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Original Contribution

Diet, Lifestyle, and Acute Myeloid Leukemia in the NIH–AARP Cohort

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The relation between diet, lifestyle, and acute myeloid leukemia was assessed in a US cohort of 491,163 persons from the NIH–AARP Diet and Health Study (1995–2003). A total of 338 incident cases of acute myeloid leukemia were ascertained. Multivariate Cox models were utilized to estimate hazard ratios and 95% confidence intervals. Compared with those for never smokers, hazard ratios were 1.29 (95% confidence interval: 0.95, 1.75), 1.79 (95% confidence interval: 1.32, 2.42), 2.42 (95% confidence interval: 1.63, 3.57), and 2.29 (85% confidence interval: 1.38, 3.79) for former smokers who smoked $\leq$1 or $>$1 pack/day and for current smokers who smoked $\leq$1 or $>$1 pack/day, respectively. Higher meat intake was associated with an increased risk of acute myeloid leukemia (hazard ratio = 1.45, 95% confidence interval: 1.02, 2.07 for the fifth vs. first quintile; *P* for trend = 0.06); however, there were no clear effects of meat-cooking method or doneness level. Individuals who did not drink coffee appeared to have a higher risk of acute myeloid leukemia than those who drank various quantities of coffee. Neither fruit nor vegetable intake was associated with acute myeloid leukemia. This large prospective study identified smoking and meat intake as risk factors for acute myeloid leukemia.

diet; leukemia, myeloid, acute; meat; smoking

Abbreviations: AML, acute myeloid leukemia; NIH, National Institutes of Health.

Acute myeloid leukemia (AML) is a group of clonal hematopoietic stem cell diseases (1). As the most frequent type of leukemia, it accounts for approximately 30% of all leukemia in adults in the United States (2). The median age at AML diagnosis is 67 years, and 55% of incident cases in the United States are 65 years of age or older (3). The incidence of AML is higher in males than in females and higher in whites than in other racial groups (4).

Although multiple risk factors have been linked to the development of AML, including age, gender, previous chemotherapy, other hematologic disorders, genetic abnormalities, cigarette smoking, and exposures to radiation and benzene (5–7), these known risk factors account for only a small number of observed cases (8). Few epidemiologic studies have explored the relation between dietary factors and the incidence of adult AML (9–11). In a prospective cohort study of women in Iowa, none of the dietary factors assessed appeared to have an impact on the risk of AML, but the findings could be falsely negative because of the small number of cases ($n = 48$, all female) (9). In a hospital-based case-control study that included 111 cases (56 males and 55 females) from New York, AML risk was negatively associated with intake of milk and positively associated with consumption of beef, wine, and beer among women (10). A hospital-based case-control study in China found no association between green tea consumption and the risk of AML ($n = 72$, gender breakdown not provided) (11). In addition, a population-based case-control study in Canada found no impact of intake of fruits and vegetables on development of AML (167 males and 140 females) (12). Because of the limited number of existing studies and the relatively small number of AML cases included in most studies, the relation between dietary factors and AML remains obscure.

We assessed the possible etiologic role of dietary factors in AML in the National Institutes of Health (NIH)–AARP (formerly the American Association of Retired Persons) Diet and Health Study. The factors evaluated included food groups, meat-cooking methods, and doneness levels, as well

Table 1. Selected Demographic and Lifestyle Factors and AML (338 Cases Among 491,163 Individuals Who Completed the Baseline Questionnaire) in the NIH–AARP Diet and Health Study, United States, 1995–2003

