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Dietary Intake of Vegetables, Fruits, and Meats/Beans as Potential Risk Factors of Acute Myeloid Leukemia: A Texas Case-Control Study

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Diet has been identified as a risk factor for some cancers, but its role in adult *de novo* acute myeloid leukemia (AML) is unclear. This study was conducted at the University of Texas MD Anderson Cancer Center to evaluate associations between consumption of vegetables, fruits, and meats with AML risk among Texas residents. All participants, 323 adult *de novo* AML cases and 380 frequency-matched controls, completed demographic and food frequency questionnaires. Overall, AML risk was significantly decreased among those who consumed the most dark green vegetables, seafood, and nuts/seeds; and it was significantly increased among greatest consumers of red meat. Among men, AML risk was lowest among those whose consumption was in the highest quartile for fruits [odds ratio (OR) = 0.25, 95% confidence interval (CI) = 0.10–0.69], poultry (OR = 0.28, 95%CI = 0.10–0.78), and seafood (OR = 0.39, 95%CI = 0.16–0.96) compared to those in the lowest. Among women, risk was lowest among those whose consumption was in the highest quartile of dark-green vegetables (OR = 0.28, 95%CI = 0.12–.68), orange vegetables (OR = 0.40, 95%CI = 0.17–.96) and nuts/beans (OR = 0.26, 95%CI = 0.11–0.60). Based on these findings, interventions can be developed to modify intake of specific dietary components to reduce cancer risk.

INTRODUCTION

Acute myeloid leukemia (AML) is the most common acute leukemia in the United States and accounts for approximately 30% of all adult leukemias. The American Cancer Society estimates that in 2013, 14,590 new cases of AML (7820 men and 6770 women) will be diagnosed, and 10,370 deaths due to AML will occur (1). The overall age-adjusted incidence rate for 2005–2009 was 3.6/100,000 person-years and was higher in males than females (4.3 vs. 3.0/100,000) (1). The etiology of AML is complex and not yet well-understood. Epidemiological studies have identified several environmental exposures associated with increased risk of *de novo* AML, including occupational solvents (2, 3), agrichemicals (4, 5), ionizing radiation (6), and cigarette smoke (7, 8).

Dietary intake has been identified as a risk factor for several different cancers. High vegetable and fish consumption have been linked to decreased risk of colorectal (9), lung (10), and breast (11) cancers. Studies examining dietary risk factors for adult *de novo* AML have been few and inconclusive. In an analysis from the NIH-AARP Diet and Health Cohort Study, researchers reported that high meat intake was associated with an increased risk of AML (12). A case-control study conducted in Canada found no association between AML risk and fruit and vegetable intake (13). Although differences in AML risk have been demonstrated by gender, few studies have explored differences by gender in associations of diet and AML risk. A small, hospital based case-control study found that among only women high consumption of milk and tea was associated with decreased risk, whereas high consumption of processed meats and wine were associated with increased risk (14). Because AML is more common among men, it is important to address the possibility that gender-differences in dietary intake may partially explain differences in risk. In a case-control study at the University of Texas MD Anderson Cancer Center (MDACC),

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we examined the association between vegetable, fruit, and meat intake and the risk of adult *de novo* AML and whether these associations differ by gender.

MATERIALS AND METHODS

Study Population and Epidemiologic Data Collection

Details of the overall study population and methods have been previously published (8). Briefly, cases were adult residents of Texas (aged 18 to 80) who registered at MDACC between 2003 and 2007 with a confirmed diagnosis of *de novo* AML, with no restrictions on gender, or ethnicity. *De novo* cases are defined as AML cases with no prior history of exposure to ionizing radiation and/or cytotoxic chemotherapies. Cases were identified to be eligible by clinical staff at their first visit and prospectively enrolled into the study, and controls were recruited using a previously described random digit dialing method (8) and frequency-matched to cases on age, gender, place of residence, and race. The overall participation rate in controls was 77%. Because dietary assessment was added after study commencement and not all subjects were requested to participate, this study only includes the 483 cases and 487 controls that were asked to complete the dietary assessment component. Eighteen percent of the cases and 5% of the controls refused to participate in the dietary component. Participants were not included in the analysis if they had incomplete FFQs (4 cases and 18 controls) or reported daily energy intake of less than 500 kcal or more than 5000 kcal (21 cases and 8 controls). In addition, 57 controls were excluded after frequency matching to the cases. After exclusionary criteria were applied, FFQs from 323 (93%) AML cases and 380 (82%) controls were included in the final analysis.

Written informed consents were obtained prior to data collection in accordance with the institutional review board requirements. Trained interviewers administered a structured risk factor questionnaire to assess sociodemographic characteristics, medical history, lifetime smoking history, occupational chemical exposure/history, family history of cancer, and anthropometric (height and weight) information (8).

Individuals who never smoked or only smoked fewer than 100 cigarettes in their lifetime were considered as "never smokers"; individuals who had quit more than 1 yr prior to diagnosis/interview were defined as "former smokers." A "current smoker" was defined as an individual who quit less than 1 yr before or was smoking at the time of diagnosis/interview. Body mass index (BMI) (kg/m^2) was calculated from self-reported height and usual weight prior to diagnosis/interview. In accordance with National Heart, Lung, and Blood Institute guidelines, participants with a BMI $\geq$ 30 kg/m^2 were considered to be obese. Using our previously described methodology (8), lifetime occupational exposure to organic solvents (benzene, gasoline, and other organic solvents) was estimated using the Job-Exposure Matrix developed by the National Cancer Institute (15). Participants were considered to have a positive family history of hematopoietic cancer if they reported having a first-degree relative (i.e., parent, sibling, or child) who had been diagnosed with hematopoietic cancer (leukemia, lymphoma, multiple myeloma, or myelodysplastic syndrome).

