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Alcohol intake and risk of breast cancer: the EURAMIC study

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Abstract

To evaluate the association of alcohol intake with the risk of breast cancer in post-menopausal women, we analyzed the data from an international case-control study conducted in five European countries (Germany, Switzerland, Northern Ireland, the Netherlands and Spain). Information on alcohol intake was available in 315 cases and 364 controls. Medians for the tertiles of alcohol intake among current drinkers were 1.7, 6.0, and 20.0 g/day. Adjusted relative risks (and 95% confidence intervals) of breast cancer for each tertile of intake in current drinkers, compared to never drinkers, were 1.00 (0.60-1.67), 1.01 (0.60-1.73), and 1.18 (0.69-2.03). The adjusted relative risk for ex-drinkers was 1.73 (1.07-2.79). Among both current drinkers and ex-drinkers, the relative risk was higher for those with body mass index above the median compared to those with body mass index below the median. These results do not support a dose-response effect of alcohol on breast cancer risk, although consumption levels were too low to exclude increased risk with high regular intake. Further research is necessary to evaluate the risk of developing breast cancer among ex-drinkers and the potential interaction between body mass index and alcohol drinking.

Keywords: breast cancer; alcohol; case-control studies

Introduction

In 1977, Williams and Horm [41] reported increased risk of cancer of the oral cavity, larynx, esophagus, colon, rectum, breast and thyroid among participants in the Third National Cancer Survey who consumed alcohol regularly compared to those who did not. Since that report, several case-control and follow-up studies have shown a small but positive increase in breast cancer risk among women who consume alcohol regularly, although other studies have failed to show any association [2, 26]. Two meta-analyses of alcohol and breast cancer have shown a weak but significant positive dose-response effect [21, 22], although a third meta-analysis concluded that the dose-response effect is evident only in hospital-based case-control studies [28], and a pooled analysis of six dietary case-control studies suggested that the association is limited to heavy drinkers [17]. Epidemiological studies have also suggested that the effect of alcohol may be stronger when consumed at young ages, in leaner women, in pre-menopausal women and under estrogen replacement therapy [9, 10, 15, 23, 30, 36, 39].

However, the causal role of alcohol on the development of breast cancer is still controversial [2, 26]. First, the relatively small increase in risk may be due to residual confounding by other unknown or unreliably measured risk factors. Second, although several mechanisms have been proposed for the carcinogenic effect of alcohol, no definitive mechanism has yet been established [26]. Finally, alcohol intake has not been found to consistenly induce cancer in experimental animals [2] and its reported co-carcinogenic effect in animal models of breast cancer [11] has been difficult to replicate consistently [13, 24, 25].

To further investigate the relation between alcohol intake and breast cancer risk and the possible interactions with age at onset of regular drinking, body mass index and estrogen replacement therapy, we have examined data from the “EURopean study on Antioxidants, Myocardial Infarction and Cancer of the breast” (EURAMIC), an international multicenter case-control study designed primarily to evaluate the effect of antioxidants on breast cancer risk in postmenopausal women [18, 37].

Materials and Methods

Study design and subject recruitment

The methods of the EURAMIC study have been described in detail elsewhere [18, 37]. Briefly, breast cancer cases and controls were recruited from 5 European countries (Germany, Northern Ireland, the Netherlands, Spain, and Switzerland). Eligible subjects were postmenopausal women, aged 50-74 years, native residents speaking the official local language of the country of recruitment. Subjects were excluded if they had a previous history of breast cancer, a history of drug or alcohol abuse, major psychiatric disorders, if they were institutionalized, or if they had modified their dietary pattern in the past year (new or altered dietary prescription for health reasons -except for low sodium or energy restricted diets-, weight loss exceeding 5 kg, or changes in the use of supplements containing α-tocopherol, β-carotene or selenium).

Cases were women with first diagnosis of breast cancer (ICD-9 code 174), histologically classified as ductal carcinoma, with tumor size < 5 cm, axillary lymph nodes stage ≤ N3, and without any clinical indication of distant metastases at discharge (M0). Cases were recruited from the surgical units of participating hospitals. Histologic diagnosis and staging were performed by medical specialists in the local pathology and clinical laboratories.

