemia (6), multiple myeloma (7-9), chronic lymphocytic leukemia (10), and various myelodysplastic syndromes (11,12). To evaluate further the quantitative relationship of acute myeloid leukemia (AML) with benzene exposure and to determine whether other types of HLD were linked with this chemical, the U.S. National Cancer Institute (NCI) and the Chinese Academy of Preventive Medicine (CAPM) collaborated in a large cohort study of benzene-exposed workers in China (13,14).

Clinicopathologic features of benzene-exposed workers developing acute myeloid leukemia (15-17), pancytopenia, and aplastic anemia (3) have been previously described in case series. Ascertainment of HLD among benzene workers in defined occupational cohorts, however, has been largely based on death certificates (18,19) in which information typically is limited only to overall diagnosis(es), often without specification of subtype (20). Therefore, a major objective of the collaborative NCI-CAPM cohort investigation was to obtain detailed clinical diagnostic information from all available medical record and laboratory sources to describe incident HLD cases (21).

In an earlier report (22), we included descriptions of salient clinicopathologic features of HLD cases for which bone marrow, lymph node or related tumor tissue, peripheral blood smears, and pathology and laboratory hematology reports were available. The goal of the present paper is to provide a comprehensive overview of the sources and types of information available for all patients and to describe clinical features. In addition to individual case descriptions (22), we also present summary statistics for selected HLD subtypes.

Methods

A detailed description of the methods for identifying and following up subjects using written factory records can be found in earlier reports (13,21). The study population includes 74,828 benzene-exposed workers and a comparison group of 35,805 nonexposed workers, with 60% of the total person-years (P-Y) contributed by workers less than 30 years of age at study entry, and 47% of the exposed and 40% of the nonexposed P-Y contributed by women (13,21). For deceased subjects and all incident cases suspected as having HLD, cause of death or diagnostic information, respectively, was first sought from medical records, then other factory records or death certificates, followed only if necessary by contacts with treating physicians and next of kin.

For all exposed and nonexposed HLD cases, medical records from diagnostic and subsequent visits, hematology and histopathology reports, and peripheral blood smears, bone marrow, lymph node, and all other tumor tissue pathology slides were sought. Information from all sources was abstracted onto standardized forms by physician investigators blinded to benzene exposure status of the patients. Abstracted data included the date and medical record diagnosis of the hematopoietic disorder; peripheral blood counts prior to therapy (including hemoglobin, hematocrit, total white blood count, a white blood cell differential count, platelet count, reticulocyte count, and date the specimen was obtained); peripheral blood morphology; diagnostic report of bone marrow aspirate and/or biopsy, lymph node or other lymphoproliferativetumor tissue and results **of** immunohistochemical stains; selected physical examination findings (including lymph node palpation, liver and spleen evaluation, and other pertinent abnormalities); diagnostic X-ray interpretation (chest and abdominal radiographs and other pertinent evaluations); surgical reports at the time of diagnostic evaluation; and stage and classification scheme used to evaluate extent of lymphoproliferative disorder. Although we searched for other laboratory data (including leukocyte alkaline phosphatase score, cytogenetic studies, serum and urine lysozyme, lactose dehydrogenase, and bilirubin), these data were rarely available in the medical records during the study period.

All abstracted forms, medical records, and available hematopathologic laboratory slides were reviewed systematically by expert U.S. and Chinese hematopathologists, from Mayo Clinic, NCI, and the Division of Hematology of the Peking Union Medical College Hospital, Beijing University School of Medicine, who were blinded to the exposure status of the cases. Most reviewers were fluent in reading Chinese, the language in which the original records were written. Details of the hematologic evaluation have been described (22). Diagnoses were assigned after evaluation of all available clinical, laboratory, and pathologic data. Published criteria were used to classify acute myeloid (also called nonlymphocytic) leukemia (23-25), acute lymphoblastic leukemia (23), chronic myeloid leukemia (26), myelodysplastic syndromes (27), and non-Hodgkin's lymphoma (28).

To summarize presenting symptoms and signs of disease and peripheral blood counts within HLD groups, we performed univariate analyses (calculating medians, means, standard deviations, etc.). We evaluated the distribution of survival times after diagnosis with product limit estimates (29). Survival was also examined according to age and exposure status, and tests of significance were performed using log-rank (30).

Results

A total of 81 HLD were diagnosed among benzene-exposed workers and 13 among nonexposed workers during 1972 to 1987. Twenty-nine (36%) of the **81** exposed cases and 3 (23%) of the 13 nonexposed cases were women. Median age at diagnosis for all cases was 40 years for exposed and **48** for nonexposed. As shown in Table 1, categories of specific disease types with the largest numbers among the Chinese benzene workers were AML and non-Hodgkin's lymphoma, followed by aplastic anemia, chronic myeloid leukemia and myelodysplastic syndromes, and then acute lymphoblastic leukemia. It is noteworthy that tumors derived from B-lymphocytes were quite rare. Confirmation of approximately **80%** of all HLD cases among both exposed and nonexposed workers was based on review of either tissue specimens or corresponding hematopathology reports. Eighty-eight percent of diagnoses were confirmed by evaluation of medical record data or hematopathology specimens/reports (Table 1).

