Alcohol Intake and Breast Cancer Risk: Effect of Exposure from 15 Years of Age

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Abstract

Research regarding the relationship between alcohol intake and breast cancer risk has suggested an association between the two, although the data are inconsistent regarding dose effects and susceptible populations.

To clarify these issues, we investigated the association of breast cancer risk with alcohol intake at various ages in a population-based case-control study nested within a screening cohort in Sweden. Subjects were women 40–75 years old who participated in a screening program in central Sweden. Information about personal characteristics, diet, and alcohol intake was obtained by a questionnaire sent out at the invitation to the screening interview and at a supplementary interview conducted among a sample of women who did and did not develop breast cancer.

Alcohol intake did not affect breast cancer risk among women under 50 years old. However, among those over 50 years of age, ever-drinking conferred a relative risk of 1.8 (95% confidence interval = 1.2–2.6). Current and former drinkers had similar increases in risk. No particular latent period of alcohol effect was identified, but drinking later in life appeared to have a bigger effect than did drinking earlier in life.

Introduction

Reports of a possible association between alcohol intake and an increased risk of breast cancer have led to considerable epidemiological debate (1). Although most studies of this issue have suggested an association (*e.g.*, Refs. 2–17), several have not (*e.g.*, Refs. 18–22). Among those analyses that have found alcohol intake to be a risk factor, there is considerable variability in the intake required to produce a measurable increase in risk; some studies have suggested that even low intake can have an impact (2–4, 11, 12), whereas others have implicated the impact of only heavier drinking (8, 14, 16). In various studies, younger women (5–7, 11) or older women (4, 15) seem to have displayed the association more strongly.

Investigating the alcohol breast cancer hypothesis is complicated because alcohol drinking may vary during a woman's adult lifetime. Many studies have measured intake in the time just before interview and have not taken into consideration the duration of drinking or the age at which subjects began to drink. The pattern of drinking during a woman's life may be relevant for several reasons: (*a*) there may be a latent period of alcohol's effect; (*b*) women who are classified as nondrinkers during interviews of recent diet may, in fact, be abstainers because of adverse effects of previous high alcohol intake; and (*c*) it is plausible that alcohol intake during adolescence is particularly important because this is a crucial period for breast development.

In this report, we present data on alcohol consumption and breast cancer risk from a case-control study nested in a screening project in Sweden. We have reported previously on the results based on current diet (23). The study offered the opportunity for information on current drinking habits to be gathered before cancer diagnosis in a large group of women with a more detailed examination of lifetime drinking patterns on a case-control basis.

Materials and Methods

This case-control study derives its cases and controls from a screening program instituted in 1987 in central Sweden. In Uppsala County (Sweden), all women ages 40–70 years were invited to receive mammography, as were all women ages 40–74 years in Västmanland county (Sweden). The invitation was mailed to eligible women, along with a food frequency questionnaire. Eighty-seven % of the women who received the invitation accepted and were screened at least once. This analysis focuses on subjects screened from March 1987 through December 1990.

Cases were members of the cohort, in whom invasive breast cancer had been diagnosed subsequently, either at the first screening, at a subsequent screen, or independently of the mammography program. Cases were identified through surveillance of pathology laboratories in the two counties and through computerized registers of cancer diagnoses at the screening centers.

Controls were members of the cohort, *i.e.*, they had completed the questionnaire and participated in the first screening round, who were found to be free of breast cancer and who did not develop breast cancer during the study period. To recruit approximately the same number of cases and controls, our monthly target sample size for controls in each county equaled the number of breast cancer cases expected in the screened population, based on the number of breast cancer diagnosis rates in the Swedish two-county mammography trial. Consequently, controls were frequency matched on the month of diagnosis, a 5-year age group, and county of residence.

In the self-administered dietary questionnaire filled out before the first screening, women were asked to report their

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usual intake of 60 foods during the most recent 6 months. For each food or beverage item, the women could choose from eight response categories: never/seldom, 1–3 times/month, once/week, 2–3 times/week, 4–6 times/week, 1 time/day, 2–3 times/day, or ≥ 4 times/day. (No information about portion sizes was obtained.) For intake of alcoholic beverages the same response categories were used. The questionnaire also requested information about age, marital status, education, parity, family history of breast cancer, weight, and height.

Women identified as cases or controls received information about the study and a request for a follow-up telephone interview. These contacts occurred about 6 months after screening for the controls or cancer diagnosis for the cases. Each interview began by identifying distinct "dietary periods," defined as time intervals during which she had more or less constant eating habits. Dietary periods usually began with life events such as marriage or childbirth or with a change toward a more "healthy" diet. The interview questions were arranged according to the woman's meal pattern and proceeded from the earliest identified dietary period to the latest (the 6-month period before breast cancer screening).

