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Original Contribution

Alcohol Consumption and Breast Cancer Risk in the Women's Health Study

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The authors assessed the association between moderate alcohol consumption and breast cancer risk in the Women's Health Study (United States, 1992–2004). During an average of 10 years of follow-up, 1,484 cases of total breast cancer (1,190 invasive and 294 in situ) were documented among 38,454 women who, at baseline, were free of cancer and cardiovascular disease and provided detailed dietary information, including alcohol consumption, for the preceding 12 months. Higher alcohol consumption was associated with a modest increase in breast cancer risk; the multivariable relative risks for ≥30 g/day of alcohol vs. none were 1.32 (95% confidence interval (CI): 0.96, 1.82) for total breast cancer and 1.43 (95% CI: 1.02, 2.02) for invasive breast cancer. An increased risk was limited to estrogen receptor (ER)– and progesterone receptor (PR)–positive tumors; the multivariable relative risks for an increment of 10 g/day of alcohol were 1.11 (95% CI: 1.03, 1.20) for ER+PR+ tumors (804 cases), 1.00 (95% CI: 0.81, 1.24) for ER+PR– tumors (125 cases), and 0.99 (95% CI: 0.82, 1.20) for ER–PR– tumors (167 cases). The association also seemed strongest among those taking postmenopausal hormones currently, but the test for interaction was not significant. The findings from this prospective study suggest that moderate alcohol consumption increases breast cancer risk.

alcohol drinking; breast neoplasms; prospective studies; receptors, estrogen; receptors, progesterone

Abbreviations: CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor.

A direct association between moderate alcohol consumption and the occurrence of breast cancer has been consistently observed in epidemiologic studies (1–5). The positive association has been noted for beer, wine, and liquor separately (2). Epidemiologic data also provide strong evidence for an influence of plasma estrogens on breast cancer risk (6, 7). In human experimental studies (8–11), alcohol consumption has been shown to affect plasma estrogens and it has thus been speculated that alcohol consumption might increase risk of breast cancer at least in part through its effect on estrogens (12). The effects of estrogen and progesterone on cell growth and differentiation are mediated through steroid hormone receptors (13, 14). Because of a lack of information on steroid hormone receptor status or limited statistical power, sparse data are available on the potential difference between alcohol consumption and risk of breast tumors of different hormone receptor status, and the findings have been inconsistent (3–5, 15–23). To better understand the mechanisms of the alcohol–breast cancer association, we examined the relation between alcohol consumption and

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breast cancer risk according to joint estrogen receptor (ER) and progesterone receptor (PR) status in the Women's Health Study.

MATERIALS AND METHODS

Study cohort

The Women's Health Study is a recently completed, randomized trial evaluating the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among 39,876 US female health professionals (registered nurses, 75 percent) aged 45 years or older (24–27). Upon enrollment in the study, all participants completed a baseline questionnaire about their medical history and lifestyle characteristics, including potential risk factors for breast cancer. As of the end of the trial, March 31, 2004, the average duration of follow-up was 10 years, and follow-up rates for morbidity and mortality were 97.2 percent and 99.4 percent, respectively (24–26).

Assessment of alcohol consumption

Information on the average frequency of consumption of alcoholic beverages including beer, wine, and liquor during the preceding 12 months was collected on the enrollment questionnaire and the food frequency questionnaire during the run-in phase. Total alcohol intake was considered the sum of the alcohol content in beer, wine, and liquor, assuming 12.8 g of ethanol for 360 ml (12 ounces) of regular beer, 11.3 g for 360 ml (12 ounces) of light beer, 11.0 g for 120 ml (4 ounces) of wine, and 14.0 g for 45 ml (1.5 ounces) of liquor. To reduce within-person variation, we used the average of alcohol intake from two reports in the present analysis. The Spearman correlation coefficient was 0.88 for alcohol intake calculated from two reports at baseline. A validation study among a subset of participants in another study, the Nurses' Health Study, indicated a high correlation ($r = 0.84$) between alcohol intake measured by the 1984 food frequency questionnaire (similar to that used for the Women's Health Study) and four 1-week dietary records in 1980 (28). In addition, alcohol consumption assessed by the 1984 food frequency questionnaire was correlated with plasma concentrations of high density lipoprotein cholesterol ($r = 0.40$), which is known to be sensitive to alcohol (28).

