

Prescription drug use and risk of acute myeloid leukemia by French-American-British subtype: Results from a Los Angeles County case-control study

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Chemotherapy is a well-established risk factor for acute myeloid leukemia (AML) but little is known about other prescription drugs and AML risk. We report data from a population-based Los Angeles County study in which 299 matched case-control pairs had complete data on prescription drug use and 88% of cases were subtyped according to the French-American-British (FAB) criteria. Cases were diagnosed between 1987 and 1994. Prescription nonsteroidal anti-inflammatory drug (NSAID) use for at least 4 weeks in the 2 to 10 years before diagnosis was associated with decreased risk (odds ratio = 0.5, 95% confidence interval = 0.3, 1.0; $p = 0.04$) with dose-response most evident for FAB subtype M2 (OR = 0.6, CI: 0.1, 2.9 for duration ≤ 6 months; OR = 0.2, CI: 0.0, 1.6 for > 6 months). For subtype M4, ORs increased with increasing duration of benzodiazepine use in the 2 to 10 years before diagnosis (OR = 1.5, CI: 0.3, 9.0 for ≤ 6 months vs. OR = 5.0, CI: 0.6, 42.8 for > 6 months). These results suggest that prescription drugs other than chemotherapy may have FAB subtype-specific effects on AML risk.

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Key words: acute myeloid leukemia; FAB type; chemotherapy; benzodiazepines; nonsteroidal anti-inflammatory drugs

Established risk factors for acute myeloid leukemia (AML) explain a small percentage of cases and include genetic diseases, such as Down syndrome¹ and Fanconi anemia,² occupational benzene exposure,^{3–6} cancer chemotherapy⁷ and ionizing radiation in heavily exposed populations.^{8–10} The association between benzene and AML as well as other bone marrow disorders such as leukopenia, aplastic anemia and myelodysplasia suggests that drugs known to cause blood dyscrasias may also be causally linked to AML. In general, nonchemotherapeutic medications have been addressed infrequently in published studies of AML risk factors.

We report results from a population-based case-control study of AML in Los Angeles County in which subjects were asked about use of prescription drugs in the 10 years before diagnosis, with emphasis on drugs known to cause blood dyscrasias. Because almost 90% of cases were FAB subtyped, we attempted to determine whether drug-related AML risk may be subtype specific.

Materials and methods

Methods for our study have been detailed previously.¹¹ Briefly, cases of adult-onset AML (ICDO, 2nd ed., codes 9861, 9864, 9866, 9867 and 9891)¹² diagnosed in Los Angeles County from January 1987 through June 1994 were identified by the University of Southern California Cancer Surveillance Program, a population-based SEER cancer registry. Proxy respondents were used for cases who were deceased or who could not otherwise be interviewed and were required to be the surviving spouse or another adult who had lived in the case's household for any 6 of the 10 years preceding the case's diagnosis.

For each case, an individually matched control was sought from among residents of the neighborhood where the patient lived at the time of diagnosis. A sequence of houses on specified street blocks surrounding the case residence, beginning with a random starting point on the street block adjacent to the case residence, was

defined, and the goal was to interview the first resident in the sequence who matched the case on birthyear (± 5 years), ethnicity (African American or white, including Hispanic) and sex. If no one was home at the time of the visit, a questionnaire was left and a follow-up visit was made several days later. If the first match refused to participate or could not be contacted, the next matched control in the sequence was located and so on. Forty housing units per case were visited and 3 return visits made before failure to secure a matched control was conceded. Controls were assigned the diagnosis dates of their matched cases as their reference dates.

Interviews were conducted from 1987 to 1997. The median time between case diagnosis and interview was 7 months for direct respondents and 14 months for proxies. The study proposal and method of obtaining informed consent from study participants were approved by the USC Institutional Review Board.

Information on prescription drug use in the 10 years before diagnosis was elicited in 2 different sections of the questionnaire to minimize reporting error. In the first section, respondents were asked about specific medications (Table I) that are known causes of or possible putative factors in development of blood disorders including neutropenia, agranulocytosis, thrombocytopenia, aplastic anemia and AML according to either one of two standard reference texts.^{13,14} If respondents answered that they had taken one of these drugs, they were further asked the month and year they started and stopped taking the drug, whether or not there were time gaps in their usage of the drug (and, if so, the actual duration of use) and the condition for which they were taking the drug. In a second section, respondents were asked about their history of specific medical conditions: arthritis, gout, tendonitis, spondylitis, thrombophlebitis, cholera, typhoid fever, urinary tract infection, acne, chronic infection, tumors or cancer, hyperthyroidism, allergies, hypertension and diabetes. If respondents answered that they had had one of these conditions or any other major medical condition, they were further asked if a doctor had prescribed any medications for that condition and, if so, the name of the drug, the months and years the drug was first and last taken and the duration of total use. Respondents were not required to know the chemical names of drugs; brand and generic names were converted to

Abbreviations: AML, acute myeloid leukemia; CI, 95% confidence interval; FAB, French-American-British; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SES, socioeconomic status.

