Research Article

Cancer Epidemiology, Biomarkers & Prevention

The Association between Alcohol Consumption and Breast Density: A Systematic Review and Meta-analysis

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Abstract

Background: Percent breast density (PBD) is a strong risk factor for breast cancer that is influenced by several other risk factors for the disease. Alcohol consumption is associated with an increased risk of breast cancer with an uncertain association with PBD. We have carried out a systematic review and meta-analysis to examine the association of alcohol consumption with PBD.

Methods: We searched nine databases to identify all relevant studies on the association between alcohol intake and breast density. Two independent investigators evaluated and selected 20 studies that were included in our analyses. We divided the studies into three groups according to the methods used to measure and analyze the association of breast density with alcohol consumption.

Results: Meta-analysis of the 11 studies that used quantitative methods to measure and analyze PBD as a continuous variable found a statistically significant difference in PBD when comparing the highest with the lowest alcohol level [$\beta = 0.84$; 95% confidence interval (CI), 0.12–1.56]. Three studies that used quantitative methods to measure PBD and categories of PBD for analysis had a summary OR = 1.81 (95% CI, 1.07–3.04). Five studies that used categories to classify PBD and analyze their association with alcohol intake had a summary OR = 1.78 (95% CI, 0.90–3.51).

Conclusions: These results suggest that there is a positive association between alcohol intake and PBD.

Impact: Alcohol may increase the risk of breast cancer associated with PBD. *Cancer Epidemiol Biomarkers Prev; 26(2); 170–8. ©2016 AACR.*

Introduction

Breast density (BD) refers to X-ray–attenuating breast tissue that appears white on a mammogram and reflects fibroglandular tissue in the breast (1). The percentage of the mammogram occupied by dense breast tissue [percentage of mammographic density (PMD)] is one of the strongest known risk factors for breast cancer. A meta-analysis by McCormack and dos Santos Silva of 42 studies with a total of more than 14,000 cases and 226,000 controls showed that greater PMD, classified by several methods, was consistently associated with an increased risk of breast cancer and that the increased risk could not be explained by the "masking" of cancers by radiologically dense breast tissue (2). In contrast to most other risk factors for breast cancer, PMD can change. Average PMD decreases with increasing age (3), is inversely associated with weight (4), decreases at menopause (5), and is increased by postmenopausal combined hormone therapy (6).

Although the clinical significance of change in PMD is at present uncertain, change in PMD may be an indicator of change in the risk of breast cancer. Alcohol is known to be associated with the risk of breast cancer, especially estrogen receptor–positive (ER^+) cancers (7–12). Risk of breast cancer has been estimated to increase by 2% to 12% for every 10 g per day increase in alcohol consumed in both pre- and postmenopausal women (9–13).

The association of alcohol consumption with BD has been previously studied; however, the results of previous studies are viewed as inconsistent (8, 14). To address this inconsistency, we have carried out a systematic review and meta-analysis of the published literature on the association of alcohol intake with BD.

Materials and Methods

Literature search and selection of studies for inclusion

We carried out our search according to a predetermined research protocol based on the PRISMA 2015 checklist (15). To assess the association of alcohol intake and BD, we searched the following nine databases: PubMed (1976–November 2015], the Cochrane Database of Systematic Reviews (2005–May 2015), the Cochrane Central Register of Controlled Trials (May 2015), Embase (1947–2015 May 28), CINAHL (from EBSCOhost), PsychINFO (1806–May week 4, 2015), MEDLINE (1946–May week 4, 2015), MEDLINE In-Process & Other Non-Indexed Citations (May 29, 2015), and the University of Toronto Library database. We used the following search terms on all databases:

Campbell Family Institute for Breast Cancer Research, Princess Margaret Comprehensive Cancer Centre, Toronto, Ontario, Canada.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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"mammographic breast density" OR "mammographic density" OR "mammary density" OR "breast density" OR "mammographic parenchyma" OR "mammary parenchyma" OR "breast parenchyma" OR "mammographic parenchymal patterns" OR "mammary parenchymal patterns" OR "breast parenchymal patterns" OR "mammographic epithelial cell proliferation" OR "mammary epithelial cell proliferation" OR "breast epithelial cell proliferation." All literature search was performed as an advanced search. In addition, a librarian literature search was also performed on MEDLINE (1946–May week 5, 2015), the Cochrane Database of Systematic Reviews (2005–May 2015), the Cochrane Central Register of Controlled Trials (May 2015), MEDLINE In-Process & Other Non-Indexed Citations (June 12, 2015), Embase (1974–2015 June 16), and CINAHL (from EBSCOhost). The librarian provided individual search strategies for each database. We implemented manual searches on review articles for other relevant studies. We completed the last search on November 30, 2015.

