Null Results in Brief

No Increased Risk of Breast Cancer Associated with Alcohol Consumption among Carriers of *BRCA1* and *BRCA2* Mutations Ages <50 Years

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Introduction

Epidemiologic studies have reported positive associations between alcohol consumption and risk of invasive breast cancer. Combined analyses suggest that breast cancer risk increases ~9% for every 10-gram increment (less than one drink) in daily alcohol consumption (1-3). A recent analysis of pooled data from 53 studies concluded that ~4% of breast cancers in developed countries may be attributable to alcohol consumption (4).

There have been some inconsistencies in both direction and strength of the observed associations, particularly in studies showing an inverse relation (see ref. 5 for example), which could reflect interstudy variability in the prevalence of factors that modify the relation between alcohol and breast cancer risk. No meaningful risk differences have been seen by menopausal status (1, 2, 6, 7) or family history (3, 8, 9). Carrying a deleterious germ-line mutation in the *BRCA1* or *BRCA2* genes could be a modifying factor. The effects of alcohol intake on breast cancer risk in women with these mutations are unknown, and we examined this issue in *BRCA1* and *BRCA2* mutation carriers ages <50 years at diagnosis or interview.

Materials and Methods

A detailed description of the study design and analytic methods is provided elsewhere.[16] Briefly, six research institutions in the United States, Canada, and Australia who were members of the Breast Cancer Family Registry (10) and from two additional sources, the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer in Australia (www.kconfab.org; ref. 11) and the Ontario Cancer Genetics Network in Canada, recruited female subjects. Study subjects were non-Hispanic white women with and without invasive breast cancer (hereafter called cases and controls, respectively) who completed the same risk factor questionnaire and who were determined to carry a deleterious mutation of *BRCA1* or *BRCA2*.

We assigned to each subject a reference date, defined for cases as the date of first diagnosis of invasive breast cancer and for controls as the date of the earliest of the following events: interview, bilateral mastectomy, bilateral oophorectomy, or diagnosis of *in situ* breast cancer. All sites collected biological samples and gathered risk factor data using epidemiologic questionnaires containing identical information. DNA was tested for *BRCA1* and *BRCA2* mutations either by full sequencing by Myriad Genetics or by one of several other methods that had been validated against full sequencing (12). We analyzed the data using unconditional logistic regression, stratified on family history of breast or ovarian cancer in first-degree relatives, restricted to women with reference age of <50 years, and who had been interviewed no later than 5 years after their reference dates. We computed the 95% confidence intervals (95% CI) for odds ratios (OR) using a robust variance estimator (13) to account for possible correlation in covariates among family members. To reduce the effects of outliers in trend tests for continuous variables, the variables were first categorized and then the reported values in each category were replaced by the median for that category. This study involved 195 cases and 302 controls with *BRCA1* mutations

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Table 1. Characteristics of non-Hispanic white *BRCA* mutation carriers with and without invasive breast cancer by mutation status

	BRCA1 mutation carriers		*BRCA2* mutation carriers	
	Cases* (*N* = 195)	Controls* (*N* = 302)	Cases* (*N* = 128)	Controls* (*N* = 179)
	n (%)	*n* (%)	*n* (%)	*n* (%)
Reference age (y)†				
<30	23 (12)	80 (27)	10 (8)	34 (19)
30-39	88 (45)	107 (35)	61 (48)	60 (34)
40-49	84 (43)	115 (38)	57 (44)	85 (47)
Year of birth				
1940-1949	16 (8)	30 (10)	16 (13)	34 (19)
1950-1959	103 (53)	87 (29)	61 (48)	53 (30)
1960-1969	65 (33)	98 (32)	49 (38)	56 (31)
1970+	11 (6)	87 (29)	2 (1)	36 (20)
Study site				
Australia	91 (47)	121 (40)	65 (51)	91 (51)
Canada	47 (24)	15 (5)	35 (27)	13 (7)
Utah	15 (8)	85 (28)	6 (5)	32 (18)
Other U.S. states	42 (21)	81 (27)	22 (17)	43 (24)
Ascertainment				
Clinic based	120 (62)	284 (94)	76 (59)	158 (88)
Population based	75 (38)	18 (6)	52 (41)	21 (12)
Family history‡	114 (58)	229 (76)	67 (52)	127 (71)
Number of full-term pregnancies				
0	49 (25)	102 (34)	27 (21)	37 (21)
1-2	99 (51)	114 (38)	64 (50)	82 (46)
>3	46 (24)	85 (28)	37 (29)	60 (33)
Ever smoker	93 (48)	97 (33)	68 (54)	61 (34)

*The totals for the different variables may not be equal to the total number of subjects in a category because of missing data.
†For cases, age at breast cancer diagnosis and, for controls, age at the earliest of these events: bilateral mastectomy, bilateral oophorectomy, diagnosis of *in situ* breast cancer, and interview.
‡Having first-degree relatives with breast cancer or ovarian cancer.

and 128 cases and 179 controls with *BRCA2* mutations. The institutional review boards at each site approved the study protocol.