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TABLE I—MEDICATIONS QUERIED¹ FOR ANALYSIS OF PRESCRIPTION DRUG USE AND RISK OF AML, LOS ANGELES COUNTY CASE-CONTROL STUDY OF AML, 1987–1994

Antibiotics for ≥2 weeks	Mephenytoin
Azolid	Mephobarbital
Bactrim	Mesantoin
Barazole	Methimazole
Bromides	Oxalid
Butazolidin	Phenobarbital
Cancer chemotherapy	Phenylbutazone/oxyphenbutazone
Chloramphenicol	Propylthiouracil (PTU)
Chloromycetin	Scopolamine
Cocaine	Sepra
Diazepam	Sterazolidin
Dilantin	Sulfa drugs
Drugs for blood dyscrasias	Tandearil
Drugs for seizures	Trimethoprim-sulfa-methoxazole (TMP- \dot{S} MX)
Drugs to suppress the thyroid gland	Topazole
Gantrisin	Urisoxin
Indocin	Urizole
Indomethacin	Valium
Magnesium sulfate	Velmatrol
Marijuana	

¹Based on known causes of or possible putative factors in development of blood disorders.

chemical names during the analysis phase. Data on specific doses taken and frequency of use were not collected.

Using the now-standard FAB classification scheme, cases were FAB-subtyped by review of pathology reports or slides by one of us, an experienced hematopathologist (P.W.N.). For cases with FAB subtype not specified on the pathology report or for whom diagnostic information was otherwise incomplete, available peripheral blood and bone marrow slides were reviewed to verify the original AML diagnosis and to establish the FAB subtype.

The primary analyses presented here report on data from “best respondents,” *i.e.*, direct respondents except for those cases for whom proxies were the only available respondents. Analyses that excluded proxies were also done when numbers of subjects were sufficient to allow meaningful results, *e.g.*, FAB-specific analyses excluding proxies were not possible due to small numbers. Chi-square tests were used to compare distributions of categorical variables. Maximum likelihood estimates of odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression conditioned on matched pairs.¹⁵

Exposure was restricted to use for at least 4 weeks in the 2 to 10 years before diagnosis. For categorical analyses of duration of exposure, 3 exposure groups were considered: 1) not exposed, 2) less than *m* exposure and 3) at least *m* exposure, where *m* was the median exposure among all exposed cases and controls. Trends were evaluated descriptively rather than by statistical testing due to small numbers. High-dose radiation exposure, smoking status and chemotherapy were evaluated as potential confounders. For this purpose, chemotherapy was defined as cancer chemotherapy in the 2 to 10 years before AML diagnosis, high-dose radiation exposure was defined as radiation treatment for cancer any time before AML diagnosis or at least 5 diagnostic imaging procedures that delivered an estimated dose of 100 mrad or more to the bone marrow in the 2 to 10 years before AML diagnosis¹⁶ and smoking was defined as ever having smoked cigarettes any time before AML diagnosis. Assessment of effect modification from these variables was not possible due to sparse data.

A 0.05 significance level was used for all statistical tests. Case-control pairs in which at least 1 member had missing data were excluded from analyses involving the corresponding variables. Analyses were done using SAS statistical software, Version 8.00 (SAS Institute, Inc., Cary, NC).

