Alcohol and Tobacco Use in Relation to Mammographic Density in 23,456 Women

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ABSTRACT

Background: Percent density (PD) is a strong risk factor for breast cancer that is potentially modifiable by lifestyle factors. PD is a composite of the dense (DA) and nondense (NDA) areas of a mammogram, representing predominantly fibroglandular or fatty tissues, respectively. Alcohol and tobacco use have been associated with increased breast cancer risk. However, their effects on mammographic density (MD) phenotypes are poorly understood.

Methods: We examined associations of alcohol and tobacco use with PD, DA, and NDA in a population-based cohort of 23,456 women screened using full-field digital mammography machines manufactured by Hologic or General Electric. MD was measured using Cumulus. Machine-specific effects were estimated using linear regression, and combined using random effects meta-analysis.

Results: Alcohol use was positively associated with PD (P_{trend} = 0.01), unassociated with DA (P_{trend} = 0.23), and inversely associated with NDA (P_{trend} = 0.02) adjusting for age, body mass index, reproductive factors, physical activity, and family history of breast cancer. In contrast, tobacco use was inversely associated with PD (P_{trend} = 0.0008), unassociated with DA (P_{trend} = 0.93), and positively associated with NDA (P_{trend}<0.0001). These trends were stronger in normal and overweight women than in obese women.

Conclusions: These findings suggest that associations of alcohol and tobacco use with PD result more from their associations with NDA than DA.

Impact: PD and NDA may mediate the association of alcohol drinking, but not tobacco smoking, with increased breast cancer risk. Further studies are needed to elucidate the modifiable lifestyle factors that influence breast tissue composition, and the important role of the fatty tissues on breast health.

Introduction

High percent density (PD) is common and is among the strongest risk factors for breast cancer (1). The prevalence of heterogeneously dense or extremely dense breasts is between 40% and 60% of screening age women, and is estimated to account for up to one third of all breast cancer diagnoses (2). PD decreases with age, body mass index (BMI), number of children, and menopause; and increases with age at menarche, age at first birth, and family history of breast cancer (1, 3, 4). Of particular interest are modifiable exposures believed to alter PD, such as the use of menopausal hormone therapy (MHT), tamoxifen (5), and alcohol (6), that could provide opportunities for women to reduce their breast cancer risk. The dense area (DA) of the breast appears radiopaque on a mammogram and contains greater proportions of collagen, epithelial, and stromal cells compared with the nondense area (NDA), which largely consists of fatty tissue (7). Recent studies have shown that NDA is inversely associated with breast cancer risk, independently of DA, suggesting that normal breast fat may play a protective role (8, 9). The underlying mechanisms through which mammographic density (MD) phenotypes are associated with breast cancer risk are poorly understood.

Alcohol drinking has been consistently associated with increased breast cancer risk (10). Plausible mechanisms underlying this association include increased sex hormone levels and carcinogenic DNA damage with greater alcohol consumption (11). Alcohol use has also been associated with higher PD (6, 12–15), but associations with absolute DA have been inconsistent (13, 15–21). It remains unknown whether alcohol influences PD by increasing DA or decreasing NDA because few prior studies have examined all three MD phenotypes. Tobacco smoke is an important human carcinogen that has been associated with increased breast cancer mortality (22), but less consistently with breast cancer incidence (23, 24). Tobacco smoke is a complex mixture of chemicals with known carcinogenic and endocrine effects (25). The effects of tobacco use on MD phenotypes are uncertain (20, 26–30).

Prior studies of alcohol and tobacco use have focused primarily on PD, due in part to the greater difficulty of quantitating the constituent measures of DA and NDA. However, to understand the mechanisms through which tobacco and alcohol influence PD, it is important to distinguish between their effects on the dense and nondense tissue components, which are likely to have distinct etiologies (31) as well as cellular interactions that influence the breast tissue microenvironment (32). In addition, few prior studies have examined interactions

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between alcohol and tobacco, or potential modifiers of their effects, due to the large sample sizes required for adequate statistical power. Finally, most prior studies have utilized screen-film mammography, which has largely been replaced by full-field digital mammography (FFDM).

In this study, we examined associations of alcohol and tobacco use with quantitative measures of PD, DA, and NDA in a population-based cohort of 23,456 women who underwent screening FFDM at Kaiser Permanente Northern California (KPNC) clinics using Hologic or General Electric (GE) machines. We further examined the combined effects of alcohol and tobacco use, and potential modification by BMI, menopausal status, and MHT use. To our knowledge, this is the largest study to date of alcohol and tobacco use and all three quantitative MD phenotypes measured on contemporary FFDM images.

Materials and Methods

Study population

This population-based study included non-Hispanic white women in the KPNC Research Program on Genes, Environment and Health (RPGEH) who participated in a genome-wide association study of MD (33, 34). The study cohort has previously been described (4, 35, 36). Briefly, eligible women were between the ages of 38 and 80 at mammography and had at least one screening FFDM exam during 2003 to 2013 at KPNC mammography clinics throughout Northern California, of which 36 clinics used Hologic ($n = 20,311$) and 11 clinics used GE ($n = 3,881$) FFDM machines. We excluded women with breast implants (3.6%), breasts that were too large to fit on a single image (1%), unreadable or unavailable images (2.6%), or history of bilateral breast cancer (0.06%) for whom no unaffected breast image was available for assessment (4, 35). Women with missing survey data for alcohol ($n = 686$) or tobacco ($n = 701$) were also excluded, yielding a final sample size of 23,456.

