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Original Contribution

Alcohol and Risk of Breast Cancer by Histologic Type and Hormone Receptor Status in Postmenopausal Women

The NIH-AARP Diet and Health Study

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Little is known about the association between alcohol and breast cancer by different tumor characteristics. The study consisted of 184,418 postmenopausal women aged 50–71 years in the National Institutes of Health-AARP Diet and Health Study (1995–2003). Alcohol use, diet, and potential risk factors for cancer were assessed with a mailed questionnaire at baseline. The relative risks and 95% confidence intervals were estimated by using Cox proportional hazards regression. Breast cancer cases and estrogen receptor and progesterone receptor status were identified through linkage to state cancer registries. During an average of 7 years of follow-up, 5,461 breast cancer cases were identified. Alcohol was significantly positively associated with total breast cancer: Even a moderate amount of alcohol (>10 g/day) significantly increased breast cancer risk. In a comparison of >35 g versus 0 g/day, the multivariate relative risks were 1.35 (95% confidence interval (CI): 1.17, 1.56) for total breast cancer, 1.46 (95% CI: 1.22, 1.75) for ductal tumors, and 1.52 (95% CI: 0.95, 2.44) for lobular tumors. The multivariate relative risks for estrogen receptor-positive/progesterone receptor-positive, estrogen receptor-positive/progesterone receptor-negative, and estrogen receptor-negative/progesterone receptor-negative tumors were 1.46 (95% CI: 1.12, 1.91) for >35 g versus 0 g/day, 1.13 (95% CI: 0.73, 1.77) for >20 g versus 0 g/day, and 1.21 (95% CI: 0.79, 1.84) for >20 g versus 0 g/day, respectively. Moderate consumption of alcohol was associated with breast cancer, specifically hormone receptor-positive tumors.

alcohol drinking; breast neoplasms; carcinoma, ductal, breast; carcinoma, lobular; receptors, estrogen; receptors, progesterone

Abbreviations: CI, confidence interval; ER+, estrogen receptor positive; ER−, estrogen receptor negative; MHT, menopausal hormone therapy; NIH, National Institutes of Health; PR+, progesterone receptor positive; PR−, progesterone receptor negative.

Most epidemiologic studies have assessed breast cancer as a single disease entity, despite the fact that cancers with different tumor characteristics clearly show divergent incidence rates. The most common type of breast cancer expresses both estrogen and progesterone receptors (estrogen receptor positive (ER+) and progesterone receptor positive (PR+)), with estrogen receptor-negative (ER−) and progesterone receptor-negative (PR−) tumors being less common (1, 2). Compared with ER+ tumors, ER− tumors tended to be diagnosed before menopause and in relatively younger women (1, 2). Some studies suggest that breast cancer risk factors differ by hormone receptor types; in particular, reproductive risk factors tend to be associated with ER+ but not ER− tumors (3, 4). In terms of histology, ductal tumors are most common, although the incidence rate of lobular carcinoma is rapidly increasing (5). Some studies suggest that ER+ lobular tumors are especially sensitive to hormone-related risk factors (5–7).

Alcohol has been consistently associated with an increased risk of breast cancer. A recent report by the World

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Cancer Research Fund concluded, "The evidence that alcoholic drinks are a cause of premenopausal and postmenopausal breast cancer is convincing" (8). However, the etiology of alcohol in relation to breast cancer is unclear. Several plausible biologic mechanisms have been postulated: 1) The interaction between alcohol and estrogen metabolism affects cellular response and differentiation of breast tissue (9); 2) by-products of alcohol metabolism such as acetaldehyde and reaction oxygen species cause DNA damage and inhibit DNA repair (10); and 3) the influence of alcohol on 1-carbon metabolism, such as folate, leads to hypomethylation and resulting DNA damage (11). In evaluating these alternative pathways, investigators have examined effect modification by menopausal hormone therapy (MHT), body mass index, and folate intake but have found inconsistent results.

In addition, little is known regarding how alcohol relates to breast cancer by various tumor characteristics. In a meta-analysis of 16 case-control studies (12), the summarized odds ratio comparing the highest and the lowest categories of alcohol intake was 1.26 (95% confidence interval (CI): 1.15, 1.37) for ER+ tumors and 1.12 (95% CI: 1.01, 1.24) for ER− tumors. On the other hand, for the highest versus the lowest category, the summarized relative risk reported from 3 cohort studies was 1.33 (95% CI: 1.06, 1.67; $P_{\text{heterogeneity}} = 0.01$) for ER+ tumors and 1.21 (95% CI: 0.84, 1.74; $P_{\text{heterogeneity}} = 0.22$) for ER− tumors. These discordant results across 3 cohort studies may be due to a narrow range of alcohol intake, a relatively small number of breast cancer cases, different covariates controlled for in the models, and a limited ability to examine effect modification by other breast cancer risk factors. In terms of breast cancer by histology, case-control studies suggested a stronger association with lobular rather than with ductal tumors (5–7), but no cohort study has examined this association.