	No. of Cases	No. of Person-Years	Age-adjusted Model			Multivariate Model[a]		
			HR	95% CI	*P* for Trend	HR	95% CI	*P* for Trend
Gender								
Male	242	1,984,127	1.00			1.00		
Female	96	1,388,580	0.57	0.45, 0.72		0.63	0.49, 0.81	
Age (years, continuous)			1.09	1.06, 1.11	<0.01	1.09	1.06, 1.11	<0.01
Race/ethnicity								
Non-Hispanic white	318	3,073,119	1.00			1.00		
Other	20	299,587	0.67	0.42, 1.05		0.72	0.46, 1.14	
Education, years					0.83			0.90
<12	29	197,038	1.00			1.00		
12–15	169	1,775,457	0.73	0.49, 1.09		0.79	0.53, 1.17	
≥16	131	1,303,003	0.80	0.53, 1.20		0.85	0.57, 1.28	
Unknown	9	97,209	0.67	0.32, 1.41		0.71	0.33, 1.49	
Smoking status					<0.01			<0.01
Never	80	1,212,541	1.00			1.00		
Quit, ≤1 pack/day	88	941,487	1.38	1.02, 1.86		1.29	0.95, 1.75	
Quit, >1 pack/day	97	705,795	2.05	1.53, 2.76		1.79	1.32, 2.42	
Current, ≤1 pack/day	37	252,314	2.40	1.62, 3.54		2.42	1.63, 3.57	
Current, >1 pack/day	19	133,601	2.49	1.51, 4.12		2.29	1.38, 3.79	
Unknown	17	126,969	1.96	1.16, 3.32		1.84	1.09, 3.11	
Body mass index, kg/m^2					0.07			0.09
<25	107	1,169,195	1.00			1.00		
25–<30	145	1,401,515	1.14	0.89, 1.46		1.04	0.81, 1.34	
≥30	80	721,918	1.30	0.97, 1.73		1.24	0.92, 1.66	
Unknown	6	80,078	0.79	0.35, 1.79		0.79	0.35, 1.80	
Vigorous physical activity					0.52			0.52
<3 times/month	97	1,048,639	1.00			1.00		
1–2 times/week	72	728,466	1.07	0.79, 1.46		1.07	0.79, 1.46	
≥3 times/week	165	1,559,693	1.08	0.84, 1.39		1.09	0.84, 1.41	
Unknown	4	35,909	1.07	0.39, 2.90		1.09	0.40, 2.99	
Coffee consumption, g/day					0.59			0.24
Never	44	362,103	1.00			1.00		
>0 and <500	104	1,109,124	0.72	0.50, 1.02		0.67	0.47, 0.96	
≥500 and <1,000	130	1,375,173	0.73	0.52, 1.03		0.62	0.44, 0.88	
≥1,000	60	526,307	0.95	0.65, 14.1		0.62	0.44, 0.88	
Tea consumption, g/day					0.86			0.95
Never	44	343,836	1.00			1.00		
>0 and <68	108	1,006,047	0.87	0.61, 1.23		0.89	0.63, 1.27	
≥68 and <332	84	1,024,842	0.67	0.46, 0.96		0.71	0.49, 1.02	
≥332	102	997,981	0.83	0.58, 1.19		0.87	0.61, 1.24	
Alcohol consumption, drinks/day					0.22			0.71
Never	77	817,478	1.00			1.00		
>0 and <1	171	1,791,622	1.05	0.80, 1.38		1.03	0.79, 1.35	
≥1 and <3	62	515,437	1.28	0.92, 1.79		1.15	0.82, 1.61	
≥3	28	248,170	1.23	0.80, 1.90		0.90	0.57, 1.42	

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; HR, hazard ratio; NIH, National Institutes of Health.

[a] Adjusted for age at baseline (continuous), gender, smoking status (never, former smoker of ≤1 pack/day, current smoker of ≤1 pack/day, and unknown), and total energy intake (continuous).

Table 2. Diet and AML (338 Cases Among 491,163 Individuals Who Completed the Baseline Questionnaire) in the NIH–AARP Diet and Health Study, United States, 1995–2003

Selected Foods[a]	Quintile of Food Intake					*P* for Trend
	1	2	3	4	5	
Fruits (servings/1,000 kcal)[b]	≤0.7	>0.7–≤1.2	>1.2–≤1.7	>1.7–≤2.5	>2.5	
No. of cases	64	72	72	63	67	
No. of person-years	670,606	672,119	675,352	676,494	678,135	
Age-adjusted model						
HR	1.00	1.08	1.06	0.92	0.98	0.65
95% CI		0.77, 1.51	0.75, 1.49	0.65, 1.32	0.69, 1.40	
Multivariate model[c]						
HR	1.00	1.20	1.25	1.15	1.29	0.28
95% CI		0.85, 1.69	0.89, 1.78	0.80, 1.66	0.90, 1.87	
Vegetables (servings/1,000 kcal)[b]	≤1.0	>1.0–≤1.4	>1.4–≤1.8	>1.8–≤2.5	>2.5	
No. of cases	71	80	66	60	61	
No. of person-years	667,453	673,184	674,606	677,901	679,561	
Age-adjusted model						
HR	1.00	1.10	0.90	0.82	0.84	0.13
95% CI		0.80, 1.51	0.64, 1.26	0.57, 1.16	0.59, 1.19	
Multivariate model[c]						
HR	1.00	1.16	0.98	0.92	1.00	0.63
95% CI		0.84, 1.60	0.70, 1.38	0.65, 1.31	0.70, 1.43	
Total meat (g/1,000 kcal)	≤41.5	>41.5–≤57.0	>57.0–≤71.9	>71.9–≤91.8	>91.8	
No. of cases	53	66	77	68	74	
No. of person-years	674,886	673,888	674,408	674,422	675,103	
Age-adjusted model						
HR	1.00	1.27	1.51	1.38	1.57	0.02
95% CI		0.88, 1.82	1.07, 2.15	0.96, 1.97	1.10, 2.23	
Multivariate model[c]						
HR	1.00	1.22	1.43	1.29	1.45	0.06
95% CI		0.85, 1.75	1.01, 2.03	0.90, 1.85	1.02, 2.07	

