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Alcohol Intake from Early Adulthood to Midlife and Mammographic Density

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Compliance with Ethical Standards

Informed written consent was obtained from all study participants for all aspects of the study and the study was approved by the institutional review boards at Columbia University Medical Center, Kaiser Permanente, Brigham and Women's Hospital, and Brown University.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical approval

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.

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Abstract

Purpose—Moderate alcohol consumption (15 grams/day) has been consistently associated with increased breast cancer risk; however, the association between alcohol and mammographic density, a strong marker of breast cancer risk, has been less consistent. Less is known about the effect of patterns of alcohol intake across the lifecourse.

Methods—Using the Early Determinants of Mammographic Density study, an adult follow-up of women born in two US birth cohorts (N=697; Collaborative Perinatal Project in Boston and Providence sites and the Childhood Health and Development Studies in California), we examined the association between alcohol intake in early adulthood (ages 20–29 years) and at time of interview and mammographic density (percent density and total dense area). We report the difference between nondrinkers and three levels of alcohol intake. We considered confounding by age at mammogram, body mass index, geographic site, race/ethnicity, and reproductive characteristics.

Results—Seventy-nine percent of women reported ever consuming alcohol. Compared to nondrinkers in early adulthood, we observed an inverse association between >7 servings/week and percent density in fully adjusted models ($\beta=-5.1$, 95% CI $-8.7, -1.5$; p for trend = <0.01). Associations with dense area were inverse for the highest category of drinking in early adulthood but not statistically significant (p for trend = 0.15). Compared to noncurrent drinkers, the association for current intake of >7 servings/week and percent density was also inverse ($\beta=-3.1$, 95% CI $-7.0, 0.8$; p for trend = 0.01). In contrast, moderate alcohol intake (>0–7 servings/week) in either time period was positively associated with dense area; but associations were not statistically significant in fully adjusted models.

Conclusions—Our study does not lend support to the hypothesis that the positive association between alcohol intake and breast cancer risk is through increasing mammographic density.

Keywords

Mammographic Density; Percent Density; Dense Area; Alcohol Intake

Introduction

Alcohol consumption of 15–30 grams/day (1–2 drinks/day) is associated with a 30–50% increase in breast cancer risk [1–4]. Even light to moderate drinkers (>7 servings/week) have a 5% increased risk of breast cancer [1]. The evidence for alcohol and mammographic density, a possible intermediate marker of breast cancer risk [5–8], is less consistent but studies have varied by type of density assessment (e.g., qualitative and quantitative assessments) and degree to which they accounted for levels of alcohol consumption across the lifecourse (also referred to as drinking patterns) (for review see [4–10]). The majority of

studies suggest a weak positive association between alcohol intake and mammographic density (for review see [4]).

We used data from an adult follow-up study of two U.S. birth cohorts to address several notable shortcomings in prior research on alcohol intake and mammographic density. First, with few exceptions [11–13], the majority of the literature does not address the association between alcohol intake in early adult life periods and mammographic density. We examined alcohol intake at age at initiation of alcohol intake and across two time periods (ages 20–29 years and current intake). In this study, current alcohol intake is measured at the time of the baseline mammogram which is usually taken in midlife (at age 40 years or later). Second, most previous studies of alcohol and mammographic density have focused on percent density, a relative measure of mammographic density which is strongly correlated with overall body mass index (BMI). Body size may positively confound the association between alcohol intake and percent density because moderate alcohol intake (< 7 servings/week) is also associated with lower BMI [14,15]. Therefore, in this study, we also measure the association of alcohol intake and dense area, an absolute measure of mammographic density that is less correlated with overall body size. Third, few studies have examined whether the type of alcoholic beverage consumed conferred different effects [16–18]; we also assess associations by beverage type. Given the relatively modest, but consistent, strength of the association between alcohol intake and breast cancer risk and the potential for family-level confounding by both socioeconomic status and body size measures, we examined siblings in our cohort to evaluate whether there was an association between differences in alcohol consumption and mammographic density using the sub-cohort of women who had a sibling in the cohort. Thus, our study addresses previous gaps by focusing on absolute and relative measures of breast density, alcohol consumption in early life, type of alcoholic beverage consumed, and examination of the associations within families.

