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ARTICLE

Alcohol Consumption and Risk of Postmenopausal Breast Cancer by Subtype: The Women's Health Initiative Observational Study

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Background Alcohol consumption is a well-established risk factor for breast cancer. This association is thought to be largely hormonally driven, so alcohol use may be more strongly associated with hormonally sensitive breast cancers. Few studies have evaluated how alcohol-related risk varies by breast cancer subtype.

Methods We assessed the relationship between self-reported alcohol consumption and postmenopausal breast cancer risk among 87 724 women in the Women's Health Initiative Observational Study prospective cohort from 1993 through 1998. Multivariable adjusted Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical tests were two-sided.

Results A total of 2944 invasive breast cancer patients were diagnosed during follow-up through September 15, 2005. In multivariable adjusted analyses, alcohol consumption was positively related to risk of invasive breast cancer overall, invasive lobular carcinoma, and hormone receptor–positive tumors (all $P_{trend} \leq .022$). However, alcohol consumption was more strongly related to risk of certain types of invasive breast cancer compared with others. Compared with never drinkers, women who consumed seven or more alcoholic beverages per week had an almost twofold increased risk of hormone receptor–positive invasive lobular carcinoma (HR = 1.82; 95% CI = 1.18 to 2.81) but not a statistically significant increased risk of hormone receptor–positive invasive ductal carcinoma (HR = 1.14; 95% CI = 0.87 to 1.50; difference in HRs per drink per day among current drinkers = 1.15; 95% CI = 1.01 to 1.32, $P = .042$). The absolute rates of hormone receptor–positive lobular cancer among never drinkers and current drinkers were, 5.2 and 8.5 per 10 000 person-years, respectively, whereas for hormne receptor–positive ductal cancer they were 15.2 and 17.9 per 10 000 person-years, respectively.

Conclusions Alcohol use may be more strongly associated with risk of hormone-sensitive breast cancers than hormone-insensitive subtypes, suggesting distinct etiologic pathways for these two breast cancer subtypes.

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Introduction

Alcohol use is an established risk factor for breast cancer. In 2002, the Collaborative Group on Hormonal Factors in Breast Cancer summarized much of the world's literature on the relationship between alcohol and breast cancer risk, utilizing data from 53 epidemiological studies that included 58 515 breast cancer case patients and 96 067 control subjects. It reported that breast cancer risk increased by 7.1% ($P < .001$) for each 10 g of alcohol (approximately equivalent to one 12 oz bottle or can of beer, one 4 oz glass of wine, or a 1.5 oz drink or shot of liquor) consumed per day (1). A more recent meta-analysis that included 98 studies reported a similar 10% increase in breast cancer risk per 10 g of alcohol consumed per day (2). Comparatively few studies have assessed how the relationship between alcohol use and breast cancer risk varies by breast cancer subtype even though alcohol is believed to influence breast cancer risk by a hormonal mechanism (3). Indeed, a controlled crossover feeding study of healthy postmenopausal women observed that alcohol consumption increases serum estrone sulfate and dehydroepiandrosterone levels in a dose-dependent fashion (4), and endogenous hormone levels are strongly linked to breast cancer risk (5). It is therefore reasonable to hypothesize that alcohol use may be more strongly related to risk of breast cancer subtypes that are hormonally sensitive than to risk of those that are not.

There is now considerable evidence across numerous observational studies that alcohol use is more strongly related to risk of hormone receptor–positive breast cancer than it is to risk of hormone receptor–negative breast cancer. A meta-analysis of 20 studies (4 cohort and 16 case–control studies) published through

April 2007 observed that risk of estrogen receptor–positive (ER+) breast cancer increased by 12% (95% confidence interval [CI] = 8% to 15%) per 10 g of alcohol consumed per day, whereas risk of estrogen receptor–negative (ER−) and progesterone receptor–negative (PR−) breast cancer increased by only 4% (95% CI = −2% to 9%) with $P_{\text{heterogeneity}} = .02$ between these two tumor types (6).

By contrast, few studies have evaluated how alcohol use is associated with risk of different histological types of breast cancer. In the United States, approximately 70% of invasive postmenopausal breast cancers are ductal carcinomas and 15%–20% are lobular carcinomas (7). Beyond differences in their histopathologic appearances, lobular carcinomas are more frequently hormone receptor–positive compared with ductal carcinomas (8) and, unlike ductal carcinomas, they almost uniformly lack expression of E-cadherin, a cell–cell adhesion molecule (9). Epidemiologically, numerous observational studies have documented that use of combined estrogen and progestin menopausal hormone therapy is more strongly related to risk of lobular than ductal carcinomas (10–12), although this difference was not statistically significant in the Women's Health Initiative (WHI) randomized trial perhaps because of the relatively short follow-up period and small number of lobular tumors (13). Overall, studies to date point to important etiologic differences between lobular and ductal tumor types. The three observational studies that have assessed the relationship between alcohol use and risk of lobular vs ductal carcinomas are consistent in finding that alcohol use may be more strongly related to risk of lobular compared with ductal carcinomas in postmenopausal women, but all three studies were based on relatively small numbers of lobular carcinoma patients (n = 152 to 308) and were limited in their abilities to evaluate dose–response relationships (14–16).

The large WHI prospective cohort Observational Study (OS) provides a unique opportunity to evaluate the relationship between alcohol use and risk of different breast cancer subtypes defined by histology and hormone receptor status. Such an assessment is relevant to public health. Because there are relatively few modifiable risk factors for breast cancer, breast cancers are heterogeneous, and treatment options and prognosis differ by tumor type, it is important to clarify which subtypes of breast cancer are most susceptible to exposure to alcohol.

Methods

This study used data collected in the WHI OS. The details of the scientific rationale, eligibility criteria, and design of the WHI OS have been published (17). Briefly, 87 724 postmenopausal women aged 50–79 years without a history of breast cancer who self-reported their alcohol use histories were enrolled between October 1, 1993 and December 31, 1998 through 40 clinical centers in the United States. All exposures used in this analysis were collected at the time of entry into the OS. Data were uniformly collected from participants according to a standardized institutional review board approved procedures and protocols by trained study staff. All participants provided written informed consent for this research study at the time of enrollment.