Food frequency questionnaire

Detailed information on dietary intake was provided by 39,345 (98.7 percent) of the randomized participants who completed and returned a self-administered, 131-item food frequency questionnaire mailed to them during the run-in phase of the trial. This dietary questionnaire, which has been used by the Nurses' Health Study and the Nurses' Health Study II, asked participants about the average frequency of consumption of specific foods and beverages during the preceding 12 months. For each food listed on the questionnaire, a commonly used unit or portion size was specified with nine responses, ranging from "never" to "6 or more times per day." Nutrient intake was computed by multiplying the frequency response by the nutrient content of the specified portion size. Values for nutrients were derived from US Department of Agriculture sources (29) and were supplemented with information from manufacturers. The validity and reliability of the food frequency questionnaires used in the Nurses' Health Study suggest that nutrient intakes calculated from the food frequency questionnaires reasonably reflect the long-term intakes of female health professionals (30–32). The current analysis was restricted to 38,454 women after excluding those who did not provide dietary information, had an implausible total energy intake (<600 kcal/day or $>3,500$ kcal/day), or reported cancers after randomization that had been diagnosed prior to randomization.

Ascertainment of breast cancer cases

Every 6 months during the first year, and then annually, women completed brief mailed questionnaires about the occurrence of newly diagnosed endpoints, including breast cancer. When a diagnosis of breast cancer was reported, we requested permission from the participant, or next of kin if deceased, to examine the relevant medical records, and we obtained medical records from the hospital or attending physicians. Deaths of participants were identified by reports from family members, postal authorities, and a search of the National Death Index.

An Endpoints Committee of physicians reviewed the medical records for final confirmation of a reported diagnosis of breast cancer. Additional details on breast cancer, including hormone receptor status, were also recorded from reports in medical records. The presence or absence of hormone receptor status was determined by laboratories affiliated with hospitals in which breast cancer cases were diagnosed. Medical records confirmed approximately 98 percent of self-reported breast cancer cases in the Women's Health Study (33). Through March 31, 2004, we ascertained 1,484 confirmed breast cancer cases (1,190 invasive and 294 in situ) and included their data in this analysis. Of the 1,190 invasive cancers, 804 (67.6 percent) were positive for both ER and PR (ER+PR+), 125 (10.5 percent) were positive for ER but negative for PR (ER+PR–), 23 (1.9 percent) were ER–PR+, 167 (14.0 percent) were ER–PR–, and 71 (6.0 percent) were unknown for ER or PR. Tumors classified as borderline positive for ER ($n = 5$) or PR ($n = 8$) were considered ER+ or PR+ in the analyses. Of the 1,190 invasive cancers, 1,101 were assayed for ER and 1,085 for PR, and nearly all assays were measured by using immunocytochemical or immunohistochemical methods (92.6 percent for ER and 92.4 percent for PR).

Statistical analysis

Person-years of observation for each participant were calculated from the date of randomization to the date of diagnosis of cancer, death, or March 31, 2004, whichever occurred first. Alcohol intake was modeled as both predetermined categories (none, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, or ≥ 30.0 g/day) and a continuous variable (a 10-g/day increment). These categories of alcohol were used in a previous

TABLE 1. Age-standardized baseline characteristics* according to alcohol consumption in the Women's Health Study, United States, 1992–2004

	Alcohol consumption (g/day)					
	None	0.1–4.9	5.0–9.9	10.0–14.9	15.0–29.9	≥30.0
No. of participants	14,249	14,745	4,321	2,420	1,908	811
Mean value						
Age (years)	54.9	54.2	54.4	55.0	55.3	56.0
Body mass index (kg/m^2)	27.0	26.0	24.8	24.3	24.4	24.7
Age at menopause (years)†	46.7	47.1	47.4	47.5	47.6	47.0
Total energy intake (kcal/day)	1,691	1,729	1,749	1,764	1,799	1,898
Physical activity (kcal/week)	865	1,009	1,094	1,087	1,057	879
Percent						
Age at menarche ≥13 years	46	47	49	51	48	52
Age at first birth ≥30 years‡	11	11	12	12	13	12
Parity ≥3	51	48	47	45	43	41
Postmenopausal	55	54	53	53	56	54
Current postmenopausal hormone use†	61	66	67	70	67	58
Current multivitamin supplement use†	29	29	29	28	29	29
Mother or sister with breast cancer	6	6	6	6	7	6
History of benign breast disease	32	35	34	37	36	32

* All factors except age were directly standardized.
† Among postmenopausal women only.
‡ Among parous women only.

meta-analysis of alcohol and breast cancer combining primary data from six large cohorts (2).

