



Risk of adult acute and chronic myeloid leukemia with cigarette smoking and cessation

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ABSTRACT

Background: Cigarette smoking is an established risk factor for adult myeloid leukemia, particularly acute myeloid leukemia (AML), but less is known about the nature of this association and effects of smoking cessation on risk.

Methods: In a large population-based case-control study of myeloid leukemia that included 414 AML and 185 chronic myeloid leukemia (CML) cases and 692 controls ages 20–79 years, we evaluated risk associated with cigarette smoking and smoking cessation using unconditional logistic regression methods and cubic spline modeling.

Results: AML and CML risk increased with increasing cigarette smoking intensity in men and women. A monotonic decrease in AML risk was observed with increasing time since quitting, whereas for CML, the risk reduction was more gradual. For both AML and CML, among long-term quitters (≥ 30 years), risk was comparable to non-smokers.

Conclusions: Our study confirms the increased risk of myeloid leukemia with cigarette smoking and provides encouraging evidence of risk attenuation following cessation.

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1. Introduction

Myeloid leukemia is a heterogeneous group of acute and chronic hematopoietic malignancies of the myeloid lineage; the two most common subgroups are AML and CML [1]. In the United States, approximately 13,800 and 5400 individuals are diagnosed annually with AML and CML, respectively, while 10,200 and 600 will die [2]. With the dismal survival for AML, prevention is a priority. Benzene, radiation and prior chemotherapy exposure are well-established risk factors for AML, although collectively they account for a small number of cases; obesity may also contribute to risk [3–5]. Importantly, cigarette smoking may account for as much as 17% of myeloid leukemias [6]. Nevertheless, while cigarette smoking has been considered an established risk factor for myeloid

leukemia for over a decade [7], the exact nature of this association in unclear (e.g. few studies have evaluated sex and leukemia classification differences, and even fewer have considered potential benefits of smoking cessation on risk). Using data from a large population-based case-control study of AML and CML, we examined effect modifiers, explored the shape and nature of the dose-response relationship, and for AML, evaluated associations by cytogenetic subtypes, for both cigarette smoking and smoking cessation.

2. Materials and methods

2.1. Subjects

Recruitment and enrollment have been described [8,9]. Incident cases were identified through the rapid case ascertainment system of the Minnesota Cancer Surveillance System from June 2005 to November 2009. Eligible cases were Minnesota residents, able to understand English or Spanish, and diagnosed between ages 20 and 79 years with AML, CML, chronic myelomonocytic leukemia (CMML), or other myeloid leukemias. A total of 907/1178

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pathologically confirmed cases were referred (230 died soon after diagnosis, 41 were not referred due to physician/patient refusal). Of the 907 referred, 833 were contacted, and 673 enrolled (83% cooperation rate; 57% overall participation rate) [10]. Non-participation reasons included participant refusal (16%) and ineligibility (3%). Cases were classified by disease subclassification; AML was further subclassified by 2001 World Health Organization (WHO) and French–American–British (FAB) systems [11,12]. All classifications involved central pathology report review including cytochemical and flow cytometric immunophenotypic data; microscopic glass slide review was performed as necessary. Cytogenetic results were also centrally reviewed and integrated with the pathologic diagnoses, per 2001 WHO guidelines. Final classification resulted in 420 AML (3 additional cases enrolled but died before questionnaire completion), 186 CML, and 64 CMML/other myeloid leukemia.

Controls were identified using the Minnesota State Driver's License/identification card list, which includes almost all adults less than 85 years of age living in Minnesota. Controls must have (a) been alive at contact time; (b) resided in Minnesota; (c) been between 20 and 79 years; (d) understood English or Spanish; and (e) had no prior myeloid leukemia diagnosis. Controls were frequency matched to cases on age in deciles. Of 1200 potentially eligible controls identified, 1020 were successfully contacted, and 701 (77% cooperation rate; 64% overall response rate) agreed to enroll [10]. Reasons for non-participation included refusal (21%) and ineligibility (10%).