Table 1. Numbers of hematopoietic and lymphoproliferative malignancies and related disorders among benzene-exposed Chinese workers by best source of diagnoses.

	Exposed			Nonexposed		
Diagnoses	Review of slides or pathology report	Medical record	Other	Review of slides or pathology report	Medical record	Other
All HLD	65(80.3%)	6(7.4%)	10(12.3%)	10(76.9%)	2(15.4%)	1(7.7%)
All leukemias	35	2	5	6	2	1
Acute myeloid	21	1	1	4	0	0
Acute lymphoblastic	4	0	1	1	0	0
Acute leukemia, NOS	3	0	1	0	0	1
Chronic myeloid	7	1	1	1	1	0
Leukemia, NOS	0	0	1	0	1	0
All nonmalignant blood disorders	16	0	2	—	—	—
Aplastic anemia	7	0	2	—	—	—
Myelodysplastic syndrome	7	0	0	—	—	—
Agranulocytosis	2	0	0	—	—	—
All lymphocytic and histiocytic	14	4	3	4	0	0
Non-Hodgkin's lymphoma	11	3	3	3	0	0
Other histiocytic	2	1	0	—	—	—
Multiple myeloma	1	0	0	1	0	0

NOS, not otherwise specified.

Presenting symptoms abstracted from medical records of benzene-exposed patients with selected HLD are listed in Table 2, but small numbers limit comparisons with nonexposed cases, except for AML. For both the exposed and nonexposed patients with AML (data for latter not shown), the most common initial complaints were abnormal bleeding (including petechiae, purpura, or hemorrhage) and persistent fevers. These symptoms are similar to those associated with de novo AML (31).

Table 2. Number and percentage (in parentheses) of exposed workers with hematopoietic and lymphoproliferative malignancies and related disorders experiencing clinical presenting symptoms and signs by type of symptom and type of disorder[a].

Diagnostic category	Bleeding	Fever, night sweats, chills	Fatigue, malaise, weakness, anemia, malnutrition	Weight loss	Lymphadenopathy	Splenomegaly	Hepat
Acute myeloid	12(57.1)	12(57.1)	8(38.1)	0(0)	9(42.9)	3(14.3)	5(2
Chronic myeloid	2(28.6)	3(42.9)	2(28.6)	—	3(42.9)	5(71.4)	5(7
Acute lymphoblastic	2(66.7)	1(33.3)	1(33.3)	—	2(66.7)	2(66.7)	2(6
Myelodysplasia	4(57.1)	5(71.4)		—	3(42.9)	1(14.3)	3(4
Aplastic anemia	7(77.8)	—	4(44.4)	—	—	—	2(2
Non-Hodgkin's lymphoma	1(7.1)	5(35.7)	4(28.6)	3(21.4)	12(857)	6(42.9)	5(3

[a]Differences in numbers of exposed patients shown in Tables 1 and 2 reflect incomplete information in medical records about symptoms and signs.

Peripheral blood cell counts at diagnosis are shown for exposed patients with six types of HLD and for nonexposed cases with acute myeloid leukemia and non-Hodgkin's lymphoma in Figures 1 through 4. For most HLD diagrammed in Figures 1 and 2, median hemoglobin concentrations and platelet counts were low at diagnosis, as expected. Consistent patterns were more difficult to identify for total white blood cell and absolute lymphocyte counts (Figures 3 and 4). For AML, median total white blood cell counts (10,000 versus 25,000 X $10^3/\mu l$) and absolute lymphocyte count (1300 versus 4000 X $10^3/\mu l$) were notably lower for benzene-exposed patients than for nonexposed cases (Figure 3). However, the median total white blood counts of benzene-exposed workers developing most other HLD conditions did not appear to differ from those described for most idiopathic cases reported in the literature (31). Benzene exposure appeared to exert a variable effect on absolute lymphocyte counts, which were low for acute and chronic myeloid leukemia cases but within the normal range for aplastic anemia, myelodysplastic syndromes and non-Hodgkin's lymphoma patients (Figure 4).