Table continues

as meat-derived heterocyclic amines and benzo[*a*]pyrene, a marker of polycyclic aromatic hydrocarbons. Because cigarette smoking has been linked to AML (6) and is known to be associated with patterns of dietary intake (13, 14), we also evaluated the possible influence of smoking and other lifestyle factors, including physical activity and consumption of coffee, tea, and alcohol.

MATERIALS AND METHODS

Study population

The NIH–AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute. Details of the study have been described previously (15). Briefly, a 16-page questionnaire eliciting information on demographic characteristics, dietary intake, and health-related behaviors was sent in 1995–1996 to 3.5 million members of AARP in 6 states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia; and Detroit, Michigan) with existing population-based cancer registries. Of 617,119 questionnaires returned (17.6% of the 3.5 million mailed), a total of 567,169 subjects satisfactorily completed the questionnaire and consented to participate in the study. Dietary habits varied considerably (dietary fat intake ranged from 20% to 40% in the first and fifth quintiles), which satisfied an original aim of the study, namely, to secure wide variation in dietary habits. Six months after the baseline questionnaire was sent, a second questionnaire that included a detailed meat-cooking module was sent to baseline respondents, and 332,913 subjects completed this second questionnaire. Respondents were primarily non-Hispanic white, highly educated, and on average 62 years of age. No data are available on the characteristics of nonrespondents to the mailing.

Table 2. Continued

Selected Foods[a]	Quintile of Food Intake					*P* for Trend
	1	2	3	4	5	
Red meat (g/1,000 kcal)[d]	≤16.1	>16.1–≤26.4	>26.4–≤36.7	>36.7–≤50.6	>50.6	
No. of cases	67	56	67	65	83	
No. of person-years	680,500	678,034	673,601	671,321	669,250	
Age-adjusted model						
HR	1.00	0.84	1.04	1.04	1.39	0.01
95% CI		0.59, 1.21	0.74, 1.46	0.73, 1.46	1.00, 1.92	
Multivariate model[c]						
HR	1.00	0.79	0.92	0.87	1.09	0.35
95% CI		0.56, 1.13	0.65, 1.30	0.62, 1.24	0.78, 1.52	
White meat (g/1,000 kcal)[d]	≤14.2	>14.2–≤22.7	>22.7–≤32.8	>32.8–≤48.8	>48.8	
No. of cases	68	68	72	60	70	
No. of person-years	668,454	672,174	674,557	677,176	680,345	
Age-adjusted model						
HR	1.00	1.00	1.06	0.90	1.09	0.72
95% CI		0.71, 1.40	0.76, 1.48	0.63, 1.27	0.78, 1.52	
Multivariate model[c]						
HR	1.00	1.05	1.15	1.00	1.23	0.29
95% CI		0.75, 1.47	0.82, 1.60	0.70, 1.42	0.88, 1.72	
Processed meat (g/1,000 kcal)[e]	≤3.1	>3.1–≤5.9	>5.9–≤9.6	>9.6–≤16.1	>16.1	
No. of cases	69	61	66	65	77	
No. of person-years	680,208	678,286	674,989	671,826	667,397	
Age-adjusted model						
HR	1.00	0.85	0.91	0.90	1.07	0.38
95% CI		0.60, 1.20	0.65, 1.29	0.64, 1.27	0.77, 1.49	
Multivariate model[c]						
HR	1.00	0.78	0.79	0.73	0.84	0.64
95% CI		0.55, 1.11	0.56, 1.12	0.52, 1.04	0.60, 1.18	

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; HR, hazard ratio; NIH, National Institutes of Health.

