Short Communication

Alcohol, Folate, Methionine, and Risk of Incident Breast Cancer in the American Cancer Society Cancer Prevention Study II Nutrition Cohort

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Abstract
Recent studies suggest that the increased risk of breast cancer associated with alcohol consumption may be reduced by adequate folate intake. We examined this question among 66,561 postmenopausal women in the American Cancer Society Cancer Prevention Study II Nutrition Cohort. A total of 1,303 incident cases had accrued during the first 5 years of follow-up. Cox proportional hazards models and stratified analysis were used to examine the relationship between alcohol, dietary and total folate intake, multivitamin use, dietary methionine, and breast cancer. We observed an increasing risk of breast cancer with increasing alcohol consumption (P for trend = 0.01). In the highest category of consumption (15 or more grams of ethanol/day), the risk of breast cancer was 1.26 (95% confidence interval, 1.04–1.53) compared with nonusers. We observed this association with higher alcohol consumption for in situ, localized, and regional disease. We found no association between risk of breast cancer and dietary folate, total folate, multivitamin use, or methionine intake. Furthermore, we found no evidence of an interaction between levels of dietary folate (P for interaction = 0.10) or total folate (P for interaction = 0.61) and alcohol. Nor did we find evidence of an interaction between alcohol consumption and recent or long-term multivitamin use (P for interaction = 0.27). Our results are consistent with a positive association with alcohol but do not support an association with folate or methionine intake or an interaction between folate and alcohol intake on risk of breast cancer.

Introduction
Women who drink on average one alcoholic beverage daily have a 10–30% higher risk of incident breast cancer than nondrinkers (1, 2). Recently, it has been suggested that the increased risk of breast cancer associated with alcohol consumption may be reduced by adequate folate intake (3). Three prospective studies and one case-control study (3–6) have examined this association, and the collective findings suggest that adequate folate levels may attenuate the risk of breast cancer associated with alcohol consumption.

Experimental evidence suggests that alcohol interferes with folate absorption, transport, and metabolism, potentially limiting tissue folate stores (7). Folate deficiency is implicated in carcinogenesis through interference with DNA synthesis and through the depletion of labile methyl groups widely used in biological methylation reactions (8). The availability of S-adenosyl-methionine, the methyl donor widely used in biomolecule methylation, is dependent on both folate and methionine, thus deficient methionine supply may increase folate requirements and possibly contribute to carcinogenesis via abnormal DNA methylation (9).

The primary objective of this study was to evaluate a possible interaction between folate and alcohol on incident breast cancer. We present data on consumption of alcohol, folate, methionine, and multivitamins as possible risk factors, in addition to examining possible interactions between those factors on breast cancer risk among 66,561 postmenopausal women in the American Cancer Society CPS2-II Nutrition Cohort after 5 years of follow-up.

Materials and Methods
Study Cohort and Follow-up. Women in this analysis were selected from the 97,787 female participants in the CPS-II Nutrition Cohort, a prospective study of cancer incidence and mortality among United States men and women established in 1992, as described in detail elsewhere (10). Participants completed a mailed questionnaire at enrollment that included information on demographic, medical, reproductive, lifestyle, and dietary factors. A follow-up questionnaire was mailed between September 1997 and August 1998 to update information and to ascertain newly diagnosed cancers (response rate > 90%).

Excluded from this analysis were women lost to follow-up from 1992 to 1997–1998 (n = 7,592), women with prevalent cancer (except non-melanoma skin cancer) at baseline (n = 11,601), and women with cirrhosis (n = 36). Women with unknown menopausal status (n = 604) or who were not postmenopausal (n = 4,247) were excluded because of the small number of cases occurring in this group (n = 105) and because our previous study had shown no association between alcohol and breast cancer in premenopausal women (11). Also excluded were women whose calculated daily energy intake was outside the range of 550–3500 kcal/day or who were missing 15% or more of the dietary questions (n = 6,779), and who had missing alcohol data (n = 257).

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2 The abbreviations used are: CPS, Cancer Prevention Study; CI, confidence interval; RR, rate ratio; FFQ, food frequency questionnaire; HRT, hormone replacement therapy; BMI, body mass index.

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expression of breast cancer risk could be increased by supplement use. Total folate did not include dietary folate or multivitamins; the multivariate trend model for ethanol excludes non drinkers.