Hazard ratios (expressed as relative risks) were calculated by dividing the incidence rate in each of the higher categories by the incidence rate in the lowest category using Cox proportional hazards regression models (34). We first estimated hazard ratios and their 95 percent confidence intervals, with adjustments for age (per-year increment) and randomized treatment assignment (aspirin vs. placebo, vitamin E vs. placebo). In multivariable analysis, we simultaneously included well-established risk factors for breast cancer, which have the potential to confound the association between alcohol and breast cancer risk, in the multivariable model, including age at menarche (<12, 12, 13, 14, or ≥15 years), age at first pregnancy lasting ≥6 months (<25, 25–29, or ≥30 years), number of pregnancies lasting ≥6 months (0, 1 or 2, 3 or 4, or ≥5), menopausal status (premenopausal, postmenopausal, or uncertain menopausal), age at menopause (<45, 45–49, 50–54, or ≥55 years), postmenopausal hormone use (never, past <5 years, past ≥5 years, current <5 years, or current ≥5 years), body mass index (<23, ≥23 to <25, ≥25 to <27, ≥27 to <30, or ≥30 kg/m^2), family history of breast cancer in the mother or a sister (yes or no), history of benign breast disease (yes or no), physical activity (quartiles of total calories expended on recreational activities and stair climbing), multivitamin supplement use (never, past, or current), and total energy intake (quintiles). We adjusted for total energy to control for confounding and to reduce measurement errors due to general over- or underreporting of food items (32).

We examined alcohol consumption in relation to risk of total breast cancer. We also performed an analysis for invasive breast cancer according to combined ER and PR status (ER+PR+, ER+PR–, ER–PR–, and unknown) using polychotomous logistic regression; ER–PR+ breast cancer cases ($n = 23$) were excluded. We modeled each specific alcoholic beverage in relation to breast cancer separately, as well as included all of them simultaneously in the model. Additional analyses of alcohol consumption further stratified women by categories of menopausal status, body mass index, postmenopausal hormone use, family history of breast cancer, history of benign breast disease, and total folate intake to assess whether the associations were stronger in subgroups, especially among those with higher estrogen exposure or with lower folate intake. Several studies have found that higher folate intake reduces the excess risk of breast cancer due to alcohol consumption (35–37). Tests for multiplicative interaction between an increment of 10 g/day of alcohol and other risk factors in relation to breast cancer risk were performed by log-likelihood ratio tests comparing the models with or without interaction terms. Tests for trend were conducted by using the median values for categories of alcohol intake as a continuous variable. All p values were two sided.

RESULTS

Approximately 13.4 percent of women drank at least 10 g/day of alcohol, which is about 0.75–1 drink per day (table 1).

TABLE 2. Relative risks and 95% confidence intervals of breast cancer according to alcohol consumption in the Women's Health Study, United States, 1992–2004

Breast cancer	Alcohol consumption (g/day)						*p* for trend*	10-g/day increment in alcohol consumption
	None	0.1–4.9	5.0–9.9	10.0–14.9	15.0–29.9	≥30.0		
Invasive and in situ tumors								
No. of cases ($n = 1,484$)	516	549	181	109	88	41		
RR†,‡	1.00	1.05	1.18	1.25	1.26	1.40	0.001	1.09
95% CI†		0.93, 1.19	1.00, 1.40	1.01, 1.53	1.00, 1.58	1.02, 1.93		1.03, 1.15
RR§	1.00	1.02	1.13	1.14	1.16	1.32	0.02	1.07
95% CI		0.90, 1.15	0.95, 1.34	0.92, 1.40	0.92, 1.45	0.96, 1.82		1.01, 1.14
Invasive tumors								
No. of cases ($n = 1,190$)	421	438	133	89	73	36		
RR‡	1.00	1.03	1.06	1.25	1.28	1.50	0.001	1.10
95% CI		0.90, 1.18	0.87, 1.29	0.99, 1.57	1.00, 1.64	1.07, 2.11		1.04, 1.17
RR§	1.00	1.00	1.03	1.16	1.19	1.43	0.01	1.09
95% CI		0.88, 1.15	0.84, 1.25	0.92, 1.47	0.93, 1.53	1.02, 2.02		1.02, 1.16
ER†+PR†+ tumors								
No. of cases ($n = 804$)	286	295	84	66	50	23		
RR‡	1.00	1.03	0.99	1.37	1.30	1.39	0.01	1.11
95% CI		0.87, 1.21	0.78, 1.27	1.04, 1.79	0.96, 1.77	0.90, 2.14		1.03, 1.19
RR§	1.00	1.00	0.96	1.29	1.23	1.39	0.02	1.11
95% CI		0.84, 1.18	0.75, 1.24	0.98, 1.70	0.91, 1.68	0.90, 2.15		1.03, 1.20
ER+PR– tumors								
No. of cases ($n = 125$)	41	49	16	8	9	2		
RR‡	1.00	1.20	1.32	1.16	1.62	0.83	0.59	1.05
95% CI		0.79, 1.82	0.74, 2.36	0.54, 2.47	0.79, 3.35	0.20, 3.43		0.86, 1.29
RR§	1.00	1.13	1.21	1.01	1.39	0.69	0.97	1.00
95% CI		0.74, 1.72	0.67, 2.18	0.47, 2.17	0.67, 2.90	0.17, 2.88		0.81, 1.24
ER–PR– tumors								
No. of cases ($n = 167$)	56	69	18	10	10	4		
RR‡	1.00	1.18	1.06	1.06	1.35	1.28	0.56	1.02
95% CI		0.83, 1.69	0.62, 1.80	0.54, 2.08	0.69, 2.65	0.46, 3.54		0.85, 1.23
RR§	1.00	1.17	1.04	1.02	1.25	1.15	0.79	0.99
95% CI		0.82, 1.67	0.60, 1.78	0.52, 2.01	0.63, 2.47	0.41, 3.19		0.82, 1.20

