ANTICANCER RESEARCH 39: 6197-6208 (2019)
doi:10.21873/anticanres.13828

Dairy Food Consumption and Mammographic Breast Density: The Role of Fat

ELISABETH CANITROT[1,2] and CAROLINE DIORIO[1,2,3]

[1]*Department of Social and Preventive Medicine, Université Laval, Québec, Canada;*
[2]*CHU de Québec-Université Laval Research Center (Oncology division), Québec, Canada;*
[3]*Université Laval Cancer Research Center, Québec, Canada*

Abstract. *Aim: This cross-sectional study aimed to evaluate the associations between low and high-fat dairy food (DF) intake and breast density (BD). Materials and Methods: A total of 775 premenopausal and 771 postmenopausal women recruited during screening mammography completed a food frequency questionnaire. Adjusted linear regression models were used to assess the associations. Results: As frequency quartiles of high-fat DF consumption increased, the adjusted mean of absolute BD increased from 31.5 to 36.1 cm^2 for all women (p_{trend}=0.0034) and from 42.4 to 50.1 cm^2 for premenopausal women (p_{trend}=0.0047). Conversely, as frequency quartiles of low-fat DF consumption increased, the adjusted mean of absolute BD decreased from 34.7 to 29.6 cm^2 for all women (p_{trend}=0.001) and from 49.7 to 40.7 cm^2 for premenopausal women (p_{trend}=0.0012). Conclusion: A higher intake of high-fat and low-fat DF is respectively associated with higher and lower BD, particularly in premenopausal women.*

Mammographic breast density (BD) is a well-known determinant of breast cancer, but also a mediator for other risk factors (1). This role as an intermediate marker may allow identifying new breast cancer risk factors and interventions to reduce BD and thus reduce breast cancer risk (2). The use of BD as a biomarker of breast cancer risk is relevant because of the ease in obtaining the measure, the acceptability of mammography in the population, and the reduction in the time required to complete studies (as compared to evaluating the effect of an intervention on disease onset) (3).

This article is freely accessible online.

Correspondence to: Caroline Diorio, Oncology Division CHU de Québec-Université Laval Research Center, 1050 Chemin Sainte-Foy, Quebec City, Qc, G1S 4L8, Canada. Tel: +1 4186827390, Fax: +1 4186827949, e-mail: caroline.diorio@crchudequebec.ulaval.ca

Key Words: Mammographic breast density, dairy food, breast cancer, nutrition.

A few studies have investigated the role of diet in relation to mammographic density. Specifically, ten studies (4-13) have examined the association between dairy food (DF) consumption and BD, but no consensus has yet been reached. Of the ten studies reviewed, seven are cross-sectional studies (4-10), two are case-control studies nested in cohorts (11, 12), and one is a prospective cohort study (13). Only five out of the ten studies found significant associations between DF intake and BD (4-7, 10), two of them favouring a positive association between DF consumption and BD (7, 10), while the other three reported a reverse association (4-6). The inconsistency between study results may be explained by the fat content in dairy products. Up to now, only two studies (5, 10) have considered the dairy fat content, and both suggested an inverse trend between low-fat dairy products consumption and BD in premenopausal women. However, only one study specifically examined the association of high-fat DF consumption with BD and reported insignificant results (5).

BD is an important factor in breast cancer risk, which can be altered by women's diet behaviours. If such an association exists for DF, then simple changes in eating habits could help reduce the risk of developing breast cancer by reducing a woman's BD. We took advantage of a cross-sectional study comprising 1546 women without breast cancer for which complete diet information was available to evaluate the influence of DF on BD. Thus, the main objective of this study was to measure the associations between dairy intake frequency, by type of DF and fat content (alone or combined), and mammographic BD in a population of premenopausal and postmenopausal women.

Materials and Methods

Study population and recruitment procedures. Study population and recruitment methods have been previously described (14, 15). The data were collected in a cross-sectional study. Briefly, women who underwent breast cancer screening mammography at two private clinics in Quebec City (province of Quebec, Canada) between February 2001 and March 2002 were recruited. Eligible women were included in the study if they met the following criteria: no contraceptive or replacement hormones taken in the 3 months preceding mammography, no Tamoxifen® or Raloxifene® treatment, no current pregnancy or breastfeeding, no personal history of cancer (all sites combined), no breast reduction or augmentation, and no endocrine diseases. There was no age limit, and menopausal status was defined according to the criteria of the Nurses' Health Study (16) based on each woman's age, menstrual cycles, smoking status and history of gynaecological surgery. Women with intellectual disabilities were ineligible for the study because of their inability to provide informed consent. Of the 1574 women (783 premenopausal and 791 postmenopausal) who participated in the original study, we excluded eleven women who did not complete the food frequency questionnaire (FFQ), three women who reported extreme daily caloric intake (<600 kcal/day or >5000 kcal/day), four women for whom the waist-to-hip ratio was not available, two for missing data on physical activity and eight who did not fill out their hormone use. In total, 1546 women were eligible in this study: 775 premenopausal and 771 postmenopausal. The study was approved by the Research Ethics Review Board – Hôpital du Saint Sacrement at the CHU of Quebec.

Data collection. Anthropometric measures were taken by a trained nurse at recruitment. Information on breast cancer risk factors and physical activity was collected by standardized phone interview within a month after recruitment. Diet was assessed with a validated self-administered semi-quantitative FFQ (97GP Copyrighted at Harvard University, Boston, MA, USA) (17, 18). Women reported their frequency of consumption of certain foods in the year prior to mammography, ranging from "never" to "6 times and more per day", with frequencies assessed in specified portions. In this FFQ, there are 11 items related to four groups of dairy products: milk (3 items), cream (3 items), yogurt (2 items), and cheese (3 items), as well as two items related more specifically to the usual fat content of dairy products consumed. These 13 items were used to assess high and low-fat dairy consumption frequency in our sample. Digitization of mammograms and assessment of mammographic density have been detailed elsewhere (15, 19). Briefly, all mammograms were digitized using a Kodak LS-85 laser film scanner. Calibration of the scanner was verified before each utilization, and all images were blindly evaluated by a trained reader. BD was measured in two ways for each participant on a craniocaudal view of the right or the left breast (randomly selected): the proportion of dense tissue in the breast (percent BD in %) and the absolute amount of dense tissue (absolute BD in cm^2). Reproducibility of measurement was assessed: the intraclass correlation coefficients were 0.98 and 0.98, and the inter-group coefficients of variation were 4% and 5% for percent and absolute BD respectively (19).

Statistical methods. Frequency of consumption for each dairy product was transformed to number of servings per week, using the middle of each category when necessary. We created fifteen groups of dairy products, according to the type of DF (milk, ice cream, yogurt, cheese) and their fat composition (low or high fat), and aggregated variables including frequency of consumption of total, low and high-fat DF. Partial Spearman correlations were estimated between the number of servings per week and BD as continuous variables. In the absence of categorizing recommendations, the number of servings per week was categorized in quartiles. Percent and absolute BD were square-root transformed (except for percent density among premenopausal women) to obtain a normal distribution (results are presented as back-transformed values). Multivariate-adjusted generalized linear models were used to estimate means of BD by quartile of DF consumption, and linear trend across quartiles was tested. Potential confounders identified *a priori* and included in the multiple regression and correlation models were: age (years), body mass index (kg/m^2), waist-to-hip ratio, menarche age (years), age at first full-term pregnancy (years), number of term pregnancies, duration of breastfeeding (years), duration of oral contraceptive use (years), duration of hormone replacement therapy use (years), family history of breast cancer (yes/no), personal history of breast biopsy (number of biopsies), smoking (non-smoker, former or current smoker), education (elementary or less, high school, college or university), physical activity (MET-h/week), alcohol consumption (drinks/week), total caloric intake (kcal/day), and menopausal status when applicable. All tests were two-sided, and a *p*-value<5% was considered statistically significant. All statistical analyses were performed using SAS9.4 Software System (SAS Institute, Inc., Cary, NC, USA).

Results

Study population. The characteristics of the 1546 women included in the analyses are presented in Table I. The 28 women excluded *a priori* had similar characteristics as those included (data not shown). Overall, the average age (±SD) of all women was 54.1 (±9.4) years, with an average of 46.7 (±4.6) years for premenopausal women compared to 61.4 (±6.8) years for postmenopausal women. As expected, BD was higher in premenopausal women than in postmenopausal women: 42.1% *versus* 18.5% and 46.6 cm^2 *versus* 23.2 cm^2, respectively. The frequency of DF consumption differed according to menopausal status. Higher consumption of milk (7.7 servings/week *versus* 7.1 servings/week) and cheese (5.3 servings/week *versus* 4.6 servings/week) was observed in premenopausal women compared to postmenopausal women. There was a slightly higher total consumption of DF in premenopausal women (16.3 servings/week on average *versus* 15.3 servings/week in postmenopausal women), with a larger observed difference for high-fat DF (average 7.1 servings/week *versus* 5.6 servings/week for postmenopausal women). Similarly, postmenopausal women tended to consume less high-fat DF than premenopausal women: 1.7 servings/week *versus* 2.2 servings/week respectively for whole milk and cream, 2.8 servings/week *versus* 3.9 servings/week for high-fat cheeses, except for ice cream (1.2 servings/week *versus* 0.8 servings/week for premenopausal).

