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Original Contribution

Alcohol and Risk of Breast Cancer in Postmenopausal Women: An Analysis of Etiological Heterogeneity by Multiple Tumor Characteristics

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Alcohol consumption is an established risk factor for breast cancer. Whether associations vary by specific tumor characteristics independent of other characteristics is unclear. We evaluated the association between alcohol consumption and breast cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort (54,562 women aged 55–74 years recruited at 10 US screening centers between 1993 and 2001; median follow-up, 8.9 years; 1,905 invasive breast cancer cases). Hazard ratios and 95% confidence intervals for subtypes defined by histological type and estrogen receptor (ER)/progesterone receptor (PR) status were calculated with standard Cox models. A novel 2-stage Cox model assessed heterogeneity in risk for individual tumor characteristics while adjusting for others. Significant trends across categories of alcohol consumption were observed, with hazard ratios for those consuming 7 or more drinks per week versus never drinkers as follows: for estrogen receptor–positive (ER+) cancer, 1.48 (95% confidence interval (CI): 1.19, 1.83); for progesterone receptor–positive (PR+) cancer, 1.64 (95% CI: 1.31, 2.06); for ER+/PR+ cancer, 1.63 (95% CI: 1.30, 2.05); and for mixed ductal/lobular cancer, 2.51 (95% CI: 1.20, 5.24). For ER+ and PR+ cancers, trends were significant for ductal and mixed ductal/lobular types. PR status explained the positive association with ER status (for ER status, $P_{\text{heterogeneity}} = 0.70$ after adjustment for PR status). Alcohol consumption was not associated with all breast cancer subtypes. Future work should emphasize large collaborative studies, precise definition of subtypes, and adjustment for correlated tumor characteristics.

alcohol; breast cancer; ductal carcinoma; estrogen receptor; lobular carcinoma; progesterone receptor

Abbreviations: CI, confidence interval; DHQ, dietary history questionnaire; ER, estrogen receptor; ER−, estrogen receptor–negative; ER+, estrogen receptor–positive; HR, hazard ratio; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PR, progesterone receptor; PR−, progesterone receptor–negative; PR+, progesterone receptor–positive.

Alcohol consumption is a well-established, modifiable risk factor for breast cancer, with pooling studies (1, 2) and meta-analyses (3) suggesting a 5%–9% increase in risk per drink per day. Breast cancer is a heterogeneous disease, however, comprising several subtypes defined by hormone receptor status and histological type, which have distinct etiological and clinical features. Most cohorts have found more convincing evidence linking alcohol intake to estrogen receptor–positive (ER+)/progesterone receptor–positive (PR+) tumors than to estrogen receptor–negative (ER−)/progesterone receptor–negative (PR−) tumors (4–10), although some have found similar effects across estrogen receptor (ER)/progesterone receptor (PR) groups (11, 12) or stronger risk for hormone receptor–negative breast cancer (13). An association with ER+/PR− tumors has been seen in most (3–5, 7, 8, 12) but not all (6) studies; however, ER/PR classifications in these studies do not reflect recent recommendations (14) that ER and PR immunohistochemical assays be considered positive if at least 1% of tumor cells stain positive.

Fewer cohorts have examined associations of alcohol intake by histological subtype (4, 5, 8, 15), with some considering mixed ductal/lobular cancer as lobular cancer (5), and

others considering it a unique histological type (4) or excluding it (8, 15). Stronger associations with alcohol intake have been suggested for lobular than for ductal cancers (5). However, because lobular and mixed ductal/lobular tumors are more frequently ER+/PR+ than are ductal tumors (16), it is not clear whether differences by histological type are due to underlying differences in hormone receptor status. Results from the few studies that have considered breast cancer subtypes defined jointly by hormone receptor status and histological type (4, 5, 15) have been variable, with one observing excess risk for ductal ER+ but not lobular ER+ disease (4), and others reporting higher risk for lobular ER+/PR+ cancers than for ductal ER+/PR+ cancers (5, 14).

Only recently have statistical approaches been developed for contrasting risk associations while simultaneously considering multiple tumor characteristics. To date, 1 study has explored alcohol associations with breast cancer by adjusting for multiple tumor receptor characteristics, specifically ER, PR, and human epidermal growth factor receptor 2 gene (*HER2*) status (17). In the current report, we use data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort (18) and apply a recently developed alternative statistical approach (19) to test for heterogeneity in alcohol-related risk by breast cancer subtypes defined by ER and PR status, as well as histological type.

METHODS

Study population

The PLCO is a multicenter randomized trial, coordinated by the National Cancer Institute (Rockville, Maryland), to evaluate the effects of screening on prostate, lung, colorectal, and ovarian cancer incidence and mortality rates. Details have been described previously (18). Briefly, women aged 55–74 years were recruited at 10 US screening centers between 1993 and 2001; those with a previous diagnosis of lung, colorectal, or ovarian cancer were ineligible. Women were randomized into either the control arm, receiving usual medical care, or the screening arm, receiving regular screening for lung, colorectal, and ovarian cancer. At randomization, participants completed a questionnaire that asked about smoking, medical and reproductive histories, cancer in family members, oral contraceptive and menopausal hormone use, and demographic and anthropometric characteristics. A 114-item dietary history questionnaire (DHQ), which included questions about current and past alcohol intakes, was introduced in December 1998 (20). New enrollees were given the DHQ at baseline; prior enrollees still in the trial were mailed the questionnaire, with an overall response rate of 82% (21). DHQs missing quantitative responses for 8 or more food items or reporting the highest or lowest 1% of sex-specific total energy intakes were considered invalid and not used. All participants provided informed consent, and institutional review boards at the National Cancer Institute and screening centers approved the study.