The primary follow-up of WHI OS participants was through self-administered questionnaires that were mailed annually after enrollment through the close-out period, April 2004 to March 2005. In our analysis, we included cohort data ascertained through September 15, 2005, by which time 2.2% of participants were lost to follow-up, 2.5% declined further follow-up, and 6.7% were deceased. Women with breast cancer were initially identified from annual questionnaires. Based on these reports, medical records were obtained and reviewed by trained study adjudicators to verify diagnoses. For the 2944 confirmed invasive breast cancer patients identified through September 15, 2005, information from medical records was forwarded to the WHI coordinating center for central adjudication, and coding of breast cancer stage, size, nodal status, grade, histology, and estrogen receptor (ER) and progesterone receptor (PR) status. Invasive histology was classified as ductal (n = 1805, *International Classification of Diseases for Oncology* [ICD-O] code 8500) or lobular (n = 720, ICD-O codes 8520 and 8522), and the 419 cancers with other ICD-O histology codes were excluded from our histology specific analyses. Data on ER and PR status were available for 88% of cancers. The 358 cancers with an unknown ER and PR status were excluded from the ER and PR analyses, as were those with ER− and progesterone receptor–positive (PR+) tumors because of insufficient statistical power (n = 37), leaving a total of 2549 invasive cancers included in the analysis focused on ER and PR status.

Cohort members completed baseline self-administered questionnaires covering a wide range of topics including demographic

CONTEXT AND CAVEATS

Prior knowledge

Few studies have examined how women's alcohol use influences breast cancer risk by cancer subtype.

Study design

This was a prospective observational study of 87 724 postmenopausal American women without prior breast cancer who were surveyed on alcohol use at enrollment in 1993 through 1998. Follow-up ended in September 2005. Associations between alcohol use and breast cancer risk by subtype were estimated using data from the 2549 women who developed invasive breast cancer by the end of follow-up and had sufficient records for the determination of tumor histology and estrogen and progesterone receptor status.

Contribution

Alcohol use at study entry was associated with higher breast cancer risk overall and higher risk of hormone receptor–positive disease. Among hormone receptor–positive breast cancers, the association between alcohol use and increased breast cancer risk was observed for invasive lobular carcinoma but not for invasive ductal carcinoma.

Implication

The association of alcohol use with hormone receptor–positive and invasive lobular breast cancers suggests a distinct etiology for these forms of the disease.

Limitations

Alcohol use was assessed only at baseline. Extensive measurement errors or changes in alcohol use could affect the study conclusions.

From the Editors

characteristics, medical history, reproductive history, lifestyle characteristics, and family history of various diseases. In addition, baseline height and weight was measured by the study staff. Alcohol consumption at the time of enrollment, our primary exposure of interest, was assessed from two sources: 1) self-administered questionnaires of personal habits at baseline that collected alcohol consumption history and 2) self-administered food-frequency questionnaires (FFQ) completed at enrollment. In the alcohol consumption questionnaires, women were asked whether they ever consumed at least 12 alcoholic drinks of any kind, and those who answered yes were asked whether they still drank alcohol so that never, former, and current drinkers could be distinguished from each other; ever drinkers were also asked how many alcoholic beverages they consumed each day, week, or month over different ages in their lives. In the data collected, one bottle or can of beer, one glass of wine, and one shot of liquor were all considered to be equivalent. Using these two data sources, summary measures of recency and frequency of alcohol consumption were obtained. If there were any discrepancies between these two measures, the FFQ data were given priority. Women were categorized as never drinkers (never consumed 12 or more alcoholic beverages of any kind in their lives), former drinkers (ever drinkers who reported having stopped drinking at the time data were collected), and current drinkers. Among current drinkers, the average number of drinks per week was computed. In our main analysis, frequency of alcohol consumption among current drinkers was then grouped into six consumption categories based on the following number of drinks consumed per week: less than 0.5, 0.5–0.9, 1.0–3.9, 4.0–6.9, 7.0–13.9, and 14.0 or more. Although most studies of alcohol use and breast cancer are limited to categories of less than 7.0 or 7.0 or more drinks per day, because of our sample size finer categories could be used to more clearly evaluate the potential dose–response relationship between alcohol use and breast cancer risk. Two approaches were used to assess the dose–response relationship. First, risk per number of drinks consumed per day among current drinkers was computed by treating the number of drinks per day consumed as a continuous term in the statistical model. Second, *P* values for trend were calculated by using the number of drinks per day consumed as a continuous variable and restricting the analyses only to women who were categorized as current drinkers. We also conducted a subanalysis of risk by alcohol type (beer, wine, and liquor) with this classification derived from FFQ data collected at baseline.

Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals as a measure of the association between history of alcohol use and breast cancer risk. Assumptions of proportionality for the Cox models were confirmed based on scaled Schoenfeld residuals. Time to breast cancer was computed from date of enrollment to date of first breast cancer diagnosis, with times for women without breast cancer censored by date of last study follow-up or September 15, 2005, whichever occurred first. All analyses were adjusted for age, race, and/or ethnicity, and women categorized as never drinkers served as the reference category. Variables considered as potential confounders or effect modifiers included the following categorical baseline characteristics using the categories shown in Table 1: education, body mass index, use of menopausal hormone therapy, smoking status, Gail model scores of 5-year breast cancer risk, and number of screening mammograms received in the past 5 years. We present risk estimates from models adjusted simply for age, race, and/or ethnicity, and the ones additionally adjusted for each of these characteristics as categorical variables according to how they are categorized in Table 1. Effect modification was assessed using likelihood ratio testing, and none of these variables were observed to be statistically significant effect modifiers (all $P_{interaction} > .05$). *P* values characterizing the difference in risk estimates between case groups were calculated through comparisons only of case patients using unconditional logistic regression (ie, a logistic regression model was fit restricted to ductal and lobular case patients' data where those with ductal carcinoma served as the reference group). All analyses were conducted using Stata 9.2 (Stata Corp, College Station, TX), and all *P* values were from two-sided tests in which values less than .05 were considered statistically significant.