MD measurements

We obtained processed FFDM images for the closest screening exam following the RPGEH survey ($n = 23,323$; 99.4%) when available, or prior to the survey date ($n = 133$; 0.6%) otherwise, from the KPNC imaging archive. The average time interval from the survey date to the mammogram was 2.9 years. For women with a diagnosis of unilateral breast cancer ($n = 1,918$; 8.2%), we selected the image of the unaffected breast from the closest prediagnostic exam following the survey when available ($n = 592$; 30.9%; ref. 35). Sensitivity analyses were performed excluding women ($n = 1,449$; 6.2%) who were diagnosed with breast cancer before the mammogram and/or surveyed after the mammogram. For women without breast cancer, we selected the left breast image except in a random 10% subset of women for whom the right breast image was selected to blind the reader to the cancer status of images. All density measurements were performed using the craniocaudal view. All FFDM images were down-sampled to a pixel size of 200 μm. Hologic images were denoised using a median filter with a radius of 3 pixels, as previously described (35).

All MD measurements were performed by a single radiological technologist (R.Y. Liang) trained by M.J. Yaffe and J.A. Lipson in the use of the Cumulus6 (37) software provided by M.J. Yaffe. Cumulus6 automatically detects the outer edge of the breast for most FFDM images. The reader is required to define the pectoral muscle boundary, and select the pixel intensity threshold for distinguishing the dense and NDA of the breast image. PD is computed by the DA divided by the total breast area, and NDA by the total area minus the DA. Reader reproducibility was assessed using random replicates within each image batch of up to 1,100 images. The intraclass correlation coefficients for PD, DA, and NDA were 0.953, 0.927, and 0.996 for Hologic images; and 0.961, 0.940, and 0.995 for GE images, respectively.

Alcohol and tobacco use

Alcohol and tobacco use were ascertained from the survey administered at enrollment into RPGEH. Information on alcohol use was obtained from the following two survey questions. (1) *On average, how many days a week do you have a drink containing alcohol?* Responses ranged from 0 to 7. (2) *On a typical day that you drink, how many drinks do you have?* Responses ranged from 0 to 8 or more drinks. The number of alcoholic drinks consumed on a typical week, drinks per week (DPW), was estimated by the product of the responses to these two questions, and categorized into tertiles: none (0 DPW), moderate (1–4 DPW), or heavy (5+ DPW). Finer categories yielded similar associations, but resulted in small numbers in some exposure categories and less robust analyses of interactions and combined alcohol and tobacco effects. Tobacco use was determined based on the responses to the following questions: (1) *Have you ever smoked one or more cigarettes per day for 6 months or longer?* (2) *Do you currently smoke or have you stopped smoking?* (3) *On average, how many packs of cigarettes do you (or did you) smoke per day (PPD)*? Response options were: *none, <0.5 packs, 0.5 to 1 pack, 1 to 1.5 packs, >1.5 packs*. Tobacco use was categorized as: none, $<^1/_2$ PPD, $^1/_2$-1 PPD, or 1+ PPD among women who smoked one or more cigarettes per day for 6 months or longer because only 3% of women reported smoking >1.5 PPD. We performed exploratory analyses to investigate associations of current or former tobacco use, and duration of smoking, with MD phenotypes.

Covariates

Model covariates were chosen *a priori* on the basis of known biologically plausible associations with MD and included: age at mammography, BMI at mammography, BMI at age 18, age at first birth, number of children, age at menarche, family history of breast cancer, menopausal status, MHT use within the 5 years prior to mammography, physical activity, and image batch. Age at mammography was determined based on date of birth and date of exam from the electronic health record (EHR). BMI was calculated using the height and weight recorded in the EHR for the patient visit closest to the mammography date. Late adolescent BMI was computed based on self-reported weight at age 18 and adult height recorded in the EHR. The KPNC pharmacy database, which records all dispensed outpatient and inpatient prescriptions, was used to determine MHT use within the 5 years prior to the mammography exam. Physical activity was defined as total metabolic equivalent (MET) hours per week and based on total MET-min/week = (8 × vigorous) + (4 × moderate) + (3.3 × walking) min/week (38). Participants were asked how many days per week they did vigorous, moderate activity or walking, and how many minutes on average each time they did the activity.

We modeled the key covariates age and BMI using polynomial terms (age, age^2, BMI, BMI^2, and BMI^3) to allow for nonlinear relationships (4). Age at menarche, age at first birth, number of children, family history of breast cancer, menopausal status, and MHT use within 5 years were modeled categorically based on the RPGEH survey and EHR data (4). To retain subjects with incomplete data for the model covariates, we included missing categories as indicated: late adolescent BMI (quartiles, missing), age at menarche (<11, 12–13, 14–15, 16+, missing), age at first birth (<20, 20–24, 25–29, 30–34, 35+ years, missing), parity (0, 1, 2, 3, 4+ children, missing), menopausal status (premenopausal, postmenopausal), MHT use (yes, no),

first-degree relative with breast cancer (yes, no), and physical activity (quartiles, missing). To evaluate effect modification, BMI strata were defined using the World Health Organization categories of normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2).

