Association of Diet and Mammographic Breast Density in the Minnesota Breast Cancer Family Cohort[1]

Celine M. Vachon, Lawrence H. Kushi, James R. Cerhan, Christopher C. Kuni, and Thomas A. Sellers[2]

Mayo Foundation, Department of Health Sciences Research [C. M. V., J. R. C., T. A. S.], and Mayo Clinic Cancer Center [J. R. C., T. A. S.], Rochester, Minnesota 55905; Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, Minnesota [L. H. K.]; and Department of Radiology, University of Colorado, Denver, Colorado [C. C. K.]

Abstract

Mammographic breast density is a significant risk factor for breast cancer. The present report analyzes the association of breast density and dietary factors in 1508 women in a historical cohort study of breast cancer families in Minnesota. Diet was assessed by a semiquantitative food frequency questionnaire. Percent breast density was estimated visually by a radiologist experienced in mammography. The association of percent breast density with quartiles of energy-adjusted dietary intakes was examined in analysis of covariance models adjusting for potential confounding effects of age, body mass index, and other covariates as well as correcting for familial correlation. Analyses were performed on all women combined and were also stratified by menopausal status. Among premenopausal women, percent breast density was positively associated with intakes of polyunsaturated fat, polyunsaturated:saturated fat ratio, and vitamins C and E and was inversely associated with saturated fat and total dairy intake. Among postmenopausal women, vitamin B_{12} was linearly associated with increased breast density. The positive associations for vitamin C and B_{12} were attributable to supplement intake only. There was a suggestive positive trend between breast density and daily alcohol consumption in both premenopausal and postmenopausal women. After adjustment for other sources of alcohol, only wine intake among postmenopausal women was significant such that white wine showed a positive association and red wine an inverse association with percent breast density. There was no association with other examined dietary factors. The cross-sectional differences in breast density across levels of dietary factors were small in magnitude but may have implications for breast cancer risk.

Introduction

Epidemiological data consistently have shown that the interindividual variability of breast tissue as pictured on the mammogram is a significant risk factor for breast cancer. Historically, the categorical parenchymal pattern has been used to characterize breast tissue into four categories ranging from fatty breasts (N1) to increasing ductal prominence (P1 and P2) to dysplasia (DY; Ref. 1). More recently, estimates of breast density, or the ratio of fibroglandular elements to total breast area, have been used to characterize the breast image (2–5). Unlike the parenchymal pattern, these estimates are semicontinuous in nature and have been calculated using both subjective and semiautomated computer-assisted algorithms. Other assessments, such as total dense area, have been used to quantify the total breast density on the mammogram (4). All of these traits have been associated with breast cancer (2, 4, 6). The strongest associations have been seen with percent breast density (2, 4, 6, 7); some studies have reported three to five times increased risks for women in high (>50%) compared with low (0% or <10%) categories of percent density; (6). Increased measures of breast density are common in the population, with roughly 30% of women having levels >50% (2, 4). This translates into an estimated population attributable risk of 28% for breast cancer (4).

Studies of correlates of percent breast density have focused primarily on factors implicated in breast cancer risk (6, 8, 9). These have been found to explain <40% of the variance in the percent breast density measure.[3] Fewer studies have examined the role of dietary factors in breast density, and the results are not consistent. Positive associations have been seen with total, saturated, and unsaturated fats in some studies (10–12) but not others (13–15). Fiber, carotenoids, vitamin A intake, carbohydrates, and dietary cholesterol have been studied to a lesser extent but also show conflicting findings (10–12). The most consistent dietary associations with percent breast density have been seen with alcohol (13, 14, 16), serum levels of high density lipoprotein cholesterol (13, 14), and urinary malonaldehyde excretions (13, 14, 17, 18); all have been positively associated with breast density.

Inconsistencies across dietary studies may be attributable to generally small sample sizes, overrepresentation of premenopausal women, and the lack of a consistent quantitative measure of breast density. Therefore, further research is necessary to clarify the possible association of dietary factors with breast density.

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[2] To whom requests for reprints should be addressed, at Health Sciences Research, Mayo Foundation, Harwick 6, 200 First Street S.W., Rochester, MN 55905. Phone: (507) 284-2511; Fax: (507) 284-1516; E-mail: sellers.thomas@mayo.edu.

