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Brief Communications

Association of Daily Alcohol Intake, Volumetric Breast Density, and Breast Cancer Risk

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Abstract

High alcohol intake and breast density increase breast cancer (BC) risk, but their interrelationship is unknown. We examined whether volumetric density modifies and/or mediates the alcohol-BC association. BC cases (n = 2233) diagnosed from 2006 to 2013 in the San Francisco Bay area had screening mammograms 6 or more months before diagnosis; controls (n = 4562) were matched on age, mammogram date, race or ethnicity, facility, and mammography machine. Logistic regression was used to estimate alcohol-BC associations adjusted for age, body mass index, and menopause; interaction terms assessed modification. Percent mediation was quantified as the ratio of log (odds ratios [ORs]) from models with and without density measures. Alcohol consumption was associated with increased BC risk (2-sided $P_{trend} = .004$), as were volumetric percent density (OR = 1.45 per SD, 95% confidence interval [CI] = 1.36 to 1.56) and dense volume (OR = 1.30, 95% CI = 1.24 to 1.37). Breast density did not modify the alcohol-BC association (2-sided $P > .10$ for all). Dense volume mediated 25.0% (95% CI = 5.5% to 44.4%) of the alcohol-BC association (2-sided $P = .01$), suggesting alcohol may partially increase BC risk by increasing fibroglandular tissue.

Increased alcohol intake (1) and high breast density (2) are breast cancer (BC) risk factors, with 4%-10% and 15%-35% of BCs attributable to each, respectively (3,4). Alcohol specifically increases risk of estrogen receptor–positive tumors (5). Most analyses of alcohol and breast density (6-11) used area density measures, which may imprecisely quantify breast density relative to volumetric measures. Few studies examined the interrelationship between alcohol, breast density, and BC risk. In one of the largest studies to do so (3392 cases and 8882 controls), percent density, measured on film screen mammography, mediated 11%-27% of the association between BC risk factors and BC (12). Because alcohol was not associated with BC in that study, mediation analyses were not performed.

This nested case-control study examined whether breast density modifies and/or mediates the association between alcohol and BC, using volumetric breast density measures with full-field digital mammography. Four facilities within the San Francisco Mammography Registry contributed data. Cases were women diagnosed with BC during 2006-2013, ascertained from the population-based California Cancer Registry, with screening mammograms acquired 6 months or more before diagnosis. Controls without BC were matched to cases on age, earliest mammogram date, race or ethnicity, facility, and mammography machine. Questionnaires administered at the time of screening ascertained alcohol intake, body mass index (BMI), family history, parity, menopausal status, and hormone therapy. Alcohol intake was assessed by asking women to select the best answer to this question on the clinical questionnaire: "On average, about how many alcoholic drinks do you have per day? None; Less than 1 or 1 a day; About 2 a day; 3 or more a day." Breast density was categorized by radiologists using the Breast Imaging Reporting and Data System (BI-RADS): almost entirely