* The test for trend was calculated by using median consumption of alcohol in each category as a continuous variable.

† RR, relative risk; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor.

‡ Models were adjusted for age and randomized treatment assignment.

§ Multivariable models were adjusted for age, randomized treatment assignment, age at menarche, age at first pregnancy lasting ≥6 months, number of pregnancies lasting ≥6 months, menopausal status, age at menopause, postmenopausal hormone use, body mass index, family history of breast cancer in the mother or a sister, history of benign breast disease, physical activity, multivitamin supplement use, and total energy intake.

Women whose alcohol consumption was higher were slightly older, weighed less, and consumed more calories. They were also more likely to have a late age at menarche and fewer births. Age at menopause, physical activity, age at first birth, menopausal status, current use of postmenopausal hormones, current use of multivitamin supplements, family history of breast cancer in the mother or a sister, and personal history of benign breast disease did not appear to differ according to alcohol consumption.

Higher alcohol consumption was associated with a modest increase in breast cancer risk; the multivariable relative risks for ≥30 g/day of alcohol versus none were 1.32 (95 percent confidence interval (CI): 0.96, 1.82) for total breast cancer and 1.43 (95 percent CI: 1.02, 2.02) for invasive breast cancer (table 2). The multivariable relative risks for an increment of 10 g/day of alcohol were 1.07 (95 percent CI: 1.01, 1.14) for total breast cancer and 1.09 (95 percent CI: 1.02, 1.16) for invasive breast cancer. To address the potential bias that breast cancer itself, before it was diagnosed, might have affected alcohol consumption, we excluded 253 total breast cancer cases diagnosed during the first 2 years of follow-up; the positive association did not change appreciably.

TABLE 3. Relative risks and 95% confidence intervals of breast cancer for a 10-g/day increment in alcohol consumption from different sources in the Women's Health Study, United States, 1992–2004

Source	RR*,†	95% CI*,†	RR‡	95% CI‡	RR§	95% CI§
Beer	1.15	1.03, 1.28	1.15	1.02, 1.29	1.14	1.02, 1.28
White wine	1.13	1.00, 1.27	1.07	0.95, 1.21	1.07	0.94, 1.21
Red wine	1.08	0.88, 1.34	1.02	0.81, 1.27	0.99	0.79, 1.24
Liquor	1.08	0.98, 1.19	1.07	0.96, 1.18	1.05	0.95, 1.17

* Models were adjusted for age and randomized treatment assignment.

† RR, relative risk; CI, confidence interval.

‡ Multivariable models were adjusted for age, randomized treatment assignment, age at menarche, age at first pregnancy lasting ≥6 months, number of pregnancies lasting ≥6 months, menopausal status, age at menopause, postmenopausal hormone use, body mass index, family history of breast cancer in the mother or a sister, history of benign breast disease, physical activity, multivitamin supplement use, and total energy intake.

§ Multivariable models were mutually adjusted for other sources of alcoholic beverages listed in the table.

The multivariable relative risks for an increment of 10 g/day of alcohol were 1.08 (95 percent CI: 1.02, 1.15) for total breast cancer and 1.10 (95 percent CI: 1.03, 1.18) for invasive breast cancer.

