Published in final edited form as:

Cancer Causes Control. 2018 August ; 29(8): 751–758. doi:10.1007/s10552-018-1053-9.

Interactions of alcohol and postmenopausal hormone use in regards to mammographic breast density

Lusine Yaghjyan¹, Graham Colditz^{2,3}, Heather Eliassen⁴, Bernard Rosner⁴, Aleksandra Gasparova¹, Rulla M. Tamimi⁴

¹University of Florida, College of Public Health and Health Professions and College of Medicine, Department of Epidemiology, Gainesville, FL, USA;

²Washington University in St. Louis School of Medicine, Department of Surgery, St. Louis, MO, USA

³Institute for Public Health, Washington University in St. Louis, St. Louis, MO, USA

⁴Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA;

Abstract

Purpose: We investigated the association of alcohol intake with mammographic breast density in postmenopausal women by their hormone therapy (HT) status.

Methods: This study included 2,100 cancer-free postmenopausal women within the Nurses' Health Study and Nurses' Health Study II cohorts. Percent breast density (PD), absolute dense (DA) and non-dense areas (NDA) were measured from digitized film mammograms using a computer-assisted thresholding technique; all measures were square-root transformed. Alcohol consumption was assessed with a food frequency questionnaire (0, <5 and ≥5 g/day). Information regarding breast cancer risk factors was obtained from baseline or biennial questionnaires closest to the mammogram date. We used generalized linear regression to examine associations between alcohol and breast density measures in women with no HT history, current and past HT users.

Results: In multivariable analyses, we found no associations of alcohol consumption with PD (p-trend=0.32) and DA (p-trend=0.53) and an inverse association with NDA ($\beta=-0.41$, 95%CI -0.73, -0.09 for ≥5 g/day, p-trend<0.01). In the stratified analysis by HT status, alcohol was not associated with PD in any of the strata. We found a significant inverse association of alcohol with NDA among past HT users ($\beta=-0.79$, 95%CI -1.51, -0.07 for ≥5 g/day, p-trend=0.02). There were

CORRESPONDING AUTHOR: Dr. Lusine Yaghjyan, 2004 Mowry Rd., Gainesville, FL 32610; phone: 352-294-5940; fax: 352-273-5365; lyaghjyan@ufl.edu.

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

This study was approved by the Institutional Review Board at the Brigham and Women's Hospital. Consent was obtained or implied by return of questionnaires.

no significant interactions between alcohol and HT in relation to PD, DA, and NDA (p-interaction=0.19, 0.42, and 0.43, respectively).

Conclusions: Our findings suggest that associations of alcohol with breast density do not vary by HT status.

Keywords

alcohol consumption; breast density; hormone therapy; breast cancer

Background

Mammographic breast density is a well-established and strong predictor of breast cancer risk [1–4]. Appearance of the breast on the mammogram is a reflection of the amount of fat, connective tissue, and epithelial tissue in the breast [3]. Light (non-radiolucent) areas on the mammogram represent the fibrous and glandular tissues (“mammographically dense”), whereas, the dark (radiolucent) areas are primarily fat. Women with breasts of 75% or greater percent density (proportion of the total breast area that appears dense on the mammogram) are at 4- to 6-fold greater risk of breast cancer compared to women with more fat tissues in the breasts [3, 5, 6]. Absolute dense area of the breast that represents fibroglandular tissue has been shown to be positively associated with breast cancer risk in both pre- and postmenopausal women [7–13], while absolute non-dense area of the breast (representing adipose tissue) has been inversely associated with breast cancer risk [7, 9, 14, 15].

Previous studies have suggested a positive association of alcohol consumption with breast cancer [16–18]. Multiple pathways were suggested as possible explanation for these associations, including alteration of estrogen levels as well as carcinogenic properties of ethanol metabolites that result from their ability to form protein and DNA adducts, disrupt normal anti-oxidative defense system and DNA repair, and cause genomic instability via indirect effect on DNA methylation [18]. Even though the findings on the association between alcohol consumption and breast density have been inconsistent across the studies, a recent meta-analysis suggests an overall positive association [19].

Postmenopausal hormones have been shown to consistently increase breast cancer risk and mammographic breast density [20–24]. Some previous studies suggest an interaction between alcohol use and postmenopausal hormones in relation to breast cancer risk (OR=4.74, 95% CI: 2.61–8.59 for those who had an intake of more than 2 drinks per day and took hormones vs. abstainers who did not use hormones) [25]. Alcohol could potentially interact with postmenopausal hormones via its stimulating effect on aromatase and subsequent increase in active estrogen levels in the peripheral tissues, including the breast [26, 27]. Further, interactions of alcohol with variety of medications attributable to its stimulating effects on CYP3A4 that metabolizes large proportion of xenobiotics have been previously reported [28, 29]. Long-term alcohol consumption also induces activity of CYP1A2, CYP2A6, CYP2E1 which together with CYP3A4 metabolize up to 90% of xenobiotics [30]. On the other hand, exogenous hormones such as hormone replacement therapy may also inhibit activity of selected CYP450 enzymes, thus further supporting

potential interaction between alcohol consumption and hormone therapy [31]. However, the data on the possible interactions of alcohol use with hormone therapy (HT) with respect to breast density is very limited. Using Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II) cohorts, we examined associations of alcohol consumption with percent density, absolute dense and non-dense areas by woman's hormone therapy status.

