

The Relationship between Alcohol Use and Risk of Breast Cancer by Histology and Hormone Receptor Status among Women 65–79 Years of Age¹

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Abstract

Alcohol consumption is associated with a moderate increase in breast cancer risk, possibly because alcohol increases estrogen levels in blood. Certain types of breast carcinomas are more hormonally responsive than others, including those that have a lobular histology or are hormone receptor positive, but few studies evaluating alcohol use and breast cancer risk have stratified results by histology or estrogen receptor (ER)/progesterone receptor (PR) status. We conducted a population-based case-control study of women 65–79 years of age in western Washington State. Women (975) diagnosed with invasive breast cancer during 1997–1999 were compared with 1007 controls. Ever-use of alcohol over the past 20 years was associated with a 1.3-fold [95% confidence interval (CI), 1.0–1.5] increased risk of breast cancer, although this increase was primarily limited to women who consumed ≥ 30.0 g/day of alcohol [odds ratio (OR), 1.7; 95% CI, 1.1–2.6]. Differences in risk by histology were observed: ever-use of alcohol was associated with a 1.8-fold (95% CI, 1.3–2.5) increased risk of lobular cancer but only a 1.2-fold (95% CI, 0.9–1.4) increased risk of ductal cancer. Ever-users of alcohol had an increase in risk of ER+/PR+ tumors (OR, 1.3; 95% CI, 1.1–1.7), but no change in their risks of ER+/PR– or ER–/PR– tumors. Alcohol use appears to be more strongly associated with risk of lobular carcinomas and hormone receptor-positive tumors than it is with other types of breast cancer. These results are consistent with there being an underlying hormonal basis for the known association between alcohol use and breast cancer incidence.

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Introduction

Reviews and meta-analyses of observational studies evaluating alcohol use and breast cancer risk have consistently shown that alcohol use is a moderate risk factor for breast cancer (1–4). Specifically, a recent pooled analysis of 53 epidemiological studies reported that breast cancer risk increases 7.1% with each additional 10 g/day of alcohol consumed (1).

One of the mechanisms thought to underlie this association is the influence that alcohol use has on hormone levels in women (2). In breast cancer cells in culture, ethanol has been shown to stimulate the proliferation of ER-positive,³ but not ER– cells (5, 6). A controlled feeding study of healthy postmenopausal women demonstrated that alcohol consumption increases blood estrone sulfate and dehydroepiandrosterone concentrations in a dose-dependent manner (7). Thus, one might expect that alcohol use may selectively increase a woman's risk of hormonally responsive breast cancers, because data suggest that hormonally related breast cancer risk factors are associated with ER+/PR-positive breast tumors, but not with ER–/PR– or ER+/PR– tumors (8). However, epidemiological data from five studies investigating the relationship between alcohol use and risk of breast tumors with different hormone receptor profiles are inconsistent. Two of these studies found that alcohol use was associated with an increased risk of ER+ but not ER– breast cancers (9, 10), one found a positive association only with risk of ER–/PR– breast cancer (11), and two found that the incidence of ER+ and ER– breast cancer was associated with alcohol use to a similar degree (12, 13). The fact that alcohol use is but a moderate risk factor for breast cancer may account for these inconsistencies, although additional investigation of these relationships is warranted.

There is also growing evidence that the hormonal responsiveness of tumors varies by histological type. For example, ILC, the second most common histological type of breast cancer, is more likely to be both ER+ and PR+ compared with the most common histological type of breast cancer, IDC (14). Five recent studies also report that use of combined estrogen and progestin HRT is associated with a 2.0–3.9-fold increased risk of ILC but has little relative impact on risk of IDC (15–19). However, only one small study has evaluated the relationship between alcohol use and risk of breast cancer of different histologies (10). It found that use of ≥ 15 g/day of alcohol was associated with a 1.76-fold (95% CI, 0.83–3.71) increased risk of ILC but with only a 1.32-fold (95% CI, 1.01–1.72) increased risk of IDC.