A total of 78,202 women participated in the trial, of whom, 57,781 (73.9%) provided valid DHQs. Our study included 54,562 participants (69.8% of total) who completed both the baseline interview and a valid DHQ, had no prior history of breast cancer at completion of the DHQ, and were followed up for at least 1 month. Participants were followed from the date of DHQ completion to the date of breast cancer diagnosis or completion of the last annual study update prior to the end of follow-up (December 31, 2009, or 13 years following enrollment in the cohort, whichever came first).

Ascertainment and classification of breast cancer cases

Participants were contacted annually by mail regarding cancer diagnoses occurring within the previous year. We obtained data on breast cancer diagnoses from self-reports, next-of-kin, physicians, death certificates, and National Death Index linkage. Tumor characteristics, including histological type and hormone receptor status, were abstracted. Among the 2,397 reported breast cancers, confirmation was obtained for 2,372 (99%); the 25 that could not be confirmed were not included as cases. Those with ductal in situ cancer ($n = 336$) or other in situ cancer ($n = 131$) were censored at the dates of diagnosis and not included as cases. Thus, this analysis is limited to 1,905 histologically confirmed, invasive breast cancers. Cases were grouped as follows: ductal (*International Classification of Diseases for Oncology, Second Edition*, histology code 8500), lobular (code 8520), mixed ductal/lobular (code 8522), and tubular/other/unknown. When quantitative immunohistochemical results were available, tumors were considered ER+ or PR+ if at least 1% of cells stained positive (14). Had we considered low positives (1%–9% of cells positive) as negative (for ER status, $n = 17$; for PR status, $n = 77$), the number of ER+/PR+ tumors would have been reduced by 5.8% (from 1,322 to 1,245), and the number of ER−/PR− and ER+/PR− tumors would have increased by 6.5% (from 247 to 263) and 37.0% (from 187 to 256), respectively. For analyses including histological type, those with tubular/other/unknown types were censored at their diagnosis dates; those missing ER or PR data were similarly censored in hormone receptor analyses.

Assessment of alcohol consumption

The DHQ contained questions on frequency of consumption (10 categories) for "beer," "wine or wine coolers," and "liquor or mixed drinks" during the preceding 12 months, as well as typical portion sizes (3 categories). It also contained questions on the frequency of consumption (10 categories) of "beer" (12-oz serving; 1 oz = 29.57 mL), "wine" (5-oz serving), and "liquor" (1.5-oz serving) during each of the following 4 periods of adult life: ages 18–24, 25–39, 40–54, and ≥55 years. We calculated alcohol intake per day from all sources (in grams) and present this as the number of alcoholic drink equivalents, with 1 drink considered to be 12 oz of beer, 5 oz of wine, or 1.5 oz of liquor. Women were considered current drinkers if, at baseline, they reported drinking any alcohol in the preceding 12 months; those who reported not drinking any alcohol in the preceding 12 months, but drinking during at least 1 of the earlier age periods, were considered former drinkers. Those who never drank in any age period, including the preceding 12 months, were considered never drinkers. Categories of alcohol consumption in this analysis included never, former, and current drinkers, with

the latter further categorized as consuming less than 0.5, 0.5 to less than 1, 1 to less than 7, or 7 or more drinks per week.

Statistical analysis

Hazard ratios and 95% confidence intervals for breast cancer subtypes defined by histological type, hormone receptor status, and their combinations were estimated using a standard Cox proportional hazards regression model in which different subtypes are treated as mutually exclusive competing events. In all analyses, attained age was used as the underlying time scale, and subjects were assumed to be left-truncated at their age at entry. Analyses were performed without adjustment for any covariates (henceforth reported as age-adjusted models) and with adjustment for known breast cancer risk factors (multivariate models), including race, educational level, body mass index (weight (kg)/height $(m)^2$) at study entry, height, family history of breast cancer, age at menarche, age at natural menopause, parity, age at first birth, oral contraceptive use, menopausal hormone use at study entry, and smoking at study entry. Tests for trends in hazard ratio by level of alcohol consumption were based on the median amount consumed in each alcohol category, and they use never drinkers as the reference category; former drinkers were excluded from trend analyses. All reported P values are 2-sided.

To analyze how the effects of alcohol vary by histological subtype or hormone receptor status while controlling for the other, we used a recently developed modification of the Cox proportional hazards model (19). In the first stage, the model incorporates distinct hazard ratio parameters for alcohol consumption for each possible subtype that could be defined by the combination of a set of tumor characteristics (e.g., histological type, ER status, and PR status). In the second stage, the subtype-specific hazard ratios are specified by a reduced set of parameters that can be used to assess heterogeneity in the effect of a risk factor by certain tumor characteristics while controlling for the others.

Because the numbers of cases of some subtypes and categories of alcohol consumption were sparse, we were unable to adjust for all tumor characteristics and all known breast cancer risk factors simultaneously. However, adjustment for each risk factor 1 at a time did not change alcohol-associated risk coefficients in any of our models by more than 15%; thus, only age adjustments were made in analyses of multiple tumor characteristics. As expected, the strongest confounding was observed when the model was adjusted for smoking, but even then, the main results highlighted in this report remained qualitatively very similar.

RESULTS

Study population characteristics

The median times from study entry to diagnosis (for breast cancer cases) and to exit (for noncases) were 8.9 years (interdecile range, 6.1–10.0) overall, 4.1 years (interdecile range, 0.8–8.0) for cases, and 9.0 years (interdecile range, 6.5–10.1), for noncases. Table 1 presents demographic and breast cancer risk factor characteristics of the study population overall and according to alcohol use at study entry. Most characteristics were distributed similarly across categories of alcohol use. Current alcohol consumers tended to be younger at study entry, non-Hispanic white, better educated, thinner, taller, older at the birth of their first child, and more likely to have used oral contraceptives than never or former drinkers.