Methods

Study population and design

Women included in this study were selected from participants of the nested case-control study within Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) cohorts. These prospective cohorts followed registered nurses in the United States who were 30–55 years (NHS) or 25–42 years old (NHSII) at enrollment. After administration of the initial questionnaire, the information on breast cancer risk factors and any diagnoses of cancer or other diseases was updated through biennial questionnaires [3, 32].

A nested case-control approach was originally used as an efficient design to examine the association between selected biomarkers and breast cancer risk within the NHS and NHS II [3, 33]. Using incidence density sampling, women without cancer history (other than non-melanoma skin cancer) at the time of the case's cancer diagnosis (controls) were matched 1:1 or 1:2 with women diagnosed with in situ or invasive breast cancer (cases). Matching variables included age at the time of blood collection, menopausal status and postmenopausal hormone use (current vs. not current) at blood draw, and day/time of blood draw; for NHS II, additional matching included race/ethnicity and day in the luteal phase [34]. Our analysis included controls from these case-control studies nested in NHSI and NHSII cohorts. We attempted to obtain mammograms closest to the time of blood collection (or ~1997 for those who did not provide blood samples). From all eligible women, 2,334 postmenopausal women provided consent and had a usable mammogram for density estimation. Of these women, 2,100 (90%) had data on recent alcohol consumption and postmenopausal hormone use. This study was approved by the Institutional Review Board at the Brigham and Women's Hospital. Consent was obtained or implied by return of questionnaires.

Assessment of alcohol consumption—Information on alcohol consumption was obtained from semi-quantitative food frequency questionnaires [35]. In NHS I, questions regarding alcohol consumption were asked in 1980, 1984, 1986, and 1990. Women reported their average consumption of beer, wine, and liquor separately in the prior year. One drink was considered equal to one can or bottle of beer, a 4-ounce glass of wine, or one drink or shot of liquor. Participants were asked to select from the following categories: almost never, 1 to 3 per month, 1 per week, 2 to 4 per week, 5 to 6 per week, 1 per day, 2 to 3 per day, 4 to 6 per day, 6 or more per day. Similarly, women in NHS II answered questions on consumption of alcohol in the 1989 and 1991 questionnaires. In 1991, the NHS II alcohol questions were expanded to include red wine, white wine, light beer, regular beer, and liquor. Total alcohol consumption per questionnaire cycle was calculated as the sum of the daily number of drinks multiplied by the average alcohol content per type of alcoholic beverage

(12.8 g for regular beer, 11.3 for light beer, 11.0 g for wine, and 14.0 g for liquor) [36, 37]. Alcohol consumption in these cohorts has been shown to be valid and highly reproducible in repeated assessments [38].

Women were assigned the alcohol exposure from the cycle closest to the date of the mammogram. If alcohol consumption was missing from the questionnaire before the mammogram date, the exposure from the preceding cycle was used [37]. In the current analysis, we used both a continuous (g/day) as well as categorical measure of alcohol consumption (0 [reference], 0–<5, and ≥5 g/day). Median levels within respective categories (0, 1.8, and 11.8) were used for the test of trend. In a secondary analysis, we considered cumulative average alcohol consumption using all available data from before the mammogram date.

Assessment of Mammographic Breast Density

To quantify mammographic density, the craniocaudal views of both breasts for all mammograms in the NHS and for the first two batches of mammograms in the NHSII were digitized at 261 µm per pixel with a Lumisys 85 laser film scanner (Lumisys, Sunnyvale, California) with bit depth of 12. The third batch of NHSII mammograms was digitized using a VIDAR CAD PRO Advantage scanner (VIDAR Systems Corporation; Herndon, VA) and comparable resolution of 150 dots per inch and 12 bit depth). The Cumulus software (University of Toronto, Toronto, Canada) was used for computer-assisted determination percent mammographic density and absolute dense area and non-dense areas on all mammograms [3, 39]. As reported previously, the measure of breast density from NHS mammograms was highly reproducible (within-person intraclass correlation coefficient=0.93) [3]. All NHSII images were read by a single reader. Although within batch reproducibility was high (intraclass correlation coefficient = 0.90) [7], density measures varied across the NHSII batches. We included a small subset of identical mammograms in all batches to account for batch drift in density measurement readings. The density measures from the second and third batches of NHSII mammograms were adjusted to account for the batch effect (whether due to intra-reader variability or scanner), as previously described [40]. Additionally, to assess the potential variability in percent density by scanner, we conducted a pilot study of 50 mammograms. These mammograms were scanned using both the Lumisys 85 laser scanner and the VIDAR CAD PRO Advantage scanner; percent density was measured by the same observer using Cumulus. The correlation between percent density as measured by the two scanners was 0.88; the mean difference was 2.3% points [41].

Percent breast density was measured as percentage of the total area occupied by epithelial/stromal tissue (absolute dense area) divided by the total breast area. Because breast densities of the right and left breast for an individual woman are strongly correlated [39], the average density of both breasts was used in this analysis.

Covariate Information

Information on breast cancer risk factors was obtained from the biennial questionnaires closest to the date of the mammogram. Women were considered to be postmenopausal if they reported: 1) no menstrual periods within the 12 months before blood collection with

natural menopause, 2) bilateral oophorectomy, or 3) hysterectomy with one or both ovaries retained, and were 54 years or older for ever smokers or 56 years or older for never smokers [42, 43].

