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EPIDEMIOLOGY

Milk intake and mammographic density in premenopausal women

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Abstract

Purpose Mammographic density is a strong risk factor for breast cancer. Although diet is associated with breast cancer risk, there are limited studies linking adult diet, including milk intake, with mammographic density. Here, we investigate the association of milk intake with mammographic density in premenopausal women.

Methods We analyzed data from 375 cancer-free premenopausal women who had routine screening mammography at Washington University School of Medicine, St. Louis, Missouri in 2016. We used Volpara to measure volumetric percent density, dense volume, and non-dense volume. We collected information on recent milk intake (past 12 months), and categorized skim milk and low/reduced-fat milk intake into 4 groups: < 1/week, 1/week, 2–6 times/week, ≥ 1/day, while whole and soy milk intake were categorized into 2 groups: < 1/week, ≥ 1/week. We used multivariable linear regression model to evaluate the associations of milk intake and log-transformed volumetric percent density, dense volume, and non-dense volume.

Results In multivariable analyses, volumetric percent density was 20% (p-value = 0.003) lower in the 1/week group, 14% (p-value = 0.047) lower in the 2–6/week group, and 12% (p-value = 0.144) lower in the ≥ 1/day group (p-trend = 0.011) compared with women who consumed low/reduced-fat milk < 1/week. Attenuated and non-significant associations were observed for low/reduced-fat milk intake and dense volume. There were no associations of whole, skim, and soy milk intake with volumetric percent density and dense volume.

Conclusions Recent low/reduced-fat milk intake was inversely associated with volumetric percent density in premenopausal women. Studies on childhood and adolescent milk intake and adult mammographic density in premenopausal women are needed.

Keywords Milk intake · Mammographic density · Dairy · Diet · Breast cancer

Abbreviations

BI-RADS	Breast imaging reporting and data system
BMI	Body mass index
CLA	Conjugated linoleic acid
ER	Estrogen receptor
IRB	Institutional review board
SD	Standard deviation

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Introduction

Mammographic density reflects the amount of epithelial and stromal tissues in relation to adipose tissue in the breast. Mammographic density is one of the strongest risk factors for breast cancer, with a 4–6 fold increased risk among women who have dense breast tissue (> 75% of the breast) compared with women who have little or no dense breast tissue [1–7]. Estimates of attributable risk suggest that having dense breasts may account for 26–39% of breast cancer cases in the US, with the population attributable risk proportion higher in premenopausal women (39.3%) than postmenopausal women (26.2%) [1, 2, 8]. About 27.6 million women aged 40–74 years in the US have extremely dense breasts, and women aged 40–49 years account for 44.3% ($N=12.3$ million) [9]. Hence, strategies to reduce mammographic density, especially in premenopausal women could be important in breast cancer prevention.

Diet is modifiable; hence, a good understanding of the associations of diet with mammographic density may provide insight into how dietary modification could be utilized in reducing mammographic density and ultimately breast cancer incidence. Nevertheless, the associations of adult diet, including dairy intake (e.g., milk) with mammographic density have been inconsistent [10–15]. Two studies reported inverse associations between dairy foods and mammographic density in premenopausal women [10, 13], while others did not [11, 12, 14, 15]. Milk has many bioactive compounds that could impact mammographic density (e.g., calcium, branched chain fatty acids, rumenic acid, and cysteine-rich whey proteins) but only three studies have investigated the associations of milk intake with mammographic density [11, 12, 14] and only one in premenopausal women [11]. One of the studies reported an inverse association between milk intake and mammographic density [14] while the other two studies found no association between milk intake and mammographic density [11, 12].To address this knowledge gap, we evaluated the associations of different types of milk (skim milk, low/reduced-fat milk, whole milk, and soy milk) intake with mammographic density in premenopausal women.

Methods

Participants

Annually, close to 5000 premenopausal women undergo mammography at the Joanne Knight Breast Health Center (BHC), Washington University School of Medicine and Siteman Cancer Center, St. Louis. We recruited 383 participants among premenopausal women who had the routine screening mammogram at the BHC in 2016. The current study is limited to 375 women with complete data. The detailed description of the study population has been provided previously [16]. Briefly, premenopausal women who were scheduled for their annual screening mammography at the BHC were mailed study flyers by research coordinators 2 weeks to 1 month in advance. Follow-up calls were made within 7 days of the scheduled appointments to screen interested individuals and to provide further details on the study. To be eligible, participants had to be (i) premenopausal at the time of mammogram. We identified women as premenopausal if they had a regular menstrual period within the preceding 12 months, no prior history of bilateral oophorectomy, and not used menopausal hormone therapy, (ii) no serious medical condition that would prevent the participant from returning for her annual mammogram in 12 months, (iii) not pregnant, (iv) no history of cancer, including breast cancer, and (v) no history of breast augmentation or reduction. Study approval was granted by the Institutional Review Board (IRB) of the Washington University School of Medicine, Saint Louis, MO. All study participants provided informed consent.