For this study, in addition to the risk factor questionnaire, a self-administered modified version of the National Cancer Institute Block Health Habits and History Questionnaire (HHHQ) (16) with more than 170 items queried was used to assess usual dietary intake (frequency and portion size) for the year prior to diagnosis (cases) or interview (controls). The HHHQ was modified to include commonly consumed ethnic foods that are major contributors to nutrient intake in Texas (17).

The frequency and portion size reported in the modified HHHQ were integrated into MyPyramid Equivalents Database, 2.0 for USDA Survey Foods, 2003–2004 (MPED 2.0) which uses standardized recipe files to determine the number of MyPyramid serving equivalents of each ingredient and then calculates the cup/ounce equivalent for each food's individual ingredients and assigns components to food groups (18). The food groups were based on the MyPyramid documented grouping of individual food items. Overall total and subgroup (dark green vegetables, orange vegetables, and white potatoes) consumption of vegetables were included in the initial analyses. The meat and beans group was divided into 4 subgroups to allow us to compare our results to previous reports (14, 34): red meat/pork, poultry, seafood (fish, shellfish), and beans/nuts/seeds. Total fruit and the MPED 2.0 groupings of citrus/melons/berries and other fruits were also analyzed as risk factors. The daily MyPyramid equivalents across all relevant food items were summed to obtain total and subgroup-specific food intakes.

Statistical Analysis

Descriptive analyses of categorical characteristics were conducted using Pearson's chi-squared (χ^2) tests. For continuous variables that were normally distributed, case-control differences in means were assessed using Student's *t*-tests. Because the distribution of the dietary intakes was skewed, median dietary intakes were compared between cases and controls using Wilcoxon rank sums tests.

The dietary intakes of each food group were categorized into quartiles based on the distributions of dietary intake in controls using overall and gender-specific cut-points for the respective analyses. Odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for associations between dietary intake and AML risk were estimated using unconditional logistic regression. For all analyses, the lowest quartile of intake was used as the referent category. Intakes of each dietary component were entered into a multivariable model for the overall population, as well as models stratified on gender. Models were constructed in a backward, stepwise manner with terms for all food groups and adjustment for potential confounders, such as, age, education, smoking, obesity, alcohol consumption, and solvent exposure (8) entered into the initial model. Total vegetable intake was not used in the multivariable models to allow us to assess the effects

of the component vegetable groups (i.e., dark green, orange, potatoes). Because the dietary intakes of foods and nutrients are correlated with total energy intake, total calorie intake was entered as a continuous variable in all multivariable models (19). All analyses were conducted for the overall sample and also stratified by gender. All statistical tests were 2-sided and statistical significance was defined as $P < 0.05$. Statistical analyses were conducted using SPSS version 21.0 (SPSS, Chicago, IL).

RESULTS

Because of successful matching, there were no significant differences between cases and controls with respect to age, gender, and ethnicity (Table 1). Compared to controls, AML cases were more likely to be obese (40.0% vs. 23.7%; $P < 0.001$) and were less likely to have completed a Bachelor's degree (36.5% vs. 62.1%; $P \leq 0.001$). Cases also had a higher mean daily energy intake than controls (2536 kcal vs. 2293 kcal; $P = 0.001$).

Table 2 compares median daily servings consumed of vegetables, fruit, and meat/beans among all cases and controls and by gender. Compared to controls, cases consumed significantly more servings of white potatoes ($P < 0.01$) and red meat/pork ($P < 0.01$). Cases compared to controls also consumed significantly fewer servings of total vegetables ($P = 0.02$), dark-green vegetables ($P < 0.01$), orange vegetables ($P < 0.01$), seafood ($P < 0.01$), and nuts/seeds ($P = 0.01$).

When we investigated differences in consumption by gender among controls, we found that women consumed greater amounts of dark green ($P = 0.05$) and orange vegetables ($P = 0.03$) than men; and men consumed more red meat ($P = 0.02$) compared to women. We found that the case-control differences seen in the overall population for intake of total and orange vegetables and nuts/seeds was limited to women ($P < 0.01$), as we found no significant case-control differences among men. Both female and male cases consumed significantly more servings of red meat compared to controls ($P = 0.02$ and <0.01); however, males consumed more servings of red meat than females among both cases and controls. Conversely, controls consumed significantly more servings of seafood compared to cases among both males and females ($P = 0.01$ and <0.01).