Statistical analysis

We used multivariate generalized linear regression to examine the associations of alcohol intake with percent density, absolute dense and non-dense areas. Because density measures were non-normally distributed, we used square root transformation to improve normality in all the regression analyses. The regression estimates were adjusted for age (continuous), body mass index (continuous), age at menarche (<12, 12–13, >13 years), parity and age at first child's birth (nulliparous, parous with age at first birth <25 years, or parous with age at first birth of ≥25 years), a confirmed history of benign breast disease (yes, no), a family history of breast cancer (yes, no), study cohort, and age at menopause (<46, 46–<50, 50–<55, 55, unknown). To assess the overall trend for alcohol consumption, we used respective medians within each category.

Stratified analysis were performed for women with no history of HT, past and current HT. Differences in the associations of alcohol consumption with breast density by hormone therapy status were evaluated with two-way interactions and using Wald Chi-square test. We used respective medians within each of the alcohol consumption categories to model the interaction. Additionally, among current hormone therapy users, we examined separately associations among women using combined estrogen plus progesterone hormone therapy. In a secondary analysis, we used cumulative average alcohol consumption to examine the associations with breast density. Statistical significance in all the analyses was assessed at 0.05 level. The analyses were performed using SAS software (version 9.2, SAS Institute, Cary, NC, USA).

Results

In this study of 2,100 cancer-free women, the average age at the mammogram was 58 years (range 35–84). Of these women, 748 (35.6%) never used hormones, 420 (20%) used HT in the past, and 932 (44.4%) were currently on HT. As compared to women who did not drink, women in the highest category of alcohol consumption (≥5 g/day) had a greater mean percent density (28.7% vs. 24.2%), larger absolute dense area (49.0 vs. 47.8 cm²), and smaller absolute non-dense area (133.9 vs. 167.8 cm²). Distributions of breast cancer risk factors by alcohol consumption are presented in Table 1. Women in the highest category of alcohol intake were more likely to be nulliparous (12 vs. 7%) and to have a lower BMI (24.8 vs. 27.0 kg/m²) as compared to women who did not drink. Distributions of other risk factors were similar across the alcohol intake categories.

In the overall analysis, we found no associations of alcohol consumption with percent density ($\beta = -0.06$, 95% CI $-0.22, 0.09$ for <5 g/day and $\beta = 0.06$, 95% CI $-0.11, 0.22$ for ≥5 g/day, p-trend 0.32) and absolute dense area ($\beta = -0.00$, 95% CI $-0.25, 0.25$ for <5 g/day and $\beta = -0.08$, 95% CI $-0.34, 0.19$ for ≥5 g/day, p-trend=0.53). Greater alcohol consumption was associated with larger absolute non-dense area ($\beta = 0.11$, 95% CI $-0.19, 0.41$ for <5 g/day and $\beta = -0.41$, 95% CI $-0.73, -0.09$ for ≥5 g/day, p-trend<0.01).

In the stratified analysis by woman's HT status, alcohol consumption was not associated with percent density or absolute dense area in any of the strata (Table 3). We found a significant inverse association of alcohol intake with non-dense area among women with past hormone therapy $\beta = -0.79$, 95% CI $-1.51, -0.07$ for ≤ 5 g/day, p -trend=0.02). There were no significant interactions between alcohol consumption and hormone therapy in relation to percent density, absolute dense and non-dense area (p -interaction=0.19, 0.42, and 0.43, respectively). Association patterns in women with current use of combined therapy were similar to those among current HT users.

In the secondary analysis, associations of cumulative average alcohol consumption with breast density by HT status were similar (Supplementary table 1). In this analysis, we found a significant interaction of alcohol use with HT in relation to percent density (p -interaction=0.04) and a marginally significant interaction in relation to absolute dense area (p -interaction=0.06).

Discussion

In this study of cancer-free postmenopausal women, we investigated the associations of alcohol intake with mammographic density by the woman's HT status. We found no associations of alcohol intake with percent density and absolute dense area. Inverse associations of regular alcohol intake with absolute non-dense area were limited to past hormone users. Our findings did not support a hypothesis that associations of alcohol consumption with breast density differs by the woman's HT status.

Previous studies have consistently found a positive association of alcohol consumption with breast cancer risk in postmenopausal women [16–18]. It has been suggested that this effects may be explained by carcinogenic properties of acetaldehyde which is formed from ethanol mainly in the liver as well as peripheral tissues, including breast. Acetaldehyde has ability to disrupt normal cellular regulation by forming protein and DNA adducts and thus interfering with normal anti-oxidative and DNA repair mechanisms [18]. Higher alcohol intake has been also linked to an increase in estrogen levels and subsequent stimulation of cell proliferation [18]. Higher levels of circulating hormones have been noted after alcohol consumption by women currently using HT [44] and several studies suggested a stronger association of alcohol intake with breast cancer risk in current HT users [25, 45, 46]. In addition, in postmenopausal women alcohol consumption has been reported to increase the levels of circulating insulin-like growth factor (IGF)-1 [47] which plays an important role in breast carcinogenesis [48]. Finally, long-term alcohol consumption has stimulating effects on CYP 450 enzymes (CYP3A4, CYP1A2, CYP2A6, and CYP2E1) which together metabolize up to 90% of xenobiotics, including those with potential endocrine disrupting properties [28–30].

