Alcohol and Postmenopausal Breast Cancer Risk Defined by Estrogen and Progesterone Receptor Status: A Prospective Cohort Study

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Background: **Alcohol intake has been reported to be positively associated with an increased risk of postmenopausal breast cancer; however, the association with the estrogen receptor (ER) and progesterone receptor (PR) status of the breast tumors remains unclear.** ***Methods:*** **Self-reported data on alcohol consumption were collected in 1987 and 1997 from 51 847 postmenopausal women in the population-based Swedish Mammography Cohort. Through June 30, 2004, 1188 invasive breast cancer case patients with known ER and PR status were identified during an average 8.3-year follow-up. We used Cox proportional hazards models to estimate multivariable relative risks (RRs) of breast cancer, adjusting for age; family history of breast cancer; body mass index; height; parity; age at menarche, first birth, and menopause; education level; use of postmenopausal hormones; and diet. Heterogeneity among groups was evaluated using the Wald test. All statistical tests were two-sided.** ***Results:*** **Alcohol consumption was associated with an increased risk for the development of ER-positive (+) tumors, irrespective of PR status (highest intake [≥10 g of alcohol per day] versus nondrinkers, multivariable RR = 1.35, 95% confidence interval [CI] = 1.02 to 1.80; P_{trend}<.049 for ER+PR+ tumors; and RR = 2.36, 95% CI = 1.56 to 3.56; P_{trend}<.001 for ER+PR− tumors). The absolute rate of ER+ breast cancer (standardized to the age distribution of person-years experienced by all study participants using 5-year age categories) was 232 per 100 000 person-years among women in the highest category of alcohol intake, and 158 per 100 000 person-years among nondrinkers. No association was observed between alcohol intake and the risk of developing ER− tumors. Furthermore, we observed a statistically significant interaction between alcohol intake and the use of postmenopausal hormones on the risk for ER+PR+ tumors ($P_{interaction}$ = .039).** ***Conclusion:*** **The observed association between risk of developing postmenopausal ER+ breast cancer and alcohol drinking, especially among those women who use postmenopausal hormones, may be important, because the majority of breast tumors among postmenopausal women overexpress ER.** **[J Natl Cancer Inst 2005;97:1601–8]**

Many epidemiologic studies demonstrate a positive association of alcohol consumption with an increased risk for breast cancer *(1–4)*. Approximately 60% of all breast cancers are hormone dependent and overexpress estrogen receptor (ER) at the time of diagnosis *(5)*. Progesterone receptor (PR) expression in breast tumors is also known to be an important prognostic and therapeutic indicator *(6)*. A number of hormone-dependent mechanisms mediated by ERs and PRs for the positive association between alcohol intake and postmenopausal breast cancer risk have been hypothesized *(7–11)*, including the induction of endogenous estrogen levels by alcohol *(7–9)*. Previous studies reported that alcohol increases a women's cumulative exposure to endogenous steroid hormones by either increasing the production of estrogens *(7,8)* or by decreasing metabolic estradiol clearance *(9)*. Furthermore, in vitro studies have shown that ethanol increases the expression of ERs itself *(10,11)*, that ethanol stimulates the proliferation of ER-positive (+) human breast cancer cells but not of ER-negative (−) cells *(11)*, and that ethanol increases ER-α activity *(10)* through the inactivation of BRCA1 *(12)*. Alternative hypotheses include activation through hormone-independent pathways, such as the induction of carcinogenesis and DNA damage by the ethanol metabolite acetaldehyde *(13)*, reactive oxygen species, and lipid peroxidation *(14)*. Several epidemiologic studies have evaluated whether the association between alcohol intake and postmenopausal breast cancer risk differs with ER and PR tumor status *(15–22)*, but the results were inconsistent. The major underlying mechanism for the positive association has not yet been clearly elucidated *(23)*.

In the present study, we investigated whether the observed association of alcohol consumption with increased risk of postmenopausal breast cancer differs across ER+/− and PR+/− tumor subtypes. We also evaluated whether there are interactions between alcohol intake and other known risk factors, such as use of postmenopausal hormones, relative body weight, and family history of breast cancer, on the risk of ER- and PR-defined postmenopausal breast cancer.

Subjects and Methods

The Swedish Mammography Cohort

The Swedish Mammography Cohort has been described in detail elsewhere *(24)*. The cohort was established in 1987–1989

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in Västmanland County and in 1988–1990 in Uppsala County in central Sweden. All women born between 1917 and 1948 in Västmanland County and between 1914 and 1948 in Uppsala County were invited to a mammography screening and completed a questionnaire that elicited information on diet, parity, age at first birth, family history of breast cancer, weight, height, and education level (response rate 74%). The information on age at menarche, age at menopause, and ever use of oral contraceptives (OCs) and postmenopausal hormones (PMHs) was obtained from a supplemental questionnaire from women in Uppsala County at their mammography examination in 1988–1990.