Table 3 presents the multivariable ORs associated with dietary intake by quartile for the population overall and by gender adjusted only for non-dietary confounding factors (i.e., age, gender, race, education, smoking, obesity, and solvent exposure). In the overall population, AML risk was decreased among those who consumed the greatest amounts (highest quartile) of total vegetables (OR = 0.23, 95% CI: 0.12–0.44), dark green vegetables (OR = 0.32, 95% CI: 0.18–0.57), orange vegetables (OR = 0.44, 95% CI: 0.25–0.76), poultry (OR = 0.56, 95% CI: 0.30–1.06), seafood (OR = 0.33, 95% CI: 0.19–0.58), and nuts/seeds (OR = 0.30, 95% CI: 0.17–0.53). Risk was increased among those who consumed the greatest amounts of white potatoes (OR = 2.51, 95% CI: 1.33–4.72) and red meats (OR = 2.11, 95% CI: 1.11–4.04). The results from stratified analyses showed differences by gender. Highest total vegetable intake (OR = 0.12, 95% CI: 0.04–0.31), orange vegetable intake (OR = 0.27, 95% CI: 0.12–0.60), and nuts/seeds (OR = 0.25, 95% CI: 0.11–0.57) significantly decreased risk only among women. High red meat (OR = 4.09, 95% CI: 1.39–12.07) was associated with increased risk only in men. When we evaluated for differences in the types of specific dark-green vegetables consumed, we found that controls ate significantly more broccoli and raw spinach than cases (data not shown). When we examined intakes of specific orange vegetables, controls consumed more winter, acorn and butternut squashes than cases (data not shown).

Based on these differences in associations with food groups by gender, 2 independent multivariable regression models were constructed with simultaneous adjustment for dietary and other

TABLE 1
Characteristics of *de novo* acute myeloid leukemia cases and controls

Characteristic	Cases ($N = 323$)	Controls (N = 380)	P^*
Age (Mean ± SD)	53.5 ± 16.6	53.3 ± 13.4	NS[#]
Range	18–87	21–82	
Sex (%)			
Male	171 (52.9)	186 (48.9)	NS
Female	152 (47.1)	194 (51.1)	
Ethnicity (%)			
White/Non-Hispanic	222 (68.7)	284 (74.7)	NS
Hispanic	61 (18.9)	48 (12.6)	
African-American	30 (9.3)	33 (8.7)	
Other	10 (3.1)	15 (3.9)	
BMI, kg/m2 (Mean ± SD)	29.4± 7.2	27.4 ± 6.2	<0.001[#]
BMI[+] (%)			
Nonobese	192(60.0)	289(76.3)	<0.001
Obese	128(40.0)	90(23.7)	
Smoking Status (%)			
Never	171 (52.9)	210 (55.3)	
Former	84 (26.0)	104 (27.4)	NS
Current	68 (21.1)	66 (21.3)	
Education (%)			
<Bachelors	205 (63.5)	144 (37.9)	<0.001
≥Bachelors	118 (36.5)	236 (62.1)	
Family history of hematopoietic cancer (%) ($n = 621$)			
Yes	16 (5.0)	5 (1.7)	
No	306 (95.0)	294 (98.3)	0.02
Solvent exposure ($n = 547$) (%)			
None	129 (48.5)	203 (72.5)	<0.001
Low	40 (15.0)	44 (15.7)	
Moderate/high	97 (36.5)	33 (11.8)	
Total energy intake (Mean kcal ± SD)	2536 ± 1032	2293 ± 915	0.001[#]

[+]BMI = body mass index.
[*]χ^2 test. [#]Student's *t*-test.

TABLE 2
Median daily servings[+] of vegetables, fruits, and meats in *de novo* AML cases and controls

	All			Women			Men		
Daily serving[+]	Cases ($n = 323$)	Controls ($n = 380$)	P^*	Cases ($n = 152$)	Controls ($n = 194$)	P^*	Cases ($n = 171$)	Controls ($n = 186$)	P^*
Total vegetables	5.46(0.6–30.0)	6.04(0.8–31.0)	0.02	4.74(0.6–30.0)	6.15(1.4–31.0)	< 0.01	5.95(0.6–21.7)	5.89(0.8–20.6)	0.72
Dark-green vegetables	0.19(0.0–5.9)	0.37(0.0–4.3)	< 0.01	0.19(0.0–5.9)	0.42(0.0–4.3)	< 0.01	0.18(0–4.3)	0.31(0.0–4.0)	< 0.01
Orange vegetables	0.18(0.0–4.4)	0.25(0.0–5.1)	< 0.01	0.17(0.0–4.4)	0.33(0.0–4.7)	< 0.01	0.19(0–2.7)	0.20(0.0–5.1)	0.31
White potatoes	0.98(0.0–13.4)	0.67(0.0–7.2)	< 0.01	0.77(0.0–13.5)	0.66(0.0–7.2)	0.02	1.19(0–11.2)	0.69(0.0–7.2)	< 0.01
Total fruits	3.04(0.0–31.5)	3.29(0.0–18.2)	0.46	3.12(0.5–31.5)	2.97(0.0–18.2)	0.75	2.93(0–20.7)	3.50(0.1–16.3)	0.18
Citrus/melons/berries	1.11(0.0–11.8)	1.27(0.0–13.3)	0.43	1.13(0.0–9.4)	1.29(0.0–8.5)	0.61	1.06(0–11.8)	1.25(0.0–13.3)	0.57
Total meat/beans	7.07(0.6–22.1)	6.32(0.2–26.8)	0.11	6.02(1.1–18.5)	5.86(0.2–26.8)	0.95	7.76(0.6–22.1)	6.68(0.8–17.7)	0.07
Red meat/pork	3.66(0.0–13.7)	2.72(0.0–11.8)	< 0.01	3.07(0.0–11.0)	2.54(0.1–8.9)	0.02	4.39(0.2–13.7)	3.12(0.0–11.8)	< 0.01
Poultry	0.97(0.0–9.7)	1.10(0.0–9.4)	0.14	0.99(0.1–9.7)	1.08(0.0–9.4)	0.79	0.95(0–6.6)	1.13(0.0–7.1)	0.06
Seafood	0.64(0.0–9.1)	0.93(0.0–14.0)	< 0.01	0.56(0.0–7.5)	0.86(0.0–14.0)	< 0.01	0.78(0–9.1)	1.08(0.0–7.9)	0.01
Nuts/seeds	0.19(0.0–3.4)	0.27(0.00–3.1)	0.01	0.11(0.0–2.2)	0.29(0.0–2.3)	< 0.01	0.28(0–3.4)	0.25(0.0–3.1)	0.53

[+]Unit is cup or ounce equivalents consumed per day based on pyramid servings.*Wilcoxan rank sums test.

