Short Communication

Alcohol and Breast Cancer Risk Defined by Estrogen and Progesterone Receptor Status: A Case-Control Study

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Abstract

Background: **Alcohol consumption increases breast cancer risk. Some studies suggested that this association is stronger or limited to tumors expressing estrogen receptors (ER).**

Methods: **We investigated the role of alcohol according to ER and progesterone receptor (PR) status in a case-control study on breast cancer conducted from 1991 to 1994 in three Italian areas. Cases were 989 women with incident, histologically confirmed breast cancer. Controls were 1,350 women admitted to hospitals in the same catchment areas for acute nonneoplastic diseases. A validated food-frequency questionnaire was used to collect information on dietary habits and lifetime consumption of various alcoholic beverages. Multiple logistic regression models were used to estimate odds ratios and 95% confidence interval (95% CI).**

Results: **Alcohol drinking was associated with ER+ tumors (odds ratio, 2.16; 95% CI, 1.68-2.76 for an intake of ≥13.8 g/d as compared with nondrinkers). The odds ratio was 1.13 (95% CI, 1.07-1.20) for a 10-g increase in daily intake. For ER- tumors, the relation with alcohol consumption was not significant (odds ratio, 1.36; 95% CI, 0.93-2.01). When breast cancers were further classified according to PR, the findings for ER+PR+ cancers were similar to those for all ER+ ones, with an odds ratio of 2.34 (95% CI, 1.81-3.04) for an intake of ≥13.8 g/d. No significant association emerged for ER-PR- tumors (odds ratio, 1.25; 95% CI, 0.81-1.94).**

Conclusion: **This study supports the hypothesis that alcohol is more strongly related to ER+ than to ER- breast tumors.** (Cancer Epidemiol Biomarkers Prev 2008;17(8):2025–8)

Introduction

Several epidemiologic studies (1) have reported on the association between alcohol and breast cancer. A possible explanation for this association includes hormone-dependent mechanisms mediated by sex hormone receptors (2).

Several studies (3-12) have investigated whether the association between alcohol intake and breast cancer risk differs depending on estrogen receptor (ER) and progesterone receptor (PR) status, but the findings have been inconsistent, possibly due to incomplete information on receptor status. Although some studies found an association limited to ER+ tumors (3), in other investigations the relation with alcohol was significant neither for ER+ nor for ER- breast cancers (4-7), or it was detectable only in women with specific characteristics such as postmenopausal status (8) or leanness (9). Fewer studies investigated PR too, usually in combination with ER, and produced inconsistent results.

We investigated the effect of alcohol according to ER and PR status and the potential modifying effect of several covariates in an Italian multicenter case-control study on breast cancer (13, 14). Our study is based on a Southern European population with relatively high alcohol consumption, where this issue has not been previously studied.

Materials and Methods

This case-control study was conducted between 1991 and 1994 in six Italian areas: the provinces of Pordenone and Forlì, the urban areas of Milan and Genoa in the North; the province of Latina in Central Italy; and the urban area of Naples in the South. The general design of the study has already been described elsewhere (13, 14). Information on ER/PR status was available in 3 centers only (Pordenone, Forlì, and Naples), representing 1,516 breast cancer cases, 59.0% of the total 2,569 cases, and 1,477 controls, 57.1% of the total 2,588 controls. After exclusion of cases with missing ER/PR status (29.1% among Pordenone, Forlì, and Naples centers) and ex-drinkers

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(8.5%), 989 cases and 1,350 controls were available for this analysis. We excluded ex-drinkers because their risk was lower than that of current drinkers (13).

Briefly, cases were 989 women (aged 23-74 years; median, 55 years) with incident, histologically confirmed breast cancer diagnosed no more than 1 year before the interview, and with no previous diagnoses of cancer. Controls were 1,350 women (aged 20-74 years; median, 56 years) admitted to hospitals in the same catchment areas for acute, nonneoplastic, nongynecologic diseases: non–alcohol related trauma (22%); orthopedic disorders (33%); eye diseases (18%); acute surgical disorders (15%); and other miscellaneous diseases related to ear, nose and throat, skin, and teeth (12%). Cases were not individually matched to controls, but were well comparable by age within study centers. Refusal rate was less than 5% of cases and controls approached for interview.