[3] C. M. Vachon, C. C. Kuni, K. Anderson, V. E. Anderson, and T. A. Sellers. Association of mammographically defined percent breast density with epidemiological risk factors for breast cancer, submitted for publication.

Using dietary data from food frequency questionnaires, coupled with risk factor and breast density measures from women in the Minnesota Breast Cancer Family Study, we investigated the association of dietary factors with breast density. Understanding the determinants of breast density may provide insight into the pathogenesis of breast cancer and potentially identify mechanisms for prevention.

Materials and Methods

Population. The study was approved by the University of Minnesota Institutional Review Board. Details of the study design and methods have been published (19). Briefly, a family study of breast cancer was initiated in 1944 at the University of Minnesota. Breast cancer probands were women ascertained at the Tumor Clinic of the University of Minnesota Hospital with microscopic diagnosis ($n = 527$) or clinical evidence ($n = 17$) of breast cancer. Information on probands and history of cancer in their relatives was obtained by interviews, medical history questionnaires, and death certificates.

A follow-up study of this cohort of families was initiated in 1990. Members eligible for that investigation included sisters, daughters, nieces, and granddaughters of the breast cancer probands and women identified as the spouses of corresponding male first- and second-degree relatives of these breast cancer probands.

Questionnaire Data. Telephone interviews were completed with all available female relatives ≥18 years of age. Specific topics covered included: history of cancer, weight history, marital status, education, occupational class, medical history of conditions associated with reproductive dysfunction, benign or malignant breast disease, mammography, menstrual and pregnancy history, oral contraceptive use, physical activity, and history of smoking and alcohol intake. Menopausal status was determined from the response to a question of whether the participant had a menstrual period within the last year, excluding periods brought on by hormones. After the telephone interview, subjects were mailed a body measurement questionnaire, which was designed to elicit replicated measures of current height and weight. Circumferences of the waist (2 inches above the umbilicus) and hips (maximal protrusion) were also determined according to a validated protocol (20).

Food Frequency Questionnaire. After the interview, participants were mailed a 153-item semiquantitative Food Frequency Questionnaire, adapted from Willett *et al*. (21), to assess usual dietary intake over the past year. Participants were asked, on average over the past year, how often they had consumed a certain portion size of food. The seven categories of foods included dairy foods, fruits, vegetables, eggs and meats, breads and cereals, beverages, and sweets. There were nine possible responses, ranging from "never or less than once per month" to "six or more times per day" to define their frequency of consumption of that portion size. Additional questions on food preparation and vitamin supplements were included. The average daily nutrient intake was then calculated by multiplying the frequency of consumption of each food portion by the nutrient content of the specified portions, according to the food composition tables from the United States Department of Agriculture, Handbook 8 (Willett Food Frequency Questionnaire Manual). The average daily intake for vitamins was calculated from both food and supplement intake.

Mammography to Detect Breast Cancer and Quantify Percent Breast Density. To verify the breast cancer status of relatives and spouses and to permit estimation of percent breast density, females ≥40 years of age were asked to provide a recent mammogram. If one had not been taken in the previous year (2 years if <50 years), they were instructed to obtain a new one through their personal physician. These women were mailed a letter for their physician that explained the study and described our need to review the mammogram after it was obtained.

Estimation of Percent Breast Density. The fraction of the volume of the breast occupied by fibroglandular tissue was estimated visually by a radiologist experienced in mammography (C. C. K.) and the estimation of breast density. The radiologist gained experience in quantitative estimation by examining radiographs of a series of calibrated breast phantoms of known densities. As mammograms arrived at the coordinating center, the mammographic films (10 × 12 inches) were scanned on a Lumiscan 200 digitizer at 2 bytes/pixel on a 1024 × 1228 matrix, yielding a pixel size of 0.248 mm (0.00976 inch) × 0.248 mm (0.00976 inch). Estimates of the subjects' breast densities were made from a video display of the digitized film-screen mammograms. Contrast and brightness of the displayed images were routinely manipulated to facilitate visual density estimation, which was made in 5% increments. The left mediolateral oblique view was used for the estimate; the right mediolateral oblique view was used if the left was unavailable. The radiologist was blinded to all risk factor and genetic information. Duplicate readings over varying time periods were made on all images, resulting in an intrareader reliability of 0.82.