[a] Adjusted for energy by using the density method.

[b] Intakes of fruits and vegetables were mutually adjusted for in the model.

[c] Adjusted for age at baseline (continuous), gender, smoking status (never, former smoker of ≤1 pack/day, current smoker of ≤1 pack/day, and unknown), and total energy intake (continuous).

[d] Red meat intake and white meat intake were mutually adjusted for in the model.

[e] Processed meat intake and nonprocessed meat intake were mutually adjusted for in the model.

In this analysis, we excluded subjects who were represented in duplicate ($n = 179$), moved out of the 8 study areas before returning the baseline questionnaire ($n = 321$), died before study entry ($n = 261$), withdrew ($n = 6$), had questionnaires completed by proxy respondents ($n = 15{,}760$), had a history of cancer before study entry ($n = 51{,}205$), were identified as having cancer through death reports only ($n = 3{,}890$), or had extreme values for energy intake (more than 2 interquartile ranges outside the 75th and 25th percentiles of log-transformed energy intake, $n = 4{,}384$). Our final analytical cohort consisted of 491,163 persons (292,724 men and 198,439 women) who completed the baseline questionnaire, among whom 307,597 persons (179,348 men and 128,249 women) also completed the second questionnaire that included the meat-cooking module.

Follow-up and ascertainment of cases

In the NIH–AARP study, vital status was ascertained through linkage of the cohort to the Social Security Administration Death Master File in the United States, the National Death Index Plus (for participants who could also be matched to the Death Master File), and cancer registry records. Participants' responses to questionnaires and other mailings were also used to confirm vital status. Follow-up time extended from study baseline (between 1995 and 1996)

Table 3. Meat-Cooking Methods, Doneness Level, Meat Mutagens, and AML (204 Cases Among 307,597 Individuals Who Completed the Second Questionnaire) in the NIH–AARP Diet and Health Study, United States, 1995–2003

	Tertile of Intake			*P* for Trend
	1	2	3	
Cooking methods[a]				
Pan-fried meat (g/1,000 kcal)[b]				
No. of cases	82	50	72	
No. of person-years	787,002	634,986	704,024	
Age-adjusted model				
HR	1.00	0.71	0.98	0.45
95% CI		0.50, 1.02	0.71, 1.36	
Multivariate model[c]				
HR	1.00	0.70	0.89	0.86
95% CI		0.48, 1.00	0.64, 1.23	
Grilled/barbecued meat (g/1,000 kcal)[b]				
No. of cases	58	74	72	
No. of person-years	708,272	709,327	708,413	
Age-adjusted model				
HR	1.00	1.41	1.55	0.04
95% CI		0.99, 2.00	1.07, 2.24	
Multivariate model[c]				
HR	1.00	1.32	1.32	0.23
95% CI		0.93, 1.88	0.91, 1.92	
Sautéed, baked, or microwaved meat (g/1,000 kcal)[b]				
No. of cases	91	34	79	
No. of person-years	926,017	489,094	710,901	
Age-adjusted model				
HR	1.00	0.65	1.14	0.09
95% CI		0.43, 0.97	0.82, 1.58	
Multivariate model[c]				
HR	1.00	0.67	1.26	0.02
95% CI		0.44, 1.00	0.91, 1.74	
Oven-broiled meat (g/1,000 kcal)[b]				
No. of cases	124	11	69	
No. of person-years	1,300,951	118,788	706,273	
Age-adjusted model				
HR	1.00	0.98	1.09	0.57
95% CI		0.53, 1.83	0.80, 1.49	
Multivariate model[c]				
HR	1.00	0.96	1.04	0.78
95% CI		0.52, 1.80	0.76, 1.43	

Table continues

to date of death, date of diagnosis of incident primary AML, participant relocation out of the registry ascertainment area, or December 31, 2003, whichever date was earliest.

Incident cancer cases were identified through linkage with state cancer registry databases, and a validation study showed that approximately 90% of all incident cancer cases in the NIH–AARP cohort were identified by using linkage to cancer registries (16). A total of 338 incident, first primary AML cases (*International Classification of Diseases for Oncology*, Third Edition, codes 9840, 9861, 9866–9867, 9870–9874, 9891, 9895–9897, 9910, 9920, 9930–9931) were identified. Of the 338 cases (242 men and 96 women), 204 (150 men and 54 women) completed the second questionnaire that included the meat-cooking module.