In 1997, a follow-up questionnaire was sent to all living cohort members. The follow-up questionnaire included questions about diet, details on reproductive factors, and history of the use of OCs and PMHs (response rate 70%).

A total of 66 651 women completed the first food frequency questionnaire (FFQ-87). We excluded women with missing (n = 707) or incorrect (n = 415) national identification numbers; women who were born before 1914 or after 1948 (n = 165); women whose questionnaires were not properly dated (n = 608); women with missing date of moving out of the study area (n = 79), date of death (n = 16), height or weight (n = 1404), age at first birth (n = 61), and parity (n = 33) and women who reported unreasonable estimates of total energy intake (n = 793). The follow-up of the cohort began in January 1988 in Uppsala County and in November 1997 in Västmanland County, because routine evaluation of ER and PR status had been implemented in Västmanland County in 1997 (during the period 1987–November 1997, ER/PR status was unknown in 72.5% of case patients; see Supplemental Table 1 available at http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol97/issue21). Women with a previous cancer diagnosis (except nonmelanoma skin cancer) that was identified by linkage to the National Swedish Cancer Registry (before the start of follow-up) were also excluded (n = 4325). In addition, we excluded all women who were pre- and perimenopausal at the start of follow-up (n = 27 722), but subsequently we reentered women who become postmenopausal during follow-up if they were cancer-free and living in the study area (n = 23 888). In the present study, we defined age at menopause as the age at cessation of menstruation (natural or due to bilateral oophorectomy) based on the information from the self-administrated supplemental form in 1988–1990 and the second questionnaire in 1997 (n = 39 727). If the information enabling us to determine age at menopause was missing on the questionnaire, we defined it as either the age at bilateral oophorectomy (from the Swedish Inpatient Register) if they were younger than 55 years of age (n = 734) or as 55 years of age if they were age 55 years and older (n = 13 750), because approximately 90% of women in the cohort stopped menstruating before age 55 years. Furthermore, all women who were more than 70 years old at baseline (n = 2364) were excluded from the analyses to avoid a potential selection bias due to the dependency of case patients with unknown receptor status on nondrinking status in this age group (see Supplemental Table 2 available at http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol97/issue21). Consequently, the final study cohort comprised 51 847 postmenopausal women.

Exposure Measurement

Dietary assessment methods and validity of the food frequency questionnaire (FFQ-87) were described in our previous study *(24)*. The FFQ-87 included 67 food items and alcoholic beverages commonly consumed in Sweden. Women were asked to report an average frequency of consumption of each food and beverage during the past 6 months before entry in the cohort. There were eight prespecified frequency categories ranging from "never/seldom" to "four or more times per day." To assess alcohol intake, the FFQ-87 included questions on five types of alcohol, i.e., light beer (1.8% alcohol), medium beer (2.8% alcohol), strong beer (4.5% alcohol), wine, and hard liquor. The second questionnaire (FFQ-97) added fortified wine to the list. To estimate alcohol (ethanol) intake from the FFQ-87, we multiplied reported frequency of consumption by age-specific (<53, 53–65, and >65 years) drink sizes based on mean values obtained from 213 randomly chosen women from the study area whose food intake (including alcoholic beverages) for 5922 days was weighed and recorded (Wolk A: personal communication). The average daily alcohol intake that was estimated from the FFQ-97 was based on consumption frequencies of specific alcoholic beverages and self-reports of average sizes for those specific drinks (in centiliters; open questions). We observed a high correlation between alcohol intake estimated by the FFQ-87 and alcohol intake calculated from four 1-week diet records obtained 3–4 months apart (Spearman rank correlation coefficient, r = .9) among 129 women in a subgroup from the Swedish Mammography Cohort, validating the accuracy of the alcohol intake estimates.

The estimated nutrient intakes based on the FFQ-87 and FFQ-97 were calculated using food composition values from the Swedish National Food Administration database *(25)* that take age-specific portion sizes into account. Nutritional covariates (dietary fiber and total fat) were adjusted for total caloric intake using the residual method *(26)*.

Ascertainment of Breast Cancer Cases and Follow-up of the Cohort

Histologically confirmed incident cases of invasive breast cancer were identified by linkage of the cohort with the National and Regional Cancer Registries (from March 1, 1987, through June 30, 2004). The Swedish Cancer Registry system is estimated to be 98% complete *(27)*. Dates of death during follow-up were ascertained through linkage with the Swedish Death Register, and dates of migration from the study area were obtained through linkage with the Swedish Population Register. The information about ER and PR status (+/−) of breast cancers was obtained by reviewing pathology laboratory work logs stored at Uppsala University Hospital (from 1987 to 1994) and by linkage with the clinical database (the Quality Register) at the Regional Oncology Centre in Uppsala (from January 1, 1992, to June 30, 2004), which was based on the patients' original medical records.