Figure 1 illustrates article selection. The search was limited to full-text articles on female participants. Prospective and retrospective cross-sectional and case–control studies were included in the study. Review articles were initially hand-searched to find other eligible articles but were excluded from the final analysis. We identified 8,593 potential articles in the literature search of databases and found one more article through hand searching of relevant review articles. We considered all languages in the literature search to exclude any language selection bias. Articles were first assessed for relevance based on title associated with lifestyle and diet and breast density during the database searches, and then by abstract and full text to find articles about alcohol intake and breast density. We screened 8,594 articles, searching for titles relating to diet or lifestyle; however, we excluded 8,428 based on irrelevant titles, leaving 166 articles for assessment of eligibility. After screening the 166 articles based on the relevancy of their abstract and full text for alcohol, 143 articles were off topic, two articles did not contain full text, and one was a duplicate, leaving 20 articles to be included in analyses.

Quality assessment

Two reviewers (S. Ziembicki and E. Tse) independently performed the data extraction and quality appraisal of articles. We assessed the quality of included studies according to the STROBE Statement Checklist, (16) a validated 22-point checklist for observational studies. Although the checklist has 22 headings to assess quality, many of the headings subdivided into other checklist points. Therefore, there was a different maximum score for the two different designs of observational studies: 32 points for case–control studies and 31 points for cross-sectional studies. Discrepancies with studies were resolved through in-person discussion between the two reviewers. The mean quality score was 27.2 for case–control studies and 25.73 for cross-sectional studies.

Extraction of data

The following data were collected from the studies: year of publication, number of subjects, number of pre- or postmenopausal subjects (if separated in the study), design, measure of nutrient intake questionnaire, method used to measure percent

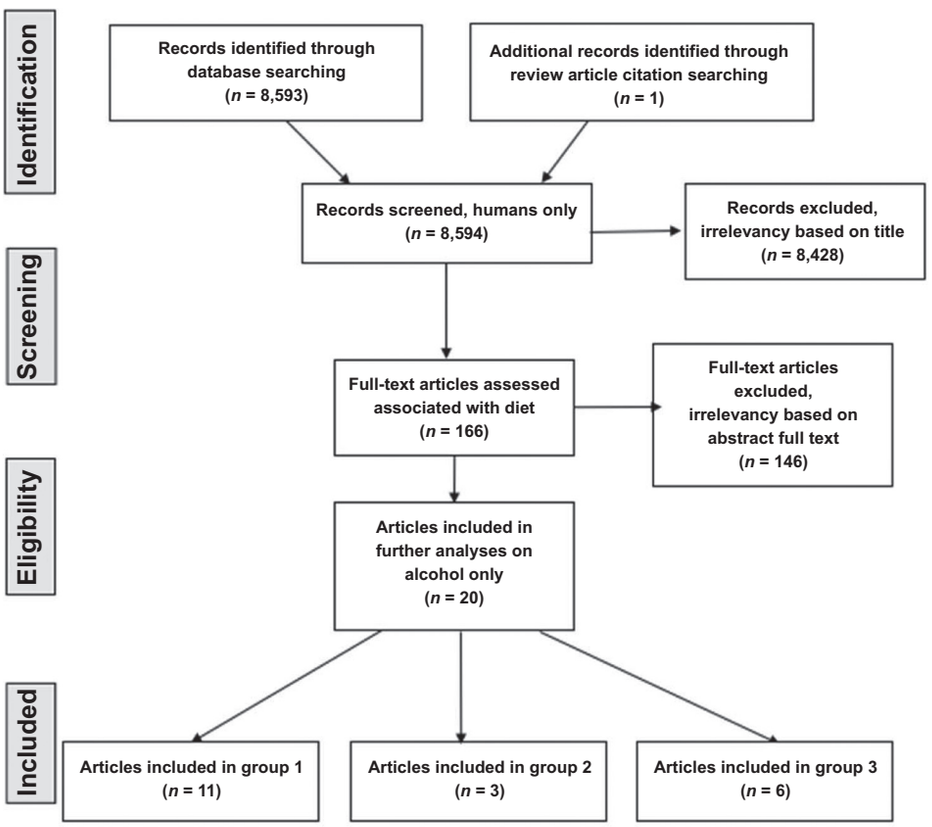

Figure 1.
Flow diagram of article selection. The figure outlines the selection of included articles. It is adapted from the PRISMA 2009 Flow Diagram.

breast density (PBD), measurement of association, and confounders included in adjustment. We extracted data on differences in PBD associated with the highest and lowest categories of alcohol consumption from tables and from the in-text results of the included studies, selecting the most adjusted measure of association.