The risk of developing ER+PR+ breast cancers increased with increasing categories of alcohol intake (p for trend = 0.02), although the risk estimates were not statistically significant, except for the category of 10.0–14.9 g/day

TABLE 4. Relative risks and 95% confidence intervals of breast cancer for a 10-g/day increment in alcohol consumption in different subgroups of women in the Women's Health Study, United States, 1992–2004

	No. of cases	RR*,†	95% CI*,†	p value for interaction*	RR‡	95% CI‡	p for interaction‡
Menopausal status							
Premenopausal	362	1.12	0.99, 1.25		1.08	0.96, 1.22	
Postmenopausal	910	1.09	1.01, 1.16	0.67	1.07	0.99, 1.15	0.68
Body mass index							
<25 kg/m^2	822	1.09	1.01, 1.17		1.08	1.01, 1.17	
≥25 kg/m^2	643	1.06	0.96, 1.17	0.65	1.04	0.94, 1.15	0.60
Postmenopausal hormone use							
Never	251	1.00	0.86, 1.15		0.99	0.86, 1.15	
Past	112	0.93	0.74, 1.18		0.91	0.72, 1.16	
Current	545	1.15	1.06, 1.26	0.09	1.15	1.05, 1.26	0.07
Family history of breast cancer							
No	1,371	1.08	1.01, 1.14		1.05	0.99, 1.12	
Yes	113	1.22	1.06, 1.40	0.15	1.23	1.05, 1.44	0.16
History of benign breast disease							
No	847	1.11	1.03, 1.19		1.09	1.01, 1.17	
Yes	637	1.07	0.97, 1.18	0.53	1.05	0.95, 1.16	0.51
Total folate intake							
<300 μg/day	490	1.08	0.99, 1.18		1.06	0.97, 1.17	
300–599 μg/day	703	1.09	1.00, 1.19		1.07	0.98, 1.17	
≥600 μg/day	291	1.12	0.98, 1.27	0.96	1.11	0.97, 1.26	0.96

* Models were adjusted for age and randomized treatment assignment.

† RR, relative risk; CI, confidence interval.

‡ Multivariable models were adjusted for age, randomized treatment assignment, age at menarche, age at first pregnancy lasting ≥6 months, number of pregnancies lasting ≥6 months, menopausal status, age at menopause, postmenopausal hormone use, body mass index, family history of breast cancer in the mother or a sister, history of benign breast disease, physical activity, multivitamin supplement use, and total energy intake. Stratified variable was excluded from each multivariable model.

TABLE 5. Epidemiologic studies of alcohol consumption and risk of breast cancer according to joint ER* and PR* status

First author (reference no.)	Geographic location	No. of cases	Alcohol consumption category	ER+PR+		ER–PR–		ER+PR–		ER–PR+	
				RR*	95% CI*	RR	95% CI	RR	95% CI	RR	95% CI
			Prospective studies								
Potter (18)	Iowa	610	None	1.00		1.00		1.00			
			Ever (median: 4.0 g/day (provided by Gapstur et al. (39)))	1.17	0.95, 1.44	1.37	0.86, 2.18	1.23	0.81, 1.87		
Suzuki (5)	Sweden	1,188	None	1.00		1.00		1.00		1.00	
			<3.4 g/day	1.07	0.89, 1.30	1.11	0.72, 1.71	1.10	0.78, 1.55	1.27	0.63, 2.57
			3.4–9.9 g/day	1.09	0.88, 1.35	1.09	0.68, 1.75	1.30	0.91, 1.87	1.30	0.58, 2.89
			≥10 g/day	1.35	1.02, 1.80	0.80	0.38, 1.67	2.36	1.56, 3.56	0.62	0.13, 2.90
Zhang†	United States	1,119	None	1.00		1.00		1.00			
			<3.4 g/day	0.99	0.83, 1.18	1.13	0.78, 1.64	1.07	0.69, 1.66		
			3.4–9.9 g/day	0.98	0.79, 1.22	1.15	0.73, 1.82	1.31	0.79, 2.18		
			≥10 g/day	1.28	1.04, 1.58	1.13	0.69, 1.84	1.10	0.63, 1.92		
Pooled estimates‡		2,917	None	1.00		1.00		1.00			
			<3.4 g/day	1.03	0.90, 1.17	1.12	0.85, 1.49	1.09	0.83, 1.43		
			3.4–9.9 g/day	1.08	0.96, 1.22	1.20	0.92, 1.57	1.28	1.01, 1.63		
			≥10 g/day	1.30	1.10, 1.54	1.02	0.68, 1.53	1.65	0.78, 3.48		
			Case-control studies								
Yoo (19)	Nagoya, Japan	455	Never	1.00		1.00		1.00		1.00	
			Ever§	1.00	0.71, 1.41	0.68	0.44, 1.05	0.96	0.60, 1.52	0.80	0.32, 2.02
Enger (20)	Los Angeles, California	406 premenopausal	None	1.00		1.00		1.00			
			1–5 g/day	0.73	0.46, 1.15	0.68	0.40, 1.16	0.45	0.18, 1.10		
			6–13 g/day	1.07	0.69, 1.65	0.90	0.53, 1.51	0.16	0.04, 0.69		
			≥14 g/day	1.10	0.67, 1.80	1.04	0.60, 1.81	0.71	0.30, 1.68		
		736 postmenopausal	None	1.00		1.00		1.00			
			1–5 g/day	0.97	0.74, 1.27	0.81	0.52, 1.26	0.75	0.49, 1.14		
			6–13 g/day	1.18	0.80, 1.75	0.91	0.47, 1.75	1.36	0.80, 2.33		
			≥14 g/day	1.76	1.14, 2.71	1.37	0.68, 2.76	1.10	0.53, 2.26		
Huang (21)	North Carolina	785	None	1.0		1.0		1.0		1.0	
			Ever§	0.8	0.6, 1.1	0.9	0.6, 1.2	1.5	0.9, 2.8	1.5	0.8, 2.8
Britton (22)	United States	1,210	None	1.00		1.00		1.00		1.00	
			<7 drinks/week	1.11	0.88, 1.41	1.08	0.81, 1.43	0.86	0.55, 1.35	0.87	0.55, 1.39
			≥7 drinks/week	1.33	0.94, 1.87	1.38	0.93, 2.06	0.94	0.47, 1.86	1.64	0.90, 2.98
Li (3)	Washington	892¶	Never	1.0		1.0		1.0			
			Ever§	1.3	1.1, 1.7	1.1	0.7, 1.7	1.1	0.7, 1.5		
Cotterchio (4)	Ontario, Canada	735 premenopausal	None	1.00		1.00					
			≤1 drinks/week	1.08	0.72, 1.60	1.31	0.78, 2.19				
			1.5–3 drinks/week	0.84	0.55, 1.28	1.36	0.81, 2.28				
			≥3.5 drinks/week	1.38	0.91, 2.10	0.92	0.51, 1.68				
		1,774 postmenopausal	None	1.00		1.00					
			≤1 drinks/week	1.03	0.23, 1.30	1.06	0.75, 1.50				