The answers were reported as absolute frequencies and were then converted into frequencies/month. The daily nutrient intake was calculated from the database at the Swedish National Food Administration (Uppsala, Sweden), including estimates of women's portion sizes and the nutrient composition of the foods in the questionnaire. For each dietary period, the woman was asked about consumption frequencies of each of the 60 foods and beverages in the questionnaire.

ORs[2] were used as the measure of association (22). These ratios and their 95% CIs were computed by using logistic regression in the statistical package, SAS (Cary, NC). All models included county of residence, month of diagnosis, and age to conform to the study design. The potential importance of a latent period of effect was investigated descriptively by using the method proposed by Goldsmith (24). This computes the OR of being exposed to drinking alcohol during successive periods of time before diagnosis. In a similar vein, we also computed the relative risks for breast cancer at any age (40–75 years) associated with drinking at various chronological ages. Unfortunately, the relative risks generated by these analyses are highly correlated; we are unaware of any method that can be used to test the statistical significance of any trends observed.

Results

A total of 380 cases and 525 controls were identified in the study cohort, and responses were obtained from 276 (73%) cases and 452 (86%) controls. The cases were comparable to controls with respect to age at screening, education, number of children, and body mass index (Table 1); cases had a family history of breast cancer almost twice as often as controls. As a consequence of the age limits applied in the screening program, only 54 cases were 50 years old or younger at the time of screening.

Ever use of alcohol was not associated with breast cancer risk among women under 50 years (unadjusted OR = 0.8; 95% CI = 0.4–1.8; Table 2). There was no suggestion that long duration of drinking, early age at start of drinking, or recent drinking conferred any measurable increase in risk. Indeed, women who had the heaviest or longest-term intake had a modest (and nonsignificant) decrease in risk.

[2] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 1 Characteristics of cases and controls

	Cases	Controls
	n (%)	*n* (%)
Identified	380	525
Agreed to interview	276	452
Age (yr)		
40–49	48 (17)	85 (19)
50–59	88 (32)	108 (24)
60–74	140 (51)	259 (57)
Education		
<9 yr primary school	225 (82)	355 (78)
>9 yr of education	45 (16)	89 (20)
unknown	6 (2)	8 (2)
No. of children		
0	35 (13)	43 (10)
1	69 (25)	98 (22)
2	91 (33)	165 (36)
>3	81 (29)	146 (32)
Body mass index (kg/m^2)		
>23.0	64 (23)	120 (26)
23.0–24.9	72 (26)	111 (25)
25.0–27.4	68 (25)	109 (24)
>27.5	65 (24)	103 (23)
Unknown	7 (2)	9 (2)
% with family history of breast cancer	31 (11)	29 (6)

Among women 50 years old or older (postmenopausal women), ever-drinkers displayed a modest increase in risk, with an unadjusted OR of 1.8 (95% CI = 1.2–2.6). Early age of first drinking had no apparent impact, but long-term drinking increased risk slightly more than short-term drinking did. Drinking >0.75 g/day increased risk for breast cancer. Current and former drinkers had similar increases in risk. Although the CIs for the older women in general did not include the point estimates for the younger group (and *vice versa*), the interaction term between age group and the alcohol variables was not statistically significant ($P = 0.72$)

The results presented in Table 2 were also analyzed in basic models where only the stratification variables of the study were accounted for. The results were very similar to the fully adjusted models. In addition, age at first use, duration of use, and currency of use were analyzed and fully adjusted for the mean alcohol dose for the overall period. The results changed very little from data shown in Table 2, and the overall pattern was the same as in the models not adjusted for dose (data not shown).

The plot of ORs for breast cancer by age at first use of alcohol does not suggest a particular "peak" latent period up to 35 years before diagnosis (Fig. 1). The variability associated with drinking for >35 years before diagnosis precludes any conclusions regarding such very long-term latent periods. The mean alcohol intake of cases and controls showed a similar pattern, a modest excess among cases, with no particular temporal pattern (data not shown).

The ORs for breast cancer by age at first use of alcohol show an increase with age, suggesting that beginning to drink at later ages may have a larger impact than beginning to drink at younger ages (Fig. 2).

