

Smoking and Risk of Acute Myeloid Leukemia: Results from a Los Angeles County Case-Control Study

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Acute myelogenous leukemia (AML) is a heterogeneous disease with distinct histologic subtypes likely to have distinct risk factors. The authors examined smoking and the risk of adult AML by French-American-British (FAB) subtype in a Los Angeles County, California, population-based case-control study of 412 cases diagnosed between 1987 and 1994 and 412 matched controls. Consistent with previous studies, smoking was not a substantial risk factor for AML overall (odds ratio (OR) = 1.2, 95% confidence interval (CI): 0.9, 1.6). However, increased risk was observed for FAB subtype M2 (OR = 2.3, 95% CI: 1.1, 4.4), particularly for subjects aged 60–75 years (OR = 3.3, 95% CI: 1.1, 10.0). For M2, significant dose-response was associated with total years smoked ($p = 0.02$), cigarettes per day ($p = 0.007$), and product filter status (filtered vs. nonfiltered; $p = 0.03$). The authors estimate that 42% (standard error = 13%) of M2 cases are attributable to smoking. There were no or weak associations between smoking and increased AML risk for other FAB subtypes. The finding by this study of an association between smoking and FAB subtype M2 confirms a previously published report and suggests that earlier findings of no or weak smoking-AML associations may have been due to lack of subtype-specific analysis. *Am J Epidemiol* 2002;155:546–53.

leukemia, myeloid; smoking

Acute myeloid leukemia (AML) is the most common of the adult-onset leukemias and is a leading cause of leukemia mortality. Established risk factors for adult AML include high-dose ionizing radiation (1), benzene (2), and some forms of chemotherapy (3), yet these factors in combination account for only a small percentage of cases. Smoking was first hypothesized as a risk factor in 1986 (4), but findings from studies examining this association were inconsistent. Some studies found no relation between smoking and AML (5–8), while others reported small elevated risks (9–14) or elevated risk confined to certain demographic subgroups (e.g., men but not women) (15, 16). A meta-analysis of case-control studies published through 1992 estimated the relative risk of AML from smoking to be 1.3 (95 percent confidence interval (CI): 1.1, 1.5) and the population attributable risk (PAR) to be 14 percent (17).

One of the most interesting recent developments regarding the AML-smoking hypothesis is the possibility that increased risk may be limited to one or more French-American-British (FAB) subtypes of the disease. Epidemiologic studies have only recently begun to consider that some risk factors may be specific to AML subtypes. The original FAB classification divided AML into seven histologic subtypes on the basis of morphologic and cytochemical criteria (18–20). More recently, 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 (21). It seems plausible that specific exposures may correlate with the acquisition of specific mutations in tumor cells, reflecting varying levels of vulnerability to particular carcinogens at different stages of white blood cell differentiation (22) and that different AML subtypes may therefore have unique risk factor profiles. The first study to consider smoking risk within FAB subtypes found that risk was limited to subtype M2, especially in persons over age 60 years (22).

We report results from a large, population-based case-control study of AML in Los Angeles County, California, in which 86 percent of all cases were FAB subtyped. We considered active use of all tobacco products as well as exposure to passive tobacco smoke. Our primary objectives were to determine overall risk of exposure to tobacco products and to assess differences in risk by FAB subtype; secondarily, we evaluated possible effect modification by age and gender.

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Abbreviations: AML, acute myelogenous leukemia; CI, confidence interval; FAB, French-American-British; OR, odds ratio; PAR, population attributable risk; SE, standard error.

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MATERIALS AND METHODS

All cases of adult-onset AML (*International Classification of Diseases for Oncology*, Second Edition, codes 9861, 9864, 9866, 9867, and 9891) (23) diagnosed in Los Angeles County from January 1987 through June 1994 who met our eligibility criteria were identified by the University of Southern California Cancer Surveillance Program, a population-based Surveillance, Epidemiology, and End Results cancer registry. During the first 5 years of the study, patients were limited to English-speaking Whites and African Americans. In 1992, these criteria were expanded to include Spanish-speaking Latino patients. One of the primary hypothesized risk factors for this study was medical radiography in the 10 years before diagnosis. Because of this and because bone marrow distribution shifts from the limbs to the trunk region around age 20 years, eligible cases had to be at least age 30 years and no older than age 69 at first AML diagnosis. We imposed the upper age limit for several reasons: 1) AML is more rapidly fatal in the elderly; 2) it is more difficult to find matched controls for elderly cases; and 3) recall is more difficult for some elderly respondents. Since exposure to radiography is dependent on access to Western medical care, we also required that study participants had resided in the United States during the previous 15 years.