Materials & Methods

Study population

The Early Determinants of Mammographic Density (EDMD) study is an adult follow-up of women born in two US birth cohorts – the Child Health and Development Studies (CHDS), which was conducted in California between 1959–1967 [19,20], and two sites of the Collaborative Perinatal Project (referred to as the New England Family Study, NEFS) conducted in Boston, Massachusetts and Providence, Rhode Island between 1959–1966 [21]. Details of this cohort have been previously published [22]. The final sample included 1,134 women - 521 singletons and 296 sibling-sets totaling 613 individuals. Sibling-sets included 277 sets of two, 17 sets of three, and 2 sets of four siblings. Informed written consent was obtained from all study participants for all aspects of the study. The study was approved by the institutional review boards at Columbia University Medical Center, Kaiser Permanente, Brigham and Women's Hospital, and Brown University and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Adult data collection

Women who agreed to participate in the adult follow-up completed a computer-assisted telephone interview [22]. The adult follow-up ascertained information on sociodemographic characteristics (age at mammogram, race), BMI (current and during ages 20–29 years calculated from self-reported height and weight), current smoking status, first degree family history of breast cancer, and reproductive events (age at menarche, menopausal status, hormonal birth control use, and pregnancy history). For race, women who self-identified as non-Hispanic white were referred to as white and women who self-identified as non-Hispanic Black, Hispanic, or non-Hispanic Asian Pacific Islander/other were referred to as non-white. Interviews also collected a detailed history of alcohol intake.

Alcohol assessment

Using a telephone survey, we asked participants if they had ever consumed an alcoholic beverage at least once a month for six months or more (yes/no). Those who reported “no” were defined as never drinkers. Women who reported “yes” were asked about the age of initiation of alcohol intake and patterns of alcohol intake in adulthood, specifically at the time of interview (hereafter referred to as current alcohol intake) and between ages 20–29 years (also referred to as early adulthood alcohol intake). Current alcohol intake was defined as consuming alcoholic beverages at least once a month for six months or more in the 12 months prior to interview. For current alcohol intake, participants reported on the frequency of consumption and the average number of servings consumed each time they drank coolers, beer, wine, and/or liquor. We calculated servings per week by beverage type and total servings per week. We combined coolers with beer because the sample size for cooler intake was small (N=24 women) and since 1991 the majority of coolers consumed in the US are made from malt liquor [23,24]. Alcohol intake between ages 20–29 years was defined as consuming alcoholic beverages at least once a month for six months or more between age 20 and 29 years. Women who reported consuming alcohol in their 20s reported on the frequency of use and average number of servings consumed by any alcoholic beverage type. For current alcohol intake and alcohol intake from age 20–29 years, the measures were categorized as servings/week equivalent to 0 (nondrinker), >0–<3, 3–7, and >7. Age at initiation of alcohol intake was defined as the age (years) a woman initiated drinking at least once a month for 6 months or longer.

Mammographic density data

If participants responded in the telephone interview that they had had or were planning on having a mammogram, we then asked them to report on the facility where they had or planned to have their mammogram. Detailed information on the procurement and assessment of the mammogram data can be found in earlier publications [22,20]. Among the 1,134 women in the sample, 87% (N=981) had a previous mammogram or planned to obtain a mammogram, and 91% of these participants consented to providing their mammogram for density assessments in this study (N=893). Mammograms for 23 participants could not be retrieved, 51 mammograms were of poor quality, and 119 participants only had digital mammograms available. As the sensitivities for digital and film mammograms may differ, we restricted our sample to those with film mammograms. Of the remaining 700 women,

three women with incomplete information on current alcohol consumption were further excluded; thus this analysis was restricted to 697 women with film mammograms and complete data on current alcohol intake. The analyses for age at initiation and intake at 20–29 years were restricted to 673 women due to missing information on these variables.

We assessed mammographic density using Cumulus, a computer assisted threshold program [25]. We measured total breast area, total dense area (cm^2), and percent density (dense area divided by breast area multiplied by 100). We calculated nondense (fat tissue) area as total breast area minus total dense area. All cranio-caudal (CC) films that were available for a participant were read in one batch and all sibling-sets were read within the same batch. Each batch included films from NEFS and CHDS cohorts. Films were read in batches of approximately 50 and 10% of the films had repeated readings from the same batch. We repeated an additional 10% of films in every batch to estimate batch-to-batch variability. The overall within-batch correlation coefficient was 0.96 for percent density and the intraclass correlation coefficient for between-batch reliability was 0.95 [22].