Using data from a population-based case-control breast

³ The abbreviations used are: ER, estrogen receptor; PR, progesterone receptor; ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; HRT, hormone replacement therapy; CI, confidence interval; OR, odds ratio; CSS, Cancer Surveillance System; BMI, body mass index.

cancer study, we assessed the relationship between alcohol use and risk of invasive breast cancer by histology and hormone receptor status to further our understanding of the hormonal basis for the well-established association between alcohol use and breast cancer risk.

Materials and Methods

We conducted a population-based case-control study of women 65–79 years of age living in the three-county Seattle-Puget Sound metropolitan area. The study protocol was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and written informed consent was obtained from all of the study subjects before each interview.

Cases. Briefly, women aged 65–79 years with no prior history of *in situ* or invasive breast cancer when diagnosed with invasive breast cancer between April 1, 1997, and May 31, 1999, were eligible as cases. The CSS, the population-based tumor registry that serves the Seattle-Puget Sound region of Washington State and participates in the Surveillance, Epidemiology, and End Results program of the National Cancer Institute, was used to identify cases. To be eligible for the study, all of the cases had to live in King, Pierce, or Snohomish counties and have a Health Care Financing Administration record, because these records were used to identify controls. Of the 1210 eligible cases identified and selected, 975 (80.6%) were interviewed.

Information on tumor histology and hormone receptor status was ascertained from CSS, which abstracts data on tumor characteristics from medical records and pathology reports from institutions serving the area. CSS classifies histology using the International Classification of Diseases for Oncology codes, and we divided cases into two groups with codes 8520 and 8522 used to define the 196 ILC cases, and code 8500 used to define the 656 IDC cases. The 123 women with other breast cancer histologies were excluded from our analyses by histological type. CSS classifies ER and PR status as positive, negative, borderline, not assessed, or unknown based on information abstracted from medical records. The 75 (7.7%) cases with an ER and/or PR status that was borderline, not assessed, or unknown were excluded from our analyses by hormone receptor status. Additionally, we did not include ER–/PR+ cases in our analysis of joint ER/PR status, because there were only 6 ER–/PR+ cases.

Controls. Health Care Financing Administration records were used to identify women from the general population who were frequency matched on age to cases to serve as controls. Of the 1365 eligible women selected as controls, 1007 (73.8%) were interviewed.

Data Collection. Subjects were interviewed in-person and were asked about a variety of factors including: menstrual, contraceptive, and reproductive histories; use of HRT; body size; smoking history; demographic information; and medical history, including family history of cancer. Our questioning was limited to exposures that occurred before the reference date of each subject. The reference date used for cases was their breast cancer diagnosis date. Controls were assigned reference years so that the distribution of control reference years was similar to that of the case diagnosis years to control somewhat for recall bias. Reference months were then randomly assigned to controls.

Information on alcohol use was collected for the 20 years before diagnosis/reference date. Alcohol drinkers were defined as women who reported that they had consumed at least 12 beverages containing alcohol during the past 20 years and had

consumed at least 1 alcohol-containing beverage a month for ≥ 6 months during the past 20 years. The age of a woman 20 years before her reference date defined the beginning of her first drinking interval. Women were asked separate questions about how many units of 12-ounce bottles or cans of beer, 4-ounce glasses of wine, and 1.5-ounce shots of liquor they consumed per day, week, month, or year. After reporting their use of these three types of alcoholic beverages, they were asked at what age their drinking habits changed. If this age was before reference age it marked the beginning of a second drinking interval, and the previous questions were repeated until women reported no additional changes in their drinking habits. A life events calendar was used to enhance recall of times when patterns of alcohol use changed. Using each of the episodes of alcohol use reported, cumulative intake of alcohol over the 20 years before reference date was calculated, and then this total was divided into a daily alcohol intake over this period. We also assessed associations between recency of alcohol use and breast cancer risk based on the alcohol consumption of subjects during the year before their reference date. Former users of alcohol were defined as ever-users who reported no use of alcohol during the year before reference date, and current users were defined as ever-users who did report consuming alcohol during this year.