Table 2 Odds ratios (with 95% confidence intervals) for breast cancer, by age group and alcohol use. Number of cases and controls given in each category

	≤ 50 yr (54 cases/97 controls)		>50 yr (222 cases/355 controls)		All (276 cases/452 controls)
	Adjusted[a]	Cases/controls	Adjusted[a]	Cases/controls	Adjusted[a]
Alcohol use					
Never	1.0	15/23	1.0	56/132	1.0
Ever	0.8 (0.4–1.9)	39/74	1.9 (1.2–2.7)	166/223	1.7 (0.2–2.4)
Age at first use					
Never	1.0	15/23	1.0	56/132	1.0
≥28 yr	0.8 (0.2–2.1)	24/37	1.8 (1.2–2.7)	117/151	1.4 (0.9–2.1)
15–27 yr	0.5 (0.2–1.3)	15/37	1.7 (1.0–2.7)	49/72	1.6 (1.1–2.4)
Duration of use					
Never	1.0	15/23	1.0	56/132	1.0
≤10 yr	0.6 (0.2–1.6)	12/29	1.5 (0.9–2.5)	42/64	1.3 (0.8–2.0)
11–20 yr	1.0 (0.3–2.4)	19/28	1.8 (1.1–3.0)	44/59	1.5 (1.0–2.4)
≥21 yr	0.4 (0.1–1.5)	8/17	1.9 (1.2–3.0)	80/100	1.8 (1.2–2.7)
Currency of use					
Never	1.0	15/23	1.0	56/132	1.0
Stopped (>2 yr)	0.3 (0.1–1.0)	3/9	1.6 (1.0–2.6)	20/38	1.7 (1.2–2.4)
Current	0.9 (0.4–2.1)	36/65	1.8 (1.2–2.8)	146/185	1.3 (0.9–2.0)
Mean alcohol dose					
Never	1.0	15/23	1.0	56/132	1.0
≤0.75 g/day	0.4 (0.1–1.5)	6/17	1.4 (0.9–2.3)	48/85	1.2 (0.8–1.8)
0.76–2 g/day	0.7 (0.3–1.8)	15/26	2.1 (1.3–3.4)	64/68	1.9 (1.2–2.9)
≥2 g/day	0.8 (0.4–1.4)	18/31	1.8 (1.1–2.9)	54/70	1.6 (1.0–2.4)

[a] In "adjusted models" the following co-variates are included: family history of breast cancer, parity, age at first birth, educational level, and body mass index.

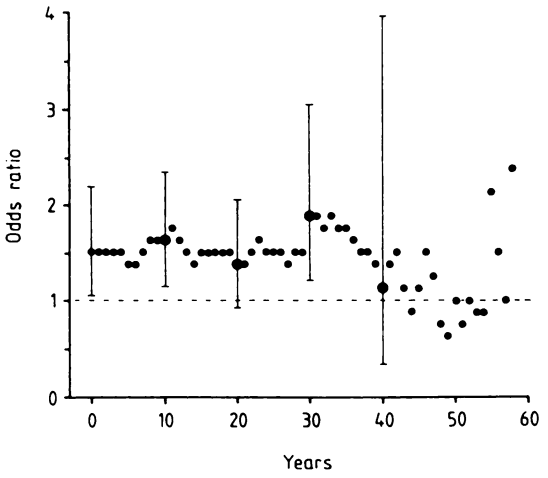

Fig. 1. ORs for breast cancer risk in ever-users of alcohol *versus* never-users plotted against duration in years of use before diagnosis. Every fifth year is marked with a larger point, and 95% CIs are given.

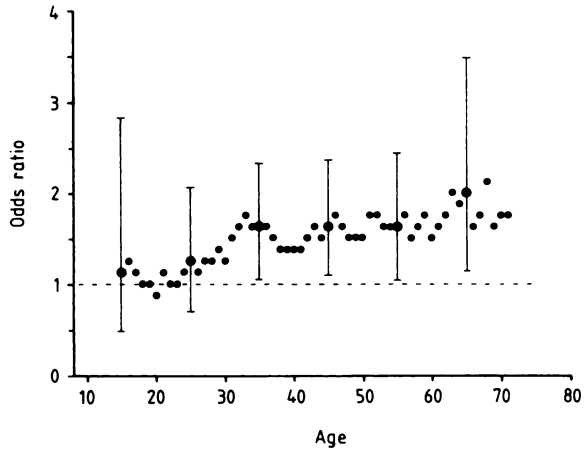

Fig. 2. ORs for breast cancer risk in ever-users of alcohol *versus* never-users plotted against age (years) of first use. Every fifth year is marked with a larger point, and 95% CIs are given.

