Dietary Folate Consumption and Breast Cancer Risk

Thomas E. Rohan, Meera G. Jain, Geoffrey R. Howe, Anthony B. Miller

Deficient dietary folate intake may predispose individuals to cancer as a consequence of disruption of DNA synthesis, repair, and methylation (1, 2). Diets deficient in methyl groups may result in the activation of oncogenes and inactivation of tumor suppressor genes (3). Relatively low intake of methionine and relatively high intake of alcohol may increase folate requirements, the former by reducing the availability of methyl groups (4) and the latter by interfering with folate metabolism (5). Epidemiologic evidence linking dietary folate, methionine, and alcohol intake with cancer risk is limited. Two prospective studies (6, 7) showed that diets low in folate and methionine and high in alcohol were associated with increased risk of colorectal adenomas and of colon cancer, respectively. Another prospective study (8) showed an increased risk of recurrence of colorectal adenoma in association with a high-alcohol, low-folate diet, and a case–control study (9) showed an increased risk of rectal cancer in association with a low-folate, high-alcohol dietary combination. A recent prospective study (10) showed some evidence for an inverse association between folate intake and breast cancer risk in women with relatively high alcohol intake; alcohol consumption by itself has been associated with an increased breast cancer risk (11). Given the paucity of currently available prospective data, we examined the association between dietary folate intake and breast cancer risk and its modification by methionine and alcohol intake in a cohort study in Canada.

A case–cohort analysis was undertaken within the cohort of 56,837 women in the Canadian National Breast Screening Study (NBSS) (12–14) who completed a self-administered, quantitative food-frequency questionnaire developed for the NBSS (15, 16). The NBSS was approved by the University of Toronto Human Subjects Review Committee. The dietary questionnaire ascertained the frequency of consumption and usual portion size of 86 food items (including alcoholic beverages) and was used to estimate daily intake of alcohol (standard servings of beer [350 mL], wine [120 mL], and spirits [45 mL] were estimated to contain 12.6 g, 13.8 g, and 17.1 g of ethanol, respectively) and calories with the use of a nutrient database developed by modifying the U.S. Department of Agriculture’s food-composition tables to include typically Canadian foods (17). Data on intake of folate, methionine, and specific carotenoids were obtained from previously published values (18–20). The values for folate intake presented here are for intake from dietary sources alone, since data on the folate content of vitamin supplements were not available. Major sources of dietary folate were liver, green leafy vegetables, and whole-grain cereals.

Case patients were the 1469 women diagnosed with incident invasive carcinoma of the breast during follow-up from recruitment (which occurred from 1980 through 1985) to December 31, 1993, and ascertained by record linkage to the Canadian Cancer Database. For the analysis, a subcohort was constructed by the selection of a random sample of 5681 women from the dietary cohort. After exclusions, the main analyses were based on 1336 case patients (1469 case patients minus 128 with no diet questionnaire available minus five with extreme values for energy intake [i.e., those subjects for whom natural log-transformed total energy intake was more than three standard deviations from the mean natural log-transformed total energy]) and 5382 women (including 144 of the case patients) in the subcohort (5681 minus 256 with no diet questionnaire available minus 43 with extreme energy values).

Incidence rate ratios (IRRs) and robust standard errors (21) for the association between folate intake and breast cancer risk were estimated with the use of Poisson regression. Case patients contributed person-time to the study from their date of enrollment until the date of diagnosis of their breast cancer, and non-case subjects contributed person-time from their date of enrollment until December 31, 1993, or death (whichever came first). The IRRs were adjusted for energy intake (22) and for the variables listed in the footnotes to the tables. Tests for trend (on 1 df) in the association between folate and breast cancer risk were performed by fitting categorized variables as continuous variables, and tests for interaction were based on likelihood ratio tests comparing models with and without product terms representing the variables of interest. All statistical tests were two-sided, and P values less than .05 were considered to be statistically significant.