Statistical Analyses

We examined the distribution of baseline characteristics by servings per week for alcohol intake. We also examined mean amount of current alcohol intake by beverage type. For all bivariable comparisons, we generated p-values using chi-square test of association and regression analyses. We examined the correlation between the mammographic density measures and BMI using the Spearman correlation test. We categorized women who were perimenopausal or postmenopausal into one category because the distribution of mammographic density was similar in the two groups (premenopausal Median (Standard Deviation (SD)) 34.4 (18.4); perimenopausal Median (SD) 28.1 (17.6); and postmenopausal Median (SD) 25.9 (19.3)).

We assessed the association between alcohol intake and continuous measures of percent density, dense area, and nondense area using generalized estimating equation (GEE) models to account for the correlated nature of the outcome among sibling sets. A priori confounders included age, BMI, geographic site, race, smoking status, breast cancer family history, and reproductive events (including hormone replacement therapy use). We also evaluated whether the association between current drinking was independent of alcohol intake in the 20s by mutually adjusting for both in a single model. Confounders were included in the final model if they altered the association between alcohol intake and the density measure by more than 10%. We modeled age at initiation of alcohol intake and mammographic density measures adjusted for age at mammogram. We estimated three models for categorical measures of alcohol intake from ages 20–29 years and current alcohol intake and each measure of mammographic density, with Model 1 adjusted for age at mammogram, Model 2 additionally adjusted for BMI, and Model 3 further adjusted for all other confounders. We also stratified Model 3 by menopausal status for the association between current alcohol intake and mammographic density and nondense area.

For our analyses we combined never drinkers with former drinkers, but first assessed whether the inferences were different when they were separately considered. We assessed

additive interactions by study cohort for models of percent density, dense area, and nondense area.

There were 120 sibling-pairs with complete information on alcohol intake. We modeled the outcome as difference in density between the sister with the highest density and the sister with the lowest density. We used the same ranking order to generate difference in alcohol intake (continuous, servings/week) between siblings. Final models included the sibling-pair difference in age and difference in BMI as potential confounders. For statistical analyses we used STATA software (STATA IC/11 for Windows).

Results

Table 1 summarizes the descriptive statistics by current alcohol intake. The average age at mammogram was 43.1 years (standard deviation (SD) 2.3; Range 30.4, 48.6) and the majority of women were premenopausal (71%) and without a family history of breast cancer (89%). Never drinkers and former drinkers did not differ on mammographic density, age, BMI, or reproductive characteristics. However, non-white women were more likely to be never drinkers (73%) compared to whites (54%). Compared to never drinkers and former drinkers, current drinkers had a lower BMI and had a current or past smoking history.

Table 1 also summarizes alcohol intake behaviors. In the 79% of women who reported ever drinking alcohol, 81% reported drinking in the past 12 months. Former drinkers initiated alcohol use at an earlier age (years) (Mean 18.1 (SD 3.1)) compared to current drinkers (Mean 22.2 (SD 7.2)). Half of the women who reported drinking in their 20s were also current drinkers, suggesting a consistent drinking behavior from early adulthood to current age. Among the total population, 13% (N=89) of current drinkers did not consume alcohol in their 20s and of the 673 women reporting drinking patterns in their 20s, 14% (N=93) were former drinkers who drank in their 20s but were not current drinkers. The majority of current drinkers consumed wine (72%) and about a third consumed beer (37%) or liquor (30%).

In age-adjusted models, age at initiation of alcohol was not associated with percent density ($\beta=0.02$, 95% CI $-0.2, 0.2$) or dense area ($\beta=0.1$, 95% CI $-0.1, 0.3$); where β represents the difference per 1-year increase in the age at initiation of alcohol intake. We present the results of multivariable analyses for percent density and dense area for drinking during ages 20–29 years and current alcohol intake in Table 2. In Table 2, β represents the difference between nondrinkers (0 servings/week) and the level of alcohol intake ($>0<3$, $3-7$, or >7 servings/week). In this table we present a combined group of never drinkers and former drinkers as we found that the inferences were not different when these groups were separately considered. As seen in Table 2, after adjusting for BMI, we observed inverse associations between >7 servings/week in early adulthood and percent density (Model 2) which remained in the fully adjusted models (Model 3); similar inverse associations were observed for current alcohol intake at >7 servings/week and percent density but did not reach significance. Percent density is closely correlated with BMI ($\rho=-0.61$) compared to dense area and BMI ($\rho=-0.14$); therefore, we also examined alcohol intake and dense area. Similar to percent density, we observed inverse associations between >7 servings/week in