After consent of the attending physician was obtained, cases who were living and were well enough to be interviewed were contacted and asked to participate in a 45-minute, in-person, highly structured interview conducted by one of two trained interviewers. Proxy respondents were used for cases who were deceased or who could otherwise not 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. Additionally, proxies were interviewed for a subset of cases who were directly interviewed to allow comparisons within pairs of direct and proxy respondents. For each case, a neighborhood control was matched by birth year (± 5 years), race (Black or White), and gender according to a previously established protocol (24). Controls were also required to speak English (or Spanish if matched to a Spanish-speaking case) and to have resided in the United States during the previous 15 years. The study proposal and method of obtaining informed consent from study participants were approved by the University of Southern California Institutional Review Board.

Interviews were conducted from 1987 to 1997. Although it was not practical to blind the interviewer as to disease status, interviewing methods were standardized, and matched pairs were interviewed by the same person and in the same manner. Interviews were also conducted with proxy respondents for most controls. In interviews, subjects were asked whether they had ever smoked cigarettes (filtered or nonfiltered), pipes, or cigars or whether they had ever used smokeless tobacco products (chewing tobacco or snuff); those who had used any of these products were further asked about the quantity and frequency of exposure and start and stop dates and whether there were any gaps in usage. Subjects were also asked whether they had ever lived with anyone who smoked; if they had, they were asked the rela-

tion of the smoker to them, the quantity and frequency of exposure, and the time periods during which they were exposed.

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

Logistic regression conditioned on matched pairs was used to compute maximum likelihood estimates of odds ratios, slopes (for trend tests in dose-response analyses), and 95 percent confidence intervals (25). Likelihood ratio tests were used to test interactions between exposure and FAB subtypes. Chi-square or Fisher's exact tests were used to test associations between exposure variables in smokers. Exposure was primarily defined as cigarettes, pipes, or cigars. Previous research suggests that pipe and cigar smokers who were ex-cigarette smokers have significantly higher levels of serum thiocyanate than do pipe and cigar smokers who never smoked cigarettes (26); on the basis of this finding, we conservatively defined pipe and cigar smokers who did not smoke cigarettes as unexposed. A secondary series of analyses restricted exposure to cigarettes only. Differences in results between the primary and secondary analyses are discussed. Total number of years smoked, average number of cigarettes per day, total number of pack-years, and filter status of products smoked (always smoked filtered vs. ever smoked nonfiltered) were used as measures of dose-response. Pipefuls and cigars were counted as two and one-half cigarettes in calculating pack-years and average cigarettes per day (26), and both were considered "nonfiltered" in analysis of filter status. Dose response was evaluated by comparing odds ratios across categories of exposure, with unexposed subjects as the reference group. For all dose variables except filter status, exposure category cutpoints were loosely based on tertiles of exposure among all exposed subjects combined (i.e., tertile values were rounded to a multiple of five). Tests of dose-response significance were performed by using the original form of continuous dose variables. In addition, odds ratios were compared by categories of time since exposure, defined by years before diagnosis; an odds ratio was computed for each time interval, with exposure defined as having smoked during that interval. Time since exposure was based on the start and stop dates reported for each tobacco product, but it was an approximation since we did not collect specific dates of gaps in usage. For age-specific analysis, the age of matched pairs was determined by the age of the control. PARs and standard errors (SEs) were calculated for dichotomous exposure (27).

A reliability analysis to compare proxy responses with those of directly interviewed respondents ("index" respondents) was performed by using the subset of subjects for whom proxy respondents were interviewed. Agreement was measured by the kappa statistic for dichotomous exposures. For continuous exposures, differences between proxy and index responses were calculated and compared with zero by

using *t* tests and signed rank tests. Differences were calculated as the index response subtracted from the proxy response; thus, negative differences represented proxy underestimation.

Subjects with missing values were excluded from relevant analyses. All statistical tests were two-sided with a 0.05 significance level.