Statistical analysis

We extracted measures of association to combine the included studies quantitatively in a meta-analysis. Studies interpreted their results in terms of regression coefficients, adjusted means, or adjusted ORs. We converted the measures of association into regression coefficients (β coefficients) with their respective 95% confidence intervals (CI) according to equations described as follows.

The value of β coefficients was calculated by subtracting the lowest adjusted mean from the highest adjusted mean. All studies in groups 1 and 2 adjusted coefficients for body mass index (BMI) or weight, and only two studies, both in group 3, did not adjust for BMI or weight (33, 36).

The SE in both the lowest and the highest adjusted mean interval was calculated by the equation: $SD_i = [(\text{upper bound}_i - \text{lower bound}_i)/1.96] \times 2$ ($i = 1, 2$). We assumed that the lowest and highest adjusted means were independent, and the SE of their difference was calculated by the equation $SD_\beta = \sqrt{(SD_1{}^2 + SD_2{}^2)}$. 95% CIs for β coefficients were then finally determined by $\beta \pm 1.96 \times SD$.

For meta-analysis, we used a forest plot to demonstrate the association between alcohol intake and BD. Data are expressed as regression coefficients, with 95% CIs using a random-effects model. Heterogeneity between the studies was measured using the I^2 statistic at a significance level at $P < 0.05$. We used a funnel plot to determine whether there is evidence of publication bias in the studies that measured PBD quantitatively and continuously using a random-effects model. We used the statistical software R 3.1.0 for windows and R package metafor 1.9-7 for our statistical analyses.

Results

Description of studies

Table 1 shows selected characteristics of the 20 studies included. Details of the individual studies are given in Supplementary Tables S1–S3. For the planned meta-analyses, studies were grouped according to the methods used to measure PBD and conduct the analysis of the association of BD with alcohol consumption.

Group 1 contained 11 studies (17–27), with a total of 61,229 subjects (of which 87.6% came from one study; ref. 25), that used quantitative methods, either computer assisted or visual estimation, to measure PBD in mammograms and used the continuous measures of PBD generated by these methods in the analysis of the association with alcohol consumption.

Group 2 included 3 studies, with 6,078 subjects, used visual estimation of PBD to group PBD into categories for analysis, and reported results as ORs and 95% CIs (28–30)

Group 3 included 6 studies (31–36) with 5,524 subjects and used the 4 categories of the Wolfe or BIRADS classifications to assess PBD. Five of these studies reported results as ORs and 95% CIs, and one gave no measure of association between alcohol and PBD.

Most studies in each of the these three groups reported adjustment for other risk factors, in particular the principal common confounding variables of age and weight or BMI. Studies in group 3 included fewer adjustments for potential confounders than studies in groups 1 and 2.

Measurement of alcohol consumption

Four studies (21, 25, 27, 35) explicitly stated that they used validated questionnaires to assess alcohol intake. Other forms of dietary assessment included in-person dietary history interviews (20, 24, 29, 30, 33, 37, 38), dietary history questionnaires (17–19, 22, 23, 26, 28, 34), and a 7-day food diary (32).

Details of the approaches taken to the classification of alcohol intake in each study are given in Supplementary Tables S1–S3. Alcohol intake was expressed variously as g/day (17, 24, 25, 27, 29, 34), no alcohol use versus alcohol use times/year (19), servings/week (20), drinks/week (21–23) g/week (26, 30), drinks/month (28), and tertiles of intake (35).

The definition of "no alcohol use" varied between studies, but in general meant that the individual did not consume alcohol at the time of the study (18, 31–33). No study used a category of "never used alcohol," and the "no alcohol use" category may thus have included former users, which is likely to attenuate associations of BD with alcohol use.

Group 1: Meta-analysis and sensitivity analysis of studies using continuous measures of PBD in analysis

Figure 2 shows the forest plot for the 11 studies using quantitative measures of PBD in analysis. Five of the 11 studies reported statistically significant positive associations between alcohol consumption and BD. There was a statistically significant positive overall association between alcohol intake and BD (summary $\beta = 0.84$; 95% CI, 0.12–1.56; $P = 0.01$). The overall heterogeneity of the studies was also significant ($I^2 = 68.18\%$, $P = 0.004$).

