Alcohol Consumption and Risk of Ductal Carcinoma In situ of the Breast in a Cohort of Postmenopausal Women

Geoffrey C. Kabat¹, Mimi Kim¹, James M. Shikany², Allison K. Rodgers³, Jean Wactawski-Wende⁴, Dorothy Lane⁵, Lynda Powell⁶, Marcia L. Stefanick⁷, Matthew S. Freiberg⁹, Rasa Kazlauskaite⁷, Rowan T. Chlebowski¹⁰, Sylvia Wastertheil-Smoller¹, and Thomas E. Rohan¹

Abstract

Background: Observational studies have commonly linked higher alcohol consumption with a modest increase in invasive breast cancer risk, but cohort studies have not examined alcohol intake in relation to ductal carcinoma in situ (DCIS).

Methods: The association between adulthood alcohol consumption assessed at baseline and subsequent DCIS risk was examined in a cohort of postmenopausal women participating in the Women's Health Initiative clinical trials, in which mammography was protocol-mandated. Alcohol intake was assessed by a semiquantitative food-frequency questionnaire. Reported DCIS cases were verified by central pathology report review. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals.

Results: The cohort consisted of 63,822 women with information on alcohol intake, among whom 489 cases of DCIS were ascertained after a median follow-up of 8.0 years. For the primary analysis, invasive breast cancer was treated as a competing risk, and follow-up time was censored at the date of diagnosis of invasive breast cancer. After adjustment for covariates, the hazard ratio for DCIS among women who consumed 14 or more servings of alcohol per week, relative to nondrinkers, was 0.87 (95% confidence interval, 0.50-1.51). In addition, alcohol intake was not associated with risk of either high-grade or low-/moderate-grade DCIS.

Conclusions: In this large cohort study of postmenopausal women, alcohol consumption was not associated with risk of DCIS.

Impact: If other studies confirm our findings, this would suggest that alcohol may have an effect later in the carcinogenic process. Cancer Epidemiol Biomarkers Prev; 19(8); 2066–72. ©2010 AACR.

Introduction

Alcohol consumption has been shown in numerous epidemiologic studies to be associated with a small increase in the risk of invasive breast cancer (1-6). Meta-analyses indicate that the risk of breast cancer increases linearly with increasing alcohol intake, with an approximately 10% increase in risk for each 10 g/d increment of ethanol (1, 3, 4), although some studies suggest that there is a threshold effect (6, 7). The positive association has been observed in both cohort studies and case-control studies (4) and has been observed in association with beer, wine, and hard liquor (3, 8). However, because of the small magnitude of the association, the potential for confounding by factors associated with alcohol intake, and the lack of an animal model for alcohol-induced mammary cancer, it is uncertain whether the association represents a causal relationship (5).

Ductal carcinoma in situ (DCIS), noninvasive breast cancer confined to the breast ducts, is a risk factor for subsequent breast cancer development and is believed to represent an intermediate step between normal breast tissue and invasive breast cancer (9-11). Characteristics of DCIS associated with increased breast cancer risk include tumor size and high nuclear grade (9, 10). Carcinogenic process.
has assessed the association of DCIS with alcohol intake or has taken histologic grade of DCIS (high grade versus low/medium grade) into account in the analysis. We used baseline data on alcohol consumption in a large cohort of postmenopausal women enrolled in the Women’s Health Initiative (WHI) clinical trial and followed for a median of 8.0 years to assess the association of alcohol intake with risk of DCIS, as well as with high-grade and low-/intermediate-grade DCIS.

Materials and Methods

The WHI is a large, multicenter, multifaceted study designed to advance the understanding of the determinants of major chronic diseases in women. It is composed of a clinical trial component and an observational study component (16). The clinical trial component included randomized controlled clinical trials to test the effects of dietary modification, evaluating a low-fat dietary pattern, and/or menopausal hormone therapy, evaluating administration of postmenopausal estrogen alone or estrogen plus progestin, on the risk of coronary heart disease, stroke, pulmonary emboli, breast cancer, colorectal cancer, and fractures. In addition, women participating in those trials were also eligible for a clinical trial evaluating calcium plus vitamin D supplementation. Women between the ages of 50 and 79 years and representing major racial/ethnic groups were recruited from the general population at 40 clinical centers throughout the United States between 1993 and 1998. Details of the design and reliability of the baseline measures have been published (17, 18).