Discussion

In this population-based case-control study, alcohol intake had a modest association with breast cancer risk among women over 50 years old but not among women under 50 years (although interpretation in the latter is hampered by the small number of subjects). Even among the older women, no strong patterns were evident in the relative risks for drinking at various time periods before the interview. In particular, drinking early in life did not increase risk.

Our study has several strengths. No previous investigation has considered alcohol intake in a series of intervals before diagnosis as we have done. Moreover, in our study population the group of never-users was relatively large, especially among the older women. Alcohol use was low overall without large fluctuations of intake. Responses regarding recent alcohol intake before and after breast cancer diagnosis agreed, indicating that response bias was unlikely. Both cases and controls had 55–60% of agreement between questionnaire and interview data with regard to classification in quartile of intake, corresponding to a κ value of 0.41. Although we could not investi-

gate, in a similar manner, the reliability of lifetime alcohol consumption patterns, these findings make response bias extremely unlikely.

Although retrospective recall of alcohol intake seems to be more accurate than the other aspects of diet (25, 26), it is still likely that we measured alcohol intake at each period of life with some imprecision. Because differential measurement error is unlikely, imprecise recall will almost certainly minimize our risk estimates. However, the imprecision may be greater at some periods of life than at others, resulting in different degrees of bias in different periods (27).

Unfortunately, we did not collect information regarding some other exposures of potential interest, such as lactation history and menopausal hormone use; thus, we cannot address how these factors may have affected our findings. The small number of women under 50 years old also, as noted above, limits our ability to draw conclusions about effects in that age group. In the case-control set as a whole, the drinkers who drink anything more than occasional beers and glasses of wine were few. Thus, we also lack power to do meaningful analyses on the type of beverage. In a detailed analysis of current diet, we explored differences by the type of alcoholic drinks but could not see any differences in risk.

The epidemiological literature regarding alcohol intake and breast cancer risk remains confusing, despite the considerable amount of published research. Some doubt exists if alcohol intake affects breast cancer risk at all; some studies have reported no relationship of alcohol intake to risk (1, 18–21), although most have found a modest relationship, typically without dose-response relationships over duration or amount consumed (1, 2–17). Even among studies that have found an increase in risk, the level of alcohol intake required for a measurable effect has varied from relatively little to very heavy drinking (1). Relatively little data are available regarding the impact of drinking at different ages. In some studies, no differences have been found (3). In other studies, drinking early in life (6, 10, 15) has been described as particularly important. Other data (9), including ours, suggest that drinking later in life carries a larger risk. In various studies, the effect of alcohol has been strongest among younger women (5–7, 11, 17). But in other studies (such as ours), the effect of alcohol had been stronger among older women (4, 15). Thus, although the association between alcohol intake and breast cancer risk seems modest, it is not clear whether the association is causal. If the effect is causal, it most likely represents a rather weak promoting effect (28).

This can mean two distinct things: (*a*) that the result among older women is a chance effect; or (*b*) that the results in both age groups do not differ. The lack of association in women under age 50 years is, however, in line with the findings in a large case-control study of 422 cases in women ages 40–49 years (21). An effect limited to the older women could also be explained by differences in the social implications of drinking between older and younger women. Most women over 50 years old in our study were young adults in the 1930s and 1940s, whereas those under age 50 years all grew up in the 1950s or later. In Sweden, drinking patterns probably differed in the two periods because of the liberalization of social practices in the decade after the second World War. Therefore, the characteristics of drinkers in the two age groups may well be different, a contrast which could lead to differences in breast cancer risk.

A concise biological theory of how alcohol intake might influence breast cancer risk is still lacking. Alcohol influences metabolism in the liver, the adrenals, and in adipose tissue, all organs involved in steriod metabolism. In several studies of postmenopausal women (29–32), both moderate and heavy alcohol consumption increased blood levels of estradiol and estrone, but other studies have contradicted these findings. In premenopausal women, the picture is even less clear (33–36). Blood levels of androstenedione also vary with alcohol consumption (37). Alcohol might enhance luteinizing hormone production and inhibit follicle-stimulating hormone secretion (35, 38). However, building theories about mechanisms of action is still considerably difficult because the relationship between plasma hormonal levels and breast cancer risk is far from clear. Moreover, most of these studies have used persons or laboratory animals with much heavier exposure to alcohol than most epidemiological studies do. Theoretically, however, the picture derived from our results is that alcohol may be a weak promoter. This fits well with the notion that the breast cancer-alcohol association is mediated via an effect of alcohol on the metabolism of sex hormones.

In summary, we find a modest association between alcohol intake and breast cancer risk. Drinking later in life may have a bigger impact than drinking earlier in life does. Whether this relationship is causal will require additional investigation.

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