Analysis. We compared all of the breast cancer cases to controls using unconditional logistic regression (20). We compared ILC and IDC cases to controls and cases with different hormone receptor profiles to controls using polytomous logistic regression (21). Both statistical approaches were used to calculate ORs as an estimate of the relative risk and to compute 95% CIs. To convert intake of beer, wine, and liquor into average daily grams of alcohol consumed over the past 20 years, the frequency with which each beverage was consumed was multiplied by the ethanol content of each beverage as estimated by the United States Department of Agriculture (13.2 g/12 oz bottle or can of beer, 10.8 g/4 oz glass of wine, and 15.1 g/1.5 oz drink or shot of liquor; Ref. 22). Alcohol intake in grams per day was then categorized into six groups, none, <1.5, 1.5–4.9, 5.0–14.9, 15.0–29.9, and ≥ 30.0 , consistent with categorizations of alcohol use published previously (4, 23).

The following variables were evaluated as potential confounders and effect modifiers: first-degree family history of breast cancer (yes/no); education (less than high school, high school graduate, some college, or college graduate or higher); type of menopause [natural, induced, or simple hysterectomy (hysterectomy without a bilateral oophorectomy)]; and age at menopause (five-year categories, note: women with an unknown age at menopause, including all women who had a simple hysterectomy, were excluded when this variable was assessed as a confounder and effect modifier). Also evaluated were age at menarche (≤ 11 , 12–13, or ≥ 14); parity; age at first full-term (> 26 weeks) pregnancy (14–19, 20–24, 25–29, or ≥ 30 years); BMI 5 years before reference date (quartiles of control population); smoking status (never, former, or current); smoking duration in pack years (0, <10, 10–29, or ≥ 30); and HRT use (never/ < 6 months, 6 months to < 5 years, or ≥ 5 years, note: users of HRT for < 6 months were included in the reference category because these very short-term users of HRT did not differ from never-users of HRT with respect to breast cancer risk; data not shown). Only adjustment for family history of breast cancer and BMI changed the risk estimates of the ORs of interest by $> 10\%$. Therefore, all of the analyses were adjusted for age (continuous), first-degree family history of

Table 1 Distribution of demographic and known risk factors for breast cancer among 1007 controls, 975 breast cancer cases, 656 ductal cases, 196 lobular cases, 796 ER+ cases, and 107 ER- cases

