Is Histological Subtype a Marker for Environmental Exposures in Acute Myelogenous Leukemia?[1]

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Abstract

The association between occupational and other environmental exposures was evaluated in 60 acute myelogenous leukemia cases and controls. Odds ratios and 95% confidence intervals for prior cytotoxic therapy and benzene exposure, adjusted for age, sex, and race by logistic regression, were 3.7 (0.7, 19.9) and 2.6 (0.4, 15.2), respectively. No other work-related associations, including employment in electrical occupations, were present. Other associations were suggestive but may have been due to biases in control selection or small numbers of subjects. The risks for prior cytotoxic therapy (odds ratio = 10.2) and benzene exposure (odds ratio = 11.4) were concentrated in 13 patients with French-American-British M4 leukemia; no environmental exposures were associated with French-American-British subtypes M1 and M2. These findings support the concept that French-American-British histological subtypes of AML may have different etiologies.

Introduction

The causes of AML[3] remain largely unknown. The best documented risk factors for AML (previous cytotoxic therapy and occupational exposure to ionizing radiation or benzene) probably account for only a small fraction of all cases. The lack of success in identifying risk factors may be due, in part, to the possibility that subtypes of leukemia may have differing etiologies, a concept emphasized by Kessler and Lillienfeld in 1969 (1) and in subsequent reviews (2, 3). Although these authors emphasized clinical (acute versus chronic) and broad histological (granulocytic versus lymphocytic) subtypes, subsequent clinicopathological and cytogenetic studies have shown great heterogeneity within AML alone (4–6). Several recent studies have reported associations for prior cytotoxic and occupational exposures in comparisons across cytogenetically defined subtypes of AML (7–10), lending further support to the notion that etiology may differ across subtypes of disease. The current study was originally designed in 1981 to examine several known or suspected risk factors for AML. The data were recently reanalyzed to determine whether occupations with possible electromagnetic exposure were more common in cases; as part of that reanalysis, two FAB histological subtypes (4) were also examined.

Materials and Methods

Patients. Newly diagnosed, pathologically confirmed cases were ascertained between May 1, 1982, and March 1, 1983, from hospitals in the Texas Medical Center, including Methodist ($n = 7$), St. Luke's ($n = 1$), Ben Taub ($n = 1$), and the Veteran's Administration Medical Center ($n = 2$) hospitals, as well as the M. D. Anderson Cancer Center ($n = 49$). Eligibility criteria were a patient-age of at least 18 years and U.S. residency. Because FAB subtype was not a major focus at the time the study was conceived, the pathology review was mainly intended to confirm the diagnosis. However, 44 patients had been assigned FAB diagnoses: M1 ($n = 8$); M2 ($n = 13$); M3 ($n = 2$); M4 ($n = 13$); M5 ($n = 6$); or M6 ($n = 2$); the remainder were acute undifferentiated leukemia ($n = 1$) or AML, not otherwise specified ($n = 15$).

Controls. Controls, located from admissions printouts, were individually matched to each case by age (±5 years), sex, race (white, nonwhite), and hospital. Eligibility criteria were the same as for cases but also included (a) lack of evidence of a hematological abnormality and (b) admitting diagnosis for a condition other than cancer. Because M. D. Anderson predominantly serves cancer patients, controls were selected from Methodist Hospital. Most ($n = 30$) comparison subjects had been hospitalized for coronary or pulmonary problems; however, other diagnoses included diabetes ($n = 7$), gastrointestinal ($n = 8$) or endocrine disorders ($n = 6$), and other miscellaneous conditions ($n = 9$). Informed consent, using procedures and documents approved by institutional review boards at each institution, was obtained from each subject prior to participation in this study.

Data Collection Procedures. Study participants were contacted through their attending physicians. Each consenting subject was interviewed by one of the first two authors using a questionnaire modified from other stud-

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[3] The abbreviations used are: AML, acute myelogenous leukemia; OR, odds ratio; FAB, French-American-British; AMML, acute myelomonocytic leukemia; NOS, not otherwise specified.

ies (11, 12). The interviewers were not blinded to the status of the patient. The interview was used to determine demographic background; residential history; use of alcohol, tobacco, and coffee; occupational or avocational exposure to chemicals, ionizing radiation, and animals; occupational history; brief medical history; and family history of cancer/leukemia.