In this large prospective cohort study, we examined among postmenopausal women whether alcohol was associated with the risk of breast cancer defined by tumor characteristics. In addition, we examined whether the association of alcohol with breast cancer was modified by folate intake, body mass index, and MHT use.

MATERIALS AND METHODS

Study population

The National Institutes of Health (NIH)-AARP Diet and Health Study cohort was established when AARP members, aged 50–71 years and residing in 1 of 6 states (California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania) or 2 metropolitan areas (Atlanta, Georgia, or Detroit, Michigan), returned a self administered questionnaire in 1995–1996. Further details of the study have been described elsewhere (13). The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute.

Of the 617,119 men and women who returned the baseline questionnaire, we excluded individuals who did not answer substantial portions of the questionnaire ($n = 27{,}552$), indicated that they were not the intended respondent ($n = 29{,}202$), had more than 10 recording errors or reported consuming less than 10 foods ($n = 8{,}127$), withdrew from the study ($n = 829$), did not provide information on gender ($n = 6$), completed duplicate questionnaires ($n = 179$), died or moved out of the study area at baseline ($n = 586$), and were men ($n = 325{,}316$). We further excluded women who had cancer, other than nonmelanoma skin cancer, at baseline ($n = 23{,}818$); had died from cancer during follow-up but that did not appear in the cancer registry data ($n = 1{,}242$); were premenopausal ($n = 3{,}849$) or of uncertain menopausal status ($n = 10{,}023$); had end-stage renal disease ($n = 371$); and reported extreme total energy intake (>2 times the interquartile ranges of log-transformed total energy intake, $n = 1{,}601$). The analytical cohort subsequently consisted of 184,418 postmenopausal women.

Assessment of alcohol and other covariates

At baseline, we assessed dietary intake, including alcohol consumption, with a self-administered 124-item food frequency questionnaire that is an early version of the National Cancer Institute's Diet History Questionnaire designed to capture usual diet by inquiring about the frequency and portion size of foods consumed over the past year (14).

The food frequency questionnaire queried consumption of beer during the summer, beer during the rest of the year, liquor or mixed drinks, or wine or wine coolers during the entire year with 10 categories of frequency, ranging from "never" to "6 or more times per day," and 3 portion sizes (<1, 1–2, >2 drinks). The portion sizes and nutrient database were constructed by using databases from the 1994–1996 US Department of Agriculture's Continuing Survey of Food Intakes by Individuals (15). One drink of alcoholic beverage was defined as one 12-fluid-ounce beer, one 5-fluid-ounce glass of wine, or one 1.5-ounce shot of liquor equaling approximately 13 g of alcohol. The food frequency questionnaire used in the study was evaluated by using 2 nonconsecutive 24-hour dietary recalls in 1,953 NIH-AARP Diet and Health Study participants (16). The Spearman correlation coefficient for alcohol intake between the food frequency questionnaire and the reference method was 0.63 in women.

We also collected demographic, anthropometric, and lifestyle information including smoking, physical activity, reproductive history, and oral contraceptive and MHT use at baseline.

Ascertainment of breast cancer

We identified breast cancer cases through probabilistic linkage to the original 8 state cancer registries and 3 additional states subsequently added to capture participants who had moved to those states (Arizona, Nevada, and Texas). The cancer registries are certified by the North American Association of Central Cancer Registries as being ≥90% complete within 2 years of cancer occurrence. The case ascertainment method used in the study was estimated to identify approximately 90% of all cancer cases in our cohort (17). Vital status was ascertained through annual linkage of the cohort to the Social Security Administration Death

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Master File, follow-up searches of the National Death Index Plus for participants who matched to the Social Security Administration Death Master File cancer registry linkage, questionnaire responses, and responses to other mailings.

We defined breast cancer cases as primary incident breast tumors that had invasive behavior and were not a metastatic site from a prevalent cancer. Histology of breast cancer was available from all 11 state cancer registries, and the hormone receptor status of breast cancer was available from 7 state cancer registries (Arizona, California, Georgia, Louisiana, New Jersey, Nevada, and North Carolina). Sixty-one percent of breast cancers were identified from states that reported hormone receptor status. Using histology codes from the *International Classification of Diseases for Oncology,* Third Edition (ICD-O-3), we classified breast cancer into ductal tumors (code 8500), lobular tumors (code 8520), ductal-lobular tumors (code 8522), and other tumors (with codes 8500, 8520, and 8522 excepted).