RESULTS

Of 726 eligible cases, 188 (26 percent) were deceased or too ill to interview and had no available proxy; 31 (4 percent) were not contacted, as advised by their physicians; 21 (3 percent) were lost to follow-up; and 74 (10 percent) refused to participate. Therefore, the study included 57 percent (412 of 726) of the originally identified cases or 85 percent (412 of 487) of the cases invited to participate. Interviews with proxy respondents were conducted for 201 deceased cases (49 percent of the total included cases). Because the study included a proxy reliability component, proxy interviews were conducted for 102 cases and 174 controls who also were directly interviewed. The primary analysis presented here reports on data from "best respondents," that is, direct respondents except for those cases for whom proxies were the only available respondents.

Distributions for demographic variables and FAB subtypes are shown in table 1. Forty-three percent of both cases and controls were aged 60 years or older. The study population was predominantly White, and cases were somewhat more likely than controls to be Hispanic. Cases also had a slightly lower socioeconomic status than did controls. Fifteen cases had myelodysplastic syndrome that was diagnosed as either refractory anemia with excess blasts or refractory anemia with excess blasts in transformation. Although these patients often transform to overt AML, they were excluded from analyses.

Sixty-five percent of the cases and 61 percent of the controls had ever smoked (table 2). Pack-years contributed by filtered cigarettes, nonfiltered cigarettes, pipes, and cigars were 55, 33, 5, and 3 percent, respectively, of all pack-years combined. The odds ratio for ever having smoked was 1.2 (95 percent CI: 0.9, 1.6), with a PAR of 11 percent (SE, 9 percent). In FAB subtype-specific analyses, the highest and only significantly increased odds ratio was for M2 (odds ratio (OR) = 2.3, 95 percent CI: 1.1, 4.4); odds ratios were also increased for M4 and M5. M3 had a significantly decreased odds ratio for ever having smoked. In comparisons of specific FAB subtypes with all other cases with known subtype (M1 cases vs. all other cases, M2 cases vs. all other cases, etc.), M2 cases were significantly more likely to have smoked ($p = 0.02$). The PARs for smoking were 42 percent (SE, 13 percent) for M2, 34 percent (SE, 15 percent) for M4, and 34 percent (SE, 30 percent) for M5.

In an analysis by age, the odds ratio for smoking was somewhat increased among subjects aged 60–75 years and older for all FAB subtypes combined. For M2, the odds ratio was significantly increased for older, but not for younger, subjects (OR = 1.8, 95 percent CI: 0.7, 4.2 for ages 25–59; OR = 3.3, 95 percent CI: 1.1, 10.0 for ages 60–75 years).

TABLE 1. Distribution of study subjects by gender, age, ethnicity, socioeconomic status, and FAB* subtype in a case-control study of AML*, Los Angeles County, California, 1987–1994

Characteristic	No. of cases		No. of controls	
	No.	%	No.	%
Gender				
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
Race/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†				
Low	217	53	193	47
High	195	47	218	53
Unknown	0	0	1	0.002
FAB subtype‡				
M1	70	20		
M2	116	33		
M3	34	10		
M4§	89	25		
M4E§	4	1		
M5¶	17	5		
M5a¶	3	1		
M5b¶	6	2		
Other#	15	4		
Unknown	58			

* FAB, French-American-British; AML, acute myelogenous leukemia.

† Based on education and occupation according to the Hollingshead Social Index (51): low, ≥ 51 ; high, ≤ 51 .

‡ Percentages = % of cases with nonmissing FAB.

§ M4 and M4E were combined for analysis purposes.

¶ M5, M5a, and M5b were combined for analysis purposes.

Includes refractory anemia with excess blasts ($n = 4$) and refractory anemia with excess blasts in transformation ($n = 11$).

For M4, the odds ratio was somewhat higher in younger compared with older subjects (OR = 2.1, 95 percent CI: 0.9, 4.9). For M5, an increased odds ratio was observed only in older subjects (OR = 4.0, 95 percent CI: 0.4, 35.8).