TABLE II—DISTRIBUTION OF STUDY SUBJECTS BY SEX, AGE, ETHNICITY, SOCIOECONOMIC STATUS AND FAB SUBTYPE., LOS ANGELES COUNTY STUDY OF AML, 1987–1994

Characteristic	Number of cases (%)	Number of controls (%)
Sex		
Male	234 (57)	234 (57)
Female	178 (43)	178 (43)
Age (years)		
25–39	54 (14)	54 (14)
40–49	66 (17)	73 (18)
50–59	108 (27)	101 (25)
60–75	169 (43)	169 (43)
Ethnicity		
Non-Hispanic white	306 (74)	334 (81)
Hispanic	65 (16)	45 (11)
African American	37 (9)	31 (8)
Other	4 (1)	2 (0.5)
Socioeconomic status ¹		
Low	217 (53)	193 (47)
High	195 (47)	218 (53)
Unknown	0 (0)	1 (0.002)
FAB Subtype		
M0	7 (2) ²	
M1	70 (19)	
M2	116 (32)	
M3	34 (9)	
M4 ³	89 (25)	
M4E ³	4 (1)	
M5 ⁴	17 (5)	
M5a ⁴	3 (1)	
M5b ⁴	6 (2)	
Other ⁵	15 (4)	
Unknown	51	

¹Based on education and occupation according to the Hollingshead Social Index⁴⁰; low = > 51, High = ≤51.–²Percentages = % of cases with non-missing FAB.–³M4/M4E combined for analysis purposes.–⁴M5/M5a/M5b combined for analysis purposes.–⁵Includes RAEB (4) and RAEB-T (11).

Results

Of 725 eligible cases, 188 (26%) were deceased or too ill for interview and had no available proxy, 31 (4%) were not contacted as advised by their physicians and 20 (3%) were lost to follow-up. Therefore, 67% (486/725) of eligible cases were invited to participate. Seventy-four (13%) invited cases refused to participate, resulting in participation rates of 57% (412/725) of originally identified cases or 85% (412/486) of invited cases. Interviews with proxy respondents were conducted for 201 (49%) deceased cases. The first known matched control was interviewed for 248 (60%) cases, the second known matched control for 86 (21%) cases, the third known matched control for 44 (11%) cases and the fourth or greater (range = 4th to 9th) known matched control for the remaining 34 (8%) cases. Fifteen interviewed cases with diagnoses of refractory anemia with excess blasts (RAEB) or RAEB-T (RAEB in transformation), also known as myelodysplastic syndrome, were excluded. These patients often transform to overt AML but can have myelodysplasia for varying lengths of time prior to evolution to AML.

Distributions for demographic variables and FAB subtype are shown in Table II. Cases were somewhat more likely to be Hispanic and to have lower socioeconomic status (SES). Fifty-one cases (12%) had unknown FAB subtypes; of these, 42 (82%) had inadequate pathology materials available, 2 (4%) had inadequate information in medical records to obtain pathology materials, 6 (12%) would not consent to release of pathology materials and 1 (2%) was unclassifiable after pathology review. Two hundred ninety-nine “best respondent” and 162 “proxy respondent” case-control pairs were available for analysis after exclusion of pairs in which at least 1 member had missing data, *e.g.*, unknown drug names or dates of use for all drugs analyzed for this report. Eight-eight percent (263/299) of cases had known FAB subtype.

No cases but 4 controls reported taking chloramphenicol. Three cases and 3 controls took phenylbutazone at least 2 years before diagnosis; 2 of these cases had FAB subtype M4 (the third case had unknown FAB). For drugs with relatively high prevalence of exposure (reported by at least 15 subjects), relative risks associated with taking the drug for at least 4 weeks in the 2 to 10 years before AML diagnosis are shown in Table III. Results are shown for both the "best respondent" analysis and for the analysis that excluded proxy respondents.

The only significant association in the "best respondent" analysis was a reduced OR for NSAIDs, which was unchanged with proxies excluded. The most commonly reported NSAIDs were ibuprofen (32%), naproxen (25%) and piroxicam (12%). There was weak evidence of dose-response with duration of use among all best respondents combined (OR = 0.8, CI: 0.3, 1.7 for ≤ 6 months vs. OR = 0.6, CI: 0.3, 1.6 for > 6 months). By FAB subtype, the association with use for at least 4 weeks and the dose-response relationship was most evident for M2 (Table IV); among these cases, the greatest reduction in OR appeared to be related to the 6- to 10-year period before diagnosis. Data were too sparse to evaluate dose-response or timing of use among M2 pairs with proxies excluded.