Positive associations of alcohol consumption with percent breast density were reported by some previous studies, though the evidence remains inconsistent [49–51]. Despite biological plausibility that associations of alcohol consumption with breast density may vary by woman's hormone therapy status, the evidence on potential interaction between alcohol consumption and HT remains very limited. A recent extreme phenotype case-control study

of 265 women with high density and 860 women with fatty breasts investigated interactions of HT with alcohol intake in a population based longitudinal cohort with 18 years of follow up and multiple mammograms per woman [52]. Breast density phenotype was defined using all mammograms available for a woman. Cases were defined as having high density equivalent to BI-RADS breast category IV (extremely dense) on any of their mammograms. Women who had low density (equivalent to BI-RADS density category I [fatty breasts]) on all of their mammograms served as controls. The HT was classified as any history of HT vs. no history and drinking was defined as none vs. any. The study has shown that the positive association of alcohol with breast density was stronger in women who ever used HT (alcohol use ever use vs. never OR=3.6, 95% CI 1.7–7.7) as compared to women with no HT history (alcohol use ever use vs. never OR=1.6, 95% CI 1.1–2.4, p-interaction<0.001)[52]. Another study of population-based sample of postmenopausal women (n=1,147) suggested that alcohol intake was positively associated with percent density and absolute dense area in current HT users but not in non-current users (p-interaction=0.06 and 0.04, respectively”) [53]. Unlike these reports, our findings did not suggest any interactions between recent alcohol consumption and HT status, though the magnitude of the associations between alcohol consumption and absolute non-dense area appeared to be the largest among past HT users. In our study, the median alcohol intake was 1.6 g/day and 75th percentile was 6.4 g/day (range 0–9.0 g/day) which along with differences in definition of alcohol consumption categories and breast density assessment may explain inconsistency of our findings as compared to previous reports.

We found an inverse association of alcohol consumption with absolute non-dense area. Though the interaction was not significant, the magnitude of the association between alcohol and absolute non-dense area appeared to be the largest among postmenopausal women who used HT in the past. An association with reduced absolute area of non-dense tissue has been previously reported [53] which could potentially be explained by its fat-reducing effect on various tissues, including breast, due to high energy demanding nature of the microsomal ethanol oxidation which dominates in women [54] as well as alcohol-associated increase in thermogenesis [53, 55]. It is unclear, however, why the largest decrease in the absolute non-dense area is seen in women with past HT and future studies are warranted to elucidate potential mechanisms behind these association patterns.

Our study is the largest study to date that systematically investigated associations of alcohol consumption with mammographic breast density among postmenopausal women and by woman’s HT status. The analysis used data from the NHS and NHS II cohorts with more than 25 years of follow-up, ascertainment of disease status, and comprehensive information on breast cancer risk factors and breast density. Our study has a few limitations. The examined associations are based on the density measures from a single mammogram which might not be reflective of the woman’s life-long density pattern, however studies have suggested that a single measure can predict breast cancer risk for up to 10 years in both pre- and postmenopausal women [6, 56]. Despite the prospective nature of the cohort, potential errors in recall of alcohol consumption are possible. However, previous validation studies suggest reasonable reproducibility and validity of the data from food frequency questionnaires for the use in studies of associations between diet and health outcomes in epidemiologic studies [57, 58]. High accuracy in self-reported alcohol consumption has been

reported in both men and women, including in Nurses' Health Study [38, 59, 60]. There was a high correlation between alcohol intake reported on food frequency questionnaire and that assessed by multiple week diet records over the same period ($r=0.90$). Moreover, four years after completing the diet record, another assessment was done to collect self-reported alcohol intake over the previous 4 years. These measures were highly correlated as well ($r=0.84$). This evidence suggests that a food frequency questionnaire provides reliable and sufficiently accurate information on alcohol intake over an extended period of time for use in epidemiologic investigations [38]. Finally, we were unable to examine the associations of alcohol with breast density for types of HT other than combined estrogen + progesterone therapy as the numbers of women in those strata were insufficient.

In conclusion, we investigated the associations of alcohol intake with percent density, absolute dense and non-dense areas by woman's HT status. Our findings suggest inverse associations of alcohol consumption with absolute non-dense area in postmenopausal women overall and in women with past HT. Further studies are warranted to confirm our findings, to elucidate potential mechanisms for stronger associations of alcohol with absolute non-dense area in this subset of postmenopausal women, and to explore the potential differences in association patterns by the type of HT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by the National Cancer Institute at the National Institutes of Health [CA131332, CA087969, CA175080 to R.M.T., UM1 CA186107 to M.S., UM1 CA176726 to W.W.], Avon Foundation for Women, Susan G. Komen for the Cure®, and Breast Cancer Research Foundation.