Results

Compared with never drinkers, current drinkers of one or more alcoholic beverages per day were somewhat more likely to be younger, non-Hispanic white, and highly educated; to have a higher Gail model score; to have received more screening mammograms within the past 5 years; to have a first-degree family history of breast cancer; to be nulliparous; to have a lower body mass index; to be currently using estrogen plus progestin menopausal hormone therapy; and to be a current smoker (Table 1). In general, former drinkers and current drinkers of less than one drink per day were in-between never drinkers and current drinkers of one or more drinks per day with respect to each of these characteristics. Among breast cancer patients, stage, nodal status, and tumor size were similarly distributed across alcohol use categories (Table 2).

In multivariable adjusted statistical models, higher quantity of alcohol intake was associated with an increased risk of invasive breast cancer overall (among current drinkers, $P_{trend} = .004$) (Table 3). Number of drinks per day consumed among current drinkers was more strongly related to the risk of invasive lobular carcinoma compared with the risk of invasive ductal carcinoma, although in the multivariable models this difference was within the limits of chance (multivariable adjusted risk per drink per day consumed among current drinkers: HR for invasive lobular carcinoma = 1.13, HR for invasive ductal carcinoma = 1.06, multivariable adjusted difference in HRs = 1.10, 95% CI = 0.99 to 1.23, *P* for difference = .080). Compared with never drinkers, consumers of 14 or more drinks per week had a (statistically significant) 2.13-fold increased risk of lobular carcinoma but not a statistically significantly increased risk of ductal carcinoma (HR = 1.04). With respect to ER and PR status, alcohol consumption was positively related to risk of both ER+PR+ and ER+PR− breast cancers (risk per drink per day consumed among current drinkers: HR = 1.08 and 1.12, respectively), and these elevations in risk were not statistically different (multivariable adjusted difference in HRs = 1.03, 95% CI = 0.89 to 1.20, $P = .661$). There was some suggestion that alcohol consumption was inversely related to risk of ER−PR− breast cancer. Whereas this observation was within the limits of chance ($P_{trend} = .12$), the risk per drink per day was statistically significantly lower

Table 1. Distribution of demographic and personal characteristics by alcohol use*

Characteristic	Never drinkers (n = 9926)	Former drinkers (n = 16,517)	Current drinkers <7 drinks per week (n = 50276)	Current drinkers ≥7 drinks per week (n = 11,005)
Age at enrollment, No. (%), y				
50–59	2609 (26.3)	5066 (30.7)	17299 (34.4)	3272 (29.7)
60–69	4348 (43.8)	7104 (43.0)	21956 (43.7)	5155 (46.8)
70–79	2969 (29.9)	4347 (26.3)	11021 (21.9)	2578 (23.4)
Race and/or ethnicity, No. (%)				
Non-Hispanic white	6579 (66.3)	12404 (75.1)	43797 (87.1)	10295 (93.5)
African American	1325 (13.3)	2377 (14.4)	3021 (6.0)	319 (2.9)
Hispanic white	693 (7.0)	824 (5.0)	1699 (3.4)	176 (1.6)
Asian or Pacific Islander	1050 (10.6)	515 (3.1)	936 (1.9)	77 (0.7)
American Indian or Alaska Native	78 (0.8)	111 (0.7)	178 (0.4)	27 (0.2)
Other	201 (2.0)	286 (1.7)	645 (1.3)	111 (1.0)
Education, No. (%)				
< High school	1166 (11.9)	1520 (9.3)	1642 (3.3)	212 (1.9)
High school graduate	2198 (22.4)	3209 (19.6)	7509 (15.1)	1250 (11.4)
Some college or vocation training	3444 (35.0)	6431 (39.3)	18224 (36.5)	3712 (34.0)
College graduate	943 (9.6)	1398 (8.5)	6038 (12.1)	1646 (15.1)
Graduate or professional school	2082 (21.2)	3807 (23.3)	16476 (33.0)	4105 (37.6)
Missing	93	152	387	80
Gail model score of 5-year risk of breast cancer, No. (%)				
<1.25	3367 (33.9)	5757 (34.9)	14101 (28.0)	2385 (21.7)
1.25–1.75	3106 (31.3)	5017 (30.4)	16831 (33.5)	3831 (34.8)
>1.75	3453 (34.8)	5743 (34.8)	19344 (38.5)	4789 (43.5)
Screening mammograms received in the past 5 years, No. (%)				
0	911 (9.4)	1190 (7.4)	2487 (5.0)	483 (4.5)
1	854 (8.8)	1331 (8.2)	2862 (5.8)	535 (4.9)
2	1373 (14.2)	2204 (13.6)	5584 (11.3)	1080 (10.0)
3	1451 (15.0)	2293 (14.2)	6727 (13.6)	1403 (13.0)
4	1545 (16.0)	2498 (15.5)	8356 (16.9)	1825 (16.9)
5	3542 (36.6)	6651 (41.1)	23395 (47.3)	5502 (50.8)
Missing	250	350	865	177
First-degree family history of breast cancer, No. (%)				
No	7708 (85.2)	12640 (84.2)	39073 (84.6)	8328 (83.2)
Yes	1,343 (14.8)	2366 (15.8)	7091 (15.4)	1677 (16.8)
Missing	875	1511	4112	1000
Parity, No. (%)				
Nulliparous	1047 (10.6)	2025 (12.3)	6277 (12.6)	1703 (15.6)
1	881 (8.9)	1620 (9.9)	4439 (8.9)	992 (9.1)
2	2489 (25.2)	4163 (25.3)	13461 (26.9)	2834 (25.9)
3	2262 (22.9)	3727 (22.7)	12367 (24.7)	2622 (24.0)
≥4	3181 (32.3)	4891 (29.8)	13443 (26.9)	2793 (25.5)
Missing	66	91	289	61
Body mass index, quartiles, No. (%), kg/m^2				
<23.21	2258 (23.0)	3303 (20.2)	12539 (25.2)	3674 (33.8)
23.21–26.09	2141 (21.8)	3407 (20.9)	12939 (26.0)	3181 (29.3)
26.10–30.03	2469 (25.2)	4051 (24.8)	12642 (25.4)	2514 (23.1)
≥30.04	2946 (30.0)	5563 (34.1)	11569 (23.3)	1501 (13.8)
Missing	112	193	587	135
Hormone therapy use, No. (%)				
Never	4614 (46.5)	7199 (43.6)	18805 (37.5)	3893 (35.4)
Former	1392 (14.0)	2506 (15.2)	6730 (13.4)	1538 (14.0)
Current unopposed estrogen	2486 (25.1)	4272 (25.9)	13299 (26.5)	2807 (25.5)
Current estrogen+progestin	1429 (14.4)	2528 (15.3)	11379 (22.7)	2758 (25.1)
Missing	5	12	63	9
Smoking status, No. (%)				
Never	8505 (86.4)	7717 (47.2)	24608 (49.5)	3308 (30.6)
Former	1119 (11.4)	7496 (45.9)	21995 (44.3)	6475 (59.8)
Current	224 (2.3)	1130 (6.9)	3083 (6.2)	1043 (9.6)
Missing	79	174	590	179