To examine potential sources of heterogeneity, we carried out a sensitivity analysis shown in Table 2, in which we examined the effect of removing each study, one at a time, on the overall heterogeneity and β estimate. The summary regression coefficient remained statistically significant after the systematic removal of each study. Overall heterogeneity remained relatively constant and statistically significant after the removal of each study and was least when the studies of Flom and colleagues (61.56%) (22) and Brisson and colleagues (61.21%;

Table 1. Summary of selected characteristics of studies

	Measurement and analysis of breast density		Number of	Number of	Risk	Adjustments of risk estimates		
Group	Method	Analysis	studies	subjects	estimates	Age	BMI/weight	Other
Group 1	Quantitative	Quantitative	11	61,229	Beta	11	11	11
Group 2	Quantitative	Qualitative	3	6,078	OR	3	3	3
Group 3	Qualitative	Qualitative	6	5,524	OR	4	4	4

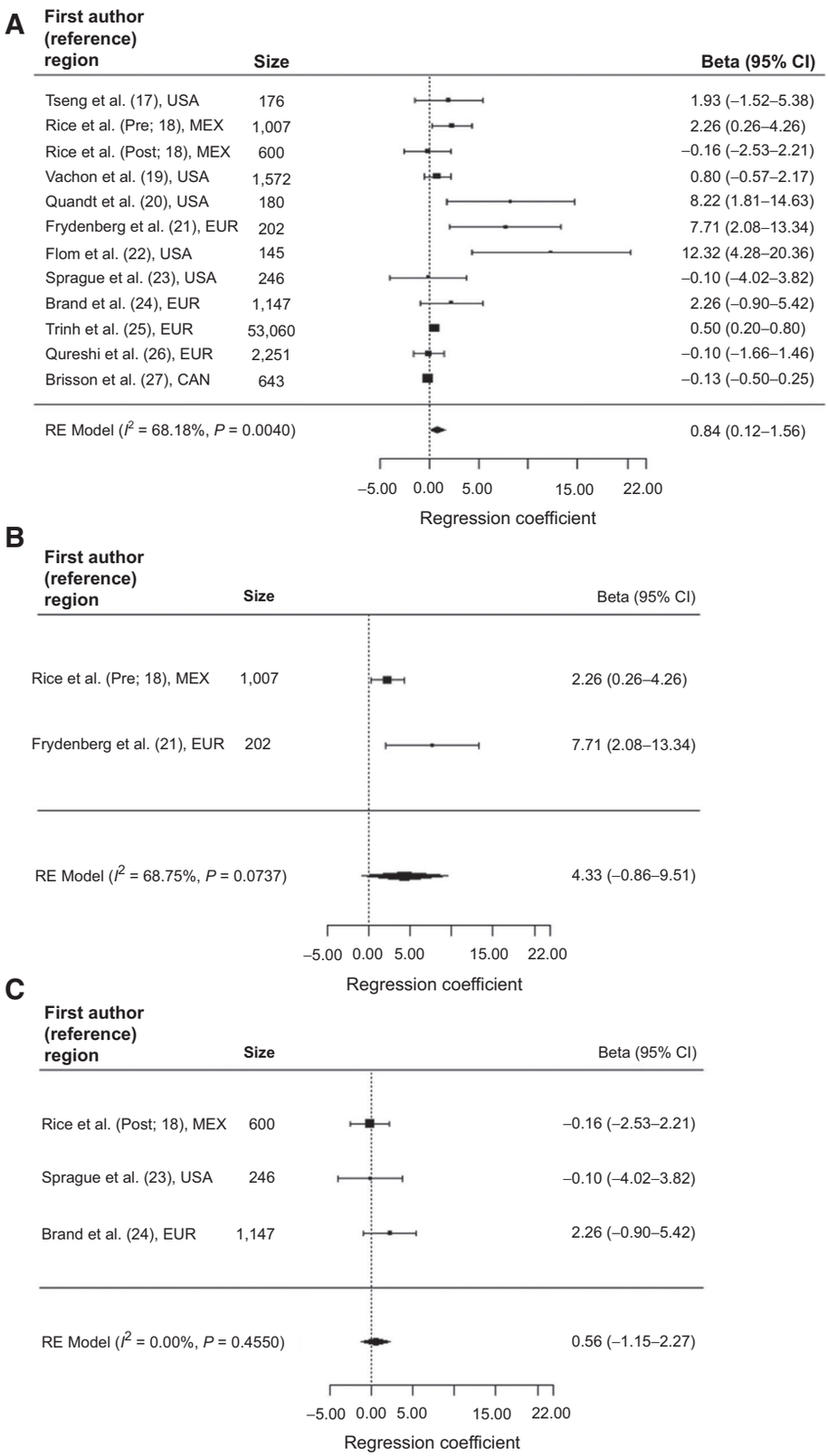

Figure 2.