Consumption of low and high-fat dairy foods. After adjusting for potential confounders, none of the subgroups of DF intake was associated with BD in the total population (p_{trend}>0.05 for consumption of milk, ice cream, yogurt, cheese or total DF – Table II). On the other hand, for all women, there were significant inverse associations between consumption of low-fat milk and percent BD [p_{trend}=0.026,

Table I. *Characteristics of the study population.*

	Overall n=1546	Premenopausal n=775	Postmenopausal n=771
Body mass index (kg/m^2), μ (SD)	26.1 (4.7)	25.2 (4.5)	27.1 (4.7)
Waist-to-hip ratio, μ (SD)	0.8 (0.1)	0.78 (0.1)	0.81 (0.1)
Age at menarche (years), μ (SD)	12.7 (1.6)	12.8 (1.6)	12.7 (1.5)
Parity (yes), n (%)	1164 (75.3%)	583 (75.2%)	581 (75.4%)
Age at first full-term pregnancy (years), μ (SD)*	25.7 (4.2)	26.3 (4.2)	25.2 (4.1)
Breastfeeding (yes), n (%)*	532 (45.7%)	363 (62.3%)	169 (29.1%)
Oral contraceptive treatment (yes), n (%)	1126 (72.8%)	711 (91.7%)	415 (53.8%)
Duration of oral contraceptive treatment (years), μ (SD)**	4.8 (4.4)	5.2 (4.3)	4 (4.4)
Substitutive hormonal treatment (yes), n (%)	346 (22.4%)	45 (5.8%)	301 (39 %)
Duration of substitutive hormonotherapy (years), μ (SD)**	3.6 (4.9)	0.7 (0.9)	4.1 (5.1)
Familial history of breast cancer (yes), n (%)	518 (33.5%)	283 (36.5%)	235 (30.5%)
History of breast biopsy (yes), n (%)	234 (15.1%)	111 (14.3%)	123 (16%)
Physical activity (MET-h/week), μ (SD)	26.3 (22.8)	27 (22.3)	25.7 (23.3)
Caloric intake (kcal/day), μ (SD)	1941 (584.6)	1909 (517.3)	1972 (644.1)
Alcohol consumption (drinks/week), μ (SD)	3 (4.1)	3.4 (3.8)	2.5 (4.4)
Education (highest degree completed), n (%)			
Primary or less	254 (16.5%)	51 (6.6%)	203 (26.3%)
Secondary	506 (32.7%)	241 (31.1%)	265 (34.4%)
College	302 (19.5%)	206 (26.6%)	96 (12.5%)
University	484 (31.3%)	277 (35.7%)	207 (26.8%)
Smoking status, n (%)			
Non-smoker	809 (52.3%)	354 (45.6%)	455 (59%)
Ex-smoker	521 (33.7%)	306 (39.5%)	215 (27.9%)
Smoker	216 (14%)	115 (14.9%)	101 (13.1%)
Percent breast density (%), μ (SD)	30.3 (24)	42.1 (24.3)	18.5 (16.7)
Absolute breast density (cm^2), μ (SD)	34.9 (27.7)	46.6 (28.7)	23.2 (20.9)
Total milk consumption (s/w), μ (SD)	7.4 (6.8)	7.7 (6.6)	7.1 (6.9)
Low-fat milk consumption (s/w), μ (SD)	5.4 (6.2)	5.4 (5.9)	5.4 (6.4)
High-fat milk consumption (s/w), μ (SD)	2.0 (3.6)	2.2 (3.8)	1.7 (3.4)
Total ice cream consumption (s/w), μ (SD)	1.0 (1.6)	0.8 (1.2)	1.2 (1.9)
Low-fat ice cream consumption (s/w), μ(SD)	0.4 (1.1)	0.4 (0.8)	0.5 (1.3)
High-fat ice cream consumption (s/w), μ (SD)	0.6 (0.9)	0.5 (0.8)	0.7 (1.0)
Total yogurt consumption (s/w), μ (SD)	2.4 (3.0)	2.5 (2.8)	2.4 (3.2)
Low-fat yogurt consumption (s/w), μ (SD)	2.0 (2.9)	2.0 (2.8)	2.0 (3.0)
High-fat yogurt consumption (s/w), μ (SD)	0.4 (3.9)	0.5 (1.4)	0.4 (1.5)
Total cheese consumption (s/w), μ (SD)	5.0 (3.9)	5.3 (4.0)	4.6 (3.8)
Low-fat cheese consumption (s/w), μ (SD)	1.6 (3.1)	1.4 (3.0)	1.7 (3.2)
High-fat cheese consumption (s/w), μ (SD)	3.3 (4.1)	3.9 (4.2)	2.8 (3.8)
Total dairy food consumption (s/w), μ (SD)	15.8 (9.3)	16.3 (8.9)	15.3 (9.7)
Low-fat dairy food consumption (s/w), μ (SD)	9.4 (8.6)	9.2 (8.1)	9.7 (8.9)
High-fat dairy food consumption (s/w), μ (SD)	6.3 (6.3)	7.1 (6.4)	5.6 (6.2)

μ, Mean; SD: standard deviation; MET-h/week, metabolic equivalent hours per week; s/w, servings per week. *Among parous women. **Among treated women.

r=–0.042 (p=0.099)], as well as between consumption of low-fat yogurt and percent BD [p_{trend}=0.021, r=–0.038 (p=0.142)] or absolute BD [p_{trend}=0.045, r=–0.034 (p=0.183)]. Also, there were strong significant positive associations between consumption of high-fat milk and percent BD [(p_{trend}=0.0004, r=0.091 (p=0.00004)] or absolute BD [p_{trend}=0.011, r=0.064 (p=0.013)], as well as between consumption of high-fat ice cream and percent BD [p_{trend}=0.043, r=0.055 (p=0.031)].

This marked difference in the direction of the associations between low and high-fat DF consumption and BD was more evident in the associations between the total consumption of low-fat and high-fat DF and BD (Table II and Figure 1). While the consumption of low-fat DF by increasing quartiles was statistically associated with lower percent BD [mean of 29.1; 28.4; 28.3 and 24.7% with p_{trend}=0.0003, r=–0.069 (p=0.007)] or absolute BD [mean 34.7; 34.5; 34.2 and 29.6 cm^2 with p_{trend}=0.001, r=–0.069 (p=0.007)], the consumption of high-

Table II. *Associations between dairy food consumption and mammographic breast density among all women*.