early adulthood. For the dense area analyses, the association with moderate alcohol intake (>0–7 servings/week) during early adulthood as well as the association with current intake were both positively associated with higher dense area in BMI adjusted (Model 2) and fully adjusted models (Model 3), although these weakly positive associations were not statistically significant.

When we mutually considered drinking during both time periods, the direction and magnitude of the associations between current alcohol intake and mammographic density measures was very similar suggesting that the association between current drinking and mammographic density was independent of drinking in the earlier time period. We also examined the association between current alcohol intake and mammographic density by menopausal status. We observed a strong inverse association between current alcohol intake and percent density in premenopausal women (servings/week of >0–<3 $\beta=-2.4$, 95% CI –5.7, 0.9; 3–7 $\beta=-4.1$, 95% CI –7.8, 0.3; >7 $\beta=-5.4$, 95% CI –9.8, –0.9; *p for trend*=0.006). In contrast, we observed a positive association in peri/post-menopausal women but estimates were not statistically significant (servings/week of >0–<3 $\beta=2.7$, 95% CI –2.3, 7.7; 3–7 $\beta=2.1$, 95% CI –4.0, 8.1; >7 $\beta=1.2$, 95% CI –5.8, 8.2; *p for trend*=0.60). There was no trend by menopausal status observed for the association between alcohol intake and dense area (premenopausal: servings/week of >0–<3 $\beta=0.7$, 95% CI –4.1, 5.4; 3–7 $\beta=2.5$, 95% CI –3.2, 8.2; >7 $\beta=-0.5$, 95% CI –7.3, 6.4; *p for trend*=0.75 and peri/post-menopausal: servings/week of >0–<3 $\beta=-0.5$, 95% CI –7.2, 6.3; 3–7 $\beta=7.3$, 95% CI –1.1, 15.6; >7 $\beta=2.1$, 95% CI –7.8, 12.0; *p for trend*=0.28).

We present the results of multivariable analyses for nondense area for drinking during ages 20–29 years and current alcohol intake in Table 3. For nondense area, there was no association between age at initiation of alcohol in age-adjusted model ($\beta=-0.4$, 95% CI –1.2, 0.4) nor an association with drinking between ages 20–29 after adjusting for age, BMI in the 20s, geographic site, hormonal birth control use, parity, and age at first birth (*P for trend*=0.1). We also observed no association with current alcohol intake and nondense area in fully adjusted models. There was no trend by menopausal status observed for the association between alcohol intake and nondense area (premenopausal *p for trend*=0.26; peri/post-menopausal *p for trend*=0.28).

Forty-six percent of our sibling-pairs were concordant on alcohol intake (categories including 0, <3, 3–7, and >7 servings/week) (Table 4). Using a sibling-pair analysis, we observed no association between sibling-pair difference in alcohol intake and percent density or dense area (Table 5). To examine the effect of timing of alcohol intake on mammographic outcomes, we examined cumulative alcohol intake between ages at menarche and first birth among parous women and observed no association between percent density or dense area in age and BMI adjusted models. There were no differences in mammographic density by beverage types including wine, liquor, or beer intake. We observed no statistically significant differences in the associations between alcohol consumption and mammographic density (percent density or dense area) or nondense area outcomes by geographic site (*P for interactions* all >0.1).

Discussion

We did not observe a positive dose response relationship between alcohol intake and mammographic density. For women who drank >7 servings/week, we observed lower percent density and dense area. There was some suggestion of a positive association between moderate alcohol intake (>0–7 servings/week) and dense area, both in the 20s and current consumption, that was not observed in percent density analyses. Body size is associated with measures of percent breast density and alcohol consumption [5,26]; however, measures of absolute total dense area are less correlated with BMI [27,28]. While BMI positively confounds the association between moderate alcohol intake (early adulthood intake and current intake) and percent density, dense area analyses are less affected by body size adjustments. However, the estimates for the association between moderate alcohol intake (early adulthood intake and current intake) and dense area were not statistically significant. Thus, our overall study does not support a positive association between alcohol intake and mammographic density. We also observed no association between alcohol intake and mammographic density in sibling analyses that controlled for fixed family-level confounding.