Occupation was coded using the Dictionary for Occupational Titles (13). Prior to coding any data, two algorithms for determining exposed occupations were developed. The first corresponded more or less to blue versus white collar and was based on general occupational categories at the two-digit level of the Dictionary for Occupational Titles system; the second was based on specific occupations thought by the authors to involve chemical exposures. A Dictionary for Occupational Titles code algorithm proposed previously (14) for possible exposure to electromagnetic radiation was also used.

Data Analysis. ORs and 95% confidence intervals for both matched (15) and unmatched (16) designs were calculated. Differences among groups for continuous variables were evaluated by either the Wilcoxon signed-rank test or, when the matching was broken, by the Mann-Whitney test. Confounding was evaluated by stratification and unconditional logistic regression (17) using the SPSS/PC and EPILOG statistical packages (18, 19).

Results

One AML patient was too ill to be interviewed, but otherwise there were no refusals in either group. Cases and controls were similar with respect to age (52.6 versus 52.6 years), sex (50% female), race (8% black), marital status (72% versus 70% married), education (14.0 versus 12.2 years of school), and mean number of lifetime jobs (4.1 versus 4.7 jobs). More cases were from Texas (38% versus 25%) or out of state (17% versus 15%), whereas 60% of controls and 45% of cases were from the local six-county region.

ORs were similar in both matched and unmatched analyses and, in order to maximize flexibility, matching was therefore dissolved for the analyses reported below.

Medical Exposures. Cases (Table 1) were more likely than controls to have had a previous diagnosis of cancer (OR = 5.8); no other statistically significant differences were present; the OR for prior cytotoxic therapy was 3.2 (0.5, 33.7).

Tobacco and Alcohol Consumption. Cases were more likely to have used tobacco products other than cigarettes (OR = 2.7) and to have consumed hard liquor (OR = 2.2). No differences were present for cigarette use, amount smoked per day, or cumulative dose (as measured by pack-years). When total alcohol consumption was converted to ounces consumed, no differences were present.

Occupation. No statistically significant differences were present; the ORs for benzene exposure in the longest occupation and the occupation at diagnosis were 2.1 (0.3, 23.6) and 4.2 (0.4, 211.0), respectively. Only one case reported the longest employment in an electrically exposed occupation as compared to four controls.

Other Factors. Controls were more likely than cases to use self-serve gas-stations (OR = 0.4), whereas cases reported more exposure to cats (OR = 2.2).

Stratified Analyses. When numbers permitted, the data in Table 1 were stratified by age (<45 years versus 45 or older), sex, and FAB subtype. Eight of the older cases reported a prior cancer versus none of the older controls; the OR was 1.0 for the younger stratum. The effect of prior cytotoxic therapy was limited to women (OR = 5.8) and was not present in men (OR = 1.0). The only other difference that emerged was a statistically significant increase in consumption of hard liquor in the younger patients (OR = 7.8). which was supported by a dose-response relationship with frequency of consumption (χ^2 = 4.99; P = 0.03). This pattern was not observed for beer or wine or for total ounces of alcohol consumed.

Histological Subtype. ORs for a history of prior cancer (OR = 12.9), prior cancer therapy (OR = 8.7), and exposure to benzene (OR = 8.7) during the longest occupation were statistically significant in comparisons involving FAB M4 patients (Table 2). There were no associations with the 21 FAB M1/M2 patients.

Unconditional logistic regression was used to evaluate confounding. There was little evidence of confounding in models that included prior cytotoxic therapy and benzene exposure at the longest occupation and the demographic matching variables for all patients, FAB-M1/M2 or FAB M4, shown in Table 3 (*A–C*, respectively). A model with selected variables that were elevated in the univariate analysis is shown in Table 3 (D). The OR for cytotoxic therapy was reduced (from 3.2 to 2.5), and the OR for benzene exposure during the longest occupation increased (from 2.1 to 3.3) in the full model. With the exception of farm residence as an adult (reduced from 9.1 to 6.7), the adjusted estimates in the full model were similar to the univariate ones.

Discussion

In this study, exposures to prior cytotoxic therapy and benzene were reported more often by cases than controls, as was use of other tobacco and residence on a farm as an adult. The latter two associations may reflect a bias in the selection of comparison subjects, since the catchment area for M. D. Anderson is both metropolitan Houston and all of east Texas (a mostly rural region), whereas the comparison hospital tends to serve patients from the Houston metropolitan area. This may be reflected in the greater proportion of patients from outside the local region (55% versus 40%). On the other hand, farming has been associated with leukemia in several studies (20), although AML has not been specifically mentioned.