Quartiles of servings per week	n=1546	Percent breast density % [95%CI]		Absolute breast density cm^2 [95%CI]	
		Unadjusted models	Adjusted models*	Unadjusted models	Adjusted models*
Total milk consumption					
[0-3.01)	376	30.0 [27.7-32.4]	28.3 [26.6-30.2]	34.7 [32.1-37.4]	34.0 [31.8-36.4]
[3.01-6.02)	359	29.4 [27.0-31.8]	27.4 [25.7-29.3]	34.4 [31.8-37.1]	33.4 [31.2-35.8]
[6.02-10.01)	418	31.5 [29.2-33.8]	28.5 [26.8-30.2]	35.9 [33.4-38.5]	34.0 [31.9-36.2]
[10.01-38.01]	393	30.3 [28.0-32.7]	26.0 [24.3-27.7]	34.6 [32.1-37.2]	31.6 [29.4-33.8]
p_{trend}		0.742	0.071	0.996	0.125
$r_{Spearman}$ (p)		0.013 (0.611)	–0.038 (0.143)	–0.002 (0.923)	–0.041 (0.108)
Low-fat milk consumption					
[0-0.70)	381	31.5 [29.1-34.0]	28.8 [27.1-30.6]	35.7 [33.1-38.4]	34.3 [32.1-36.7]
[0.70-3.01)	174	30.8 [27.3-34.4]	28.3 [25.8-31.0]	35.7 [31.9-39.8]	34.1 [30.9-37.6]
[3.01-7.00)	463	30.6 [28.5-32.8]	27.8 [26.3-29.4]	35.9 [33.5-38.3]	34.0 [32.0-36.1]
[7.00-35.00]	528	29.1 [27.1-31.1]	26.2 [24.8-27.7]	33.3 [31.2-35.5]	31.5 [29.7-33.4]
p_{trend}		0.140	**0.026**	0.132	0.053
$r_{Spearman}$ (p)		–0.037 (0.144)	–0.042 (0.099)	–0.036 (0.160)	–0.040 (0.116)
High-fat milk consumption					
[0-0.14)	429	24.6 [22.7-26.6]	25.4 [23.9-27.1]	29.4 [27.2-31.6]	31.1 [29.0-33.2]
[0.14-0.28)	355	31.3 [28.9-33.8]	26.9 [25.2-28.7]	36.3 [33.6-39.1]	33.3 [31.1-35.7]
[0.28-3.01)	353	30.8 [28.4-33.3]	27.8 [26.0-29.6]	35.3 [32.6-38.1]	33.0 [30.7-35.4]
[3.01-31.01]	409	35.1 [32.6-37.6]	30.2 [28.5-32.0]	39.3 [36.6-42.0]	35.7 [33.5-38.0]
p_{trend}		**<0.0001**	**0.0004**	**<0.0001**	**0.011**
$r_{Spearman}$ (p)		**0.158 (<0.0001)**	**0.091 (0.0004)**	**0.132 (<0.0001)**	**0.064 (0.013)**
Total ice cream consumption					
[0-0.28)	355	31.5 [29.1-34.1]	26.8 [25.0-28.6]	35.2 [32.5-38.0]	32.1 [29.8-34.4]
[0.28-0.56)	337	33.1 [30.5-35.9]	27.3 [25.5-29.2]	37.7 [34.9-40.7]	33.2 [30.8-35.6]
[0.56-1.12)	427	29.5 [27.4-31.8]	27.2 [25.6-28.9]	34.4 [32.0-36.9]	33.1 [31.0-35.2]
[1.12-21.00]	427	27.9 [25.8-30.0]	28.8 [27.1-30.5]	33.0 [30.7-35.5]	34.5 [32.3-36.7]
p_{trend}		**0.003**	0.112	**0.044**	0.175
$r_{Spearman}$ (p)		**–0.071 (0.005)**	0.044 (0.088)	–0.047 (0.066)	0.036 (0.156)
Low-fat ice cream consumption					
[0-0.14)	598	29.3 [27.5-31.2]	27.2 [25.8-28.6]	33.2 [31.2-35.2]	32.2 [30.4-33.9]
[0.14-0.56)	538	33.5 [31.4-35.6]	27.7 [26.3-29.2]	38.4 [36.1-40.8]	34.0 [32.1-35.9]
[0.56-0.98)	233	28.3 [25.5-31.3]	28.0 [25.8-30.3]	33.6 [30.5-37.0]	33.8 [31.0-36.8]
[0.98-14.00]	177	26.6 [23.5-30.0]	27.9 [25.4-30.5]	32.0 [28.5-35.7]	34.0 [30.8-37.5]
p_{trend}		**0.011**	0.672	0.096	0.475
$r_{Spearman}$ (p)		–0.017 (0.503)	0.024 (0.339)	0.008 (0.761)	0.033 (0.201)
High-fat ice cream consumption					
[0-0.14)	172	30.3 [26.9-34.0]	25.8 [23.4-28.4]	33.6 [29.9-37.5]	31.2 [28.1-34.5]
[0.14-0.56)	676	31.5 [29.7-33.3]	27.2 [25.9-28.5]	36.1 [34.2-38.2]	32.8 [31.2-34.5]
[0.56-0.98)	427	30.4 [28.2-32.7]	27.9 [26.3-29.6]	35.6 [33.1-38.1]	34.2 [32.1-36.4]
[0.98-7.00]	271	27.3 [24.8-30.1]	29.1 [27.0-31.3]	31.7 [28.9-34.7]	34.1 [31.4-36.9]
p_{trend}		0.075	**0.043**	0.230	0.149
$r_{Spearman}$ (p)		–0.045 (0.080)	**0.055 (0.031)**	–0.030 (0.243)	0.046 (0.075)
Total yogurt consumption					
[0-0.14)	300	28.0 [25.5-30.6]	27.2 [25.2-29.2]	31.6 [28.9-34.5]	31.8 [29.4-34.3]
[0.14-0.98)	373	30.8 [28.4-33.2]	29.1 [27.3-30.9]	35.9 [33.3-38.6]	35.0 [32.7-37.4]
[0.98-3.15)	458	31.0 [28.8-33.2]	28.2 [26.6-29.8]	36.7 [34.2-39.2]	34.8 [32.7-36.9]
[3.15-21.00]	415	30.9 [28.6-33.2]	25.9 [24.2-27.5]	34.6 [32.1-37.1]	31.1 [29.0-33.2]
p_{trend}		0.195	0.095	0.316	0.259
$r_{Spearman}$ (p)		0.037 (0.151)	–0.027 (0.292)	0.032 (0.213)	–0.023 (0.379)
Low-fat yogurt consumption					
[0-0.14)	623	31.5 [29.6-33.4]	28.0 [26.6-29.4]	35.4 [33.4-37.5]	33. [31.6-35.1]
[0.14-0.70)	199	27.9 [24.9-31.1]	28.3 [25.9-30.8]	33.5 [30.0-37.1]	34.3 [31.2-37.6]
[0.70-3.15)	373	30.5 [28.2-33.0]	28.9 [27.1-30.7]	36.4 [33.8-39.2]	35.4 [33.1-37.8]
[3.15-21.00]	351	29.4 [27.0-31.9]	25.1 [23.4-26.9]	33.3 [30.7-36.0]	30.2 [28.0-35.2]
p_{trend}		0.809	**0.021**	0.639	0.045
$r_{Spearman}$ (p)		–0.032 (0.202)	–0.038 (0.142)	–0.021 (0.409)	–0.034 (0.183)

Table II. *Continued*

Table II. *Continued*

Quartiles of servings per week	n=1546	Percent breast density % [95%CI]		Absolute breast density cm^2 [95%CI]	
		Unadjusted models	Adjusted models*	Unadjusted models	Adjusted models*
High-fat yogurt consumption					
[0-0.14)	1230	29.1 [27.8-30.4]	27.3 [26.3-28.2]	33.8 [32.4-35.3]	32.8 [31.6-34.1]
[0.14-0.98)	132	33.3 [29.2-37.8]	28.8 [25.8-31.9]	37.6 [33.1-42.4]	34.5 [30.8-38.5]
[0.98-14.00]	184	36.3 [32.6-40.2]	28.8 [26.3-31.5]	40.4 [36.4-44.6]	35.1 [31.8-38.5]
p_{trend}		**0.010**	0.524	**0.030**	0.429
$r_{Spearman}$ (p)		**0.101 (<0.0001)**	0.036 (0.161)	**0.085 (0.001)**	0.037 (0.149)
Total cheese consumption					
[0-1.96)	378	27.6 [25.4-29.9]	27.4 [25.6-29.2]	32.5 [30.1-35.1]	33.3 [31.0-35.7]
[1.96-3.71)	344	29.7 [27.3-32.2]	26.7 [25.0-28.5]	34.7 [32.1-37.5]	32.8 [30.5-35.2]
[3.71-7.00)	421	31.4 [29.2-33.8]	28.2 [26.5-29.9]	35.9 [33.4-38.4]	33.5 [31.3-35.6]
[7.00-21.14]	403	32.2 [29.9-34.7]	27.8 [26.1-29.6]	36.4 [33.8-39.0]	33.4 [31.2-35.7]
p_{trend}		**0.003**	0.508	**0.031**	0.879
$r_{Spearman}$ (p)		**0.078 (0.002)**	0.028 (0.277)	**0.059 (0.021)**	0.011 (0.666)
Low-fat cheese consumption					
[0-0.14)	1010	31.9 [30.4-33.4]	27.7 [26.7-28.8]	36.4 [34.7-38.0]	33.3 [32.0-34.7]
[0.14-3.57)	245	26.0 [23.4-28.7]	27.8 [25.7-30.1]	31.9 [28.9-35.1]	34.7 [31.9-37.8]
[3.57-17.57]	291	28.3 [25.8-31.0]	26.8 [24.8-28.7]	32.4 [29.6-35.3]	31.6 [29.2-34.2]
p_{trend}		0.233	0.367	0.109	0.148
$r_{Spearman}$ (p)		**–0.089 (0.001)**	–0.016 (0.532)	**–0.071 (0.005)**	–0.011 (0.681)
High-fat cheese consumption					
[0-0.14)	564	27.0 [25.2-28.8]	27.1 [25.7-28.5]	31.9 [30.0-34.0]	32.9 [31.1-34.8]
[0.14-2.94)	220	29.7 [26.7-32.9]	27.4 [25.2-29.8]	33.8 [30.6-37.3]	32.3 [29.4-35.3]
[2.94-5.88)	362	32.2 [29.8-34.8]	27.3 [25.5-29.1]	36.6 [33.9-39.4]	32.8 [30.6-35.2]
[5.88-21.14]	400	33.6 [31.2-36.1]	28.6 [26.9-30.4]	38.2 [35.6-41.0]	34.7 [32.4-37.0]
p_{trend}		**0.0001**	0.219	**0.001**	0.185
$r_{Spearman}$ (p)		**0.119 (<0.0001)**	0.031 (0.223)	**0.098 (0.0001)**	0.023 (0.380)
Total dairy food consumption					
[0-8.68)	374	27.3 [25.1-29.6]	27.1 [25.3-29.0]	31.9 [29.5-34.5]	32.6 [30.3-35.1]
[8.68-14.28)	398	31.3 [29.0-33.8]	28.5 [26.8-30.2]	36.7 [34.1-39.4]	34.7 [32.5-37.0]
[14.28-21.56)	385	32.1 [29.7-34.6]	29.2 [27.4-31.0]	36.6 [34.0-39.4]	34.5 [32.3-36.8]
[21.56-54.04]	389	30.4 [28.1-32.8]	25.5 [23.8-27.3]	34.3 [31.8-36.9]	31.1 [28.9-33.4]
p_{trend}		0.104	0.194	0.357	0.261
$r_{Spearman}$ (p)		**0.048 (0.060)**	–0.015 (0.551)	**0.027 (0.291)**	–0.023 (0.378)
Low-fat dairy food consumption					
[0-3.01)	342	31.7 [29.2-34.3]	29.1 [27.2-31.0]	35.9 [33.2-38.8]	34.7 [32.3-37.2]
[3.01-7.14)	427	31.2 [28.9-33.5]	28.4 [26.7-30.1]	36.3 [33.8-38.9]	34.5 [32.4-36.7]
[7.14-14.00)	387	31.3 [29.0-33.8]	28.3 [26.6-30.0]	36.3 [33.7-39.0]	34.2 [32.0-36.5]
[14.00-46.76]	390	27.1 [25.0-29.4]	24.7 [23.1-26.4]	31.2 [28.8-33.6]	29.6 [27.6-31.8]
p_{trend}		**0.004**	0.0003	**0.003**	**0.001**
$r_{Spearman}$ (p)		**–0.064 (0.012)**	–0.069 (0.007)	**–0.062 (0.015)**	**–0.069 (0.007)**
High-fat dairy food consumption					
[0-1.12)	386	26.1 [24.0-28.3]	25.8 [24.1-27.5]	30.9 [28.5-33.3]	31.5 [29.3-33.7]
[1.12-4.41)	386	27.6 [25.5-29.9]	26.7 [25.1-28.4]	32.3 [29.9-34.9]	32.0 [29.9-34.2]
[4.41-8.96)	388	31.8 [29.4-34.2]	28.0 [26.3-29.7]	36.3 [33.7-39.0]	33.5 [31.3-35.7]
[8.96-41.02]	386	35.7 [33.2-38.4]	29.8 [28.0-31.7]	40.2 [37.4-43.1]	36.1 [33.7-38.5]
p_{trend}		**<0.0001**	**0.0012**	**<0.0001**	**0.0034**
$r_{Spearman}$ (p)		**0.156 (<0.0001)**	**0.074 (0.0039)**	**0.134 (<0.0001)**	**0.065 (0.011)**