References

1. Boyd NF, Rommens JM, Vogt K, Lee V, Hopper JL, Yaffe MJ, and Paterson AD (2005). Mammographic breast density as an intermediate phenotype for breast cancer. *Lancet Oncol.* 6:798–808. [PubMed: 16198986]
2. Ginsburg OM, Martin LJ, and Boyd NF (2008). Mammographic density, lobular involution, and risk of breast cancer. *Br J Cancer.* 99:1369–74. [PubMed: 18781174]
3. Tamimi RM, Byrne C, Colditz GA, and Hankinson SE (2007). Endogenous hormone levels, mammographic density, and subsequent risk of breast cancer in postmenopausal women. *J Natl Cancer Inst.* 99:1178–87. [PubMed: 17652278]
4. Harvey JA and Bovbjerg VE (2004). Quantitative assessment of mammographic breast density: relationship with breast cancer risk. *Radiology.* 230:29–41. [PubMed: 14617762]
5. Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, Lockwood GA, Tritchler DL, and Yaffe MJ (1995). Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *J Natl Cancer Inst.* 87:670–5. [PubMed: 7752271]
6. Byrne C, Schairer C, Wolfe J, Parekh N, Salane M, Brinton LA, Hoover R, and Haile R (1995). Mammographic features and breast cancer risk: effects with time, age, and menopause status. *J Natl Cancer Inst.* 87:1622–9. [PubMed: 7563205]
7. Pettersson A, Hankinson S, Willett W, Lagiou P, Trichopoulos D, and Tamimi R (2011). Nondense mammographic area and risk of breast cancer. *Breast Cancer Research.* 13:R100. [PubMed: 22017857]

8. Aitken Z, McCormack VA, Highnam RP, Martin L, Gunasekara A, Melnichouk O, Mawdsley G, Peressotti C, Yaffe M, Boyd NF, and dos Santos Silva I (2010). Screen-Film Mammographic Density and Breast Cancer Risk: A Comparison of the Volumetric Standard Mammogram Form and the Interactive Threshold Measurement Methods. *Cancer Epidemiology Biomarkers & Prevention*. 19:418–428.
9. Stone J, Ding J, Warren RM, Duffy SW, and Hopper JL (2010). Using mammographic density to predict breast cancer risk: dense area or percentage dense area. *Breast Cancer Res*. 12:R97. [PubMed: 21087468]
10. Ursin G, Ma H, Wu AH, Bernstein L, Salane M, Parisky YR, Astrahan M, Siozon CC, and Pike MC (2003). Mammographic Density and Breast Cancer in Three Ethnic Groups. *Cancer Epidemiology Biomarkers & Prevention*. 12:332–338.
11. Maskarinec G, Pagano I, Lurie G, Wilkens LR, and Kolonel LN (2005). Mammographic Density and Breast Cancer Risk. *American Journal of Epidemiology*. 162:743–752. [PubMed: 16150892]
12. Boyd N, Martin L, Gunasekara A, Melnichouk O, Maudsley G, Peressotti C, Yaffe M, and Minkin S (2009). Mammographic Density and Breast Cancer Risk: Evaluation of a Novel Method of Measuring Breast Tissue Volumes. *Cancer Epidemiology Biomarkers & Prevention*. 18:1754–1762.
13. Vachon CM, Brandt KR, Ghosh K, Scott CG, Maloney SD, Carston MJ, Pankratz VS, and Sellers TA (2007). Mammographic Breast Density as a General Marker of Breast Cancer Risk. *Cancer Epidemiology Biomarkers & Prevention*. 16:43–49.
14. Lokate M, Peeters PH, Peelen LM, Haars G, Veldhuis WB, and van Gils CH (2011). Mammographic density and breast cancer risk: the role of the fat surrounding the fibroglandular tissue. *Breast Cancer Res*. 13:R103. [PubMed: 22030015]
15. Pettersson A, Graff RE, Ursin G, Santos Silva ID, McCormack V, Baglietto L, Vachon C, Bakker MF, Giles GG, Chia KS, Czene K, Eriksson L, Hall P, Hartman M, Warren RM, Hislop G, Chiarelli AM, Hopper JL, Krishnan K, Li J, Li Q, Pagano I, Rosner BA, Wong CS, Scott C, Stone J, Maskarinec G, Boyd NF, van Gils CH, and Tamimi RM (2014). Mammographic Density Phenotypes and Risk of Breast Cancer: A Meta-analysis. *J Natl Cancer Inst*.
16. Scoccianti C, Lauby-Secretan B, Bello PY, Chajes V, and Romieu I (2014). Female breast cancer and alcohol consumption: a review of the literature. *Am J Prev Med*. 46:S16–25. [PubMed: 24512927]
17. Boyle P and Boffetta P (2009). Alcohol consumption and breast cancer risk. *Breast Cancer Res*. 11 Suppl 3:S3. [PubMed: 20030878]
18. McDonald JA, Goyal A, and Terry MB (2013). Alcohol Intake and Breast Cancer Risk: Weighing the Overall Evidence. *Current breast cancer reports*. 5:10.1007/s12609-013-0114-z.
19. Ziembicki S, Zhu J, Tse E, Martin LJ, Minkin S, and Boyd NF (2017). The Association between Alcohol Consumption and Breast Density: A Systematic Review and Meta-analysis. *Cancer Epidemiology Biomarkers & Prevention*. 26:170–178.
20. Conner P, Svane G, Azavedo E, Soderqvist G, Carlstrom K, Graser T, Walter F, and von Schoultz B (2004). Mammographic breast density, hormones, and growth factors during continuous combined hormone therapy. *Fertil Steril*. 81:1617–23. [PubMed: 15193485]
21. Greendale GA, Palla SL, Ursin G, Laughlin GA, Crandall C, Pike MC, and Reboussin BA (2005). The association of endogenous sex steroids and sex steroid binding proteins with mammographic density: results from the Postmenopausal Estrogen/Progestin Interventions Mammographic Density Study. *Am J Epidemiol*. 162:826–34. [PubMed: 16177147]
22. Pettersen PC, Raundahl J, Loog M, Nielsen M, Tanko LB, and Christiansen C (2008). Parallel assessment of the impact of different hormone replacement therapies on breast density by radiologist- and computer-based analyses of mammograms. *Climacteric*. 11:135–43. [PubMed: 18365856]
23. Vachon CM, Sellers TA, Vierkant RA, Wu FF, and Brandt KR (2002). Case-control study of increased mammographic breast density response to hormone replacement therapy. *Cancer Epidemiol Biomarkers Prev*. 11:1382–8. [PubMed: 12433715]
24. Shah NR, Borenstein J, and Dubois RW (2005). Postmenopausal hormone therapy and breast cancer: a systematic review and meta-analysis. *Menopause*. 12:668–78. [PubMed: 16278609]