Another potential source of bias in this study, besides referral patterns, is the fact that the interviewers were not blinded. Over 80% of the time, cases and controls were interviewed by the same individual, and attempts were made to restrict the study to well-defined, objective outcomes. It is also reassuring that previously known risk factors were identified in this study; however, the possibility of an unconscious bias cannot be excluded.

The proportion of AML cases secondary to prior cytotoxic therapy in this series may be higher than in

Table 1 Relative odds for environmental exposures in 60 leukemia cases and controls

	Number of exposed			95% confidence interval
	Cases (n = 60)	Controls (n = 60)	Odds ratio	
Prior medical conditions				
Shingles	6	3	2.1	(0.4, 13.6)
Hepatitis, any	3	4	0.7	(0.1.4.6)
Infectious mononucleosis	3	1	2.0	(0.1, 122.01
Cancer (any)[a]	10	7	5.8	(1.1, 56.2)
Cytotoxic cancer therapy	6	7	3.2	(0.5, 33.7)
Leukemia in relatives	3	2	1.0	(0.1. 14.2)
Tobacco or alcohol use, ever				
Cigarettes	34	41	0.6	(0.3, 1.4)
Other tobacco	14	6	2.7	(0.9, 9.4)
Beer	28	22	1.5	(0.7, 3.4)
Wine	18	16	1.2	(0.5, 2.8)
Hard liquor	30	19	2.2	(1.0, 4.9)
Occupation at diagnosis				
Benzene exposure	4	1	4.2	(0.4, 211.0)
Pesticide exposure	2	2	1.0	(0.1, 14.2)
Dyes, glues, etc.[b]	1	5	0.2	(0.0, 1.8)
Ionizing radiation	1	3	0.3	(0.0, 4.2)
Electrical occupations	0	4	0.0	(0.0. 2.3)
Specific occupations'	3	4	0.7	(0.1, 4.3)
General categories[d]	16	9	2.1	(0.8, 5.8)
Longest occupation				
Benzene exposure	4	2	2.1	(0.3, 23.6)
Pesticide exposure	1	2	0.5	(0.0, 9.7)
Dyes, glues, etc.[b]	3	7	0.4	(0.1, 1.9)
Ionizing radiation	1	2	0.5	(0.1. 9.7)
Electrical occupations	1	4	0.2	(0.0, 2.5)
Specific occupations'	5	4	1.3	(0.3, 6.8)
General categories"	17	14	1.3	(0.5, 3.2)
Other factors				
Farm residence < age 16	24	22	1.2	(0.5, 2.6)
Adult farm residence	8	1	9.1	(1.1, 409.4)
Self-serve gas for car	32	44	0.4	(0.2, 1.0)
Possibly exposed hobbies	6	4	1.6	(0.4, 7.9)
Exposure to cats	29	18	2.2	(1.0, 5.0)
Coffee use	45	47	0.9	(0.3, 2.3)

[a] Excludes skin cancer.
[b] Includes contact with dyes, glues, lacquers, and varnishes.
[c] Based on decision rule for specific occupations.
[d] Based on two-digit DOT codes using decision rule described in the text.

population-based series due to the fact that M. D. Anderson is a major referral center. if so, this would tend to bias the point estimate upward. However, the point estimate (OR = 3.0) for secondary AML was generally compatible with estimates derived from a relatively short follow-up of Surveillance, Epidemiology and End Results patients, which ranged from 2.5 to 4.5 (21), but the risk may be considerably higher for FAB-M4.

Although a low risk (relative risk < 2.0) for cigarette smoking and leukemia (predominantly AML) has been shown in several studies (22, 23), the current study did not permit a reasonable evaluation of this issue because (a) most of the controls had been hospitalized for smoking-related conditions and (b) statistical power to detect an association was limited. Other case-control studies have failed to document this association (24, 25), including one at M. D. Anderson that used patients with nontobacco-related cancers as controls (26).

There was no evidence for an increased risk of AML in persons employed in electrical or chemically exposed occupations (27). The wide confidence intervals around ORs for the occupational analyses reflect the low power of this study to detect any but very strong risks. Furthermore, the lack of sensitivity and misclassification that occur with the use of job titles may have diluted any occupational effect that may have been present and may account for the lack of results in larger studies (28). It is noteworthy that these data were collected prior to a concern for electrically exposed occupations in AML.

