

Association of daily alcohol intake, volumetric density and breast cancer risk

Vachon CM¹, Scott CG¹, Winham S¹, Shepherd JA², Brandt KR¹, Norman, A¹, Jensen M¹, Hruska C¹, Heine J³, Pankratz VS⁴, Kerlikowske K⁵

¹Mayo Clinic, Rochester, MN; ²University of Hawaii, Honolulu, HI; ³Moffitt Cancer Center, Tampa, FL; ⁴University of New Mexico Health Sciences Center, Albuquerque, NM .

⁵University of California at San Francisco, San Francisco, CA.

Background

- Alcohol intake and breast density are two established risk factors for breast cancer.
 - 4-10% of breast cancers estimated to be attributable to alcohol intake.
- A few studies have examined the association between alcohol, breast density and breast cancer. These suggest:
 - Breast density may be on the causal pathway between alcohol and breast cancer.
 - Alcohol may be more strongly related with breast cancer among women with dense breasts or with higher background risk.
- More recent volumetric measures of breast density are robust breast cancer risk factors.
- Mechanism through which alcohol influences breast cancer is not clear but hypothesized to be due to:
 - Increased circulating estrogen levels
 - Carcinogenic role of ethanol metabolites (i.e. acetaldehyde).
- A better understanding of how alcohol consumption increases breast cancer risk is crucial for developing breast cancer prevention strategies.

Objective

To evaluate the interrelationship of alcohol, volumetric breast density and breast cancer risk. Specifically, we examined:

- Whether alcohol is a differential risk factor in women with dense vs. non-dense breasts.
- Whether breast density is on the causal pathway between alcohol intake and breast cancer.

Materials and Methods

Study Design: Nested case-control study within the San Francisco Mammography Registry (4 screening centers)

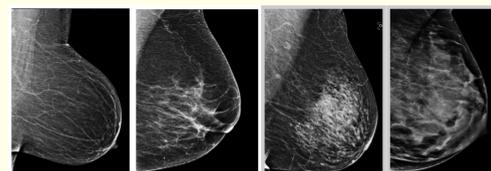
- Cases:** 2572 women diagnosed with breast cancer who had screening mammograms performed at least six months prior to diagnosis. Identified from linkage to CA state cancer registry.
- Controls:** 5119 women without breast cancer matched to cases on age, date of earliest mammogram, race/ethnicity, facility, and mammography machine.

Daily alcohol intake

- Assessed from clinical form at screening mammogram
- None, one or less, two or more drinks per day
 - Available on 88% of cases and controls
 - n=2233 cases, 4562 matched controls

Mammographic density measures

- 4-category clinical BI-RADS density measure (a-d)
 - Almost entirely fatty (a), Scattered areas of density (b), Heterogeneously dense (c), Extremely dense (d)
 - BI-RADS c and d categories define dense breasts
- Digital mammograms (raw-format) obtained at least 6 months prior to diagnosis
 - 3.1 years prior to cancer on average
- Volpara™ commercial software to assess volumetric density
 - Volumetric percent density, absolute dense and non-dense volume



Fatty → Dense

Statistical Methods

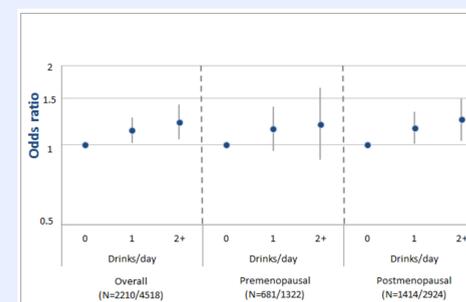
- Volumetric density measures were log-transformed
- Examined the associations of daily alcohol intake and volumetric density phenotypes (per 1 SD of log-transformed measures) with breast cancer risk using logistic regression
 - Odds ratios, OR; 95% confidence intervals, CI; and trend tests)
- Assessed deviation from multiplicative interaction using chi-squared tests
- Estimated mediation of the alcohol and breast cancer association by volumetric density measures
 - Logistic regression estimated association between alcohol use and breast cancer with and without adjustment for density measures.
 - Percent mediation estimated using the differences in the log OR estimates from the two models
- Models were adjusted for age, 1/BMI and menopause (all women)
- Analyses were stratified by menopausal status

Results

Table 1. Study characteristics of cases and matched controls.