Statistical analysis

We estimated the relative risk and 95% confidence interval using Cox proportional hazards regression (18). Person-years of follow-up were calculated from the scan date of the baseline questionnaire to the date of cancer diagnosis, death, emigration out of the study area, or end of follow-up (December 31, 2003), whichever occurred first. We confirmed that the proportional hazard assumption was met for the main exposure by including interaction terms with time and using the Wald chi-square procedure to test whether all coefficients equaled 0.

The relative risks were estimated according to categories of 0, >0–5, >5–10, >10–20, >20–35, and >35 g/day of alcohol intake. Tests for linear trend across those categories were conducted by using the mean alcohol intake in each category as a single continuous variable in the model.

In multivariate models, we adjusted for age; race/ethnicity; family history of breast cancer; number of breast biopsies in the past 3 years; combined age at birth of first child and number of children; duration of oral contraceptive use; age at menopause; duration of MHT use; body mass index; height; smoking history; physical activity; and intakes of total folate (from both diet and supplements), total fat, and total energy. We assigned missing values for covariates to their respective reference category after checking that individuals with such missing values did not show breast cancer risks that were statistically significantly different from individuals in the reference category. Those missing body mass index and height measurements were assigned the mean values in the study population (19). The proportion of missing values for each covariate in the multivariate model was less than 3%.

We tested whether the association between alcohol and breast cancer was modified by family history of breast cancer, history of breast biopsy, smoking, body mass index, MHT use, duration of MHT use, and total folate intake. The test for interaction was performed by using the likelihood ratio test with alcohol intake as a continuous variable.

SAS, version 9.1, statistical software (SAS Institute, Inc., Cary, North Carolina) was used for all analyses. All statistical tests were 2 sided; P values less than 0.05 were considered statistically significant.

RESULTS

During an average of 7 years of follow-up, we identified 5,461 breast cancer cases (3,531 ductal, 550 lobular, 424 ductal-lobular, and 956 other tumors). A total of 3,341 breast cancers were identified from state cancer registries that reported hormone receptor status, with 1,641 ER+/PR+, 336 ER+/PR−, 48 ER−/PR+, and 366 ER−/PR− tumors and 950 tumors with either unknown estrogen receptor or progesterone receptor status. The distribution of the various subtypes of breast cancer was consistent with those reported in other studies (1, 2). We do not present results for ER−/PR+ tumors because of the small number of cases.

Thirty percent of women did not consume alcohol, while 54% and 16% of women consumed ≤10 g and >10 g of alcohol per day, respectively. Compared with nondrinkers, women who consumed alcohol tended to be physically active, to smoke more, to be nulliparous, to use MHT, and to have lower intakes of total folate and total fat (Table 1). The characteristics of women in states for which hormone receptor status was available did not differ from those of women in states where hormone receptor status was not available (data not shown).

Alcohol intake was significantly positively associated with total breast cancer (Table 2). The significantly increased risk of total breast cancer was found in both moderate and heavy drinkers: Compared with nondrinkers, women who consumed 10–<20, 20–35, and >35 g/day of alcohol showed risk increases of 13%, 23%, and 35%, respectively ($P_{trend} < 0.001$). The association between alcohol intake and total breast cancer did not differ by ascertainment of hormone receptor status. The multivariate relative risk for >35 g versus 0 g/day of alcohol was 1.40 (95% CI: 1.16, 1.69) among women in states with available hormone receptor status information and 1.30 (95% CI: 1.03, 1.63) among women in those states without hormone receptor status data. This positive association of alcohol with breast cancer was observed for all different histologic types of breast cancer. For >35 g versus 0 g/day of alcohol, the multivariate relative risks were 1.46 (95% CI: 1.22, 1.75; $P_{trend} < 0.001$) and 1.52 (95% CI: 0.95, 2.44; $P_{trend} = 0.04$) for ductal and lobular tumors, respectively. The multivariate relative risks for an increment of 10 g/day of alcohol were 1.04 (95% CI: 1.02, 1.05) for total breast cancers, 1.04 (95% CI: 1.02, 1.06) for ductal tumors, 1.03 (95% CI: 0.98, 1.08) for lobular tumors, and 1.03 (95% CI: 0.97, 1.09) for ductal-lobular tumors. For an increment of 1 drink/day, the multivariate relative risks were 1.05 (95% CI: 1.03, 1.07) for total breast cancer, 1.05 (95% CI: 1.03, 1.08) for ductal tumors, 1.04 (95% CI: 0.98, 1.11) for lobular tumors, and 1.04 (95% CI: 0.96, 1.12) for ductal-lobular tumors. When we examined the associations after excluding breast cancer cases diagnosed within the first 2 years of follow-up, the results did not change.