ER and PR status was determined from fresh tumor samples directly after surgery. An Abbott immunoassay was used for evaluating ER and PR status *(28)*. Only two laboratories, the Departments of Pathology and Cytology at Västerås Central Hospital and at Uppsala University Hospital, were involved in this evaluation. Cases coded as borderline (≥0.1 fmol of receptor per μg of cytosol DNA) were considered as hormone receptor–positive for this analysis. In analyses we only included the first invasive breast cancer case patients with known receptor status. Patients with synchronous cancers with different receptor status (n = 4) or patients with missing ER and/or PR status were classified into the ER and/or PR unknown group and were excluded

from the analysis. The study was approved by the Regional Ethical Committee at Uppsala University Hospital and by the Regional Ethical Committee at Karolinska Institutet. Obtaining written information about the study and completion of the questionnaire were considered to imply informed consent.

Statistical Analysis

Subjects were entered into the study on the administration date of the FFQ-87 in Uppsala and that of the FFQ-97 in Västmanland if they were postmenopausal, the date of becoming postmenopausal during follow-up as recorded in 1997 for those who were premenopausal at baseline, the date of bilateral oophorectomy during follow-up, or the woman's 55th birthday for those with missing dates of menopause. Follow-up was censored at the date of death, at the date of migration out of the study area, at the date of diagnosis for any other type of cancer including other subtypes of breast tumors, or at the end of the follow-up (June 30, 2004), whichever occurred first.

To improve statistical efficiency and to reduce misclassification of exposure, we used time-dependent multivariable Cox proportional hazards regression models to estimate relative risks (RRs) and 95% confidence intervals (CIs) with age as the time scale *(29)*. The data conformed to proportional hazards assumptions as verified by a graphical method using Kaplan–Meier curves *(30)*. We subdivided the consumption of alcohol into four categories: nondrinker, <3.4 g, 3.4–9.9 g, and ≥10.0 g of ethanol per day. The cut points of 3.4 and 10.0 g of ethanol per day correspond to the median value among drinkers in the cohort and to approximately one alcoholic drink, respectively. The multivariable model simultaneously included first-degree family history of breast cancer, body mass index [BMI (weight in kilograms divided by height in meters squared), based on the World Health Organization classification *(31)*], height, age at menarche (≤12 years, 13 years = median in the cohort, or ≥14 years), parity (nulliparous, 1–2, or ≥3 children), age at first birth (nulliparous, <26, 26–30, or ≥31 years), educational level (<12 or ≥12 years of education), use of OCs, age at menopause (<51 or ≥51 years; 51 years = median age at menopause in the study cohort), type of menopause, use of PMHs, and history of benign breast disease. Total energy intake, energy-adjusted dietary fiber intake, and energy-adjusted total fat intake were also included in the model as nutritional covariates. Alcohol intake was included in the model as a time-dependent variable, which means that for the time period between the start of follow-up and the FFQ-97, estimates of alcohol intake were based on the FFQ-87 data and thereafter on the FFQ-97 data. Similarly, data for other covariates changing with time such as BMI, use of PMHs, family history of breast cancer, and nutritional variables were updated in the analysis when the information in the FFQ-97 was available.

We tested heterogeneity of the observed associations across ER and PR status by comparing three pairs of regression coefficients that corresponded to three alcohol intake levels derived from separate Cox regression models. Differences of the results between the different tumor subtypes were tested by the Wald statistic *(32)*. A combined Wald statistic for this purpose has asymptotic chi-squared distribution with 3 degrees of freedom. We also applied the Wald statistic for testing heterogeneity of risk estimates between the different subtypes of cancer for each alcohol intake level separately (paired comparisons with 1 degree of freedom). Trend tests were conducted by using the median value for each category of alcohol intake as a continuous variable in the model.

We conducted analyses stratified by use of PMHs, BMI, and family history of breast cancer to assess possible interactions with these factors. The cross-product terms of these factors (PMHs, ever or never; BMI, <25 or ≥25 kg/m^2; family history, yes or no) and four categories of alcohol intake (nondrinker, < median among drinkers, median to 9.9 g/day, or ≥10.0 g/day) were introduced into the Cox proportional hazard regression model. Participants with missing values for the factors of interest were excluded from these analyses. The *P* value for interaction was calculated by a likelihood ratio test comparing models with and without the interaction terms.