Subject Selection. Women who completed a telephone interview and participated in both the mammogram and food frequency questionnaire components of the study were eligible for these analyses. Women were excluded if they reported an infeasible caloric intake (<600 kcal/day or >5000 kcal/day) or if they left 30 or more food questions unanswered on the food frequency questionnaire. Additionally, women with a history of breast cancer were excluded, because their diets may have changed as a result of their diagnoses.

Statistical Analysis. Descriptive statistics and daily mean nutrient intakes were compared between the study sample and women who completed the food frequency questionnaire but did not participate in the mammogram component. Additionally, breast cancer risk factors were compared between the study sample and women not participating in either the dietary component of the study or the mammogram component or both. These comparisons were performed using χ^2 and t tests.

Dietary factors previously shown (10, 11) or hypothesized (10, 13–15) to be associated with breast density were evaluated. These included total, saturated, polyunsaturated, and monounsaturated fats (alone and as a percentage of total fat), vitamin A, retinol, carotene, crude and dietary fiber, calcium, total carbohydrates, alcohol, and cholesterol. Additional dietary exposures hypothesized to be associated with breast cancer, including vitamins C, D, and E, total protein, and total energy, were also evaluated to determine whether these factors are correlated with breast density. Also, because vitamin B_{12} and folate are involved in DNA and cell membrane synthesis and lipid metabolism, it is plausible that they have a role in breast cancer; we investigated their association with breast density as well.

In all analyses of the dietary factors, adjustment for total energy intake was performed by regression techniques (22). Briefly, each dietary factor was entered into a regression model as the dependent variable, with total calories as the independent variable. The residuals from this model were then added to the expected nutrient value for the mean level of energy intake in the sample to arrive at an individual-adjusted nutrient score.

All energy-adjusted dietary factors were then categorized into quartiles of daily intake, except for alcohol, which was categorized into three categories: one for nondrinkers and two categories of energy-adjusted alcohol intake. To investigate the association between the dietary variables and breast density, each energy-adjusted dietary factor was analyzed in an analysis of covariance model, using PROC GLM in SAS (23), with total energy intake, age, and potential confounders as independent variables and mammographic breast density in semicontinuous, five-unit intervals as the response. Multivariate-adjusted breast density means for each quartile of nutrient intake were estimated, and tests for trend were performed on the adjusted breast density means, using linear contrasts.

If significant associations were detected with a dietary factor, foods or food groups that were a major source of that factor were examined. This approach was designed to provide insight into the actual food source influencing breast density. Food groups were formed using a classification scheme extended from initial work done by Smith-Warner *et al.* (24) on vegetable and fruit food groups. Multivariate-adjusted mean levels of breast density for tertiles of food or food group intake were calculated.

Potential confounders of the diet and breast density association were included in the model. These included body mass index, WHR[4] (measured in quintiles with an additional category for women with missing values), education as a five-category variable (grade school, some high school, high school graduate, vocational school or some college, and college graduate or post-graduate), smoking (never smoker, former smoker with <20 pack-years, former smoker with ≥ 20 pack-years, current smoker with <20 pack-years, and current smoker with ≥ 20 pack-years), physical activity index (low, moderate, and high), oral contraceptive use (never, former, and current), hormone replacement therapy (never, former, and current), age at menarche (≤ 10 years, 11–13 years, and 14+ years), and a combined variable for age at first birth and number of live births (nulliparous, age at first birth ≤ 20 years and 1–2 births, age at first birth >20 years and 1–2 births, age at first birth ≤ 20 years and 3+ births, and age at first birth >20 years and 3+ births).

To compensate for the family-based sampling design of this study (in which individuals are not independent observations), we applied a bootstrap macro using PROC GLM in SAS (23). The bootstrapping procedure repeatedly selected random samples of families (with replacement) from the total number of families under study. For each randomly selected sample, a generalized linear model was fit to the data, and parameter estimates from this model were saved. The overall bootstrap estimate and SE were approximated by the mean and SE of the parameter estimates from each of the individual analyses. The SEs, as well as the pooled parameter estimate, were then used for hypothesis testing and calculation of confidence intervals according to standard parametric approaches.