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Table 1. Baseline Characteristics by Categories of Alcohol Intake Among Postmenopausal Women in the NIH-AARP Diet and Health Study, 1995–2003 ($n = 184,418$)

	Alcohol, g/day					
	0	>0–5	>5–10	>10–20	>20–35	>35
No. of participants	55,146	86,363	13,199	16,558	7,305	5,847
Alcohol, g/day[a]	0	1.4	7.2	14.3	26.2	71.2
Age, years	63	62	62	62	62	62
White, non-Hispanic, %	85	90	92	95	95	94
Height, m[a]	1.6	1.6	1.6	1.6	1.6	1.6
Body mass index, kg/m^2 [a]	27.9	27.0	25.6	24.9	25.0	25.5
Physical activity ≥3 times/week, %	38	40	47	49	46	39
Smoking, %						
Never	56	48	40	35	28	22
Past (≤20 cigarettes/day)	21	27	33	33	33	25
Past (>20 cigarettes/day)	11	11	12	15	17	19
Current (≤20 cigarettes/day)	8	10	11	12	15	20
Current (>20 cigarettes/day)	3	3	3	5	7	13
Age at birth of first child and parity, %						
Nulliparous	15	15	16	17	19	22
<30 years and ≤2 children	30	32	32	32	32	30
<30 years and ≥3 children	50	48	46	45	43	42
≥30 years	5	6	6	6	6	5
Age at menopause, %						
<50 years	64	59	58	57	58	61
50–<55 years	30	33	35	36	35	32
≥55 years	7	7	7	7	7	7
Family history of breast cancer (yes), %	12	12	12	13	12	13
Breast biopsies in previous 3 years (yes), %	24	24	24	24	23	23
Oral contraceptive use (ever), %	32	39	45	44	45	45
Menopausal hormone therapy use, %						
Never	52	45	42	41	42	48
<5 years	18	20	21	19	18	19
5–<10 years	11	14	15	15	15	12
≥10 years	19	21	23	24	24	21
Total folate, μg/day[a]	603	619	628	620	587	523
Total fat, % of energy[a]	31	31	30	29	29	25
Total energy, kcal/day[a]	1,577	1,531	1,565	1,568	1,653	2,027
Energy excluding energy from alcohol, kcal/day[a]	1,577	1,521	1,514	1,468	1,470	1,529

Abbreviation: NIH, National Institutes of Health.
[a] Mean values.

The positive association between alcohol and breast cancer risk was observed for all types of alcoholic beverages. In a comparison of ≥3 and 0 drinks/day, the multivariate relative risks were 1.36 (95% CI: 1.16, 1.59; $P_{trend} < 0.001$; median intake = 4.4 drinks/day) for total alcoholic beverages, 1.73 (95% CI: 1.22, 2.47; $P_{trend} < 0.001$; median intake = 7.2 drinks/day) for beer, 1.39 (95% CI: 0.86, 2.24; $P_{trend} = 0.004$; median intake = 5.6 drinks/day) for wine, and 1.24 (95% CI: 1.03, 1.49; $P_{trend} = 0.001$; median intake = 5.2 drinks/day) for liquor, with mutual adjustment for each alcoholic beverage type.

When we subdivided breast cancers according to their hormone receptor status, alcohol intake was significantly positively associated with ER+ and PR+ tumors, but not with ER− and PR− tumors. In a comparison of women who consumed >35 g/day of alcohol with nondrinkers, the

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Table 2. Relative Risks and 95% Confidence Intervals of Total Breast Cancer and Breast Cancer by Histologic Type for Categories of Alcohol Intake, NIH-AARP Diet and Health Study, 1995–2003