Table 3. Continued

	Tertile of Intake			*P* for Trend
	1	2	3	
Doneness level[a]				
Well-done/very-well-done meat (g/1,000 kcal)[d]				
No. of cases	64	69	71	
No. of person-years	708,299	708,394	709,320	
Age-adjusted model				
HR	1.00	1.19	1.32	0.16
95% CI		0.84, 1.70	0.92, 1.91	
Multivariate model[c]				
HR	1.00	1.14	1.26	0.24
95% CI		0.80, 1.62	0.87, 1.82	
Rare/medium-done meat (g/1,000 kcal)[d]				
No. of cases	65	59	80	
No. of person-years	710,825	707,954	707,234	
Age-adjusted model				
HR	1.00	0.97	1.48	0.01
95% CI		0.68, 1.39	1.04, 2.12	
Multivariate model[c]				
HR	1.00	0.93	1.32	0.06
95% CI		0.65, 1.33	0.92, 1.89	
Meat mutagens[a]				
2-Amino-3,4,8-dimethylimidazo [4,5-*f*] quinoxaline (ng/1,000 kcal)				
No. of cases	79	57	68	
No. of person-years	767,289	650,816	707,907	
Age-adjusted model				
HR	1.00	0.83	0.96	0.92
95% CI		0.59, 1.17	0.70, 1.33	
Multivariate model[c]				
HR	1.00	0.84	0.91	0.81
95% CI		0.59, 1.18	0.66, 1.27	
2-Amino-1-methyl-6-phenylimidazo [4,5-*b*] pyridine (ng/1,000 kcal)				
No. of cases	56	70	78	
No. of person-years	709,891	706,834	709,288	
Age-adjusted model				
HR	1.00	1.31	1.54	0.02
95% CI		0.92, 1.86	1.09, 2.17	
Multivariate model[c]				
HR	1.00	1.16	1.33	0.13
95% CI		0.82, 1.66	0.94, 1.88	

Table continues

Data collection and dietary assessment

The baseline questionnaire was used to obtain information on a number of demographic and lifestyle factors, including age; gender; race; height; weight; smoking status; consumption of coffee, tea, and alcohol; and vigorous physical activity (activity that lasted 20 minutes or more and caused either increases in breathing or heart rate or working up a sweat). For participants, each type of beverage was categorized into 4 levels: nondrinkers and drinkers whose

Table 3. Continued

	Tertile of Intake			*P* for Trend
	1	2	3	
2-Amino-3,8-dimethylimidazo [4,5-*f*] quinoxaline (ng/1,000 kcal)				
No. of cases	67	58	79	
No. of person-years	710,358	709,573	706,082	
Age-adjusted model				
HR	1.00	0.89	1.26	0.08
95% CI		0.62, 1.26	0.91, 1.74	
Multivariate model[c]				
HR	1.00	0.83	1.11	0.29
95% CI		0.58, 1.18	0.80, 1.54	
Benzo[*a*]pyrene (ng/1,000 kcal)				
No. of cases	66	66	72	
No. of person-years	706,139	711,257	708,615	
Age-adjusted model				
HR	1.00	1.03	1.20	0.24
95% CI		0.73, 1.44	0.86, 1.68	
Multivariate model[c]				
HR	1.00	1.02	1.06	0.71
95% CI		0.72, 1.43	0.76, 1.49	
Mutagen activity (revertant colonies/1,000 kcal)				
No. of cases	66	66	72	
No. of person-years	709,970	707,437	708,605	
Age-adjusted model				
HR	1.00	1.05	1.20	0.26
95% CI		0.74, 1.47	0.86, 1.68	
Multivariate model[c]				
HR	1.00	0.93	1.04	0.69
95% CI		0.66, 1.32	0.74, 1.46	

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; HR, hazard ratio; NIH, National Institutes of Health.

[a] Adjusted for energy by using the density method.

[b] Pan-fried meat; grilled/barbecued meat; sautéed, baked, or microwaved meat; and oven-broiled meat were mutually adjusted for in the model.

[c] Adjusted for age at baseline (continuous), gender, smoking status (never, former smoker of ≤1 pack/day, current smoker of ≤1 pack/day, and unknown), and total energy intake (continuous).

[d] Well-done/very-well-done meat and rare/medium-done meat were mutually adjusted for in the model.

levels of consumption were in the first, second, and third tertiles.