25. Nielsen NR and Grønbæk M (2008). Interactions between intakes of alcohol and postmenopausal hormones on risk of breast cancer. *International Journal of Cancer*. 122:1109–1113. [PubMed: 17966122]
26. Onland-Moret NC, Peeters PH, van der Schouw YT, Grobbee DE, and van Gils CH (2005). Alcohol and endogenous sex steroid levels in postmenopausal women: a cross-sectional study. *J Clin Endocrinol Metab*. 90:1414–9. [PubMed: 15572431]
27. Zhu BT and Conney AH (1998). Functional role of estrogen metabolism in target cells: review and perspectives. *Carcinogenesis*. 19:1–27. [PubMed: 9472688]
28. Rahmioglu N, Heaton J, Clement G, Gill R, Surdulescu G, Zlobecka K, Hodgkiss D, Ma Y, Hider RC, Smith NW, and Ahmadi KR (2011). Genetic epidemiology of induced CYP3A4 activity. *Pharmacogenet Genomics*. 21:642–51. [PubMed: 21750469]
29. Weathermon R and Crabb DW (1999). Alcohol and medication interactions. *Alcohol Res Health*. 23:40–54. [PubMed: 10890797]
30. Tanaka E (1998). Clinically important pharmacokinetic drug-drug interactions: role of cytochrome P450 enzymes. *J Clin Pharm Ther*. 23:403–16. [PubMed: 10048501]
31. Hong C-C, Tang B-K, Hammond GL, Trichtler D, Yaffe M, and Boyd NF (2004). Cytochrome P450 1A2 (CYP1A2) activity and risk factors for breast cancer: a cross-sectional study. *Breast Cancer Research*. 6:R352–R365. [PubMed: 15217502]
32. Colditz GA and Hankinson SE (2005). The Nurses' Health Study: lifestyle and health among women. *Nat Rev Cancer*. 5:388–96. [PubMed: 15864280]
33. Tworoger SS, Sluss P, and Hankinson SE (2006). Association between plasma prolactin concentrations and risk of breast cancer among predominately premenopausal women. *Cancer Res*. 66:2476–82. [PubMed: 16489055]
34. Bertrand KA, Rosner B, Eliassen AH, Hankinson SE, Rexrode KM, Willett W, and Tamimi RM (2015). Premenopausal plasma 25-hydroxyvitamin D, mammographic density, and risk of breast cancer. *Breast Cancer Res Treat*. 149:479–87. [PubMed: 25543181]
35. Farvid MS, Cho E, Chen WY, Eliassen AH, and Willett WC (2014). Dietary protein sources in early adulthood and breast cancer incidence: prospective cohort study. *BMJ*. 348:g3437. [PubMed: 24916719]
36. Chen WY, Rosner B, Hankinson SE, Colditz GA, and Willett WC (2011). Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. *Jama*. 306:1884–1890. [PubMed: 22045766]
37. Tamimi RM, Byrne C, Baer HJ, Rosner B, Schnitt SJ, Connolly JL, and Colditz GA (2005). Benign breast disease, recent alcohol consumption, and risk of breast cancer: a nested case-control study. *Breast Cancer Research*. 7:R555. [PubMed: 15987462]
38. Giovannucci E, Colditz G, Stampfer MJ, Rimm EB, Litin L, Sampson L, and Willett WC (1991). The Assessment of Alcohol Consumption by a Simple Self-administered Questionnaire. *American Journal of Epidemiology*. 133:810–817. [PubMed: 2021148]
39. Byng JW, Boyd NF, Little L, Lockwood G, Fishell E, Jong RA, and Yaffe MJ (1996). Symmetry of projection in the quantitative analysis of mammographic images. *Eur J Cancer Prev*. 5:319–27. [PubMed: 8972250]
40. Bertrand K, Eliassen AH, Hankinson S, Gierach G, Xu X, Rosner B, Ziegler R, and Tamimi R (2012). Urinary estrogens and estrogen metabolites and mammographic density in premenopausal women. *Breast Cancer Research and Treatment*. 136:277–287. [PubMed: 23053640]
41. Rice MS, Rosner BA, and Tamimi RM (2017). Percent mammographic density prediction: development of a model in the nurses' health studies. *Cancer Causes Control*. 28:677–684. [PubMed: 28478536]
42. Willett W, Stampfer MJ, Bain C, Lipnick R, Speizer FE, Rosner B, Cramer D, and Hennekens CH (1983). Cigarette smoking, relative weight, and menopause. *Am J Epidemiol*. 117:651–8. [PubMed: 6859020]
43. Stampfer MJ, Willett WC, Colditz GA, Rosner B, Speizer FE, and Hennekens CH (1985). A Prospective Study of Postmenopausal Estrogen Therapy and Coronary Heart Disease. *New England Journal of Medicine*. 313:1044–1049. [PubMed: 4047106]

