***Short Communication***

# Diet and Risk of Leukemia in the Iowa Women's Health Study[1]

**Julie A. Ross,[2] Christine M. Kasum, Stella M. Davies, David R. Jacobs, Aaron R. Folsom, and John D. Potter**

Division of Pediatric Epidemiology & Clinical Research, University of Minnesota Department of Pediatrics [J. A. R.], University of Minnesota Cancer Center [J. A. R., S. M. D.], and Division of Epidemiology [C. M. K., D. R. J., A. R. F.], University of Minnesota School of Public Health, Minneapolis, Minnesota 55455; Institute for Nutrition Research, University of Oslo, Norway 0316 [D. R. J.]; and Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington 98104 [J. D. P.]

## Abstract

**Nearly 30,000 individuals ages over 21 years are diagnosed with leukemia each year in the United States. Other than benzene, radiation, and chemotherapy, which account for a small proportion of cases, there are few identified risk factors for adult leukemia. Although recent data from animal studies indicate a potentially protective role for dietary restriction in leukemogenesis, few data exist on dietary relationships in adult leukemia. Food frequency data collected at baseline (1986) were analyzed from the prospective Iowa Women's Health Study to begin to address the role of diet in adult leukemia. Data from 35,221 women ages 55–69 years were analyzed. A total of 138 women developed leukemia during the 14-year follow-up period of 1986 to 1999. With the exception of an inverse association (*P* trend = 0.08) with increasing consumption of all vegetables (relative risk, 0.56 and 95% confidence interval, 0.36–0.88; relative risk, 0.69 and 95% confidence interval, 0.44–1.07 for medium and high consumption, respectively), there was little evidence of an important role for other dietary factors in leukemogenesis. Analyses that excluded cases diagnosed in the first 2 years from baseline did not notably alter the results. Leukemia subgroups, including acute myeloid leukemia and chronic lymphoblastic leukemia, were also analyzed, but no statistically significant associations with dietary factors were revealed. This study provides evidence that increased vegetable consumption may decrease the risk of adult leukemia. However, given that our study focused on older women from a defined geographical area, analyses of prospective studies in other populations are needed to confirm or refute these results.**

## Introduction

Leukemia accounts for ~3% of all newly diagnosed cancer cases in the United States each year; approximately 31,000 Americans are expected to be diagnosed in 2001 (1). The incidence of particular subgroups of leukemia varies with age, which may suggest differences in etiology. ALL[3] is the most common type of leukemia diagnosed in children in the United States, with a ~4-fold higher incidence rate than AML (reviewed in Ref. 2); chronic leukemias are extremely rare in childhood. In contrast, the most common leukemias in adults are AML, chronic myeloid leukemia, and CLL (reviewed in Ref. 3).

Prior cancer chemotherapy and exposure to radiation and benzene are established risk factors for adult leukemia, primarily AML (3). However, these risk factors account for only a small proportion of adult cases. Cigarette smoking has been linked with adult leukemia, although the relative risk estimates are quite small, ~1.2 (4). Risk factors that have been explored and have produced inconsistent associations with leukemia include farming, proximity to nuclear plants, hair dye use, and alcohol consumption (3). By and large, little is known about the etiology of adult leukemia.

Epidemiological studies have suggested an important role for diet in the etiology of several adult malignancies. In a systematic review of 196 case-control studies and 21 cohort studies, an international panel of experts reported that there was convincing or probable evidence that increased vegetable consumption is associated with a decreased risk of colon, breast, pancreas, bladder, lung, larynx, stomach, esophageal, and oral cancer (5). High red meat intake has been associated with an increased risk of colon cancer and non-Hodgkin's lymphoma (5, 6). Animal studies have suggested that dietary restriction (low energy intake) is associated with a decreased risk of leukemia (7, 8), but few epidemiological studies have explored associations between diet and leukemia in adults. We analyzed data from the IWHS, a prospective study of >40,000 women ages 55–69 years.