While several studies of mammographic density and early adulthood alcohol intake have observed no association [12,13,12], studies that report associations between alcohol intake and mammographic density generally support stronger associations between higher current alcohol intake and higher mammographic density [12,12,13,18]. Our results agree with other studies that have found weak or no association between alcohol intake and breast density [17,29,16,30], which like ours reported a low average alcohol intake (average intake range of <0.1–5.35 g/day (<0.5 servings/day)) [17] or a low percentage of women consuming 7 drinks/week (<5%) [29]. In our study, 64% of women were current drinkers; however, only 13% consumed >7 servings/week. In contrast, other studies that observed an association reported higher levels of alcohol consumption. For example, the New York site of the National Collaborative Perinatal Project (NCPP, N=145) had an average alcohol intake level of 4.4 servings/week (>0.5 servings/day) and reported that alcohol intake (>7 drinks/week) was associated with a 12% increase and a 16 cm² increase in mammographic density compared to nondrinkers [12]. In a Mediterranean population (N=1,668), premenopausal women in the highest tertile of alcohol intake (consuming >12 grams/day (>1 serving/day)) had 1.3 greater odds of having higher mammographic density using Wolfe patterns (P2/DY compared to N1/P1) compared to women in the lowest tertile of alcohol intake [18]. In addition, in a Swedish population-based cohort study, authors found the most pronounced association between alcohol intake and mammographic density were among heavy drinkers, or those consuming more than 20 grams of alcohol per day (approximately 2 servings/day) [31].

Nondense area is associated with an approximate 2-fold increase in breast cancer risk and limited studies examine the association of nondense area with breast cancer risk factors [32]. In a Swedish cohort of postmenopausal women (n=1,147), increasing current alcohol intake was associated with higher nondense area (*P for trend*=0.02) [33]. We did not observe an association between nondense area and early adulthood or current alcohol intake; therefore, the associations we observe with alcohol intake are driven by dense area. Moreover, our

cohort consists of primarily premenopausal women who would typically have higher density and lower breast fat compared to postmenopausal women [34].

Genetic and family based studies demonstrate a genetic inheritance to mammographic density patterns [35]. Within our sibling analyses, which only partially controls for genetics, difference in current alcohol was not associated with mammographic density. Sibling-pair drinking concordance may explain the lack of effect. Within sibling-pairs, 46% were concordant on alcohol intake (categories including 0, 7, and >7 servings/week).

The strengths of our large study include high reliability across our density measures and the sibling analysis enabling us to rule out any fix-level family confounding. Although we observed no overall positive dose response between alcohol intake (early adulthood or current intake) and mammographic density outcomes, we did see a positive trend in the association between moderate alcohol intake and dense area but not percent density. Nevertheless, our study suggests that if alcohol intake is associated with mammographic density, the effect is weak and that the consistent effect observed between alcohol intake and breast cancer risk may be through other pathways such as the acetaldehyde carcinogenic pathway rather than the hormonal pathway [9]. In the carcinogenic pathway, ethanol metabolites have been associated with modulating estrogen levels and having a role in breast cancer carcinogenesis [9]. In summary, the majority of studies between alcohol intake and mammographic density suggest a weak positive association, or no association, primarily in postmenopausal women. In our cohort of primarily premenopausal women, we did not observe any strong positive associations between alcohol consumption and mammographic density suggesting that the role of alcohol on breast cancer risk may be through other pathways including its carcinogenic effects, and only minimally through changing mammographic density. Studies focused on measuring the impact of alcohol during particular windows of susceptibility when the breast is more susceptible to oncogenic onslaughts, as well as whether modifying alcohol intake over time changes mammographic density over time will provide additional evidence on the pathways linking alcohol to breast cancer risk.