	Cases (N=2233)	Controls (N=4562)
Mean age (SD)	57.2 (11.5)	57.1 (11.5)
Menopausal Status		
Pre	684 (30.6%)	1326 (29.1%)
Post	1434 (64.2%)	2934 (64.3%)
Unknown	115 (5.2%)	302 (6.6%)
Mean BMI (SD)	25.3 (5.3)	24.9 (5.1)
Daily alcohol intake (drinks)		
0	1069 (47.9%)	2328 (51.0%)
1	834 (37.3%)	1634 (35.8%)
2+	330 (14.8%)	600 (13.2%)
BI-RADS density		
a	183 (8.2%)	573 (12.6%)
b	731 (32.7%)	1658 (36.3%)
c	863 (38.6%)	1666 (36.5%)
d	379 (17.0%)	523 (11.5%)
Missing	77 (3.4%)	142 (3.1%)
Volumetric Percent Density (%)		
Median (Q1, Q3)	9.5 (5.8, 15.5)	8.4 (5.2, 14.0)
Dense Volume (cm ³)		
Median (Q1, Q3)	58 (41.0, 83.2)	50.9 (36.5, 72.5)
Non-Dense Volume (cm ³)		
Median (Q1, Q3)	556.7 (337.8, 926.2)	557.4 (331.9, 883.4)

Figure 1. Association of daily alcohol intake and breast cancer.



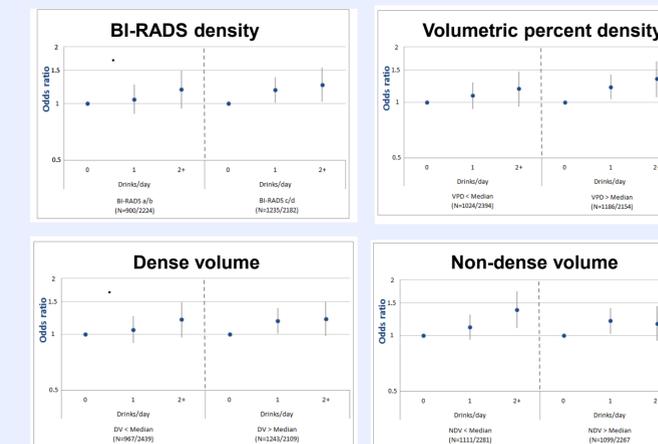
- Positive association for daily alcohol intake and breast cancer among all women and by menopausal status.

Table 2. Association (odds ratios, 95% CI)* of breast density measures with breast cancer risk.

	All women	Premenopausal	Postmenopausal
BI-RADS density (c/d vs. a/b)	1.64 (1.46, 1.84)	1.98 (1.56, 2.51)	1.51 (1.31, 1.74)
Volumetric percent density (per SD)	1.45 (1.36, 1.56)	1.54 (1.36, 1.73)	1.39 (1.26, 1.52)
Dense Volume (per SD)	1.30 (1.24, 1.37)	1.40 (1.28, 1.52)	1.25 (1.16, 1.34)
Non-Dense Volume (per SD)	0.93 (0.86, 1.01)	0.99 (0.85, 1.16)	0.92 (0.84, 1.02)

*Adjusted for age, 1/BMI and menopausal status (for all women)

Figure 2. Association of alcohol (per drink) with breast cancer by BI-RADS density and volumetric density measures. All women.



- No evidence of an interaction of alcohol and breast density measures on BC.
- Similar findings among pre and post-menopausal women (not shown).

Table 3. Mediation of alcohol and breast cancer association by dense volume (DV).

	OR (95% CI) Per drink	OR (95% CI) Per drink Adjusted for DV	Percent mediated	P-value
All women	1.11 (1.04, 1.20)	1.08 (1.01, 1.17)	25%	0.01
Premenopausal	1.12 (0.97, 1.29)	1.07 (0.93, 1.24)	36%	0.17
Postmenopausal	1.12 (1.03, 1.23)	1.10 (1.01, 1.20)	19%	0.03

- Evidence for mediation of the alcohol and breast cancer association by dense volume among all women and postmenopausal women.
- No evidence for mediation by other volumetric density measures.

Summary

- Alcohol and breast cancer association was similar among women with dense and non-dense breasts (Figure 2).
- Mediation of alcohol and breast cancer association by dense volume suggests that alcohol partially influences breast cancer risk through changes in breast tissue composition (Table 3).
 - Lack of evidence for mediation by non-dense volume or volumetric percent density implies these changes results from fibroglandular and not fatty tissue.