Short Communication

Interaction of Dietary Folate Intake, Alcohol, and Risk of Hormone-Receptor-defined Breast Cancer in a Prospective Study of Postmenopausal Women

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Abstract

Alcohol intake is an established risk factor for breast cancer, but the underlying mechanism remains unknown. Four recent studies have described interactions of alcohol and low folate intake. We examined this interaction on the risk of postmenopausal breast cancer stratified by tumor receptor status for estrogen (ER) and progesterone (PR). The Iowa Women’s Health Study is a prospective cohort study of 34,393 at-risk women. Alcohol use and folate intake from diet and supplements were estimated at baseline in 1986 through a semiquantitative food frequency questionnaire. Through 1999, 1,875 cases of breast cancer were identified through linkage to the Iowa Surveillance, Epidemiology, and End Results registry. Compared with nondrinkers with folate intakes above the 50th percentile, women with low folate and high alcohol were at a 1.43-fold greater risk (1.02–2.02). When stratified by tumor receptor status for ER or PR, the risks for low folate/low alcohol were 2.1 (1.18–3.85), 1.0 (0.76–1.42), 1.2 (0.88–1.70), and 1.2 (0.69–2.02) for ER−, ER+, PR+, and PR− tumors, respectively. Because the results were limited primarily to ER− tumors, one plausible interpretation of these data is that alcohol influences breast cancer through its metabolite, acetaldehyde, rather than through effects on ER levels and receptor-mediated pathways.

Introduction

There is consistent evidence that alcohol intake increases risk of breast cancer (1). A recent pooled analysis of >300,000 women and 4,335 cases suggests that intake of 2–5 drinks/day increases risk by roughly 40% (2). The underlying mechanisms through which this occurs are not firmly established (3) but may include an influence on circulating levels of estrogens (4), immune function, enhanced permeability of chemical carcinogens, decreased absorption of essential nutrients (5), or through metabolism of alcohol to acetaldehyde, a known carcinogen (6).

There are now four large epidemiological studies that suggest that risks associated with intake of alcohol may be greater in women with low intakes of dietary folate. The original report, from the Nurses Health Study (7), was quickly replicated with analyses of the Canadian National Breast Cancer Screening Trial (8), a case-control study from Italy (9), and the Iowa Women’s Health Study (10). The consistency of this interaction lends credence to the possibility that the results are real and not merely a chance observation.

The current report describes an updated analysis of the Iowa Women’s Health Study. We reported previously that alcohol is a risk factor for breast cancer (11), primarily for tumors lacking receptors for ER (3) and PR (12), and corroborated the interaction between low folate intake and alcohol consumption (13). The current analyses bring together these previous observations to examine the interaction within strata defined by tumor receptors for ER and PR.

Materials and Methods

Definition of Cohort. Detailed methods of the Iowa Women’s Health Study have been published elsewhere (13). Briefly, the cohort represents 41,836 licensed drivers ages 55–69 years who responded to a mailed survey.

Diet and Risk Factor Assessment. The questionnaire solicited information on factors known or suspected to be relevant to breast cancer risk, including alcohol use, and a 127-item semiquantitative food frequency questionnaire that included use of multivitamins and supplements. Average daily alcohol intake over the previous year was assessed by summing the products of frequency of use of specific beverages by their ethanol content. The reliability and accuracy of the instrument is good (14).

Exclusion Criteria. We excluded women at baseline if they were not postmenopausal (n = 569), had a total or partial mastectomy (n = 1,870), or had any cancer other than skin cancer (n = 2,293). We also excluded women if ≥30 items on the food frequency questionnaire were left blank or if their responses resulted in extreme energy intake values (<600 or ≥5,000 kcal/day; n = 2,712). These exclusions left a total of 34,393 women eligible for follow-up.

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3 The abbreviations used are: ER, estrogen; PR, progesterone; RR, risk ratio; CI, confidence interval.
Follow-Up. We mailed questionnaires in 1987, 1989, 1992, and 1997 to establish vital status and change of address. We ascertained cancer incidence and ER/PR status through annual record linkage to the Iowa Cancer Registry. We ascertained deaths in Iowa through the Cancer Registry supplemented through linkage with the National Death Index.

Through 14 years of follow-up, we identified 1875 cases of breast cancer (1,633 invasive and 242 in situ) among the cohort at risk. Of these, 1191 (63.5%) were ER+; 989 (52.8%) were PR+, and 225 (12.0%) were PR−. Of these, 1191 (63.5%) were ER+ through linkage with the National Death Index.