Characteristic	Controls (n = 1007)		All cases (n = 975)		Ductal (n = 656)		Lobular (n = 196)		ER+ (n = 796)		ER- (n = 107)	
	N	%	N	%	N	%	N	%	N	%	N	%
Reference age												
65-69	330	32.8	300	30.8	204	31.1	58	29.6	240	30.2	41	38.3
70-74	381	37.8	381	39.1	252	38.4	85	43.4	319	40.1	33	30.8
75-79	296	29.4	294	30.2	200	30.5	53	27.0	237	29.8	33	30.8
Race												
White	925	91.9	929	95.3	623	95	188	95.9	759	95.4	104	97.2
Black	37	3.7	16	1.6	11	1.7	3	1.5	13	1.6	2	1.9
Asian/Pacific Islander	29	2.9	19	1.9	18	2.7	1	0.5	17	2.1	0	0.0
Other/unknown	16	1.6	11	1.1	4	0.6	4	2.0	7	0.9	1	0.9
Income												
<\$15,000	191	21.7	177	21.3	124	22.1	30	17.9	145	21.3	22	24.4
\$15-25,000	214	24.3	198	23.9	139	24.8	39	23.2	166	24.4	20	22.2
\$25-50,000	296	33.6	296	35.7	204	36.4	60	35.7	239	35.1	36	40.0
>\$50,000	180	20.4	159	19.2	94	16.8	39	23.2	131	19.2	12	13.3
Missing	126		145		95		28		115		17	
Parity												
Nulliparous	94	9.3	88	9.0	57	8.7	20	10.2	71	8.9	11	10.3
Parous	913	90.7	887	91.0	599	91.3	176	89.8	725	91.1	96	89.7
Type of menopause												
Natural	607	61.6	583	61.4	400	62.8	113	59.8	483	62.6	58	55.2
Induced	148	15.0	129	13.6	78	12.2	29	15.3	96	12.4	18	17.1
Simple hysterectomy	231	21.6	237	25.0	159	25.0	47	24.9	193	25.0	29	27.6
Missing	21		26		19		7		24		2	
First-degree family history of breast cancer												
No	771	82.9	703	77.2	469	77.1	146	78.5	564	76.0	83	82.2
Yes	159	17.1	208	22.8	139	22.9	40	21.5	178	24.0	18	17.8
Missing	77		64		48		10		54		6	
BMI, quartiles												
≤23.32	261	27.1	209	22.3	139	22.0	51	27.1	166	21.6	25	24.3
23.33-26.20	241	25.0	240	25.6	164	25.9	43	22.9	196	25.5	28	27.2
26.21-30.11	230	23.9	245	26.1	162	25.6	52	27.7	200	26.0	26	25.2
≥30.12	231	24.0	245	26.1	168	26.5	42	22.3	206	26.8	24	23.3
Missing	44		36		23		8		28		4	
Smoking status												
Never	523	51.9	450	46.2	301	45.9	89	45.4	373	46.9	48	44.9
Former	369	36.6	396	40.6	269	41.0	79	40.3	321	40.3	46	43.0
Current	115	11.4	129	13.2	86	13.1	28	14.3	102	12.8	13	12.1
Smoking duration, pack years												
0	523	52.0	450	46.3	301	46.1	89	45.4	373	47.0	48	45.3
<10	107	10.6	89	9.2	56	8.6	21	10.7	70	8.8	10	9.4
10-29	143	14.2	166	17.1	119	18.2	30	15.3	136	17.1	18	17.0
≥30	233	23.2	267	27.5	177	27.1	56	28.6	215	27.1	30	29.3
Missing	1		3		3		0		2		1	
Ever-use of HRT												
Never/<6 months	413	41.1	352	36.3	243	37.3	59	30.1	285	35.9	40	38.1
6 months-5 years	156	15.5	119	12.3	87	13.4	22	11.2	97	12.2	16	15.2
≥5 years	435	43.3	499	51.4	321	49.3	115	58.7	411	51.8	49	46.7
Missing	3		5		5		0		3		2	

breast cancer (yes/no), and BMI (quartiles). Of note, we did not observe a synergistic effect between alcohol and HRT use on breast cancer risk as has been reported previously (11). All of the *P*s for linear trend were estimated using grams/day of alcohol use as a continuous term in each model and excluding women who were never-users of alcohol. Never-users of alcohol were excluded from the trend tests because of concern that unmeasurable bias could result in a uniform elevation of ORs for the exposed groups relative to the never user group. This is because there may be factors that are related to breast cancer risk that result in a woman choosing to be a regular user of alcohol or not.

Results

Lobular, ductal, and ER+ cases had a similar age distribution as controls, but ER- cases tended to be younger than controls (Table 1). Controls were more likely than cases to be non-white. ILC cases had higher incomes compared with both controls and the other case groups. Women in each case group were more likely to have had a hysterectomy without a bilateral oophorectomy and to have a first-degree family history of breast cancer compared with controls. Both IDC and ER+ cases were somewhat more likely than controls to have a higher BMI. All of the cases were more likely to be former or current

Table 2 Relationship between alcohol use and risk of overall and specific histologic types of breast cancer