Breast cancer cases

The majority of the 1,905 incident, histologically confirmed, invasive breast cancer cases were stage 1 (63.3%), less than 2 cm in diameter (75.1%), and without nodal involvement (70.2%). Additionally, 75.8% were ductal carcinoma, 12.2% lobular carcinoma, and 5.7% mixed ductal/lobular carcinoma; 69.4% were ER+/PR+, 13.0% were ER−/PR−, and 9.8% were ER+/PR− (Table 2). Lobular and mixed ductal/lobular tumors were more likely to be ER+/PR+ than were ductal tumors (76.8% and 80.7%, respectively, vs. 66.4%).

Breast cancer risk by alcohol consumption, overall and by subtype

Overall, current drinkers experienced higher risk with a greater number of drinks consumed per week ($P_{trend} = 0.01$), with the multivariate hazard ratio reaching 1.35 (95% CI: 1.12, 1.64) for those who reported consuming 7 or more drinks per week compared with never drinkers (Table 3). Similar results were obtained from the age-adjusted models ($P_{trend} = 0.01$). Former drinkers had a nonsignificant 16% higher risk compared with never drinkers. Risk increased steadily with increasing amount of alcohol consumption for ER+ and PR+ cancers ($P_{trend} = 0.0039$ and 0.0004, respectively), but not for ER− or PR− cancer (Table 4). For subtypes defined jointly by ER and PR status (Table 5), higher risks by alcohol intake were observed only for ER+/PR+ cancer ($P_{trend} = 0.0003$), with approximately 60% higher risk associated with consumption of 7 or more drinks/week relative to never drinkers. When we considered tumors with 1%–9% staining as hormone receptor–negative rather than positive, the associations with alcohol intake were essentially unchanged for ER+/PR+ and ER−/PR− breast cancers. The hazard ratio for ER+/PR− tumors went from less than 1.0 for nearly all levels of alcohol intake to greater than 1.0 for all levels, but both trends were nonsignificant (Web Table 1, available at http://aje.oxfordjournals.org/).

For all histological types, risks were higher with higher alcohol consumption (Table 6). Although women consuming at least 0.5 drinks per week were at significantly higher risk of ductal breast cancer than were never drinkers, trends were significant only for mixed ductal/lobular cancer, largely because of the higher risk associated with the small number of women consuming at least 7 drinks per week.

Breast cancer risk by alcohol consumption in subtypes jointly defined by histological type, ER status, and PR status

For women with ductal or mixed ductal/lobular cancer, higher risks were seen only for those with ER+/PR+ disease (for ductal cancer, $P_{trend} = 0.03$; for mixed ductal/lobular

Table 1. Participant Characteristics in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Cohort, Overall and By Alcohol Consumption at Study Entry, 1993–2001

Characteristic	All ($n = 54,562$)		Alcohol Consumption, %		
	No.	%	Never ($n = 7,463$)	Former ($n = 9,362$)	Current ($n = 37,737$)
Age at study entry, years					
55–59	10,246	18.8	13.9	16.8	20.2
60–69	30,151	55.3	54.7	54.9	55.4
70–74	14,165	26.0	31.4	28.3	24.3
Race/ethnicity					
White (non-Hispanic)	49,816	91.3	86.6	86.4	93.4
Black (non-Hispanic)	2,061	3.8	4.8	6.7	2.8
Asian/Pacific Islander	1,903	3.5	7.5	5.0	2.3
Hispanic/American Indian/missing	782	1.4	1.0	1.8	1.4
Educational level					
<12 years	2,831	5.2	6.6	9.5	3.8
Completed high school	15,198	27.9	31.3	31.1	26.4
Some college/post–high school	19,739	36.2	35.9	36.0	36.3
College graduate	8,514	15.6	14.9	11.7	16.7
Postgraduate	8,185	15.0	11.2	11.5	16.6
BMI at study entry[a]					
<20	2,101	3.9	3.9	3.6	3.9
20–24.9	19,441	35.6	32.6	28.6	38.0
25–29.9	19,162	35.1	34.8	34.6	35.3
≥30	8,584	15.7	17.8	18.0	14.8
Height, inches[b]					
<63	430	0.8	0.8	0.8	0.8
63–64	530	1.0	0.7	0.9	1.0
65	301	0.6	0.5	0.5	0.6
66	275	0.5	0.4	0.4	0.6
≥67	358	0.7	0.5	0.6	0.7
Family history of breast cancer					
No	46,499	85.2	85.2	84.7	85.4
Yes (first-degree female relative)	7,624	14.0	14.4	14.5	13.8
Yes (first-degree male relative only)	83	0.2	0.1	0.2	0.2
Age at menarche, years					
<12	10,947	20.1	19.5	22.1	19.7
12–13	29,527	54.1	54.2	52.8	54.4
14–15	11,612	21.3	21.6	20.4	21.4
≥16	2,368	4.3	4.6	4.5	4.3

Table continues

cancer, $P_{trend} = 0.003$), although the trend for mixed ductal/lobular cancer was mainly driven by a small number of women consuming at least 7 drinks per week (Table 7). Ductal ER+/PR− and ER−/PR− tumors were not associated with alcohol intake, and too few cases were available to explore ER+/PR− and ER−/PR− status among lobular and mixed ductal/lobular subtypes.

To further explore the effect of simultaneously adjusting for multiple tumor characteristics, we present ratios of the alcohol risks in which the hazard ratio of 1 tumor subtype is compared with another (Web Table 2). For each comparison, results are presented from an age-adjusted model in which the tumor characteristic was analyzed by itself and also from models in which multiple tumor characteristics were analyzed simultaneously. For these analyses, additional adjustment for known breast cancer risk factors was not possible. Thus, for example, in the comparison of ER+ versus ER− tumors, the hazard ratio of 1.62 (95% CI: 0.93, 2.81)