* Due to rounding, not all column percentages sum to exactly 100.0%.

Table 2. Tumor characteristics of invasive breast cancer by alcohol use*

Characteristic	Never drinkers (n = 279)	Former drinkers (n = 485)	Current drinkers <7 drinks per week (n = 1713)	Current drinkers ≥7 drinks per week (n = 467)
Stage				
Localized	198 (74.4)	340 (73.6)	1228 (74.5)	343 (75.9)
Regional or distant	68 (25.6)	122 (26.4)	421 (25.5)	109 (24.1)
Missing	13	23	64	15
Nodal status				
Negative	199 (76.0)	334 (73.7)	1201 (74.4)	340 (76.4)
Positive	63 (24.0)	119 (26.3)	413 (25.6)	105 (23.6)
Missing	17	32	99	22
Tumor size, cm				
<2.0	149 (76.4)	266 (75.8)	918 (74.3)	247 (74.0)
2.0–4.9	39 (20.0)	75 (21.4)	276 (22.3)	74 (22.2)
≥5.0	7 (3.6)	10 (2.8)	41 (3.3)	13 (3.9)
Missing	84	134	478	133

* Due to rounding, not all column percentages sum to exactly 100.0%. Stage was assessed from Surveillance Epidemiology, and End Results program summaries and nodal status and tumor size from abstracted medical records.

for ER−PR− breast cancer than it was for ER+PR+ breast cancer (multivariable adjusted difference in HRs = 0.74, 95% CI = 0.58 to 0.93, P = .010).

Because of the greater frequency of hormone receptor–positivity among lobular tumors compared with ductal tumors, we further explored the relationship between alcohol use and risk of lobular and ductal tumors and restricted our analysis to tumors that were ER+PR+. Similar to our findings in analyses by histological type regardless of ER and PR status, the association between number of drinks consumed per day among current drinkers and risk of ER+PR+ lobular carcinoma was stronger than it was for risk of ER+PR+ ductal carcinoma (multivariable adjusted risk per drink per day consumed among current drinkers (HR for ER+PR+ lobular carcinoma = 1.16, HR for ER+PR+ ductal carcinoma = 1.05, multivariable adjusted difference in HRs = 1.15, 95% CI = 1.01 to 1.32, $P_{\text{difference}}$ = .042) (Table 4). Additionally, compared with never drinkers, women who consumed one or more drinks per day had an increased risk of ER+PR+ lobular carcinoma (HR = 1.82, 95% CI = 1.18 to 2.81), but not a statistically significant increased risk of ER+PR+ ductal carcinoma (HR = 1.14, 95% CI = 0.87 to 1.50). On an absolute scale, the incidence rates of ER+PR+ lobular cancer among never drinkers and current drinkers were 5.2 and 8.5 per 10 000 person-years, respectively, whereas for ER+PR+ ductal cancer they were 15.2 and 17.9 per 10 000 person-years, respectively. In addition, these risk estimates did not vary to a statistically significant degree when they were stratified by use of menopausal hormone therapy. Specifically, the multivariable adjusted risks of ER+PR+ ductal carcinoma per drink per day among current users of unopposed estrogens (HR = 1.12; 95% CI = 0.96 to 1.31) and current users of combined estrogens and progestins (HR = 0.97; 95% CI = 0.83 to 1.14) were similar to those for never users (HR = 1.06; 95% CI = 0.92 to 1.21) and former users of menopausal hormone therapy (HR = 1.09; 95% CI = 0.87 to 1.37). The multivariable adjusted risks of ER+PR+ lobular carcinoma per drink per day among current users of unopposed estrogens (HR = 1.17; 95% CI = 0.96 to 1.43) and current users of combined estrogens and progestins (HR = 1.04; 95% CI = 0.84 to 1.28) were also similar to those for never users (HR = 1.17; 95% CI = 1.04 to 1.32) and former users 1.26 (95% CI = 1.02 to 1.56) of menopausal hormone therapy.