Methionine (g/day)
0 to 60.4 1.00 0.1 1.00 0.10 1.00
0.64 to <0.76 1.00 0.1 1.00 0.10 1.00
0.76 to <0.88 1.00 0.1 1.00 0.10 1.00
0.88 to <1.04 1.00 0.1 1.00 0.10 1.00
1.04+ 1.00 0.1 1.00 0.10 1.00

Multivitamin use
None in 1982 or 1992 1.00 0.1 1.00 0.10 1.00
Any use in 1982, none in 1992 1.00 0.1 1.00 0.10 1.00
Any use in 1982 and in 1992 1.00 0.1 1.00 0.10 1.00
None in 1982, any in 1992 1.00 0.1 1.00 0.10 1.00

Table 1 Risk of incident breast cancer among postmenopausal women by ethanol, folate, methionine, and multivitamin intake in the CPS-II Nutrition Cohort, 1992–1997

<table>
<thead>
<tr>
<th>Variable</th>
<th>Censor</th>
<th>Case</th>
<th>RR</th>
<th>95% CI</th>
<th>RR</th>
<th>95% CI</th>
<th>P trend</th>
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<tr>
<td>Ethanol (g/day)</td>
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<td></td>
<td></td>
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<tr>
<td>None</td>
<td></td>
<td>31,296</td>
<td>598</td>
<td>1.00</td>
<td>1.00</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>0.1 to &lt;5</td>
<td></td>
<td>17,936</td>
<td>353</td>
<td>1.03</td>
<td>0.90–1.17</td>
<td>1.00</td>
<td>0.88–1.15</td>
</tr>
<tr>
<td>5 to &lt;10</td>
<td></td>
<td>5,922</td>
<td>109</td>
<td>0.96</td>
<td>0.78–1.18</td>
<td>0.94</td>
<td>0.77–1.16</td>
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<tr>
<td>10 to &lt;15</td>
<td></td>
<td>4,642</td>
<td>109</td>
<td>1.21</td>
<td>0.99–1.49</td>
<td>1.18</td>
<td>0.96–1.46</td>
</tr>
<tr>
<td>15+</td>
<td></td>
<td>5,462</td>
<td>134</td>
<td>1.29</td>
<td>1.07–1.55</td>
<td>1.26</td>
<td>1.04–1.53</td>
</tr>
<tr>
<td>Dietary folate (µg/day)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;178.8</td>
<td></td>
<td>16,220</td>
<td>297</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
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<tr>
<td>178.8 to &lt;230.9</td>
<td></td>
<td>16,257</td>
<td>340</td>
<td>1.13</td>
<td>0.97–1.32</td>
<td>1.11</td>
<td>0.95–1.30</td>
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<tr>
<td>230.9 to &lt;294.3</td>
<td></td>
<td>16,359</td>
<td>339</td>
<td>1.11</td>
<td>0.95–1.30</td>
<td>1.10</td>
<td>0.93–1.29</td>
</tr>
<tr>
<td>294.3+</td>
<td></td>
<td>16,422</td>
<td>327</td>
<td>1.07</td>
<td>0.92–1.25</td>
<td>1.07</td>
<td>0.91–1.27</td>
</tr>
<tr>
<td>Total folate (µg/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;209.8</td>
<td></td>
<td>16,261</td>
<td>307</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
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<tr>
<td>209.8 to &lt;319.8</td>
<td></td>
<td>16,335</td>
<td>317</td>
<td>1.02</td>
<td>0.87–1.19</td>
<td>0.99</td>
<td>0.85–1.17</td>
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<tr>
<td>319.8 to &lt;603.7</td>
<td></td>
<td>16,216</td>
<td>331</td>
<td>1.08</td>
<td>0.92–1.26</td>
<td>1.04</td>
<td>0.89–1.22</td>
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<tr>
<td>603.7+</td>
<td></td>
<td>16,446</td>
<td>348</td>
<td>1.11</td>
<td>0.95–1.29</td>
<td>1.10</td>
<td>0.94–1.29</td>
</tr>
<tr>
<td>Methionine (g/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.64</td>
<td></td>
<td>13,320</td>
<td>262</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.64 to &lt;0.76</td>
<td></td>
<td>12,855</td>
<td>259</td>
<td>1.02</td>
<td>0.86–1.21</td>
<td>1.01</td>
<td>0.85–1.20</td>
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<tr>
<td>0.76 to &lt;0.88</td>
<td></td>
<td>13,006</td>
<td>280</td>
<td>1.10</td>
<td>0.93–1.30</td>
<td>1.08</td>
<td>0.91–1.28</td>
</tr>
<tr>
<td>0.88 to &lt;1.04</td>
<td></td>
<td>13,132</td>
<td>265</td>
<td>1.03</td>
<td>0.86–1.22</td>
<td>1.01</td>
<td>0.84–1.20</td>
</tr>
<tr>
<td>1.04+</td>
<td></td>
<td>12,945</td>
<td>237</td>
<td>0.93</td>
<td>0.78–1.11</td>
<td>0.92</td>
<td>0.77–1.11</td>
</tr>
<tr>
<td>Multivitamin use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None in 1982 or 1992</td>
<td>28,150</td>
<td>542</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any use in 1982, none in 1992</td>
<td>9,440</td>
<td>186</td>
<td>1.03</td>
<td>0.87–1.22</td>
<td>1.01</td>
<td>0.85–1.19</td>
<td></td>
</tr>
<tr>
<td>Any use in 1982 and in 1992</td>
<td>10,553</td>
<td>227</td>
<td>1.13</td>
<td>0.96–1.31</td>
<td>1.12</td>
<td>0.96–1.30</td>
<td></td>
</tr>
<tr>
<td>No use in 1982, any in 1992</td>
<td>17,115</td>
<td>348</td>
<td>1.06</td>
<td>0.92–1.21</td>
<td>1.02</td>
<td>0.89–1.17</td>
<td></td>
</tr>
</tbody>
</table>