		1.5–3 drinks/week	0.90	0.69, 1.15	0.90	0.62, 1.32						
		≥3.5 drinks/week	1.27	1.00, 1.64	1.13	0.79, 1.64						
Terry (23)	New York	None	1.00		1.00							
		351 with a body mass index of <25 kg/m^2										
		<15 g/day	1.53	1.09, 2.15	1.07	0.66, 1.71						
		≥15 g/day	1.80	1.14, 2.83	1.30	0.69, 2.47						
		437 with a body mass index of ≥25 kg/m^2										
		None	1.00		1.00							
		<15 g/day	0.84	0.64, 1.12	0.91	0.57, 1.45						
		≥15 g/day	0.59	0.37, 0.95	1.56	0.88, 2.76						
Pooled estimates‡		7,781										
		None	1.00		1.00		1.00			1.00		
		<14 g/day	1.05	0.95, 1.17	0.98	0.88, 1.09	0.92	0.69, 1.22	1.02		0.71, 1.47	
		≥14 g/day	1.23	0.85, 1.80	1.32	1.04, 1.69	0.93	0.60, 1.43				

* ER, estrogen receptor; PR, progesterone receptor; RR, relative risk; CI, confidence interval.

† Data are presented in the text of this paper.

‡ The pooled estimates were obtained by using DerSimonian and Laird's random-effects model (51). On the basis of available information on the range or average amount of alcohol consumed in each category reported in previous studies, alcohol intake was categorized into four and three groups for cohort and case-control studies, respectively, in our meta-analysis. We first converted the different units for alcohol consumed to grams per day according to the conversion factors provided in studies that reported alcohol data as drinks (a drink defined as 14 g of alcohol). When nondrinkers were considered the reference group, each RR reported from each individual study was assigned to our standardized category. If the average alcohol intake for more than one category in a single study was in one category in our meta-analysis, we pooled these RRs in this category first and then pooled results across all studies.

§ Ever use was included in the category of <14 g/day of alcohol.