At baseline, dietary intakes were assessed with a self-administered, 124-item food frequency questionnaire, which was based on the National Cancer Institute Diet History Questionnaire. Participants reported their usual frequency of intake and portion size over the past 12 months according to 3 predefined categories of portion size and 10 predefined frequency categories ranging from ''never'' to ''≥6 times/day'' for beverages and from ''never'' to ''≥2 times/day'' for foods. The food items, portion sizes, and nutrient database for this food frequency questionnaire were constructed by using the US Department of Agriculture 1994–1996 Continuing Survey of Food Intake by Individuals (17). We excluded white potatoes from the vegetable group. The total meat category included all types of beef, poultry, fish, pork, and processed meats. The red meat category included bacon, beef, cold cuts, ham, hamburger, regular hot dogs, liver, pork, sausage, and steak. The white meat category included all forms of poultry, fish, and low-fat hot dogs and sausages, which are usually made from turkey. All types of cold cuts, bacon, ham, hot dogs, and sausages from red and white meats were included in the processed meat variable.

The second questionnaire with a meat-cooking module queried the consumption of hamburgers, steak, bacon, and chicken; usual cooking method (pan fried; grilled/barbecued; oven broiled; other such as sautéed, baked, or microwaved); and level of doneness on the outside and inside. For individuals who completed the second questionnaire (307,597 subjects, 204 cases), 2 doneness levels (rare/medium and well/very well done) were derived for this analysis. In addition, the CHARRED database was used to estimate daily intake of meat mutagens, including an overall meat mutagenic activity index, benzo[*a*]pyrene, and heterocyclic amines: 2-amino-3,4,8-dimethylimidazo[4,5-*f*] quinoxaline, 2-amino-3,8-dimethylimidazo[4,5-*f*] quinoxaline, and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*] pyridine. All meats queried on the meat-cooking module were used to create these variables. Details about the methods used to develop the CHARRED database are described elsewhere (18–21).

Statistical analysis

Servings/day or grams/day of the food variables were adjusted for energy by using the multivariate nutrient density method (22) and were then split into quintiles based on the distribution of the entire cohort ($n = 491{,}163$). Because of the relatively small number of cases with data from the second questionnaire, we used tertiles instead of quintiles for these analyses.

Cox proportional hazards models with follow-up time as the underlying time metric were used to estimate hazard ratios and 95% confidence intervals of AML according to intake of foods and beverages, as well as meat mutagens. Using age as the underlying time metric led to essentially the same results.

Two models were used. An age-adjusted model conservatively adjusted for age at entry (continuous). A multivariate model adjusted for variables that were significantly associated with the risk of AML in the univariate analysis, including age at entry (continuous), gender, and smoking status. In this paper, we present risk estimates from both models in tables but describe estimates from only the multivariate model in the text. We attempted to include in the multivariate model additional variables that have been reported as risk factors for AML in previous studies, including race/ethnicity, education, and body mass index (9, 23), but including the additional variables had no appreciable impact on the results. Foods in the same broader group (e.g., red meat and white meat) were simultaneously included in the same model, whereas the individual heterocyclic amines and benzo[*a*]pyrene were modeled independently of each other.

To maintain a relatively large sample size, we grouped participants who had missing values for education, smoking, body mass index, or physical activity in a separate category rather than excluding them. To evaluate the impact of this analytical strategy, we conducted sensitivity analyses by excluding participants who had missing values for any of these variables and compared the results with those derived from analyses including participants with missing values. Tests for trend for smoking, education, and physical activity were conducted by modeling categorical variables as ordinal variables (excluding the unknown category). Tests for trend for age and body mass index were conducted by using the original values in their continuous format. For all other variables, tests for trend were performed by using the median value of each category (quintile or tertile).

Because subjects included in the analyses of meat-cooking methods, doneness level, and meat mutagens were a subset of the subjects included in the analyses of foods and beverages, we conducted a sensitivity analysis to assess the relation of foods and beverages with AML among subjects who completed the second questionnaire. In addition, we conducted analyses for males and females separately. To minimize potential effects of latent disease on responses, we also conducted additional analyses by omitting patients diagnosed in the first year of follow-up ($n = 44$) or the first 2 years of follow-up ($n = 70$).

All analyses were performed with SAS version 9.1 software (SAS Institute, Inc., Cary, North Carolina). An alpha level of 0.05 was considered statistically significant, and all tests were 2-sided.