There also was no evidence of an association between AML and selected viral diseases or avocational exposure to chemicals. Although the Third National Cancer Survey suggested a possible association between AML and alcohol use (29), it was not present in these data.

A surprising and unanticipated finding was that both prior cytotoxic therapy and benzene exposure were clustered in the FAB-M4 (AMML) patients. These results may be chance associations due to the number of compari-

Table 2 Odds ratios for selected environmental exposures in FAB subtypes

	Number of exposed		Odds ratio[a]	95% confidence interval
	Patients	Controls		
FAB-M1/M2[b]	(n = 21)	(n = 60)		
Cancer (any)[c]	0	2	0.0	(0.0. 12.2)
Cancer therapy	0	2	0.0	(0.0. 12.2)
Cigarettes, ever	5	23	0.5	(0.1. 1.7)
Other tobacco, ever	6	6	3.6	(0.9. 15.3)
Alcohol use, current	12	40	0.7	(0.2, 2.1)
Benzene exposure, occupation at diagnosis	2	1	6.2	(0.4, 184.2)
Benzene exposure, longest occupation	1	2	1.5	(0.0, 22.2)
General categories, occupation at diagnosis	4	5	2.6	(0.5, 13.0)
General categories, longest occupation	6	9	2.3	(0.3, 8.6)
FAB-M4[d]	(n = 13)	(n = 60)		
Cancer (any)[c]	4	2	12.9	(1.6, 122.4)
Cancer therapy	3	2	8.7	(1.0, 88.2)
Cigarettes, ever	4	23	0.7	(0.2, 3.0)
Other tobacco, ever	3	6	2.7	(0.5, 15.2)
Alcohol use. current	11	40	2.8	(0.5, 19.9)
Benzene exposure, occupation at diagnosis	2	1	10.7	(0.7, 330.2)
Benzene exposure, longest occupation	3	2	8.7	(1.0, 88.2)
General categories, occupation at diagnosis	1	5	0.9	(0.0, 9.6)
General categories, longest occupation	3	9	1.7	(0.3, 8.8)

[a] Matching was broken and comparisons are for each subtype *versus* all controls. Numbers of patients with each subtype are in parentheses.
[b] Acute myeloblastic leukemia with (M2) and without (M1) maturation.
[c] Excludes skin cancer.
[d] Acute myelomonocytic leukemia (M4).

Table 3 Odds ratios for selected risk factors using unconditional logistic regression

	Odds ratio	95% confidence intervals
A. Known AML risk factors, all patients[a]		
Prior cancer therapy	3.7	(0.7, 19.9)
Benzene exposure, longest occupation	2.6	(0.4, 15.2)
B. Known AML risk factors, FAB-M1/M2 patients[b]		
Prior cancer therapy	No exposed cases	
Benzene exposure, longest occupation	1.5	(0.1, 17.6)
C. Known AML risk factors, FAB-M4 patients[c]		
Prior cancer therapy	10.2	(1.4, 74.6)
Benzene exposure, longest occupation	11.4	(1.6, 83.8)
D. Selected variables with elevated ORs in the univariate analysis, all patients[c]		
Prior cancer therapy	2.5	(0.4, 15.6)
Benzene exposure, longest occupation	3.3	(0.5, 22.3)
Other tobacco	3.4	(0.9, 12.7)
Farm residence as an adult	6.7	(0.7, 65.0)
Exposure to cats	2.0	(0.9, 4.6)
General categories, occupation at diagnosis	2.7	(0.9. 8.2)
Liquor	2.2	(0.9, 5.4)

[a] Model included age as a continuous variable, sex (male = 1), prior cytotoxic therapy (yes = 1), and benzene exposure at longest occupation (yes = 1).
[b] Same model as in A, except there were no cases of persons with prior cytotoxic exposure.
[c] Model was the same as A, with each exposure coded as a zero-one variable.

sons made in this study, but it has been noted that AMML predominates in therapy-related AML (30). On the other hand, a review of the data from the Fourth Workshop on Chromosomes and Leukemia (31) indicates that the proportions of FAB-M4 patients in de novo (22%) versus therapy-related AML (20%) were similar.