Effects of time since tobacco exposure and dose for all M2 subjects combined and for older M2 subjects are shown in table 3. For all M2 subjects combined, risk increased with increasing time since exposure, and dose-response was significant for total years smoked (p for trend = 0.02), cigarettes smoked per day (p for trend = 0.007), and filter status of products smoked (p for trend = 0.03). Odds ratios were significantly increased for M2 subjects who smoked for longer than 20 years (OR = 2.5, 95 percent CI: 1.1, 5.8 for 21–35

TABLE 2. Odds ratios and 95% confidence intervals for risk of AML* by smoking status stratified by age at diagnosis and FAB* subtype in a case-control study of AML, Los Angeles County, California, 1987–1994

FAB subtype	All ages				Ages 25–59 years			Ages 60–75 years		
	No. of cases	No. of controls	OR*	95% CI*	No. of cases	OR	95%CI	No. of cases	OR	95% CI
All types†										
Never smoked	137	150	1.0		91	1.0		46	1.0	
Ever smoked	250	232	1.2	0.9, 1.6	130	1.0	0.7, 1.5	120	1.6	1.0, 2.6
M1										
Never smoked	32	20	1.0		21	1.0		12	1.0	
Ever smoked	37	45	0.5	0.3, 1.1	15	0.4	0.1, 1.2	22	0.7	0.3, 1.8
M2										
Never smoked	30	45	1.0		20	1.0		10	1.0	
Ever smoked	81	68	2.3	1.1, 4.4	47	1.8	0.7, 4.2	34	3.3	1.1, 10.0
M3										
Never smoked	23	8	1.0		21	1.0		2	1.0	
Ever smoked	11	24	0.1	0.0, 0.6	5	0.1	0.0, 0.6	6	0.5	0.0, 5.5
M4/M4E										
Never smoked	25	37	1.0		16	1.0		9	1.0	
Ever smoked	65	53	1.9	1.0, 3.9	39	2.1	0.9, 4.9	26	1.5	0.4, 5.3
M5/M5a/M5b										
Never smoked	6	9	1.0		4	1.0		2	1.0	
Ever smoked	20	16	1.8	0.5, 6.0	9	1.0	0.2, 5.0	11	4.0	0.4, 35.8

* AML, acute myelogenous leukemia; FAB, French-American-British; OR, odds ratio; CI, confidence interval.

† Includes subjects with missing FABs.

years; OR = 2.9, 95 percent CI: 1.1, 7.2 for >35 years), those who smoked more than a pack per day (OR = 3.4, 95 percent CI: 1.4, 8.2), and those who smoked nonfiltered products (OR = 2.3, 95 percent CI: 1.1, 4.9). In older M2 subjects, the exposure time period associated with the highest odds ratio was more than 25 years before diagnosis (OR = 3.0, 95 percent CI: 1.0, 9.3), and dose-response was most evident for total years smoked (OR = 3.5, 95 percent CI: 0.9, 12.9 for >35 years) and filter status (OR = 2.9, 95 percent CI: 0.6, 14.2 for filtered products and OR = 3.3, 95 percent CI: 1.1, 10.6 for nonfiltered products; p for trend = 0.04). However, in this older subgroup, there was no dose-response associated with filter status when analysis was restricted to cigarettes only. Odds ratios were generally higher for older M2 subjects than for all M2 subjects combined.

For all FAB subtypes combined, time since exposure had no effect, and there was weak evidence of dose-response. For M4 and M5, significantly increased risk was not associated with exposure during any particular time interval before diagnosis. For M4, dose-response was evident for filter status of the product smoked (OR = 1.2, 95 percent CI: 0.5, 2.8 for filtered products and OR = 2.9, 95 percent CI: 1.2, 7.1 for nonfiltered products; p = 0.03). For M5, there was no clear-cut evidence of dose-response. By age, dose-response was more evident in younger than in older M4 subjects; age-stratified dose-response analyses for M5 were limited by sparse data.

Separation of timing and dose effects was not possible because of significant relations among the exposure vari-

ables. Among all smokers combined, average cigarettes per day was positively correlated with total years smoked (p < 0.0001; figure 1). There was a trend of increasing likelihood of smoking nonfiltered products (at some time) with increasing number of cigarettes per day: 72 percent of the subjects who smoked more than a pack per day used nonfiltered products compared with 49 percent of those who smoked 10 or fewer cigarettes per day (p = 0.0002). Similarly, 88 percent of those who smoked for more than 35 years used nonfiltered products at some time compared with 43 percent of those who smoked for 20 years or less (p < 0.0001). Those who smoked for more than 25 years before diagnosis were more likely to have greater total years of exposure, to have smoked more cigarettes per day, and to have smoked nonfiltered products (p < 0.0001 for all tests).