Questionnaire data

Participants completed a detailed questionnaire on the day of the screening mammogram. The questionnaire requested detailed demographic, reproductive and anthropometric information on breast cancer risk factors, including age (years), age at menarche (years), age at first birth (years), race (non-Hispanic White, Black/African American, others), education (pre-college, post-college), body mass index (BMI) (kg/m^2), menstrual and reproductive history included parity (0, 1, 2, ≥ 3), use of oral contraceptive (yes/no), family history of breast cancer (yes/no), etc.

Milk intake

Participants were asked, on the questionnaire, how many servings do they typically consume of the following types of milk in the past 12 months: skim milk, low/reduced-fat milk, whole milk, and soy milk. A serving of milk is 1 cup or 1 regular 8-ounce container. Servings of milk intake were categorized into seven groups: (i) Never or < 1/week, (ii) 1/week, (iii) 2–6/week, (iv) 1/day, (v) 2–3/day, (vi) 4–5/day, and (vii) ≥ 6/day. Milk intake was low in our study population; hence, we re-categorized servings of milk intake based on the distribution in our study population. We re-categorized skim milk and low/reduced-fat milk fat milk into 4 groups: < 1/week, 1/week, 2–6/week, and ≥ 1/day, while whole milk and soy milk were re-categorized into 2 groups: < 1/week and ≥ 1/week because of the small number.

Skim milk is fat free milk; 1% milk (low fat milk) contains 1% milk fat; 2% milk (reduced-fat milk) contains 2% milk fat; and whole milk contains 3.25% milk fat by weight. Soy milk is made from soybeans and low in saturated fat.

Volumetric mammographic density measures

We used Volpara [version 1.5, (Matakina Technology Ltd, Wellington, New Zealand)] to determine volumetric measures of mammographic density: volumetric percent density, dense volume, and non-dense volume. Volumetric percent density is calculated as the ratio of fibroglandular tissue volume to total breast volume. The method underlying Volpara has been described in detail [17]. Volpara volumetric percent density values range from 0.5 to 34.5% [17, 18]. In comparison with clinical two-dimensional methods, Breast

Imaging Reporting and Data System (BI-RADS) density categories (5th edition), Volpara is mapped to an automated density grade using preset thresholds (automated density grade 1: < 3.5%; grade 2: ≥ 3.5 and < 7.5%; grade 3 ≥ 7.5 and < 15.5%; and grade 4: ≥ 15.5%) [16].

Statistical analysis

Descriptive statistics are presented as mean and standard deviation (SD) for continuous variables and percentages (%) for categorical variables. The parametric p-value was calculated using ANOVA for numerical variables and Chi square test for categorical variables. Volumetric percent density, dense volume, and non-dense volume were all natural log-transformed to ensure the normality of the residuals in all regression models. Multivariable linear regression models were used to evaluate the associations between categories of milk intake and log-transformed volumetric percent density, dense volume, and non-dense volume. All models were adjusted for age (continuous), BMI (continuous), parity (0, 1, 2, ≥ 3), oral contraceptive use (yes/no), family history of breast cancer (yes/no), and race (non-Hispanic White/African American/others). The variables were selected as potential confounders based on their associations with mammographic density and/or breast cancer risk in previous studies, and they retained significance in the multivariable model. BMI was calculated as current weight (kg) divided by current height squared (m^2). Beta coefficients (β) and 95% confidence intervals from the regression models were evaluated and back-transformed for easier interpretation. The back-transformed coefficients are presented as percentage difference (%), which is estimated as $\text{Diff }\% = (\exp(\beta) - 1) \times 100$, and comparing each group to the reference group. Trend across categories of milk intake was tested using Wald statistic by including the medians of milk intake categories as continuous variables in multivariable models. All the analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). All tests were two-tailed, and $p < 0.05$ was considered to be statistically significant.