	Alcohol, g/day						P_{trend}
	0	>0–5	>5–10	>10–20	>20–35	>35	
Total breast cancer							
Cases, no.	1,493	2,531	395	550	265	227	
Person-years, no.	382,931	607,663	93,051	115,752	50,694	40,064	
RR, age adjusted (95% CI)	1.00	1.08 (1.02, 1.16)	1.11 (0.99, 1.24)	1.23 (1.11, 1.35)	1.35 (1.18, 1.54)	1.47 (1.28, 1.69)	<0.001
RR, multivariate (95% CI)[a]	1.00	1.04 (0.97, 1.10)	1.04 (0.93, 1.16)	1.13 (1.02, 1.25)	1.23 (1.08, 1.41)	1.35 (1.17, 1.56)	<0.001
Histologic type							
Ductal tumors							
Cases, no.	947	1,646	263	352	170	153	
Person-years, no.	380,888	604,371	92,537	115,040	50,310	39,763	
RR, age adjusted (95% CI)	1.00	1.11 (1.02, 1.20)	1.16 (1.01, 1.33)	1.24 (1.09, 1.40)	1.37 (1.16, 1.61)	1.56 (1.32, 1.86)	<0.001
RR, multivariate (95% CI)[a]	1.00	1.06 (0.98, 1.15)	1.10 (0.95, 1.26)	1.16 (1.02, 1.31)	1.27 (1.07, 1.50)	1.46 (1.22, 1.75)	<0.001
Lobular tumors							
Cases, no.	135	253	48	63	29	22	
Person-years, no.	377,943	599,247	91,767	113,987	49,804	39,316	
RR, age adjusted (95% CI)	1.00	1.22 (0.99, 1.50)	1.51 (1.09, 2.11)	1.57 (1.16, 2.11)	1.65 (1.11, 2.47)	1.61 (1.02, 2.52)	0.01
RR, multivariate (95% CI)[a]	1.00	1.13 (0.91, 1.40)	1.36 (0.97, 1.90)	1.38 (1.02, 1.88)	1.47 (0.97, 2.21)	1.52 (0.95, 2.44)	0.04
Ductal-lobular tumors							
Cases, no.	98	210	33	43	27	13	
Person-years, no.	377,783	599,167	91,720	113,921	49,800	39,284	
RR, age adjusted (95% CI)	1.00	1.36 (1.07, 1.73)	1.40 (0.94, 2.08)	1.46 (1.02, 2.09)	2.10 (1.37, 3.21)	1.29 (0.72, 2.29)	0.17
RR, multivariate (95% CI)[a]	1.00	1.27 (0.99, 1.62)	1.27 (0.85, 1.90)	1.28 (0.89, 1.85)	1.86 (1.20, 2.87)	1.21 (0.66, 2.20)	0.35
Other tumors							
Cases, no.	313	422	51	92	39	39	
Person-years, no.	378,511	598,840	91,782	114,082	49,846	39,366	
RR, age adjusted (95% CI)	1.00	0.87 (0.75, 1.01)	0.69 (0.51, 0.92)	0.98 (0.78, 1.24)	0.95 (0.68, 1.33)	1.22 (0.87, 1.70)	0.12
RR, multivariate (95% CI)[a]	1.00	0.84 (0.73, 0.98)	0.65 (0.48, 0.88)	0.90 (0.71, 1.15)	0.85 (0.61, 1.20)	1.01 (0.71, 1.43)	0.68

Abbreviations: CI, confidence interval; NIH, National Institutes of Health; RR, relative risk.

[a] Multivariate model adjusted for race, height (quintile), body mass index (<25, 25–<30, and ≥30), age at birth of first child and number of children (nulliparous, first birth <30 years and ≤2 children, first birth <30 years and ≥3 children, and first birth ≥30 years), family history of breast cancer (yes and no), age at menopause (<50, 50–54,and ≥55 years), physical activity (never, rarely, 1–3 times per month, 1–2 times per week, 3–4 times per week, and ≥5 times per week), smoking (never, past ≤20 cigarettes/day, past >20 cigarettes/day, current ≤20 cigarettes/day, and current >20 cigarettes/day), past oral contraceptive use (never or <1 year, 1–4 years, 5–9 years, and ≥10 years), menopausal hormone therapy use (never, <5, 5–10, and ≥10 years), number of breast biopsies (none, 1, 2, and 3), and intakes of total folate (continuous), total fat (quintiles), and total energy (continuous).

multivariate relative risks were 1.50 (95% CI: 1.19, 1.90; $P_{trend} < 0.01$; 2,074 cases) for ER+, 1.46 (95% CI: 1.12, 1.90; $P_{trend} = 0.003$; 1,700 cases) for PR+, 0.81 (95% CI: 0.42, 1.58; $P_{trend} = 0.90$; 418 cases) for ER−, and 1.17 (95% CI: 0.76, 1.81; $P_{trend} = 0.25$; 704 cases) for PR− tumors. When hormone receptor status was further defined by both estrogen receptor and progesterone receptor, a statistically significant positive association with alcohol was found for ER+/PR+ tumors but not for ER−/PR− tumors (Table 3). However, the association between alcohol intake and breast cancer did not differ statistically by hormone receptor status. The multivariate relative risks for an increment of 10 g/day of alcohol were 1.04 (95% CI: 1.01, 1.08) for ER+/PR+ tumors and 1.00 (95% CI: 0.93, 1.08) for

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Table 3. Relative Risks and 95% Confidence Intervals of Breast Cancer Risk by Hormone Receptor Status for Categories of Alcohol Intake, NIH-AARP Diet and Health Study, 1995–2003