RESULTS

Compared with females, males had a significantly higher risk of AML, and older age was linked to a higher AML incidence (Table 1). Compared with those for never smokers, the hazard ratios were 1.29 (95% confidence interval: 0.95, 1.75), 1.79 (95% confidence interval: 1.32, 2.42), 2.42 (95% confidence interval: 1.63, 3.57), and 2.29 (85% confidence interval: 1.38, 3.79) for former smokers of $\leq$1 pack/day, former smokers of $>$1 pack/day, current smokers of $\leq$1 pack/day, and current smokers of $>$1 pack/day, respectively. Compared with coffee drinkers, those who did not drink coffee appeared to have a higher risk of AML. Race/ethnicity, education, body mass index, vigorous physical activity, and consumption of tea or alcohol did not seem to be significant determinants of AML risk in this cohort (Table 1). Specific types of alcohol (i.e., wine, beer, and liquor) were also not associated with AML (data not shown).

Compared with individuals whose total meat intake was in the first quintile, those whose meat intake was higher appeared to have an increased risk of AML (hazard ratio = 1.45, 95% confidence interval: 1.02, 2.07 for the fifth quintile vs. the first quintile); the *P* for trend was 0.06 (Table 2). No association was observed with intake of fruits, vegetables, red meat, white meat, or processed meat (Table 2). In the subcohort for whom we had meat-cooking information, there were no clear effects of cooking method or doneness level (Table 3).

When analyses were stratified by gender, being obese (i.e., having a body mass index of $\geq$30 kg/m^2) was not associated with AML in males, but the association between obesity and AML was borderline statistically significant among females (hazard ratio = 1.58, 95% confidence interval: 0.97, 2.57 for obese vs. normal weight; *P* for trend = 0.07). Intake of the meat mutagen 2-amino-1-methyl-6-phenylimidazo[4,5-*b*] pyridine was positively associated with AML incidence in males; the hazard ratio for the

third tertile versus the first tertile was 1.55 (95% confidence interval: 1.04, 2.31), and the P for trend was 0.03, whereas no association between 2-amino-1-methyl-6-phenylimidazo[4,5-*b*] pyridine and AML was observed among females. For both obesity and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*] pyridine, tests for interaction with gender were not statistically significant ($P > 0.50$).

Analyses excluding subjects who had missing values for education, smoking, body mass index, or vigorous physical activity generated essentially the same results (data not shown). The relation between foods and beverages and AML did not appear to be different between subjects in the original cohort who completed the baseline questionnaire ($n = 491{,}163$) and subjects in the smaller cohort who also completed the second questionnaire ($n = 307{,}597$) (data not shown). Omitting patients diagnosed in the first year or first 2 years of follow-up did not substantially change the point estimates and did not affect our study conclusions (data not shown).

DISCUSSION

In this large, prospective cohort study, smoking and total meat intake were risk factors for AML. Those who did not drink coffee appeared to have a higher risk of AML. Although there was some indication of possible gender differences with regard to obesity and the meat mutagen 2-amino-1-methyl-6-phenylimidazo[4,5-*b*] pyridine, the findings were difficult to interpret, given that there were only a small number of female cases ($n = 96$) and statistical tests for interaction were not statistically significant.

Previous studies on smoking and AML have generated inconsistent findings, but a meta-analysis published in 1993 reported a summary odds ratio of 1.3 (ever smoking vs. never smoking, 95% confidence interval: 1.1, 1.5) (6). Pogoda et al. (24) found that smoking (measured as ever vs. never) was associated with AML occurring in individuals 60–75 years of age (odds ratio = 1.6, 95% confidence interval: 1.0, 2.6) and a subtype of AML known as M2 (odds ratio = 2.3, 95% confidence interval: 1.1, 4.4), although not AML as a group. A case-control study in Canada observed increased risk of AML for active smokers, with a clear dose-response relation (P for trend = 0.02) (12). In the current analysis, we found a positive association between smoking and AML, and the magnitude of association was stronger for current smokers than former smokers. Using limited-use data (1973–2006) from the Surveillance, Epidemiology, and End Results Program, we did not see a decrease of age-adjusted AML incidence following the reduced prevalence of smoking in the United States. However, the absence of time trend should probably not be interpreted as evidence against a smoking–AML association. The etiology of AML is obscure. It is possible that other risk factors for AML have also changed over time, therefore complicating the picture.