CI, Confidence interval; $r_{Spearman}$, Spearman correlation coefficient; p_{trend}, p-value for linear test trend. *All models (linear regression and correlation models) were adjusted for: menopausal status, age at mammography, age at menarche, age at first full-term pregnancy, parity, breastfeeding, duration of hormonal contraceptive treatment, duration of substitutive hormonal treatment, total caloric intake, body mass index, waist-to-hip ratio, alcohol intake, physical activity, family history of breast cancer, number of breast biopsy, smoking status and education. The statistically significant results are in bold.

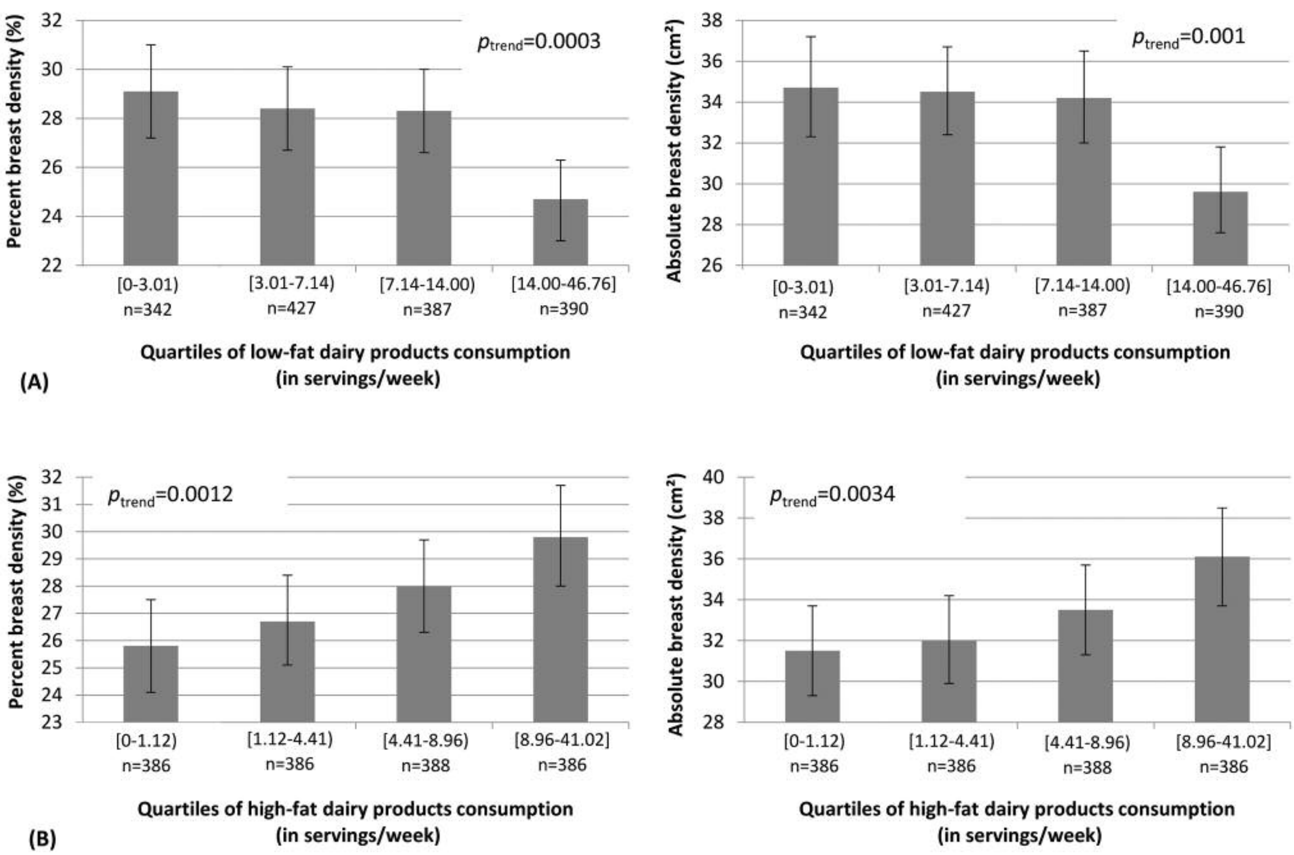

Figure 1. *Associations between mammographic breast density and (A) low-fat or (B) high-fat dairy products consumption among premenopausal and postmenopausal women (N=1546).*

fat DF by increasing quartiles was significantly associated with higher percent BD [mean of 25.8; 26.7 ; 28.0 and 24.7% with p_{trend}=0.0012, r=0.074 (p=0.0039)] or absolute BD [averages of 31.5; 32.0; 33.5 and 36.1 cm^2 with p_{trend}=0.034, r=0.065 (p=0.011)] among total women.

Table III presents the results of associations between DF consumption frequencies with BD according to menopausal status. Among the 775 premenopausal women, trends were similar to those found in all women. An inverse association was observed between the consumption of low-fat milk in quartiles and percent BD [p_{trend}=0.015, r=–0.071 (p=0.051)] or absolute BD [p_{trend}=0.013, r=–0.064 (p=0.078)], while the consumption of high-fat milk was significantly associated with high percent BD [p_{trend}=0.001, r=0.106 (p=0.004)] and with high absolute BD [p_{trend}=0.020, r=0.071 (p=0.052)], as well as the consumption of high-fat cheese [p_{trend}=0.030, r=0.067 (p=0.066) for percent BD; p_{trend}=0.021, r=0.084 (p=0.022) for absolute BD]. Ice cream consumption was significantly positively correlated with high absolute BD in premenopausal women [r=0.085 (p=0.020)] but in a non-linear manner (p_{trend}=0.600). On the other hand, an inverse linear trend association was found between the consumption of low-fat yogurt and percent BD (p_{trend}=0.031) or absolute BD (p_{trend}=0.042), but with insignificant Spearman correlation tests [r=–0.024 (p=0.508) and r=–0.048 (p=0.190)].

In general, for premenopausal women, we observed reversed trends between DF intake and BD according to the fat content consumed. Low-fat DF consumption by increasing quartiles was statistically associated with lower percent BD [mean densities of 44.8; 43.5; 42.0 and 38.1% with p_{trend}=0.0012, r=–0.082 (p=0.024)] and lower absolute BD [mean of 49.7; 48.2; 45.8 and 40.7 cm^2 with p_{trend}=0.012, r=–0.098 (p=0.007)], while the consumption of high-fat DF by quartiles was significantly associated with high percent BD [mean of 39.0; 40.6; 42.3 and 45.0% with p_{trend}=0.0033, r=0.084 (p=0.021)] and with higher absolute BD [mean of 42.4; 43.8; 46.2 and 50.1 cm^2 with p_{trend}=0.0047, r=0.100 (p=0.006)] in premenopausal women (Table III and Figure 2).