	Alcohol, g/day						P_{trend}
	0	>0–5	>5–10	>10–20	>20–35	>35	
ER+/PR+							
Cases, no.	430	759	131	165	89	67	
Person-years, no.	225,108	347,717	55,951	71,842	31,531	22,820	
RR, age adjusted (95% CI)	1.00	1.16 (1.03, 1.31)	1.25 (1.03, 1.52)	1.21 (1.01, 1.45)	1.49 (1.19, 1.87)	1.55 (1.20, 2.01)	<0.001
RR, multivariate (95% CI)[a]	1.00	1.07 (0.95, 1.21)	1.13 (0.93, 1.38)	1.07 (0.89, 1.29)	1.34 (1.06, 1.69)	1.46 (1.12, 1.91)	0.003
	0	>0–5	>5–10	>10–20	>20		
ER+/PR−							
Cases, no.	85	151	27	45	28		
Person-years, no.	223,855	345,454	55,586	71,421	53,852		
RR, age adjusted (95% CI)	1.00	1.18 (0.91, 1.54)	1.32 (0.85, 2.03)	1.68 (1.17, 2.41)	1.39 (0.91, 2.13)		0.08
RR, multivariate (95% CI)[a]	1.00	1.08 (0.83, 1.42)	1.15 (0.74, 1.78)	1.39 (0.96, 2.02)	1.13 (0.73, 1.77)		0.51
ER−/PR−							
Cases, no.	102	162	29	42	31		
Person-years, no.	223,915	345,500	55,608	71,398	53,842		
RR, age adjusted (95% CI)	1.00	1.02 (0.80, 1.31)	1.14 (0.75, 1.72)	1.29 (0.90, 1.85)	1.26 (0.84, 1.88)		0.15
RR, multivariate (95% CI)[a]	1.00	1.01 (0.79, 1.30)	1.12 (0.74, 1.71)	1.28 (0.88, 1.85)	1.21 (0.79, 1.84)		0.25

Abbreviations: CI, confidence interval; ER+, estrogen receptor positive; ER−, estrogen receptor negative; NIH, National Institutes of Health; PR+, progesterone receptor positive; PR−, progesterone receptor negative; RR, relative risk.

[a] Multivariate model adjusted for race, height (quintile), body mass index (<25, 25–<30, and ≥30), age at birth of first child and number of children (nulliparous, first birth <30 years and ≤2 children, first birth <30 years and ≥3 children, and first birth ≥30 years), family history of breast cancer (yes and no), age at menopause (<50, 50–54,and ≥55 years), physical activity (never, rarely, 1–3 times per month, 1–2 times per week, 3–4 times per week, and ≥5 times per week), smoking (never, past ≤20 cigarettes/day, past >20 cigarettes/day, current ≤20 cigarettes/day, and current >20 cigarettes/day), past oral contraceptive use (never or <1 year, 1–4 years, 5–9 years, and ≥10 years), menopausal hormone therapy use (never, <5, 5–10, and ≥10 years), number of breast biopsies (none, 1, 2, and 3), and intakes of total folate (continuous), total fat (quintiles), and total energy (continuous).

ER−/PR− tumors. For an increment of 1 drink/day, the multivariate relative risks were 1.05 (95% CI: 1.01, 1.09) and 1.02 (95% CI: 0.93, 1.11) for ER+/PR+ and ER−/PR− tumors, respectively.

We examined alcohol intake in relation to breast cancer defined by both histologic types and estrogen receptor status. The multivariate relative risks for an increment of 10 g/day of alcohol were 1.05 (95% CI: 1.02, 1.08) for ER+ ductal tumors, 1.00 (95% CI: 0.91, 1.09) for ER+ lobular tumors, 0.98 (95% CI: 0.90, 1.07) for ER− ductal tumors, and 1.03 (95% CI: 0.82, 1.30) for ER− lobular tumors.

The association between alcohol and total breast cancer was not modified by total folate intake, body mass index, or MHT use (Table 4). Although the interactions with MHT use were not statistically significant, the association between alcohol and total breast cancer appeared stronger in long-term MHT users. When we examined the association by the combination of MHT status and duration of use, we found that the association was stronger in long-term current users. In a comparison of >35 g and 0 g/day of alcohol, the multivariate relative risks were 1.66 (95% CI: 1.25, 2.22) in current MHT users for ≥10 years, 1.18 (95% CI: 0.88, 1.58) in current MHT users for <10 years, and 1.11 (95% CI: 0.64, 1.94) in former MHT users for <10 years (data not shown for former MHT users for ≥10 years because of the small number of cases). We also found no effect modification of the alcohol and breast cancer relation by family history of breast cancer, history of breast biopsy, or smoking status (data not shown).

DISCUSSION

In this large prospective cohort of postmenopausal women, we found a significantly positive relation between alcohol and breast cancer, regardless of the type of alcoholic beverage consumed. The significantly increased risk of breast cancer was found even among women who consumed a moderate amount of alcohol (>10 g/day), and the risk increased linearly as alcohol consumption increased. Alcohol intake was positively related to ductal and lobular tumors and to hormone receptor-positive tumors.