## Materials and Methods

The IWHS has been described in detail elsewhere (6, 9, 10). Briefly, the IWHS consists of a prospective cohort of Iowa women ages 55–69 years selected from the State of Iowa automobile driver's license list in 1985. A questionnaire was mailed to a random sample of 98,030 women in January 1986, followed by reminder mailings 1 and 4 weeks later. Completed self-administered questionnaires, which included information on weight history, health habits, diet assessment, medical history, and family medical history, were returned by 41,836 women (42.7%). Using information from the driver's license list and 1980 United States Census information, nonresponders

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[2] To whom requests for reprints should be addressed, at University of Minnesota Department of Pediatrics, MMC 422, 420 Delaware St., Southeast, Minneapolis, MN 55455. Phone: (612) 626-2902; Fax: (612) 626-4842; E-mail: ross@epi.umn.edu.

[3] The abbreviations used are: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphoblastic leukemia; IWHS, Iowa Women's Health Study; RR, relative risk; CI, confidence interval; BMI, body mass index.

were found to differ only slightly from responders at baseline; they were 3 months younger than responders, 0.4 $kg/m^2$ heavier, and slightly less likely to live in a rural, less affluent county. Moreover, nonresponders had somewhat higher rates of smoking-related diseases (9).

The 1986 baseline self-administered questionnaire included a slightly modified version of the 126-item food frequency questionnaire developed by Willett *et al.* (11). Validity and reproducibility of the questionnaire for selected nutrients have been examined in 44 women from the IWHS (12). For protein, the correlation was 0.27; food groups were not evaluated.

Deaths were ascertained using Iowa death certificates and the National Death Index. Incident cancers were ascertained through the State Health Registry of Iowa, one of the National Cancer Institute's Surveillance Epidemiology and End Results program sites (13). Surveillance Epidemiology and End Results sites achieve at least 98% case ascertainment. Incident cases were identified through computer matching on name, zip code, birth date, and social security number between the 1986 and 1999 registry cases and the study participants. Data from follow-up surveys indicate that the migration rate from Iowa among cohort members is <1% annually. Topographic and morphological data from the International Classification of Diseases for Oncology (14) were used to classify incident leukemia in the cohort and included codes 9801, 9821, 9823, 9861, 9863, 9867, 9868, 9874, 9940, and 9891.

Before data analysis, women were excluded if they left ≥30 food items blank on the food frequency questionnaire or had implausible daily energy intakes (<600 or ≥5000 kcal/day; $n = 3096$). In addition, we excluded women who self-reported, at baseline, a cancer at any site other than skin or prior use of cancer chemotherapy ($n = 3519$). Of the remaining cohort of 35,221 women, a total of 138 developed leukemia during the 14 years of follow-up.

Baseline distributions of certain characteristics, with respect to leukemia status, were evaluated. $\chi^2$ tests (for categorical variables) and *t* tests (for continuous variables) were performed to determine whether these characteristics differed according to leukemia status. Associations were examined between reported consumption of intake (tertiles) of specific foods and incident leukemia using Cox proportional hazards regression (15). Food groupings were also created[4]; as an example, the total vegetable variable consisted of 66 items, including legumes, tomatoes in sauces, and potatoes (including French fries) but not vegetables in meat mixtures. Finally, selected nutrients, including vitamins C, E, A, and $\beta$-carotene, were evaluated. RRs and 95% CIs were calculated. For each analysis, the RR for a given category of food intake was estimated by exponentiation of the proportional hazards regression coefficient for that level of intake. A Wald $\chi^2$ test for trend was determined across categories of intake, treating the categorical variable as a continuous variable in the models. The SAS statistical package was used in all analyses (16).

## Results

Of the cohort of 35,221 women, >447,294 people years of observation, 138 women developed leukemia during the period from 1986 to 1999. Leukemia diagnoses included 58 CLL, 48 AML, and 12 chronic myeloid leukemia. The remaining leukemias included 3 ALL, 3 acute leukemias, 6 chronic myelogenous leukemias, 4 hairy-cell leukemias, and 4 basophilic leukemias.