Data collection

At study entry, information was collected on demographics; medical, reproductive, and family history; and dietary and lifestyle factors, including smoking history and alcohol consumption with self-administered questionnaires. Clinical outcomes (including cancer diagnoses) were updated semiannually in the clinical trial by mailed or telephone questionnaires. Self-reported in situ invasive breast cancers were verified by centralized review of medical records and pathology reports (19). As of September 12, 2005, a total of 526 incident cases of carcinoma in situ and 2,214 cases of invasive breast cancer had been diagnosed among 68,132 clinical trial participants after a median of 8.0 years of follow-up.

Information obtained in two different questionnaires was combined to characterize women’s alcohol consumption. In a health habits questionnaire, women were asked whether they had ever consumed at least 12 drinks of any alcoholic beverage over their lifetime and whether they currently (at baseline) still drank alcohol. In addition, in the food frequency questionnaire, women were asked about their intakes of beer, wine, and hard liquor during the past 3 months. Frequency categories for number of servings per unit time were “never or less than once per month,” “1-3 per month,” “1 per week,” “2-4 per week,” “5-6 per week,” “1 per day,” “2-3 per day,” “4-5 per day,” and “6+ per day.” Serving size was also queried. A medium serving was defined as a 12-oz. can or bottle of beer, a 6-oz. glass of wine, or 1 shot (1.5 oz.) of hard liquor. The Pearson correlation coefficient between alcohol intake assessed by the food frequency questionnaire versus 8-day dietary intake (four 24-hour recalls and a 4-day food record) was 0.89 in a validation study carried out in a subsample of 113 participants (20). Two variables were created to describe the frequency of total alcohol intake: a categorical variable (nondrinker, past drinker, <1 drink/mo, <1 drink/wk, 1 to <7 drinks/wk, and 7+ drinks/wk) and a continuous variable (alcoholic drinks per week). In addition, intakes of beer, wine, and hard liquor (servings per week) were also examined.

Of 68,132 clinical trial participants, we excluded 3,428 women who reported a history of any cancer (except nonmelanoma skin cancer) at baseline, 216 women who were missing information on breast cancer as an outcome, 385 women who had either only a positive mammogram or no mammogram during follow-up, and 244 women who were missing information on alcohol consumption. In addition, we excluded in situ cases missing detailed histology (n = 2) and cases of lobular carcinoma in situ (LCIS; n = 35). After exclusions, 63,822 women were available for analysis, among whom 489 DCIS cases were identified. DCIS cases were further classified into high grade (n = 122) and low/medium grade (n = 367).

Women in the hormone therapy trial were mandated to receive yearly mammograms (21), whereas women in the dietary modification trial were required to receive biennial mammograms (22). Compliance with these requirements was good (21, 22), and the majority of women (83.8%) in both trials had annual mammograms. Mammogram results were classified by WHI as “negative,” “benign finding—negative,” “probably benign finding—short interval follow-up suggested,” “suspicious abnormality—biopsy should be considered,” and “highly suggestive of malignancy,” and laterality was coded. We considered the latest mammogram to be negative if the results were characterized as “negative,” “benign finding—negative,” or “probably benign finding.”

Statistical analysis

Our main analysis focused on women diagnosed with DCIS, and invasive breast cancer was treated as a competing risk, with follow-up time censored at the date of diagnosis of invasive breast cancer. This approach is supported by studies indicating that DCIS and invasive breast cancer can develop independently (23, 24). However, because the natural history of DCIS is poorly understood (9, 10), we also carried out two sensitivity analyses. First, the main analysis was repeated with censoring of follow-up time for the invasive breast cancer cases and other noncases at the date of the last negative mammogram preceding diagnosis. Second, to take account of the possibility that invasive cancers passed through an earlier in situ stage (10, 25-27), we reclassified invasive ductal...
carcinoma cases as DCIS, which was assumed to occur at the midpoint between the date of the last negative mammogram and the date of diagnosis of the invasive breast cancer. Noncases in this second sensitivity analysis were censored at the date of the last negative mammogram.

Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for associations of alcohol consumption and risk of DCIS. We classified women according to frequency of alcohol intake (nondrinker, >0 to <1 drink/wk, 1 to <3 drinks/wk, 3 to <7 drinks/wk, 7 to <14 drinks/wk, ≥14 drinks/wk) at baseline. In addition, we examined the association of beer, wine, and hard liquor intakes separately with DCIS. For analyses of high-grade and low-/medium-grade DCIS, due to reduced numbers of cases, alcohol frequency was categorized as nondrinker, >0 to <3 drinks/wk, and ≥3 drinks/wk. To assess confounding, age-adjusted and multivariable-adjusted results were compared. The following covariates were included in multivariable models: age (continuous), age at menarche (continuous), age at first full-term pregnancy (<20, 20-29, ≥30), parity (continuous), age at menopause (<50, ≥50, missing), body mass index [BMI (kg/m²); continuous], waist circumference (cm; continuous), use of oral contraceptives (ever, never), use of hormone therapy (ever, never), history of breast biopsy (never, ever, missing), mammogram in the past 2 years (no, yes), family history of breast cancer in a first-degree relative (absent, present), dietary folate intake, and dietary methionine intake and breast cancer risk by comparing the fit of models with and without the product terms representing the variables of interest with a likelihood ratio test. All P values are two-sided.

Results

Cases and controls were generally similar in terms of age, ethnicity, BMI, age at menarche, age at first birth, age at menopause, oral contraceptive use, physical activity, and pack-years of smoking (Table 1). Cases had lower parity and were more likely than noncases to be ever users of hormone therapy, to have a family history of breast cancer in a first-degree relative, to have a postcollege education, and to have had a mammogram within the past 2 years.

Table 1. Baseline characteristics of DCIS cases and noncases in the WHI clinical trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 489)</th>
<th>Noncases (n = 63,333)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>62.6 ± 6.9</td>
<td>62.7 ± 7.0</td>
<td>0.84</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.9 ± 6.0</td>
<td>28.9 ± 5.9</td>
<td>0.93</td>
</tr>
<tr>
<td>Parity</td>
<td>2.5 ± 1.6</td>
<td>2.7 ± 1.7</td>
<td>0.006</td>
</tr>
<tr>
<td>Age at menopause (y)</td>
<td>47.7 ± 6.7</td>
<td>47.1 ± 6.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Alcohol intake (servings/wk)</td>
<td>2.2 ± 5.2</td>
<td>2.2 ± 4.4</td>
<td>0.76</td>
</tr>
<tr>
<td>Physical activity (METs/wk)*</td>
<td>10.0 ± 12.3</td>
<td>9.6 ± 12.3</td>
<td>0.57</td>
</tr>
<tr>
<td>Age ≤11 y at menarche (%)</td>
<td>21.9</td>
<td>21.8</td>
<td>0.68</td>
</tr>
<tr>
<td>Age ≥30 y at first birth (%)</td>
<td>10.5</td>
<td>8.5</td>
<td>0.12</td>
</tr>
<tr>
<td>Oral contraceptive use (% ever)</td>
<td>44.8</td>
<td>43.6</td>
<td>0.58</td>
</tr>
<tr>
<td>Hormone therapy use (% ever)</td>
<td>59.5</td>
<td>51.5</td>
<td>0.0004</td>
</tr>
<tr>
<td>Breast cancer in a first-degree relative (% yes)</td>
<td>20.9</td>
<td>16.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Education (% postcollege)</td>
<td>31.1</td>
<td>26.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Ethnicity (% non-Hispanic white)</td>
<td>83.6</td>
<td>81.6</td>
<td>0.72</td>
</tr>
<tr>
<td>Pack-years of smoking (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>54.2</td>
<td>52.3</td>
<td></td>
</tr>
<tr>
<td>&gt;0 to &lt;20</td>
<td>26.4</td>
<td>28.6</td>
<td></td>
</tr>
<tr>
<td>20 to &lt;40</td>
<td>10.7</td>
<td>11.2</td>
<td></td>
</tr>
<tr>
<td>≥40</td>
<td>8.8</td>
<td>7.9</td>
<td>0.90</td>
</tr>
<tr>
<td>Mammogram in the last 2 y (%)</td>
<td>86.7</td>
<td>80.0</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

*METs, metabolic equivalent tasks (defined as caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram of body weight per hour at rest) per hour per week.
In both age-adjusted and multivariable-adjusted analyses, alcohol consumption was not associated with risk of DCIS (Table 2). Most HRs were below unity, and there were no trends with increasing level of intake. Relative to nondrinkers, the HR for drinkers of ≥14 servings of alcohol per week was 0.87 (95% CI, 0.50-1.51). When the number of servings of alcohol per week was entered into a separate model as a continuous variable, the HR was 1.00 (95% CI, 0.97-1.02) for an increase of 1 drink/wk. Intakes of beer, wine, and hard liquor individually showed no association with DCIS (data not shown). Furthermore, alcohol intake showed no association with risk of either high-grade or low-/moderate-grade DCIS (Table 2). Results were similar when past drinkers were excluded (data not shown).