Factor	Controls n = 998		Overall n = 967		OR ^a	95% CI	Ductal n = 651		OR	95% CI	Lobular n = 195		OR	95% CI
	N	%	N	%			N	%			N	%		
	Alcohol use (g/day)													
Never ^b	514	51.5	459	47.5	1.0	(ref)	319	49.0	1.0	(ref)	77	39.5	1.0	(ref)
Ever	484	48.5	508	52.5	1.3	(1.0–1.5) ^c	332	51.0	1.2	(0.9–1.4)	118	60.5	1.8	(1.3–2.5) ^c
<1.5	59	5.9	60	6.2	1.2	(0.8–1.8)	41	6.3	1.2	(0.8–1.9)	14	7.2	1.5	(0.8–3.0)
1.5–4.9	121	12.2	128	13.2	1.6	(0.9–1.7)	85	13.0	1.2	(0.9–1.7)	31	15.9	1.9	(1.2–3.1) ^c
5.0–14.9	167	16.6	161	16.6	1.1	(0.9–1.5)	100	15.4	1.0	(0.7–1.3)	36	18.5	1.6	(1.0–2.5) ^c
15.0–29.9	91	9.2	96	9.9	1.3	(0.9–1.7)	68	10.4	1.2	(0.9–1.8)	20	10.3	1.7	(1.0–2.9)
≥30.0	46	4.6	63	6.5	1.7	(1.1–2.6) ^c	38	5.8	1.5	(0.9–2.3)	17	8.7	2.6	(1.3–4.9) ^c
<i>P</i> for trend ^d					0.673				0.931				0.614	
Former ^b	77	7.7	70	7.2	1.1	(0.8–1.7)	43	6.6	1.0	(0.6–1.5)	16	8.2	1.5	(0.8–2.8)
Current ^b	407	40.8	438	45.3	1.3	(1.0–1.6) ^c	289	44.4	1.2	(1.0–1.5)	102	52.3	1.8	(1.3–2.6) ^c
<1.5	67	6.7	79	8.2	1.3	(0.9–1.9)	52	8.0	1.2	(0.8–1.9)	20	10.3	2.1	(1.2–3.7) ^c
1.5–4.9	87	8.7	90	9.3	1.2	(0.9–1.7)	56	8.6	1.1	(0.7–1.6)	23	11.8	2.1	(1.2–3.5) ^c
5.0–14.9	138	13.8	133	13.8	1.1	(0.9–1.5)	91	14.0	1.1	(0.8–1.5)	27	13.8	1.4	(0.9–2.4)
15.0–29.9	78	7.8	78	8.1	1.2	(0.8–1.7)	56	8.6	1.2	(0.8–1.8)	14	7.2	1.4	(0.8–2.7)
≥30.0	37	3.7	58	6.0	1.8	(1.2–2.9) ^c	34	5.2	1.5	(0.9–2.6)	18	9.2	3.3	(1.7–6.4) ^c
<i>p</i> for trend ^d					0.419				0.638				0.453	

^a All odds ratios (ORs) are adjusted for age (continuous), family history of breast cancer (yes/no), and body mass index (quartiles).

^b Women who drank <12 beverages containing alcohol during the past 20 years, or who did not consume at least one beverage containing alcohol a month for 6 months during the past 20 years, were classified as never-users of alcohol. Former users were defined as ever-users of alcohol who reported no alcohol consumption during the year prior to their reference date. Current users were defined as users of alcohol who reported using alcohol during the year prior to their reference date.

^c *P* < 0.05.

^d *P* for trend were evaluated by treating alcohol use (g/day) as a continuous variable and excluding subjects who were never-users of alcohol.

smokers and to have ever used HRT for ≥5 years, with the ILC case group having the highest proportion of HRT users.

Ever-use of alcohol was associated with a 1.3-fold (95% CI, 1.0–1.5) increased risk of breast cancer. Although women who consumed ≥30.0 g/day of alcohol had the highest risk of breast cancer (OR, 1.7; 95% CI, 1.1–2.6), no clear linear trend in risk among drinkers was observed (*P* for trend = 0.673; Table 2). When examined by histology, ever-use of alcohol was associated with a relatively greater increase in risk of ILC, than IDC (OR, 1.8; 95% CI, 1.3–2.5 and OR, 1.2; 95% CI, 0.9–1.4, respectively). Women who used ≥30.0 g/day of alcohol had the highest risk of ILC (OR, 2.6; 95% CI, 1.3–4.9), but again no linear trend was observed (*P* for trend = 0.614). Although within the limits of chance, a modest elevation in risk of IDC was seen among users of ≥30.0 g/day of alcohol (OR, 1.5; 95% CI, 0.9–2.3). Risks varied little by type of alcohol use. Ever-use of beer, wine, and liquor were associated with 1.2 (95% CI, 1.0–1.5), 1.3 (95% CI, 1.0–1.5), and 1.2-fold (95% CI, 1.0–1.4) elevations in risk of breast cancer overall, respectively; 1.1 (95% CI, 0.9–1.4), 1.2 (95% CI, 1.0–1.5), and 1.1-fold (95% CI, 0.9–1.4) elevations in risk of IDC, respectively; and 1.7 (95% CI, 1.2–2.4), 1.6 (95% CI, 1.1–2.2), and 1.5-fold (95% CI, 1.1–2.1) elevations in risk of ILC, respectively. Risks of breast cancer associated with alcohol use were primarily limited to current users. Current alcohol users had 1.3, 1.2, and 1.8-fold increased risks of breast cancer overall, IDC, and ILC, respectively, but former users had 1.1, 1.0, and 1.5-fold changes in risks of breast cancer overall, IDC, and ILC, respectively. Similar to what was observed among ever-users, current users of ≥30.0 g/day of alcohol had the highest risks of breast cancer.