When we analyzed only FFQ data collected at study enrollment regarding the amounts and types of alcoholic beverages (beer, wine, and/or liquor) consumed, again, differences were observed between the alcohol-related risks of invasive ductal vs invasive lobular carcinomas, though none reached statistical significance primarily because of limited statistical power (multivariable adjusted risks for current drinkers: for beer, invasive ductal carcinoma HR = 1.14, invasive lobular carcinoma HR = 1.70, multivariable adjusted difference in HRs = 1.51, 95% CI = 0.92 to 2.47; P = .100; for wine, invasive ductal carcinoma HR = 1.04, invasive lobular carcinoma HR = 1.58, multivariable adjusted difference in HRs = 1.48, 95% CI = 0.98 to 2.23; P = 0.63; and for liquor, invasive ductal carcinoma HR = 1.05, invasive lobular carcinoma HR = 1.68, multivariable adjusted difference in HRs = 1.57, 95% CI = 0.98 to 2.51; P = .059) (Table 5). Some variation in the HRs associated with beer, wine, and liquor consumption were observed, but none of the differences were statistically significant.

Discussion

In this largest single study to date, to our knowledge, of the relationship between alcohol use and risk of different subtypes of invasive breast cancer based on histology and ER and PR status in postmenopausal women, we document that alcohol use (regardless of type) is more strongly related to risk of lobular carcinoma than to risk of ductal carcinoma, and that it is more strongly related to risk of hormone receptor–positive than it is to hormone receptor–negative tumors. These findings add further support to the central importance of hormonal mechanisms in mediating the relationship between alcohol use and breast cancer risk. Clinically, survival rates for lobular carcinomas are higher than those for ductal carcinomas (18), and survival rates for hormone receptor–positive tumors are higher than those for hormone receptor–negative tumors (19).

To our knowledge, this is the first prospective cohort study to assess the relationship between alcohol use and risk of different histological types of invasive breast cancer, and its results are consistent with the three previous case–control studies in identifying a stronger association with lobular carcinoma than with ductal

Table 3. Risk of breast cancer associated with alcohol use*

Average number of alcohol-containing beverages consumed per week at baseline	Number of incident cancers	Adjusted for age, race, and ethnicity HR (95% CI)	Multivariable adjusted† HR (95% CI)
All invasive cancers (n = 2944)			
Never drinker	279	1.00 (ref)	1.00 (ref)
Former drinker	485	1.04 (0.89 to 1.20)	0.98 (0.83 to 1.15)
Current drinker	2180	1.19 (1.05 to 1.35)‡	1.08 (0.94 to 1.25)
<0.5 drinks per week	708	1.08 (0.94 to 1.24)	1.02 (0.87 to 1.18)
0.5–0.9 drinks per week	180	1.13 (0.93 to 1.36)	1.05 (0.85 to 1.28)
1.0–3.9 drinks per week	604	1.21 (1.05 to 1.40)‡	1.1 (0.94 to 1.30)
4.0–6.9 drinks per week	221	1.25 (1.04 to 1.49)‡	1.12 (0.91 to 1.36)
7.0–13.9 drinks per week	307	1.39 (1.18 to 1.64)‡	1.27 (1.05 to 1.53)‡
≥14.0 drinks per week	160	1.4 (1.15 to 1.71) ‡	1.24 (1.00 to 1.55)
Risk per drink per day among current drinkers		1.09 (1.05 to 1.14)‡	1.07 (1.02 to 1.12)‡
P for trend across current drinkers		<.001	.004
Invasive ductal carcinoma (n = 1805)			
Never drinker	185	1.00 (ref)	1.00 (ref)
Former drinker	314	1.02 (0.85 to 1.22)	0.94 (0.77 to 1.15)
Current drinker	1306	1.09 (0.93 to 1.27)	0.99 (0.83 to 1.18)
<0.5 drinks per week	436	1.01 (0.85 to 1.20)	0.93 (0.77 to 1.13)
0.5–0.9 drinks per week	110	1.05 (0.82 to 1.33)	0.99 (0.76 to 1.28)
1.0–3.9 drinks per week	358	1.10 (0.92 to 1.31)	1.00 (0.81 to 1.22)
4.0–6.9 drinks per week	130	1.12 (0.89 to 1.40)	1.06 (0.82 to 1.35)
7.0–13.9 drinks per week	184	1.28 (1.04 to 1.58)‡	1.21 (0.96 to 1.52)
≥14.0 drinks per week	88	1.18 (0.91 to 1.53)	1.04 (0.78 to 1.39)
Risk per drink per day among current drinkers		1.07 (1.02 to 1.14)‡	1.06 (1.00 to 1.13)
P for trend across current drinkers		.011	.055
Invasive lobular carcinoma (n = 720)			
Never drinker	50	1.00 (ref)	1.00 (ref)
Former drinker	106	1.25 (0.89 to 1.75)	1.25 (0.86 to 1.82)
Current drinker	564	1.66 (1.24 to 2.22)‡	1.50 (1.08 to 2.09)
<0.5 drinks per week	167	1.39 (1.01 to 1.91)‡	1.35 (0.95 to 1.93)
0.5–0.9 drinks per week	45	1.53 (1.02 to 2.29)‡	1.46 (0.93 to 2.28)
1.0–3.9 drinks per week	149	1.61 (1.16 to 2.23)‡	1.52 (1.05 to 2.19)‡
4.0–6.9 drinks per week	63	1.91 (1.31 to 2.78)‡	1.55 (1.01 to 2.39)‡
7.0–13.9 drinks per week	90	2.17 (1.53 to 3.08)‡	1.87 (1.25 to 2.79)‡
≥14.0 drinks per week	50	2.35 (1.58 to 3.49)‡	2.13 (1.36 to 3.33)‡
Risk per drink per day among current drinkers		1.16 (1.09 to 1.24)‡	1.13 (1.05 to 1.23)‡
P for trend across current drinkers		<.001	.002
P for ductal vs lobular difference§		.007	.080
Invasive ER+PR+ cancers (n = 1803)			
Never drinker	162	1.00 (ref)	1.00 (ref)
Former drinker	290	1.07 (0.88 to 1.30)	0.96 (0.78 to 1.19)
Current drinker	1351	1.25 (1.06 to 1.47)‡	1.07 (0.89 to 1.28)
<0.5 drinks per week	429	1.11 (0.93 to 1.34)	1.00 (0.82 to 1.22)
0.5–0.9 drinks per week	105	1.11 (0.87 to 1.43)	1.00 (0.77 to 1.30)
1.0–3.9 drinks per week	370	1.25 (1.04 to 1.51)‡	1.08 (0.88 to 1.33)
4.0–6.9 drinks per week	139	1.32 (1.05 to 1.66)‡	1.08 (0.84 to 1.40)
7.0–13.9 drinks per week	203	1.54 (1.25 to 1.90)‡	1.32 (1.04 to 1.66)‡
≥14.0 drinks per week	105	1.55 (1.21 to 1.99)‡	1.27 (0.96 to 1.68)
Risk per drink per day among current drinkers		1.11 (1.06 to 1.17)‡	1.08 (1.02 to 1.15)‡
P for trend across current drinkers		<.001	.009
Invasive ER+PR− cancers (n = 373)			
Never drinker	34	1.00 (ref)	1.00 (ref)
Former drinker	57	0.99 (0.64 to 1.51)	0.92 (0.57 to 1.49)
Current drinker	282	1.21 (0.84 to 1.74)	1.11 (0.74 to 1.69)
<0.5 drinks per week	80	0.97 (0.65 to 1.46)	0.98 (0.63 to 1.54)
0.5–0.9 drinks per week	20	1.00 (0.57 to 1.74)	0.90 (0.49 to 1.67)
1.0–3.9 drinks per week	79	1.25 (0.83 to 1.88)	1.21 (0.77 to 1.92)
4.0–6.9 drinks per week	36	1.59 (0.99 to 2.56)	1.46 (0.86 to 2.48)
7.0–13.9 drinks per week	42	1.50 (0.94 to 2.37)	1.21 (0.71 to 2.05)
≥14.0 drinks per week	25	1.73 (1.02 to 2.91)‡	1.45 (0.80 to 2.63)
Risk per drink per day among current drinkers		1.17 (1.06 to 1.28)‡	1.12 (1.00 to 1.25)
P for trend across current drinkers		.001	.060