*Table 1* Baseline characteristics in 1986 of the IWHS by follow-up leukemia status

| | Cases (138)[a] | Noncases (35,221)[a] | *P* |
|---|---|---|---|
| Education, no. (%) | | | |
| <High school | 34 (24.6) | 6,284 (17.9) | |
| High school | 51 (37.0) | 14,739 (42.1) | |
| >High school | 53 (38.4) | 13,992 (40.0) | 0.11 |
| Marital Status, no. (%) | | | |
| Current | 101 (73.7) | 26,996 (77.4) | |
| Former | 32 (23.4) | 7,024 (20.1) | |
| Never | 4 (2.9) | 859 (2.5) | 0.72 |
| Residence, no. (%) | | | |
| Nonfarm | 132 (95.6) | 33,547 (95.6) | |
| Farm | 6 (4.4) | 1,536 (4.4) | 0.99 |
| Blood transfusion, no. (%) | | | |
| No | 86 (63.2) | 24,919 (71.4) | |
| Yes | 43 (31.6) | 8,875 (25.4) | |
| Not sure | 7 (5.2) | 1,080 (3.1) | 0.08 |
| Cigarette smoking (%) | | | |
| Current | 26 (19.3) | 5,156 (14.9) | |
| Past | 21 (15.6) | 6,727 (19.4) | |
| Never | 88 (65.2) | 22,731 (65.7) | 0.91 |
| Mean total energy | | | |
| Intake, kcal/day | 1,862.0 | 1,798.3 | 0.27 |
| Alcohol consumption | | | |
| Servings/wk | 1.7 | 2.0 | 0.36 |
| BMI | | | |
| Baseline, $kg/m^2$ | 27.9 | 27.0 | 0.03 |

[a] Participants with missing values for certain characteristics are excluded in the totals.

Overall, the women who developed leukemia were not different from the cohort with respect to marital status, alcohol consumption, or farm residence (Table 1). Women who developed leukemia had a statistically significantly higher BMI. There was also a suggestion that women who developed leukemia were less well-educated and more likely to report current smoking, higher energy intake, and a previous blood transfusion; none of these variables, however, was statistically significantly different from the women who did not develop leukemia. Since these variables have been associated with leukemia in past studies, they were included in the analyses (along with age) as potential confounders. The results did not change substantially, however, with or without these additional adjustments.

Table 2 shows the overall results for dietary factors and leukemia. Increasing consumption of all vegetables was associated with a decreased risk of leukemia (RR, 0.56 and 95% CI, 0.36–0.88; RR, 0.69 and 95% CI, 0.44–1.07 for medium and high consumption, respectively; *P* trend, 0.08), which was not accounted for by consumption of either cruciferous (including broccoli, cabbage, cauliflower, brussel sprouts) or carotene-rich vegetables (including carrots, yellow squash, yams, spinach). Additional analyses did not identify any single vegetable group that accounted for this overall decreased risk. Moreover, none of the nutrients examined, including vitamins C, A, E, or $\beta$-carotene, were associated significantly with risk (data not shown). No other notable associations were observed. Given that underlying disease could affect diet, we excluded cases ($n = 26$) diagnosed during the first 2 years of follow-up (1986–87). Although fewer relationships approached statistical significance, there were no notable differences in the results (data not shown).

[4] Food groupings available upon request.

*Table 2* Relative risk of leukemia among Iowa women according to level of intake of various food groups, adjusted for age, energy intake, blood transfusion status, education, BMI, and smoking status IWHS,[a] 1986 to 1999