In the first sensitivity analysis, in which invasive breast cancer was treated as a competing risk and follow-up time was censored at date of the last negative mammogram, results were similar to those of the primary analysis, in which the invasive breast cancer cases were followed to the date of diagnosis of the invasive cancer: 0.89 (95% CI, 0.51-1.54) for consumers of ≥7 drinks/wk, 0.96 (95% CI, 0.71-1.29) for 4 to <7 drinks/wk, 0.95 (95% CI, 0.61-1.49) for 1 to <4 drinks/wk, and 1.00 (reference) for ≤1 drinks/wk. In the second sensitivity analysis in which invasive breast cancer cases were reclassified as in situ, which was assumed to occur at the midpoint between the last negative mammogram and the date of diagnosis of invasive breast cancer, and in which noncases were censored at the date of the last negative mammogram, risk of DCIS was not associated with level of alcohol intake: 0.97 (95% CI, 0.86-1.08) for <1 drink/wk, 0.95 (95% CI, 0.82-1.09) for 3 to <7 drinks/wk, 0.85 (95% CI, 0.75-0.97) for 7 to ≤14 drinks/wk, and 0.86 (95% CI, 0.69-1.07) for ≥14 drinks/wk (P-trend = 0.75).

In subgroup analyses in which the association of alcohol intake and risk of DCIS was stratified by hormone therapy use, BMI, family history of breast cancer, and dietary folate and methionine intakes, most HRs for the highest drinking category were close to or below unity. The highest drinking category was defined as ≥14 servings of alcohol per week. In the WHI clinical trial, our primary analyses showed no significant associations or trends with alcohol intake. The results were similar in the first sensitivity analysis, in which invasive breast cancer cases were reclassified as in situ, which was assumed to occur at the midpoint between the last negative mammogram and the date of diagnosis of invasive breast cancer, and in which noncases were censored at the date of the last negative mammogram, risk of DCIS was not associated with level of alcohol intake: 0.97 (95% CI, 0.86-1.08) for <1 drink/wk, 0.95 (95% CI, 0.82-1.09) for 3 to <7 drinks/wk, 0.85 (95% CI, 0.75-0.97) for 7 to ≤14 drinks/wk, and 0.86 (95% CI, 0.69-1.07) for ≥14 drinks/wk (P-trend = 0.75).

Discussion

We found no evidence of an association of alcohol intake in adulthood with risk of DCIS among postmenopausal women in the WHI clinical trial. Our primary analysis, treating invasive breast cancer as a competing risk and censoring invasive breast cancer at the date of diagnosis, showed no significant associations or trends with alcohol intake. The results were similar in the first sensitivity analysis, in which follow-up time for the invasive breast cancer cases and noncases was calculated to the date of the last negative mammogram. The second sensitivity analysis, in which invasive breast cancer cases were reclassified as in situ, also provided no evidence of a positive association. Finally, no association was seen with high- or low-/moderate-grade DCIS or in analyses within strata of hormone therapy use, BMI, family history of breast cancer in a first-degree relative, folate intake, and methionine intake.

Four previous studies (all case-control) have examined the association of alcohol intake and in situ breast cancer or DCIS (12-15). Only one study presented analyses for DCIS and LCIS (13), whereas the remaining studies combined all in situ cases into one category. The numbers of cases in the studies were 214 in situ (12), 875 DCIS and 123 LCIS (13), 301 in situ (14), and 1,878 in situ (15). Three of the studies categorized alcohol intake into four or five levels of drinks per week or grams per week (12, 14, 15), whereas the remaining study categorized alcohol intake into four levels (13).