Statistical methods

We applied a square-root transformation to PD, DA, and NDA to reduce skew and heteroscedasticity of residuals in linear regression models. $\sqrt{}$DA and $\sqrt{}$NDA can be interpreted as the length (cm) of the side of a square area of dense or nondense tissue, respectively, whereas $\sqrt{}$PD can be interpreted as the width (cm) of the dense square within a 10 cm × 10 cm breast area (39). To facilitate comparison with prior studies of quantitative area-based MD measures, we transformed the main parameter estimates back to units of percentage for PD and cm^2 for DA and NDA using the delta method (40). This nonlinear transformation depends on the baseline value of the original phenotype, and the overall means of 21.08%, 28.06 cm^2, and 135.11 cm^2 for PD, DA, and NDA, respectively, were used for this purpose.

Linear regression models were used to evaluate the association of the exposure and outcomes, adjusted for covariates, separately for each FFDM machine manufacturer (Hologic or GE). Machine-specific estimates were then combined by restricted maximum likelihood (REML) random effects meta-analysis using the R metafor package. The REML random effects meta-analysis method may be more robust than the DerSimonian and Laird method in accounting for the error associated with parameter estimation when the number of study groups is small (41). We used the Q statistic to test for study heterogeneity by machine type, and I^2 to quantify the degree of heterogeneity (42). We performed global tests for statistical interactions using a likelihood ratio test to compare the linear mixed-effects models with and without the interaction terms, where machine type was modeled as a random intercept, and all other covariates were modeled as fixed effects using the R lme4 package. Mediation analyses were conducted to evaluate the relative contribution of DA and NDA to associations with PD (43, 44). Standard errors of the indirect effect estimates were computed using 2,000 bootstrap replicates, and the machine-specific effects were combined by REML random effects meta-analysis. All analyses were implemented in SAS version 9.4 (SAS Inc.) and R version 3.5 (R Foundation for Statistical Computing).

Results

Subject characteristics

The study included 23,456 women screened at KPNC clinics that used Hologic (84%) or GE (16%) FFDM machines (**Table 1**). Women screened at clinics using Hologic machines were 2.6 years older and had 0.8 kg/m^2 higher BMI, on average, compared with women screened at clinics using GE machines. In addition, the Hologic cohort was slightly more likely to be postmenopausal, use MHT, and have higher parity and older age at first birth. The distributions of alcohol and tobacco use, and square-root–transformed values of PD, DA, and NDA were generally comparable in the Hologic and GE cohorts. PD was strongly correlated with DA ($R = 0.8$) and NDA ($R = -0.8$) as expected, and DA and NDA were moderately negatively correlated ($R = -0.35$) in both cohorts. Less than 3% of women were excluded because of missing alcohol or tobacco data, and these women did not have significantly different distributions of age, BMI, or other covariates.

Table 1. Study population characteristics, by digital mammography machine manufacturer.

Characteristic	Hologic study $N = 19{,}699$		GE study $N = 3{,}757$	
	n	%	*n*	%
Age (years), mean ± SD	61.9	± 8.6	59.3	± 8.9
Age at menarche (years)				
<11	4,200	21.3	777	20.7
12–13	10,729	54.5	2,079	55.3
14–15	3,417	17.4	635	16.9
16+	722	3.7	166	4.4
Missing	631	3.2	100	2.7
BMI (kg/m^2), mean ± SD	27.7	± 6.2	26.9	± 5.8
Late adolescent BMI (kg/m^2), mean ± SD				
1st quartile	18.1	± 0.9	18.1	± 0.9
2nd quartile	20.0	± 0.4	19.9	± 0.4
3rd quartile	21.4	± 0.4	21.4	± 0.5
4th quartile	25.0	± 3.1	24.9	± 3.4
Missing, *n*	1,883		361	
Age at first birth (years)				
<20	2,111	10.7	360	9.6
20–24	5,516	28.0	990	26.4
25–29	4,553	23.1	785	20.9
30–34	2,267	11.5	411	10.9
35–40	926	4.7	177	4.7
>40	209	1.1	36	1.0
Missing	2,302	11.7	558	14.8
Number of births				
None	1,815	9.2	440	11.7
1	3,006	15.3	545	14.5
2	7,633	38.8	1,314	35.0
3	3,409	17.3	608	16.2
4+	1,648	8.4	309	8.2
Missing	2,188	11.1	541	14.4
MHT use within 5 years prior to mammogram				
Yes	4,662	23.7	1140	30.3
No	15,037	76.3	2617	69.7
Menopausal status				
Premenopause	4,676	23.7	1,031	27.4
Postmenopause	15,023	76.3	2,726	72.6
First-degree relative with breast cancer				
Yes	1,865	9.5	358	9.5
No	17,834	90.5	3,399	90.5
Breast cancer diagnosis prior to mammogram				
Yes	1,127	5.7	199	5.3
No	18,572	94.3	3,558	94.7
Physical activity (METs), mean ± SD				
1st quartile	61.7	± 69.4	64.7	± 70.0
2nd quartile	411.8	± 122.1	413.6	± 120.0
3rd quartile	953.1	± 204.0	950.5	± 196.8
4th quartile	2,243.9	± 749.9	2,187.4	± 693.8
Missing, *n*	396		72	
Alcohol use (drinks per week)				
None	7,926	40.2	1,487	39.6
1–4	6,122	31.1	1,116	29.7
5+	5,651	28.7	1,154	30.7
Tobacco use (packs per day)				
Never	11,969	60.8	2,264	60.3
<1/2	2,507	12.7	436	11.6
1/2–1	2,980	15.1	607	16.2
1+	2,243	11.4	450	12.0
MD phenotypes, mean ± SD				
PD (%)	20.4	± 14.9	24.4	± 17.1
DA (cm^2)	27.9	± 17.9	29.0	± 20.9
NDA (cm^2)	140.0	± 77.7	109.2	± 61.0