¶ Estimated from the number of breast cancer cases with PR assays.

of alcohol. However, alcohol consumption was not significantly associated with risk of ER+PR– (p for trend = 0.97) or ER–PR– breast tumors (p for trend = 0.79) (table 2). The multivariable relative risks for an increment of 10 g/day of alcohol were 1.11 (95 percent CI: 1.03, 1.20) for ER+PR+ tumors, 1.00 (95 percent CI: 0.81, 1.24) for ER+PR– tumors, and 0.99 (95 percent CI: 0.82, 1.20) for ER–PR– tumors. When alcohol was classified into four categories (0, >0 to <3.4, 3.4 to 9.9, ≥10 g/day) used in the Swedish Mammography Cohort (5), the multivariable relative risks comparing the higher three categories of alcohol with none were 0.99 (95 percent CI: 0.83, 1.18), 0.98 (95 percent CI: 0.79, 1.22), and 1.28 (95 percent CI: 1.04, 1.58) for ER+ PR+ tumors; 1.07 (95 percent CI: 0.69, 1.66), 1.31 (95 percent CI: 0.79, 2.18), and 1.10 (95 percent CI: 0.63, 1.92) for ER+PR– tumors; and 1.13 (95 percent CI: 0.78, 1.64), 1.15 (95 percent CI: 0.73, 1.82), and 1.13 (95 percent CI: 0.69, 1.84) for ER–PR– tumors.

Positive associations between alcohol consumption and breast cancer risk existed for alcohol derived from different beverages (beer, white wine, and liquor), although the associations for white wine and liquor were not statistically significant (table 3). These associations did not noticeably change after mutually controlling for other sources of alcoholic beverages. Red wine consumption was not associated with breast cancer risk. The positive associations between alcohol and breast cancer risk did not differ appreciably according to categories of other risk factors, except that there appeared to be a stronger risk among women who were current users of postmenopausal hormones, although the test for interaction was not significant (p for interaction = 0.07) (table 4). When we examined alcohol intake and postmenopausal hormone use in combination, the multivariable relative risk of total breast cancer was 1.84 (95 percent CI: 1.37, 2.46) for women who consumed ≥10 g/day of alcohol and used postmenopausal hormones currently compared with women who were both nondrinkers of alcohol and never users of postmenopausal hormones.

DISCUSSION

In this large cohort of women, we found a modest and significant positive association between alcohol consumption and breast cancer risk. This association was mostly limited to ER+PR+ tumors or those women using postmenopausal hormones. The prospective design and high follow-up rates minimize the possibility that our findings are due to methodological biases. Because controlling for established risk factors for breast cancer had minimal effect on the relative risks, our results are unlikely to be explained by confounding. Our results are also unlikely to be explained by the potential bias that breast cancer itself, before it was diagnosed, might have affected alcohol consumption, because the relative risks after excluding breast cancer cases diagnosed within the first 2 years of follow-up were similar to those for the entire cohort.

In this study, daily consumption of 10 g/day of alcohol (about 0.75–1 drink) was significantly associated with a 9 percent increase in risk of invasive breast cancer, and

the risk increased with increasing categories of alcohol; consumption of ≥30 g/day of alcohol was significantly associated with a 43 percent increase in risk. These magnitudes of association are consistent with the findings from a pooled analysis using primary data from six prospective cohorts, in which an increment of 10 g/day of alcohol was significantly associated with a 9 percent increase in risk of invasive breast cancer, and alcohol intakes of ≥30 to <60 g/day vs. none were significantly associated with a 41 percent increase in risk (2). Similarly, in a meta-analysis of 38 case-control and cohort studies, daily consumption of one alcoholic drink was statistically associated with an 11 percent increase in the risk of breast cancer, and the risk increased with increasing number of drinks of alcohol per day (1). Consistent with the previous investigations (2), the positive association was noted for beer, wine, and liquor separately in the present study, suggesting alcohol per se rather than some congener is responsible for the increase in risk. In this study, alcohol from white, rather than red, wine accounted for the positive association; although this finding could be related to the more frequent consumption of white wine than red wine in this population, it warrants further investigation.

To our knowledge, the Iowa Women's Health Study and the Swedish Mammography Cohort study are the only two other large prospective studies that have examined the association of alcohol intake with joint ER and PR status, and the results were mixed. In the Swedish Mammography Cohort, alcohol intake was associated with an elevated risk of both ER+PR+ and ER+PR– breast tumors, but not with ER–PR+ and ER–PR– breast tumors (5). In contrast, alcohol intake was most strongly associated with ER–PR– tumors in the Iowa Women's Health Study (18). Our findings that alcohol was associated with ER+PR+ tumors, but not with ER–PR– and ER+PR– tumors, are in general consistent with the results from the Swedish Mammography Cohort. The small number of cases in the present analysis, however, precluded us from calculating precise estimates of the association between alcohol and ER+PR– tumors. We also did not have enough cases to evaluate the association between alcohol and ER–PR+ tumors. Overall pooled estimates from these three prospective studies showed a significant positive association for ER+PR+ tumors, but not for ER–PR– and ER+PR– tumors (table 5). Although our data on the presence or absence of hormone receptors were determined from laboratories affiliated with hospitals in which breast cancer cases were diagnosed and not from a single reference laboratory, the measurement of hormone receptors has been standardized, and the distribution of hormone receptors in the Women's Health Study is comparable to those reported in previous studies for postmenopausal women (38, 39).