Table 1. Continued

Characteristic	All ($n = 54,562$)		Alcohol Consumption, %		
	No.	%	Never ($n = 7,463$)	Former ($n = 9,362$)	Current ($n = 37,737$)
Age at natural menopause, years					
<40	2,302	4.2	4.9	5.1	3.8
40–44	4,373	8.0	8.0	8.8	7.8
45–49	10,510	19.3	18.5	19.5	19.4
50–54	19,056	34.9	33.0	31.6	36.1
≥55	5,957	10.9	10.4	9.7	11.3
No. of livebirths					
Nulliparous	4,817	8.8	6.6	8.5	9.4
1	3,915	7.2	6	7.6	7.3
2	15,752	28.9	27.8	45.3	25
3	13,624	25	29.3	17.2	26.1
4	8,358	15.3	22.3	6	16.2
≥5	7,905	14.5	25.4	0.5	15.8
Age at first birth, years					
Nulliparous	4,817	8.8	6.6	8.5	9.4
<20	8,862	16.2	18.8	22.5	14.2
20–24	25,887	47.4	49.9	45.3	47.5
25–29	11,049	20.3	17.9	17.2	21.5
≥30	3,685	6.8	6.4	6	7
Ever oral contraceptive use	30,189	55.3	44.5	52.3	58.2
Menopausal hormone use at study entry					
Never	17,037	31.2	33.6	35.3	29.7
Former	28,607	52.4	49	46.9	54.5
Current	8,604	15.8	16.7	17.3	15.2
Smoking status at study entry					
Never	31,051	56.9	89.4	55	51
Former	4,660	8.5	2.3	10.1	9.4
Current	18,841	34.5	8.3	34.9	39.6

Abbreviation: BMI, body mass index.
[a] Weight (kg)/height (m)^2.
[b] One inch = 2.54 cm.

for consuming 7 drinks or more per week implies that breast cancer risk associated with this amount of drinking (in reference to never drinkers) was 62% higher for women with ER+ tumors relative to those with ER− tumors. In the age-adjusted models, alcohol-associated risks differed by ER status ($P_{\text{heterogeneity}} = 0.06$), by PR status ($P_{\text{heterogeneity}} = 0.01$), and between mixed ductal/lobular and ductal subtypes ($P_{\text{heterogeneity}} = 0.001$). However, in the model with simultaneous adjustment for ER status, PR status, and histological type, differences in alcohol-associated hazard ratios were suggested for PR status ($P_{\text{heterogeneity}} = 0.1$) but not ER status. The observed difference in alcohol-associated risks between mixed ductal/lobular and ductal tumors, driven mainly by risk among women consuming 7 or more drinks per week, persisted in the model that accounted for both ER and PR status.

DISCUSSION

Our finding that breast cancer is linked to moderate alcohol consumption is consistent with a large body of evidence from epidemiologic studies (1–3). However, suggestions that the strength of this association differs by histological type (5, 15) and hormone receptor status (4–10, 13) are not conclusive and may be due to correlated tumor characteristics (16). We applied a novel statistical approach that simultaneously adjusted for ER status, PR status, and histological type, which allowed us to explore alcohol-associated risks by each distinct tumor characteristic (19). In our data, positive associations were limited to ER+/PR+ tumors, and within this subgroup, risks were observed for ductal and mixed ductal/lobular cancers. Analyses incorporating multiple tumor characteristics indicated that PR status, and not necessarily ER

Table 2. Distribution of Breast Cancer Cases by Histological Type and Hormone Receptor Status

Histological Type	ER+/PR+		ER+/PR−		ER−/PR+		ER−/PR−		Unknown		Total	
	No.	%[a]	No.	%	No.	%	No.	%	No.	%	No.	%
Ductal	959	50.3	136	7.1	19	1.0	229	12.0	101	5.3	1,444	75.8
Lobular	179	9.4	37	1.9	0		6	0.3	11	0.6	233	12.2
Mixed ductal/lobular	88	4.6	6	0.3	0		5	0.3	10	0.5	109	5.7
Tubular/other/unknown	96	5	8	0.4	0		7	0.4	8	0.4	119	6.2
Total	1,322	69.4	187	9.8	19	1.0	247	13.0	130	6.8	1,905	100.0

Abbreviations: ER−, estrogen receptor–negative; ER+, estrogen receptor–positive PR−, progesterone receptor–negative; PR+, progesterone receptor–positive.

[a] Percent of total invasive breast cancer cases; numbers do not sum to 100% because of rounding.

status, may characterize alcohol-associated etiological heterogeneity for breast cancer subtypes. Differences in ER/PR status did not account for differences by histological type.

Contrary to our results, most (3–5, 7, 8, 12), but not all (6), studies link alcohol consumption to ER+/PR− disease. Only 1 study has assessed whether ER+ status and PR+ status are independently associated with alcohol intake (17), but unlike our results, that study found the ER+ association was not attributable to PR status. In our study, PR status was more informative in parsing out the alcohol association because risks were seen only for ER+/PR+ cancers and not for ER+/PR− or ER−/PR− cancers. The 2-stage Cox model supported these observations, although the finding that women with PR+ tumors experienced higher risk with higher alcohol intake compared to women with PR− tumors, even after adjustment for ER status, was of borderline significance. One possible explanation for our unusual findings is our reliance on recent American Society of Clinical Oncology and College of American Pathologists guidelines (14), in which immunohistochemical staining in 1%–9% cells is considered hormone receptor positive. Had we considered the low positive ER and PR readings as negative, the number of ER+/PR− tumors would have declined dramatically from 248 to 187, with the direction of the alcohol association for this subgroup switching from negative to positive, although the strength of the associations was not significant in either instance. Whether these new guidelines are useful for etiological research is not clear, because the new criteria were based on tumor responsiveness to endocrine therapy, which included instances in which ER and/or PR positivity was low (14). It is not known whether the resulting subgroups accurately reflect tumor molecular biology or etiology (22–24). When we use earlier conventions, in which less than 10% positive staining is considered hormone receptor–negative, etiological and clinical differences between ER+/PR+ and ER−/PR− cancers are clear (25, 26); however, the literature on

Table 3. Hazard Ratios for Breast Cancer by Alcohol Consumption in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Cohort, 1993–2001

Alcohol Consumption	No. of Cases[a]	Age-Adjusted HR	95% CI	Multivariate HR[b]	95% CI
Never	218	1.00	Referent	1.00	Referent
Former	306	1.15	0.96, 1.36	1.16	0.97, 1.39
Current, drinks/week					
<0.5	432	1.16	0.99, 1.37	1.15	0.97, 1.36
0.5–<1	197	1.28	1.06, 1.55	1.25	1.03, 1.53
1–<7	495	1.28	1.09, 1.51	1.26	1.07, 1.49
≥7	257	1.38	1.15, 1.65	1.35	1.12, 1.64
P_{trend}[c]		0.01		0.04	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Women missing data on educational level, age at menarche, height, or body mass index (weight (kg)/height $(m)^2$) ($n = 35$) were included in the age-adjusted model but excluded from the multivariate-adjusted model.