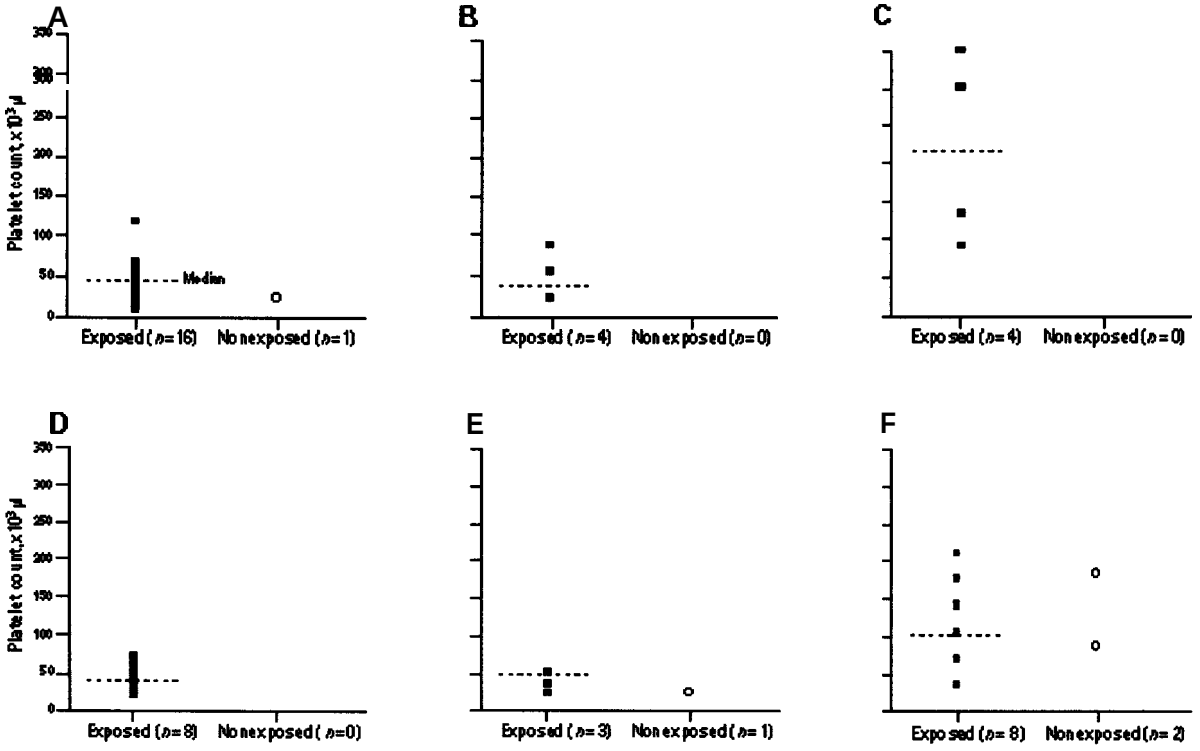

Figure 2. Platelet counts at diagnosis of patients with six hematopoietic and lymphoproliferative malignancies and related disorders by type of HLD and exposure status.

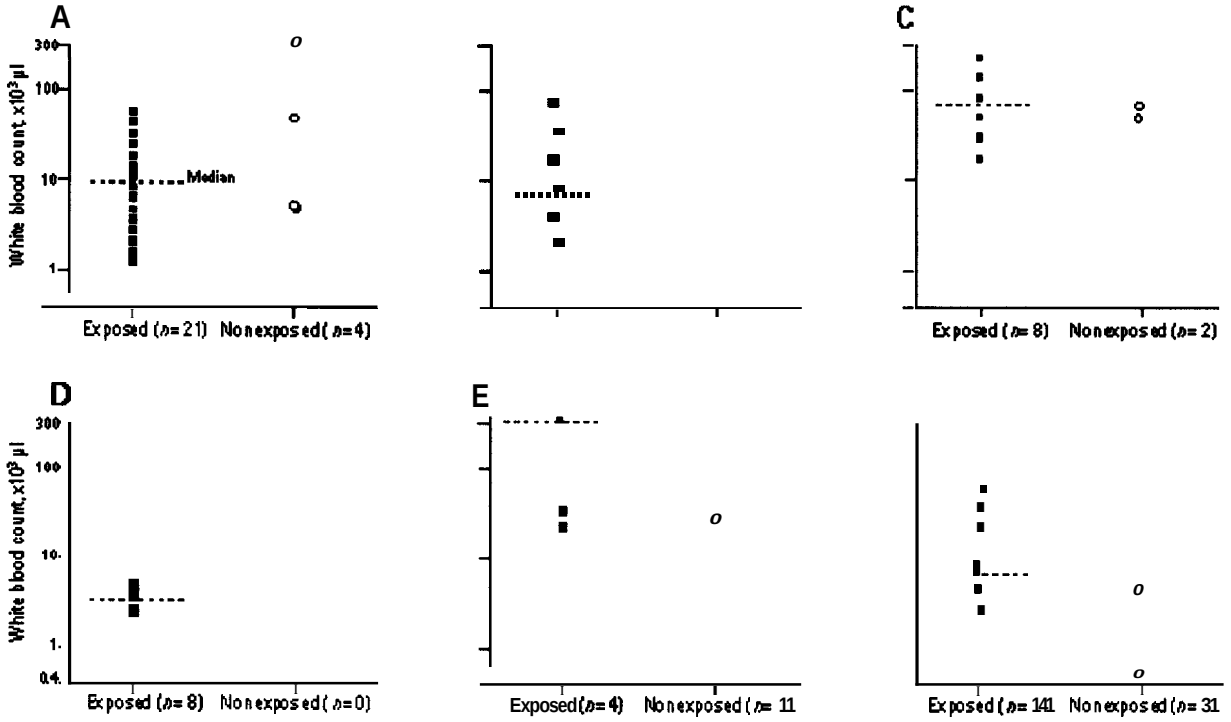

Figure 3. Total white blood cell counts of patients with six hematopoietic and lymphoproliferative malignancies and related disorders by type of HLD and exposure status.