44. Ginsburg ES, Mello NK, Mendelson JH, and et al. (1996). Effects of alcohol ingestion on estrogens in postmenopausal women. *JAMA*. 276:1747–1751. [PubMed: 8940324]
45. Chen WY, Colditz GA, Rosner B, and et al. (2002). Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. *Annals of Internal Medicine*. 137:798–804. [PubMed: 12435216]
46. Zhang SM, Lee I-M, Manson JE, Cook NR, Willett WC, and Buring JE (2007). Alcohol Consumption and Breast Cancer Risk in the Women's Health Study. *American Journal of Epidemiology*. 165:667–676. [PubMed: 17204515]
47. Vrieling A, Voskuil DW, de Mesquita HBB, Kaaks R, van Noord PAH, Keinan-Boker L, van Gils CH, and Peeters PHM (2004). Dietary Determinants of Circulating Insulin-like Growth Factor (IGF)-I and IGF Binding Proteins 1, –2 and –3 in Women in the Netherlands. *Cancer Causes & Control*. 15:787–796. [PubMed: 15456992]
48. Christopoulos PF, Msaouel P, and Koutsilieris M (2015). The role of the insulin-like growth factor-I system in breast cancer. *Molecular Cancer*. 14:43. [PubMed: 25743390]
49. Quandt Z, Flom JD, Tehranifar P, Reynolds D, Terry MB, and McDonald JA (2015). The association of alcohol consumption with mammographic density in a multiethnic urban population. *BMC Cancer*. 15:124.
50. Lindgren J, Dorgan J, Savage-Williams J, Coffman D, and Hartman T (2013). Diet across the Lifespan and the Association with Breast Density in Adulthood. *Int J Breast Cancer*. 2013:808317. [PubMed: 23431461]
51. Singletary KW and Gapstur SM (2001). Alcohol and breast cancer: Review of epidemiologic and experimental evidence and potential mechanisms. *JAMA*. 286:2143–2151. [PubMed: 11694156]
52. Yaghjian L, Mahoney MC, Succop P, Wones R, Buckholz J, and Pinney SM (2012). Relationship between breast cancer risk factors and mammographic breast density in the Fernald Community Cohort. *Br J Cancer*.
53. Brand JS, Czene K, Eriksson L, Trinh T, Bhoo-Pathy N, Hall P, and Celebioglu F (2013). Influence of lifestyle factors on mammographic density in postmenopausal women. *PLoS One*. 8:e81876. [PubMed: 24349146]
54. Lands WE and Zakhari S (1991). The case of the missing calories. *The American Journal of Clinical Nutrition*. 54:47–8. [PubMed: 2058586]
55. Westerterp KR (2004). Diet induced thermogenesis. *Nutrition & Metabolism*. 1:5–5. [PubMed: 15507147]
56. Yaghjian L, Colditz GA, Rosner B, and Tamimi RM (2013). Mammographic breast density and subsequent risk of breast cancer in postmenopausal women according to the time since the mammogram. *Cancer Epidemiol Biomarkers Prev*. 22:1110–7. [PubMed: 23603205]
57. Hu FB, Rimm E, Smith-Warner SA, Feskanich D, Stampfer MJ, Ascherio A, Sampson L, and Willett WC (1999). Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. *The American Journal of Clinical Nutrition*. 69:243–249. [PubMed: 9989687]
58. WILLETT WC, SAMPSON L, STAMPFER MJ, ROSNER B, BAIN C, WITSCHI J, HENNEKENS CH, and SPEIZER FE(1985). REPRODUCIBILITY AND VALIDITY OF A SEMIQUANTITATIVE FOOD FREQUENCY QUESTIONNAIRE. *American Journal of Epidemiology*. 122:51–65. [PubMed: 4014201]
59. Del Boca FK and Darkes J (2003). The validity of self-reports of alcohol consumption: state of the science and challenges for research. *Addiction*. 98:1–12.
60. Feunekes GI, van 't Veer P, van Staveren WA, and Kok FJ (1999). Alcohol intake assessment: the sober facts. *Am J Epidemiol*. 150:105–12. [PubMed: 10400547]

Table 1.