[b] Adjusted for race (white, other), educational level (≤12 years, beyond high school, missing), body mass index at study entry (<25, 25–29.9, ≥30, missing), height, family history of breast cancer (yes in a first-degree female relative, no), age at menarche (<12, 12–13, ≥14 years, missing), age at natural menopause (<45, 45–49, ≥50 years, missing)/surgical menopause, reproductive history (nulliparous, first birth at <30 years of age and 1–2 children, first birth at <30 years of age and ≥3 children, first birth at ≥30 years of age), oral contraceptive use (ever, never), menopausal hormone use at study entry (never, former, current), and smoking at study entry (never, former, current).

[c] P_{trend} calculated using median value in each drinking category and includes never drinkers but not former drinkers.

Table 4. Hazard Ratios for Breast Cancer by Alcohol Consumption and Hormone Receptor Status in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Cohort, 1993–2001

Alcohol Consumption, by Hormone Receptor Status	No. of Cases[a]	Age-Adjusted HR	95% CI	Multivariate HR[b]	95% CI
ER+					
Never	175	1.00	Referent	1.00	Referent
Former	235	1.10	0.90, 1.34	1.14	0.93, 1.4
Current, drinks/week					
<0.5	341	1.14	0.95, 1.37	1.15	0.95, 1.39
0.5–<1	158	1.28	1.04, 1.59	1.29	1.03, 1.61
1–<7	397	1.29	1.08, 1.54	1.29	1.07, 1.56
≥7	219	1.47	1.20, 1.79	1.48	1.19, 1.83
P_{trend}[c]		0.0006		0.0039	
ER–					
Never	33	1.00	Referent	1.00	Referent
Former	50	1.22	0.79, 1.90	1.10	0.70, 1.73
Current, drinks/week					
<0.5	60	1.05	0.69, 1.61	0.98	0.63, 1.51
0.5–<1	29	1.22	0.74, 2.00	1.08	0.65, 1.81
1–<7	68	1.14	0.75, 1.72	1.05	0.68, 1.62
≥7	26	0.91	0.54, 1.52	0.84	0.49, 1.44
P_{trend}[c]		0.47		0.24	
PR+					
Never	147	1.00	Referent	1.00	Referent
Former	201	1.12	0.90, 1.38	1.14	0.92, 1.42
Current, drinks/week					
<0.5	302	1.20	0.99, 1.47	1.20	0.98, 1.48
0.5–<1	143	1.38	1.09, 1.73	1.37	1.08, 1.74
1–<7	345	1.32	1.09, 1.61	1.33	1.09, 1.63
≥7	203	1.62	1.31, 2.00	1.64	1.31, 2.06
P_{trend}[c]		0.0001		0.0004	
PR–					
Never	60	1.00	Referent	1.00	Referent
Former	80	1.09	0.78, 1.52	1.08	0.76, 1.53
Current, drinks/week					
<0.5	93	0.91	0.66, 1.26	0.88	0.63, 1.24
0.5–<1	42	0.99	0.67, 1.48	0.95	0.63, 1.43
1–<7	117	1.10	0.81, 1.51	1.05	0.75, 1.47
≥7	42	0.82	0.55, 1.22	0.76	0.5, 1.16
P_{trend}[c]		0.37		0.15	

Abbreviations: CI, confidence interval; ER–, estrogen receptor–negative; ER+, estrogen receptor–positive; HR, hazard ratio; PR–, progesterone receptor–negative; PR+, progesterone receptor–positive.

[a] Women missing data on educational level, age at menarche, height, or body mass index (weight (kg)/height $(m)^2$) ($n = 35$) were included in the age-adjusted model but excluded from the multivariate-adjusted model.

[b] Adjusted for race (white, other), educational level (≤12 years, beyond high school, missing), body mass index at study entry (<25, 25–29.9, ≥30, missing), height, family history of breast cancer (yes= in a first-degree female relative, no), age at menarche (<12, 12–13, ≥14 years, missing), age at natural menopause (<45, 45–49, ≥50 years, missing)/surgical menopause, reproductive history (nulliparous, first birth at <30 years of age and 1–2 children, first birth at <30 years of age and ≥3 children, first birth at ≥30 year of age), oral contraceptive use (ever, never), menopausal hormone use at study entry (never, former, current), and smoking at study entry (never, former, current).

[c] P_{trend} calculated using median value in each drinking category and includes never drinkers but not former drinkers.