For the 771 postmenopausal women, most associations between DF consumption frequencies and BD were not statistically significant. Only high-fat milk, represented by whole milk and cream, was statistically positively associated with linearly increasing percent BD [p_{trend}=0.036, r=0.101

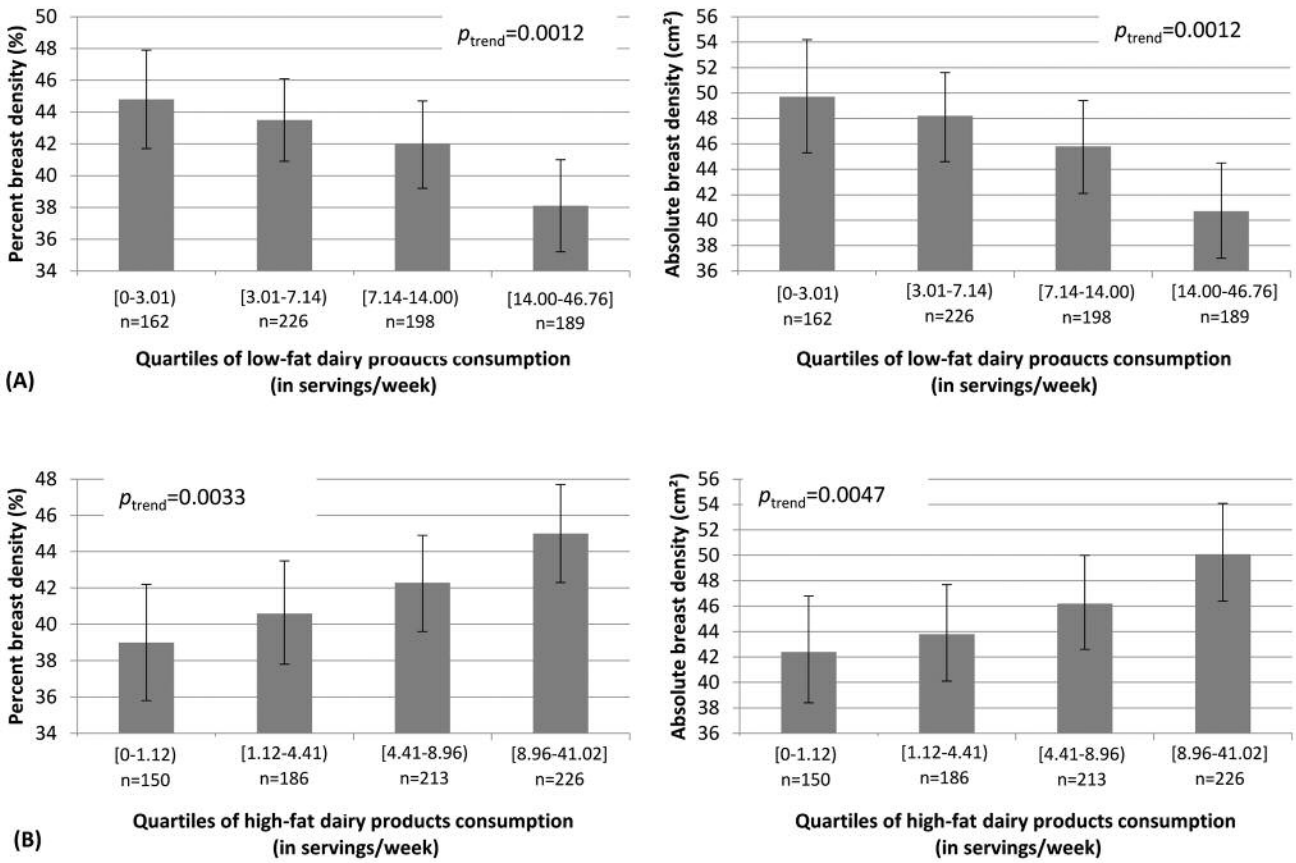

Figure 2. *Associations between mammographic breast density and (A) low-fat or (B) high-fat dairy products consumption among premenopausal women (N=775).*

(p=0.006)] and positively correlated with absolute BD [r=0.078 (p=0.034)]. Finally, total consumption of high-fat DF was associated with percent BD (p_{trend}=0.0465) but with a low correlation [r=0.070 (p=0.056)], and not with absolute BD [p_{trend}=0.149, r=0.054 (p=0.137)].

Discussion

In our population of premenopausal and postmenopausal women, we observed an inverse association between separate or combined low-fat DF intake and BD, and a positive association between separate or combined high-fat DF intake and BD. These associations seem limited to premenopausal women only. These opposing associations of DF fat content consumed with BD are interesting and could be significant in the prevention of breast cancer. In our study, premenopausal women who consumed 14 or more servings/week of low-fat DF had an average BD decreased by 6.7% compared to those who consumed less than 3 servings/week, while premenopausal women who consumed 9 or more servings/week of high-fat DF had an average BD approximately 6% higher than those who consumed little or no high-fat DF. In comparison, Tamoxifen®, which is associated with a 30 to 50% decrease in breast cancer risk (20, 21), is also associated with a 6.4% decrease in BD (22).

Our observation of an inverse association between low-fat DF consumption and BD among premenopausal women is consistent with previous studies (5, 10). In 2019, Han *et al*. (10) found that low/reduced-fat milk was inversely associated with volumetric percent density in 375 premenopausal women (p_{trend}=0.011). In 2000, Vachon *et al*. (5) found that total low-fat DF intake was negatively associated with visual estimation of BD in 283 premenopausal women, but this trend was not statistically significant (p_{trend}=0.14) possibly due to the relatively small sample size. These findings are in line with two meta-analyses suggesting a protective effect of low-fat DF intake on breast cancer risk among premenopausal women (23, 24).

Conversely, our results showing a positive association between high-fat DF intake and BD are not supported by the

Table III. *Associations between dairy food consumption and mammographic breast density according to menopausal status.*

Quartiles of servings per week	Premenopausal women (n=775)			Postmenopausal women (n=771)		
	n	Percent BD % [95%CI]	Absolute BD cm² [95%CI]	n	Percent BD % [95%CI]	Absolute BD cm² [95%CI]
Total milk consumption						
[0-3.01)	173	43.6 [40.6-46.6]	48.2 [44.0-52.5]	203	17.0 [15.2-18.9]	22.4 [20.2-24.9]
[3.01-6.02)	171	42.3 [39.3-45.2]	47.1 [43.1-51.4]	188	16.9 [15.1-18.8]	22.1 [19.8-24.7]
[6.02-10.01)	221	42.0 [39.4-44.6]	45.7 [42.4-49.3]	197	18.9 [17.1-20.9]	24.2 [21.7-26.8]
[10.01-38.01]	210	40.7 [37.9-43.4]	43.8 [40.2-47.6]	183	16.6 [14.8-18.5]	22.0 [19.5-24.6]
p_{trend}		0.187	0.120		0.756	0.855
$r_{Spearman}$ *(p)*		–0.052 (0.155)	–0.052 (0.152)		0.019 (0.607)	0.003 (0.942)
Low-fat milk consumption						
[0-0.70)	181	43.5 [40.6-46.4]	47.3 [43.3-51.5]	200	18.1 [16.3-20.1]	23.4 [21.0-26.0]
[0.70-3.01)	88	44.4 [40.2-48.6]	50.6 [44.8-56.9]	86	16.2 [13.7-19.1]	20.6 [17.3-24.3]
[3.01-7.00)	243	42.9 [40.5-45.4]	47.3 [43.9-50.9]	220	17.3 [15.6-19.1]	23.0 [20.7-25.4]
[7.00-35.00]	263	39.5 [37.0-41.9]	42.5 [39.4-45.8]	265	17.2 [15.7-18.9]	22.5 [20.2-24.8]
p_{trend}		**0.015**	**0.013**		0.917	0.854
$r_{Spearman}$ *(p)*		–0.071 (0.051)	–0.064 (0.078)		0.002 (0.967)	–0.005 (0.894)
High-fat milk consumption						
[0-0.14)	157	39.4 [36.2-42.5]	43.3 [39.2-47.6]	272	15.9 [14.4-17.4]	21.1 [19.2-23.2]
[0.14-0.28)	192	40.4 [37.6-43.2]	45.6 [41.9-49.6]	163	17.3 [15.4-19.4]	23.1 [20.5-25.9]
[0.28-3.01)	194	41.5 [38.7-44.3]	44.5 [40.9-48.4]	159	17.8 [15.8-20.0]	23.2 [20.5-26.1]
[3.01-31.01]	232	45.7 [43.2-48.2]	49.5 [46.0-53.3]	177	19.3 [17.3-21.5]	24.2 [21.6-27.0]
p_{trend}		**0.001**	**0.020**		**0.036**	0.227
$r_{Spearman}$ *(p)*		**0.106 (0.004)**	0.071 (0.052)		**0.101 (0.006)**	**0.078 (0.034)**
Total ice cream consumption						
[0-0.28)	187	40.9 [38.0-43.8]	44.4 [40.6-48.4]	168	17.0 [15.0-19.0]	22.0 [19.4-24.7]
[0.28-0.56)	199	42.1 [39.3-44.9]	45.7 [42.0-49.6]	138	16.9 [14.8-19.1]	22.7 [19.9-25.8]
[0.56-1.12)	207	41.9 [39.2-44.6]	46.2 [42.6-50 0]	220	17.0 [15.3-18.8]	22.4 [20.1-24.7]
[1.12-21.00]	182	43.4 [40.5-46.4]	47.9 [43.9-52.2]	245	18.3 [16.6-20.0]	23.5 [21.2-25.8]
p_{trend}		0.280	0.256		0.265	0.464
$r_{Spearman}$ *(p)*		0.052 (0.154)	0.054 (0.136)		0.043 (0.238)	0.028 (0.451)
Low-fat ice cream consumption						
[0-0.14)	280	40.8 [38.4-43.1]	43.4 [40.3-46.6]	318	17.5 [16.1-19.0]	22.7 [20.9-24.7]
[0.14-0.56)	318	43.2 [40.9-45.4]	47.8 [44.7-51.0]	220	16.6 [14.9-18.3]	22.2 [20.0-24.6]
[0.56-0.98)	106	43.2 [39.3-47.0]	47.6 [42.4-53.1]	127	17.8 [15.6-20.2]	22.8 [19.8-25.9]
[0.98-14.00]	71	40.5 [35.8-45.2]	46.4 [40.2-53.1]	106	18.2 [15.7-20.9]	23.3 [20.0-26.9]
p_{trend}		0.740	0.600		0.421	0.688
$r_{Spearman}$ *(p)*		0.062 (0.090)	**0.085 (0.020)**		0.005 (0.885)	–0.007 (0.855)
High-fat ice cream consumption						
[0-0.14)	83	41.4 [37.1-45.7]	45.0 [39.4-51.1]	89	15.6 [13.2-18.3]	20.6 [17.3-24.2]
[0.14-0.56)	378	41.5 [39.5-43.6]	45.5 [42.8-48.3]	298	17.2 [15.7-18.7]	22.3 [20.4-24.4]
[0.56-0.98)	207	42.6 [39.9-45.3]	47.6 [43.9-51.4]	220	17.7 [16.0-19.5]	23.3 [21.0-25.8]
[0.98-7.00]	107	43.4 [39.5-47.3]	45.9 [40.7-51.3]	164	18.3 [16.3-20.5]	23.7 [20.9-26.6]
p_{trend}		0.420	0.738		0.119	0.165
$r_{Spearman}$ *(p)*		0.028 (0.445)	0.026 (0.472)		0.056 (0.123)	0.047 (0.195)
Total yogurt consumption						
[0-0.14)	136	39.9 [36.5-43.3]	43.2 [38.8-47.8]	164	17.8 [15.8-20.0]	22.3 [19.7-25.1]
[0.14-0.98)	180	44.7 [41.7-47.6]	47.8 [43.7-52.0]	193	17.8 [16.0-19.8]	23.8 [21.3-26.5]
[0.98-3.15)	238	43.3 [40.8-45.8]	48.9 [45.4-52.6]	220	17.7 [16.0-19.5]	23.4 [21.1-25.8]
[3.15-21.00]	221	39.9 [37.3-42.6]	43.3 [39.8-46.9]	194	16.2 [14.4-18.1]	21.1 [18.7-23.6]
p_{trend}		0.399	0.687		0.217	0.317
$r_{Spearman}$ *(p)*		–0.019 (0.605)	–0.027 (0.462)		–0.036 (0.319)	–0.019 (0.600)
Low-fat yogurt consumption						
[0-0.14)	319	42.1 [39.9-44.2]	46.3 [43.4-49.4]	304	17.9 [16.4-19.5]	22.5 [20.6-24.6]
[0.14-0.70)	87	45.6 [41.3-49.8]	49.4 [43.5-55.7]	112	16.7 [14.4-19.2]	22.4 [19.3-25.8]
[0.70-3.15)	184	43.4 [40.5-46.2]	48.2 [44.3-52.4]	189	18.4 [16.5-20.4]	24.8 [22.2-27.5]
[3.15-21.00]	185	39.1 [36.2-42.0]	41.8 [38.1-45.7]	166	15.7 [13.8-17.7]	20.8 [18.3-23.5]
p_{trend}		**0.031**	**0.042**		0.266	0.477
$r_{Spearman}$ *(p)*		–0.024 (0.508)	–0.048 (0.190)		–0.046 (0.211)	–0.021 (0.571)