2.2. Data collection

Tobacco and alcohol use was obtained from the self-administered questionnaire, as were demographics, physical activity, medication use, medical and reproductive history, family cancer history, occupational history, and history of various job and home chemical exposures. To account for disease-related changes in smoking status, cigarette smoking history was assessed up to two years prior to questionnaire completion for participants who smoked cigarettes for at least six months during their lifetime. For comparison with previous studies and evaluation of effect modification, participant smoking was categorized as “never versus ever smokers” and “never, former, or current smokers”. Additional variables combined smoking intensity (usual cigarettes/day prior to quitting or 2 years prior to questionnaire completion) and status or duration: never smokers, former smoker <1 pack/day, former smoker ≥1 pack/day, current smoker <1 pack/day, and current smoker ≥1 pack/day. For duration, a similar variable was created using ≤20 and >20 years in place of former and current smokers. Pack-years (packs/day times years smoked) were also calculated to explore dose response. Smoking cessation included current smokers, former smokers who quit smoking <15 years ago, 15–29 years ago, and ≥30 years ago, and never smokers; dose-response among ever smokers was evaluated using years since quitting as a continuous variable. If a former smoker had not quit for at least a year, 0.5 years was assigned. All current smokers were assigned ‘0’. While other tobacco products (e.g., pipe, cigar, snuff, and chewing tobacco) were queried, frequency and intensity were not assessed; they were not considered further.

2.3. Statistical analysis

All analyses were performed using SAS 9.2 statistical software (Cary, NC). Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CIs) for smoking main effects. Demographic variables (Table 1) including sex, race, income, education level, body mass index (BMI), alcohol consumption, occupational benzene exposure, occupational/therapeutic

Table 1

Selected characteristics of adult myeloid leukemia cases and population-based controls.

	Controls (N = 692)	AML cases (N = 414)	CML cases (N = 185)
	N (%)	N (%)	N (%)
Age			
20–29	45 (7)	26 (6)	12 (6)
30–39	52 (8)	32 (8)	15 (8)
40–49	101 (15)	63 (15)	33 (18)
50–59	155 (22)	88 (21)	48 (26)
60–69	201 (29)	126 (30)	47 (25)
70–79	138 (20)	79 (19)	30 (16)
Sex			
Female	354 (51)	170 (41)	79 (43)
Male	338 (49)	244 (59)	106 (57)
Race/ethnicity			
Non-Hispanic White	663 (96)	388 (94)	171 (92)
Other	29 (4)	26 (6)	14 (8)
Income ^a			
Up to \$40,000	253 (37)	148 (37)	79 (43)
\$40,000–\$80,000	275 (40)	162 (40)	64 (35)
Over \$80,000	154 (23)	95 (23)	39 (21)
Marital status			
Married/cohabitating	507 (73)	311 (75)	121 (65)
Other	185 (27)	103 (25)	64 (35)
Education			
≤High school graduate	229 (33)	118 (29)	66 (36)
Some post HS	236 (34)	159 (38)	55 (40)
College graduate	227 (33)	137 (33)	64 (36)
BMI ^b			
Normal/underweight	224 (33)	94 (23)	41 (22)
Overweight	238 (35)	146 (35)	59 (32)
Obese	227 (33)	173 (42)	84 (46)
Current alcohol use ^c			
Heavy	20 (3)	19 (5)	7 (4)
Moderate	183 (27)	76 (19)	38 (21)
Light	200 (29)	132 (33)	52 (29)
Abstainer	276 (41)	179 (44)	85 (47)
Benzene/solvent exposure			
No	642 (93)	339 (82)	163 (88)
Yes	47 (7)	73 (18)	22 (12)
Radiation exposure			
No	671 (97)	386 (93)	174 (95)
Yes	18 (3)	27 (7)	10 (5)
Chemotherapy exposure			
No	679 (99)	383 (93)	177 (96)
Yes	10 (1)	30 (7)	7 (4)

^a Income may include retirement income.

^b BMI based on weight 2 years prior to questionnaire completion.

^c Current alcohol use was defined as follows: abstainer (<1 drink/month); light (<3 drinks/week); moderate (<3 drinks/day); heavy (3+ drinks/day).

radiation exposure, and chemotherapy were evaluated and retained as confounders if they altered the effect estimate by ≥10%; the frequency matching variable (age) was included as a continuous variable. Analyses were repeated stratified by sex, age (<60 vs. ≥60 years), leukemia subtype, and AML WHO subtypes; effect modification was evaluated by Wald test. WHO subtypes were evaluated using categories defined by Vardiman et al. [12], with further delineation by differentiation pattern for the “not otherwise categorized” subtypes (Table 2).

Dose-response between leukemia and pack-years smoked and time since quitting was evaluated using restricted cubic splines. The number and position of knots were determined by minimizing the Akaike's information criterion (AIC), allowing for comparison of multiple models while penalizing complexity. To prevent estimation bias in the right tail, we excluded individuals in the top 5th percentile of pack-years. The best fitting spline regression models for pack-years smoked included knots at the 40th, 60th, and 80th percentiles, corresponding to 13.75, 23, and 40 pack-years for AML, and 20th, 40th, and 60th percentiles, corresponding to 4, 12, and 22.2 pack-years for CML. For time since quitting, final

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