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Table 4. Multivariate Relative Risks[a] and 95% Confidence Intervals of Breast Cancer for Categories of Alcohol Intake, Stratified by Total Folate Intake, Body Mass Index, and Menopausal Hormone Therapy, NIH-AARP Diet and Health Study, 1995–2003

	Alcohol (g/day)											
	0	>0–5		>5–10		>10–20		>20–35		>35		P_{trend}	$P_{interaction}$
		Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval		
Total folate intake, μg/day													
<300 (n = 563)[b]	1.00	0.92	0.76, 1.13	1.08	0.75, 1.54	0.94	0.67, 1.31	1.17	0.81, 1.69	1.08	0.77, 1.51	0.40	
300–<600 (n = 2,053)	1.00	1.04	0.94, 1.16	0.93	0.76, 1.12	1.15	0.98, 1.36	1.25	1.00, 1.57	1.28	0.98, 1.67	0.02	
600–<800 (n = 1,685)	1.00	1.04	0.92, 1.17	0.95	0.77, 1.17	1.17	0.98, 1.39	1.15	0.91, 1.45	1.54	1.20, 1.96	<0.001	
≥800 (n = 1,160)	1.00	1.07	0.93, 1.23	1.34	1.07, 1.67	1.09	0.88, 1.37	1.36	1.00, 1.87	1.41	0.91, 2.17	0.04	0.13
Body mass index, kg/m^2													
<25 (n = 2,269)	1.00	1.07	0.96, 1.19	1.07	0.90, 1.26	1.18	1.02, 1.36	1.23	1.02, 1.48	1.26	1.02, 1.57	0.01	
25–<30 (n = 1,885)	1.00	1.00	0.90, 1.12	1.13	0.94, 1.36	1.09	0.92, 1.30	1.28	1.02, 1.61	1.52	1.20, 1.93	<0.001	
≥30 (n = 1,307)	1.00	1.04	0.92, 1.17	0.78	0.58, 1.05	1.07	0.81, 1.40	1.21	0.84, 1.75	1.27	0.88, 1.83	0.19	0.27
MHT use													
Never (n = 2,187)	1.00	1.01	0.91, 1.11	0.95	0.78, 1.14	1.09	0.93, 1.29	1.09	0.87, 1.37	1.31	1.04, 1.64	0.01	
Former (n = 440)	1.00	0.86	0.69, 1.08	1.01	0.68, 1.51	0.98	0.69, 1.39	1.36	0.88, 2.11	1.22	0.73, 2.03	0.12	
Current (n = 2,834)	1.00	1.09	0.99, 1.20	1.09	0.94, 1.27	1.16	1.01, 1.33	1.30	1.09, 1.55	1.40	1.14, 1.71	<0.001	0.10
Duration of MHT use													
Never (n = 2,187)	1.00	1.01	0.91, 1.11	0.95	0.78, 1.14	1.09	0.93, 1.29	1.09	0.87, 1.37	1.31	1.04, 1.64	0.01	
<5 years (n = 1,036)	1.00	0.97	0.83, 1.13	1.03	0.80, 1.32	1.11	0.88, 1.39	1.22	0.90, 1.65	1.08	0.75, 1.53	0.27	
5–<10 years (n = 865)	1.00	1.03	0.86, 1.22	1.01	0.76, 1.33	1.10	0.86, 1.41	1.11	0.80, 1.55	1.27	0.87, 1.87	0.18	
≥10 years (n = 1,376)	1.00	1.15	1.01, 1.32	1.19	0.96, 1.48	1.18	0.97, 1.44	1.53	1.20, 1.95	1.70	1.28, 2.26	<0.001	0.26

Abbreviation: MHT, menopausal hormone therapy; NIH, National Institutes of Health.

[a] Multivariate model adjusted for race, height (quintile), body mass index (<25, 25–<30, and ≥30), age at birth of first child and number of children (nulliparous, first birth <30 years and ≤2 children, first birth <30 years and ≥3 children, and first birth ≥30 years), family history of breast cancer (yes and no), age at menopause (<50, 50–54,and ≥55 years), physical activity (never, rarely, 1–3 times per month, 1–2 times per week, 3–4 times per week, and ≥5 times per week), smoking (never, past ≤20 cigarettes/day, past >20 cigarettes/day, current ≤20 cigarettes/day, and current >20 cigarettes/day), past oral contraceptive use (never or <1 year, 1–4 years, 5–9 years, and ≥10 years), menopausal hormone therapy use (never, <5, 5–<10, and ≥10 years), number of breast biopsies (none, 1, 2, and 3), and intakes of total folate (continuous), total fat (quintiles), and total energy (continuous). The stratified variable was excluded from each multivariate model.

[b] Number of cases.

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The positive dose-response relation between alcohol consumption, regardless of alcoholic beverage type, and breast cancer risk found in our study is consistent with results from previously reported studies (20). The World Cancer Research Fund report (8), summarizing the results from 11 cohort studies, found that the relative risk of breast cancer was 1.08 (95% CI: 1.05, 1.10) for a 10-g/day increment of alcohol consumption in postmenopausal women. In our study, the relative risk of breast cancer for a 10-g/day increment of alcohol was 1.04 (95% CI: 1.02, 1.05).