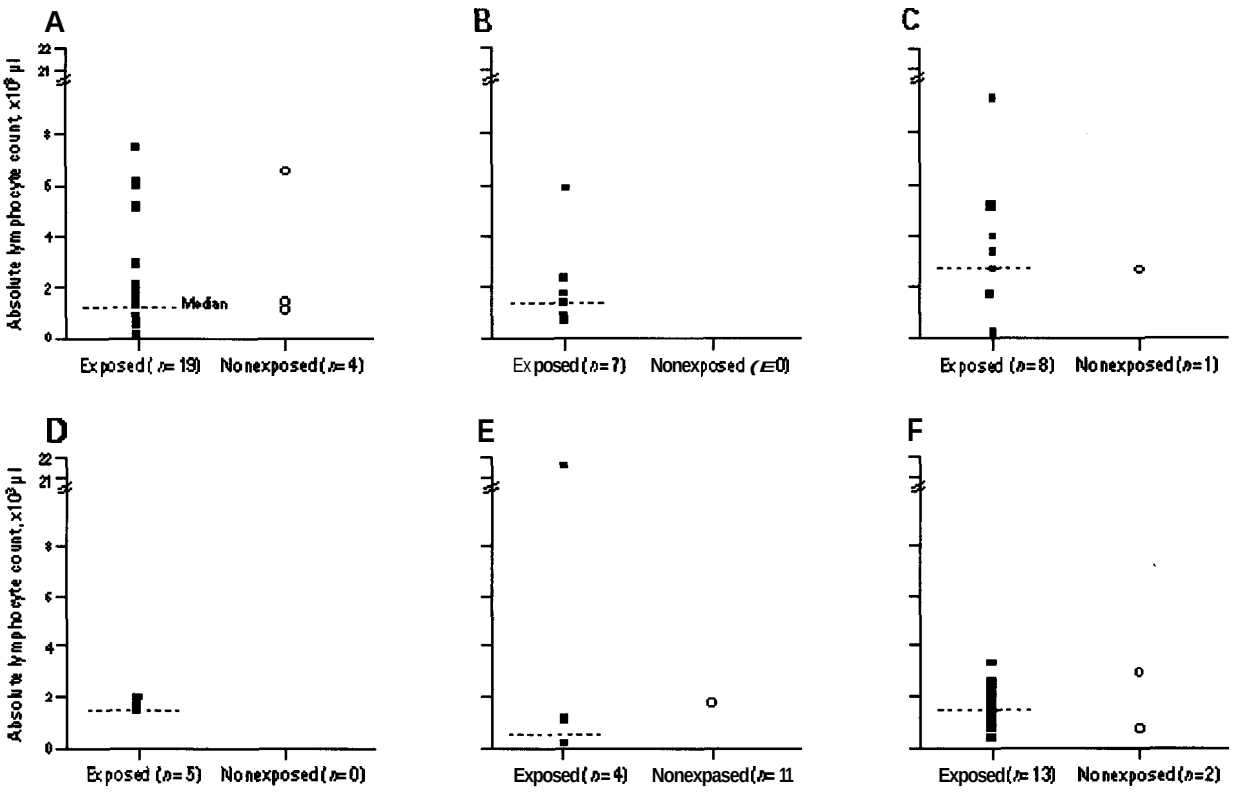

Figure 4. Absolute lymphocyte counts of **patients with six hematopoietic and lymphoproliferative malignancies and related disorders by type of** HLD **and exposure status.**

Among subjects with available pathology material or records, morphologic features in the peripheral blood and/or bone marrow of benzene-exposed workers with AML commonly included anemia, thrombocytopenia, increased bone marrow cellularity, and dyspoiesis (data not shown). Basophilia was evident in some patients with AML. The most common subtypes for cases with adequate information to determine French-American-Britishclassification were AML-M2 and AML-M3, but one patient was believed to have either a myelomonocytic or monocytic leukemia and another possibly megakaryoblastic leukemia (the latter classified as acute leukemia not otherwise specified **(NOS)** because pertinent immunohistochemical stains of bone marrow were not performed). Several other patients were also classified as acute leukemia **NOS** because of unavailability of additional immunohistochemical stains. Nevertheless, some AMLs and acute leukemias **NOS** demonstrated dysplastic changes in peripheral blood and bone marrow. Myelodysplastic syndromes, evident among seven patients based on review of histopathologic tissue or reports, included refractory anemia, refractory anemia with excess blasts, and chronic myelomonocytic leukemia, with subclassification not possible in three cases. Overall, findings for benzene-exposed workers with myelodysplastic syndromes included bone marrow hypocellularity and marked dyserythropoietic features such as multinuclearity, megaloblastoid changes, impaired hemoglobinization, abnormal nuclear shape, and dimorphic morphology of red cells. Of benzene-exposed patients with chronic myeloid leukemia, most also demonstrated dyserythropoiesis and dysgranulopoiesis, as described earlier (22).