Age-adjusted characteristics of postmenopausal women in the study, by alcohol use status at mammogram (NHS and NHSII)

Characteristic	Alcohol consumption		
	None n=774	0-<5 g/day n=713	5 g/day n=613
Mean (SD)			
Percent mammographic density	24.2 (17.0)	24.5 (17.1)	28.7 (19.4)
Dense area (cm ²)	47.8 (39.5)	49.0 (40.6)	49.0 (40.6)
Non-dense area (cm ²)	167.8 (99.2)	163.7 (89.8)	133.9 (79.9)
Age at mammogram (years) ^a	58.2 (8.3)	57.8 (7.7)	58.9 (7.4)
Age at menarche (years)	12.5 (1.4)	12.4 (1.4)	12.5 (1.4)
Age at menopause (years)	47.5 (6.1)	47.8 (5.9)	48.0 (5.5)
Body Mass Index (kg/m ²)	27.0 (5.9)	26.6 (5.4)	24.8 (3.9)
Percentages			
Parity/age at first birth			
Nulliparous	7	8	12
Parous, age<25 years	49	48	44
Parous, age ≥25 years	44	43	44
Family history of breast cancer	11	13	12
Benign breast disease	22	25	21
Never used HT	37	34	36
Past HT use	20	20	19
Current HT use	42	46	45

Abbreviations: SD – standard deviation; HT – hormone therapy

^aValue is not age adjusted

Table 2.Overall associations of alcohol consumption with postmenopausal breast density^a

	N	Percent density (β and 95% CI)	Absolute dense area (β and 95% CI)	Non-dense area (β and 95% CI)
Alcohol use at mammogram				
0	764	Ref	Ref	Ref
0–<5	707	–0.06 (–0.22; 0.09)	0.00 (–0.25; 0.25)	0.11 (–0.19; 0.41)
5	611	0.06 (–0.11; 0.22)	–0.08 (–0.34; 0.19)	–0.41 (–0.73; –0.09)
P for trend	2082	0.32	0.53	<0.01
Continuous, per 10g	2082	0.02 (–0.06; 0.09)	–0.08 (–0.20; 0.04)	–0.21 (–0.35; –0.06)

^aAdjusted for age (continuous), BMI (continuous), age at menarche (<12, 12, 13, >13), a family history of breast cancer (Yes/No), a history of benign breast disease (Yes/No), NHS cohort (NHSI, NHSII), postmenopausal hormone use status (none, past, current, past/unknown current), age at menopause (<46, 46–<50, 50–<55, 55, unknown), and parity and age at first child's birth (nulliparous, parous with age at first birth <25, parous with age at first birth ≥25)

Table 3.Associations of alcohol with breast density measures by woman's postmenopausal hormone therapy status^a

	N	Percent density (β and 95% CI)	Absolute dense area (β and 95% CI)	Non-dense area (β and 95% CI)
Never used hormones				
Alcohol use				
0	282	Ref	Ref	Ref
0–<5	244	–0.16 (–0.42, 0.10)	–0.08 (–0.49, 0.34)	0.11 (–0.39, 0.61)
5	216	–0.15 (–0.43, 0.12)	–0.40 (–0.83, 0.04)	–0.32 (–0.84, 0.21)
P for trend	742	0.42	0.06	0.14
Continuous, per 10g	742	–0.09 (–0.21, 0.03)	–0.23 (–0.42, –0.03)	–0.15 (–0.38, 0.08)
Current HT				
Alcohol use				
0	326	Ref	Ref	Ref
0–<5	326	–0.02 (–0.25, 0.22)	0.03 (–0.35, 0.41)	0.18 (–0.26, 0.63)
5	273	0.16 (–0.09, 0.41)	0.23 (–0.18, 0.63)	–0.23 (–0.72, 0.25)
P for trend	925	0.15	0.25	0.17
Continuous, per 10g	925	0.08 (–0.03, 0.20)	0.04 (–0.14, 0.22)	–0.20 (–0.42, 0.01)
Past HT				
Alcohol use				
0	156	Ref	Ref	Ref
0–<5	137	–0.00 (–0.37, 0.36)	0.02 (–0.51, 0.56)	–0.11 (–0.80, 0.57)
5	122	0.12 (–0.27, 0.50)	–0.26 (–0.83, 0.31)	–0.79 (–1.51, –0.07)
P for trend	415	0.51	0.30	0.02
Continuous, per 10g	415	0.01 (–0.19, 0.22)	–0.12 (–0.43, 0.18)	–0.24 (–0.63, 0.15)
Current E+P				
Alcohol use				
0	105	Ref	Ref	Ref
0–<5	109	–0.16 (–0.58; 0.25)	0.15 (–0.52; 0.82)	0.81 (–0.04; 1.66)
5	116	0.15 (–0.27; 0.56)	0.37 (–0.29; 1.03)	–0.00 (–0.84; 0.84)
P for trend	330	0.26	0.29	0.41
Continuous, per 10g	330	0.05 (–0.12; 0.22)	0.06 (–0.21; 0.33)	–0.15 (–0.49; 0.20)

Abbreviations: HT – hormone therapy; E+P – estrogen + progesterone therapy

^a Adjusted for age (continuous), BMI (continuous), age at menarche (<12, 12, 13, >13), a family history of breast cancer (Yes/No), a history of benign breast disease (Yes/No), NHS cohort (NHSI, NHSII), age at menopause (<46, 46–<50, 50–<55, 55, unknown), and parity and age at first child's birth (nulliparous, parous with age at first birth <25, parous with age at first birth ≥25)

Note: p-values for Interactions of alcohol with HT: percent density p=0.19; absolute dense area p=0.42; non-dense area p=0.43