There was very little difference in smoking-related risk by gender for all subjects combined or for any specific FAB subtype (data not shown). Too few subjects (seven cases and 12 controls) reported use of smokeless products to perform meaningful analyses. There was no evidence of increased risk from exposure to passive smoke, either as a child or as an adult, for all subjects combined or for any specific FAB subtype (data not shown).

Agreement between proxy and index respondents on ever having smoked was very high (kappa = 0.91, 95 percent CI: 0.85, 0.96); there were no instances of proxy-, but not index-, reported exposure. Proxies tended to underestimate total years smoked (mean difference = -1.2, 6.9 standard deviation) and overestimate cigarettes smoked per day (mean dif-

TABLE 3. Odds ratios and 95% confidence intervals for timing of exposure and dose response associated with smoking and risk of AML† among subjects with FAB‡ subtype M2 in a case-control study of AML, Los Angeles County, California, 1987–1994

Exposure	All M2 subjects				M2 subjects aged 60–75 years‡		
	No. of cases	No. of controls	OR†	95% CI†	No. of cases	OR	95% CI
Timing (years before diagnosis)							
Within 2							
Did not smoke	71	80	1.0		31	1.0	
Smoked	40	32	1.6	0.8, 3.1	13	2.3	0.6, 9.0
2–10							
Did not smoke	53	67	1.0		23	1.0	
Smoked	58	45	2.0	1.1, 3.7	21	2.6	0.9, 7.3
11–25							
Did not smoke	38	54	1.0		18	1.0	
Smoked	73	59	2.3	1.2, 4.6	26	2.0	0.7, 5.9
>25							
Did not smoke	42	57	1.0		11	1.0	
Smoked	69	56	2.5	1.2, 5.2	33	3.0	1.0, 9.3
Total no. of years smoked							
Nonsmoker	30	45	1.0		10	1.0	
1–20	18	21	1.4	0.6, 3.4	6	1.9	0.4, 7.9
21–35	31	24	2.5	1.1, 5.8	7	3.3	0.6, 18.8
>35	28	19	2.9	1.1, 7.2*	18	3.5	0.9, 12.9
Average no. of cigarettes/day§							
Nonsmoker	30	45	1.0		10	1.0	
1–10	17	15	1.9	0.8, 4.8	6	3.6	0.7, 17.8
11–20	29	32	1.7	0.8, 4.0	10	1.1	0.2, 5.6
>20	33	20	3.4	1.4, 8.2**	17	4.4	1.1, 17.6
Total no. of pack-years§							
Nonsmoker	30	45	1.0		10	1.0	
1–15	19	20	1.5	0.7, 3.6	4	1.8	0.4, 9.2
16–40	28	20	2.4	1.0, 5.4	14	3.5	0.9, 14.0
>40	29	24	2.3	0.9, 5.6	12	2.1	0.5, 8.1
Type of product smoked							
Nonsmoker	30	45	1.0		10	1.0	
Filtered only	27	23	2.1	1.0, 4.8	5	2.9	0.6, 14.2
Nonfiltered	53	44	2.3	1.1, 4.9*	29	3.3	1.1, 10.6*

* *p* for trend < 0.05.** *p* for trend < 0.01.

† AML, acute myelogenous leukemia; FAB, French-American-British; OR, odds ratio; CI, confidence interval.

‡ Based on the age of the control for each matched pair.

§ 1 cigar or pipeful = 2.5 cigarettes among smokers who also ever smoked cigarettes regularly.

ference = 0.6, 12.2 standard deviation). However, neither differed significantly from zero. Although FAB-specific analyses restricted to case-control pairs for which the case was directly interviewed were limited by sparse numbers, we performed all analyses using “direct interview” M2 pairs only (all ages combined) and observed results very similar to those reported above for the best respondent M2 pairs.