Several case-control studies have also examined the relation of alcohol consumption with breast cancer risk by joint ER and PR status; two reported that alcohol was more clearly associated with ER+PR+ breast cancer than with ER–PR– breast cancer (4, 23); two reported an increased risk for ER+PR+ tumors, but not for ER+PR– and ER–PR– tumors (3, 20); one reported an increased risk for ER+PR+, ER–PR–, and ER–PR+ tumors, except for ER+PR– tumors (22); but two other studies reported no association irrespective of joint ER and PR status, in which alcohol consumption was categorized into only two levels (ever vs. never) (19, 21). Overall pooled estimates from these case-control studies were similar for ER+PR+ and ER–PR– tumors, but the relative risk was significant for ER–PR– tumors (table 5). Three other case-control studies observed positive associations of alcohol consumption with risk of either ER+ or ER– tumors (15, 16) or with ER+ tumors only (17).

Clinically, breast cancer is a heterogeneous group of tumors (40). The hormone receptor status of breast cancer has been used to predict a patient's response to hormonal manipulation and clinical course, select patients for adjuvant hormonal therapy, and define types of breast tumors (18, 38). The etiology of hormone receptor–defined breast cancers may also be heterogeneous (41). Reproductive factors that increase breast cancer risk tended to be associated with ER+ but not ER– tumors (41). However, it is less clear whether there is a different association of alcohol with breast cancer by hormone receptor status.

A potential mechanism for the alcohol–breast cancer association is through the estrogen pathway (42); therefore, alcohol may be predominantly associated with breast cancers expressing hormone receptors. In cell culture, addition of alcohol stimulated ER signaling (43, 44) and cell proliferation of ER+ human breast cancer cells but not of ER– cells (43). In an intervention study among premenopausal women, consumption of two alcoholic drinks daily for 3 months significantly increased plasma and urinary levels of total and bioavailable estrogens (45). In an intervention study among postmenopausal women not using hormone replacement therapy, consumption of 15 or 30 g/day of alcohol for 8 weeks was associated with a nonsignificant 5–10 percent increase in estrone sulfate and dehydroepiandrosterone sulfate levels (8). Consistent with these data, the present study found that alcohol consumption was positively associated with ER+PR+ breast cancers, but not with ER–PR– cancers, suggesting that alcohol may act in part through the estrogen pathway to affect breast cancer risk. We recognize that, in the Women's Health Study, the number of cases in higher alcohol intake categories in the analyses of ER+PR– and ER–PR– was still small and thus may have reduced statistical power to observe a significant association. Alcohol may also affect breast cancer risk by acting as a co-carcinogen, increasing permeability of cell membranes to carcinogens, being mutagenic through acetaldehyde, inhibiting detoxification of carcinogens, activating pro-carcinogens, inducing oxidative stress (46), and affecting folate metabolism (47).

Along with three other large cohorts—the Nurses' Health Study (48), the Iowa Women's Health Study (49), and the Swedish Mammography Cohort (5)—the present analysis in the Women's Health Study also showed a stronger association between alcohol consumption and breast cancer risk among those using postmenopausal hormones, although the interaction was not statistically significant. Studies of acute effects of alcohol on estrogen metabolism among postmenopausal women indicate that alcohol has a much more pronounced effect in women using estrogen replacement therapy than in those who do not (12). In three studies of postmenopausal women using transdermal estradiol or oral

estrogen, alcohol ingestion caused an acute, dramatic increase in circulating estradiol levels (9–11) and prolonged half-life of estradiol (10). However, alcohol does not appear to have a marked acute effect on circulating estradiol or estrone levels in normal-weight postmenopausal women who do not use estrogen replacement therapy (11). A recent study has also shown that mammographic density was strongest among women consuming high levels of alcohol and taking estrogens (50). These data suggest that alcohol can alter estrogen metabolism, and the use of both estrogen and alcohol may increase risk of breast cancer more than the use of either one alone (12).

In summary, the findings from this study concur with those from other studies in showing that moderate alcohol consumption is associated with increased risk of breast cancer. Furthermore, the present data suggest that the alcohol–breast cancer association may be at least partly mediated by the estrogen pathway. Given that breast cancer is considered more than one entity biologically, future epidemiologic research needs to consider hormone receptor status to better understand the mechanisms of the associations.

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