Table 2. Association of alcohol consumption (servings per week) with risk of DCIS in the WHI clinical trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. cases</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCIS (n = 489)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol frequency (servings/wk)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>216</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>&gt;0 to &lt;1</td>
<td>102</td>
<td>0.96 (0.76-1.21)</td>
<td>0.91 (0.71-1.15)</td>
</tr>
<tr>
<td>1 to &lt;3</td>
<td>66</td>
<td>0.92 (0.70-1.21)</td>
<td>0.85 (0.64-1.13)</td>
</tr>
<tr>
<td>3 to &lt;7</td>
<td>56</td>
<td>0.95 (0.71-1.28)</td>
<td>0.84 (0.62-1.15)</td>
</tr>
<tr>
<td>7 to &lt;14</td>
<td>34</td>
<td>0.93 (0.65-1.33)</td>
<td>0.84 (0.58-1.23)</td>
</tr>
<tr>
<td>≥14</td>
<td>15</td>
<td>0.93 (0.55-1.56)</td>
<td>0.87 (0.50-1.51)</td>
</tr>
<tr>
<td>P-trend</td>
<td></td>
<td>0.52</td>
<td>0.44</td>
</tr>
<tr>
<td>High-grade DCIS (n = 122)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol frequency (servings/wk)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>52</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>&gt;0 to &lt;3</td>
<td>47</td>
<td>1.09 (0.73-1.61)</td>
<td>1.08 (0.72-1.62)</td>
</tr>
<tr>
<td>≥3</td>
<td>23</td>
<td>0.85 (0.52-1.39)</td>
<td>0.74 (0.43-1.27)</td>
</tr>
<tr>
<td>P-trend</td>
<td></td>
<td>0.43</td>
<td>0.20</td>
</tr>
<tr>
<td>Low-/medium-grade DCIS</td>
<td>(n = 367)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol frequency (servings/wk)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>164</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>&gt;0 to &lt;3</td>
<td>121</td>
<td>0.89 (0.71-1.13)</td>
<td>0.82 (0.65-1.05)</td>
</tr>
<tr>
<td>≥3</td>
<td>82</td>
<td>0.97 (0.74-1.26)</td>
<td>0.88 (0.66-1.17)</td>
</tr>
<tr>
<td>P-trend</td>
<td></td>
<td>0.99</td>
<td>0.65</td>
</tr>
</tbody>
</table>

*Adjusted for age only.
†Adjusted for the following variables: age (continuous), education (3 levels), ethnicity (3 levels), BMI (kg/m²; continuous), waist circumference (cm; continuous), oral contraceptive use (ever, never), hormone therapy (ever, never), age at menarche (continuous), age at first birth (4 levels), age at menopause (3 levels), family history of breast cancer (yes, no), history of breast biopsy (ever, never, missing), mammograms in the past 2 y (yes, no), pack-years of smoking (0, >0 to <20, 20 to <40, ≥40), physical activity (METs/wk; continuous), observational study (yes, no), and randomization status in hormone therapy, calcium plus vitamin D, and dietary modification trials.
one study contrasted “ever drinkers” with “never drinkers” (13). In three of the studies (12-14), risk estimates were adjusted for frequency of mammographic screening. Three of the studies (12, 14, 15) found no association, whereas the fourth (13) provided suggestive evidence of a positive association of alcohol consumption with risk (odds ratio for drinking ≥183 g of alcohol per week relative to nondrinkers was 2.34; 95% CI, 1.32-4.16); however, the trend was not statistically significant.

In addition, a large case-control study (6) and a cohort study (28) analyzed invasive and in situ cases combined (without further specification as to DCIS and LCIS), but did not present results for in situ cases separately. Terry et al. (6) reported a positive association of lifetime alcohol intake in women with BMI <25 kg/m2 who drank at least 15 g of alcohol per day, which was seen only with invasive and not in situ breast cancer. Current alcohol intake was not associated with increased risk. In an analysis of the Women’s Health Study, Zhang et al. (28) observed a significant positive association of alcohol consumption with invasive and in situ tumors combined (relative risk for intake of ≥30.0 g/d relative to none, 1.32; 95% CI, 0.96-1.82) and a slightly stronger association for invasive tumors only (relative risk for intake of ≥30 g/d relative to none, 1.43; 95% CI, 1.02-2.02). These results suggest that the relative risk for in situ cases only was closer to 1.0 than the overall estimate and was statistically nonsignificant. Thus, our results seem to be consistent with those of most previous studies.