Ever-use of alcohol was associated with elevations in risk of ER+ and PR+ tumors (OR, 1.3; 95% CI, 1.0–1.6 and OR, 1.3; 95% CI, 1.1–1.7, respectively), but not with risks of ER– and PR– tumors (OR, 1.1; 95% CI, 0.7–1.7 and OR, 1.1; 95% CI, 0.8–1.4, respectively; Table 3). The greatest elevations in risk of ER+ and PR+ tumors were seen among women who used ≥30.0 g/day of alcohol (OR, 1.7; 95% CI, 1.1–2.7 and

OR, 1.8; 95% CI: 1.1–2.8, respectively), although no clear linear trends were observed. Similarly, ever-use of alcohol was associated with an elevation in risk of ER+/PR+ tumors (OR, 1.3; 95% CI, 1.1–1.7), but not with elevations in risk of ER+/PR– or ER–/PR– tumors (OR, 1.1; 95% CI, 0.7–1.5 and OR, 1.1; 95% CI, 0.7–1.7, respectively). Risks of ER+, PR+, and ER+/PR+ breast cancers were higher among current users of alcohol than former users, and current users of ≥30.0 g/day of alcohol had the greatest risks.

Discussion

Certain limitations of our study should be considered when interpreting these results. We did not conduct independent pathology reviews or test all of the tumors for hormone receptor status in a centralized manner. Instead we relied on the assessments made by the numerous pathologists and laboratories serving the Seattle-Puget Sound area. Misclassification of tumor histology and hormone receptor status may have resulted. We were also limited by a relatively small number of ILC cases, providing us with limited power to assess the effects of different types of alcohol or of recency of alcohol use on risk of this histological type, and precluding our ability to consider the effect of alcohol on histology and ER/PR status in combination. Finally, we were unable to adjust for certain unmeasured factors, such as energy intake, that could confound the relationships we observed.

Additionally, we interviewed only 80.6% of all of the eligible cases and 73.8% of all of the eligible controls. Our results could be biased if the women we were unable to interview differed from those who did participate with regard to their use of alcohol. We also relied on participant recall of their alcohol use over the past 20 years. However, it has been documented that the recall bias associated with data on alcohol use collected retrospectively from both cases and controls has minimal effects on alcohol risk estimates when compared with prospectively collected data (24).

Table 3 Relationship between alcohol use and risk of breast cancer by ER and PR status