(Table continues)

Table 3 (Continued).

Average number of alcohol-containing beverages consumed per week at baseline	Number of incident cancers	Adjusted for age, race, and ethnicity HR (95% CI)	Multivariable adjusted† HR (95% CI)
Invasive ER-PR− cancers (n = 359)			
Never drinker	46	1.00 (ref)	1.00 (ref)
Former drinker	74	0.94 (0.65 to 1.36)	1.11 (0.73 to 1.70)
Current drinker	239	0.82 (0.59 to 1.13)	0.94 (0.64 to 1.37)
<0.5 drinks per week	86	0.80 (0.56 to 1.15)	0.88 (0.58 to 1.34)
0.5–0.9 drinks per week	30	1.16 (0.73 to 1.85)	1.26 (0.74 to 2.15)
1.0–3.9 drinks per week	69	0.87 (0.59 to 1.27)	0.98 (0.63 to 1.53)
4.0–6.9 drinks per week	22	0.78 (0.46 to 1.30)	1.02 (0.58 to 1.79)
7.0–13.9 drinks per week	25	0.73 (0.45 to 1.20)	0.91 (0.52 to 1.59)
≥14.0 drinks per week	7	0.39 (0.17 to 0.86)‡	0.46 (0.19 to 1.12)
Risk per drink per day among current drinkers		0.82 (0.67 to 1.00)‡	0.85 (0.68 to 1.05)
P for trend across current drinkers		.048	.12
P for ER+PR+ vs ER+PR− difference§		.236	.661
P for ER+PR+ vs ER-PR- difference§		<.001	.010

* HR = hazard ratio; CI = confidence interval; ER = estrogen receptor; PR = progesterone receptor.

† Multivariable adjusted hazard ratios and 95% confidence intervals are adjusted for age, race, and/or ethnicity, education, body mass index, hormone therapy use, smoking status, Gail model 5-year risk of breast cancer, first-degree family history of breast cancer, parity, and number of mammograms in the past 5 years.

‡ For the indicated associations Cox regression two-sided $P < .05$

§ *P* for difference compares risk estimates per drink per day among current drinkers between the two case groups being compared.

carcinoma (14–16). Although each of these studies provided some indication that the risk of breast cancer was stronger for lobular compared with ductal tumors, each had limited power to make this assessment or did not report on the statistical significance of this difference. Hence, comparative strengths of our report include our substantially larger number of lobular cancer patients and sufficient statistical power to assess differences across tumor types and dose–response relationships. When we assessed this association in terms of the number of drinks consumed per day, the risk estimate for lobular carcinoma was twofold greater than the risk estimate for ductal carcinoma. Another noteworthy difference that we found was that although current drinkers of seven or more drinks per week had an 82% increased risk of ER+PR+ lobular carcinoma compared with never drinkers, they had only a nonsignificant 14% increased risk of ER+PR+ ductal carcinoma. Thus, just as the literature suggests that use of combined estrogen and progestin hormone therapy is more strongly related to the risk of lobular than ductal carcinoma (10–12,20–25), our data suggest that another established risk factor for breast cancer, alcohol use, is also differentially associated with risk of these two breast cancer subtypes.