All analyses were performed using the SAS statistical package version 9.1 (SAS Institute, Cary, NC). All statistical tests were two-sided, and statistical significance was defined as $P<.05$.

Results

After an average 8.3-year follow-up, corresponding to 430 583 person-years, 1284 invasive breast cancer cases were diagnosed among 51 847 postmenopausal women in the cohort. Information about combined ER and PR status was available for 1188 case patients (92.5% of the total). Among them, the tumors of 716 case patients (60.3%) were ER+PR+, 279 (23.5%) were ER+PR−, 50 (4.2%) were ER−PR+, and 143 (12.0%) were ER−PR−. Either ER or PR status or both were missing for 96 tumors. The study cohort had relatively low alcohol consumption; 26.7% of subjects were nondrinkers, 36.9% consumed on average less than 3.4 g/day, 28.5% consumed 3.4–9.9 g/day, and 7.9% consumed 10 g/day or more. The women who did not consume alcohol were older than the drinkers. There were no differences in the percentage distribution of women with different characteristics across categories of alcohol intake (Table 1). The distribution of case patients with known and unknown receptor status was not different overall according to alcohol intake, PMH use, BMI, family history of breast cancer, and other major potential confounding factors (see Supplemental Table 3 available at http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol97/issue21).

We observed an association with alcohol intake and breast cancer risk that was dependent upon ER status. In the study cohort, alcohol intake was statistically significantly associated with elevated risk for both ER+PR+ and ER+PR− tumors; the multivariable adjusted risk ratios comparing the highest alcohol intake group (≥10 g/day) with nondrinkers were 1.35 (95% CI = 1.02 to 1.80, $P_{trend}<.049$) and 2.36 (95% CI = 1.56 to 3.56, $P_{trend}<.001$), respectively (Table 2). In contrast, no statistically significant associations were observed for ER−PR+ or for ER−PR− tumors (RR = 0.62, 95% CI = 0.13 to 2.90 and RR = 0.80, 95% CI = 0.38 to 1.67, respectively). No statistically significant difference was observed in the risk estimates between the ER+PR+ and ER+PR− tumors ($P_{heterogeneity} = .10$) or between ER−PR+ and ER−PR− tumors ($P_{heterogeneity} = .94$), which allowed us to perform analysis with all ER+ subtypes and all ER− subtypes combined to increase statistical power. The absolute rate of all ER+ breast cancers (standardized to the age distribution of person-years experienced by all study participants using 5-year age categories) among women in the highest category of alcohol intake was 232 per 100 000 person-years and 158 per 100 000 person-years among nondrinkers.

Table 1. Age-standardized prevalence of risk factors for breast cancer according to alcohol intake among 51 847 postmenopausal women in the Swedish Mammography Cohort*

Characteristic	Categories of alcohol consumption, g of ethanol per day				
	Nondrinkers n = 13 857 (26.7%)	<3.4 n = 19 151 (36.9%)†	3.4–9.9 n = 14 762 (28.5%)	≥10 n = 4077 (7.9%)	P‡
Age at entry, y mean (standard deviation)	63 (8.3)	60 (7.9)	57 (6.7)	57 (6.6)	
Body mass index, %					
Lean and normal (<25 kg/m^2)	45.7	52.1	60.7	59.4	
Overweight (25–29.9 kg/m^2)	37.7	36.2	31.8	32.2	
Obesity (≥30 kg/m^2)	16.6	11.7	7.5	8.4	.24
Family history of breast cancer, %§	8.3	8.5	8.8	9.0	1.00
≥12 years of education, %	6.3	8.5	10.7	14.6	.24
Ever taken postmenopausal hormones, %‖	36.5	43.7	48.9	49.8	.21
Ever taken oral contraceptives, %‖	42.9	45.4	50.0	50.2	.67
Age at menarche, %‖					
≤12 y	24.5	24.0	23.9	20.3	
13 y	34.8	37.3	39.5	39.6	
≥14 y	40.7	38.7	36.6	40.1	.98
Parity, %					
No. of children					
0	11.8	10.6	11.1	12.2	
1–2	49.9	55.8	57.4	55.8	
≥3	38.3	33.6	31.5	32.0	.95
Age at first birth					
Nulliparous	11.8	10.6	11.1	12.2	
≤25 y	59.6	58.3	54.3	53.7	
26–30 y	19.9	22.4	25.5	25.9	
≥31 y	8.7	8.7	9.1	8.2	1.00

*Age standardized to the distribution of person-time of follow-up among nondrinkers.
†3.4 g of ethanol per day is the median alcohol intake among drinkers.
‡P values (two-sided) were from chi-square tests.
§A family history of breast cancer in mother, sister, or daughter.
‖Among those with complete information.