TABLE 3
Multivariable analysis food groups and *de novo* acute myeloid leukemia (AML) risk overall and by gender

	All AML		Female		Male	
Variable[#]	Odds ratio[*] (95% CI)	*P* trend	Odds ratio[+] (95% CI)	*P* trend	Odds ratio[+] (95% CI)	*P* trend
Total vegetable						
1st quartile	1.00		1.00		1.00	
2nd quartile	0.48 (0.28–0.82)		0.36 (0.17–0.73)		0.57 (0.25–1.31)	
3rd quartile	0.37 (0.21–0.64)		0.21 (0.10–0.47)		0.71 (0.30–1.68)	
4th quartile	0.23 (0.12–0.44)	<0.001	0.12 (0.04–0.31)	<0.001	0.37 (0.14–0.94)	0.07
Dark-green vegetable						
1st quartile	1.00		1.00		1.00	
2nd quartile	0.91 (0.55–1.50)		0.64 (0.32–1.25)		0.70 (0.32–1.51)	
3rd quartile	0.36 (0.21–0.63)		0.34 (0.16–0.72)		0.39 (0.17–0.88)	
4th quartile	0.32 (0.18–0.57)	<0.001	0.23 (0.10–0.51)	<0.001	0.35 (0.15–0.81)	0.005
Orange vegetable						
1st quartile	1.00		1.00		1.00	
2nd quartile	0.75 (0.46–1.23)		0.66 (0.34–1.29)		0.68 (0.32–1.46)	
3rd quartile	0.37 (0.21–0.65)		0.43 (0.21–0.89)		0.73 (0.31–1.70)	
4th quartile	0.44 (0.25–0.76)	<0.001	0.27 (0.12–0.60)	0.001	0.41 (0.17–0.96)	0.06
White potatoes						
1st quartile	1.00		1.00		1.00	
2nd quartile	1.77 (0.97–3.22)		1.79 (0.82–3.91)		1.73 (0.67–4.48)	
3rd quartile	1.70 (0.92–3.14)		1.57 (0.70–3.53)		1.95 (0.77–4.95)	
4th quartile	2.51 (1.33–4.72)	0.01	2.18 (0.93–5.11)	0.13	3.01 (1.15–7.90)	0.03
Total fruits						
1st quartile	1.00		1.00		1.00	
2nd quartile	0.98 (0.59–1.63)		0.70 (0.34–1.45)		1.31 (0.58–2.94)	
3rd quartile	0.65 (0.38–1.11)		0.80 (0.39–1.64)		0.60 (0.27–1.32)	
4th quartile	0.64 (0.36–1.16)	0.07	1.15 (0.51–2.55)	0.81	0.24 (0.09–0.65)	0.002
Citrus/melon/berries						
1st quartile	1.00		1.00		1.00	
2nd quartile	0.86 (0.52–1.44)		0.73 (0.36–1.46)		1.63 (0.74–3.60)	
3rd quartile	0.71 (0.42–1.20)		0.68 (0.33–1.37)		0.93 (0.40–2.17)	
4th quartile	0.64 (0.36–1.13)	0.09	0.67 (0.29–1.53)	0.28	0.78 (0.33–1.87)	0.36
Total meat/beans						
1st quartile	1.00		1.00		1.00	
2nd quartile	0.54 (0.30–0.96)		0.39 (0.18–0.86)		0.60 (0.22–1.59)	
3rd quartile	0.70 (0.38–1.27)		0.51 (0.23–1.12)		1.35 (0.52–3.49)	
4th quartile	0.63 (0.31–1.28)	0.31	0.56 (0.22–1.42)	0.26	0.68 (0.23–2.04)	0.86
Red meat/pork						
1st quartile	1.00		1.00		1.00	
2nd quartile	1.01 (0.56–1.82)		1.06 (0.50–2.27)		1.56 (0.59–4.15)	
3rd quartile	1.07 (0.58–1.96)		0.65 (0.28–1.52)		2.55 (0.90–7.21)	
4th quartile	2.11 (1.11–4.04)	0.02	1.44 (0.61–3.37)	0.51	4.09 (1.39–12.07)	0.005
Poultry						
1st quartile	1.00		1.00		1.00	
2nd quartile	1.34 (0.79–2.27)		1.35 (0.66–2.73)		0.76 (0.33–1.74)	
3rd quartile	0.82 (0.47–1.45)		0.82 (0.38–1.81)		0.68 (0.29–1.57)	
4th quartile	0.56 (0.30–1.06)	0.02	0.68 (0.29–1.58)	0.21	0.22 (0.08–0.60)	0.005

(Continued on next page)

TABLE 3
Multivariable analysis food groups and *de novo* acute myeloid leukemia (AML) risk overall and by gender *(Continued)*