Table III. *Continued*

Table III. *Continued*

Quartiles of servings per week	n=1546	Percent breast density % [95%CI]			Absolute breast density cm^2 [95%CI]	
		Unadjusted models	Adjusted models*		Unadjusted models	Adjusted models*
High-fat yogurt consumption						
[0-0.14)	595	41.6 [40.1-43.2]	45.3 [43.2-47.5]	635	17.2 [16.2-18.2]	22.6 [21.3-24.0]
[0.14-0.98)	73	43.1 [38.5-47.7]	45.6 [39.6-53.5]	59	18.1 [14.8-21.7]	24.0 [19.7-28.9]
[0.98-14.00]	107	43.6 [39.8-47.4]	50.4 [45.1-56.0]	77	18.3 [15.4-21.5]	22.4 [18.6-26.5]
p_{trend}		0.546	0.113		0.669	0.713
$r_{Spearman}$ (*p*)		0.020 (0.583)	0.044 (0.225)		0.044 (0.227)	0.026 (0.474)
Total cheese consumption						
[0-1.96)	155	39.8 [36.6-43.1]	42.5 [38.3-46.8]	223	18.4 [16.6-20.3]	24.7 [22.2-27.2]
[1.96-3.71)	176	42.2 [39.2-45.1]	47.5 [43.5-51.7]	168	15.7 [13.9-17.6]	20.7 [18.2-23.3]
[3.71-7.00)	217	43.6 [40.9-46.2]	47.1 [43.5-50.8]	204	17.5 [15.7-19.4]	22.5 [20.1-25.0]
[7.00-21.14]	227	42.0 [39.4-44.7]	46.4 [42.8-50.1]	176	17.5 [15.6-19.6]	22.4 [19.8-25.1]
p_{trend}		0.260	0.245		0.918	0.442
$r_{Spearman}$ (*p*)		0.040 (0.268)	0.048 (0.193)		0.003 (0.940)	–0.019 (0.604)
Low-fat cheese consumption						
[0-0.14)	556	42.8 [41.4-44.4]	46.9 [44.6-49.2]	454	17.1 [15.9-18.3]	22.2 [20.6-23.8]
[0.14-3.57)	84	39.0 [334.7-43.4]	44.3 [38.7-50.3]	161	18.8 [16.7-21.0]	25.1 [22.2-28.1]
[3.57-17.57]	135	41.0 [37.7-44.4]	43.6 [39.3-48.2]	156	16.8 [14.8-18.9]	21.6 [19.0-24.4]
p_{trend}		0.724	0.336		0.515	0.381
$r_{Spearman}$ (*p*)		–0.042 (0.247)	–0.045 (0.215)		0.014 (0.694)	0.014 (0.697)
High-fat cheese consumption						
[0-0.14)	227	40.1 [37.5-42.7]	43.7 [40.3-47.2]	337	17.6 [16.2-19.1]	23.3 [21.4-25.2]
[0.14-2.94)	110	40.2 [36.4-44.0]	42.3 [37.5-47.5]	110	18.4 [15.9-21.0]	23.7 [20.4-27.2]
[2.94-5.88)	206	43.1 [40.4-45.8]	47.8 [44.0-51.6]	156	15.7 [13.9-17.8]	20.3 [17.8-23.0]
[5.88-21.14]	232	43.9 [41.3-46.6]	48.6 [45.0-52.4]	168	17.8 [15.8-19.9]	23.1 [20.5-25.9]
p_{trend}		**0.030**	**0.021**		0.791	0.723
$r_{Spearman}$ (*p*)		0.067 (0.066)	**0.084 (0.022)**		–0.013 (0.713)	–0.023 (0.530)
Total dairy food consumption						
[0-8.68)	152	42.7 [39.4-46.0]	46.3 [41.9-51.0]	222	16.3 [14.6-18.1]	21.6 [19.3-24.1]
[8.68-14.28)	216	42.7 [40.0-45.4]	46.8 [43.1-50.6]	182	18.4 [16.5-20.5]	24.4 [21.9-27.2]
[14.28-21.56)	199	43.8 [41.0-46.6]	47.9 [44.1-51.9]	186	18.7 [16.8-20.7]	23.5 [21.1-26.2]
[21.56-54.04]	208	39.3 [36.4-42.2]	43.4 [39.6-47.3]	181	16.3 [14.4-18.3]	21.3 [18.8-24.1]
p_{trend}		0.158	0.352		0.817	0.631
$r_{Spearman}$ (*p*)		–0.036 (0.328)	–0.026 (0.470)		0.013 (0.722)	–0.004 (0.923)
Low-fat dairy food consumption						
[0-3.01)	162	44.8 [41.7-47.9]	49.7 [45.3-54.2]	180	17.7 [15.8-19.8]	22.5 [20.0-25.2]
[3.01-7.14)	226	43.5 [40.9-46.1]	48.2 [44.6-51.9]	201	17.6 [15.8-19.5]	23.2 [20.8-25.7]
[7.14-14.00)	198	42.0 [39.2-44.7]	45.8 [42.1-49.7]	189	18.6 [16.7-20.6]	24.6 [22.1-27.3]
[14.00-46.76]	189	38.1 [35.2-41.0]	40.7 [37.0-44.5]	201	15.7 [14.0-17.5]	20.5 [18.3-23.0]
p_{trend}		**0.0012**	**0.0012**		0.111	0.204
$r_{Spearman}$ (*p*)		**–0.082 (0.024)**	**–0.098 (0.007)**		–0.045 (0.223)	–0.038 (0.296)
High-fat dairy food consumption						
[0-1.12)	150	39.0 [35.8-42.2]	42.4 [38.4-46.8]	236	16.6 [15.0-18.3]	22.1 [19.9-24.4]
[1.12-4.41)	186	40.6 [37.8-43.5]	43.8 [40.1-47.7]	200	16.4 [14.7-18.2]	21.8 [19.5-24.3]
[4.41-8.96)	213	42.3 [39.6-44.9]	46.2 [42.6-50.0]	175	18.0 [16.1-20.0]	22.8 [20.3-25.5]
[8.96-41.02]	226	45.0 [42.3-47.7]	50.1 [46.4-54.1]	160	19.1 [16.9-21.4]	24.5 [21.7-27.5]
p_{trend}		**0.0033**	**0.0047**		**0.0465**	0.149
$r_{Spearman}$ (*p*)		**0.084 (0.021)**	**0.100 (0.006)**		0.070 (0.056)	0.054 (0.137)