(Continued on the following page)

Table 1. Study population characteristics, by digital mammography machine manufacturer. (Cont'd)

Characteristic	Hologic study N = 19,699		GE study N = 3,757	
	n	%	*n*	%
MD phenotypes (square-root), mean ± SD				
PD	4.2	± 1.6	4.6	± 1.8
DA	5.0	± 1.6	5.0	± 1.9
NDA	11.3	± 3.3	10.0	± 2.9

Alcohol use and MD phenotypes

Associations of alcohol use with PD, DA, and NDA in adjusted models were similar in the Hologic and GE cohorts (Supplementary Fig. S1). There was no evidence of significant heterogeneity by machine type (Q statistic $P > 0.05$), and I^2 was below 50% for all effect estimates except for the highest category of alcohol use in the NDA model ($I^2 = 68\%$, $P = 0.08$). We found a positive trend ($P_{trend} = 0.01$) of higher PD with higher levels of alcohol use (**Table 2**). Specifically, women who reported drinking 5+ alcoholic beverages per week had higher PD than nondrinkers by approximately half a percent (95% confidence interval: 0.07, 0.83). However, alcohol use was not significantly associated with DA. In contrast, there was an inverse trend of lower NDA with higher levels of alcohol use ($P_{trend} = 0.02$). Women who reported drinking 5+ alcoholic beverages per week had lower NDA than nondrinkers by approximately 4 cm^2 (−7.06, −0.35).

The association of alcohol use with higher PD was explained mostly by lower NDA, rather than higher DA. Specifically, the positive association of alcohol drinking with PD was no longer significant after adjusting for NDA ($P_{trend} = 0.60$), but was only slightly attenuated by adjusting for DA ($P_{trend} = 0.059$). Consistent with these results, mediation analysis showed that the indirect effect of alcohol on PD through NDA was statistically significant ($P = 0.001$), whereas the indirect effect through DA was not significant ($P = 0.88$). Approximately 69% of the total effect of alcohol on PD was explained by NDA in the fully adjusted mediation model.

Stratification by BMI (**Fig. 1**; Supplementary Table S1) showed that alcohol use was positively associated with PD and inversely associated with NDA in overweight or normal weight women, but these associations were not statistically significant in obese women. The global tests of interactions between alcohol and BMI categories reached statistical significance for PD ($P_{interaction} = 0.04$) and NDA ($P_{interaction} = 0.02$). Stratification by menopausal status (**Fig. 1**; Supplementary Table S2) showed that alcohol use was positively associated with PD, except for a nonsignificant inverse association among postmenopausal women who drank 1 to 4 DPW ($P_{interaction} = 0.016$). However, there was no evidence that menopausal status significantly modified the associations of alcohol use with either NDA or DA, suggesting that the interaction found for PD may be due to chance. Further stratification by MHT use among postmenopausal women (**Fig. 1**; Supplementary Table S3) showed that the effects of alcohol were not significantly modified by MHT use for PD ($P_{interaction} = 0.70$), DA ($P_{interaction} = 0.86$), or NDA ($P_{interaction} = 0.77$).

Tobacco use and MD phenotypes

Associations of tobacco use with PD, DA, and NDA in adjusted models were similar in the Hologic and GE cohorts (Supplementary Fig. S1). There was no evidence of significant heterogeneity by machine type (Q statistic $P > 0.05$ and $I^2 < 20\%$). Tobacco use was inversely associated with PD and positively associated with NDA (**Table 2**). Women who reported smoking $^1/_2$ to 1 PPD and 1+ PPD, respectively, had lower PD by approximately half (−0.89, −0.04) and three quarters (−1.23, −0.28) of a percent than nonsmokers ($P_{trend} = 0.0008$). Tobacco use was not significantly associated with DA ($P_{trend} = 0.93$), except for a small positive association in the lowest (<$^1/_2$ PPD) category that is likely due to chance. In contrast, women who reported smoking $^1/_2$ to 1 PPD and 1+ PPD, respectively, had higher NDA by approximately 3 (0.64, 5.03) and 4 (2.33, 6.40) cm^2 compared with nonsmokers ($P_{trend} < 0.0001$).

The association of tobacco use with lower PD was explained mostly by higher NDA, rather than lower DA. Specifically, the inverse association of smoking with PD was no longer significant after adjusting for NDA ($P_{trend} = 0.74$), but remained significant after adjusting for DA ($P_{trend} < 0.0001$). Consistent with these results, mediation analysis showed that the indirect effect of smoking on PD through NDA was statistically significant ($P < 0.0001$), whereas the indirect effect through DA was not significant ($P = 0.39$). Approximately 83% of the total effect of smoking on PD was explained by NDA in the fully adjusted mediation model.

Exploratory analyses of smoking status indicated that the inverse association with PD and positive association with NDA were stronger among current (3.8%) versus former (35.4%) smokers (Supplementary

Table 2. Association of alcohol and tobacco use with MD phenotypes.