For all ER+ tumors, the multivariable adjusted risk ratio among women in the high alcohol intake group (≥10.0 g/day) was higher than that among nondrinkers (RR = 1.65, 95% CI = 1.31 to 2.07, P_{trend}<.001). The corresponding risk ratio for all ER− tumors in the high alcohol intake group was 0.77 (95% CI = 0.40 to 1.49, P_{trend} = .36). Heterogeneity between observed risk estimates for all ER+ and all ER− tumors was observed in the high alcohol intake group (≥10 g/day) ($P_{heterogeneity}$ = .034).

Because age 55 years was used as a cut point of menopausal status for 26% of the women in the study cohort, we performed sensitivity analyses and changed the assumed postmenopausal age from 55 years to either 53 or 57 years. When we used 53 or 57 years of age as the cut point for postmenopausal status, the multivariable adjusted risk for all ER+ tumors was higher among women in the high alcohol intake group (≥10.0 g/day) than among nondrinkers (for 53 years, RR = 1.65, 95% CI = 1.31 to 2.07, P_{trend}<.001 and for 57 years, RR = 1.66, 95% CI = 1.31 to 2.10, P_{trend}<.001); in contrast, the corresponding relative risks for all ER− tumors were not statistically significant. Further sensitivity analyses based on the data excluding all women with missing values on age at menopause, use of OCs, and use of PMHs or including women with synchronous cancers with different receptor status in different ER- and PR-defined subgroups gave risk estimates similar to those presented in Table 2 (data not shown). An additional sensitivity analysis based on the data from the Uppsala County subcohort (including women older than 70 years of age at baseline), in which the routine evaluation of ER/PR status was introduced before the start of the cohort, gave similar results (Table 2).

We then evaluated whether risk factors influencing estrogen exposure in postmenopausal women (use of PMHs and BMI >25 kg/m^2) and family history of breast cancer modified the observed association between alcohol intake and breast cancer risk. Among nondrinkers, we found no evidence of an overall positive association between ever PMH use and invasive breast cancer risk. The multivariable adjusted risk ratios for nondrinkers who were ever PMH users compared with those nondrinkers who never used PMHs were not statistically significantly different for any of the three tumor subtypes (Table 3). The number of case patients with ER−PR+ tumors was too small (n = 33) to analyze separately; therefore, we performed the analysis with all ER− tumors. Among women who consumed alcohol, ever PMH use was positively associated with increased risk for the development of ER+PR+ tumors and of ER+PR− tumors but not for that of ER− tumors. The risk of developing ER+PR+ breast cancer among women with alcohol intake ≥10.0 g/day and ever PMH users was approximately 80% higher than that among nondrinkers who never used PMHs; the risk of developing ER+PR− tumors was greater than 3.5-fold higher (Table 3). The corresponding risk estimates for women in the high alcohol intake group (≥10.0 g/day) and ever PMH use were heterogeneous between ER+PR+ and all ER− tumors ($P_{heterogeneity}$ = .005) and between ER+PR− and all ER− tumors ($P_{heterogeneity}$<.001).

The interaction between alcohol intake and PMH use for ER+PR+ tumors was statistically significant ($P_{interaction}$ = .039). For the sensitivity analysis based on the Uppsala County subcohort, the corresponding interaction was also statistically significant ($P_{interaction}$ = .038). Overall, the results for the interaction of alcohol intake with high BMI and with history of breast cancer

Table 2. Multivariable relative risks (RRs)* and 95% confidence intervals (CIs) for the effects of alcohol intake on postmenopausal breast cancer risk by receptor-defined subtype among 51 847 postmenopausal women in the Swedish Mammography Cohort (the Uppsala County subcohort = 30 143 women)