Forest plots of alcohol intake and PBD for group 1 studies. The forest plot demonstrates the association between alcohol intake and PBD from studies that measured density quantitatively and continuously. Data are expressed as regression coefficients with 95% CIs using a random-effects model. Heterogeneity between the studies was measured using the I^2 statistic at a significance level at $P < 0.05$. **A,** Overall forest plot of alcohol intake and PBD. **B,** Forest plot of alcohol intake and percent BD in premenopausal populations. **C,** Forest plot of alcohol intake and PBD in postmenopausal populations.

Table 2. Sensitivity test of studies included in meta-analysis

Article removed[a]	I^2 heterogeneity value (*P*)	β estimate (*P*)
Tseng et al. (17)	70.36% (0.0002)	0.8007 (0.0335)
Rice et al. (Pre; ref. 18)	67.71% (0.0006)	0.6846 (0.0669)
Rice et al. (Post; ref. 18)	70.93% (0.0002)	0.9285 (0.0166)
Vachon et al. (19)	70.68% (0.0002)	0.8743 (0.0312)
Quandt et al. (20)	65.22% (0.0014)	0.6968 (0.0430)
Frydenberg et al. (21)	64.22% (0.0018)	0.6718 (0.0483)
Flom et al. (22)	61.56% (0.0037)	0.6627 (0.0427)
Sprague et al. (23)	71.03% (0.0002)	0.8811 (0.0200)
Brand et al. (24)	69.82% (0.0003)	0.7726 (0.0393)
Trinh et al. (25)	68.64% (0.0004)	1.3969 (0.0198)
Qureshi et al. (26)	70.81% (0.0002)	0.9866 (0.0139)
Brisson et al. (27)	61.21% (0.0040)	1.3771 (0.0099)

[a]One article was removed at a time to observe the effects of its removal on the overall heterogeneity of the result and the overall regression coefficient result.

ref. 27) were removed. The subjects in the Flom and colleagues' study were predominantly non-Caucasian (25.8% non-Hispanic white, 34.4% non-Hispanic black, and 39.8% Hispanic), and breast tissue characteristics and mean BMI differed substantially between these groups. The study of Brisson and colleagues was the only study in this group not to use a computer-assisted measure of PBD.

We also examined mean age, mean BMI, and smoking status (% yes) for each study as potential modifiers of effect using a mixed-effects model. BMI and smoking status were not statistically significant ($P = 0.73$ for BMI, $P = 0.22$ for smoking), but mean age was significant ($P = 0.008$).

We also carried out a meta-analysis of the association of alcohol consumption with PBD according to menopausal status (shown in Supplementary Fig. S2B and S2C). Six studies (17, 19, 20, 22, 25, 26) did not separate their data by menopausal status. Two studies in group 1 reported separate results for premenopausal women (summary OR = 4.33; 95% CI, −0.86 to 9.41; refs. 18, 21), and three in group 1 for postmenopausal women (summary OR = 0.56; 95% CI, −1.15 to 2.27; refs. 18, 23, 24).

The two forest plots report nonsignificant results; however, the summary β values are consistent with a positive association between alcohol intake and BD and a stronger effect was seen in premenopausal women.

Group 2: Meta-analysis of studies using quantitative measures of PBD and categorical measures of PBD in analysis

There were three studies that measured BD quantitatively but categorized percentage of BD into mutually exclusive groups and expressed the association of alcohol intake with BD using ORs (Supplementary Table S2; refs. 28–30). All reported statistically significant associations between alcohol use and BD. The forest plot is shown in Figure 3. There was a statistically significant positive overall association between alcohol intake and BD (summary OR = 1.81; 95% CI, 1.07–3.04). The overall heterogeneity of the studies was also significant ($I^2 = 80.13\%$, $P = 0.01$).

Group 3: Meta-analysis of studies using qualitative measures of PBD

Six studies assessed BD qualitatively and categorically and expressed the associations in ORs (Supplementary Table S3; refs. 31–36). Three studies (32, 35, 36) used Wolfe's classification of parenchymal patterns and three (31, 33, 34) used the BIRADS classification of PBD. Three of the six studies reported positive statistically significant associations between alcohol consumption and PBD. One study did not give a measure of the association but stated that it was nonsignificant (31, 34–36). The forest plot is shown in Fig. 3B. The summary OR for the overall association between alcohol intake and PBD was similar to that seen in group 2 but was not statistically significant (summary OR = 1.78; 95% CI, 0.90–3.51). The overall heterogeneity of the studies was statistically significant ($I^2 = 92.23\%$, $P < 0.0001$).