	N	%	PD (%) β (95% CI)	*P*	DA (cm^2) β (95% CI)	*P*	NDA (cm^2) β (95% CI)	*P*
Alcohol use								
None	9,413	40.1	Referent					
1–4 DPW	7,238	30.9	0.08 (−0.58–0.74)	0.8073	−0.30 (−1.29–0.69)	0.5542	−1.94 (−3.41 to −0.47)	0.0098
5+ DPW	6,805	29.0	0.45 (0.07–0.83)	0.0195	0.28 (−0.41–0.96)	0.4250	−3.71 (−7.06 to −0.35)	0.0314
P for trend				0.0149		0.2323		0.0189
Tobacco use								
Never	14,233	60.7	Referent					
<1/2 PPD	2,943	12.6	−0.02 (−0.48–0.45)	0.9436	0.69 (0.03–1.34)	0.0383	1.77 (−0.14–3.69)	0.0693
1/2–1 PPD	3,587	15.3	−0.47 (−0.89 to −0.04)	0.0322	0.08 (−0.52–0.68)	0.7984	2.83 (0.64–5.03)	0.0110
1+ PPD	2,693	11.5	−0.76 (−1.23 to −0.28)	0.0021	−0.20 (−0.88–0.49)	0.5731	4.37 (2.33–6.40)	<0.0001
P for trend				0.0008		0.9340		<0.0001

Note: All models were adjusted for age, age^2, BMI, BMI^2, BMI^3, late adolescent BMI, age at menarche, age at first birth, parity, menopausal status, MHT use, first-degree relative with breast cancer, physical activity, and image batch. Effects were estimated using separate linear regression models of the square-root–transformed phenotype in the Hologic and GE cohorts, and combined using REML random effects meta-analysis. Coefficients (β) and 95% confidence intervals (CI) were back-transformed to the original scale.

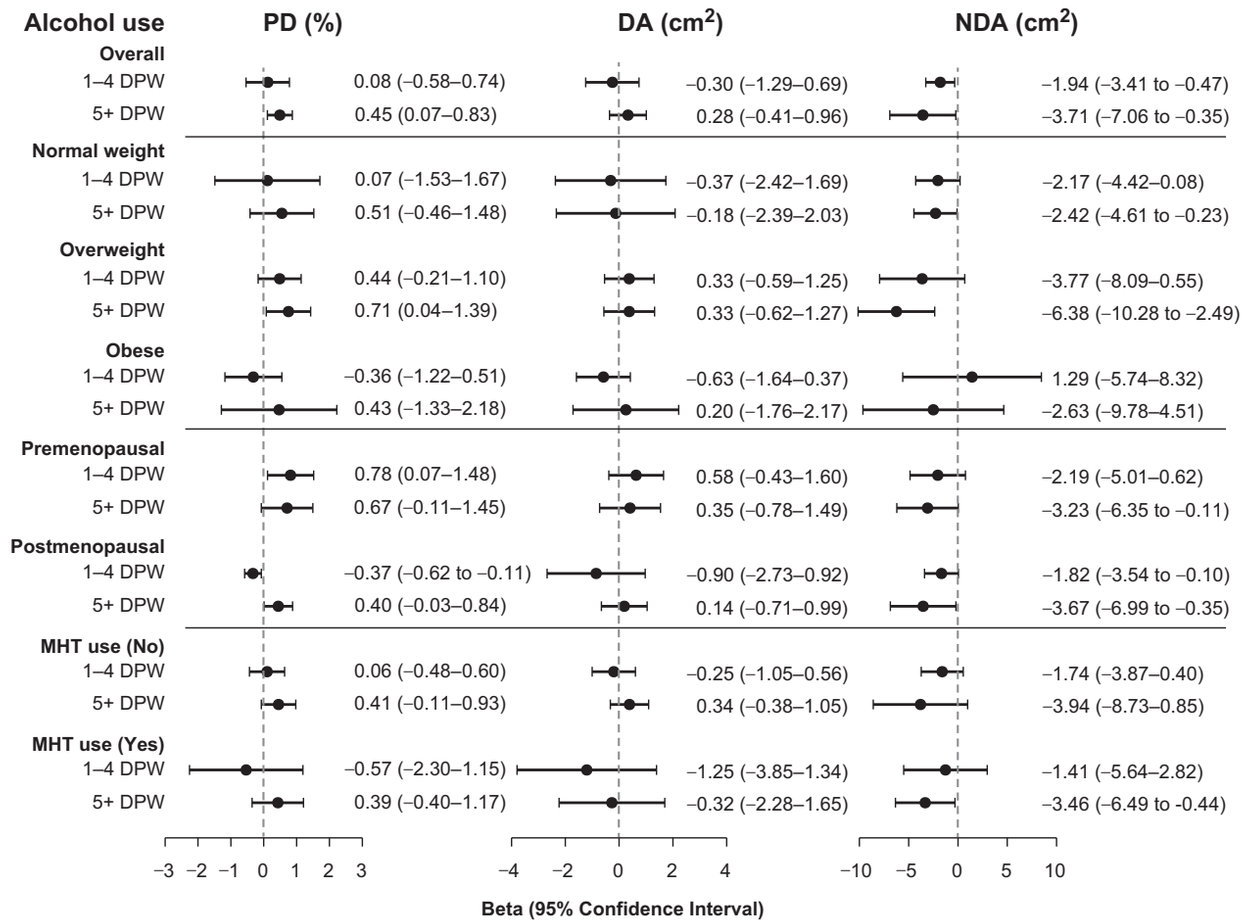

Figure 1.

Associations of alcohol drinking with MD phenotypes compared with nondrinkers, overall and stratified by BMI category, menopausal status, and MHT use. All models were adjusted for tobacco use, age, age^2, BMI, BMI^2, BMI^3, late adolescent BMI, age at menarche, age at first birth, parity, menopausal status, MHT use, first-degree relative with breast cancer, physical activity, and image batch. Effects were estimated using separate linear regression models of the square-root–transformed phenotype in the Hologic and GE cohorts, and combined using REML random effects meta-analysis. Coefficients (β) and 95% confidence intervals (CI) were back-transformed to the original scale.