Three cohort studies have examined the relation of alcohol to breast cancer by hormone receptor status (21–23). Consistent with our study, 2 cohort studies (21, 22) found that alcohol was positively associated with hormone receptor-positive tumors but not with -negative tumors. In the Swedish Mammography Cohort Study (22), the multivariate relative risks comparing >10 g and 0 g/day were 1.35 (95% CI: 1.02, 1.80; $P_{\text{trend}} = 0.049$) for ER+/PR+ tumors, 2.36 (95% CI: 1.56, 3.56; $P_{\text{trend}} < 0.001$) for ER+/PR− tumors, and 0.80 (95% CI: 0.38, 1.67; $P_{\text{trend}} = 0.45$) for ER−/PR− tumors. For every 10-g/day increment of alcohol consumption, the Woman's Health Study (23) found the multivariate relative risks were 1.11 (95% CI: 1.03, 1.20) for ER+/PR+ tumors, 0.99 (95% CI: 0.82, 1.20) for ER+/PR− tumors, and 1.00 (95% CI: 0.81, 1.24) for ER−/PR− tumors. In contrast to results from our study and those 2 cohort studies, the Iowa Woman's Health Study (21) found a significant positive association of alcohol with ER− tumors (for ≥4 g vs. 0 g/day, multivariate relative risk = 1.64, 95% CI: 1.14, 2.35) but not with ER+ tumors (for ≥4 g vs. 0 g/day, multivariate relative risk = 1.07, 95% CI: 0.90, 1.26). Experimental studies have shown that alcohol increases the levels of estrogen metabolites, and chronic exposure to alcohol and estrogen metabolites significantly increases the proliferation of ER+ tumor cells but not that of ER− tumor cells (9).

To our knowledge, our study is the first prospective cohort study to examine the relation between alcohol and different histologies of breast cancer. Case-control studies that examined different histologic types of breast cancer found that the association of alcohol was stronger with lobular tumors than with ductal tumors (5–7, 24). In a comparison of the highest alcohol consumption group with the nondrinking group in 3 case-control studies of women aged 20–79 years (6), 65–79 years (24), and postmenopausal women (5), the odds ratios of ductal tumors were 1.32 (95% CI: 1.01, 1.72), 1.5 (95% CI: 0.9, 2.3), and 1.2 (95% CI: 1.0, 1.6), respectively, whereas the odds ratios of lobular tumors were 1.76 (95% CI: 0.83, 3.71), 2.6 (95% CI: 1.3, 4.9), and 1.9 (95% CI: 1.2, 3.1), respectively. In contrast, we found a positive association of alcohol with both ductal and lobular tumors.

Several cohort studies observed that the association between alcohol and breast cancer was modified by folate intake: High folate intake attenuated the risk of breast cancer associated with high alcohol consumption (25–28). On the other hand, other cohort studies (29, 30) and ours found no significant interaction between alcohol consumption and folate intake. In our study, we observed that alcohol was significantly related to an increased risk of breast cancer even among women who had >800 μg/day of total folate intake. The cutpoint for the highest total folate intake group in most studies was between 400 and 600 μg/day.

The alcohol and breast cancer relation was also postulated to be modified by MHT use. Several experimental studies suggested that alcohol may be related to breast cancer through the estrogen pathway (9, 11, 31), and MHT use may jointly increase the risk of breast cancer (32, 33). Epidemiologic studies, however, have found inconsistent results (20–23, 34, 35). Among the cohort studies examining the interaction between alcohol and MHT use with breast cancer risk, about half found a statistically significant interaction by MHT use (22, 34, 36); the other cohort studies, including ours, did not find a statistically significant interaction, but the association between alcohol and breast cancer appeared stronger in MHT users than in nonusers among postmenopausal women (12, 23, 35).

The strengths of our study include a large number of breast cancer cases and a wide range of alcohol consumption, which allowed us to examine the effect of alcohol on breast cancer in not only moderate drinkers but also heavy drinkers. We also investigated breast cancer defined by histology and hormone receptors status, taking into consideration that breast cancer has heterogeneous tumor characteristics. Our study has several limitations. Because alcohol consumption was assessed only at baseline in our study, we were not able to examine the effect of lifetime alcohol consumption and consumption during earlier life times. In addition, we could not evaluate the effects of changes in drinking patterns on breast cancer.

In conclusion, we found that alcohol consumption was significantly positively associated with breast cancer in postmenopausal women. The risk of breast cancer was elevated even among moderate alcohol drinkers (>10 g/day) and rose linearly as alcohol consumption increased. A significant positive association of alcohol appeared to be stronger with hormone receptor-positive tumors and among long-term MHT users. Our finding confirms that alcohol is a modifiable risk factor for postmenopausal breast cancer.

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