Benzodiazepine use for at least 4 weeks was associated with an elevated but nonsignificant increased OR among best respondents, but this association was not evident with proxies excluded. Ninety percent of benzodiazepine exposure among both cases and controls was from diazepam. No subjects reported exposure to both benzodiazepines and chemotherapy. There was weak evidence of increasing risk with increasing duration of use among all best respondents combined (OR = 1.3, CI: 0.5, 3.3 for ≤ 6 months vs. OR = 1.5, CI: 0.6, 3.7 for > 6 months). In FAB subtype-specific analyses, the OR for benzodiazepine use for at least 4 weeks was nonsignificantly elevated for M4 (Table IV), and risk increased with increasing duration of use among these cases. Data were too sparse to evaluate dose-response or timing of use among M4 pairs with proxies excluded. There were 3 pairs of M3 subjects in which the case but not the control used benzodiazepines; there were no M3 pairs in which the control but not the case used benzodiazepines.

The only association that strengthened with proxies excluded was a reduced OR for thiazides. However, there was no evidence of dose-response and the effect was not specific to any one FAB subgroup.

There was no evidence of confounding from high-dose radiation, smoking or cancer chemotherapy on risk estimates associated with benzodiazepines or NSAIDs.

Discussion

In studies of low-prevalence risk factors such as certain prescription drugs for a rare disease such as AML, achieving adequate statistical power for FAB subtype specific analyses requires very large populations from which to draw cases. Even drawing from a population as large as Los Angeles County (about 10 million), too few of our subjects took the drugs that were of most interest for us to provide convincing evidence of associations with specific FAB subtypes. However, we report some notable observations that may generate hypotheses for future study.

Chloramphenicol and phenylbutazone have been linked previously to AML^{14,17,18} but were reported too infrequently in our study to draw conclusions. We observed marginally increased risk for only one class of nonchemotherapeutic drug: benzodiazepines, mostly in the form of diazepam. Benzodiazepines have been prescribed extensively in the US since the 1960s for anxiety-related disorders. There are contradictory animal data regarding the possible carcinogenicity of benzodiazepines,¹⁹⁻²³ and previous human studies have not found a consistent increase in risk for any malignancy.²⁴ However, some benzodiazepines, including diazepam, are suspected aneugens and are therefore biologically plausible carcinogens.²⁵ We noted a possible dose-response relationship for

TABLE IV—ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR AML RISK AND BENZODIAZEPINE AND NSAID USE IN THE 2-10 YEARS BEFORE DIAGNOSIS FOR SPECIFIC FAB SUBTYPES, LOS ANGELES COUNTY CASE-CONTROL STUDY OF AML, 1987-1994

	Number of pairs	Number of discordant pairs	OR	CI
Benzodiazepines, M4				
Use for ≥ 4 weeks	61	8/3	2.7	0.7,10.1
Total number of months used	59			
0		—	1.0	
≤ 6		3/2	1.5	0.3,9.0
> 6		5/1	5.0	0.6,4.9
Timing of use				
2-5 yrs pre-dx	55	6/1	6.0	0.7,49.8
6-10 yrs pre-dx	57	7/2	3.5	0.7,16.8
NSAIDs, M2				
Use for ≥ 4 weeks	77	2/8	0.3	0.1,1.2
Total number of months used	75			
0		—	1.0	
≤ 6		2/4	0.6	0.1,2.9
> 6		1/4	0.2	0.0,1.6
Timing of use				
2-5 yrs pre-dx	69	2/4	0.5	0.1,2.7
6-10 yrs pre-dx	69	1/5	0.2	0.0,1.7

TABLE III—ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) ASSOCIATED WITH AML AND FREQUENTLY REPORTED DRUGS KNOWN TO CAUSE OR TO POSSIBLY BE RELATED TO BLOOD DYSCRASIAS, EXPOSURE FOR AT LEAST 4 WEEKS IN THE 2-10 YEARS BEFORE DIAGNOSIS, LOS ANGELES COUNTY CASE-CONTROL STUDY OF AML, 1987-1994

Drug	Best respondents				Proxies excluded			
	Number of pairs	Number of discordant Pairs	OR	CI	Number of pairs	Number of discordant pairs	OR	CI
ACE inhibitors ¹	270	8/11	0.7	0.3,1.8	148	7/5	1.4	0.4,4.4
Benzodiazepines	264	24/14	1.7	0.9,3.3	145	11/9	1.2	0.5,2.9
Beta blockers	270	16/14	1.1	0.6,2.3	148	9/7	1.3	0.5,3.5
Calcium blockers	263	7/10	0.7	0.3,1.8	145	5/7	0.7	0.2,2.3
H ₂ blockers ²	270	13/8	1.6	0.7,3.9	147	8/6	1.3	0.5,3.8
NSAIDs ³	265	12/24	0.5	0.3,1.0	146	7/13	0.5	0.2,1.4
Penicillin	267	0/2	—	—	146	0/1	—	—
Sulfa antibiotics	269	9/9	1.0	0.4,2.5	148	4/6	0.7	0.2,2.4
Sulfonylurea	269	5/4	1.3	0.3,4.7	146	3/3	1.0	0.2,5.0
Thiazides	270	13/21	0.6	0.3,1.2	148	6/17	0.4	0.1,0.9

¹Angiotensin converting enzyme inhibitor. ²H₂ histamine receptor antagonist. ³Nonsteroidal anti-inflammatory drug.

duration of benzodiazepine use among subjects with M4 FAB subtype.