Table S4). Exploratory analyses of smoking duration showed that women who smoked for >15 years (16.3%) had significantly lower PD, and women who smoked for >5 years (29.2%) had significantly higher NDA (Supplementary Table S4). These results indicate that the associations with PD and NDA may be stronger among current smokers who have smoked for at least 5 years.

Stratification by BMI (**Fig. 2**; Supplementary Table S1) showed that the inverse association of tobacco use with PD was strongest in overweight women, whereas no statistically significant trends were found in obese or normal weight women. Similarly, the positive association of tobacco use with NDA was stronger in normal (P_{trend} = 0.0015) and overweight (P_{trend} < 0.0001) women than in obese women (P_{trend} = 0.69). Global tests of the interaction of tobacco and BMI categories were statistically significant for PD ($P_{interaction}$ = 0.0017) and NDA ($P_{interaction}$ < 0.0001), suggesting that estimated associations with tobacco use are attenuated in obese women. Stratification by menopausal status (**Fig. 2**; Supplementary Table S2) showed that the association of tobacco use with PD ($P_{interaction}$ = 0.50) and NDA ($P_{interaction}$ = 0.24) was similar in premenopausal and postmenopausal women. Stratification by MHT use in postmenopausal women (**Fig. 2**; Supplementary Table S3) likewise yielded no evidence of significant modification of tobacco effects.

Sensitivity and exploratory analyses of alcohol and tobacco use

Exploratory analyses of alcohol and tobacco use stratified by both menopausal status and BMI were comparable with the results stratified by BMI only, although the sample size and statistical power were reduced in each substratum. Among both premenopausal (Supplementary Table S5) and postmenopausal (Supplementary Table S6) women who were overweight or normal weight, alcohol use was inversely associated with NDA, and tobacco use was positively associated with NDA, whereas no significant trends were found in obese women. Sensitivity analyses (Supplementary Table S7) excluding 1,449 (6.2%) women who were diagnosed with breast cancer before the mammogram and/or surveyed after the mammogram showed no meaningful differences compared with the main results including all 23,456 women (**Table 2**; Supplementary Table S8). These results indicated that associations of alcohol and tobacco use with MD phenotypes were not unduly influenced by breast cancer treatment or reverse temporality.