	All AML		Female		Male	
Variable[#]	Odds ratio* (95% CI)	*P* trend	Odds ratio[+] (95% CI)	*P* trend	Odds ratio[+] (95% CI)	*P* trend
Seafood						
1st quartile	1.00		1.00		1.00	
2nd quartile	0.46 (0.27–0.78)		0.41 (0.19–0.85)		0.61 (0.27–1.37)	
3rd quartile	0.46 (0.27–0.78)		0.39 (0.19–0.80)		0.36 (0.15–0.84)	
4th quartile	0.33 (0.19–0.58)	<0.001	0.36 (0.16–0.77)	0.005	0.34 (0.15–0.79)	0.006
Nuts/seeds						
1st quartile	1.00		1.00		1.00	
2nd quartile	0.57 (0.34–0.96)		0.34 (0.17–0.68)		1.14 (0.48–2.69)	
3rd quartile	0.46 (0.27–0.78)		0.16 (0.07–0.36)		1.32 (0.57–3.06)	
4th quartile	0.30 (0.17–0.53)	<0.001	0.25 (0.11–0.57)	<0.001	0.49 (0.20–1.20)	0.15

[#]Cut-off values for the quartiles-total vegetables: 4.12, 6.04, 8.59; dark-green vegetables: 0.14, 0.37, 0.71; orange vegetables: 0.12, 0.25, 0.51; total fruits: 1.76, 3.29, 5.23; total meats/beans: 4.24, 6.32, 8.93; red meat/pork: 1.44, 2.72, 4.44; poultry: 0.51, 1.10, 1.93; seafood: 0.50, 0.93, 1.69; nuts/seeds: 0.10, 0.27, 0.54.

*Adjusted for total energy intake, age, gender, race, education, smoking, obesity, and solvent exposure.

[+]Adjusted for total energy intake, age, race, education, smoking, obesity, and solvent exposure.

confounding factors (Tables 4A and 4B) to allow us to assess confounding between food groups. We found that associations between AML risk and intake of some vegetables differed by gender even after adjustment. Among women, AML risk decreased among those who had high intakes of dark green vegetables (OR = 0.28, 95% CI: 0.12–0.68), orange vegetables (OR = 0.40, 95% CI: 0.17–0.96), and nuts/seeds (OR = 0.26, 95% CI: 0.11–0.60). Among men, greater consumption of total fruits (OR = 0.26, 95% CI: 0.10–0.69), poultry (OR = 0.28, 95% CI: 0.10–0.78), and seafood (OR = 0.39, 95% CI: 0.16–0.96) were associated with decreased AML risk. In summary, we found no commonalities in the food groups associated with risk in men and women.

DISCUSSION

To the best of our knowledge, our study is the first large case-control study to evaluate the overall and gender-specific roles of dietary intake by food groups with risk of adult *de novo* AML. We found that higher consumption of dark green vegetables, seafood, and nuts/seeds decreased adult *de novo* AML risk and greater intake of red meat was associated with increased risk in the overall study population. Notably, the factors associated with gender-specific AML risk differed from those identified in the overall analysis. Among women, greater intake of dark green vegetables, orange vegetables, and nuts/seeds were associated with decreased risk; and among men, greater intake of fruits, poultry, and seafood were associated with decreased risk. These differences in risk by gender may in part be attributable to differences in dietary consumption as noted in our study. Based on the Third NHANES data, Berrigan et al. reported that women were more likely than men to consume greater amounts of fruits and vegetables (34). In addition, Berrigan et al. noted that higher education, age, and income were associated with higher adherence to dietary recommendations (i.e., consume at least 5 fruits and vegetables per day) (34). Given the case-control differences observed in education in our data, it is possible that some of

TABLE 4A
Final multivariable model of dietary factors and *de novo* acute myeloid leukemia (AML) risk among women

Food group (servings/day)	Odds ratio* (95% confidence interval)	*P* trend
Dark-green vegetable		
1st quartile (<0.17)	1.00	
2nd quartile (0.17–0.42)	0.72 (0.35–1.46)	
3rd quartile (0.42–0.79)	0.40 (0.18–0.88)	
4th quartile (>0.79)	0.28 (0.12–0.68)	0.001
Orange vegetable		
1st quartile (<0.12)	1.00	
2nd quartile (0.12–0.33)	0.76 (0.37–1.55)	
3rd quartile (0.33–0.63)	0.59 (0.27–1.28)	
4th quartile (>0.63)	0.40 (0.17–0.96)	0.04
Nuts/seeds		
1st quartile (<0.10)	1.00	
2nd quartile (0.10–0.29)	0.38 (0.19–0.78)	
3rd quartile (0.29–0.51)	0.17 (0.08–0.39)	
4th quartile (>0.51)	0.26 (0.11–0.60)	<0.001

*Adjusted for age, education, obesity, solvent exposure, alcohol consumption, dark-green vegetable intake, orange vegetable intake, and nuts/seeds intake.