Funnel plot

We assessed the risk of publication bias in group 1 studies using a funnel plot shown in Fig. 4 (groups 2 and 3 were judged to have too few studies for this to be useful). The overall plot was not symmetrical, with many studies outside the bounds of the 95% confidence limits, suggesting that the heterogeneity of the result does not fit with the assumptions of the fixed-effects model, and/or there is evidence of publication bias. There are four studies outside the limits. The three studies (20–22) outside the triangle on the right had very diverse, non-Caucasian populations that differed from the rest of the studies except for Frydenberg and colleagues' study (21); however, these studies did not change the significance of the overall result when they were individually removed in the sensitivity analysis. Brisson and colleagues' study appeared just outside of the triangle at the top left, which is due to its small SE (27).

Dense breast area

The associations between alcohol consumption and PBD shown above must exert their effect though associations with either dense or nondense areas of the mammogram (or both). We carried out an additional meta-analysis on the association of alcohol consumption with the dense breast area (in cm^2). Only five studies (20–22, 24, 26) separately reported associations with untransformed units of cm^2. The overall summary β coefficient for the association of alcohol consumption and the dense area of the mammogram was positive and statistically significant (β = 6.51; 95% CI, 0.38–12.63; $P = 0.04$).

Discussion

The results of this systematic review of the literature and meta-analysis suggest that there is a positive association between alcohol intake and percent mammographic density. This association was observed in group 1 studies that used quantitative and continuous measures of PBD measure meta-analysis in which PMD was approximately 0.84% greater in the highest alcohol intake category compared with the lowest category (β = 0.84; 95% CI, 0.12–1.56). Alcohol and PBD were also associated in group 2 studies that analyzed qualitative measures of PBD in categories (summary OR = 1.81; 95% CI, 1.07–3.04). Group 3 studies, that used categorical methods of classification for breast density and analysis, had a summary OR (OR = 1.78; 95% CI, 0.90–3.51) of similar magnitude to group 2 studies, but that was not statistically significant.

The association of alcohol consumption with PBD appears to be principally the result of an association with the dense area of the mammogram. The dense area reflects fibroglandular tissue in the breast and is positively associated with the risk of breast cancer (39).