Our findings are generally consistent with the results of the meta-analysis (6) of 20 studies that have evaluated the relationship

Table 4. Risk of ER+PR+ ductal and lobular carcinomas associated with alcohol use*

Average number of alcohol-containing beverages consumed per week at baseline	Number of incident cancers	Adjusted for age, race, and ethnicity, HR (95% CI)	Multivariable adjusted† HR (95% CI)
Invasive ER+PR+ ductal cancers (n = 1105)			
Never drinker	109	1.00 (ref)	1.00 (ref)
Former drinker	179	0.98 (0.77 to 1.25)	0.86 (0.66 to 1.11)
Current drinker	817	1.12 (0.91 to 1.37)	0.95 (0.76 to 1.19)
<6.9 drinks per week	633	1.06 (0.86 to 1.31)	0.92 (0.73 to 1.15)
≥7.0 drinks per week	184	1.37 (1.08 to 1.74)‡	1.14 (0.87 to 1.50)
Risk per drink per day among current drinkers		1.09 (1.02 to 1.17)‡	1.05 (0.97 to 1.14)
P for trend across current drinkers		0.016	0.194
Invasive ER+PR+ lobular cancers (n = 497)			
Never drinker	37	1.00 (ref)	1.00 (ref)
Former drinker	75	1.21 (0.81 to 1.79)	1.17 (0.76 to 1.80)
Current drinker	385	1.55 (1.10 to 2.19)‡	1.39 (0.95 to 2.03)
<6.9 drinks per week	290	1.44 (1.02 to 2.03)‡	1.32 (0.90 to 1.94)
≥7.0 drinks per week	95	2.08 (1.41 to 3.05)‡	1.82 (1.18 to 2.81)‡
Risk per drink per day among current drinkers		1.18 (1.09 to 1.27)‡	1.16 (1.06 to 1.26)‡
P for trend across current drinkers		<.001	.001
P for ER+PR+ ductal vs ER+PR+ lobular difference§		.030	.042

* HR = hazard ratio; CI = confidence interval; ER = estrogen receptor; PR = progesterone receptor.

† Multivariable adjusted hazard ratios are adjusted for age, race/ethnicity, education, body mass index, hormone therapy use, smoking status, Gail model 5-year risk of breast cancer, first-degree family history of breast cancer, parity, and number of mammograms in the past 5 years.

‡ For the indicated associations Cox regression two-sided $P < .05$.

§ Two-sided *P* for difference using Cox regression compares risk estimates per drink per day among current drinkers between the two cancer groups being compared.

Table 5. Risk of invasive breast cancer overall, invasive ductal carcinoma, and invasive lobular carcinoma associated with use of different types of alcoholic beverages based on food-frequency questionnaire data*

Average number of alcohol-containing beverages consumed per day at baseline	Beer HR† (95% CI)	Wine HR† (95% CI)	Liquor HR† (95% CI)
All invasive cancers			
Never drinker	1.00 (ref)	1.00 (ref)	1.00 (ref)
Current drinker	1.23 (1.03 to 1.47)‡	1.11 (0.95 to 1.29)	1.14 (0.96 to 1.36)
<1 drink per day	1.20 (1.00 to 1.44)‡	1.10 (0.95 to 1.29)	1.11 (0.93 to 1.32)
≥1 drink per day	1.90 (1.34 to 2.70)‡	1.15 (0.94 to 1.41)	1.45 (1.14 to 1.83)‡
Invasive ductal carcinoma			
Never drinker	1.00 (ref)	1.00 (ref)	1.00 (ref)
Current drinker	1.14 (0.92 to 1.43)	1.04 (0.86 to 1.26)	1.05 (0.84 to 1.29)
<1 drink per day	1.12 (0.90 to 1.41)	1.04 (0.86 to 1.26)	1.02 (0.82 to 1.26)
≥1 drink per day	1.65 (1.04 to 2.60)‡	1.05 (0.81 to 1.36)	1.28 (0.94 to 1.72)
Invasive lobular carcinoma			
Never drinker	1.00 (ref)	1.00 (ref)	1.00 (ref)
Current drinker	1.70 (1.13 to 2.54)‡	1.58 (1.11 to 2.25)‡	1.68 (1.14 to 2.47)‡
<1 drink per day	1.62 (1.08 to 2.43)‡	1.55 (1.09 to 1.21)‡	1.59 (1.07 to 2.35)‡
≥1 drink per day	3.55 (1.85 to 6.82)‡	1.87 (1.22 to 2.87)‡	2.46 (1.51 to 4.00)‡
P for ductal vs lobular difference§	.100	.063	.059

* HR = hazard ratio; CI = confidence interval.

† Hazard ratios are adjusted for age, race/ethnicity, education, body mass index, hormone therapy use, smoking status, Gail model 5-year risk of breast cancer, first-degree family history of breast cancer, parity, and number of mammograms received in the past 5 years.

‡ For the indicated associations Cox regression two-sided $P < .05$.

§ *P* for difference compares risk estimates associated with current drinkers between the two cancer groups being compared.

between alcohol use and risk of breast cancer subtypes defined by ER and PR status. We observed that risk of ER+PR+ and ER+PR− breast cancer increased by 8% and 12%, respectively, per drink consumed per day among current drinkers, which is comparable to the 12% increase in risk of ER+ tumors per 10 g per day of alcohol consumed reported in the meta-analysis. Interestingly, the meta-analysis also reported some evidence that alcohol use may be more strongly related to risk of ER+PR− tumors compared with ER+PR+ tumors, though this difference was neither statistically significant in that study nor in ours. Similarly, neither study found a relationship between alcohol use and risk of ER−PR− breast cancer. The observation that alcohol use is related to risk of hormone receptor–positive, but not hormone receptor–negative tumors, further suggests that influence of alcohol on steroid hormones mediates its association with breast cancer risk.

The primary limitation of this study is that alcohol use was only assessed at baseline, so histories of alcohol use before baseline were not assessed and changes in alcohol use patterns after baseline were not incorporated. Lack of data on past use is less of a concern than subsequent changes in patterns of alcohol use after baseline because both our data and those of others (14) find breast cancer risk to be elevated only among current drinkers (although past users comprise a heterogeneous group of women that includes some who did and some who did not quit for health-related reasons). Measurement errors in alcohol consumption assessments could also affect hazard ratio estimates. A study of measurement characteristics of the WHI FFQ yielded an estimate of 0.86 for the correlation between alcohol consumption (grams per day) as measured by this FFQ and as measured using 8 days of food records (26). This suggests that the "noise" aspect of measurement error could attenuate hazard ratio estimates by a factor of about $(0.86)^2 = 0.74$, though more complex distortions would be possible if there are shared systematic biases between the food-frequency and food-record assessments. In addition, data on tumor characteristics were based on information abstracted from local pathology reports, which resulted in an unknown degree of misclassification because of variations in the ways histology is assessed and ER and PR status are determined by pathologists across the United States. Finally, this is an observational study and although efforts were made to adjust all analyses for relevant confounders, residual confounding may still exist.