| Dietary factor | Tertile of intake | | | *P* for trend[b] |
|---|---|---|---|---|
| | 1 | 2 | 3 | |
| Protein (g/day) | | | | |
| Range | <66.2 | 66.2–89.0 | >89.0 | |
| No. of cases | 42 | 44 | 52 | |
| RR | 1.00 | 1.03 | 1.13 | |
| 95% CI | | 0.64–1.66 | 0.61–2.10 | 0.70 |
| % Carbohydrates (total calories) | | | | |
| Range | <45.7 | 45.7–51.9 | >51.9 | |
| No. of cases | 52 | 49 | 37 | |
| RR | 1.00 | 0.91 | 0.72 | |
| 95% CI | | 0.61–1.36 | 0.46–1.11 | 0.14 |
| % Total fat (total calories) | | | | |
| Range | <31.6 | 31.6–36.4 | >36.4 | |
| No. of cases | 43 | 46 | 49 | |
| RR | 1.00 | 1.00 | 1.14 | |
| 95% CI | | 0.65–1.54 | 0.75–1.74 | 0.53 |
| All meats (servings/wk) | | | | |
| Range | <10.3 | 10.3–15.0 | >15.0 | |
| No. of cases | 45 | 50 | 43 | |
| RR | 1.00 | 1.09 | 0.84 | 0.52 |
| 95% CI | | 0.71–1.68 | 0.50–1.41 | |
| Red meat (servings/wk) | | | | |
| Range | <4.0 | 4.0–6.5 | >6.5 | |
| No. of cases | 37 | 48 | 53 | |
| RR | 1.00 | 1.33 | 1.14 | 0.62 |
| 95% CI | | 0.85–2.09 | 0.71–1.86 | |
| Processed meat (servings/wk) | | | | |
| Range | <1.0 | 1.0–1.5 | >1.5 | |
| No. of cases | 54 | 32 | 52 | |
| RR | 1.00 | 0.63 | 0.80 | 0.28 |
| 95% CI | | 0.40–0.99 | 0.52–1.21 | |
| Fish and seafood (servings/wk) | | | | |
| Range | <1.0 | 1.0–1.5 | >1.5 | |
| No. of cases | 41 | 51 | 46 | |
| RR | 1.00 | 0.88 | 1.00 | 0.98 |
| 95% CI | | 0.58–1.35 | 0.64–1.55 | |
| Chicken with skin (servings/wk) | | | | |
| Range | <0.5 | 0.5 | >0.5 | |
| No. of cases | 49 | 26 | 63 | |
| RR | 1.00 | 0.82 | 1.23 | 0.28 |
| 95% CI | | 0.50–1.35 | 0.83–1.81 | |
| Chicken without skin (servings/wk) | | | | |
| Range | <0.5 | 0.5 | >0.5 | |
| No. of cases | 53 | 25 | 60 | |
| RR | 1.00 | 0.77 | 0.86 | 0.45 |
| 95% CI | | 0.47–1.25 | 0.58–1.25 | |
| Skim milk (servings/wk) | | | | |
| Range | <3.0 | 3.0–7.0 | >7.0 | |
| No. of cases | 46 | 53 | 39 | |
| RR | 1.00 | 0.92 | 1.01 | 0.97 |
| 95% CI | | 0.61–1.36 | 0.64–1.58 | |
| Whole milk (servings/wk)[c] | | | | |
| Range | <0.5 | 0.5 | | |
| No. of cases | 109 | 29 | | |
| RR | 1.00 | 0.94 | | 0.77 |
| 95% CI | | 0.62–1.43 | | |
| All dairy products (servings/wk) | | | | |
| Range | <10.5 | 10.5–20.0 | >20.0 | |
| No. of cases | 44 | 36 | 58 | |
| RR | 1.00 | 0.75 | 1.01 | 0.91 |
| 95% CI | | 0.48–1.17 | 0.65–1.58 | |

*Table 2* Continued

| Dietary factor | Tertile of intake | | | *P* for trend[b] |
|---|---|---|---|---|
| | 1 | 2 | 3 | |
| All fruits (servings/wk) | | | | |
| Range | <13.1 | 13.1–20.9 | >20.9 | |
| No. of cases | 50 | 45 | 43 | |
| RR | 1.00 | 0.94 | 0.77 | 0.25 |
| 95% CI | | 0.62–1.43 | 0.49–1.20 | |
| All vegetables (servings/wk) | | | | |
| Range | <18.1 | 18.1–28.0 | >28.0 | |
| No. of cases | 56 | 34 | 48 | |
| RR | 1.00 | 0.56 | 0.69 | 0.08 |
| 95% CI | | 0.36–0.88 | 0.44–1.07 | |
| Cruciferous vegetables (servings/wk) | | | | |
| Range | <2.0 | 2.0–3.5 | >3.5 | |
| No. of cases | 41 | 51 | 46 | |
| RR | 1.00 | 1.12 | 0.99 | 0.96 |
| 95% CI | | 0.74–1.71 | 0.64–1.54 | |
| Carotene-rich vegetables (servings/wk) | | | | |
| Range | <1.5 | 1.5–3.0 | >3.0 | |
| No. of cases | 37 | 53 | 48 | |
| RR | 1.00 | 1.05 | 1.02 | 0.93 |
| 95% CI | | 0.68–1.62 | 0.65–1.62 | |
| Whole grains (servings/wk) | | | | |
| Range | <6.9 | 6.9–12.5 | >12.5 | |
| No. of cases | 51 | 41 | 46 | |
| RR | 1.00 | 0.88 | 0.86 | 0.49 |
| 95% CI | | 0.58–1.35 | 0.56–1.32 | |