Table 5. Hazard Ratios for Breast Cancer by Alcohol Consumption and Joint Estrogen/Progesterone Receptor Status in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Cohort, 1993–2001

Alcohol Consumption, by Hormone Receptor Status	No. of Cases[a]	Age-Adjusted HR	95% CI	Multivariate HR[b]	95% CI
ER+/PR+					
Never	147	1.00	Referent	1.00	Referent
Former	201	1.12	0.90, 1.38	1.15	0.92, 1.43
Current, drinks/week					
<0.5	296	1.18	0.97, 1.44	1.18	0.97, 1.45
0.5–<1	141	1.36	1.08, 1.72	1.36	1.07, 1.72
1–<7	336	1.29	1.06, 1.57	1.30	1.06, 1.59
≥7	201	1.60	1.30, 1.98	1.63	1.30, 2.05
P_{trend}[c]		0.0001		0.0003	
ER+/PR−					
Never	27	1.00	Referent	1.00	Referent
Former	30	0.92	0.54, 1.54	1.04	0.60, 1.79
Current, drinks/week					
<0.5	39	0.86	0.52, 1.40	0.88	0.52, 1.48
0.5–<1	15	0.81	0.43, 1.52	0.85	0.44, 1.63
1–<7	58	1.24	0.78, 1.96	1.24	0.75, 2.04
≥7	18	0.79	0.44, 1.44	0.74	0.39, 1.42
P_{trend}[c]		0.63		0.39	
ER−/PR−					
Never	33	1.00	Referent	1.00	Referent
Former	50	1.23	0.79, 1.91	1.11	0.70, 1.74
Current, drinks/week					
<0.5	54	0.95	0.62, 1.46	0.88	0.57, 1.38
0.5–<1	27	1.14	0.69, 1.90	1.01	0.60, 1.72
1–<7	59	0.99	0.65, 1.52	0.91	0.58, 1.43
≥7	24	0.84	0.50, 1.43	0.78	0.44, 1.36
P_{trend}[c]		0.45		0.66	

Abbreviations: CI, confidence interval; ER−, estrogen receptor–negative; ER+, estrogen receptor–positive; HR, hazard ratio; PR−, progesterone receptor–negative; PR+, progesterone receptor–positive.

[a] Women missing data on educational level, age at menarche, height, or body mass index (weight (kg)/height $(m)^2$) ($n = 35$) were included in the age-adjusted model but excluded from the multivariate-adjusted model.

[b] Adjusted for race (white, other), educational level (≤12 years, beyond high school, missing), body mass index at study entry (<25, 25–29.9, ≥30, missing), height, family history of breast cancer (yes= in a first-degree female relative, no), age at menarche (<12, 12–13, ≥14 years, missing), age at natural menopause (<45, 45–49, ≥50 years, missing)/surgical menopause, reproductive history (nulliparous, first birth at <30 years of age and 1–2 children, first birth at <30 years of age and ≥3 children, first birth at ≥30 year of age), oral contraceptive use (ever, never), menopausal hormone use at study entry (never, former, current), and smoking at study entry (never, former, current).

[c] P_{trend} calculated using median value in each drinking category and includes never drinkers but not former drinkers.

ER+/PR− disease is more limited (27). Despite being somewhat responsive to hormonal therapy, ER+/PR− tumors have more aggressive clinicopathological characteristics than ER+/PR+ tumors (27, 28), and results from the largest pooling study to date do not implicate reproductive and hormonal risk factors in their etiology (25). In future studies, the adoption of the new American Society of Clinical Oncology and College of American Pathologists criteria may help elucidate the molecular and etiological characteristics of ER+/PR+ breast cancer, including a potential role for alcohol consumption.

In terms of histological type, stronger positive associations were noted for lobular than for ductal tumors, although the differences were not statistically significant; whereas, the risk for women consuming 7 or more drinks weekly among the mixed ductal/lobular group was significantly higher compared with the corresponding risk for ductal cancer. This difference remained significant even after controlling for ER and

Table 6. Hazard Ratios for Breast Cancer by Alcohol Consumption and Histological Type in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Cohort, 1993–2001

Alcohol Consumption, drinks/week, by Histological Type	No. of Cases[a]	Age-Adjusted HR	95% CI	Multivariate HR[b]	95% CI
Ductal					
Never	165	1.00	Referent	1.00	Referent
Former	224	1.11	0.90, 1.35	1.12	0.91, 1.38
<0.5	332	1.18	0.97, 1.42	1.16	0.96, 1.41
0.5–<1	155	1.32	1.06, 1.65	1.30	1.04, 1.63
1–<7	389	1.32	1.10, 1.59	1.32	1.09, 1.59
≥7	179	1.26	1.02, 1.56	1.26	1.00, 1.58
P_{trend}[c]		0.25		0.48	
Lobular					
Never	27	1.00	Referent	1.00	Referent
Former	38	1.16	0.71, 1.90	1.19	0.72, 1.98
<0.5	58	1.27	0.80, 2.01	1.25	0.78, 2.01
0.5–<1	20	1.07	0.60, 1.91	0.98	0.54, 1.80
1–<7	54	1.15	0.72, 1.82	1.06	0.65, 1.73
≥7	36	1.58	0.96, 2.61	1.42	0.83, 2.43
P_{trend}[c]		0.09		0.41	
Mixed ductal/lobular					
Never	12	1.00	Referent	1.00	Referent
Former	21	1.45	0.71, 2.95	1.59	0.77, 3.28
<0.5	16	0.80	0.38, 1.68	0.83	0.39, 1.78
0.5–<1	10	1.22	0.53, 2.83	1.27	0.54, 2.98
1–<7	25	1.21	0.61, 2.42	1.20	0.58, 2.45
≥7	25	2.51	1.26, 4.99	2.51	1.20, 5.24
P_{trend}[c]		0.0001		0.0003	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Women missing data on educational level, age at menarche, height, or body mass index (weight (kg)/height $(m)^2$) ($n = 35$) were included in the age-adjusted model but excluded from the multivariate-adjusted model.

[b] Adjusted for race (white, other), educational level (≤12 years, beyond high school, missing), body mass index at study entry (<25, 25–29.9, ≥30, missing), height, family history of breast cancer (yes= in a first-degree female relative, no), age at menarche (<12, 12–13, ≥14 years, missing), age at natural menopause (<45, 45–49, ≥50 years, missing)/surgical menopause, reproductive history (nulliparous, first birth at <30 years of age and 1–2 children, first birth at <30 years of age and ≥3 children, first birth at ≥30 year of age), oral contraceptive use (ever, never), menopausal hormone use at study entry (never, former, current), and smoking at study entry (never, former, current).