Epidemiologic studies have suggested that coffee intake may decrease the risk of cancer, including cancer of the liver (25), colorectum (26), breast (27), and endometrium (28). Coffee may help protect against cancer through the activity of its anticarcinogenic constituents (29–32) or polyphenolic compounds (33), which inhibit carcinogenesis through antioxidant, antihormonal, and antiinflammatory mechanisms (34). Cafestol and kahweal, 2 coffee-specific diterpenes, can reduce the genotoxicity of multiple carcinogens (31). In this analysis, individuals who did not drink coffee had a higher risk of AML than coffee drinkers did. However, the small number of noncoffee drinkers, the lack of a dose-response relation, and the fact that no other studies are known to have reported such an association suggest that this finding should be interpreted with caution.

Studies on dietary factors and AML are scarce and usually include a small number of cases. In contrast, the current analysis included 242 male and 96 female cases. The study by Ross et al. (9) found that overall vegetable intake was associated with a decreased risk of leukemia as a group (138 cases) but not AML in particular (48 cases). In a large case-control study, Kasim et al. (12) did not observe any association between intake of fruits and vegetables and the risk of adult leukemia overall (1,068 cases) or AML in particular (307 cases). In the current analysis, we did not observe an association between intake of fruits and vegetables and AML. The study by Li et al. (10) reported that AML risk was positively associated with consumption of beef, wine, and beer among women, which we were unable to confirm in the current analysis. Hu et al. (35) reported that the risk of leukemia was associated with intake of meat and processed meat, but no results were presented specifically for AML. The study by Zhang et al. (11) found no association between green tea consumption and the risk of AML. We also found no association with tea consumption, although we were unable to evaluate green tea specifically.

Because total meat intake appeared to be a risk factor for AML, we evaluated the role of meat-cooking methods, doneness level, and meat mutagens. Meat cooked at high temperature and for increased duration is a source of heterocyclic amines and polycyclic aromatic hydrocarbons (18–20, 36). In animal models, heterocyclic amines and polycyclic aromatic hydrocarbons can generate DNA adducts (37) and induce a variety of malignancies, including leukemia (38–40). Meats prepared by common household cooking practices generally contain heterocyclic amines at trace levels (in the low parts-per-billion range) (41); thus, the distribution of consumed cooking-related meat mutagens is skewed, with most populations exposed to very low concentrations (42). It is possible that the adverse effects of these mutagens may be observed only when biologic thresholds have been reached (43), which may explain why we observed no clear effects of meat mutagens.

The prospective cohort design, the large number of individuals included in the cohort, and the detailed assessment of dietary intake were major strengths of this study. Of the few previous studies on dietary factors and AML, only one was a cohort study, which included only women and a fairly small number of cases ($n = 48$) (9). In the current study, recall bias and reverse causality were minimized because diet and other important factors such as smoking were assessed at baseline. The large number of participants, the high follow-up rate (more than 95%), and the relatively long

follow-up time (median, 7.5 years) resulted in a total of 338 cases, which is quite large given the rarity of AML. Because of our detailed dietary assessment, this study is the first known to evaluate the role of meat-cooking methods and meat mutagens in relation to AML. The nutrient density adjustment method we used for dietary factors was also important, considering that intake of many types of foods, such as meat, is correlated with energy intake (44, 45). In addition, we were able to control for several potential confounders in the multivariate analyses of dietary factors.

Since the NIH–AARP study enrolled individuals aged 50–71 years at baseline, our findings may not be applicable to AML occurring in younger individuals. However, AML is predominantly a disease of older adults and is rare among persons younger than age 40 years (7). Because the focus of the study was dietary intake in late adulthood, we were unable to evaluate possible changes in diet over the entire lifetime. Compared with the general US population, participants in our cohort were less likely to be current smokers, and they consumed less fat and red meat and more fiber and fruits and vegetables (15), which may be the result of the relatively low response to the initial mailing or the AARP membership. Nevertheless, the distributions of dietary factors in our cohort were wider than those in the national surveys; for example, the median intake of red meat among study cohort members in the top quintile was more than 7 times (for men) and 9 times (for women) that of members in the bottom quintile. Even though the total number of cases included in this study was fairly large for a disease as rare as AML, statistical power was probably limited, especially for females. In addition, we did not further classify AML into subtypes because of concerns about statistical power.

In this large, prospective cohort study, smoking and total meat intake were associated with an increased risk of AML. Given the limited understanding of the risk factors for AML and the small number of studies on dietary factors and AML, it is important to further evaluate the role of diet and lifestyle in the etiology of AML in well-designed, large studies.

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