[a] Subjects with missing values for any of the covariates were not included in the final regression models.
[b] Tests for trend were performed by treating the categorical variable as a continuous variable in the model.
[c] No consumption was >0.5 servings per week.

Finally, because leukemia is a heterogeneous malignancy, we explored associations with CLL (58 cases) and AML (48 cases) separately, recognizing that the sample sizes reduce confidence in interpretation (Table 3). For CLL, and to a lesser extent AML, increasing consumption of dietary fat was associated with increased risk. There was a suggestion that increasing dietary protein was positively associated with AML but not CLL. Consumption of all vegetables appeared to be associated with a decreased risk of AML but was not as apparent for CLL. Finally, there was a slight suggestion of a greater risk of CLL associated with increasing consumption of cruciferous vegetables.

## Discussion

Numerous cohort and case-control studies have demonstrated that increased vegetable (and to some extent fruit) consumption is associated with a decreased risk of many adult malignancies, including cancers of the stomach, colon, esophagus, and lung, although some studies have found no association (reviewed in Ref. 5). Several animal studies have demonstrated that dietary restriction delays the onset of leukemia but does not reduce its progression (7, 8, 17, 18). However, few epidemiological studies have considered relationships between diet and adult leukemia. An ecologic study of international data showed some positive correlations between energy intake and leukemia incidence, particularly with lymphoblastic leukemia, but no analytic study has examined this association (19). Kwiatkowski (20), in a case-control study of 119 adult patients with acute

*Table 3* Relative risk of AML and CLL among Iowa women according to level of intake of various food groups, adjusted for age, energy intake, blood transfusion status, education, BMI, and smoking status