Based on available tissue and/or pathology reports, we were often unable to update diagnoses of non-Hodgkin's lymphoma (assigned during 1972-87) to reflect recent advances in disease classification, since immunohistochemical stains and other appropriate tests had not been performed. Frequently we could only maintain the original diagnoses. In benzene-exposed subjects, diagnoses included diffuse, cleaved, mixed-cell lymphoma or lymphosarcoma (four cases of each); gastric lymphoma, T-cell non-Hodgkin's lymphoma, malignant lymphoma NOS (two each); and poorly differentiated non-Hodgkin's lymphoma (one case). Among nonexposed workers, diagnoses of gastric lymphoma, diffuse, cleaved, mixed lymphoma, and lymphosarcoma were each apparent in one patient. Assigned diagnoses reflected the evolution of classification schemes over several decades as well as differences in

levels of expertise among pathologists in hospitals throughout China.

Sixty-five (80%) of benzene-exposed patients with HLD died during the study period, including 39 of 42 with leukemia, 17 of 21 with lymphocytic/histiocytic disorders, and 9 of 18 with nonmalignant hematopoietic conditions. Similarly, all but one of the 13 nonexposed HLD cases died. Overall, benzene-exposed HLD patients had somewhat, though not significantly, shorter age-adjusted relative survival (median 0.8 year) than nonexposed patients with these disorders (median 1.0 year); survival did not vary by age (older versus younger than the median) among exposed HLD patients (median 0.7 year for both age groups), but among nonexposed cases, younger persons survived substantially longer (median 2.4 years) than older subjects (median 0.4 year). Older benzene-exposed workers with AML demonstrated no difference in survival by exposure status (median 0.1 year for benzene-exposed and for nonexposed), but younger exposed patients had notably shorter survival (median 0.2 years) than nonexposed cases (median 1.0 year), although none of these differences are statistically significant. There were too few nonexposed workers with non-Hodgkin's lymphoma and related tumors to evaluate survival, but exposed older and younger workers with these neoplasms had similar survival (median approximately 1.0 year for both age groups). For subjects with all nonmalignant hematopoietic disorders (all were exposed), younger workers survived substantially longer (median 9.6 years) than older subjects (median 3.3 years).

Discussion

In one of the largest cohort studies of benzene-exposed workers ever carried out, we sought to validate and characterize clinicopathologically all cases of HLD among the exposed study population and the nonexposed comparison group. Key among the findings was a notable diversity of malignant and nonneoplastic hematopoietic and lymphoproliferative disorders, documentation of excess myelodysplastic syndromes among benzene workers, and widespread dyspoiesis involving all hematopoietic cell lines among numerous patients. Overall, survival of patients diagnosed with HLD was poor but slightly (nonsignificantly) shorter among benzene-exposed compared with nonexposed patients, though somewhat (nonsignificantly) longer among younger than older patients. Survival differences must be interpreted cautiously, however, because of small numbers and multiple comparisons.

Table 3. Characterization of hematolymphoproliferative disorder outcomes by number, type, and source of diagnoses among cohort studies of workers exposed to benzene or in n

Reference	Study population (Person-years)	Study period	Number and type HLD: Leukemia	Lymphoma	Other	Source diagnos
Chemical manufacturing						
Thorpe, 1974 (32)	383 276	1962–71	CML-2; AML-1; MYEL-1; ACUTE, NOS-1; LEUK, NOS12			Reporte ipatin
Ott et al., 1976 (33)	n=8,171[a]	1915–54:1973	All LEU(-10		OM HLD 18	Death c
Decoufle et al.. 1983(7)	5,943	1947–60:1977[b]	AMoL-1; CLL-1		MM-2	Death c and m
Bond et al.. 1985(35)	407,094	1940–80	All LEUK-30	LS-13; HD-10	OTH-18	Death c
Bond et al., 1986 (36)	24,571	1938–78:1982	" EL-4	LY-2	AA-1; MYFIB-1	Death c
Pifer et al., 1986 (37)	94,524	1971:1982	All LEUK-7	LY-11		Death c
Wong, 1987 (5)	133,968	1946–75:1977	All LEUK-7	LY-5; HD3	OTH-7; DBFO-2	Death c
O'Berg et al., 19871383	2,489,390 (males) 463,939 (females)	1956–84	All LEU(-169M, 22F	LS-111M. 16F; HD-109M, 15F		Compar registr retirea
Rinsky et al., 1988 (39)	691,183	1940-78	All LEUK-54	LY-48; HD-9	OM 18; DBFO-7	Death c
Ott et al., 1989 (40)	Nested case–control[c] study of HLD from Rinsky et al.. 1988	1940–78	NLL-39; LL-18	NHL-52	MM-7	Death c
Olsen et al., 1989 (41)	27,405 (est.)	1956–80	AML-1; ALL-1; CML-1			Death c
Rubber manufacturing						
McMichael et al., 1974[a] (42) (studied 1 company)	51,356	1964–72	All LEU(-16	LY-14		Death c
McMichael et al., 1975[a] (43)	Nested case–control study of HLD	1964–72	AML-7; CML-8; NLL-2; ALL-4; CLL-11; LL-3; LEUK,NOS-7	LY-16; HD-10; OM LYM-9	MMIO: MYFIB-1	Death c
Fox and Collier. 1976(44)	n=40,867	1968–74	All LEUK-28			Death c
Andjelkovich et al.. 1977 (47)	n=8,418	1964–73	MoL-3; NLL-5; LL-8; LEUK, M S 4	LY-5; HD-2; OM LYM-10		Death c group
Monson and Fine, 1978 (48)	n=13,570	1940-76	All LEUK-78	OM HLD 55		Death c Akron regist
Delzell and Monson, 1981(49)	441,995 (NWM union) 28,729 (NWM union) 134397 (F union) 110,987 (M salaried) 82012 (F salaried)	1940–78	Pop. Group WM union-68 NWM union-0 F union-8 M salaried-10 F salaried-1	All L E N 68 0 8 10 1	LYM and MM: 76 6 11 15 7	Death c
Wolff et al., 1981(51)	Nested case–control study of leukemias	1964–73	NLL-27; LL-31; OM LEUK-14			Death c
Parkes et al., 1982 (52)	n=33,815	1946–60;1975	All LEUK-31			Death c