Controls were women without breast cancer, frequency-matched for age in 5-year intervals and center. In two centers, random samples from local population registries were used (Germany, Switzerland). Where it was thought that low response rates from population based samples would compromise internal validity, control subjects were selected via a random sample by the patient's general practitioner (Netherlands, Northern Ireland, Spain).

Cases and controls were recruited concurrently during 1991 and 1992. Response rates were 85.9% and 41.3% for cases and controls, respectively. Informed consent was obtained from study participants in accordance with the ethical standards of the responsible committees on human experimentation for each center.

Data collection

Information on smoking habits, reproductive and medical history and anthropometric measures was collected for all subjects by interview. Specific items related to the reproductive and hormonal history included age at menarche, age at first childbirth, parity, use of oral contraceptives or estrogen replacement therapy, age at menopause and type of menopause. Socioeconomic status, family history of breast cancer and alcohol intake were assessed through locally-developed questionnaires. Study participants were asked about the frequency and amount of alcoholic drinks usually consumed during work days and during the weekend in the past year, as well as the age at starting regular drinking and past drinking habit. To obtain the total amount of alcohol consumed per week, we calculated the total number of units of alcohol consumed per week and assumed that each unit was equivalent to 10 g of alcohol. In Germany, no information was available on past drinking habits. Therefore, this center was not included in the estimates of risk for ex-drinkers.

Statistical methods

Among cases and controls, summary statistics for alcohol intake and established risk factors of breast cancer were calculated for each center. Cases and controls were grouped with respect to their alcohol intake in never drinkers, ex-drinkers and current drinkers. The distribution of alcohol levels in control subjects was used to compute cutoff points and medians for tertiles of alcohol among current drinkers. For intra-center comparisons, tertiles were based on the control distribution for each center, while the combined sample was used for categorizations in overall analyses. The levels of breast cancer risk factors across tertiles of alcohol intake were evaluated among controls by one-way analysis of variance and χ^2 tests [33].

For risk analysis, multiple logistic regression was used to estimate the association of alcohol intake with the risk of developing breast cancer, adjusting for potential confounders. Relative risks were estimated as odds ratios in alcohol intake categories compared to never drinkers. To assess the presence of a linear trend of risk across categories of alcohol intake, tests for trend were computed by including in the logistic models a variable with the median value for the corresponding tertile of intake [3]. All P-values reported are two-tailed. Statistical analysis were performed using the SAS package [29].

Results

Information on alcohol intake was available in 315 cases and 364 controls (94.2% of study participants). As expected, cases had higher body mass index, age at first childbirth, family history of breast cancer and history of benign breast disease, but only age at first childbirth and family history of breast cancer reached statistical significance. Age at menarche, age at menopause and parity were similar among cases and controls (table 1).

The proportion of current drinkers and ex-drinkers, as well as alcohol intake among current drinkers varied markedly across centers. In the control group, Zeist had the highest proportion of current drinkers (78.7 %), Málaga had the lowest (5.9 %), and Coleraine had the highest proportion of ex-drinkers (33.7 %). There were only 3 ex-drinkers in Málaga, all of them cases (table 2). Berlin and Zeist had the highest average alcohol intake among current drinkers (14.0 and 13.1 g/day respectively), while Málaga had the lowest (3.0 g/day). The overall mean concentration of alcohol intake in controls was 11.8 g/day (table 3).

The relation between breast cancer risk factors and alcohol intake was examined among controls (table 4). Ex-drinkers had the highest age at first childbirth, frequency of use of estrogen replacement therapy and frequency of personal history of benign breast disease and the lowest body mass index and proportion of low socioeconomic status. Never drinkers had the highest body mass index and proportion of parous women, and the lowest proportion of smokers, family history of breast cancer and low socioeconomic status. As an indirect evidence of the validity of the assessment of alcohol intake in the EURAMIC study, we examined the proportion of smokers by category of alcohol intake. The proportion of smokers increased steadily from never drinkers (7.5%) to heavy drinkers (36.1%; ANOVA $p < 0.001$). The proportion of smokers among ex-drinkers (12.0%) was similar to that in light drinkers (11.5%).