Tumors according to receptor status	Categories of alcohol consumption, g of ethanol per day				P_{trend}§
	Nondrinkers	< Median†	Median–9.9	≥10.0‡	
Study cohort					
All invasive tumors‖					
No. of person-years	104 515	164 567	114 828	46 673	
No. of patients	314	476	343	151	
RR (95% CI)	1.00 (referent)	1.08 (0.94 to 1.25)	1.10 (0.94 to 1.29)	1.43 (1.16 to 1.76)	.0012
ER+PR+ tumors					
No. of patients	184	269	186	77	
RR (95% CI)	1.00 (referent)	1.07 (0.89 to 1.30)	1.09 (0.88 to 1.35)	1.35 (1.02 to 1.80)	.049
ER+PR− tumors					
No. of patients	54	90	81	54	
RR (95% CI)	1.00 (referent)	1.10 (0.78 to 1.55)	1.30 (0.91 to 1.87)	2.36 (1.56 to 3.56)	<.001
ER−PR+ tumors					
No. of patients	13	21	14	2	
RR (95% CI)	1.00 (referent)	1.27 (0.63 to 2.57)	1.30 (0.58 to 2.89)	0.62 (0.13 to 2.90)	.57
ER−PR− tumors					
No. of patients	35	56	42	10	
RR (95% CI)	1.00 (referent)	1.11 (0.72 to 1.71)	1.09 (0.68 to 1.75)	0.80 (0.38 to 1.67)	.45
Uppsala County subcohort					
All invasive tumors¶					
No. of person-years	81 649	120 728	81 321	33 263	
No. of patients	279	352	249	110	
RR (95% CI)	1.00 (referent)	1.00 (0.85 to 1.18)	1.04 (0.87 to 1.25)	1.49 (1.17 to 1.89)	<.001
ER+PR+ tumors					
No. of patients	167	206	137	60	
RR (95% CI)	1.00 (referent)	0.99 (0.81 to 1.22)	0.99 (0.78 to 1.26)	1.41 (1.02 to 1.94)	.030
ER+PR− tumors					
No. of patients	29	45	47	34	
RR (95% CI)	1.00 (referent)	1.09 (0.68 to 1.74)	1.49 (0.91 to 2.43)	3.05 (1.76 to 5.28)	<.0001
ER−PR+ tumors					
No. of patients	16	24	13	2	
RR (95% CI)	1.00 (referent)	1.30 (0.68 to 2.47)	1.16 (0.53 to 2.53)	0.74 (0.16 to 3.39)	.67
ER−PR− tumors					
No. of patients	32	40	31	8	
RR (95% CI)	1.00 (referent)	1.01 (0.63 to 1.61)	1.12 (0.66 to 1.89)	1.03 (0.45 to 2.33)	.83

*Multivariable Cox proportional hazards models with age as the time scales were adjusted for body mass index (<18.5, 18.5–24.9, 25–29.9, or ≥30 kg/m^2), height (continuous), education (<12 years of education or ≥12 years of education), parity (nulliparous, 1–2, or ≥3 children), age at first birth (nulliparous, <26, 26–30, or ≥31 years), age at menarche (≤12 years, 13 years, ≥14 years, or missing), age at menopause (<51 or ≥51 years), type of menopause (natural or surgery), use of oral contraceptives (ever, never, or missing), use of postmenopausal hormones (ever, never, or missing), first-degree of family history of breast cancer (yes or no), history of benign breast disease (yes or no), quartiles of total energy intake, energy-adjusted dietary fiber and total fat intake. ER = estrogen receptor; PR = progesterone receptor.

†The median alcohol intake among drinkers is approximately 3.4 g of ethanol per day in the study cohort and in the Uppsala County subcohort.

‡10 g ethanol corresponds to approximately one drink of alcohol.

§Two sided *P* values for trend were calculated using the Wald statistic using the median values for each category of alcohol intake as a continuous variable.

‖Includes 96 patients with unknown ER/PR status.

¶Includes 99 patients with unknown ER/PR status.

in first-degree relatives were not statistically significant (data not shown).

Discussion

In this population-based prospective cohort study of postmenopausal women, we found that alcohol consumption is statistically significantly positively associated in a dose–response manner with increased risk for the development of ER+PR+ tumors and ER+PR− tumors but not for development of ER−PR+ tumors or ER−PR− tumors. We observed a statistically significant interaction between alcohol intake and use of PMHs for the risk of ER+PR+ tumors and an additive risk relationship for ER+PR− tumors. These results suggest that both alcohol consumption and PMH use may be involved in the etiology of ER+ tumors but not that of ER− tumors.

A possible biologic explanation for the association between alcohol and breast cancer risk is that ethanol stimulates the expression of ER and/or the proliferation of ER+ human breast cancer cells as shown in mechanistic studies *(10,11)*. The observed results for ER+PR+ tumors also support a possibility that alcohol-induced endogenous estrogen may contribute to the increased risk *(7–9)*, given that higher frequency of PR expression indicates ER-mediated estrogen action in the tumors *(33)*.

We did not observe an association between alcohol intake and the risk of ER− breast cancer. ER− breast cancer has been proposed to have characteristics different from those of ER+ breast cancer, and previous studies indicate that tumors with BRCA1 mutations are generally ER−PR− *(34–38)*.