TABLE 4B
Final multivariable model of dietary factors and *de novo* acute myeloid leukemia (AML) risk among men

Food group (servings/day)	Odds ratio+ (95% confidence interval)	*P* trend
Total fruits		
1st quartile (<1.77)	1.00	
2nd quartile (1.77–3.50)	1.51 (0.66–3.47)	
3rd quartile (3.50–5.57)	0.49 (0.22–1.11)	
4th quartile (>5.57)	0.25 (0.10–0.69)	0.002
Poultry		
1st quartile (<0.60)	1.00	
2nd quartile (0.60–1.12)	0.91 (0.38–2.17)	
3rd quartile (1.12–2.12)	0.69 (0.28–1.69)	
4th quartile (>2.12)	0.28 (0.10–0.78)	0.03
Seafood		
1st quartile (<0.51)	1.00	
2nd quartile (0.51–1.08)	0.61 (0.26–1.42)	
3rd quartile (1.08–1.75)	0.33 (0.14–0.79)	
4th quartile (>1.75)	0.39 (0.16–0.96)	0.02

+Adjusted for age, education, obesity, solvent exposure, alcohol consumption, fruit intake, poultry intake, and seafood intake.

the differences in consumption may be attributable to residual effects despite adjustment for education in the multivariable models. In addition, the association with red meat intake found in the overall population was not seen in the final gender-specific models; and the decreases in AML risk with high fruit intake and poultry noted in men were only discernible in the stratified analysis. The lack of association with red meat in the multivariable models may be due to the protective effects associated with greater vegetable and alternative protein source intake (e.g., greater poultry, seafood, and/or nuts and seeds). However, our findings highlight the need for gender specific analyses in future research.

Our review of the literature revealed only 4 previous studies that have evaluated the relationship between dietary intake by food group and AML risk (12–14, 35). Although the previous studies all reported no significant associations with vegetable intake, we found that greater vegetable consumption was associated with decreased risk of AML in the overall study population. Our finding that red meat consumption was associated with increased overall risk is consistent with previous reports (12,14). In contrast to the findings reported by Li et al. that AML risk was increased only among women who consumed the most red meat (14), we found that risk was significantly increased only in the overall population who consumed the greatest amounts of red meat/pork. Our findings are similar to those of Ma et al. which used the NIH-AARP cohort to demonstrate greater total and red meat consumption increased overall risk; however, they did not explore gender-specific differences (12). Analyses restricted to the 48 female AML cases included in the Iowa Women's Health Study (IWHS) cohort found no significant association with all, red, or processed meat intake and AML risk (35). The study by Kasim et al. did not include meat intake in the results (13).

Differences in findings across studies could possibly be due to differences in methodology and study populations. Differences in the instruments as well as the groupings used for analysis may account for some of the differences. The current study used a comprehensive validated FFQ with more than 170 items that was modified from the HHHQ to include foods commonly consumed in the Southwestern diet whereas other studies used FFQs querying for fewer food items (12–14, 35).

In addition, differences in the study populations with respect to inclusion criteria (*de novo* vs. all AML), gender and age, as well as sample size may all play a role in explaining different results. For example, compared to the current study, the AARP cohort is significantly older (mean age = 62 vs. 53 in this study) and largely male (72% vs. 53%) (12). The IWHS includes only 48 female AML cases. The study by Kasim et al. was most similar to ours (13); however, it was not restricted to *de novo* cases. Li et al. demonstrated some gender-specific risk associations, and the population was similar in age and gender composition to the current study; however, it was not limited to *de novo* cases (14).

The specific mechanisms by which food intake may affect AML risk has not been investigated for specific food groups. However, extensive evidence in the literature from in vivo, in vitro, and population studies suggest that dietary intake may play a significant role in cancer risk. Fruits and vegetables have been shown to contain a number of compounds with potentially anti-carcinogenic properties, including lycopene, carotenoids, dietary fiber, lutein, isothiocyanates, flavonoids, folic acid, and vitamins C and E (24, 29–31, 36). Human and animal models suggest that the anticarcinogenic effects of these compounds are likely the result of several complementary and overlapping mechanisms (24). The inverse association we demonstrated with greater consumption of dark green vegetables, notably spinach and broccoli, and decreased AML risk, suggest that higher folate consumption may be protective. Folate has been shown to be an important co-factor in DNA methylation and maintenance (37–40), as well as plays a protective role in several cancers (40, 41). Polymorphisms in folate metabolism genes, such as methylenetetrahydrofolate reductase have been associated with risk of cancers including leukemias (42, 43). Several mechanisms by which meat may induce carcinogenesis have been suggested. The metabolism of red meat can produce phenols and hydroquinones which have been shown to have hematotoxic effects similar to benzene, one of the few well-established causes of leukemia (44). Consumption of red and processed meats has also been shown to stimulate the production of N-nitroso compounds and nitrosamines, which have been hypothesized to be carcinogenic (14, 45). This same mechanism may explain why greater consumption of poultry and seafood were not associated

with increased risk, because both poultry and seafood contain lower concentrations of nitrosamines and are less likely than red meat to form N-nitroso compounds when cooked (29).

As a case-control study, there were limitations inherent in our study. In all retrospective studies, recall bias may have a confounding effect; however, to minimize this possibility, the same trained interviewers were used to administer personal interviews to both cases and controls using the same data collection instruments. Although our analyses controlled for smoking, obesity, education, age, gender, race, family history of hematopoietic cancers, total energy intake, and organic solvent exposure in multivariable models, there may also be residual confounding from imperfect assessment (e.g., education, occupation) or other unknown factors. The gender differences observed for different food groups may also be attributable to residual confounding. The use of vitamin and other dietary supplements may also play a role in AML risk; however, these data were not available for this population.