						Lance
Arp et al., 1983[a] (54)	Nested case–control study of lymphocytic leukemia	1964–73	LL-15			Deathc
Checkoway et al., 1984 (55)	Nested case–control study of lymphocytic leukemia	1964–73	LL-11			Deathc
Gustavsson et al., 1986 (57)	179,894	1952–75:1980	All LEK-7		MM-5	Swedis Cance
Bernardinelli et al., 1987 (58)	69,233	1962–R:1983	MYEL-2; OTH LEUK-1	HD-2		Death c
Rinsky et al., 1987 (8)	31,612	1940–65:1981	AML-6; MoL-1; MYEL-1; CML-1		MM-4; OTH HLD 2	Deathc hospit record pathol
Sorahan and Pope, 1993 (59)	e2,410	1955–84	All LEUK-4	LYM3		Death c
Printers and related workers						
Greenberg, 1972 (60)	*n*=670	Deaths during 1954–66	ALL LEUK-4	LS-3; HD-1		Deathc
Lloyd et al., 1977 (61)	*n*=2,604	Deaths during 1966–68	ALL LEUK-21			Deathc
Greene et al., 1979 (62)	*n*=347	Deaths during 1948–77	ALL LEUK-16	NHL-7; HD-7	MMIO	Death c
Paganini-Hill et al., 1980 (63)	*n*=1,361	1949–65:1978	AMMoL-6; MYEL-1		MYFIB-1	Deathc
Zoloth et al., 1986 (64)	*n*=1,401	Deaths during 1958–81	ALL LEUK-9	NHL-11	MYFIB-3	Deathc
Leon, 1994 (65)	NGA *n*=4,702 NATSOPA *n*=4,530	1949–63 83	Union NGA LEUK-4; NATSOPA LEUK-4	NHL-6 NHL-6		Deathc
Painters and paint manufacturing						
Chiazze et al., 1980 (66)	*n*=226	Deaths during 1970–76	ALL LEUK-2	LYM3		Deathc
Englund, 1980 (67)	152,754	1966–71	LL-13			Swedis Regist
Morgan et al., 1981 (69)	*n*=16,243	1946–76	ALL LEUK-20	LS-15; HD-7; OTH LYM-9		Deathc
Whorton et al., 1983 (70)	*n*=2,200	1976–78	ALL LEUK-2			Populat cancer
Matanoski et al., 1986 (71)	257222	1975–79	ALL LEUK-44			Death c

Abbreviations: LS, lymphosarcoma; NHL, non-Hodgkin's lymphoma; LY, lymphoma, not otherwise specified or lymphosarcoma plus reticulosarcoma; HD, Hodgkin's disease; All LEU CLL, chronic lymphocytic leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; AML, acute myeloid leukemia; AMoL, acute monocytic leukemia; AMMoL HLD: AA, aplastic anemia; PA, pernicious anemia; MYFIB, myelofibrosis; NLL, nonlymphocytic leukemia; LL, lymphocytic leukemia; DBFO, disease of blood-forming organs: LEUK, and histiocytic neoplasms; OTH HLD, all HLD except leukemia; ACUTE, NOS, acute leukemia, not otherwise specified; WM, white males; NWM, nonwhite males; M, males; F, fema of Operative Printers, Graphical, and Media Personnel. [a]*n*=5,994 workers, since person-years not provided. [b]Ever employed during years to left of colon(:) and followed up throu

Compared with other cohort studies of benzene-exposed workers or workers in major occupational categories included in the current series (4,5,7,18,19,32-71), the present investigation is one of very few using all available sources in addition to death certificates to review HLD diagnoses (Table **3).** If one considers only the key studies of benzene workers (3,5,7,8,16-19) there is an impression that only two hematopoietic disorders (AML and aplastic anemia) are indisputably associated with benzene exposure. Despite the limited and generally qualitative nature of data demonstrating a link between benzene exposure and HLD outcomes, Table 3 reveals that the specific industries included in the present investigation are characterized by mortality outcomes that include a wide range **of** HLD (32-71). Relatively few studies have attempted to evaluate quantitatively the relationship between benzene or other specific solvents and HLD (5,8,14,18,51,54,56) and none of these evaluated HLD other than the leukemias. Thus, the absence of clinical, hematologic, and/or pathologic data in conjunction with few detailed investigations of specific benzene measures in relation to various HLD types has limited the

opportunity to draw inferences with regard to hematopoietic cell lines targeted by benzene.