The number of replications for samples of families selected from the total pool of samples was set at 1000, because this number provided a stable estimate of the parameter and confidence intervals (25).

Because there is evidence that an association between diet and percent breast density may differ by menopausal status (15), we performed analyses for all women combined and within strata of menopausal status.

[4] The abbreviations used are: WHR, waist:hip ratio; P:S, polyunsaturated:saturated fat ratio; CI, confidence interval.

Table 1 Daily dietary intake measures for 1,508 women with percent breast density readings from the Minnesota Breast Cancer Family Study

Daily dietary intake	Mean	SD	5% tail values	
			5th	95th
Total energy (kcal)	1,933	668	1,010	3,141
Protein (g)	83	32	39	141
Animal protein (g)	57	26	23	103
Total fat (g)	65	28	29	118
Saturated fat (g)	22	10	9	41
Monounsaturated fat (g)	25	11	11	46
Polyunsaturated fat (g)	12	6	5	23
ω-3 fatty acids (g)	0.22	0.22	0.02	0.65
Cholesterol (mg)	235	118	94	443
Total carbohydrate (g)	257	99	126	430
Dietary fiber (g)	24	10	11	42
Crude fiber (g)	6	3	3	11
Alcohol (g)	4	9	0	19
Caffeine (mg)	269	267	2	828
Carotene (IU)	13,124	12,466	2,723	33,854
Vitamin A (IU)	17,408	13,987	4,199	42,764
Retinol (IU)	4,284	5,162	535	12,001
Vitamin D (IU)	398	291	63	931
Vitamin E (IU)	112	201	4	446
Folate (μg)	467	260	156	946
Vitamin B_{12} (μg)	11	14	2	25
Vitamin C (mg)	345	348	61	1,168

Results

The follow-up study of the cohort of breast cancer families ascertained between 1944 and 1952 at the University of Minnesota included 6194 living women from 426 families who participated in the telephone interview. Of these women, 5219 (84.2%) were ≥ 40 years of age and eligible for a mammogram. Mammograms ($n = 2491$; 47.8%) were returned to the coordinating center to be read by the radiologist. For the food frequency component of the study, 3598 (57.9%) women returned the mailed questionnaire. Of the 2491 women participating in the mammogram component of the study, 1679 also participated in the food frequency component of the study; however, 92 women were excluded for leaving 30 or more food questions unanswered or for reporting an infeasible total caloric intake. Additionally, 79 women with breast cancer were excluded. Thus, 1508 women formed the study sample for this analysis. Women ranged from 40 to 90 years in age and had a mean ($\pm$ SD) percent breast density of 34.3% ($\pm$ 15.3%). 60.3% of the women were relatives of the 426 probands with breast cancer, and 81.2% of the sample were postmenopausal. The means ($\pm$ SD) of daily dietary intakes (food and supplements combined) for this sample of women are shown in Table 1.

Among women who completed a food frequency questionnaire, those who also provided a mammogram had slightly higher daily mean intakes of crude fiber (6.3 g *versus* 5.9 g), dietary fiber (24.0 g *versus* 22.8 g), carotene (13,115.7 IU *versus* 11,008.5 IU), vitamin A (17,417 IU *versus* 15,247 IU), vitamin C (345.1 mg *versus* 323.2 mg), and vitamin E (112.0 IU *versus* 92.0 IU) and a slightly lower intake of saturated fat (22.0 g *versus* 22.8 g; all $P < 0.05$) than women who did not provide mammograms. However, there were no differences in total calorie intake, protein, animal protein, total and other types of fat (than saturated), cholesterol, carbohydrates, alcohol, caffeine, retinol, folate, vitamin B_{12}, or calcium.

To further evaluate the possibility that the analytic sample reflected a selection bias, additional analyses were performed

of non-diet factors. Women who responded to both the mammogram and food frequency components of the study were compared with other women in the cohort who did not provide a mammogram, food frequency questionnaire, or either. As shown in Table 2, women completing both components of the study were more likely to be blood relatives of the breast cancer proband (60% *versus* 51%), ever users of oral contraceptives (48% *versus* 43%), ever users of hormone replacement therapy (47% *versus* 35%), moderate to high frequency exercisers (67% *versus* 61%), never smokers (58% *versus* 52%), and have percent density >40% (23% *versus* 19%). Women in the study group also had a higher body mass index than other women in the cohort (27.1 *versus* 26.6; all $P < 0.05$). There were no differences in menopausal status, ages at first birth, last birth, and menarche, number of live births, age, WHR, weight, and alcohol.