[c] P_{trend} calculated using median value in each drinking category and includes never drinkers but not former drinkers.

PR status. This finding, which has not been reported previously, needs to be interpreted with caution because the result was driven by a small number of women in that category of alcohol intake. Whether mixed ductal/lobular breast cancer is a unique histological type that borrows etiological and clinical characteristics from ductal and lobular breast cancer is not known (15, 16). In prior studies, classifications have differed, with some considering mixed ductal/lobular cancer as lobular cancer (5), and others considering it its own histological subtype (4, 15). Future studies with larger sample sizes are needed to explore this subtype on its own.

Our study had several limitations. Information on hormone receptor status and histological type was abstracted from hospital records, and there was no central review of pathological findings; thus, misclassification of subtypes is possible. Because we enrolled participants before the routine adoption of *HER2* testing in early-stage breast cancer, our findings are limited to the differential impact of alcohol on breast cancer subtypes distinguished only by ER and PR status. Alcohol consumption was not high, with less than 12% of the cohort reporting current consumption of 7 or more drinks per week at study entry, and information on changes in alcohol use over the follow-up period was not available. Finally, although the PLCO cohort included a relatively large number of breast cancers cases overall, the small numbers of cases of specific subtypes limited the power of tests for heterogeneity and produced imprecise risk estimates.

Table 7. Hazard Ratios for Breast Cancer by Alcohol Consumption, Hormone Receptor Status, and Histological Type in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Cohort, 1993–2001

Alcohol Consumption, drinks/week, by Histological Type	No. of Cases[a]	Age-Adjusted HR	95% CI	Multivariate HR[b]	95% CI
		ER+/*PR*+			
Ductal					
Never	105	1.00	Referent	1.00	Referent
Former	145	1.13	0.88, 1.45	1.16	0.90, 1.50
<0.5	218	1.21	0.96, 1.53	1.22	0.96, 1.55
0.5–<1	104	1.40	1.06, 1.83	1.41	1.07, 1.86
1–<7	254	1.36	1.08, 1.71	1.39	1.09, 1.76
≥7	133	1.48	1.14, 1.91	1.52	1.16, 2.00
P_{trend}[c]		0.02		0.03	
Lobular					
Never	18	1.00	Referent	1.00	Referent
Former	27	1.23	0.68, 2.23	1.16	0.63, 2.13
<0.5	48	1.57	0.91, 2.70	1.45	0.83, 2.51
0.5–<1	17	1.35	0.69, 2.62	1.14	0.57, 2.27
1–<7	39	1.23	0.70, 2.16	1.07	0.60, 1.92
≥7	30	1.97	1.09, 3.53	1.67	0.89, 3.12
P_{trend}[c]		0.07		0.32	
Mixed ductal/lobular					
Never	12	1.00	Referent	1.00	Referent
Former	11	0.76	0.34, 1.73	0.84	0.37, 1.93
<0.5	15	0.75	0.35, 1.60	0.80	0.37, 1.73
0.5–<1	9	1.11	0.47, 2.63	1.18	0.49, 2.86
1–<7	18	0.88	0.42, 1.83	0.89	0.41, 1.92
≥7	23	2.31	1.15, 4.65	2.47	1.16, 5.26
P_{trend}[c]		0.0002		0.0003	
		ER+/*PR*–			
Ductal					
Never	20	1.00	Referent	1.00	Referent
Former	16	0.66	0.34, 1.27	0.73	0.37, 1.46
<0.5	28	0.82	0.46, 1.46	0.86	0.47, 1.58
0.5–<1	13	0.93	0.46, 1.87	0.97	0.47, 2.02
1–<7	45	1.28	0.76, 2.18	1.29	0.73, 2.29
≥7	14	0.82	0.42, 1.63	0.79	0.38, 1.65
P_{trend}[c]		0.75		0.52	
Lobular[d]					
Never	5				
Former	9				
<0.5	7				
0.5–<1	2				
1–<7	10				
≥7	4				

Table continues

In summary, by using data from a large cohort study in which classification of hormone receptor subtypes relied on recent guidelines, we used novel statistical methods to characterize alcohol-associated risks for breast cancer associated with multiple tumor characteristics. Our results indicate that PR status may be more informative than ER status as a

Table 7. Continued

Alcohol Consumption, drinks/week, by Histological Type	No. of Cases[a]	Age-Adjusted HR	95% CI	Multivariate HR[b]	95% CI
Mixed ductal/lobular[d]					
Never	0				
Former	4				
<0.5	0				
0.5–<1	0				
1–<7	2				
≥7	0				
		ER–/PR–			
Ductal					
Never	31	1.00	Referent	1.00	Referent
Former	45	1.17	0.74, 1.86	1.05	0.65, 1.68
<0.5	50	0.93	0.60, 1.46	0.86	0.54, 1.37
0.5–<1	26	1.17	0.69, 1.97	1.03	0.60, 1.77
1–<7	56	1.00	0.64, 1.55	0.91	0.58, 1.45
≥7	21	0.78	0.45, 1.36	0.72	0.40, 1.29
P_{trend}[c]		0.32		0.16	
Lobular[d]					
Never	2				
Former	0				
<0.5	1				
0.5–<1	0				
1–<7	2				
≥7	1				
Mixed ductal/lobular[d]					
Never	0				
Former	3				
<0.5	0				
0.5–<1	0				
1–<7	1				
≥7	1				

Abbreviations: CI, confidence interval; ER–, estrogen receptor–negative; ER+, estrogen receptor–positive; HR, hazard ratio; PR–, progesterone receptor–negative; PR+, progesterone receptor–positive.

[a] Women missing data on educational level, age at menarche, height, or body mass index (weight (kg)/height $(m)^2$) ($n = 35$) were included in the age-adjusted model but excluded from the multivariate-adjusted model.