Fatal aplastic anemia was first reported among benzene-exposed workers nearly 100 years ago (72), while leukemia was initially linked with benzene exposure in 1928 (73). During the subsequent half century, important series of leukemia cases were described among benzene-exposed printers in rotogravure plants and shoemakers in cottage shoe factories in Milan and Pavia, Italy (15,74,75), exposed workers in small shoe and handbag factories in Istanbul, Turkey (3,16,17,76), and hospitalized patients reporting prior occupational exposure to benzene (77). Case-control studies have also linked benzene exposure (primarily occupational) with leukemia (10,78,79). These clinical series, case-control studies, and two important cohort investigations (18,19,80) were considered to provide sufficient evidence to link benzene with leukemia, particularly AML, in humans (2). Subsequent cohort investigations of benzene-exposed workers within chemical manufacturing, petroleum refinery, or other industries in the United States, the United Kingdom, Italy, and China have confirmed the benzene-leukemia association (Table 3) (81,82). Although acute myeloid leukemia, not otherwise characterized, has been the type of malignancy most consistently associated with benzene exposure, other unusual variants of acute myeloid leukemia, particularly erythroleukemia and to a lesser extent acute myelomonocytic leukemia, appear to occur disproportionately in some studies of benzene-related leukemia (15,83-85). While chronic myeloid leukemia has been mentioned in clinical reports (86,87), the only previous cohort investigation in which this leukemia type was noted was the first cohort study by Yin et al. in China (6).

Lymphopoietic malignancies (including chronic lymphocytic leukemia, acute lymphoblastic leukemia, malignant lymphoma, and multiple myeloma) have only infrequently been directly associated with benzene exposure. More commonly, reports indirectly suggest a possible link. For example, two case-control investigations imply that benzene may be related to increased risk of chronic lymphocytic leukemia (10,78), a neoplasm observed in excess in cohort and nested case-control studies of rubber industry workers (43,51,54,56) and long-term petroleum industry workers (88-90). Hodgkin's disease has been observed in a few cohorts of rubber industry workers (43,47,58). Reports of benzene-related acute lymphoblastic leukemia have been limited to occasional case descriptions (73), while speculation (9,85), but few analytic investigations, has linked benzene with multiple myeloma (7,8,85) or non-Hodgkin's lymphoma (5,91-93). Explanations for the diversity of HLD within the present study include additional workplace and possibly residential exposure to other solvents and chemicals as well as differences in genetic or other susceptibility factors between populations. Population-based cancer registration data have shown that Asians are characterized by low incidence of chronic B-cell malignancies, including chronic lymphocytic leukemia, multiple myeloma, and subtypes of non-Hodgkin's lymphoma of B-cell origin (94). While the types of HLD among benzene-exposed workers in our survey were compared with those among a nonexposed comparison group, there were no specific features that distinguished HLD associated with benzene exposure from those among nonexposed subjects, with the possible exception of dyspoietic findings.

Aksoy (84) has noted that some case series of benzene-related HLD include a substantial proportion of individuals with preleukemia (3,76). Yet, reports of preleukemia among benzene-exposed workers only rarely include descriptions of dyspoietic features such as megaloblastoid dyserythropoiesis (17). There have also been reports of benzene-exposed workers with varying degrees of pancytopenia, among whom a few have been observed to develop aplastic anemia, then a preleukemic phase, followed by a transformation to overt acute myeloid leukemia (3,85). Honda and colleagues (95) and Cowles et al. (96) recently reported excess myelodysplastic syndromes and myelofibrosis during 1985 to 89 in conjunction with a deficit in leukemia during the same period among workers at a petroleum manufacturing and refining plant, where excesses of leukemia (as well as myelofibrosis though based on only two cases) had been observed during 1940 to 84 (97-99). Changes in diagnostic or reporting practices were postulated to explain the apparent shifts from leukemia to myelodysplastic syndromes and myelofibrosis (95). Additional deceased workers employed in this factory had myelofibrosis or preleukemia reported as contributing causes rather than underlying causes of death (the latter coded as the official cause of death) (95). Two workers from the same facility whose cause of death was specified as "neoplasm of uncertain behavior" were also found to have myeloproliferative disease listed elsewhere on death certificates (95). One other study of petroleum refinery workers has also reported excess deaths from myelofibrosis (100). Recent modifications to rules for coding death certificates, revisions in the