In summary, this study provides prospective evidence that the relationship between alcohol use and breast cancer risk varies by breast cancer subtype, with risks most pronounced for invasive lobular and hormone receptor–positive tumors. Hence, alcohol is another established breast cancer risk factor that appears to be differentially associated among breast cancer subtypes, and this pattern of associated risks indicates that tumors defined by both histology and hormone receptor status have somewhat different etiologic determinants. These findings highlight the importance of incorporating breast cancer subtype information in etiologic studies of the disease. Alcohol use is known to have important health risks as well as potential benefits. Although one of well-known risks of alcohol is an increased risk of breast cancer, this study suggests that alcohol primarily increases risk of lobular and hormone receptor–positive breast cancer.

Supplementary Data

Supplementary data can be found at http://www.jnci.oxfordjournals.org/.

References

1. Collaborative Group on Hormonal Factors in Breast Cancer. Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer*. 2002;87(11):1234–1245.

2. Key J, Hodgson S, Omar RZ, Jensen TK, Thompson SG, Boobis AR, et al. Meta-analysis of studies of alcohol and breast cancer with consideration of the methodological issues. *Cancer Causes Control.* 2006;17(6):759–770.
3. Singletary KW, Gapstur SM. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. *JAMA.* 2001;286(17):2143–2151.
4. Dorgan JF, Baer DJ, Albert PS, Judd JT, Brown ED, Corle DK, et al. Serum hormones and the alcohol-breast cancer association in postmenopausal women. *J Natl Cancer Inst.* 2001;93(9):710–715.
5. Key T, Appleby P, Barnes I, Reeves G. Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst.* 2002;94(8):606–616.
6. Suzuki R, Orsini N, Mignone L, Saji S, Wolk A. Alcohol intake and risk of breast cancer defined by estrogen and progesterone receptor status—a meta-analysis of epidemiological studies. *Int J Cancer.* 2008;122(8):1832–1841.
7. Li CI, Daling JR. Changes in breast cancer incidence rates in the United States by histologic subtype and race/ethnicity, 1995 to 2004. *Cancer Epidemiol Biomarkers Prev.* 2007;16(12):2773–2780.
8. Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. *Br J Cancer.* 2005;93(9):1046–1052.
9. Acs G, Lawton TJ, Rebbeck TR, LiVolsi VA, Zhang PJ. Differential expression of e-cadherin in lobular and ductal neoplasms of the breast and its biologic and diagnostic implications. *Am J Clin Pathol.* 2001;115(1):85–98.
10. Li CI, Malone KE, Porter PL, Weiss NS, Tang MT, Cushing-Haugen KL, et al. Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. *JAMA.* 2003;289(24):3254–3263.
11. Li CI, Malone KE, Porter PL, Lawton TJ, Voigt LF, Cushing-Haugen KL, et al. Relationship between menopausal hormone therapy and risk of ductal, lobular, and ductal-lobular breast carcinomas. *Cancer Epidemiol Biomarkers Prev.* 2008;17(1):43–50.
12. Reeves GK, Beral V, Green J, Gathani T, Bull D. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. *Lancet Oncol.* 2006;7(11):910–918.
13. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA.* 2003;289(24):3243–3253.
14. Li CI, Malone KE, Porter PL, Weiss NS, Tang MT, Daling JR. The relationship between alcohol use and risk of breast cancer by histology and hormone receptor status among women 65-79 years of age. *Cancer Epidemiol Biomarkers Prev.* 2003;12(10):1061–1066.
15. Li CI, Daling JR, Malone KE, Bernstein L, Marchbanks PA, Liff JM, et al. Relationship between established breast cancer risk factors and risk of seven different histologic types of invasive breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2006;15(5):946–954.
16. Rosenberg LU, Einarsdottir K, Friman EI, Wedren S, Dickman PW, Hall P, et al. Risk factors for hormone receptor-defined breast cancer in postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2006;15(12):2482–2488.
17. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials.* 1998;19(1):61–109.
18. Li CI, Moe RE, Daling JR. Risk of mortality by histologic type of breast cancer among women aged 50 to 79 years. *Arch Intern Med.* 2003;163(18):2149–2153.
19. Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. *Breast Cancer Res.* 2007;9(1):R6.
20. Chen CL, Weiss NS, Newcomb P, Barlow W, White E. Hormone replacement therapy in relation to breast cancer. *JAMA.* 2002;287(6):734–741.
21. Daling JR, Malone KE, Doody DR, Voigt LF, Bernstein L, Coates RJ, et al. Relation of regimens of combined hormone replacement therapy to lobular, ductal, and other histologic types of breast carcinoma. *Cancer.* 2002;95(12):2455–2464.
22. Li CI, Weiss NS, Stanford JL, Daling JR. Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. *Cancer.* 2000;88(11):2570–2577.
23. Newcomer LM, Newcomb PA, Potter JD, Yasui Y, Trentham-Dietz A, Storer BE, et al. Postmenopausal hormone therapy and risk of breast cancer by histologic type (United States). *Cancer Causes Control.* 2003;14(3):225–233.
24. Rosenberg LU, Magnusson C, Lindstrom E, Wedren S, Hall P, Dickman PW. Menopausal hormone therapy and other breast cancer risk factors in relation to the risk of different histological subtypes of breast cancer: a case-control study. *Breast Cancer Res.* 2006;8(1):R11.
25. Ursin G, Tseng CC, Paganini-Hill A, Enger S, Wan PC, Formenti S, et al. Does menopausal hormone replacement therapy interact with known factors to increase risk of breast cancer? *J Clin Oncol.* 2002;20(3):699–706.
26. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol.* 1999;9(3):178–187.

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