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Table 1

Distribution of baseline characteristics by current alcohol intake, EDMD, 2001–2006

	Never drinker (N=147), Mean $\pm$ SD or N (%)	Former drinker (N=104), Mean $\pm$ SD or N (%)	>0–<3 servings/week (N=210) Mean $\pm$ SD or N (%)	3–7 servings/week (N=147), Mean $\pm$ SD or N (%)	>7 servings/week (N=89), Mean $\pm$ SD or N (%)	<i>p</i> ^a
Age at mammogram (years)	43.01 $\pm$ 2.20	42.79 $\pm$ 2.26	43.10 $\pm$ 2.41	43.21 $\pm$ 2.20	43.17 $\pm$ 2.35	0.28
Percent density	30.90 $\pm$ 21.01	28.99 $\pm$ 18.43	33.69 $\pm$ 18.63	33.71 $\pm$ 16.37	29.71 $\pm$ 18.05	0.46
Dense area (cm ²)	33.98 $\pm$ 22.01	34.87 $\pm$ 23.34	35.24 $\pm$ 20.03	39.35 $\pm$ 22.14	35.64 $\pm$ 24.11	0.14
Nondense area (cm ²)	113.69 $\pm$ 86.24	117.62 $\pm$ 79.36	94.34 $\pm$ 78.16	90.62 $\pm$ 57.24	99.08 $\pm$ 61.54	0.005
Body mass index (kg/m ²) (Current)	29.23 $\pm$ 7.77	29.19 $\pm$ 8.16	26.76 $\pm$ 5.64	25.87 $\pm$ 4.38	27.10 $\pm$ 5.46	<0.001
Body mass index (kg/m ²) (During ages 20–29 years)	23.36 $\pm$ 5.79	22.81 $\pm$ 4.29	22.36 $\pm$ 4.07	21.71 $\pm$ 2.82	22.67 $\pm$ 4.18	0.02
Age at menarche	12.53 $\pm$ 1.67	12.48 $\pm$ 1.43	12.79 $\pm$ 1.65	12.80 $\pm$ 1.62	12.98 $\pm$ 1.40	0.01
EDMD Birth Cohort						
NEFS	68 (46.26)	58 (55.77)	94 (44.76)	74 (50.34)	56 (62.92)	0.03
CHDS	79 (53.74)	46 (44.23)	116 (55.24)	73 (49.66)	33 (37.08)	
Adult race						
Non-Hispanic White	98 (66.67)	85 (82.52)	157 (74.76)	126 (85.71)	79 (89.77)	<0.001
Non-White	49 (33.33)	18 (17.48)	53 (25.24)	21 (14.29)	9 (10.23)	
Adult smoking status						
Never	102 (69.39)	47 (45.19)	121 (57.62)	70 (47.62)	36 (40.45)	
Former	31 (21.09)	38 (36.54)	59 (28.10)	55 (37.41)	36 (40.45)	<0.001
Current	14 (9.52)	19 (18.27)	30 (14.29)	22 (14.97)	17 (19.10)	
Menopausal status						
Premenopausal	100 (70.42)	63 (63.64)	149 (72.33)	107 (74.83)	59 (68.60)	
Perimenopausal/menopausal transition	20 (14.08)	20 (20.20)	35 (16.99)	19 (13.29)	15 (17.44)	0.66
Postmenopausal	22 (15.49)	16 (16.16)	22 (10.68)	17 (11.89)	12 (13.95)	
Hormonal birth control use						
Never	27 (18.49)	13 (12.50)	25 (11.90)	15 (10.27)	12 (13.48)	0.29
Ever	119 (81.51)	91 (87.50)	185 (88.10)	131 (89.73)	77 (86.52)	
Age at first birth ^b	25.73 $\pm$ 5.16	27.11 $\pm$ 6.18	28.26 $\pm$ 5.16	28.76 $\pm$ 5.84	26.90 $\pm$ 5.90	0.003
Parity						