Analytic Approach. We calculated the length of follow-up for each individual from baseline until the date of breast cancer diagnosis, estimated date of move from Iowa, date of death, or December 31, 1999.

We calculated RR and 95% CIs using Cox proportional hazards regression, with survival modeled as a function of age (15). To isolate those at the extreme of low folate intake, we defined four percentile categories: >50th (referent), 31st-50th, 11th-30th, and ≤10th. We categorized use of alcohol into three levels: never drinkers, ≤4 grams/day, >4 grams/day. The cut-point among drinkers was approximately the median of use. Models considered dietary folate alone and folate including supplements. Two sets of regression models were fit to the data: one adjusting only for age and total caloric intake, one adjusting for additional potential confounding variables.

Results

A cross-tabulation of folate intakes (with and without supplements) with reported alcohol consumption confirmed that the two exposures were independent. Table 1 presents multivariate-adjusted RRs for folate and alcohol by tumor hormone receptor status. Low folate intake from diet alone is associated primarily with breast cancers with missing data on ER or PR. Note that most of these 459 cases were either in situ (41.2%) or localized (42.5%). When folate from supplements is considered, the same general pattern remains. The possible exception is the pattern with ER− tumors in which the graded dose-response trend disappears. Conversely, use of alcohol is associated primarily with ER− and PR− tumors.

Table 2 presents the joint effects of alcohol and folate (including supplements) by receptor status. A formal test for interaction between alcohol and total folate was not statistically significant (P = 0.49). To improve the stability of the risk estimates, the total folate intake categories were decreased from four to three (50:25:25 percentile split). Alcohol use was not associated with risk of any receptor-defined category of breast cancer if folate intake was above the median. Similarly, at all levels of folate and alcohol there was no appreciable association with risk of ER+ tumors. Rather, the largest RR was observed for ER− tumors among women with low total folate and alcohol above the median (RR = 2.14; 95% CI, 1.18–3.85). Notably, the risks for ER− tumors were also elevated when alcohol intake was above the median and folate intake was between the 25th and 50th percentiles.

Because methionine intake may play a role similar to folate in methylation pathways, we also examined the joint effects of alcohol and methionine. Overall, low methionine and high alcohol intakes were associated with a RR of 1.3 (0.90–1.92). Because this was weaker than the alcohol × folate joint effect, no additional analyses were performed.

Discussion

Epidemiological studies of folate and breast cancer have yielded inconsistent results (16, 17). A clearer picture began to emerge when studies examined the joint effects of folate and alcohol (7–10). The current report provides evidence that this interaction may apply primarily to tumors lacking the ER receptor. Because this is the first report to examine the interaction by hormone receptor status, caution is warranted until this observation can be replicated, as it may reflect a chance finding.

There are at least two possible mechanisms that could account for the apparent joint effects of alcohol and folate on risk of ER− breast cancers. The first mechanism takes into consideration the direct carcinogenic effect of the primary metabolite of alcohol, acetaldehyde. Recent experimental evidence suggests that non-neoplastic human mammary epithelial cells treated with alcohol at physiologically relevant concentrations have increased rates of benzo(a)pyrene-DNA adduct formation (18). Rates of DNA adduct formation were even greater when cells were exposed to alcohol before administra-
tion of acetaldehyde. This type of genetic damage is independent of receptor-mediated events, and is, therefore, a plausible explanation for an association of alcohol with ER− breast cancers. Because folate is critical to certain DNA repair pathways (19), it should not be surprising that the association of alcohol and low folate (including supplements) with risk of hormone receptor-specific postmenopausal breast cancer

<table>
<thead>
<tr>
<th>Daily intakes</th>
<th>Alcohol (g)</th>
<th>ER+</th>
<th>RR (95% CI)</th>
<th>ER−</th>
<th>RR (95% CI)</th>
<th>PR+</th>
<th>RR (95% CI)</th>
<th>PR−</th>
<th>RR (95% CI)</th>
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<tr>
<td>Folate (µg/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;351</td>
<td>0</td>
<td>329</td>
<td>1.00 (ref)</td>
<td>50</td>
<td>1.00 (ref)</td>
<td>270</td>
<td>1.00 (ref)</td>
<td>88</td>
<td>1.00 (ref)</td>
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<td>1.32 (0.83–2.11)</td>
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<td>0.99 (0.79–1.25)</td>
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<td>1.04 (0.72–1.52)</td>
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<td>0.65 (0.36–1.14)</td>
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<td>54</td>
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<tr>
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<td>19</td>
<td>1.18 (0.69–2.02)</td>
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References


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