Results

The baseline characteristics of participants are shown in Table 1. The mean age at the time of screening mammogram was 47.5 years (SD 4.8, range 32–58 years). The mean BMI was 30.8 kg/m^2 (range 17.9–63.1 kg/m^2), consistent with the BMI of women attending screening mammogram at the Joanne Knight Breast Health Center. Most (65.6%) of the participants were non-Hispanic White; 29.3% were Black/African American. The mean volumetric percent density was 9.5% (SD 6.5), the mean dense volume was 80.7 cm^3 (SD 42.7), and the mean non-dense volume was 1079.0 cm^3 (SD

Table 1 Characteristics of 375 premenopausal women recruited during annual screening mammogram at the Joanne Knight Breast Health Center (BHC) at Washington University School of Medicine, St. Louis, Missouri

	Number	Mean ± SD/percentage (%)
Age (years)	375	47.5 ± 4.8
Age at menarche (years)	373	12.8 ± 2.2
Age at first birth (years)	302	26.0 ± 6.1
BMI (kg/m^2)	375	30.8 ± 8.1
Parity		
0	70	18.8%
1	67	18.0%
2	138	37.1%
≥ 3	97	26.1%
Ever breastfeed		
Yes	216	70.8%
No	89	29.2%
Ever use of oral contraceptive		
Yes	333	88.8%
No	42	11.2%
Family history of breast cancer		
Yes	88	23.5%
No	287	76.5%
Race		
Non-Hispanic White	246	65.6%
Black/African American	110	29.3%
Others	19	5.1%
Education		
Pre-college	54	14.4%
Post-college	319	85.1%
Mammographic density		
Volumetric percent density (%)	375	9.5 ± 6.5
Dense volume (cm^3)	375	80.7 ± 42.7
Non-dense volume (cm^3)	375	1079.0 ± 743.0
Milk consumption		
Skim milk		
< 1/week	220	67.5%
1/week	34	10.4%
2–6/week	39	12.0%
≥ 1/day	33	10.1%
Low/reduced-fat milk		
< 1/week	188	56.8%
1/week	50	15.1%
2–6/week	53	16.0%
≥ 1/day	40	12.1%
Whole milk		
< 1/week	271	89.4%
≥ 1/week	32	10.6%
Soy milk		
< 1/week	269	90.3%
≥ 1/week	29	9.7%

BMI Body mass index, *SD* standard deviation

743.0). Milk intake was low among women in our study: 56.8% participants consumed low/reduced-fat milk < 1/week, 67.5% participants consumed skim milk < 1/week, 90.3% participants consumed soy milk < 1/week, 89.4% participants drank whole milk < 1/week.

Because low/reduced-fat milk was the most frequently consumed milk in our study population, we examined the distribution of mammographic density and known breast cancer risk factors among participants by categories of low/reduced-fat milk intake (Table 2). We observed significant differences in parity ($p = 0.030$) and breastfeeding history ($p = 0.005$) by categories of low/reduced-fat milk intake.

In multivariable adjusted analyses (adjusted for age, BMI, parity, oral contraceptive use, family history of breast cancer, and race), we observed an inverse association between low/reduced-fat milk and volumetric percent density (Table 3). Volumetric percent density was 20% (β = 0.80, 95% CI 0.68–0.93) lower in the 1/week group; 14% (β = 0.86, 95% CI 0.74–1.00) lower in the 2–6/week group; and 12% (β = 0.88, 95% CI 0.75–1.04; *p*-trend = 0.011) lower in the ≥ 1/day group compared with < 1/week group. There were no associations between whole, skim, and soy milk and volumetric percent density (Table 3).

The associations of low/reduced-fat milk intake with dense volume were attenuated in multivariable adjusted analyses (adjusted for age, BMI, parity, oral contraceptive use, family history of breast cancer, and race) (Table S1). Dense volume was 15% (β = 0.85, 95% CI 0.74–0.98; *p*-value = 0.026) lower among women who drank low/reduced-fat milk 1/week compared with women who drank < 1/week, but no associations were observed for higher intake groups (2–6/week, and ≥ 1/day). There were no associations between whole, skim, and soy milk and dense volume (Table S1).