We observed significantly reduced AML risk with use of prescription NSAIDs, and this was most evident in subjects with FAB subtype M2. Although our controls were of somewhat higher SES than our cases, NSAIDs use was actually more prevalent among low SES subjects in our study. Furthermore, the majority of both cases and controls took NSAID use for arthritis, back pain, gout or tendonitis; there were no reported prophylactic uses of prescription NSAIDs. Therefore, it seems unlikely that this finding is due to a control group that was more health conscious or had better access to healthcare than cases.

A protective effect of NSAIDs on colon, breast, stomach and esophageal cancer is well documented.²⁶ Part of this effect has been attributed to the inhibition of the cyclooxygenase-2 (COX-2) enzyme, which is overexpressed in most cancer cells. COX-2 stimulates cellular division and angiogenesis and inhibits apoptosis. Angiogenesis, the natural process of blood vessel production, is typically associated with solid tumors. However, it has been shown that angiogenesis and angiogenic factors, such as vascular endothelial growth factor (VEGF), also play a significant role in hematological malignancies.^{27–29,30–34} The inhibition of COX-2 by NSAIDs may decrease the risk of AML by reducing the formation of angiogenic factors that are necessary for tumor growth. A recent report on a cohort study of post-menopausal women indicated a significantly reduced risk of AML (and other leukemias) associated with aspirin use.³⁵ Future studies of AML and NSAIDs should consider both prescription and nonprescription use.

Many of the limitations of our study, such as small numbers, are due to the generally poor prognosis of most patients with AML. While we were able to interview 85% of cases invited to participate, only 67% of all registered cases of AML in Los Angeles County were invited because of the rapid progression of this disease; thus, our results may be biased towards longer-term survivors. Furthermore, we had to rely on a relatively large amount of data from proxy respondents, and we did not have enough index respondents to perform FAB-specific analyses that excluded proxies. Nonetheless, we performed analyses for specific FAB subtypes because few epidemiological studies have reported FAB-specific findings.

Another potential limitation in our study is the possibility that prescription drug use was related to disease status. We minimized

the potential for this by excluding exposure during the 2 years before diagnosis. With self-reported data not validated through medical records, another potential bias could arise if cases link prescription drug use to their disease development and therefore provide biased estimates of exposure. This is less likely to play a factor in FAB subtype-specific analyses. The reduced risk we observed for prescription NSAIDs, a class of medications typically used for painful conditions, suggests that our results are not due to either recall bias or cases using more medications than controls to treat early symptoms of their illness.

We relied on self-reported exposure ascertainment rather than physician or pharmacy records, and past research has shown that self-reported data on medication use can be relatively accurate.³⁶

Advances in cytogenetics and diagnostic technologies have led to an AML classification scheme proposed by the World Health Organization that is based on the original FAB scheme but also attempts to correlate morphologic, biologic, genetic and clinical features of the disease.³⁷ We did not have cytogenetic data available for our study, but future studies of AML risk from medications should aim to investigate associations not only by FAB subtype but also by cytogenetic abnormalities. The general poor prognosis of AML patients requires a large study population and a mechanism for immediate case ascertainment. The incorporation of pharmacy or medical records to supplement or confirm self-reports would improve exposure assessment. To reduce the number of comparisons and thus the likelihood of chance findings, hypotheses should focus exclusively on drugs previously associated with major forms of bone marrow toxicity. A dose-response relationship for a particular drug and a consistent link with specific FAB subtype(s) and/or cytogenetic abnormalities in various populations would strengthen the evidence for an etiological association. The established leukemogens benzene and cancer chemotherapy appear to induce leukemia through specific molecular alterations such as deletions in chromosome 5 or 7, or both.^{38,39} It is reasonable to hypothesize that if other drugs play a role in the etiology of AML, the pathogenesis may involve similar molecular mechanisms.

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