Information was collected in the hospital by trained interviewers on socioeconomic variables and lifestyle habits, anthropometric measures, history of selected diseases, menstrual and reproductive history, use of oral contraceptives and hormone replacement therapy in menopause, and dietary habits using a validated food-frequency questionnaire (15). A specific section collected information on lifetime consumption of alcohol: the weekly number of drinks for the five most commonly consumed alcoholic beverages or groups of beverages (that is, wine, beer, herb liquors, grappa, whisky/brandy, and other spirits) was investigated. Taking into account the different ethanol concentrations, 1 drink corresponded to approximately 125 mL of wine, 330 mL of beer, and 30 mL of hard liquor (that is, about 15 g of ethanol). Total alcohol intake was the sum of all alcoholic beverages reported. Age at starting drinking and, for ex-drinkers, age at quitting were also recorded. Former drinkers had abstained from any type of drinking for at least 12 months. A satisfactory level of reproducibility and validity of the pattern of alcoholic consumption across different levels and types of alcoholic beverage intake was observed (16).

The information about ER and PR status of breast cancers was obtained by reviewing pathology laboratory work logs at local level. ER and PR status were determined from fresh tumor samples directly after surgery by biochemical analysis.

To estimate odds ratios, we used multiple logistic regression models, including terms for age, center, education, parity, menopausal status, age at menarche, family history of breast cancer, body mass index (BMI), and energy intake. We used unordered polytomous logistic regression to test the heterogeneity of risk in different ER and PR subtypes.

Results

Table 1 presents selected characteristics of the population according to ER subtypes. ER+ and ER- cases were not substantially different with regard to study center; age; education; family history of breast cancer; menstrual, reproductive, and hormonal variables; BMI; and energy intake. There was no difference in alcohol intake between women with breast cancer with available data on hormone receptor status and those without (χ^2, 1.324; 2 *df*; $P = 0.516$).

Table 2 gives the distribution of cases and controls according to the level of alcohol intake, and the odds ratios for light and heavy drinkers as compared with nondrinkers in selected combinations of ER and PR subtypes. Alcohol intake was directly associated with ER+ tumor subtypes [odds ratio, 2.16; 95% confidence interval (95% CI), 1.68-2.76 for an intake of ≥13.8 g/d as compared with nondrinkers]. The odds ratio was 1.13 (95% CI, 1.07-1.20) for a 10-g increase in daily intake. For ER- cancers, the relation with alcohol consumption was not significant (odds ratio, 1.36; 95% CI, 0.93-2.01 for an intake of ≥13.8 g/d as compared with nondrinkers). There was a significant heterogeneity between the

Table 1. Distribution of 989 breast cancer cases and 1,350 controls according to age, center, and selected covariates (Italy; 1991-1994)

Characteristics	ER- cases	ER+ cases	Controls
Center			
Pordenone	154 (67.84)	544 (71.39)	918 (68.00)
Forlì	38 (16.74)	108 (14.17)	191 (14.15)
Napoli	35 (15.42)	110 (14.44)	241 (17.85)
χ^2 test, *df* (*P*)	1.21, 2 (0.547)		
Age group (y)			
<45	59 (25.99)	154 (20.21)	289 (21.41)
45-49	28 (12.33)	139 (18.24)	169 (12.52)
50-54	44 (19.38)	116 (15.22)	213 (15.78)
55-59	32 (14.10)	93 (12.20)	203 (15.04)
60-64	28 (12.33)	113 (14.83)	177 (13.11)
65-69	24 (10.57)	93 (12.20)	189 (14.00)
70-74	12 (5.29)	54 (7.09)	110 (8.15)
χ^2 test, *df* (*P*)	10.70, 6 (0.098)		
Education (y)			
<5	29 (12.78)	114 (14.96)	306 (22.67)
5-7	77 (33.92)	292 (38.32)	646 (47.85)
8-12	85 (37.44)	237 (31.10)	299 (22.15)
≥13	36 (15.86)	119 (15.62)	99 (7.33)
χ^2 test, *df* (*P*)	3.65, 3 (0.302)		
Age at menarche (y)			
<13	102 (44.93)	315 (41.34)	524 (38.81)
13-14	93 (40.97)	321 (42.13)	580 (42.96)
>14	32 (14.10)	126 (16.54)	246 (18.22)
χ^2 test, *df* (*P*)	1.24, 2 (0.537)		
Menopausal status			
Pre-/perimenopausal	102 (44.93)	333 (43.70)	499 (36.96)
Postmenopausal	125 (55.07)	429 (56.30)	851 (63.04)
χ^2 test, *df* (*P*)	0.11, 1 (0.743)		
Parity (number of births)			
Nulliparae	33 (14.54)	111 (14.57)	164 (12.15)
1-2	128 (56.39)	467 (61.29)	709 (52.52)
≥3	66 (29.07)	184 (24.15)	477 (35.33)
χ^2 test, *df* (*P*)	2.38, 2 (0.305)		
Family history of breast cancer			
Yes	13 (5.73)	72 (9.45)	64 (4.74)
No	214 (94.27)	690 (90.55)	1,286 (95.26)
χ^2 test, *df* (*P*)	3.08, 1 (0.079)		
BMI			
<22	50 (22.03)	182 (23.98)	264 (19.64)
22 to <25	71 (31.28)	231 (30.43)	407 (30.28)
25 to <28	47 (20.70)	172 (22.66)	314 (23.36)
≥28	59 (25.99)	174 (22.92)	359 (26.71)
χ^2 test, *df* (*P*)	1.32, 3 (0.724)		
Energy intake (kcal/d)			
<1,934	61 (26.87)	235 (30.84)	450 (33.33)
1,934 to <2,445	79 (34.80)	258 (33.86)	450 (33.33)
≥2,445	87 (38.33)	269 (35.30)	450 (33.33)
χ^2 test, *df* (*P*)	1.41, 2 (0.494)		