Factor	Controls n = 998		ER+ n = 789		OR ^a	95% CI	ER- n = 106		OR	95% CI	PR+ n = 648		OR	95% CI	PR- n = 244		OR	95% CI	
	N	%	N	%			N	%			N	%			N	%			
Alcohol use (g/day)																			
Never	514	51.5	370	47.0	1.0	(ref)	53	50.0	1.0	(ref)	300	46.3	1.0	(ref)	122	49.8	1.0	(ref)	
Ever	484	48.5	419	53.1	1.3	(1.0–1.6) ^b	53	50.0	1.1	(0.7–1.7)	348	53.7	1.3	(1.1–1.7) ^b	122	50.0	1.1	(0.8–1.4)	
<1.5	59	5.9	48	6.1	1.2	(0.8–1.8)	6	5.7	1.1	(0.4–2.7)	41	6.3	1.2	(0.8–1.9)	13	5.3	1.0	(0.5–1.9)	
1.5–4.9	121	12.2	109	13.8	1.6	(1.0–1.8)	12	11.3	1.1	(0.5–2.1)	92	14.2	1.4	(1.0–2.0) ^b	29	11.9	1.0	(0.6–1.6)	
5.0–14.9	167	16.6	133	16.9	1.2	(0.9–1.6)	18	17.0	1.0	(0.6–1.9)	107	16.5	1.2	(0.9–1.6)	43	17.6	1.1	(0.7–1.6)	
15.0–29.9	91	9.2	76	9.6	1.2	(0.9–1.8)	12	11.3	1.4	(0.7–2.7)	65	10.0	1.3	(0.9–1.9)	22	9.0	1.1	(0.6–1.8)	
≥30.0	46	4.6	53	6.7	1.7	(1.1–2.7) ^b	5	4.7	1.2	(0.5–3.2)	43	6.6	1.8	(1.1–2.8) ^b	15	6.1	1.4	(0.7–2.7)	
P for trend					0.705					0.544					0.998				
Former	77	7.7	57	7.2	1.1	(0.8–1.7)	8	7.5	1.1	(0.5–2.5)	47	7.3	1.2	(0.8–1.8)	18	7.4	1.0	(0.6–1.8)	
Current	407	40.8	362	45.9	1.3	(1.1–1.6) ^b	45	42.5	1.1	(0.7–1.8)	301	46.5	1.4	(1.1–1.7) ^b	104	42.6	1.1	(0.8–1.5)	
<1.5	67	6.7	61	7.7	1.3	(0.9–1.8)	10	9.4	1.5	(0.7–3.2)	50	7.7	1.3	(0.9–1.9)	21	8.6	1.3	(0.8–2.2)	
1.5–4.9	87	8.7	76	9.6	1.3	(0.9–1.8)	8	7.5	1.0	(0.4–2.1)	67	10.3	1.4	(1.0–2.1) ^b	17	7.0	0.8	(0.5–1.4)	
5.0–14.9	138	13.8	114	14.4	1.2	(0.9–1.7)	10	9.4	0.8	(0.4–1.6)	94	14.5	1.3	(0.9–1.8)	29	11.9	0.9	(0.5–1.4)	
15.0–29.9	78	7.8	61	7.7	1.2	(0.8–1.7)	12	11.3	1.5	(0.7–3.0)	50	7.7	1.2	(0.8–1.8)	22	9.0	1.2	(0.7–2.1)	
≥30.0	37	3.7	50	6.3	1.9	(1.2–3.1) ^b	5	4.7	1.5	(0.5–4.0)	40	6.2	2.0	(1.2–3.2) ^b	15	6.1	1.7	(0.9–3.3)	
P for trend					0.386					0.902					0.508				
Alcohol use (g/day)																			
Never	514	51.5	298	46.4	1.0	(ref)	71	49.3	1.0	(ref)	51	51.0	1.0	(ref)					
Ever	484	48.5	344	53.6	1.3	(1.1–1.7) ^b	73	50.7	1.1	(0.7–1.5)	49	49.0	1.1	(0.7–1.7)					
<1.5	59	5.9	41	6.4	1.2	(0.8–1.9)	7	4.9	0.9	(0.4–2.1)	6	6.0	1.1	(0.5–2.7)					
1.5–4.9	121	12.2	90	14.0	1.4	(1.0–2.0) ^b	19	13.2	1.0	(0.6–1.8)	10	10.0	0.9	(0.4–1.9)					
5.0–14.9	167	16.6	106	16.5	1.2	(0.9–1.6)	26	18.1	1.1	(0.7–1.9)	17	17.0	1.0	(0.5–1.8)					
15.0–29.9	91	9.2	64	10.0	1.3	(0.9–1.9)	11	7.6	0.9	(0.4–7.8)	11	11.0	1.3	(0.6–2.6)					
≥30.0	46	4.6	43	6.7	1.8	(1.1–2.8) ^b	10	6.9	1.5	(0.7–3.3)	5	5.0	1.2	(0.5–3.3)					
P for trend					0.945					0.330					0.656				
Former	77	7.7	46	7.2	1.2	(0.8–1.8)	11	7.6	1.1	(0.5–2.2)	7	7.0	0.9	(0.4–2.3)					
Current	407	40.8	298	46.4	1.4	(1.1–1.7) ^b	62	43.1	1.1	(0.7–1.6)	42	42.0	1.1	(0.7–1.7)					
<1.5	67	6.7	50	7.8	1.3	(0.9–1.9)	11	7.6	1.1	(0.5–2.3)	10	10.0	1.6	(0.7–3.3)					
1.5–4.9	87	8.7	64	10.0	1.4	(1.0–2.0) ^b	12	8.3	1.0	(0.5–1.9)	5	5.0	0.6	(0.2–1.6)					
5.0–14.9	138	13.8	94	14.6	1.3	(0.9–1.8)	19	13.2	0.9	(0.5–1.7)	10	10.0	0.8	(0.4–1.6)					
15.0–29.9	78	7.8	50	7.8	1.2	(0.8–1.8)	10	6.9	1.0	(0.5–2.1)	12	12.0	1.5	(0.7–3.1)					
≥30.0	37	3.7	40	6.2	2.0	(1.2–3.3) ^b	10	6.9	1.8	(0.8–4.0)	5	5.0	1.5	(0.6–4.1)					
P for trend					0.439					0.548					0.367				