[b] Adjusted for race (white, other), educational level (≤12 years, beyond high school, missing), body mass index at study entry (<25, 25–29.9, ≥30, missing), height, family history of breast cancer (yes= in a first-degree female relative, no), age at menarche (<12, 12–13, ≥14 years, missing), age at natural menopause (<45, 45–49, ≥50 years, missing)/surgical menopause, reproductive history (nulliparous, first birth at <30 years of age and 1–2 children, first birth at <30 years of age and ≥3 children, first birth at ≥30 year of age), oral contraceptive use (ever, never), menopausal hormone use at study entry (never, former, current), and smoking at study entry (never, former, current).

[c] P_{trend} calculated using median value in each drinking category and includes never drinkers but not former drinkers.

[d] Hazard ratios were not estimated for instances in which the reference category had 5 or fewer cases.

marker for alcohol-associated risk for breast cancer, and that information on histological type may provide additional specificity. In the future, however, large collaborative efforts combining data from multiple studies are needed to corroborate these findings. Our analysis further points to the value of novel analytical strategies, such as the one used here, for identifying potentially distinct etiological pathways of breast and other cancers using data on multiple tumor characteristics, including new molecular markers that continue to emerge.

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REFERENCES

1. Hamajima N, Hirose K, Tajima K, et al. 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. Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA*. 1998;279(7):535–540.
3. Suzuki R, Orsini N, Mignone L, et al. 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.
4. Lew JQ, Freedman ND, Leitzmann MF, et al. Alcohol and risk of breast cancer by histologic type and hormone receptor status in postmenopausal women: the NIH-AARP Diet and Health Study. *Am J Epidemiol*. 2009;170(3):308–317.
5. Li CI, Chlebowski RT, Freiberg M, et al. Alcohol consumption and risk of postmenopausal breast cancer by subtype: the Women's Health Initiative Observational Study. *J Natl Cancer Inst*. 2010;102(18):1442–1431.
6. Zhang SM, Lee IM, Manson JE, et al. Alcohol consumption and breast cancer risk in the Women's Health Study. *Am J Epidemiol*. 2007;165(6):667–676.
7. Suzuki R, Ye W, Rylander-Rudqvist T, et al. Alcohol and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status: a prospective cohort study. *J Natl Cancer Inst*. 2005;97(21):1601–1608.
8. Chen WY, Rosner B, Hankinson SE, et al. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. *JAMA*. 2011;306(17):1884–1890.
9. Bassett JK, Baglietto L, Hodge AM, et al. Dietary intake of B vitamins and methionine and breast cancer risk. *Cancer Causes Control*. 2013;24(8):1555–1563.
10. Horn-Ross PL, Canchola AJ, Bernstein L, et al. Alcohol consumption and breast cancer risk among postmenopausal women following the cessation of hormone therapy use: the California Teachers Study. *Cancer Epidemiol Biomarkers Prev*. 2012;21(11):2006–2013.
11. Setiawan VW, Monroe KR, Wilkens LR, et al. Breast cancer risk factors defined by estrogen and progesterone receptor status: the Multiethnic Cohort Study. *Am J Epidemiol*. 2009; 169(10):1251–1259.
12. Park SY, Kolonel LN, Lim U, et al. Alcohol consumption and breast cancer risk among women from five ethnic groups with light to moderate intakes: the Multiethnic Cohort Study. *Int J Cancer*. 2014;134(6):1504–1510.
13. Sellers TA, Vierkant RA, Cerhan JR, et al. Interaction of dietary folate intake, alcohol, and risk of hormone receptor–defined breast cancer in a prospective study of postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2002;11(10 Pt 1): 1104–1107.
14. Hammond MEH, Hayes DF, Dowsett M, et al. ASCO-CAP guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010;28(16):2784–2795.
15. Kotsopoulos J, Chen WY, Gates MA, et al. Risk factors for ductal and lobular breast cancer: results from the Nurses' Health Study. *Breast Cancer Res*. 2010;12(6):R106.
16. Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. *Br J Cancer*. 2005;93(9): 1046–1052.
17. Rosner B, Glynn RJ, Tamimi RM, et al. Breast cancer risk prediction with heterogeneous risk profiles according to breast cancer tumor markers. *Am J Epidemiol*. 2013;178(2): 296–308.
18. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials*. 2000;21(6 suppl): 273S–309S.
19. Chatterjee N, Sinha S, Diver WR, et al. Analysis of cohort studies with multivariate and partially observed disease classification data. *Biometrika*. 2010;97(3): 683–698.
20. Subar AF, Ziegler RG, Thompson FE, et al. Is shorter always better? Relative importance of questionnaire length and cognitive ease on response rates and data quality for two dietary questionnaires. *Am J Epidemiol*. 2001;153(4): 404–409.
21. Sue LY, Schairer C, Ma X, et al. Energy intake and risk of postmenopausal breast cancer: an expanded analysis in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort. *Cancer Epidemiol Biomarkers Prev*. 2009; 18(11):2842–2450.
22. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol*. 2010;28(3): 509–518.
23. Hefti MM, Hu R, Knoblauch NW, et al. Estrogen receptor negative/progesterone receptor positive breast cancer is not a reproducible subtype. *Breast Cancer Res*. 2013; 15(4):R68.
24. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomized trials. *Lancet*. 2011;378(9793): 771–784.
25. Yang XR, Chang-Claude J, Goode EL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled

analysis from the Breast Cancer Association Consortium studies. *J Natl Cancer Inst*. 2011;103(3):250–263.
26. 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.
27. Thakkar JP, Mehta DG. A review of an unfavorable subset of breast cancer: estrogen receptor positive progesterone receptor negative. *Oncologist*. 2011;16(3):276–285.
28. Cui X, Schiff R, Arpino G, et al. Biology of progesterone receptor loss in breast cancer and its implications for endocrine therapy. *J Clin Oncol*. 2005;23(30):7721–7735.