a Univariate Cox model, stratified by age.
b Multivariate Cox model, stratified by age, includes ethanol, dietary folate, methionine, multivitamin use, race, education, first-degree family history of breast cancer, history of breast lump, mammographic history, HRT use, parity and age at first birth, age at menopause, age at menarche, physical activity, BMI, adult weight gain, and energy.
c Multivariate trend model for ethanol excludes non drinkers.
d Multivariate model for total folate does not include dietary folate or multivitamin use.

This analysis included 1303 incident breast cancer cases, 1246 initially identified through self-report and 57 identified as interval deaths. Self-reported cases were verified through medical records (n = 1063) or state tumor registries (n = 183). Deaths were identified through linkage with the National Death Index. The death certificate listed breast cancer as a primary or contributory cause of death (International Classification of Diseases, Ninth Revision, codes 174.0–174.9) during the interval from the date of enrollment in 1992 or 1993 through August 31, 1997, in women who had not reported having breast cancer at enrollment. We obtained additional information for 32 of the 57 incident deaths, including date of death, from tumor registries. For the remaining 25 deaths, we used the date of death as a proxy for date of diagnosis. We excluded an additional 108 self-reported breast cancers for which confirmed diagnosis was not obtained and 2 cases with missing year of diagnosis from this analysis.

Dietary Assessment. Usual dietary intake of folate and ethanol was assessed using a semiquantitative 68-item FFQ, which is a modification of the brief “Health Habits and History Questionnaire” developed by Block et al. (10, 12). Dietary and total nutrient intakes were estimated using the Diet Analysis System version 3.8a (13). Nutrient estimates were adjusted for total energy using the residuals method (14). Energy-adjusted correlations between the FFQ and four 24-h recalls were 0.77 for ethanol and 0.43 for dietary folate (overall nutrient mean r = 0.62; Ref. 15).

Because folic acid from supplements is more bioavailable than that from dietary sources (especially after the legal limit on folic acid in multivitamins was raised to 400 µg in 1973 and before regular folate supplementation of grains beginning in 1996; Ref. 16), we also examined whether an interaction was present among users of multivitamins, using estimates of total folate and long-term supplement use. Total folate was estimated by adding dietary and supplemental sources reported on the FFQ, assuming that each multivitamin tablet contains 400 µg of folic acid. Respondents were asked to record how many vitamin tablets they took per day or per week. The two top quartiles of total folate almost exclusively represent folate from supplements (319.8 µg/day and higher). To assess long-term exposure to high folate levels, information on multivitamin use was taken from both the historical 1982 CPS-II questionnaire and the 1992 Nutrition Cohort questionnaire (17). Multivitamin use was classified into four categories: (a) none use reported in both 1982 and 1992; (b) past use (any use reported in 1982, but none in 1992); (c) current use (any use 1992, but none in 1982); and (d) long-term use (any use reported in both 1982 and 1992). Blank multivitamin questions were interpreted as none.