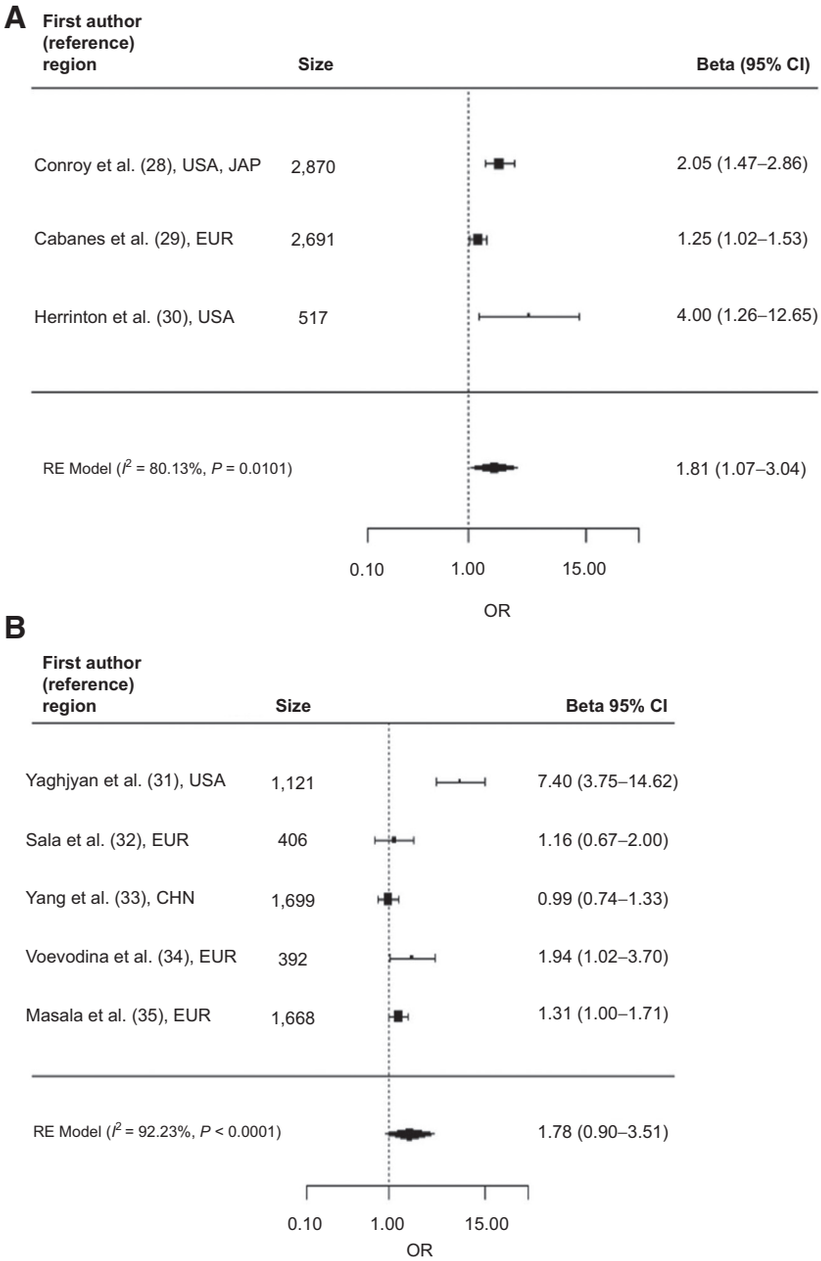

Figure 3.
Forest plots of alcohol intake and PBD for qualitative analysis studies. The forest plot demonstrates the association between alcohol intake and PBD from studies that measured density quantitatively and continuously. Data are expressed as regression coefficients with 95% CIs using a random-effects model. Heterogeneity between the studies was measured using the I^2 statistic at a significance level at $P < 0.05$. **A,** Overall forest plot of alcohol intake and percent BD in group 2 studies. **B,** Overall forest plot of alcohol intake and percent BD in group 3 studies.

Limitations of our systematic review include our reliance on previously published observational studies that may be subject to biases in the design, conduct, or analysis of the original studies or in their publication. Not all studies adjusted for age and weight or BMI, which are potentially important confounders in any association with BD. The β values and ORs used in the meta-analyses may not be comparable, as they are influenced by the variables used in adjustment in the original studies. There was also variability between studies in the questions used to assess alcohol intake, and in the units in which alcohol intake was measured. Several studies (19, 24, 26, 28–30, 33) noted that alcohol consumption was low within the study population, which may have influenced the results, and there were six studies (20–23, 36, 40) with less than 300 participants. These uncontrolled sources of variation are reflected in the tests of heterogeneity that were statistically significant in all three groups of studies and remained significant in the sensitivity analyses.

Strengths of the current study include our inclusion of non-English publications, our use of two independent reviewers to examine independently the quality of all included studies, and to extract data from the studies included. Our systematic review included several studies with more than 1,000 participants and a total in all studies of more than 70,000 subjects. Furthermore, the sensitivity analyses in groups 1 and 2 further gave consistent support for a positive association between alcohol intake and PBD.