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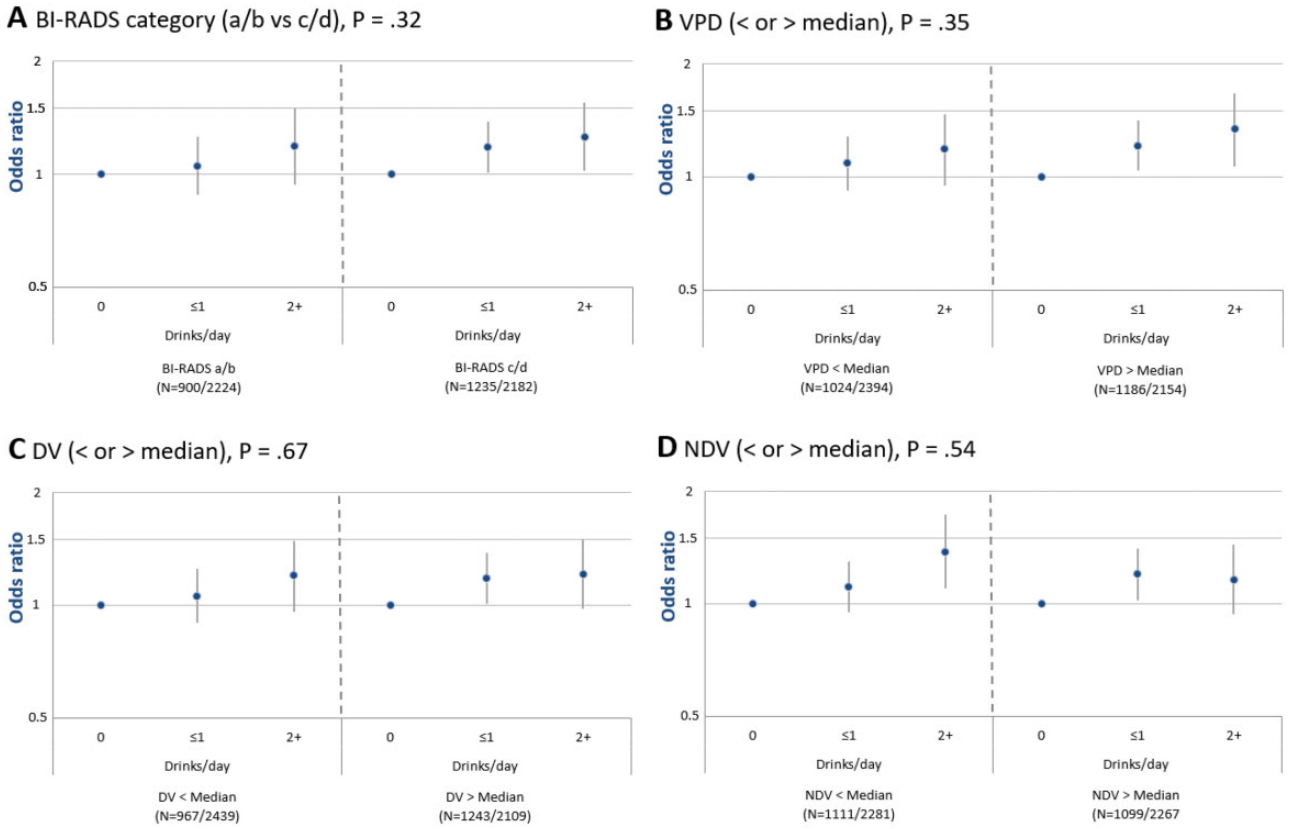

Figure 1. Association of alcohol (per drink per day) with breast cancer by Breast Imaging Reporting and Data System (BI-RADS) density and volumetric density measures for all women. Two-sided *P* values are listed for the interaction term of each density measure with alcohol . DV = dense volume; NDV = nondense volume; VPD = volumetric percent density.

fatty (category a), scattered areas of density (category b), heterogeneously dense (category c), or extremely dense (category d). Volpara commercial software was used to calculate volumetric percent density (VPD), absolute dense volume (DV), and nondense volume (NDV) as previously described (13). Participants provided passive permission for research. The University of California-San Francisco institutional review board approved the study, which was Health Insurance Portability and Accountability Act United Stated Preventive Services Task Force (HIPAA) compliant.