^a All odds ratios (ORs) are adjusted for age (continuous), family history of breast cancer (yes/no), and body mass index (quartiles).

^b $P < 0.05$

Alcohol consumption has been shown to be a moderate but consistent risk factor for breast cancer in both observational studies and meta-analyses (1–4), and in the present study we confirm this association. The influence alcohol has on increasing hormone levels, particularly estrone sulfate and dehydroepiandrosterone, is believed to be one of the mechanisms underlying this association (2). Consistent with this mechanism, we found that alcohol consumption, particularly current use and heavy alcohol consumption (≥ 30.0 g/day), is primarily associated with breast cancers that are particularly hormone sensitive, both ILC and ER+/PR+ tumors.

Whereas our results certainly need to be confirmed by others, data from the one study that has evaluated the relationship between alcohol use and risk of ILC and IDC were suggestive of a similar difference by histology, although this study included a limited number of ILC cases (10). This finding is particularly interesting in light of recent studies demonstrating that use of combined estrogen and progestin HRT is more strongly associated with risk of ILC than it is with risk of IDC (15–19). Our data suggest that alcohol use may be another hormonally related risk factor for breast cancer that exerts a stronger effect on risk of ILC than it does on risk of IDC.

We also found ever-use of alcohol, and particularly current use and heavy use, to be associated with an elevation in risk of

hormone receptor-positive tumors, but not with risk of hormone receptor-negative tumors. The other studies evaluating this association have been inconclusive (9–13). However, one of the strengths of our study is that data on ER/PR status were missing for only 7.7% of cases, whereas 16%–60% of the cases in these other studies had missing data on ER and/or PR status, and four of these five studies had data missing on $>25\%$ of cases. Additionally, these inconsistencies may be because the magnitude of the increase in breast cancer risk associated with alcohol use is modest. Despite the inconsistencies within the epidemiological literature, data from our study and others suggest that heavy alcohol use is associated with an increased risk of hormone receptor-positive tumors. There is laboratory evidence in support of this hypothesis, because ethanol has been shown to stimulate the proliferation of ER+, but not ER-, breast cancer cells in culture (5, 6).

Taken as a whole, our results add to the evidence that alcohol is likely involved in pathways contributing to hormonal carcinogenesis of the breast. We found that ever and current alcohol use increases risk of ILC and hormone receptor-positive tumors. Breast cancer is a heterogeneous disease, and additional research focusing on different types of breast cancer has the potential to be a valuable approach

toward gaining a clearer understanding of mechanisms involved in breast carcinogenesis.

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The Relationship between Alcohol Use and Risk of Breast Cancer by Histology and Hormone Receptor Status among Women 65–79 Years of Age

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