Overall, as well as in postmenopausal women alone, there was no association between dietary folate intake and breast cancer risk (Table 1). There was some suggestion of an increased risk at the uppermost quintile level of folate intake in premenopausal women, but the associated 95% confidence interval (CI) included unity. Risk varied little in association with folate intake among women in the lowest 80% of the distribution of alcohol consumption (intakes of ≤14 g of alcohol/day) (Table 2, A), but there were marked reductions in risk associated with folate intake among those consuming more than 14 g of alcohol/day, and the associated test for trend was statistically significant (P = .004) [the adjusted IRR associated with an intake of >14 g of alcohol/day versus that associated with an intake of ≤14 g of alcohol/day was 1.12 (95% CI = 0.94–1.34); risk was greater at higher levels of intake (16)]. This pattern, while evident in both menopausal strata, was more pronounced in postmenopausal women. However, on formal testing, there was no evidence for an interaction between folate and alcohol [e.g., in the total study population, χ²(1) = 1.380; P = .24]. There was little evidence for variations...
Table 1. Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for the association between dietary folate intake and risk of breast cancer*  

<table>
<thead>
<tr>
<th>Study group</th>
<th>Quintile level of folate intake</th>
<th>1 (low)†</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 (high)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>Case patients/pyr‡</td>
<td>258/113 868</td>
<td>1</td>
<td>263/113 501</td>
<td>266/111 799</td>
<td>264/113 626</td>
<td>285/113 397</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>Case patients/pyr‡</td>
<td>69/5792</td>
<td>1</td>
<td>61/4931</td>
<td>52/4153</td>
<td>41/4284</td>
<td>64/4688</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>Case patients/pyr‡</td>
<td>151/82 565</td>
<td>1</td>
<td>157/84 306</td>
<td>157/87 153</td>
<td>176/90 039</td>
<td>176/89 433</td>
</tr>
</tbody>
</table>

*Adjusted for energy intake, age, age at menarche, number of live births, menopausal status, family history of breast cancer in a first-degree relative, practice of breast self-examination, alcohol consumption, randomization group, and study center. All P values are two-sided and, if less than .05, are considered to be statistically significant.
†Reference category. Quintile cut points for folate were 224.78, 266.83, 305.01, and 354.28 μg/day.
‡Number of case patients/estimated person-years of follow-up.

Table 2. Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for the association between dietary folate intake and risk of breast cancer by levels of alcohol consumption, overall, and by menopausal status (A) and by levels of methionine consumption, overall, and by menopausal status (B)*  

<table>
<thead>
<tr>
<th>Study group</th>
<th>Quintile level of folate intake</th>
<th>1 (low)†</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 (high)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) By levels of alcohol consumption, overall, and by menopausal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol intake, ≤14 g/day</td>
<td>Case patients/pyr‡</td>
<td>182/92 657</td>
<td>1</td>
<td>217/89 798</td>
<td>191/89 654</td>
<td>207/92 335</td>
<td>285/91 425</td>
</tr>
<tr>
<td>Alcohol intake, &gt;14 g/day</td>
<td>Case patients/pyr‡</td>
<td>76/21 211</td>
<td>1</td>
<td>46/23 703</td>
<td>75/22 145</td>
<td>57/21 291</td>
<td>44/21 972</td>
</tr>
<tr>
<td>Premenopausal and alcohol intake, ≤14 g/day</td>
<td>Case patients/pyr‡</td>
<td>47/4278</td>
<td>1</td>
<td>46/5346</td>
<td>40/2938</td>
<td>33/3202</td>
<td>52/3479</td>
</tr>
<tr>
<td>Premenopausal and alcohol intake, &gt;14 g/day</td>
<td>Case patients/pyr‡</td>
<td>22/1514</td>
<td>1</td>
<td>15/1384</td>
<td>12/1214</td>
<td>8/1082</td>
<td>12/1209</td>
</tr>
<tr>
<td>Postmenopausal and alcohol intake, ≤14 g/day</td>
<td>Case patients/pyr‡</td>
<td>108/67 376</td>
<td>1</td>
<td>130/67 055</td>
<td>111/70 664</td>
<td>137/74 197</td>
<td>153/72 556</td>
</tr>
<tr>
<td>Postmenopausal and alcohol intake, &gt;14 g/day</td>
<td>Case patients/pyr‡</td>
<td>43/15 190</td>
<td>1</td>
<td>27/17 251</td>
<td>46/16 489</td>
<td>39/15 842</td>
<td>23/16 877</td>
</tr>
</tbody>
</table>