Logistic regression quantified the odds ratios (ORs) of alcohol and density measures with BC risk, adjusting for age, 1/BMI, and menopausal status. The alcohol-BC association was tested through an ordinal trend across the 3 categories (P_{trend}), with categories defined to categorize women into nondrinkers and those whose alcohol intake was in accordance with USPSTF guidelines of 1 or fewer drinks per day on average for women (14). Multiplicative interaction terms between alcohol categories and density measures (dichotomized at the median, or category c and d for BI-RADS) were added to test for modification by breast density. To quantify the percent of the alcohol-BC association mediated by density, we calculated the ratio of log (odds ratio) with and without adjustment for each density measure, assessed continuously (volumetric measures) or categorically (BI-RADS), with the SAS macro developed by Spiegelman and colleagues (15) (https://www.hsph.harvard.edu/donna-spiegelman/software/mediate). Analyses were repeated within prespecified subgroups by menopausal status. Analyses used SAS version 9.4. All *P* values were 2-sided. The cutoff for statistical significance was *P* less than .05. To calculate *P* values for mediation analysis, the standard error was estimated according to an equation by Lin (16), and the *P* value was calculated from the estimated standard error per our prior work (12).

Of 2572 cases and 5119 controls who met inclusion criteria, alcohol intake was available on 88%, leaving 2233 cases and 4562 controls in the analysis. Mammograms were obtained on average 3.1 (SD = 1.7) years before diagnosis for cases or matched date for controls. Cases were similar to controls in many demographic characteristics (Supplementary Table 1, available online), including menopausal status and BMI. Cases were more likely to have a family history of BC, be nulliparous, and take hormone therapy. More cases drank alcohol than controls (52% vs 49%). Cases had higher breast density as measured by BI-RADS (18% vs 12% for category d), VPD (median = 9.5% vs 8.4%), and DV (median = 58.0 vs 50.9 cm^3). NDV was similar between cases and controls (median = 556.7 vs 557.4 cm^3).

Alcohol intake was associated with BC for all women (OR = 1.22, 95% CI = 1.05 to 1.42 for ≥2 drinks per day vs none; 2-sided P_{trend} = .004) and when stratified by menopausal status (Supplementary Tables 2 and 3, available online). Breast density measured by BI-RADS, VPD (OR = 1.45 per SD, 95% CI = 1.36 to 1.56), and DV (OR = 1.30, 95% CI = 1.24 to 1.37) was associated with BC risk. NDV was associated with a modest reduction in BC risk, although not statistically significant (OR = 0.93, 95% CI = 0.86 to 1.01).

Table 1. Mediation of the association between alcoholic drinks per day[a] and BC by breast density, as measured by BI-RADS density, DV, VPD, and NDV, for all women, restricted cases with ER-positive cancers and their controls, and stratified by menopausal status[b]

Group	No. of cases/controls	OR (95% CI)	Mediated, % (95% CI)	*P*
All women				
Baseline OR	2210/4080	1.11 (1.04 to 1.20)	—	—
Adjusted for				
BI-RADS	2135/3953	1.10 (1.03 to 1.19)	8 (−8 to 25)	.31
VPD	2210/4080	1.14 (1.06 to 1.23)	Not mediated	N/A
DV	2210/4080	1.08 (1.01 to 1.17)	25 (6 to 44)	.01
NDV	2210/4080	1.13 (1.05 to 1.21)	Not mediated	N/A
All ER+ women				
Baseline OR	1404/2579	1.12 (1.03 to 1.23)	—	—
Adjusted for				
BI-RADS	1355/2499	1.11 (1.01 to 1.21)	12	.23
VPD	1404/2579	1.16 (1.06 to 1.27)	Not mediated	N/A
DV	1404/2579	1.10 (1.00 to 1.20)	22	.04
NDV	1404/2579	1.13 (1.03 to 1.24)	Not mediated	N/A
Premenopausal women				
Baseline OR	681/1200	1.12 (0.97 to 1.29)	—	—
Adjusted for				
BI-RADS	659/1163	1.12 (0.97 to 1.29)	Not mediated	N/A
VPD	681/1200	1.16 (1.01 to 1.34)	Not mediated	N/A
DV	681/1200	1.07 (0.93 to 1.24)	36 (−15 to 88)	.17
NDV	681/1200	1.12 (0.97 to 1.29)	Not mediated	N/A
Postmenopausal women				
Baseline OR	1414/2603	1.12 (1.03 to 1.23)	—	—
Adjusted for				
BI-RADS	1365/2525	1.11 (1.01 to 1.21)	12 (−7 to 31)	.21
VPD	1414/2603	1.14 (1.04 to 1.25)	Not mediated	N/A
DV	1414/2603	1.10 (1.01 to 1.20)	19 (2 to 36)	.03
NDV	1414/2603	1.13 (1.04 to 1.24)	Not mediated	N/A