This study has several major strengths. To our knowledge, it is the first large case-control study in the United States that examines risk for AML according to the food groups defined by the dietary guidelines of the USDA. This is a relatively large case-control study from Texas, and the cases are restricted to *de novo* AML cases. In addition, we used a comprehensive FFQ to capture food intake for the year prior to diagnosis/interview for cases and controls, respectively. As well as the food groups, we were able to identify some of the specific foods that underlie the differences between cases and controls. These findings could assist in the development of intervention programs to target increasing (e.g., broccoli, raw spinach) or decreasing (e.g., red meat) consumption of specific foods especially in high risk groups, such as myelodysplastic syndrome patients.

CONCLUSION

In conclusion, we identified multiple dietary risk factors for AML, several of which differed between genders. This study adds to the sparse literature examining the dietary risk factors for adult *de novo* AML and may have important potential implications in the prevention of AML. Future studies should investigate the mechanisms by which some foods affect cancer risk, evaluate specific nutrients and other compounds that may underlie the effects seen here. As diet is a modifiable risk factor, community interventions can be developed to encourage healthy dietary changes.

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REFERENCES

1. American Cancer Society: *Cancer Facts & Figures 2013*. Atlanta: American Cancer Society, 2013.
2. Aksoy M: Benzene and leukemia. *Environmental Health Perspectives* **91,** 165–166, 1991.
3. Ciccone G, Mirabelli D, Levis A, Gavarotti P, Rege-Cambrin G, et al.: Myeloid leukemias and myelodysplastic syndromes: Chemical exposure, histologic subtype and cytogenetics in a case-control study. *Cancer Genetics and Cytogenetics* **68,** 135–139, 1993.
4. Sperati A, Rapiti E, Settimi L, Quercia A, Terenzoni B, and Forastiere F: Mortality among male licensed pesticide users and their wives. *American Journal of Industrial Medicine* **36,** 142–146, 1999.
5. Cantor KP and Silberman W: Mortality among aerial pesticide applicators and flight instructors: Follow-up from 1965–1988. *American Journal of Industrial Medicine* **36,** 239–247, 1999.
6. Yardley-Jones A and Gray A: Haematopoietic effects of workplace exposures: anaemias, leukemias and lymphomas. In *Hunter's Diseases of Occupations*, Baxter P, Aw TC, Cockroft A, Durrington P, Harrington, JM (eds.). London: Hodder Arnold, 2001, pp. 901–913.
7. Kane EV, Roman E, Cartwright R, Parker J, and Morgan G: Tobacco and the risk of acute leukaemia in adults. *British Journal of Cancer* **81,** 1228–1233, 1999.
8. Strom SS, Oum R, Elhor Gbito KY, Garcia-Manero G, and Yamamura Y: De novo acute myeloid leukemia risk factors: a Texas case-control study. *Cancer* **118,** 4589–4596, 2012.
9. Aune D, Lau R, Chan DS, Vieira R, Greenwood DC, et al.: Nonlinear reduction in risk for colorectal cancer by fruit and vegetable intake based on meta-analysis of prospective studies. *Gastroenterology* **141,** 106–118, 2011.
10. Wakai K, Matsuo K, Nagata C, Mizoue T, Tanaka K, et al.: Lung cancer risk and consumption of vegetables and fruit: an evaluation based on systematic review of epidemiological evidence in Japan. *Japanese Journal of Clinical Oncology* **41,** 693–708, 2011.
11. Zhang C, Ho SC, Fu J, Cheng SZ, Chen YM, et al.: Dietary patterns and breast cancer risk among Chinese women. *Cancer Causes and Control* **22,** 115–124, 2011.
12. Ma X, Park Y, Mayne ST, Wang R, Sinha R, et al.: Diet, lifestyle, and acute myeloid leukemia in the NIH-AARP cohort. *American Journal of Epidemiology* **171,** 312–322, 2010.
13. Kasim K, Levallois P, Abdous B, Auger P, and Johnson KC: Lifestyle factors and the risk of adult leukemia in Canada. *Cancer Causes and Control* **16,** 489–500, 2005.
14. Li Y, Moysich KB, Baer MR, Weiss JR, Brasure J et al. Intakes of selected food groups and beverages and adult acute myeloid leukemia. *Leukemia Research* **30,** 1507–1515, 2006.
15. Dosemeci M, Cocco P, Gomez M, Stewart PA, and Heineman EF: Effects of three features of a job-exposure matrix on risk estimates. *Epidemiology* **5,** 124–127, 1994.
16. Block G, Hartman A, Dreser C, Carroll M, Gannon J, et al.: A data-based approach to diet questionnaire design and testing. *American Journal of Epidemiology* **124,** 453–469, 1986.
17. Pillow PC, Hursting SD, Duphorne CM, Jiang H, Honn SE, et al.: Case-control assessment of diet and lung cancer risk in African Americans and Mexican Americans. *Nutrition and Cancer* **29,** 169–173, 1997.
18. Bowman SA, Friday JE, and Moshfegh AJ: *MyPyramid Equivalents Database, 2.0 for USDA Survey Foods, 2003–2004*. Beltsville, MD: Food Surveys Research Group. Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, 2011 Retrieved from http://www.ars.usda.gov/SP2UserFiles/Place/12355000/pdf/mped/mped2_doc.pdf
19. Kipnis V, Freedman LS, Brown CC, Hartman A, Schatzkin A, et al.: Interpretation of energy adjustment models in nutritional epidemiology. *American Journal of Epidemiology* **137,** 1376–1380, 1993.