Results

Table 1 shows selected characteristics for carriers of *BRCA1* or *BRCA2* mutations. Cases were older than controls, were more likely to be ascertained through clinic-based study centers, and were less likely than controls to have a family history for breast or ovarian cancer.

Table 2 shows ORs relating breast cancer risk to alcohol consumption, adjusted for age, study site, family history, smoking, and number of full-term pregnancies. Compared with never users of alcohol, ever users were not at increased risk for breast cancer regardless of whether they were *BRCA1* carriers (OR, 1.06; 95% CI, 0.73-1.52) or *BRCA2* carriers (OR, 0.66; 95% CI, 0.45-0.97). There was no evidence for a linear trend in risk with drink-years among *BRCA1* carriers ($P = 0.5$)

Table 2. Risk of invasive breast cancer among white non-Hispanic *BRCA1* and *BRCA2* mutation carriers according to alcohol consumption for women under 50 years of age by gene

Alcohol consumption	*BRCA1* mutation carriers			*BRCA2* mutation carriers		
	Cases* (*N* = 195)	Controls* (*N* = 302)	OR (95% CI)†	Cases* (*N* = 128)	Controls* (*N* = 179)	OR (95% CI)†
	n (%)	*n* (%)		*n* (%)	*n* (%)	
Ever use‡						
No	99 (51)	170 (58)	1.00	60 (47)	86 (48)	1.00
Yes	95 (49)	123 (42)	1.06 (0.73-1.52)	68 (53)	93 (52)	0.66 (0.45-0.97)
Current use‡						
No	126 (65)	203 (69)	1.00	78 (61)	125 (70)	1.00
Yes	68 (35)	90 (31)	0.96 (0.67-1.37)	50 (39)	54 (30)	1.11 (0.76-1.63)
Drink-years‡						
Nonusers	99 (54)	170 (60)	1.00	60 (49)	86 (52)	1.00
1-29	26 (14)	38 (13)	1.07 (0.64-1.76)	14 (11)	27 (16)	0.40 (0.21-0.74)
>29	57 (31)	76 (27)	0.93 (0.62-1.39)	49 (40)	51 (31)	0.89 (0.59-1.34)
Trend/ 10 drink-years			0.98 ($P = 0.5$)			1.02 ($P = 0.4$)
Intake/d (g)‡						
Nonusers	99 (53)	170 (58)	1.00	60 (47)	86 (49)	1.00
1-4	14 (7)	32 (11)	0.63 (0.34-1.18)	11 (9)	24 (14)	0.41 (0.22-0.77)
>4	75 (40)	91 (31)	1.14 (0.77-1.69)	55 (44)	66 (37)	0.79 (0.52-1.18)
Trend/10 g			1.02 ($P = 0.4$)			1.00 ($P = 0.9$)

*The totals for the different variables may not be equal to the total number of subjects in a category because of missing data.
†OR, odds ratio; CI, confidence interval.
‡Stratified on age (<40 years and >40-49 years) and study sites (Australia, Canada, Utah, other U.S. states) and adjusted for age (continuous), family history (number of first-degree relatives with breast or ovarian cancer), smoking (ever and never), and number of full-term pregnancies (continuous).

or *BRCA2* carriers ($P = 0.4$). Similarly, there was no evidence for a linear trend in risk with increasing rates of alcohol consumption, measured as grams daily ($P = 0.4$ and 0.9 for *BRCA1* and *BRCA2* carriers, respectively), although modest alcohol intake (<4 grams daily) was associated with a nominally significant decrease in breast cancer risk for *BRCA2* mutation carriers (OR, 0.41; 95% CI, 0.22-0.77). We observed no significant differences in risks by type of alcohol (beer, wine, or spirits; data not shown).

Discussion

The present data do not support a positive association between alcohol intake and breast cancer risk for women who carry a germ-line mutation of *BRCA1* or *BRCA2* but suggest a possible reduction in risk in *BRCA2* mutation carriers for modest alcohol intake. Several study limitations warrant consideration in interpreting these findings. We included only data from living affected carriers because of the difficulty of obtaining accurate histories of alcohol consumption from relatives of deceased patients. To minimize the potential for survival and recall bias, we restricted the analysis to carrier cases who were interviewed within 5 years of their breast cancer diagnosis (~85% of these women were interviewed within 3 years of diagnosis). We also duplicated major analyses for a subset of more recent cases and did not find substantial differences in the magnitudes of ORs. The study subjects were not a random sample of all mutation carriers specific for disease status but were recruited mainly from members of families with multiple cases of breast cancer and, in some instances, ovarian cancer. The association between alcohol and breast cancer risk in these carriers may not be the same as that among carriers in the general population.

These potential limitations must be balanced against the strengths of this study. These include the large numbers of premenopausal carriers available, the uniform way, in which lifestyle characteristics were ascertained using a common questionnaire, and the inclusion only of young women who carried deleterious mutations. These findings should be further investigated to clarify the relation, if any, between breast cancer risk and alcohol intake among genetically susceptible women.

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