Statistical Analysis. Cox proportional hazards modeling (18) was used to calculate RR and 95% CIs for the relationship between total grams of ethanol/day, dietary and total folate intake (µg/day), dietary methionine (g/day), multivitamin use, and incident breast cancer while adjusting for potential founders. Ethanol was categorized as none, 0.1 to <5, 5 to <10, 10 to <15, and 15+ g/day. Dietary folate (µg/day) and total folate (µg/day) were categorized in quartiles; methionine (g/day) was categorized in quintiles. The multivariate model for total folate did not include dietary folate or multivitamins; the
multivariate model for multivitamin use did not include total folate.

Cox models were stratified by single year of age at enrollment. Potential confounders included in the multivariate models were race, education, family history of breast cancer (first-degree relative related by blood), history of a breast lump, mammographic history, HRT use, parity and age at first live birth, age at menarche, age at menopause, BMI, physical activity (hours of exercise/week in metabolic equivalents), adult weight gain, and energy (kcal/day) in quintiles.

Stratified analysis and multiplicative interaction terms for each main exposure were used to test the a priori hypothesis that high folate consumption would attenuate the positive association between alcohol use and breast cancer. The likelihood ratio test (19) was used to test for significance.

Results

The mean age of women included in this analysis was 62.6 years (range, 40–87 years) and did not differ by alcohol or folate consumption. Those with the highest alcohol consumption tended to have lower intakes of folate and methionine. Nondrinkers were more likely to report never using HRT or multivitamins, fewer years of education, and to have a higher BMI and less physical activity than drinkers.

Results from multivariate models are shown in Table 1. We observed an increased risk of breast cancer for ≥10 g ethanol/day when controlling for other breast cancer risk factors (P for trend = 0.01). In the highest category of ethanol consumption (≥15 g/day), the relative risk of breast cancer was 1.26 (95% CI, 1.04–1.53) compared with nonusers. We found no association between risk of breast cancer and intake of dietary folate, total folate, methionine, or multivitamins. We found similar increases in breast cancer risk among women consuming ≥15 g alcohol/day for in situ (RR = 1.26), localized (RR = 1.24), and regional breast cancer (RR = 1.25; data not shown).

We examined the possible interaction between alcohol and folate consumption on risk of breast cancer in several ways. Table 2 shows the risk of breast cancer by categories of ethanol for dietary folate, total folate, and multivitamin use. We found no evidence of an interaction between ethanol consumption and levels of dietary folate (P for interaction = 0.10), total folate (P for interaction = 0.61), or long-term multivitamin use (P for interaction = 0.27). We also found no interaction when multivitamin use in 1992 was evaluated separately, when only regular multivitamin use (at least 3 times/week) was considered, or when in situ cases were excluded from the analysis (data not shown).

Finally, we used stratified analysis to examine whether women with both low folate and methionine levels (less than median values of 300 μg/day and 0.8 g/day, respectively) were at higher risk if they consumed alcohol compared with women with folate ≥ 300 μg/day and methionine ≥ 0.8 g/day. We found no statistically significant difference in breast cancer risk among these groups (RR = 1.22 and RR = 1.13 for 15+ g ethanol/day in low and high groups, respectively; data not shown).

Discussion

In the CPS-II Nutrition Cohort, alcohol use is associated with increased risk of postmenopausal breast cancer, as has been observed in most previous studies (1, 2). Our results are also consistent with three other large prospective studies (3–5) that do not find a direct association between breast cancer and folate intake. However, these three previous studies all suggest that adequate folate intake may protect against the increased risk of breast cancer associated with alcohol consumption. In contrast,
our data do not suggest an interaction between folate and alcohol intake with respect to breast cancer risk.

There are at least two possible reasons that our findings differ from those of the other published cohort studies. It is possible that our assessment of folate consumption is incomplete, given the brief FFQ that was used in our study relative to others (3–5). Our FFQ may not accurately capture dietary folate consumption. However, multivitamin use, which is likely to be recorded with less error than specific foods, did not modify the association with alcohol; thus, it is unlikely that measurement error can entirely explain our results.

It is also possible that our length of follow-up is too short. It is hypothesized that folate acts early in carcinogenesis, so cases occurring within the first 5 years of follow-up may not benefit from a protective effect of high folate intake. However, when we looked at women who reported multivitamin use in both 1982 and 1992 (assuming that use was continuous), we still saw no evidence of a protective effect for long-term multivitamin use.

In summary, although we observed a positive association between the consumption of alcohol and risk of breast cancer, we cannot corroborate previous reports of an interaction between folate and alcohol consumption. Given the important public health implications for reducing the risk of breast cancer through adequate folate intake, it will be important to reevaluate this question in the future as our follow-up time increases.

Acknowledgments

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References

Cancer Epidemiology, Biomarkers & Prevention

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