BD, Breast density; CI, confidence interval; $r_{Spearman}$, Spearman correlation coefficient; p_{trend}, *p*-value for linear test trend. *All models (linear regression and correlation models) were adjusted for: menopausal status, age at mammography, age at menarche, age at first full-term pregnancy, parity, breastfeeding, duration of hormonal contraceptive treatment, duration of substitutive hormonal treatment, total caloric intake, body mass index, waist-to-hip ratio, alcohol intake, physical activity, family history of breast cancer, number of breast biopsy, smoking status and education. The statistically significant results are in bold.

litterature. Although Vachon *et al*. observed a similar trend among premenopausal women, their results were not significant (p_{trend}=0.08) (5). The inconsistencies observed in the associations of DF intake and BD reported in other studies may be explained by the fact that none explored the role of fat. Indeed, when introduced simultaneously into the same model, low-fat and high-fat total DF intake were independent co-factors, and trend tests remained statistically significant among all or premenopausal women (data not shown). Thus, an antagonistic mechanism related to fat could explain the null associations observed in our study, when considering the total intake of DF not stratified on fat content, as well as results observed in previous studies not focusing on DF fat content.

Several mechanisms could explain our results. On the one hand, the inverse association found between the consumption of low-fat DF and BD among premenopausal women can be attributed to the protective effects of calcium and vitamin D (14, 25). In a systematic review published in 2016, Ekpo *et al*. also found an inverse association between dietary intakes of vitamin D and calcium and BD in premenopausal women (26). Further adjustment of our linear models for calcium or vitamin D intake resulted in a slight decrease in the average BD per DF consumption; thus, the strength of our associations decreased slightly but remained significant (data not shown). In other words, part of the association between the consumption of low-fat DF and BD is mediated by calcium or vitamin D, but each of these intermediate factors does not totally explain the observed associations. However, vitamin D intake is subject to misclassification in our study, which could generate residual confounding bias explaining the persistence of the observed associations (14, 27).

On the other hand, another biological explanation for our results could be associated with the role of fat. One explanation could be provided by Nelson *et al*., who showed some evidence of the harmful role of 27-hydrocholesterol, a metabolite contained in cholesterol whose level increases following the consumption of trans and saturated fat, on cell proliferation in the breast gland (28). This hypothesis could be consistent with previous observations in breast cancer epidemiology studies (29, 30). Inflammatory mechanisms related to fat intake are also associated with altered levels of circulating hormones and insulin resistance (31), factors known to promote breast cell proliferation (32, 33). In addition, Hanna *et al*. found in 2017 that inflammatory markers may be associated with breast carcinogenesis through their effects on BD. High expression levels of the proinflammatory markers were associated with higher percent BD among premenopausal women, whereas higher expression levels of anti-inflammatory markers were associated with lower percent BD among all and postmenopausal women, which could logically explain our results based on fat intake (34). Finally, the fact that these results are observed mainly in premenopausal women is consistent with an important role of sex hormones (oestrogens and progesterone) on BD (31, 35, 36).

Our study has several strengths. First, the quality of mammography was maximized, with most images taken with the same device (LORAD M4), in the same clinic, accredited by the Canadian Radiological Association, and according to the Quebec breast cancer screening program quality criteria. Second, quantitative BD measurements were obtained without any information on the participants, by computer-assisted method, over a short period, and by a single operator whose reliability and accuracy of the measurements were demonstrated, thus minimizing the probability of measurement bias. Also, the BD measurements between the left and right breasts were in agreement which minimizes the probability of misclassification bias since one of the two breast images for each woman was randomly chosen. Third, the characteristics of the women included and excluded in this study were not significantly different, thus, limiting possible selection bias related to the exclusion of 28 subjects. Fourth, several factors known or suspected to be associated with BD and/or DF consumption were documented and included in the analyses to account for their likely confounding effects. As all participants were Caucasian, no adjustment for ethnic status was required. Finally, the sample size is relatively large, making us confident in our findings and interpretation of results. Nonetheless, although our sample size allowed us to explore differences between menopausal groups, we may have lacked power when stratifying for body mass index and physical activity, which may explain the null results obtained in these additional analyses (data not shown).

However, there are several limitations. The use of a self-administered food frequency questionnaire requiring the recall of consumption frequencies over a year can lead to memorization and misclassification bias. Nonetheless, the validity and accuracy of the questionnaire used have been demonstrated in several studies (17, 18). Also, if a recall bias is present, it would be non-differential, since women were not informed of the specific objectives of this study at the time the questionnaire was completed. In the same way, non-differential misclassification bias may have occurred when assessing DF fat composition. Indeed, milk was the only dairy product where whole milk was specifically distinguished from low-fat or skimmed milk. Other items like yogurt or cheese were crossed with a general question about the fat composition of items consumed. In both cases, these measurement biases will only have the effect of underestimating the associations observed. In addition, participants in our study were recruited for screening mammography, so, logically, women with a family history of breast cancer should be more represented, which would explain why the percentage of women with a family history of breast cancer is higher than in other studies of similar cohorts. Similarly, since BD increases with family history of breast cancer, it is possible that our study population also has a higher average BD than the general population of Quebec women, thus limiting the inference of observed results to the population of women participating in mammography screening. To explore this possibility, we conducted a sensitivity analysis in which we investigated the association between high- and low-fat DF consumption and BD based on family history of breast cancer in premenopausal women. The correlations between high-fat DF intake and BD were found to be similar in women with and without a family history of breast cancer. Correlations between low-fat DF consumption and BD were more nuanced, with higher correlations observed in women with no history. Thus, these results favour a limited selection bias, suggesting that our findings could be generalized to Caucasian women. The cross-sectional design of the study does not allow us to make causal judgements about the observed associations, and prospective cohort studies will be required to determine the causality and sustainability of the observed associations. Finally, the multiplicity of the associations tested may lead to significant first-order risk inflation (type I errors, or false positive results). Therefore, we cannot exclude that the associations observed may be due to chance. It is interesting to note, however, that the reverse trends observed between total high-fat and low-fat DF intake and BD are also observed for each group of DF (by fat content) and BD, so our results cannot be completely random.

Conclusion

To our knowledge, this study is the first to observe antagonistic associations of low-fat and high-fat DF intake with mammographic density among a large sample of premenopausal women, regardless of the DF group consumed. Given the increase in fat intakes in the world's diet and the health problems attributed to it, it is important to continue the research on this subject and to inform women so that they adopt healthy and beneficial eating practices. However, while this study provides interesting elements for positioning oneself in the debate on the role of diet in relation to breast cancer risk, new studies will be needed to further explore the associations observed. In addition, excessive consumption of high-fat DF could lead to significant health problems depending on a woman's susceptibility, and thus threaten her quality of life and life expectancy, just like breast cancer. Possible recommendations in terms of frequency of consumption of specific dairy products, resulting from this work or subsequent research, would necessarily have to be adapted according to the health status of each woman.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

EC designed the study, performed the statistical analyses, interpreted the results and drafted the manuscript. CD had the original idea, contributed to the study design and the interpretation of the results, and revised the manuscript. All Authors approved the final version.

References

1 Nazari SS and Mukherjee P: An overview of mammographic density and its association with breast cancer. Breast Cancer *25(3)*: 259-267, 2018. PMID: 29651637. DOI: 10.1007/s12282-018-0857-5

2 Brisson J, Berube S and Diorio C: Breast density: A biomarker to better understand and prevent breast cancer. Bull Cancer *93(9)*: 847-855, 2006. PMID: 16980227.

3 Boyd NF, Rommens JM, Vogt K, Lee V, Hopper JL, Yaffe MJ and Paterson AD: Mammographic breast density as an intermediate phenotype for breast cancer. Lancet Oncol *6(10)*: 798-808, 2005. PMID: 16198986. DOI: 10.1016/S1470-2045(05)70390-9

4 Thomson CA, Arendell LA, Bruhn RL, Maskarinec G, Lopez AM, Wright NC, Moll CE, Aickin M and Chen Z: Pilot study of dietary influences on mammographic density in pre-and postmenopausal hispanic and non-hispanic white women. Menopause *14(2)*: 243-250, 2007. PMID: 17091096. DOI: 10.1097/01.gme.0000235362.72899.7b

5 Vachon CM, Kushi LH, Cerhan JR, Kuni CC and Sellers TA: Association of diet and mammographic breast density in the minnesota breast cancer family cohort. Cancer Epidem Biomarkers Prev *9(2)*: 151-160, 2000. PMID: 10698475.