International Classification of Diseases classification schemes, failure to recognize these rare disorders, and other problems may have affected ascertainment of these and possibly other specific HLD types. Aksoy (84) and others (101) have pointed out that defined criteria often were not used for myelodysplastic syndromes until an internationally recognized classification scheme was published in the early 1980s (27). With one recent exception (102), population-based incidence data for the myelodysplastic syndromes have not been published, nor have these disorders been evaluated systematically in cohorts of benzene-exposed workers. In small case-control studies (12,103) and a case series (11), however, myelodysplastic syndromes have been linked with prior exposure to gasoline or diesel exhaust within the United Kingdom (12), to pesticides or chemicals within the United States (103), and to organic solvents within Italy (11). These hematopoietic disorders also develop after treatment with alkylating agents or may precede transformation to overt AML in chemotherapy-treated patients developing secondary leukemia (104).

Characteristic hematotoxic effects of benzene have been described for several decades, although specific mechanisms of action are still being elucidated. The most common reported abnormalities are peripheral pancytopenias, although anemia, leukopenia, and thrombocytopenia individually have been noted (105). As early as 1941, Goldwater (106) observed that an absolute lymphocytopenia was a relatively frequent and early manifestation of benzene hematotoxicity. Recently, we observed a decreased absolute lymphocyte count among healthy workers with moderate-to-high exposures to benzene compared with nonexposed controls in Shanghai (107). Though the finding of benzene-associated lymphocytopenia has been confirmed by some (108), others have failed to find this result (109,110). However, administration of benzene to rats, mice, and rabbits has been shown to produce a dose-dependent decrease in the number of lymphocytes, which may precede the drop in levels of other blood cells (111). Similarly, lymphocytes are extremely sensitive to ionizing radiation, another known leukemogen (112). Unfortunately, few workers within the present study underwent systematic evaluation prior to onset of symptoms associated with HLD. Also, no patient with AML had been previously diagnosed with aplastic anemia, nor did any of those diagnosed with myelodysplastic syndromes subsequently develop acute myeloid leukemia. It should be noted, however, that several patients died of complications related to myelodysplastic syndromes.

As we pointed out earlier (22), we observed considerable overlap in hematologic features present within several AMLs within our survey and those described for leukemias secondary to alkylating agents or radiotherapy (104). These findings included dysmyelopoietic changes (113,114) and the common occurrence of anemia, thrombocytopenia, and increased bone marrow cellularity. While some of these features have been observed in previous descriptions of benzene-related AML, we were the first to report dyspoiesis among benzene workers with a variety of HLD (22). We also observed basophilia among several patients with acute myeloid leukemia, although this finding has not been considered to be characteristic of chronic benzene toxicity (84,108). Treatment-related leukemias are distinct clinicopathologic entities based on morphologic and cytogenetic abnormalities (104,115). Although cytogenetic studies were not performed as part of the routine diagnostic evaluation of HLD cases arising among Chinese benzene-exposed workers, morphologic and hematologic similarities between our cases and treatment-related AMLs suggest possible similarities in pathogenesis, perhaps involving damage to marrow stem cells and/or extra-medullary mediators of carcinogenesis. Similarly, a recent clinicopathologic description of AML following exposure to organic solvents revealed comparable types of abnormalities (116).

The major limitation of our study is the historical nature inherent within retrospective cohort investigations. Particularly for workers within early years of the study period, incomplete characterization of HLD diagnoses at initial presentation was common. Ideally, work-up of patients with newly diagnosed HLD should include immunohistochemical stains on histopathologic specimens in addition to cytogenetic, immunophenotypic, and other studies. Currently, we are initiating extended follow-up of this cohort, and efforts are being made to implement up-to-date evaluation of all HLD.

Nevertheless, our study of benzene-exposed workers is one of the first occupational investigations in which HLD outcomes for a large proportion (close to 90%) of cases have been validated through standardized review of medical records or diagnostic pathology-related data. As routine clinicopathologic characterization of individual patients and classification schemes for all categories of

HLD have become increasingly sophisticated, it is hoped that future epidemiologic investigations of benzene workers will incorporate the approach for outcome assessment that we have described. In the extended follow-up of this cohort, we will continue to utilize all available clinical, laboratory hematologic, and pathologic data as well as cytogenetic and biochemical markers to characterize HLD outcomes. Workers diagnosed with aplastic and myelodysplastic syndromes will also continue to be followed after diagnosis for evolution of these conditions to acute myeloid leukemia. We are also considering a prospective evaluation of workers diagnosed with benzene poisoning by means of various biochemical and molecular markers that might be associated with the subsequent development of HLD. It is hoped that these studies might eventually lead to identification of patients who are particularly susceptible to benzene toxicity and carcinogenesis, and, conversely, description of molecular/biochemical profiles that correlate with resistance to these end points. These facets of our investigations are designed to provide further clarification of underlying molecular mechanisms of leukemogenesis and development of HLD, with possible implications for other hematopoietic carcinogens such as ionizing radiation and chemotherapeutic agents.

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