NOTE: The sum may not add up to the total because of some missing values.

Table 2. Odds ratio of breast cancer and 95% CI according to levels of alcohol intake by receptor status of the tumor (Italy; 1991-1994)

	Never drinkers	<Median* (13.8 g/d)	≥Median (13.8 g/d)	Per 10 g increased
Categories of alcohol consumption (g of ethanol per day)				
Controls [*n* (%)]	491 (36.4)	429 (31.8)	430 (31.9)	
Cases [*n* (%)]	244 (24.7)	337 (34.1)	408 (41.3)	
OR (95% CI)	1†	1.55 (1.24-1.93)	1.96 (1.57-2.47)	1.11 (1.05-1.17)
ER status				
ER−				
Cases [*n* (%)]	65 (28.6)	90 (39.7)	72 (31.7)	
OR (95% CI)	1†	1.57 (1.09-2.26)	1.36 (0.93-2.01)	not given‡
ER+				
Cases [*n* (%)]	179 (23.5)	247 (32.4)	336 (44.1)	
OR (95% CI)	1†	1.51 (1.18-1.93)	2.16 (1.68-2.76)	1.13 (1.07-1.20)
P heterogeneity = 0.006				
ER and PR status combined				
ER-PR-				
Cases [*n* (%)]	50 (29.24)	68 (39.77)	53 (30.99)	
OR (95% CI)	1†	1.54 (1.02-2.32)	1.25 (0.81-1.94)	not given‡
ER+PR−				
Cases [*n* (%)]	31 (30.69)	33 (32.67)	37 (36.63)	
OR (95% CI)	1†	1.02 (0.60-1.74)	1.30 (0.76-2.24)	1.07 (0.95-1.21)
ER−PR+				
Cases [*n* (%)]	15 (26.79)	22 (39.29)	19 (33.93)	
OR (95% CI)	1†	1.63 (0.81-3.28)	1.72 (0.83-3.59)	1.11 (0.95-1.28)
ER+PR+				
Cases [*n* (%)]	148 (22.39)	214 (32.38)	299 (45.23)	
OR (95% CI)	1†	1.60 (1.24-2.08)	2.34 (1.81-3.04)	1.14 (1.07-1.20)

Derived from multiple logistic regression, including terms for age, center, education, parity, menopausal status, age at menarche, family history of breast cancer, BMI, and energy intake. Abbreviation: OR, odds ratio.
*Computed on the distribution of control drinkers.
†Reference category = nondrinkers (ex-drinkers were excluded).
‡Not given because of the lack of linearity in the categorical analysis.

odds ratios for alcohol in ER+ and ER- breast cancers ($P = 0.006$).