We also observed an inverse association between soy milk intake and non-dense volume (β = 0.81 for ≥ 1/week; *p*-value = 0.039) (Table S1). This finding should be interpreted cautiously, however, given the small proportion

Table 2 Distribution of risk factors in 375 premenopausal women by low/reduced-fat milk intake

	Low/reduced-fat milk intake								
	< 1/week		1/week		2–6/week		≥ 1/day		*p*-value
	N	Mean ± SD/percentage (%)	*N*	Mean ± SD/percentage (%)	*N*	Mean ± SD/percentage (%)	*N*	Mean ± SD/percentage (%)	
Age (years)	188	47.5 ± 5.0	50	46.6 ± 4.9	53	47.4 ± 4.7	40	48.5 ± 4.0	0.358
Menarche (years)	187	12.7 ± 2.6	50	12.7 ± 1.4	52	12.9 ± 1.8	40	13.3 ± 1.7	0.488
Age at first birth (years)	139	26.6 ± 6.0	43	25.3 ± 5.3	50	25.9 ± 6.1	33	24.9 ± 7.6	0.394
BMI (kg/m^2)	188	30.1 ± 8.5	50	31.8 ± 8.5	53	31.6 ± 8.3	40	32.37 ± 7.0	0.271
Parity									
0	48	25.67%	7	14.0%	3	5.7%	5	13.2%	0.030
1	36	19.25%	5	10.0%	10	18.9%	9	23.7%	
2	58	31.02%	24	48.0%	23	43.4%	13	34.2%	
3	45	24.06%	14	28.0%	17	32.1%	11	29.0%	
Ever breastfeed									
Yes	100	71.4%	24	55.8%	43	86.0%	20	57.1%	0.005
No	40	28.6%	19	44.2%	7	14.0%	15	42.9%	
Ever use of oral contraceptive									
Yes	165	87.8%	45	90.0%	49	92.5%	37	92.5%	0.687
No	23	12.2%	5	10.0%	4	7.6%	3	7.5%	
Family history of breast cancer									
Yes	45	23.9%	15	30.0%	13	24.5%	5	12.5%	0.271
No	143	76.1%	35	70.0%	40	75.5%	35	87.5%	
Race									
Non-Hispanic White	123	65.4%	32	64.0%	32	60.4%	24	60.0%	0.818
Black/African American	54	28.7%	17	34.0%	19	35.9%	13	32.5%	
Others	11	5.9%	1	2.0%	2	3.8%	3	7.5%	
Education level									
Pre-college	21	11.2%	10	20.0%	8	15.1%	6	15.0%	0.195
Post-college	167	88.8%	39	78.0%	45	84.9%	34	85.0%	

BMI Body mass index, *SD* standard deviation

Table 3 Multivariable adjusted associations of milk intake and volumetric percent density in 375 premenopausal women

Servings of milk intake	Number	Volumetric percent density (%)		
		β (95% CI)[a]	*p*-value	*p*-trend
Low/reduced-fat milk				
< 1/week	188	Reference		
1/week	50	0.80 (0.68, 0.93)	0.003	
2–6/week	53	0.86 (0.74, 1.00)	0.047	
≥ 1/day	40	0.88 (0.75, 1.04)	0.144	0.011
Skim milk				
< 1/week	220	Reference		
1/week	34	0.84 (0.70, 1.01)	0.069	
2–6/week	39	1.01 (0.85, 1.20)	0.869	
≥ 1/day	33	1.06 (0.88, 1.27)	0.571	0.817
Soy milk				
< 1/week	269	Reference		
≥ 1/week	29	1.13 (0.93, 1.36)	0.216	–
Whole milk				
< 1/week	271	Reference		
≥ 1/week	32	0.98 (0.82, 1.18)	0.870	–

β beta coefficient, *95% CI* 95% confidence intervals, *SD* standard deviation

[a]Adjusted for age (continuous), body mass index (continuous), parity (0, 1, 2, ≥ 3), oral contraceptive use (yes/no), family history of breast cancer (yes/no) and race (non-Hispanic White/African American/others)

(9.7%) of our participants who consumed soy milk ≥ 1/week. There were no associations between other types of milk and non-dense volume.

Discussion

Our study is one of the few to investigate the associations of milk intake with mammographic density in premenopausal women. We observed that consumption of low/reduced-fat milk was inversely associated with volumetric percent density. Whole, skim, and soy milk intake were not associated with volumetric percent density.