| Food group | AML = 48 cases | | | | | CLL = 58 cases | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (RR 2nd tertile) | 95% CI | (RR 3rd tertile) | 95% CI | ($P$ trend) | (RR 2nd tertile) | 95% CI | (RR 3rd tertile) | 95% CI | ($P$ trend) |
| Protein | 1.30 | 0.58–2.94 | 1.45 | 0.51–4.13 | 0.49 | 1.01 | 0.49–2.09 | 0.93 | 0.34–2.55 | 0.90 |
| Carbohydrates | 1.04 | 0.53–2.03 | 0.72 | 0.34–1.53 | 0.41 | 0.62 | 0.32–1.18 | 0.56 | 0.28–1.09 | 0.08 |
| Fat | 1.02 | 0.48–2.17 | 1.43 | 0.70–2.91 | 0.30 | 1.68 | 0.84–3.38 | 1.53 | 0.75–3.13 | 0.26 |
| All meats | 1.77 | 0.83–3.74 | 0.98 | 0.38–2.50 | 0.95 | 0.89 | 0.46–1.73 | 0.74 | 0.33–1.69 | 0.48 |
| Red meat | 1.42 | 0.65–3.13 | 1.47 | 0.66–3.34 | 0.38 | 1.19 | 0.59–2.39 | 1.18 | 0.56–2.50 | 0.67 |
| Processed meat | 0.67 | 0.32–1.40 | 0.73 | 0.36–1.49 | 0.39 | 0.60 | 0.30–1.23 | 0.81 | 0.42–1.56 | 0.49 |
| Fish/seafood | 0.62 | 0.31–1.25 | 0.73 | 0.36–1.50 | 0.40 | 1.06 | 0.53–2.11 | 1.25 | 0.62–2.54 | 0.52 |
| Chicken w/ skin | 0.93 | 0.44–2.11 | 1.05 | 0.54–2.03 | 0.89 | 0.96 | 0.44–2.08 | 1.43 | 0.77–2.65 | 0.25 |
| Chicken w/o skin | 0.35 | 0.29–1.54 | 0.77 | 0.41–1.45 | 0.43 | 0.54 | 0.24–1.20 | 0.68 | 0.38–1.24 | 0.22 |
| Skim milk | 0.31 | 0.36–1.39 | 0.88 | 0.45–1.97 | 0.79 | 1.28 | 0.68–2.40 | 1.08 | 0.50–2.32 | 0.78 |
| Whole milk | 0.85 | 0.43–1.69 | | | 0.64 | 0.86 | 0.45–1.65 | | | 0.65 |
| All dairy products | 0.79 | 0.36–1.73 | 1.32 | 0.62–2.79 | 0.42 | 0.81 | 0.40–1.64 | 1.09 | 0.54–2.21 | 0.80 |
| All fruits | 0.92 | 0.45–1.88 | 0.88 | 0.41–1.85 | 0.73 | 0.95 | 0.49–1.82 | 0.72 | 0.35–1.49 | 0.39 |
| All vegetables | 0.58 | 0.28–1.18 | 0.54 | 0.25–1.16 | 0.10 | 0.74 | 0.37–1.47 | 0.86 | 0.42–1.76 | 0.66 |
| Cruciferous | 1.13 | 0.58–2.16 | 0.61 | 0.28–1.33 | 0.23 | 1.57 | 0.77–3.23 | 1.73 | 0.84–3.57 | 0.15 |
| Carotene-rich | 1.02 | 0.51–2.05 | 0.78 | 0.36–1.69 | 0.52 | 0.86 | 0.44–1.70 | 1.00 | 0.49–2.02 | 0.99 |
| Whole grains | 0.42 | 0.19–0.92 | 0.66 | 0.34–1.31 | 0.21 | 1.38 | 0.71–2.67 | 1.06 | 0.52–2.15 | 0.88 |

leukemia (91 AML and 28 ALL), reported possible increased risk with consumption of milk, poultry, and soft water. Moreover, risk was statistically significantly decreased with increasing consumption of raw vegetables.

In our prospective study of >35,000 postmenopausal women, we found an inverse association of leukemia with vegetable consumption. There was little evidence that any other dietary factor was notably associated with leukemia risk. We also explored potential associations with the two leukemic subgroups for which we had a reasonable number of cases. With the exception of weak positive associations with cruciferous vegetables and CLL, and between total protein and AML, there was little evidence of potentially important leukemia-specific associations.

There are some limitations to this study that need to be discussed. First, although this is the first prospective study to examine dietary relationships in adult leukemia, the results are based on only 138 cases. In particular, our power to detect statistically significant associations is diminished when exploring associations with leukemia subgroups. Second, given these data were based on a single measure of diet using a food frequency questionnaire, reporting errors are likely (21, 22). However, because information on diet was collected prospectively, all types of reporting errors are likely to be nondifferential with respect to outcome and thus should bias the RR estimates toward the null. Third, the narrow range of intake observed for some dietary variables may have precluded the identification of important associations. Fourth, because many dietary variables were explored, it is possible that our finding with total vegetable consumption is attributable to chance. In fact, the apparent lack of an association with the majority of dietary variables examined may suggest that diet is unlikely to play a major role in the development of leukemia. Finally, this study included mostly white, postmenopausal women. Although a relatively homogeneous population decreases the potential for residual confounding, the results are not necessarily generalizable to other populations.

A strength of this study is the prospective nature of the data collection. Many epidemiological studies of diet and cancer use the case-control approach, and it is often difficult to interpret study findings because of recall bias or issues related to control selection. There is also the potential that underlying disease could influence recent eating habits. In our study, we evaluated the latter possibility by restricting the analyses to cases diagnosed 2 years from baseline. Finally, we were able to consider several potential confounders in the final analysis, including age, education, BMI, total energy intake, blood transfusion, and smoking status. Given that this is the largest prospective study to date to consider dietary factors in adult leukemia, it will be important for other large prospective studies to evaluate dietary relationships and leukemia risk to confirm or refute these findings.

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