	Never drinker (N=147), Mean $\pm$ SD or N (%)	Former drinker (N=104), Mean $\pm$ SD or N (%)	>0–<3 servings/week (N=210) Mean $\pm$ SD or N (%)	3–7 servings/week (N=147), Mean $\pm$ SD or N (%)	>7 servings/week (N=89), Mean $\pm$ SD or N (%)	<i>p</i> ^a
Nulliparous	32 (21.92)	23 (22.12)	42 (20.00)	31 (21.38)	27 (30.68)	
Parous/ 1 full-term birth	114 (78.08)	81 (77.88)	168 (80.00)	114 (78.62)	61 (69.32)	0.37
Age at initiation of alcohol		18.08 $\pm$ 3.05	22.76 $\pm$ 8.01	21.96 $\pm$ 6.53	21.31 $\pm$ 6.32	0.009
Alcohol intake between 20–29 years (servings/week)						
0	147 (100)	8 (7.92)	49 (24.87)	26 (18.44)	14 (16.09)	
<3		39 (38.61)	74 (37.56)	30 (21.28)	14 (16.09)	
3–7		19 (18.81)	47 (23.86)	51 (36.17)	25 (28.74)	<0.001
>7		35 (34.65)	27 (13.71)	34 (24.11)	34 (39.08)	
Current alcohol by beverage type (servings/week) ^c						
Beer			0.21 $\pm$ 0.48	1.10 $\pm$ 1.74	4.62 $\pm$ 7.31	<0.001
Wine			0.65 $\pm$ 0.71	3.03 $\pm$ 2.52	6.35 $\pm$ 5.76	<0.001
Liquor			0.20 $\pm$ 0.47	0.68 $\pm$ 1.46	2.86 $\pm$ 7.90	<0.001

Abbreviations: BMI, body mass index; EDMD, Early Determinants of Mammographic Density; *P*, *P*-value

^aThe *p*-values corresponding to the categorical variables are from Chi² Test of Associations and the *p*-values corresponding to the continuous variables are from regression analysis.

^bSignificance was calculated among parous women only.

^cSignificance calculated among current alcohol consumers only.

Adjusted associations for mammographic density and alcohol intake, EDMD, 2001–2006

Table 2

	Model 1: Age Adjusted			Model 2: Age And BMI Adjusted			Model 3: Fully Adjusted					
	Percent Density		Dense Area	Percent Density		Dense Area	Percent Density		Dense Area			
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI		
Alcohol intake between age 20–29 years (servings/week) ^a												
0	Ref	--	Ref	--	Ref	--	Ref	--	Ref	--		
<3	1.18	-2.60, 4.95	1.50	-3.10, 6.10	-0.67	-3.94, 2.59	0.85	-3.66, 5.37	-1.33	-4.60, 1.93	0.26	-4.29, 4.83
3–7	1.71	-2.10, 5.52	1.91	-2.70, 6.52	-0.24	-3.71, 3.23	1.20	-3.36, 5.77	-1.69	-5.19, 1.82	0.52	-4.20, 5.23
>7	-4.03	-8.12, 0.06	-3.01	-7.38, 1.36	-3.96	-7.60, -0.33	-2.99	-7.31, 1.32	-5.11	-8.71, -1.52	-4.00	-8.25, 0.24
<i>P for trend</i>	0.16		0.39		0.07		0.33		<0.01		0.15	
Current alcohol intake (servings/week) ^b												
0	Ref	--	Ref	--	Ref	--	Ref	--	Ref	--	Ref	--
<3	3.75	0.30, 7.19	1.12	-2.82, 5.06	-0.57	-3.38, 2.24	0.07	-3.87, 4.02	-0.75	-3.53, 2.03	0.30	-3.65, 4.25
3–7	3.86	0.31, 7.42	5.37	0.77, 9.97	-2.13	-5.34, 1.09	4.12	-0.65, 8.88	-2.00	-5.20, 1.20	3.79	-0.99, 8.58
>7	-0.18	-4.72, 4.37	1.61	-4.32, 7.53	-3.64	-7.53, 0.24	1.29	-4.69, 7.27	-3.13	-7.03, 0.77	0.14	-5.79, 6.06
<i>P for trend</i>	0.44		0.14		0.04		0.26		0.08		0.44	

Abbreviation: EDMD, Early Determinants of Mammographic Density; CI, confidence interval;