Compared to never drinkers, the overall center- and age-adjusted relative risk (RR) for current drinkers was 1.00 (95% confidence interval [CI]: 0.70 to 1.43; $p = 0.98$) (table 2). The RR for current drinkers ranged from 0.66 in Zurich to 2.76 in Málaga, but the confidence intervals for the individual centers were wide and overlapped one another. There was also no evidence of effect of alcohol when current drinkers were analyzed by amount of alcohol intake. The overall center- and age-adjusted RR estimates for current drinkers in the first, second and third tertile of alcohol intake compared to never drinkers were 1.00, 0.98 and 1.06, respectively (table 5). The overall center- and age-adjusted RR for ex-drinkers compared to never drinkers was 1.66 (95% CI: 1.06 to 2.62; $p = 0.028$). In the three centers with sizable numbers of ex-drinkers, the RR for ex-drinkers were all above unity (Zürich 1.09, Coleraine 1.22 and Zeist 4.01).

Adjustment for age, center, body mass index, smoking, parity, age at menarche, age at menopause, estrogen replacement therapy, family history of breast cancer, history of benign breast disease and age at first childbirth did not materially affect the results (table 5). The risk factor-adjusted RR for current drinkers in the first, second and third tertile of alcohol intake compared to never drinkers were 1.00, 1.01 and 1.18, while the RR for ex-drinkers was 1.73 (95% CI: 1.07 to 2.79; $p= 0.026$). Exclusion of centers with few ex-drinkers or without information on past drinking habits gave very similar estimates of risk (table 5).

To evaluate the possibility that changes in drinking habits were a consequence of pre-existing predisposing conditions for breast cancer, we re-analyzed the data in parous women without family history of breast cancer and without personal history of benign breast disease (269 cases and 336 controls). The RR of breast cancer for current drinkers and ex-drinkers, compared to never drinkers, were 1.02 and 1.68 respectively.

The effect of age at onset of drinking was examined in the 175 cases and 174 controls who provided this information. Among current drinkers, breast cancer risk estimates were higher for those who began drinking before age 40 compared to those who began drinking after age 40 (RR compared to never drinkers 1.36, 95% CI: 0.96 to 1.91 vs. 0.94, 95% CI: 0.53 to 1.66, respectively). Similarly, among ex-drinkers, women who began drinking before age 40 appeared to be at greater risk than those who began drinking after that age (1.83, 95% CI: 1.11 to 3.00 vs. 1.55, 95% CI: 0.62 to 3.87), although none of these differences was statistically significant.

To evaluate whether the effect of alcohol depended on obesity, we examined the RR of alcohol intake among women below and above the median of body mass index (figure 1). No indication of increased risk among current drinkers was evident either in women with body mass index below (RR compared to lean never drinkers = 0.69) or above the median (RR = 1.08). However, the RR for ex-drinkers with body mass below the median was 1.07 while in those above median was 2.07. The p-value for the alcohol intake by body mass interaction was 0.08. When the RR for alcohol intake was examined by reported use of estrogen replacement therapy, no systematic differences of effect were found between users and nonusers (p-value for the alcohol intake by estrogen replacement therapy = 0.15).

Discussion

In this large, international case-control study in postmenopausal women, we detected a 1.7-fold increased risk of breast cancer among ex-drinkers, but no increase among current drinkers. Several issues need to be considered in the interpretation of these results. First, disease development may modify the pattern of alcohol intake. Specifically, women with benign breast disease or with early signs of breast cancer may stop drinking, which would result in overestimation of RR among ex-drinkers. However, when we limited our analysis to women without family history of breast cancer and without personal history of benign breast disease the results were unchanged. Furthermore, the potential association of alcohol and breast cancer did not receive extensive press coverage prior to data collection [16].

Second, differential recall may bias the effect of alcohol on breast cancer risk. In the Nurses Health Study, prospective data was used to evaluate selection and recall bias in case-control studies of alcohol and breast cancer [12]. Although underreporting of alcohol intake in cases relative to controls biased estimates of effect towards the null, the magnitude of the bias would be too small to substantially modify our conclusions [9].

Third, information on nutrient intake was not available in this study, making it impossible to obtain calorie- and nutrient-adjusted estimates of risk [38], but in studies in which dietary information was collected, adjustment for energy intake and other dietary factors had no substantial effect on risk estimates for alcohol [6, 9, 23, 35, 36, 39].