B) By levels of methionine consumption, overall, and by menopausal status | | | | | | | |
| Methionine intake, ≤1.5 g/day | Case patients/pyr‡ | 73/36 155 | 1 | 65/30 523 | 67/28 075 | 55/25 626 | 56/22 393 | 1 | 0.90 (0.56–1.45) | 0.87 (0.54–1.41) | 0.85 (0.52–1.38) | 1.04 (0.62–1.74) | .96 |
| Methionine intake, >1.5 g/day | Case patients/pyr‡ | 185/77 713 | 1 | 198/82 978 | 199/83 724 | 209/88 000 | 229/91 004 | 1 | 0.99 (0.75–1.30) | 0.92 (0.68–1.26) | 0.97 (0.74–1.27) | 0.97 (0.74–1.27) | .77 |
| Premenopausal and methionine intake, ≤1.5 g/day | Case patients/pyr‡ | 21/1661 | 1 | 13/1310 | 11/1203 | 8/959 | 14/1096 | 1 | 0.38 (0.11–1.33) | 0.38 (0.11–1.33) | 0.12 (0.01–1.43) | 1.00 (0.16–6.42) | .39 |
| Premenopausal and methionine intake, >1.5 g/day | Case patients/pyr‡ | 48/1431 | 1 | 48/3621 | 41/2950 | 33/3235 | 50/3593 | 1 | 1.34 (0.67–2.63) | 1.52 (0.75–3.06) | 0.99 (0.50–1.97) | 2.20 (1.15–4.22) | .09 |
| Postmenopausal and methionine intake, ≤1.5 g/day | Case patients/pyr‡ | 45/26 797 | 1 | 43/23 078 | 39/22 030 | 36/20 959 | 33/18 402 | 1 | 0.92 (0.55–1.53) | 0.90 (0.53–1.52) | 0.83 (0.48–1.43) | 0.89 (0.50–1.60) | .61 |
| Postmenopausal and methionine intake, >1.5 g/day | Case patients/pyr‡ | 106/55 769 | 1 | 114/61 228 | 118/65 123 | 140/69 081 | 143/71 032 | 1 | 0.93 (0.68–1.27) | 0.88 (0.65–1.20) | 0.95 (0.70–1.29) | 0.94 (0.69–1.27) | .81 |

*Adjusted for energy intake, age, age at menarche, number of live births, menopausal status, family history of breast cancer in a first-degree relative, practice of breast self-examination, alcohol consumption, randomization group, and study center. All P values are two-sided and, if less than .05, are considered to be statistically significant.
†Reference category. Quartile cut points for folate were 224.78, 266.83, 305.01, and 354.28 μg/day.
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in risk with folate intake by levels of methionine intake overall and in postmenopausal women; in premenopausal women, although risk was decreased at the mid-level of folate intake in those with relatively low methionine intake and increased at the highest level of folate intake in those with relatively high methionine intake, the overall patterns were not clear and the estimates of risk had relatively wide CIs (Table 2, B).

The study findings were similar after additional adjustment for years of education, ever use of oral contraceptives and cigarettes, and Quetelet’s index (i.e., body mass index [weight in kg/height in m²]); after adjustment for α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein, vitamin C, vitamin E, and fiber; after exclusion of subjects who reported having used multivitamin supplements; after exclusion of case patients diagnosed within 1 year of recruitment; after exclusion of subjects with a history of nonmalignant breast disease; and after exclusion of subjects with a history of another cancer before the development of breast cancer. Furthermore, there was no evidence for differences in the association between folate consumption and breast cancer risk by NBSS randomization group and when examined separately for screen- and interval-detected cases (although some estimates in premenopausal women had relatively wide CIs).

Potential sources of bias in this study have been discussed elsewhere (16). In brief, recall bias is not an issue, since the study was prospective in design and selection bias arising from loss to follow-up seems unlikely, given that outcome was ascertained by passive follow-up through national databases with complete population coverage. However, some individuals might have been misclassified with respect to nutrient intake because of the intrinsic limitations of food-frequency questionnaires, with consequent attenuation of the true associations (23). Also, uncontrolled confounding by other (dietary) factors cannot be excluded.

Our results, although possibly chance findings, suggest that dietary folate consumption might be associated with reduced risk of breast cancer at relatively high levels of alcohol intake, particularly in postmenopausal women. Zhang et al. (10) observed a similar phenomenon in association with total folate intake (dietary plus supplemental) in both premenopausal and postmenopausal women. Other epidemiologic studies of folate and breast cancer have not examined risk by levels of alcohol: Two case-control studies (24, 25) showed some evidence for inverse associations between dietary folate and risk, whereas another study (26) showed no association, and a prospective study (27) showed no association between serum folate levels and risk. Clearly, further data are required, but our findings suggest that the adverse effects of alcohol on breast cancer risk might be ameliorated by adequate intake of folate from dietary sources alone.

REFERENCES


NOTES

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