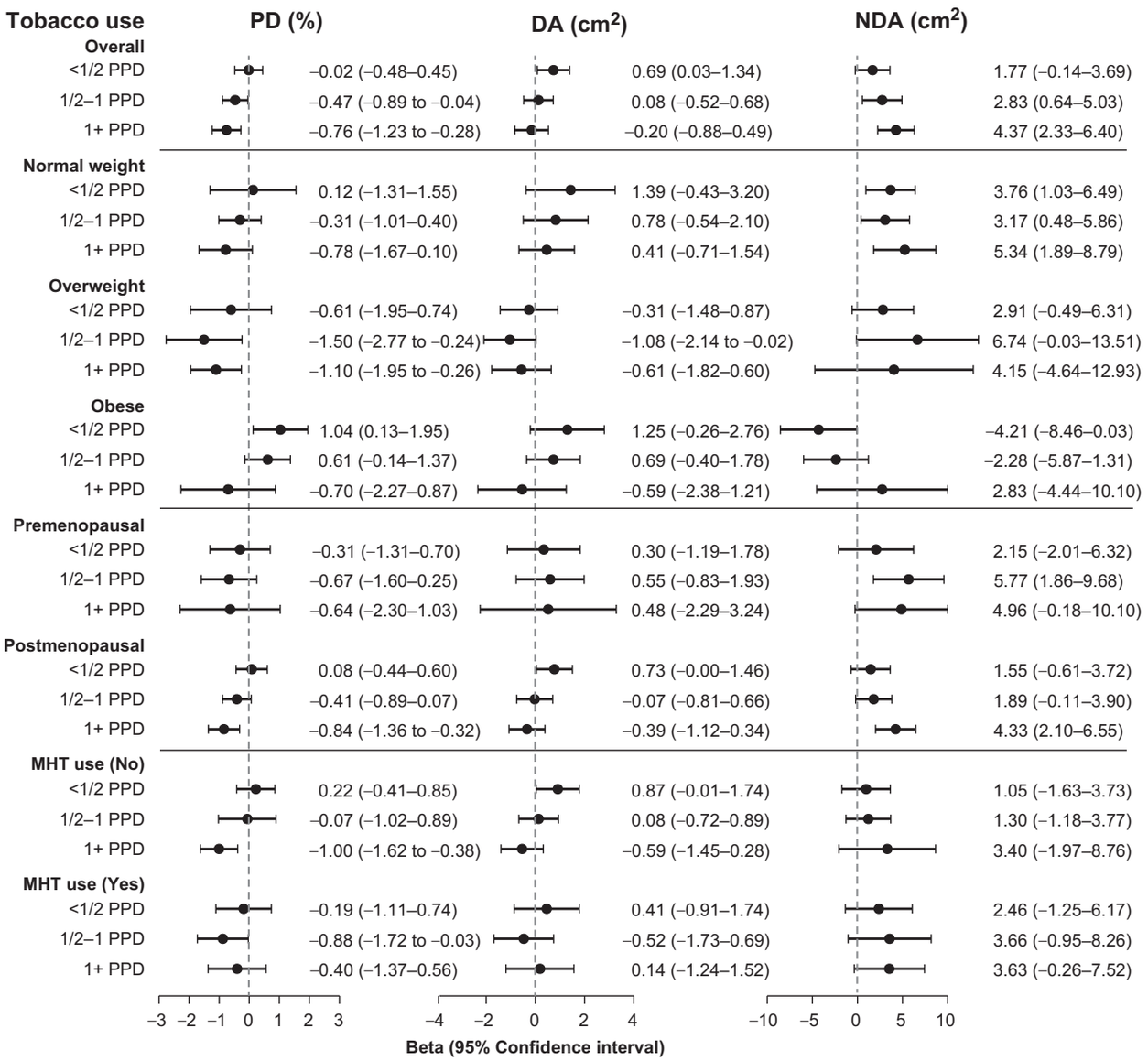

Figure 2.

Associations of tobacco smoking with MD phenotypes compared with nonsmokers, overall and stratified by BMI category, menopausal status, and MHT use. All models were adjusted for tobacco use, age, age^2, BMI, BMI^2, BMI^3, late adolescent BMI, age at menarche, age at first birth, parity, menopausal status, MHT use, first-degree relative with breast cancer, physical activity, and image batch. Effects were estimated using separate linear regression models of the square-root–transformed phenotype in the Hologic and GE cohorts, and combined using REML random effects meta-analysis. Coefficients (β) and 95% confidence intervals (CI) were back-transformed to the original scale.

Combined effects of alcohol and tobacco use

In light of the opposite directions of association of tobacco and alcohol use with MD phenotypes, and the correlation between the two behaviors, it is important to consider their combined effects. Comparison of adjusted models including both alcohol and tobacco to models with only one of the two exposures showed evidence of negative confounding (Supplementary Table S8). Specifically, the magnitude of the effects for the most extreme categories of alcohol (5+ DPW) and tobacco use (1+ PPD) on PD and NDA increased by >10% when both exposures were included in the model. We found no evidence of departure from an additive model ($P_{interaction}$ = 0.98) for the combined effects of alcohol and tobacco use on MD phenotypes (Supplementary Table S9). Specifically, for NDA the effects of heavy alcohol use in nonsmokers, and heavy tobacco use in nondrinkers, were of similar magnitude and in opposite directions, and no significant association was found among women with heavy use of both alcohol and tobacco.

Discussion

In this large population-based study of 23,456 women, we found that alcohol use was positively associated with PD, unassociated with

DA, and inversely associated with NDA, whereas tobacco use was inversely associated with PD, unassociated with DA, and positively associated with NDA. These associations were strongest among normal and overweight women, and were attenuated in obese women. We did not find evidence of interactions between alcohol and tobacco use, nor modification of their effects by menopausal status and MHT use. This study provides evidence that associations of alcohol and tobacco use with PD may be mediated mostly through their associations with NDA rather than DA, and motivates future studies to examine the biological role of breast adipocytes in MD and breast cancer risk.

Comparison with prior studies

The finding that higher alcohol consumption is associated with higher PD is consistent with a recent meta-analysis of 11 studies that reported a significant difference in PD of 0.84% when comparing the highest with the lowest categories of alcohol use (6). In a subset of five studies (13, 15–18) with absolute DA measurements, a positive association was found overall (6). However, the three positive studies had a combined sample size of 542 (13, 15, 16), whereas the two studies with no significant overall associations were comparatively larger studies of 1,147 and 2,251 women, respectively, in Sweden (17) and Norway (18). Two more recent Scandinavian studies found that alcohol use was positively associated with fully automated measures of DA (20) or dense volume (21) in models adjusted only for age, BMI, and menopausal status (20) or with additional adjustment for education and number of pregnancies (21). To our knowledge, only two previous studies have examined alcohol use in relation to NDA (17, 19). Consistent with our findings, both studies reported nonsignificant positive associations with PD, null associations with DA, and significant inverse associations with NDA. NDA was 10.6 cm^2 lower when comparing ≥10 g of alcohol per day with none (17), and 0.41 lower on the square-root scale when comparing ≥5 g of alcohol per day with none among 2,100 postmenopausal women within the Nurses' Health Study (19). These reported effect sizes were larger than our parameter estimates of −0.16 (−3.71 cm^2) for NDA and 0.05 (0.45%) for PD comparing 5+ DPW with none, which could be due in part to our tighter adjustment for BMI using three polynomial terms instead of a single linear term, or differences in the alcohol consumption categories.

The finding that tobacco use was associated with lower PD is consistent with most prior studies (14, 21, 26, 27, 45–48). The few studies that reported null associations used dichotomous measures of tobacco use and PD (28–30), which could have obscured a dose–response relationship. To our knowledge, only one prior study of 1,147 women in Sweden examined associations of tobacco use with NDA in addition to PD and DA (17). Although no significant associations were reported, NDA was 2.3 cm^2 higher comparing current with never smokers (17). Women in the Swedish study had a similar prevalence of smoking, but lower smoking intensity (8.5% >0.5 PPD) than in our study (26.5% >0.5 PPD), which may explain the larger NDA difference of 5.4 cm^2 comparing current with never smokers in our study.