Reviews of AML and benzene exposure have not assessed histological subtype (32). The proportions of FAB-M4 in exposed and unexposed cases were similar (11% versus 17%) in Aksoy's series (33), and erythroleukemia (FAB-M6) was excessive. Other reports of benzene-exposed cases do not cite myelomonocytic or monocytic leukemia as excessive (34–36). It is interesting to note that Fanconi's anemia patients almost exclusively develop AMML (37). A cluster of AMML in Turkish children, frequently accompanied by chloroma of the eye, was reported in 1971; no cause was determined, in spite of intense study (38, 39).

The results of this study must be interpreted in light of the relatively small number of cases and the problem of an appropriate comparison group for M. D. Anderson patients. The extent to which the catchment areas for M. D. Anderson and the Methodist Hospital overlap is not known; however, it is unclear whether using other cancer patients from M. D. Anderson would improve matters substantially, because referral patterns vary by site and severity of disease. Thus it is difficult to state any definitive conclusions, but some leads for future epidemiological studies of AML have been suggested. This study also

reinforces the importance of histological and cytogenetic subclassification, noted in several reviews (6, 40–42), for future etiological studies of these diseases.

Appendix: listing of Exposed Cases and Controls

A. Cytotoxic Therapy for a Prior Disease

Cases

1. Breast cancer—diagnosed 3/75, treated with radiation and chemotherapy (5-fluorouracil, Adriamycin, cytoxan, methotrexate); AML diagnosed 11/82 (M4).
2. Ovarian cancer—diagnosed in 1978, treated with chemotherapy (alkeran) for 1 year; AML diagnosed 11/82 (NOS).
3. Chronic lymphocytic leukemia—diagnosed in 1973, no treatment; AML diagnosed 8/82 (M4).
4. Endometrial cancer—diagnosed 1975 and treated surgically; AML diagnosed 7/82 (M5).
5. Hodgkin's disease—diagnosed 10/78, treated with chemotherapy (cytoxan, nitrogen mustard, oncovin, procarbazine) and radiation through 2/80; complete remission until AML diagnosed in 3/82 (M4).
6. Poorly differentiated lymphoma—diagnosed 1976, treated with chemotherapy (cytoxan, mustard, oncovin, procarbazine, Adriamycin, bleomycin, VP-16 (etoposide), methyl-Gag, ifosfamide, methotrexate); AML diagnosed 1/83 (M4).
7. Ovarian cancer—diagnosed 1/81, treated with chemotherapy (cisplatin, hexamethylmelamine, Adriamycin, cytoxan); AML diagnosed 6/82 (NOS).
8. Breast cancer—diagnosed 9/72, treated with chemotherapy (5-fluorouracil, Adriamycin, cytoxan, methotrexate, cyclophosphamide, velban, thiotepa) and radiation; AML diagnosed 9/82 (NOS).
9. Chronic lymphocytic leukemia—diagnosed in 1973, no therapy; treated 6 months with i.v. methotrexate for psoriasis in 1967; diagnosed with AML in 9/82 (NOS).
10. Prostate cancer—diagnosed in 1955, treated surgically; diagnosed with AML in 8/82 (NOS).

Controls

1. Thyroid cancer—thyroidectomy in 1972 and ^{131}I therapy in 1978; interviewed in 4/83.
2. Pituitary adenoma—diagnosed in 1970, treated with external brain radiation of unknown dose; interviewed in 4/83.

B. Benzene-exposed Occupations

Cases

1. Railroad freight car repairman (20 years)—used benzene and other solvents while spray-painting cars in poorly ventilated area (M4).
2. Quality control laboratory technician at a refinery (20 years)—benzene was among a variety of solvents used in the laboratory (M2).
3. Research associate in biochemistry (11 years)—trained in organic chemistry, used several solvents, including benzene, at work; concurrent exposures to a variety of mutagens in molecular genetics research (M4).
4. Pipefitter apprentice (1 year)—worked at a petrochemical company; was intermittently exposed, with heavy exposure during cleaning operations in storage tanks (M4).

Controls

1. Instrumentation and guidance engineer (20 years but retired at time of interview)—used benzene to clean instruments.
2. House painter (14 years)—used oil-based paints in new house construction; also spray-painting.

C. Electrical Occupations (Assessed by JobTitle Alone)

Cases

1. Electrician (20 years) and electric train operator in a coal mine for 4 years prior to diagnosis—same as AS above (M4).

Controls

1. Instrumentation engineer at an oil company (16 years).
2. Instrumentation and guidance engineer (20 years)—same as B5 above.
3. Computer sales (25 years).
4. Electronicstechnician (6 years).

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