[a]Alcohol was assessed by asking women to select the best answer choice to this question on the clinical questionnaire: "On average, about how many alcoholic drinks do you have per day? None; Less than 1 or 1 a day; About 2 a day; 3 or more a day." For the analysis, the 2 highest categories were combined. BC = breast cancer; BI-RADS = Breast Imaging Reporting and Data System; BMI = body mass index; CI = confidence interval; DV = dense volume; ER = estrogen receptor; NDV = nondense volume; OR = odds ratio; VPD = volumetric percent density.

[b]Baseline odds ratios adjusted for age and 1/BMI. Adjusted odds ratios additionally include the variable named in each row. Percent mediation is not possible to report for analyses in which the fully adjusted odds ratio is greater than the odds ratio without the mediation variable.

Breast density did not modify the alcohol-BC relationship; odds ratios by alcohol intake were similar across BI-RADS categories and below or above median VPD, DV, and NDV (Figure 1; $P > .10$ for all).

In mediation analyses, DV explained 25.0% (95% CI = 5.5% to 44.4%) of the association between alcohol intake and BC ($P = .01$), a finding that persisted among postmenopausal but not premenopausal women. Restricted to ER+ cases and their controls, DV remained a statistically significant mediator (22%; $P = .04$). BI-RADS category did not mediate the association between alcohol and BC risk (8%; $P = .31$). There was no evidence of mediation by VPD or NDV (Table 1).

In this study, we found DV mediated 25% of the association between alcohol intake and BC risk, suggesting that DV may lie on the causal pathway between alcohol consumption and increased BC risk. The magnitude of this mediation is consistent with those observed for other BC risk factors (12). Together, these findings suggest that identified BC risk factors may act in part through a common pathway, that is, breast density, in particular for ER+ tumors, which are known to be more strongly associated with alcohol intake (5). Our study found that NDV was similar between cases and controls in contrast with other area-based studies that suggest that alcohol increases BC risk via reduction in nondense tissue (8,10), albeit using measures of area not volume. If replicated, the lack of mediation by NDV or VPD observed here may imply that alcohol influences fibroglandular rather than fatty breast tissue. This is biologically plausible, because alcohol's proestrogenic effects (6) may induce proliferation of mammary cells (17). However, further studies of the mediation of alcohol and BC by volumetric measures are necessary, in particular investigations by menopausal status.

This study is one of the largest to date to evaluate the interrelationship between alcohol, breast density, and BC, and the only one to our knowledge that uses volumetric density measures. DV may more accurately and precisely approximate true breast density, thus increasing the precision of associations. Finally, this study included a relatively ethnically diverse cohort, and therefore its results may be more generalizable than studies with racially homogenous cohorts (8) or those in which race or ethnicity was not reported (10,12), although women in the study were more likely to be White and were younger compared with all women diagnosed with BC in the state of California (18).

Paralleling other studies (6,10,12), we assessed alcohol intake and mammographic density cross-sectionally on average 3 years before cancer diagnosis. However, prior research that quantified alcohol intake before breast density showed a

statistically significant association (8), a relationship that is biologically plausible, as detailed above.

These data suggest that alcohol may influence BC risk in part via its effect on breast composition, as measured by DV. Notification laws (19) have increased public awareness of breast density and factors that modify it. Based on this study, future research is needed to quantify the extent to which limiting alcohol intake might alter breast density and possibly reduce BC risk.

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Data Availability

Data available upon request to the corresponding author.

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