Reported alcohol intake in the WHI cohort was relatively low. Only 10% of women in the clinical trial reported drinking 7 or more alcoholic drinks per week. However, this level of drinking is comparable to that in other studies of middle-income, White populations (6, 7, 28) in which weak evidence of an association with invasive breast cancer has been observed.

The choice of an appropriate reference group is a critical issue in studies of the health effects of alcohol intake, and this issue is also addressed in the WHI study. The reference group was chosen to be current drinkers who drank ≥3 drinks/wk, as this group had the highest risk of breast cancer among the different categories of alcohol intake. The results for this group were then compared to the results for nondrinkers, who were considered to be at the lowest risk.

### Table 3. Association of alcohol intake with DCIS by breast cancer risk factors in the WHI clinical trial

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>HR (95% CI)*</th>
<th>HR (95% CI)*</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone therapy status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinker</td>
<td>Never user (n_cases = 198)</td>
<td>Past user (n_cases = 76)</td>
<td>Current user (n_cases = 215)</td>
</tr>
<tr>
<td>&gt;0 to &lt;3 drinks/wk</td>
<td>1.16 (0.84-1.59)</td>
<td>0.74 (0.43-1.28)</td>
<td>0.72 (0.52-0.98)</td>
</tr>
<tr>
<td>≥3 drinks/wk</td>
<td>0.95 (0.63-1.44)</td>
<td>0.88 (0.46-1.66)</td>
<td>0.73 (0.50-1.05)</td>
</tr>
<tr>
<td>P-interaction</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 (n_cases = 130)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinker</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>&gt;0 to &lt;3 drinks/wk</td>
<td>0.73 (0.47-1.13)</td>
<td>0.83 (0.59-1.17)</td>
<td>1.07 (0.77-1.48)</td>
</tr>
<tr>
<td>≥3 drinks/wk</td>
<td>1.10 (0.71-1.70)</td>
<td>0.69 (0.46-1.05)</td>
<td>0.79 (0.48-1.28)</td>
</tr>
<tr>
<td>P-interaction</td>
<td>0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent (n_cases = 387)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinker</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>&gt;0 to &lt;3 drinks/wk</td>
<td>0.95 (0.75-1.20)</td>
<td>0.65 (0.40-1.05)</td>
<td>1.06 (0.61-1.78)</td>
</tr>
<tr>
<td>≥3 drinks/wk</td>
<td>0.79 (0.59-1.06)</td>
<td>1.01 (0.61-1.68)</td>
<td></td>
</tr>
<tr>
<td>P-interaction</td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary folate intake (μg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;216.8 (n_cases = 238)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinker</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>&gt;0 to &lt;3 drinks/wk</td>
<td>0.81 (0.60-1.09)</td>
<td>0.96 (0.72-1.28)</td>
<td>0.81 (0.57-1.14)</td>
</tr>
<tr>
<td>≥3 drinks/wk</td>
<td>0.91 (0.60-1.09)</td>
<td>0.81 (0.57-1.14)</td>
<td></td>
</tr>
<tr>
<td>P-interaction</td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary methionine intake (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.53 (n_cases = 234)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinker</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>&gt;0 to &lt;3 drinks/wk</td>
<td>0.81 (0.60-1.10)</td>
<td>0.96 (0.72-1.28)</td>
<td>0.89 (0.63-1.25)</td>
</tr>
<tr>
<td>≥3 drinks/wk</td>
<td>0.80 (0.55-1.18)</td>
<td>0.89 (0.63-1.25)</td>
<td></td>
</tr>
<tr>
<td>P-interaction</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for the following variables (except for stratifying variables): age (continuous), education (3 levels), ethnicity (3 levels), BMI (kg/m2; continuous), waist circumference (cm; continuous), oral contraceptive use (ever, never), hormone therapy (ever, never), age at menarche (continuous), age at first birth (4 levels), age at menopause (3 levels), pack-years of smoking (0, >0 to <20, 20 to <40, ≥40), family history of breast cancer (yes, no), history of breast biopsy (ever, never, missing), mammogram in the past 2 y (yes, no), physical activity (METs/wk; continuous), and randomization status in hormone therapy, calcium plus vitamin D, and dietary modification trials.
consumption (29). Use of a one-time assessment to classify women as “abstainers,” “past drinkers,” and “occasional drinkers” may result in misclassification of lifetime alcohol intake due to misreporting of current and past drinking patterns (29, 30). Furthermore, abstainers tend to differ from occasional drinkers and from past drinkers on a range of sociodemographic and lifestyle factors, and these differences may distort the observed effects of alcohol. However, when we controlled for a large number of sociodemographic factors and breast cancer risk factors, the multivariable-adjusted HRs tended to be farther below unity than the age-adjusted HRs (Table 2). Another issue is that some past drinkers may have quit due to illness (“sick quitters”), and inclusion of this group in the reference group could make light/moderate drinking seem protective (29, 30). Conversely, if those who quit were more health-conscious than continuing drinkers, it could create a spurious positive association with alcohol intake. However, when past drinkers were excluded from the analysis, the results were basically unchanged.