Hypothesized mechanisms

The associations of alcohol and tobacco use with NDA in this study were unlikely to be explained by residual confounding by BMI, which reflects overall weight rather than adipose tissue distribution, because we adjusted for BMI using a flexible nonlinear model with three polynomial terms, and also adjusted for quartiles of BMI at age 18, in all models. Moreover, stratification by BMI showed that the associations of alcohol and tobacco use with NDA persisted even in normal or overweight women, within a narrow BMI range that was further adjusted using the same saturated covariate model. The attenuated associations with NDA found in obese women may have been due to smaller numbers, greater measurement error (49), or biological differences in this subgroup.

The associations of alcohol and tobacco use with MD phenotypes may be mediated partly through their effects on sex hormone levels. Alcohol use has been shown to increase estrogen signaling via upregulation of aromatase expression and activity, increased estrogen receptor expression and activity, and decreased hepatic clearance of circulating estrogens (50, 51). In contrast, tobacco use has been reported to have antiestrogenic effects via increased hepatic metabolism due to the induction of cytochrome P450 enzymes, and decreased bioavailability due to aromatase inhibition and increased sex hormone binding globulin levels (25, 52). Estrogen has been hypothesized to increase DA and thereby PD by stimulating the proliferation of mammary cells (53). Moreover, estrogen is known to regulate adipose tissue metabolism, and has been shown to decrease adipose tissue mass by decreasing lipogenesis and stimulating lipolysis (54, 55), which plausibly could decrease the adipose tissues of the breast. Consistent with this hypothesis, menopause which naturally reduces sex hormone levels has been associated with decreased PD and DA, as well as increased NDA, independently of age and BMI (3, 56). The effects of sex hormones on breast tissue composition are likely to be mediated not only through direct effects on epithelial cells, stromal cells, and adipocytes but also through their cellular interactions (32).

The associations of alcohol and tobacco use with BMI-adjusted NDA may also be mediated through their effects on lipid metabolism, weight change, and adipose tissue distribution. Alcohol drinking has been associated with higher high density lipoprotein (HDL) levels (57), and cigarette smoking with lower HDL levels (58) in women. Furthermore, higher HDL levels have been associated with higher PD (57, 59) and lower NDA (60), supporting the hypothesis that alcohol and tobacco use may influence MD phenotypes through their effects on lipid metabolism. Moderate alcohol use has also been associated with decreased weight in women (61), believed to be due to the higher metabolic demands of microsomal ethanol oxidation, the primary route through which women process alcohol (62). Furthermore, weight loss has been associated with decreased NDA, independently of BMI and waist circumference (63). In contrast, smoking cessation has been associated with weight gain in women, whereas current smokers tend to have lower weight compared with never smokers (64). Over 90% of the smokers in this study were former smokers, and weight gain is another plausible mechanism for the association of tobacco use with higher BMI-adjusted NDA. Adipose tissues are also a source of estrogens, particularly in postmenopausal women (65), which could counter the antiestrogenic effects of smoking and contribute to the weaker associations of smoking with NDA found in obese premenopausal and postmenopausal women.

Strengths and limitations

This large population-based study had high statistical power to detect modest associations of alcohol and tobacco use with MD phenotypes. RPGEH participants were unselected for breast cancer or other disease phenotypes, which improves the generalizability of the study findings. Quantitative measures of PD, DA, and NDA were centrally measured from contemporary FFDM images using the well-established Cumulus (37) method, and were highly reproducible. Nonetheless, we cannot exclude the possibility that measurement error could have obscured modest associations of alcohol or tobacco use with DA. The inclusion of all three MD phenotypes in this study was an important strength because it enabled disentangling the effects

of alcohol and tobacco use on the dense and nondense tissue components of the breast that are combined in the PD measure.

A limitation of this study is that minority women were not included because it was ancillary to a genome-wide association study. Future studies in minority women are needed. There was also potential for recall bias in the alcohol and tobacco information collected on the RPGEH survey. However, the resulting misclassification is likely to be nondifferential with respect to MD phenotypes and lead to bias toward the null hypothesis. Like most studies, we did not have detailed information regarding smoking and drinking behaviors over the life course, such as age at initiation and cessation, which would enable more precise evaluation of associations with cumulative exposures or the timing of the exposure on MD phenotypes. We also did not have measures of adiposity, other than breast fat and BMI, and were unable to assess the extent to which associations with BMI-adjusted NDA were correlated with fat depots outside of the breast.

Conclusions

This large population-based study confirms that alcohol drinking is associated with a modest increase in PD, and provides significant evidence that this association may result mostly from lower amounts of nondense fatty tissues in the breast, rather than higher amounts of dense fibroglandular tissues. These findings are consistent with the association of alcohol drinking with increased breast cancer risk being mediated in part through lower NDA and support a protective role of breast adipocytes in maintaining healthy breasts. This study also provides significant evidence that tobacco smoking is associated with a modest decrease in PD, mainly through its association with higher NDA. Different components of tobacco smoke may have either carcinogenic or antiestrogenic effects, complicating the relationship of smoking with breast cancer risk. Our findings suggest that any association of tobacco smoking with increased breast cancer risk is unlikely to be mediated through MD phenotypes. Future studies of modifiable lifestyle factors and MD, which include NDA as well as PD and DA, are needed to improve our understanding of the underlying biology, and enable better preventive interventions to reduce breast cancer risk.

Disclosure of Potential Conflicts of Interest

J.A. Lipson is Medical Director at and has an ownership interest (including patents) in GRAIL. No potential conflicts of interest were disclosed by the other authors.

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Alcohol and Tobacco Use in Relation to Mammographic Density in 23,456 Women

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