^a Alcohol intake age 20–29 years when modeling for *Percent Density* are as follows: Model 1 is adjusted for age at mammogram (years); Model 2 includes model 1 adjustments and BMI in 20s (continuous); and Model 3 includes model 2 adjustments, geographic site, current smoking status (never (referent), former, current), parity (nulliparous, parous), and age at first birth modeled at the mean.Alcohol intake age 20–29 years when modeling for *Dense Area* are as follows: Model 1 is adjusted for age at mammogram (years); Model 2 includes model 1 adjustments and BMI in 20s (continuous); and Model 3 includes model 2 adjustments, geographic site, hormonal birth control use (never, ever), parity (nulliparous, parous), and age at first birth modeled at the mean.^b Current alcohol intake when modeling for *Percent Density* are as follows: Model 1 is adjusted for age at mammogram (years); Model 2 includes model 1 adjustments and current BMI; Model 3 includes model 2 adjustments, geographic site, and race. Current alcohol intake when modeling for *Dense Area* models are as follows: Model 1 is adjusted for age at mammogram (years); Model 2 includes model 1 adjustments and current BMI (continuous); Model 3 includes model 2 adjustments, geographic site, and menopausal status (premenopausal, per/post-menopausal).

Table 3

Adjusted associations for nondense area and alcohol intake, EDMD, 2001–2006

	Model 1: Age Adjusted		Model 2: Age And BMI Adjusted		Model 3: Fully Adjusted	
	Nondense Area		Nondense Area		Nondense Area	
	β	95% CI	β	95% CI	β	95% CI
Alcohol intake between age 20–29 years (servings/week) ^a						
0	Ref	--	Ref	--	Ref	--
<3	-9.86	-24.61, 4.88	-1.39	-13.43, 10.65	-0.34	-12.46, 11.79
3–7	-8.04	-22.59, 6.50	1.17	-11.27, 13.61	5.72	-6.94, 18.38
>7	11.01	-5.79, 27.81	10.35	-4.07, 24.77	12.35	-2.78, 27.47
<i>P for trend</i>	0.37		0.18		0.09	
Current alcohol intake (servings/week) ^b						
0	Ref	--	Ref	--	Ref	--
<3	-21.22	-35.57, -6.87	-0.23	-10.61, 10.16	-0.17	-10.38, 10.04
3–7	-25.07	-38.93, -11.22	4.19	-5.30, 13.69	4.18	-5.39, 13.75
>7	-16.56	-33.38, 0.25	-0.80	-11.33, 9.74	-0.24	-10.95, 10.47
<i>P for trend</i>	<0.01		0.55		0.69	

Abbreviation: EDMD, Early Determinants of Mammographic Density; CI, confidence interval;

^a Alcohol intake age 20–29 years Model 1 is adjusted for age at mammogram (years); Model 2 includes model 1 adjustments and BMI in 20s (continuous); and Model 3 includes model 2 adjustments, geographic site, race, current smoking status (never (referent), former, current), menopausal status (premenopausal (referent), peri/post-menopausal), parity (nulliparous, parous), and age at first birth modeled at the mean.

^b Current alcohol intake Model 1 is adjusted for age at mammogram (years); Model 2 includes model 1 adjustments and current BMI; Model 3 includes model 2 adjustments, geographic site, parity (nulliparous, parous), and age at first birth modeled at the mean.

Table 4

Current drinking patterns between sibling-pairs, EDMD, 2001–2006^a

	Sister 1 Current alcohol intake (servings/week) (N)				
	0	<3	3–7	>7	
Sister 2 Current alcohol intake (servings/week) (N)	0	22	13	8	3
	<3	8	16	11	5
	3–7	5	7	10	1
	>7	3	4	3	7

Abbreviation: EDMD, Early Determinants of Mammographic Density

^aThe numbers represent the total cell count for current drinking patterns between sibling-pairs.

Adjusted associations of the difference in current drinking patterns between sibling-pairs and mammographic density, EDMD, 2001–2006

Table 5

	Percent Density			Dense Area		
	Model 1 ^a		Model 2 ^b	Model 1 ^a		Model 2 ^b
	β	95% CI	β	95% CI	β	95% CI
Alcohol Intake (servings/week)	0.03	−0.32, 0.38	0.04	−0.29, 0.37	0.27	−0.20, 0.75

Abbreviation: EDMD, Early Determinants of Mammographic Density; CI, confidence interval

The multivariable regression models for percent density (Model 1 and 2) and dense area (Model 3 and 4) and current alcohol difference between sibling-pairs.

^aModel 1 is adjusted for difference in age at mammogram (continuous) between sibling-pairs.

^bModel 2 is adjusted for difference in age at mammogram (continuous) and difference in current BMI (continuous) between sibling-pairs.