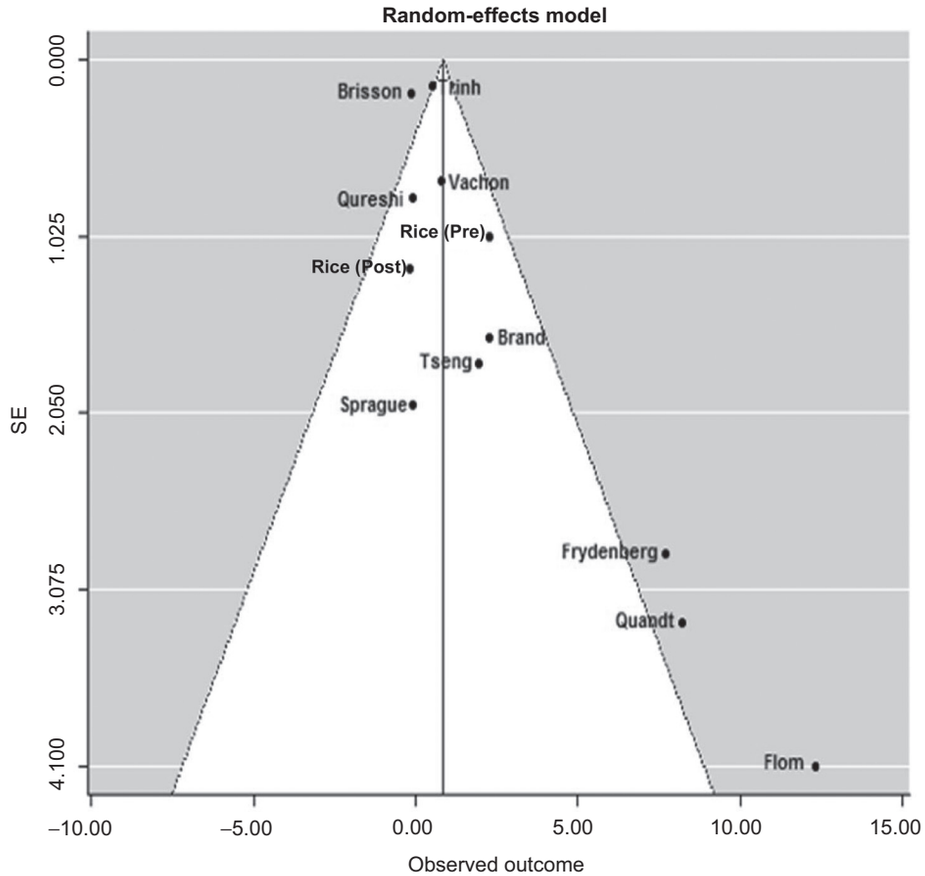

Figure 4.
Funnel plot of alcohol intake and PBD for group 1 studies. The funnel plot demonstrates whether there is evidence of publication bias in the studies that measured BD quantitatively and continuously using a random-effects model. Solid line, pooled estimate expressed as a regression coefficient; dotted lines, pseudo 95% confidence limits.

Biological mechanisms that may explain the association between alcohol consumption and PBD include an increase in endogenous estrogen (21), increased aromatase activity (26), and the components of the growth hormone insulin-like growth factor (IGF) axis (41), all of which may increase epithelial cell proliferation in the breast and increase the radiologically dense tissue in the breast that reflects fibroglandular tissue and is a risk factor for breast cancer (39). As shown above, the limited available evidence suggests that alcohol intake is associated with PMD through an association with radiologically dense tissue in the breast.

Most studies to date have not shown an association of serum levels of estradiol with mammographic density, and not all studies have shown an association of the growth hormone IGF axis and BD (reviewed in ref. 42).

The association of alcohol use with breast cancer according to the molecular phenotype of the tumor was examined in a meta-analysis of 20 cohort studies, with more than a million subjects, 21,624 ER^+ tumors, and 5,113 ER^- tumors. Risk of both tumor types was associated with alcohol use, and the summary ORs were 1.35 (95% CI, 1.23–1.48) for ER^+ tumors and 1.28 (95% CI, 1.10–1.49; ref. 43). The findings of a similar increase in risk of ER-positive and -negative tumors with alcohol use suggests that hormonal mechanism may not be the sole mechanism that links alcohol use with risk of breast cancer. Mammographic density is also associated with an increased risk of both ER-positive and -negative tumors (37).

Zhao and colleagues (44) showed in cell culture of breast cancer cells without receptors for estrogen, progesterone, or EGF (triple negative) that a low concentration of alcohol increased cell proliferation, migration, and invasiveness that might increase radiologically dense breast tissue. These effects were associated with alcohol-induced reactive oxygen species production and increased p38 and JNK phosphorylation. There is now evidence that changing alcohol consumption over a period of 5 years changes risk of breast cancer (45). It remains to be determined whether the changing alcohol consumption will change mammographic density.

These results suggest that the association of alcohol consumption with risk of breast cancer may be, in part, mediated through an effect of breast tissue composition that is reflected in mammographic density, and there is some evidence to support this possibility (28). Further examination of this possibility will require a direct examination of alcohol consumption and mammographic density in relation to risk of breast cancer. Each of the three groups of studies considered here gave statistically significant evidence of heterogeneity. This may be due in part to the inclusion of a number of distinct ethnic groups, as well as differences in the approach taken to classify alcohol intake and measure mammographic density. Examination of the potential role of PMD in mediating the effects of alcohol on risk of breast cancer is likely to benefit if these sources of heterogeneity can be avoided in study design.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L.J. Martin, N.F. Boyd
Development of methodology: J. Zhu, L.J. Martin, S. Minkin
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Ziembicki
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Zhu, L.J. Martin, S. Minkin
Writing, review, and/or revision of the manuscript: S. Ziembicki, J. Zhu, E. Tse, L.J. Martin, S. Minkin, N.F. Boyd
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E. Tse
Study supervision: L.J. Martin, N.F. Boyd

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