20. Baglietto L, Krishnan K, Severi G, Hodge A, Brinkman M, et al.: Dietary patterns and risk of breast cancer. *British Journal of Cancer* **104,** 524–531, 2011.
21. Tantamango YM, Knutsen SF, Beeson WL, and Fraser G: Food and food groups associated with the incidence of colorectal polyps: the Adventist Health Study. *Nutrition and Cancer* **63,** 565–572, 2011.
22. Magalhaes B, Bastos J, and Lunet N: Dietary patterns and colorectal cancer: a case-control study from Portugal. *European Journal of Cancer Prevention* **20,** 389–395, 2011.
23. Shahar S, Shafurah S, Hasan Shaari NS, Rajikan R, Rajab NF, et al.: Roles of diet, lifetime physical activity and oxidative DNA damage in the occurrence of prostate cancer among men in Klang Valley, Malaysia. *Asian Pacific Journal of Cancer Prevention* **12,** 605–611, 2011.
24. Steinmetz KA and Potter JD: Vegetables, fruit, and cancer II. *Mechanisms*. *Cancer Causes and Control* **2,** 427–442, 1991.
25. Nomura AM, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, et al.: Association of vegetable, fruit, and grain intakes with colorectal cancer: the Multiethnic Cohort Study. *American Journal of Clinical Nutrition* **88,** 730–737, 2008.
26. Steevens J, Schouten LJ, Goldbohm RA, and van den Brandt PA: Vegetables and fruits consumption and risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study. *International Journal of Cancer* **129,** 2681–2693, 2011.
27. Ganesh B, Sushama S, Monika S, and Suvarna P: A case-control study of risk factors for lung cancer in Mumbai, India. *Asian Pacific Journal of Cancer Prevention* **12,** 357–362, 2011.
28. Corpet DE: Red meat and colon cancer. *Meat Science* **89,** 310–316, 2011.
29. Cross AJ, Pollock JRA, and Bingham SA: Haem, not protein or inorganic iron, is responsible for endogenous intestinal *N*-nitrosation arising from red meat. *Cancer Research* **63,** 2358–2360, 2003.
30. Aune D, De Stefani E, Ronco A, Boffetta P, Deneo-Pellegrini H, et al.: Meat consumption and cancer risk: a case-control study in Uruguay. *Asian Pacific Journal of Cancer Prevention* **10,** 429–436, 2009.
31. Hu J, La Vecchia C, DesMeules M, Negri E, and Mery L: Meat and fish consumption and cancer and Canada. *Nutrition and Cancer* **60,** 313–324, 2008.
32. John EM, Stern MC, Sinha R, and Koo J: Meat consumption, cooking practices, meat mutagens, and risk of prostate cancer. *Nutrition and Cancer* **63,** 525–537, 2011.
33. Salem S, Salahi M, Mohseni M, Ahmadi H, Mehrsai A, et al.: Major dietary factors and prostate cancer risk: a prospective multicenter case-control study. *Nutrition and Cancer* **63,** 21–27, 2011.
34. Berrigan D, Dodd K, Troiano RP, Krebs-Smith SM, and Barbash RB: Patterns of health behavior in US adults. *Prev Med* **36,** 615–623, 2003.
35. Ross JA, Kasum CM, Davies SM, Jacobs DR, Folsom AR, et al.: Diet and risk of leukemia in the Iowa Women's Health Study. *Cancer Epidemiology, Biomarkers and Prevention* **11,** 777–781, 2002.
36. Steinmetz KA and Potter JD: Vegetables, fruit, and cancer prevention: a review. *Journal of the American Dietetic Association* **96,** 1027–1039, 1996.
37. Morgan GJ and Smith MT: Metabolic enzyme polymorphisms and susceptibility to acute leukemia in adults. *Am J Pharmacogenomics* **2,** 79–92, 2002.
38. Ly A, Hoyt L, Crowell J, and Kim YI: Folate and DNA methylation. *Antioxid Redox Signal* **17**(2), 302–326, 2012.
39. Lim U and Song MA: Dietary and lifestyle factors of DNA methylation. *Methods Mol Biol* **863,** 359–376, 2012.
40. Williams EA: Folate, colorectal cancer and the involvement of DNA methylation. *Proc Nutr Soc* **71,** 592–597, 2012.
41. Lin HL, An QZ, Wang QZ, and Liu CX: Folate intake and pancreatic cancer risk: an overall and dose-response meta-analysis. *Public Health* 2013. doi:10.1016/j.puhe.2013.04.008
42. Kim HN, Kim YK, Lee IK, Yang DH, Lee JJ, et al.: Association between polymorphisms of folate-metabolizing enzymes and hematological malignancies. *Leuk Res* **33,** 82–87, 2009.
43. Galbiatti Al, Ruiz MT, Maniglia JV, Raposo LS, Pavarino-Bertelli EC, et al.: Head and neck cancer: genetic polymorphisms and folate metabolism. *Braz J Otorhinolaryngol* **78**(1), 132–139, 2012.
44. McDonald TA, Holland NT, Skibola C, Duramad P, and Smith MT: Hypothesis: Phenol and hydroquinone derived mainly from diet and gastrointestinal flora activity are causal factors in leukemia. *Leukemia* **15,** 10–20, 2001.
45. Tsai H, Cross AJ, Graubard BI, Oken M, Schatzkin A, et al.: Dietary factors and risk of chronic lymphocytic leukemia and small lymphocytic lymphoma: a pooled analysis of two prospective studies. *Cancer Epidemiology, Biomarkers and Prevention* **19,** 2680–2684, 2010.