One possible explanation for the lack of an association of alcohol consumption with DCIS, in contrast to the consistent association observed with invasive cancer, is that only a small proportion of DCIS cases progress to invasive breast cancer and that an association with alcohol may only be seen in cases that progress. If this were true, the association would be diluted when all DCIS cases are analyzed as a group. We saw no suggestion of an association of alcohol consumption with high-grade DCIS, which has a greater probability of progression (9, 10); however, the number of cases was small, and the highest category of alcohol intake was only ≥3 drinks/wk, limiting the power to detect an effect.

Strengths of the present study include its prospective nature, large number of in situ cancers, centralized pathology review, high level of mammographic screening of women in the clinical trials throughout the follow-up period, and availability of information on a wide range of breast cancer risk factors and potential confounding variables. Our primary analysis and the sensitivity analysis involving the reclassification of invasive cases as in situ represent two extreme alternatives: that (a) DCIS and invasive ductal carcinoma are independent outcomes, and (b) all invasive ductal carcinomas pass through a DCIS stage. The fact that neither analysis indicated any association suggests that alcohol consumption is not associated with risk of DCIS in postmenopausal women.

Our study has several limitations. Alcohol intake was based on self-report at baseline in women who were 50 to 79 years old at recruitment and therefore did not take into account past drinking habits or change in drinking habits over the follow-up period. In addition, women who were heavier drinkers may underreport their intake. If the misclassification from these two sources is nondifferential, it would be expected to reduce the risk estimate toward the null. However, because an association between alcohol intake and invasive breast cancer was observed in the WHI observational study (7), it is unlikely that women who subsequently developed DCIS would underreport heavy alcohol intake to a greater extent than women who developed invasive breast cancer. It is possible that the results were biased due to the fact that a significantly greater proportion of DCIS cases had a mammogram in the past 2 years compared with non-cases, and that women who had mammograms were more likely to be educated and, hence, consumers of alcohol. However, this seems unlikely given that adjustment for the frequency of mammography in the 2 years before baseline did not alter the association of alcohol intake with DCIS.

Additionally, the number of high-grade DCIS cases was small, and therefore, the power to detect an association with alcohol in this subgroup was limited. Because there were few heavy drinkers in the study population, our results apply only to the effects of relatively light drinking, as opposed to the effects of regular heavy drinking or binge drinking. Finally, because we lacked information on drinking earlier in life, our results are pertinent to the effects of current drinking later in life.

In conclusion, we found no support for an association of moderate alcohol consumption and risk of DCIS in postmenopausal women within the WHI clinical trial cohort. This finding suggests that alcohol use may have differential effects on noninvasive as compared with invasive breast cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received 04/14/2010; revised 06/02/2010; accepted 06/03/2010; published OnlineFirst 07/20/2010.

References

Cancer Epidemiol Biomarkers Prev; 19(8) August 2010

Published OnlineFirst July 20, 2010; DOI: 10.1158/1055-9965.EPI-10-0388

Kabat et al.

Alcohol Consumption and Risk of Ductal Carcinoma In situ of the Breast in a Cohort of Postmenopausal Women

Geoffrey C. Kabat, Mimi Kim, James M. Shikany, et al.


Updated version
Access the most recent version of this article at:
doi:10.1158/1055-9965.EPI-10-0388

Cited articles
This article cites 29 articles, 1 of which you can access for free at:
http://cebp.aacrjournals.org/content/19/8/2066.full#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.