6 Masala G, Ambrogetti D, Assedi M, Giorgi D, Del Turco MR and Palli D: Dietary and lifestyle determinants of mammographic breast density. A longitudinal study in a mediterranean population. Int J Cancer *118(7)*: 1782-1789, 2006. PMID: 16231317. DOI: 10.1002/ijc.21558

7 Tseng M, Byrne C, Evers KA, London WT and Daly MB: Acculturation and breast density in foreign-born, us chinese women. Cancer Epidem Biomarkers Prev *15(7)*: 1301-1305, 2006. PMID: 16835327. DOI: 10.1158/1055-9965.EPI-06-0159

8 Sellers T, Vachon CM, Pankratz V, Janney C, Fredericksen Z, Brandt KR, Huang Y, Couch FJ, Kushi L and Cerhan JR: Association of childhood and adolescent anthropometric factors, physical activity, and diet with adult mammographic breast density. Am J Epidem *166(4)*: 456-464, 2007. PMID: 17548785. DOI: 10.1093/aje/kwm112

9 Alipour S, Saberi A, Alikhassi A, Bayani L and Hosseini L: Association of mammographic breast density with dairy product consumption, sun exposure, and daily activity. ISRN Oncol 2014, 2014. PMID: 24729894. DOI: 10.1155/2014/159049

10 Han Y, Zong X, Li Y, Colditz GA and Toriola AT: Milk intake and mammographic density in premenopausal women. Breast Cancer Res Treat *174(1)*: 249-255, 2019. PMID: 30456438. DOI: 10.1007/s10549-018-5062-x

11 Takata Y, Maskarinec G, Park SY, Murphy SP, Wilkens LR and Kolonel LN: Mammographic density and dietary patterns: The multiethnic cohort. Eur J Cancer Prev *16(5)*: 409-414, 2007. PMID: 17923811. DOI: 10.1097/01.cej.0000243852.05104.02

12 Sala E, Warren R, Duffy S, Welch A, Luben R and Day N: High risk mammographic parenchymal patterns and diet: A case-control study. Br J Cancer *83(1)*: 121-126, 2000. PMID: 10883679. DOI: 10.1054/bjoc.2000.1151

13 Mishra G, McCormack V, Kuh D, Hardy R, Stephen A and dos Santos Silva I: Dietary calcium and vitamin d intakes in childhood and throughout adulthood and mammographic density in a british birth cohort. Br J Cancer *99(9)*: 1539-1543, 2008. PMID: 18827811. DOI: 10.1038/sj.bjc.6604697

14 Berube S, Diorio C, Masse B, Hebert-Croteau N, Byrne C, Cote G, Pollak M, Yaffe M and Brisson J: Vitamin d and calcium intakes from food or supplements and mammographic breast density. Cancer Epidemiol Biomarkers Prev *14(7)*: 1653-1659, 2005. PMID: 16030097. DOI: 10.1158/1055-9965.EPI-05-0068

15 Diorio C, Pollak M, Byrne C, Masse B, Hebert-Croteau N, Yaffe M, Cote G, Berube S, Morin C and Brisson J: Insulin-like growth factor-i, igf-binding protein-3, and mammographic breast density. Cancer Epidemiol Biomarkers Prev *14(5)*: 1065-1073, 2005. PMID: 15894654. DOI: 10.1158/1055-9965.EPI-04-0706

16 London SJ, Colditz GA, Stampfer MJ, Willett WC, Rosner B and Speizer FE: Prospective study of relative weight, height, and risk of breast cancer. JAMA *262(20)*: 2853-2858, 1989. PMID: 2810620.

17 Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH and Speizer FE: Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol *122(1)*: 51-65, 1985. PMID: 4014201. DOI: 10.1093/oxfordjournals.aje.a114086

18 Caan BJ, Slattery ML, Potter J, Quesenberry CP Jr., Coates AO and Schaffer DM: Comparison of the block and the willett self-administered semiquantitative food frequency questionnaires with an interviewer-administered dietary history. Am J Epidemiol *148(12)*: 1137-1147, 1998. PMID: 9867257. DOI: 10.1093/oxfordjournals.aje.a009598

19 Duchaine CS, Dumas I and Diorio C: Consumption of sweet foods and mammographic breast density: A cross-sectional study. BMC Public Health *14(1)*: 554, 2014. PMID: 24969543. DOI: 10.1186/1471-2458-14-554

20 Cuzick J, Forbes J, Edwards R, Baum M, Cawthorn S, Coates A, Hamed A, Howell A, Powles T and Investigators I: First results from the international breast cancer intervention study (ibis-i): A randomised prevention trial. Lancet *360(9336)*: 817-824, 2002. PMID: 12243915. DOI: 10.1016/s0140-6736(02)09962-2

21 Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L and Wolmark N: Tamoxifen for prevention of breast cancer: Report of the national surgical adjuvant breast and bowel project p-1 study. J Natl Cancer Inst *90(18)*: 1371-1388, 1998. PMID: 9747868. DOI: 10.1093/jnci/90.18.1371

22 Cuzick J, Warwick J, Pinney E, Warren RM and Duffy SW: Tamoxifen and breast density in women at increased risk of breast cancer. J Natl Cancer Inst *96(8)*: 621-628, 2004. PMID: 15100340. DOI: 10.1093/jnci/djh106

23 Dong JY, Zhang L, He K and Qin LQ: Dairy consumption and risk of breast cancer: A meta-analysis of prospective cohort studies. Breast Cancer Res Treat *127(1)*: 23-31, 2011. PMID: 21442197. DOI: 10.1007/s10549-011-1467-5

24 Zang J, Shen M, Du S, Chen T and Zou S: The association between dairy intake and breast cancer in western and asian populations: A systematic review and meta-analysis. J Breast Cancer *18(4)*: 313-322, 2015. PMID: 26770237. DOI: 10.4048/jbc.2015.18.4.313

25 Berube S, Diorio C, Verhoek-Oftedahl W and Brisson J: Vitamin d, calcium, and mammographic breast densities. Cancer Epidemiol Biomarkers Prev *13(9)*: 1466-1472, 2004. PMID: 15342447.

26 Ekpo EU, Brennan PC, Mello-Thoms C and McEntee MF: Relationship between breast density and selective estrogen-receptor modulators, aromatase inhibitors, physical activity, and diet: A systematic review. Integr Cancer Ther *15(2)*: 127-144, 2016. PMID: 27130722. DOI: 10.1177/1534735416628343

27 Diorio C, Berube S, Byrne C, Masse B, Hebert-Croteau N, Yaffe M, Cote G, Pollak M and Brisson J: Influence of insulin-like growth factors on the strength of the relation of vitamin d and calcium intakes to mammographic breast density. Cancer Res *66(1)*: 588-597, 2006. PMID: 16397276. DOI: 10.1158/0008-5472.CAN-05-1959

28 Nelson ER, Wardell SE, Jasper JS, Park S, Suchindran S, Howe MK, Carver NJ, Pillai RV, Sullivan PM, Sondhi V, Umetani M, Geradts J and McDonnell DP: 27-hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology. Science *342(6162)*: 1094-1098, 2013. PMID: 24288332. DOI: 10.1126/science.1241908

29 Boyd NF, Connelly P, Byng J, Yaffe M, Draper H, Little L, Jones D, Martin LJ, Lockwood G and Tritchler D: Plasma lipids, lipoproteins, and mammographic densities. Cancer Epidemiol Biomarkers Prev *4(7)*: 727-733, 1995. PMID: 8672989.

30 Tseng M, Byrne C, Evers KA and Daly MB: Dietary intake and breast density in high-risk women: A cross-sectional study. Breast Cancer Res *9(5)*: R72, 2007. PMID: 17949495. DOI: 10.1186/bcr1781

31 Martin LJ and Boyd NF: Mammographic density. Potential mechanisms of breast cancer risk associated with mammographic density: Hypotheses based on epidemiological evidence. Breast Cancer Res *10(1)*: 201, 2008. PMID: 18226174. DOI: 10.1186/bcr1831

32 Kulendran M, Salhab M and Mokbel K: Oestrogen-synthesising enzymes and breast cancer. Anticancer Res *29(4)*: 1095-1109, 2009. PMID: 19414351.

33 Soguel L, Durocher F, Tchernof A and Diorio C: Adiposity, breast density, and breast cancer risk: Epidemiological and biological considerations. Eur J Cancer Prev *26(6)*: 511-520, 2017. PMID: 27571214. DOI: 10.1097/CEJ.0000000000000310

34 Hanna M, Dumas I, Orain M, Jacob S, Têtu B, Sanschagrin F, Bureau A, Poirier B and Diorio C: Association between expression of inflammatory markers in normal breast tissue and mammographic density among premenopausal and postmenopausal women. Menopause *24(5)*: 524-535, 2017. PMID: 28002200. DOI: 10.1097/GME.0000000000000794

35 Oza AM and Boyd NF: Mammographic parenchymal patterns: A marker of breast cancer risk. Epidemiol Rev *15(1)*: 196-208, 1993. PMID: 8405204. DOI: 10.1093/oxfordjournals.epirev.a036105

36 Boyd NF, Greenberg C, Lockwood G, Little L, Martin L, Tritchler D, Byng J and Yaffe M: Effects at two years of a low-fat, high-carbohydrate diet on radiologic features of the breast: Results from a randomized trial. J Natl Cancer Instit *89(7)*: 488-496, 1997. PMID: 9086005. DOI: 10.1093/jnci/89.7.488

Received September 12, 2019
Revised September 18, 2019
Accepted September 19, 2019