The results from seven case–control studies *(15–21)* and two cohort studies, the Iowa Women's Health Study cohort *(22,39)* and the Nurses' Health Study *(40,41)*, are relevant to our findings. The positive association between alcohol intake and ER+ breast tumors observed in our study is in agreement with three case–control studies *(15–17)* but in disagreement with four

Table 3. Multivariable relative risks (RRs)* and 95% confidence intervals (CIs) of ER/PR-defined breast cancer according to alcohol consumption and PMH use among 41 817 postmenopausal women with complete information for PMH use in the Swedish Mammography Cohort (the Uppsala County subcohort = 23 590 women)

	Study cohort						Uppsala County subcohort				
	Never PMH use		Ever PMH use				Never PMH use		Ever PMH use		
Alcohol intake, g of ethanol per day	No. of patients	RR (95% CI)	No. of patients	RR (95% CI)	$P_{interaction}$†	$P_{heterogenity}$‡	No. of patients	RR (95% CI)	No. of patients	RR (95% CI)	$P_{interaction}$†
All invasive tumors§											
Nondrinkers	158	1.00 (referent)	59	0.90 (0.67 to 1.22)			137	1.00 (referent)	42	0.80 (0.56 to 1.13)	
< Median‖	192	1.01 (0.82 to 1.25)	168	1.41 (1.13 to 1.76)			152	0.93 (0.74 to 1.18)	102	1.10 (0.85 to 1.43)	
Median–9.9	129	1.05 (0.83 to 1.34)	135	1.31 (1.03 to 1.67)			85	0.92 (0.70 to 1.22)	84	1.15 (0.86 to 1.52)	
≥10.0¶	49	1.31 (0.94 to 1.81)	84	1.72 (1.30 to 2.28)	.11		30	1.11 (0.74 to 1.66)	64	1.76 (1.28 to 2.42)	.07
ER+PR+ tumors											
Nondrinkers	94	1.00 (referent)	28	0.71 (0.47 to 1.09)			81	1.00 (referent)	21	0.67 (0.41 to 1.09)	
< Median‖	110	1.01 (0.76 to 1.33)	97	1.42 (1.06 to 1.89)			87	0.92 (0.68 to 1.25)	64	1.19 (0.85 to 1.66)	
Median–9.9	71	1.05 (0.77 to 1.44)	71	1.26 (0.91 to 1.74)#			46	0.88 (0.61 to 1.28)	45	1.09 (0.75 to 1.60)	
≥10.0¶	24	1.20 (0.76 to 1.90)	47	1.80 (1.24 to 2.60)**	.039	.079	16	1.06 (0.61 to 1.83)	39	1.92 (1.28 to 2.88)	.038
ER+PR− tumors											
Nondrinkers	23	1.00 (referent)	16	1.63 (0.86 to 3.10)††			14	1.00 (referent)	9	1.64 (0.71 to 3.81)	
< Median‖	35	1.17 (0.69 to 1.98)	36	1.88 (1.11 to 3.19)			21	1.13 (0.57 to 2.23)	13	1.20 (0.56 to 2.57)	
Median–9.9	27	1.31 (0.74 to 2.30)	40	2.20 (1.29 to 3.74)‡‡			15	1.30 (0.62 to 2.73)	20	2.08 (1.02 to 4.22)	
≥10.0¶	17	2.54 (1.33 to 0.86)§§	31	3.51 (1.98 to 6.21)‖‖	.96	.001	8	2.30 (0.94 to 5.64)	20	4.01 (1.93 to 8.32)	.76
All ER− tumors											
Nondrinkers	28	1.00 (referent)	6	0.53 (0.22 to 1.27)			24	1.00 (referent)	6	0.66 (0.27 to 1.62)	
< Median‖	31	0.88 (0.53 to 1.48)	23	1.06 (0.60 to 1.85)			27	0.95 (0.54 to 1.65)	14	0.89 (0.46 to 1.75)	
Median–9.9	26	1.09 (0.63 to 1.89)	11	0.56 (0.27 to 1.14)			19	1.18 (0.63 to 2.20)	8	0.65 (0.29 to 1.49)	
≥10.0¶	6	0.79 (0.32 to 1.95)	2	0.21 (0.05 to 0.89)	.09		5	1.10 (0.41 to 2.98)	1	0.17 (0.02 to 1.29)	.31

*Multivariable Cox proportional hazards models with age as the time scale were adjusted for body mass index (<18.5, 18.5–24.9, 25–29.9, or ≥30 kg/m^2), height (continuous), education (<12 years of education or ≥12 years of education), parity (nulliparous, 1–2, or ≥3 children), age at first birth (nulliparous, <26, 26–30, or ≥31 years), age at menarche (≤12 years, 13 years, ≥14 years, or missing), age at menopause (<51 or ≥51 years), type of menopause (natural or surgery), use of oral contraceptives (ever, never, or missing), first-degree family history of breast cancer (yes or no), history of benign breast disease (yes or no), quartiles of total energy intake, energy-adjusted dietary fiber and total fat intake. ER = estrogen receptor; PR = progesterone receptor.