Milk contains many bioactive compounds (e.g., calcium), which may be associated with breast density [19]. Calcium is involved in cell apoptosis, proliferation, and differentiation [20, 21], and may thus play a role breast physiology and influence mammographic density [22]. Studies have shown that calcium intake is inversely associated with percentage mammographic breast density in premenopausal women [10, 12, 23–26]. In addition, milk contains branched chain fatty acids, rumenic acid, and cysteine-rich whey proteins, which are associated with mammary cancer prevention in mice models [27]. Rumenic acid is a conjugated linoleic acid (CLA). CLA might exert anticarcinogenic effects in mammary tissues by targeting initiated epithelial cells within ducts, alveoli, and terminal end buds, or in transformed epithelial cells resulting in an inhibition of cell growth, alterations in differentiation, or induction of cell death [28].

Three other studies have previously investigated the associations of milk intake with mammographic density with conflicting results. Garcia-Arenzana et al. reported a positive association of whole milk intake, but no association of semi-skimmed milk with mammographic density [14], while the other two studies observed no associations of milk intake with mammographic density. These studies did not, however, evaluate various types of milk [11, 12]. The differences in our results when compared to previous studies may be due to differences in study population and how mammographic density was assessed (Table S2). Our study was limited to premenopausal women, hence, study population is younger (mean age 47.5 years), while the other studies included both premenopausal and postmenopausal women, all with mean age > 50 years, and analyses were not stratified by menopausal status [12, 14]. In addition, African Americans, who are more likely to have lactose intolerance, and hence consume less milk, constitute 29.3% of our study, while participants in the others were mainly White-Hispanic, and Japanese ancestry. Further, our study determined mammographic density using Volpara which provides automated volumetric measures, while other studies used semi-quantitative [12, 14], or quantitative area-based methods [11]. We also evaluated types of milk intake (skim milk, low/reduced-fat milk, whole milk, and soy milk), similar to the study by Garcia-Arenzana et al. (whole milk, skimmed milk, and semi-skimmed milk), while Masala et al. did not categorize milk into different types [12], and Takata evaluated 'fruit and milk' together [11].

We observed no association between soy milk and volumetric percent density and dense volume. Similar to our findings, Maskarinec et al. reported no significant differences in mammographic density after 2 years of soy food intervention among premenopausal women [29]. Interestingly, the authors also reported that soy consumption was positively associated with mammographic density during early life but inversely associated with mammographic density during adulthood suggesting that soy intake at different periods in life may have differential effects on mammographic density [29]. Soy contains isoflavones, which are structurally similar to 17-beta-estradiol. Hence, soy isoflavones may compete with endogenous estrogens in binding with estrogen receptor (ER) [30, 31]. As noted, soy milk intake was low in our study, which is similar to what has been reported in other western population [32].

Our study has some limitations. First, it is cross-sectional, which limits causal inference. Second, although we adjusted for potential confounders, residual confounding of unmeasured factors cannot be ruled out. Next, we examined milk intake only, but it is possible that milk intake might be a proxy for other dietary factors (e.g., dairy intake) that might influence mammographic density, thus evaluating the effects of dietary patterns on and mammographic density may provide more valuable insight. Further, the overall intake of milk in our study is low. Close to 30% of our study participants are African Americans, hence, there might be lactose intolerance which limits the amount of milk they consume [33]. In addition, milk intake was self-reported; nevertheless, we have no reason to believe there will be differential recall of milk intake based on mammographic density. Several studies have shown that self-administered dietary questionnaire can provide reproducible information on specific dietary intakes and milk intake over 1 year is a good proxy for long-term intake [34, 35], hence, our assessment of recent milk intake (past 12 months) should reflect long-term intake. Growing epidemiological evidence suggests that childhood and adolescent exposures (e.g., adolescent body size, physical activity, and dietary intake) influence breast density and can affect susceptibility of breast tissue to cancer development in adulthood [16, 36–40], thus milk intake in earlier life should be evaluated in future studies.

Despite the limitations, our study has some strengths. Participants were recruited from women attending annual routine screening mammography at the Joanne Knight Breast Health Center, which enhances generalizability. To the best of our knowledge, this is the first study to investigate the associations of various types of milk intake with mammographic density in premenopausal women using Volpara, which provides volumetric measures of density and has been found to be highly reproducible [41]. Further, we adjusted for known confounders in multivariable analysis.

Conclusion

In summary, we observed that low/reduced-fat intake was inversely associated with volumetric percent density in premenopausal women. Further studies on childhood and adolescent milk intake and adult mammographic density in premenopausal women are needed.

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Data availability The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval Ethical approval for this study was provided by the Washington University School of Medicine, Saint Louis, MO Institutional Review Board.

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