Finally, the EURAMIC study was not designed primarily to evaluate the association of alcohol and breast cancer. Information on alcohol consumption was derived through locally developed questionnaires, reflecting the different patterns of intake in the different countries, but without a formal validation procedure. Previous studies, however, suggest that even simple questionnaires provide useful estimates of regular alcohol intake over extended periods of time [12]. Furthermore, the strong correlation between reported alcohol intake and prevalence of smoking in our data reinforces the validity of our questionnaires to discriminate groups of participants with different consumption habits.

The epidemiologic evidence linking alcohol intake to breast cancer is persuasive, although some studies have shown little or no association [21, 26, 28]. With intakes of alcohol below 30 g/day, however, the estimated effect is small and may be difficult to detect [19, 35, 36]. In our study, the median intake of alcohol among current drinkers was 6.0 g/day and the median of the highest tertile of intake was 20.0 g/day, due in part to the exclusion of patients with a history of drug or alcohol abuse from the study sample in the EURAMIC centers. Thus, we cannot rule out an excess breast cancer risk among regular heavy drinkers.

In previous studies, the relative risk estimates for ex-drinkers range from 0.6 to 2.4 [4, 15, 27, 34]. In our study, the excess risk found among ex-drinkers could be explained if this group were composed of past heavy drinkers. Unfortunately, information on past level of intake among ex-drinkers is not available in our dataset. The differences in risk estimates for ex-drinkers across the EURAMIC centers reflects both the small number of ex-drinkers in each center and culture specific differences in

drinking habits. Further research is needed to determine the risk profile and its determinants among ex-drinkers.

Although some studies have found an excess risk for breast cancer with alcohol intake both in pre- and postmenopausal women [10], others have found that the excess risk in postmenopausal women is lower [30, 42] or even null [9, 36]. Since our study was limited to postmenopausal women, this fact may also contribute to the lack of effect among current drinkers in our dataset.

Contrary to other studies showing an increased risk of breast cancer among drinkers with low body mass index [10, 30, 35, 39], our data suggests a higher risk among ex-drinkers above median levels of body mass index. This interaction was almost significant ($p = 0.08$), but the variability of risk estimates in each individual category of drinking status by body mass index group makes it difficult to interpret this finding. In our study, no interaction was evident between alcohol intake and estrogen replacement therapy on the risk of breast cancer. Further research is thus necessary to clarify the potential interactions between alcohol intake and other breast cancer risk factors, such as obesity and estrogen use [8].

The effect of alcohol on breast cancer risk seems to be higher among drinkers who began drinking at younger ages [14, 30, 36], suggesting higher susceptibility of the mammary gland to carcinogens in adolescence, the importance of the duration of exposure or an accumulative effect of alcohol intake throughout life. In our study, we found higher risk both among current drinkers and ex-drinkers who began drinking before age 40 compared to those who began after age 40, but the differences were small and did not reach statistical significance. Hiatt *et al*. [15] found higher risk among current drinkers who began drinking before age 30, but not among ex-drinkers. As in our study, the small number of past drinkers in each of these categories makes risk estimates less reliable.

Several biological mechanisms have been suggested to explain the causal role of the alcohol in the etiology of breast cancer. Hormone-related mechanisms include stimulation of prolactin secretion [40], altered production or metabolism of estrogens and androgens, and reduced melatonin production. Although increased blood levels of estrogens have been found in women with high regular consumption of alcohol [5], the effect of moderate alcohol consumption on estrogen levels in postmenopausal women remain unclear [20]. Other potential mechanisms are direct alteration of cell membranes [7], liberation of mutagenic and co-carcinogenic metabolites, such as acetaldehyde [1], increased lipid peroxidation and reduction of antioxidant capacity , and the presence of carcinogens in alcoholic drinks [11]. However, none of these mechanisms clearly explains the association between alcohol and breast cancer. In addition, experimental studies of the carcinogenic or co-carcinogenic effect of alcohol intake in animal models are also inconsistent [11, 13, 24, 25, 31, 32].

In conclusion, our results do not support a dose-response effect of alcohol on breast cancer risk, although consumption levels were too low to exclude increased risk with high regular intake. Further research is necessary to evaluate the risk of developing breast cancer among ex-drinkers and the potential interaction between body mass index and alcohol drinking.

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