†*P* values (two-sided) for interaction were calculated based on −2 log likelihood test.

‡*P* values (two-sided) for heterogeneity from the Wald test compared with seven pairs of β-coefficients of all ER− tumors.

§Includes seven patients with ER+PR unknown tumors and 67 patients with ER/PR unknown status in the study cohort. Includes six patients with ER+PR unknown tumors and 67 patients with ER/PR unknown status in the Uppsala County subcohort.

‖3.2 and 3.4 g of ethanol per day were approximately the medians among drinkers in the study cohort and the Uppsala County subcohort, respectively.

¶10 g of ethanol corresponds to approximately one drink of alcohol.

#$P_{heterogeneity}$ = .042 from the Wald test for heterogeneity of respective β-coefficients between ER+PR+ and all ER− tumors.

**$P_{heterogeneity}$ = .005 as above.

††$P_{heterogeneity}$ = .042 from the Wald test for heterogeneity of respective β-coefficients between ER+PR− and all ER− tumors.

‡‡$P_{heterogeneity}$ = .003 as above.

§§$P_{heterogeneity}$ = .039 as above.

‖‖$P_{heterogeneity}$<.001 as above.

others *(18–21)* and one cohort study *(22)*. Among the last five studies, one relatively large study encompassed 1774 case patients and 2311 control subjects, but its assay method for evaluating ER and PR status was not standardized *(21)*. The relatively small size of the other studies [from 238 to 610 postmenopausal case patients with known receptor status *(18–20,22)*] may limit their power to detect a weak association. Statistically significant interaction between alcohol intake and use of PMHs was not observed either for total breast cancer risk *(40)* or for ER/PR-defined breast cancer in the Nurses' Health Study *(41)*. In the Iowa Women's Health Study cohort *(39)*, there was a statistically significant interaction of alcohol with the risk of developing ER+PR+ tumors and even ER−PR− tumors with PMH use, but not for ER+PR− tumors, which is only in partial agreement with our results. These conflicting results require further studies of ER- and PR-defined breast cancer.

There are some limitations in the present study. First, the measurement of alcohol intake, although based on a long-term exposure, did not reflect lifetime consumption and total duration of alcohol consumption. This incomplete information could lead to attenuation of the observed risk. Second, we had no information about the type of PMH preparation nor the duration and the recency of use. These variables are of importance for specific and precise estimates of the breast cancer risk associated with PMH use and with the combined effect of alcohol and PMH use. Because of the lack of complete information on PMH use in our study, women using different PMH preparations, those with short as well as long use, women who stopped use many years ago, and those who were still using PMHs—i.e., women with a varying risk due to PMH use *(42)*—were placed into the same category as ever users. However, our crude information about PMH use in general would tend to attenuate the observed association with PMH use and the observed interaction of alcohol with PMH use in relation to ER+PR+ breast cancer risk as well as the observed risk additive relation for ER+PR− tumors and thus could not explain our results. Nevertheless, the observed interaction between alcohol and PMH use for ER+PR+ tumors and the lack of a positive association between PMH use and risk of breast cancer among nondrinkers have to be considered with caution because of the lack of optimal exposure information on these two factors.

The major strengths of our study include its population-based design, the completeness of identification of all breast cancer cases through the Swedish Cancer Registries *(27)*, and the large number of breast cancer case patients with defined ER/PR status (92.5%) based on the concentrations of ER and PR that were evaluated by the same immunoassay during the entire follow-up period. Furthermore, the prospective design of our study makes it unlikely that the associations we observed were due to recall bias, which can lead to spurious associations in case–control studies. Repeated measurements of alcohol intake during follow-up and high validity of self-reported alcohol intake contribute to the precision of our estimates.

In conclusion, findings from this prospective population-based study show that alcohol consumption is positively associated with increased risk for ER+ tumors, irrespective of PR status. The observation that alcohol was associated with the risk of developing ER+ tumors but not ER− tumors implies that alcohol may affect postmenopausal breast cancer through the ER-signaling pathway. Our findings are biologically relevant because the majority of breast tumors among postmenopausal women are ER+. In the future, large studies with complete and detailed information on lifelong alcohol consumption and on lifelong specific exogenous hormone use need to further investigate the issue of alcohol and PMH use in the development of ER+ breast cancer, which is of great clinical and public health importance. Molecular epidemiologic studies also need to further identify susceptibility factors for alcohol-associated breast cancer, such as inherited differences in the capacity to metabolize and detoxify alcohol.

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NOTES

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