DISCUSSION

For FAB subtype M2, we observed results strikingly similar to those of Sandler et al. (22), who reported increased risk of M2 from smoking, with a more pronounced effect in older than in younger subjects. In the paper by Sandler et al.,

the odds ratios for ever having smoked were 1.7 (95 percent CI: 1.0, 2.9) and 3.5 (95 percent CI: 1.5, 8.0) for younger and older M2 subjects, respectively; we assume that these odds ratios were for cigarette exposure only (i.e., excluding pipes and cigars). In our study, the analogous odds ratios were 1.8 (95 percent CI: 0.7, 4.2) and 3.3 (95 percent CI: 1.1, 9.7). The only measure of dose-response reported by Sandler et al. was pack-years, and they found a more than fivefold increase in risk for older subjects in the highest exposure category (>40 pack-years). We found a clearer dose-response relation by using total years smoked rather than pack-years and observed a 3.5-fold increase in risk for older M2 subjects with the highest exposure (>35 years) to cigarettes, pipes, and/or cigars. We also found that older M2 smokers who

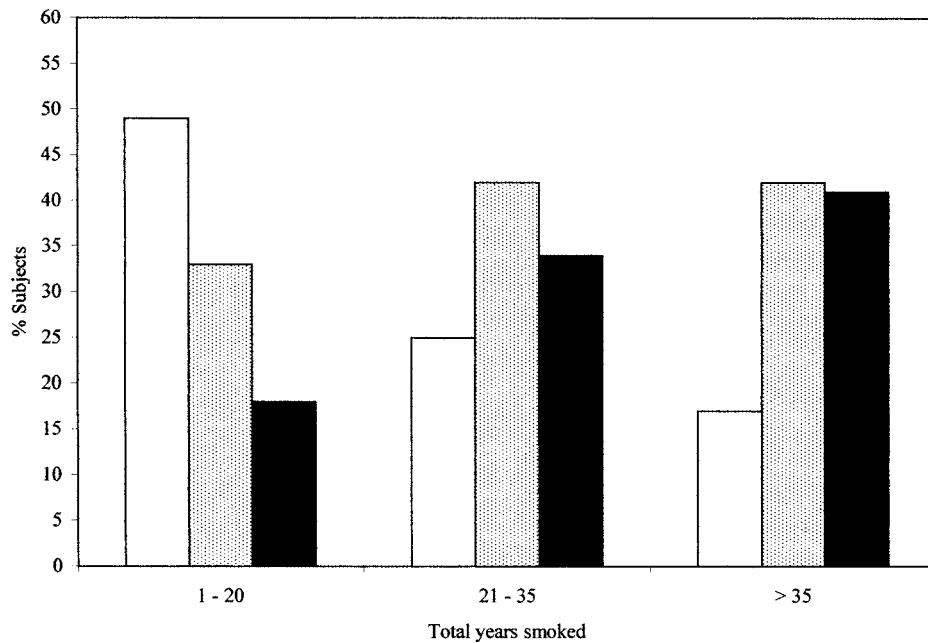


FIGURE 1. Relation between total years smoked and average cigarettes per day among smokers in a case-control study of AML in Los Angeles County, California, 1987–1994. In the calculation of cigarettes per day, one pipeful or one cigar was counted as 2.5 cigarettes among smokers who also had ever smoked cigarettes regularly. □ = 1–10 cigarettes per day; ▨ = 11–20 cigarettes per day; ■ = >20 cigarettes per day.

used filtered products exclusively had higher risk than did nonsmokers (OR = 2.9, 95 percent CI: 0.6, 14.2) but not as high as smokers who used nonfiltered products, including pipes and cigars (OR = 3.3, 95 percent CI: 1.1, 10.6). This is consistent with studies of other smoking-related cancers that have looked at the effects of filtered versus nonfiltered tobacco products (28–30). Further, an association between smoking nonfiltered products and chromosomal aberrations in AML cases has been reported previously (31). However, it must be noted that in our study smokers of nonfiltered products were more likely to be “heavy” smokers, i.e., to have smoked for a greater number of years and to have smoked more cigarettes per day. Similarly, we observed that risk of M2 increased with increasing time since exposure; however, subjects with distant exposure were also more likely to be heavy smokers and to have smoked nonfiltered products. We observed increased risk for FAB subtypes M4 and M5 combined, but to a lesser degree than for M2. Risk of ever having smoked was significantly decreased for M3 subjects. M3 is associated with Hispanic race (32), and in our study, Hispanics were significantly less likely to smoke than were other races (46 percent of Hispanics vs. 65 percent of all other races combined).