When breast cancers were further classified according to PR, the findings for ER+PR+ cancers were similar to those for all ER+ cancers, with an odds ratio of 2.34 (95% CI, 1.81-3.04) for an intake of ≥13.8 g/d and an odds ratio of 1.14 (95% CI, 1.07-1.20) for a 10-g increase per day. No significant association emerged for ER-PR- cancers (odds ratio, 1.25; 95% CI, 0.81-1.94 for an intake of ≥13.8 g/d as compared with nondrinkers).

The association between alcohol and breast cancer risk did not differ appreciably across strata of covariates, except that there was a stronger risk of ER+ subtypes per 10 g of alcohol increase daily in pre-perimenopausal age (odds ratio per 10 g of alcohol increase per day, 1.21; 95% CI, 1.10-1.32) and a significant risk increase of ER+ tumors among women reporting high folate intake (odds ratio, 1.20; 95% CI, 1.11-1.30 for ≥264.4 μg/d).

Discussion

This study, conducted in a population with relatively high alcohol consumption, found a stronger association between alcohol and breast cancer for ER+ and ER+PR+ cancers than for ER− ones. We observed a dose-response relation for ER+ tumors but not for ER−. The fact that the estimates for ER+ and ER− tumors were heterogeneous when using continuous and predefined categories further strengthens the result. This finding is consistent with the results of some studies (3, 8, 10, 11), but not of other studies (4-7). Differences in several methodologic aspects may, at least in part, explain the different findings, including the measure of alcohol consumption (yes/no versus grams per day) and the inclusion of ex-drinkers in the nondrinker category. The difference between ER+ and ER- tumors was seen only at higher levels of alcohol consumption. This may have not emerged in populations where average intake is lower.

Moreover, our population differs in terms of hormonal characteristics given the inclusion of both pre- and postmenopausal women and the low prevalence of hormone replacement therapy use.

A possible biological explanation for the association between alcohol and ER+ breast cancer is given by in vitro experiments that show a specific mitogenic activity of ethanol for ER+ human breast cancer cells but not for ER- cells (17). Moreover, ethanol can increase the transcriptional activity of the liganded ER (18). This supports the suggestion that the mechanisms contributing to alcohol-related breast cancer are due to increased estrogen responsiveness. Limited current evidence suggests that women with ER-PR+ tumors seem to fit a profile that strongly resembles that observed in ER+PR+ tumors, and that these tumors may represent a subset of ER+PR+ cancers or false negative for ER status (4). A three-group classification was therefore proposed (PR+, ER+/PR-, and ER-/PR-). However, in agreement with most recent work on risk factors for breast cancer by receptor status (19), we chose to present a classification that kept separate all combinations of ER and PR status. The similarity of ER-/PR+ and ER+/PR+ with respect to the effect of alcohol, if not due to chance, may confirm, however, the proposal made by Potter et al. (4). Only

a few studies investigated whether other hormonal, dietary, and anthropometric variables affect the positive association between alcohol and ER+ tumors: the most commonly studied factors were menopausal status (3, 5, 7-10), hormone replacement therapy (3, 6, 8-10), BMI (3, 8-10), and folate intake (10, 12). The low rate of hormone replacement therapy use in our population did not allow us to compute odds ratio in this stratum. We found a stronger risk for ER+ tumors in pre- and perimenopausal women and in women with high folate intake, in contrast with the results of Enger et al. (8) and Sellers et al. (12), respectively. In the light of these contrasting results, it is possible that these differences may simply be due to chance findings in subgroup analysis (20).

The major strengths of this study are the large sample size, the practically total participation of cases (96%) and controls (96%) approached for interview, the frequent high alcohol consumption among Italian women, and the use of a validated questionnaire for alcohol consumption (15), besides allowance for a large number of potential confounding factors, including total energy intake (21). Although only three of the original centers had information on receptor status, within these centers the information was satisfactorily complete. Moreover, we assessed case-case differences, and individuals were blinded to tumor phenotype when recalling alcohol exposure. A possible limitation of this study is that hospital controls could differ from the general population with regard to alcohol consumption. However, we paid particular attention to exclude from the study those subjects who were admitted for diseases related to alcohol drinking. In addition, our results on alcohol are well compatible with the present general knowledge on the issue (1).

In summary, our results concur with those from other studies in supporting the hypothesis that ER+ and ER- tumors may have partially different etiologic determinants.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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