There are limitations that must be considered in the interpretation of our findings. We had relatively small sample sizes for some FAB subtypes, particularly for age-specific analyses, despite a very large population base (Los Angeles County) from which to draw cases. We are currently conducting a follow-up case-control study that will include an additional 5 years of case ascertainment. Combining data from both studies will substantially improve the stability of our risk

estimates and allow us to confirm or refute results from the first study. Another limitation is report inaccuracy or, more problematic, recall bias that is inherent in all retrospective studies. Although it is possible that cases may link smoking to their disease development and therefore provide biased estimates of exposure, this is less likely to play a factor in FAB subtype-specific analyses. Finally, we had to rely on a relatively large amount of data from proxy respondents because of the rapid fatality of patients with AML. On the basis of our proxy reliability analysis, proxy responses agreed relatively well with index responses, and results were generally unchanged when proxy cases were excluded altogether.

Although a specific mechanism has yet to be identified, smoking as a causal factor for AML seems biologically plausible. Tobacco smoke contains two of the three known occupational or environmental leukemogens, benzene and ionizing radiation. It has been shown that the concentration of benzene is significantly higher in the urine of smokers than in that of nonsmokers (33). One recent report estimates that as much as 58 percent of the smoking-induced mortality among AML cases could be due to benzene in cigarette smoke (34). Ionizing radiation is present in tobacco smoke in the forms of lead-210 and polonium-210, which primarily originate from high-phosphate fertilizers used in tobacco farming (35). Lead-210 decays to bismuth-210, which in turn decays to polonium-210; polonium-210 emits high-energy alpha particles and gamma radiation during its decay process and is readily taken up by bone tissue (36). It has been estimated that smokers are exposed to up to 0.2 Sv/year from polonium-210 radiation (37), which is about eight times higher exposure than that received from natural background

radiation (38). Compared with gamma radiation, which is similar to X-radiation used medically, alpha radiation is relatively low in its ability to penetrate tissue. For this reason, it is thought that inhalation of alpha particles is likely to increase the risk of respiratory cancers but not of cancers that develop at distant sites such as the active bone marrow; this is supported by uranium miner studies, which have shown no increased incidence of leukemia in these cohorts (39, 40). However, this view has been contested (41–44). Animal studies suggest that polonium-210 interacts with benzene in tobacco smoke to promote carcinogenesis (45).

Certain cytogenetic characteristics in AML patients have been shown to have both diagnostic and prognostic value. Less clear is the role played by environmental agents in the development of chromosome abnormalities, although results from studies of cytotoxic therapy exposure suggest that specific agents induce specific abnormalities (46). Unlike lymphomas and most types of solid cancers, as many as 55 percent of AML cases have only a single abnormality (47), and most abnormalities found in AML cases are leukemia specific (48). Certain chromosome abnormalities have been observed more frequently in smokers than in nonsmokers: those involving chromosome 8 (31, 46), loss of chromosomes 7 and Y, and trisomy 13 (22). Although these specific aberrations are not strongly linked to FAB subtype M2, translocation of chromosomes 8 and 21 is associated with M2 (48) and is frequently seen in cases with Y chromosome loss (49).

Possible reasons for increased risk of AML from smoking among older subjects include decreased ability to repair DNA damage, higher exposure levels due to smoking habits that differ from those of younger subjects, and long latency for the smoking effect on AML (22). In our study, older subjects smoked more cigarettes per day and were more likely to smoke nonfiltered products. Our analysis of time since exposure suggests that distant exposure results in higher AML risk than exposure that occurs closer to AML diagnosis.

Our findings of substantially increased risk for subtype M2 associated with smoking, which confirms a previously published report (22), and somewhat increased risk for subtypes M4 and M5 suggest the strong possibility that other environmental agents might induce specific FAB morphologic subtypes. Classification by specific cytogenetic abnormalities is also likely to be important. The most recent revision of the World Health Organization's *International Classification of Diseases for Oncology* (the Third Edition) attempts to incorporate FAB subtyping and cytogenetic abnormalities into its morphologic classification scheme for acute leukemias (50). Clearly, additional epidemiologic studies of AML should avoid categorization of this disease as a single entity.

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