Fats, Cholesterol, and Total Caloric Intake. Table 3 presents the results from analyses of fats, cholesterol, and total caloric intake with percent breast density. No association was evident for total fat, total caloric intake, cholesterol, or ω-3 fatty acid intakes. Additionally, examination of types of fat alone (monounsaturated, polyunsaturated, and saturated) revealed no associations with breast density (data not shown). In contrast, examining saturated and unsaturated fats as percentages of total fat, saturated fat was inversely associated with breast density ($P_{trend} = 0.03$; see Table 3), whereas polyunsaturated fat was positively associated ($P_{trend} = 0.05$) among premenopausal women. The P:S was also positively associated with breast density among premenopausal women ($P_{trend} = 0.03$).

Dairy and meat food groups were examined as food sources of saturated fat intake in premenopausal women (Table 4). Of the dairy food groups, only total dairy intake had a significant linear trend ($P_{trend} = 0.01$) with decreasing breast density, although the inverse association of density with high fat dairy intake was suggestive ($P_{trend} = 0.08$). Of the meat food groups evaluated, none showed significant associations with breast density. Margarine intake was examined as a food source for polyunsaturated fat intake in premenopausal women; no association of breast density was seen with quartiles of margarine intake (Table 4).

Vitamins. Table 5 presents the associations of quartiles of vitamin intakes with breast density among all women combined and stratified by menopausal status. There were no associations with breast density and vitamins A, retinol, carotene, vitamin D, or folate. Among premenopausal women only, there were linear trends of increasing breast density with increasing quartiles of vitamin C intake ($P_{trend} = 0.03$) and vitamin E ($P_{trend} = 0.05$). For postmenopausal women and all women combined, there was a linear trend of increasing breast density with increasing vitamin B_{12} ($P = 0.03$ for postmenopausal women), but the difference between upper and lower quartiles was only 2%.

Food and supplement intakes from these three vitamins were examined separately in association with breast density (Table 6). Vitamin C supplement intake was positively associated with multivariate-adjusted breast density among premenopausal women ($P_{trend} = 0.02$). There was no association with vitamin C from foods. There were suggestions of positive linear trends with breast density and vitamin E from both food and supplement intake in premenopausal women, and in postmenopausal women, there was a linear trend of increasing breast density with increasing vitamin B_{12} supplement intake ($P_{trend} = 0.05$) but not with B_{12} from food intake.

Alcohol. There was a suggestion of a trend of increasing breast density with alcohol consumption in both premenopausal

Table 2 Comparison of breast cancer risk factors between study participants and nonrespondents to the mammogram and/or food frequency components of the Minnesota Breast Cancer Family Study

	Study sample[a] ($n = 1679$)	Nonrespondents[b] ($n = 3540$)	P[c]
	Mean ± SD		
Age (yr)	61.4 ± 11.4	62.2 ± 13.2	0.06
Anthropometric variables			
Body mass index (kg/m^2)	27.1 ± 5.8	26.6 ± 5.5	0.002
WHR	0.85 ± 0.08	0.85 ± 0.11	0.457
Weight	156.1 ± 33.7	154 ± 32.9	0.095
Hormone-related variables			
Age at first birth	23.0 ± 4.2	22.0 ± 5.3	0.63
Age at last birth	31.1 ± 5.5	31.1 ± 7.1	0.78
Number of live births	3.1 ± 1.96	3.1 ± 4.04	0.07
Age at menarche	13.2 ± 5.5	13.5 ± 6.8	0.09
	%		
Menopausal status			
Premenopausal	17.5	19.5	0.07
Postmenopausal	82.5	80.5	
Oral contraceptive use			
Never	51.5	57.3	0.001
Former	47.8	42.0	
Current	0.7	0.7	
Hormone replacement use			
Never	53.5	65.4	0.001
Former	17.4	15.3	
Current	29.1	19.3	
Mammographic density (%)			
0–20	25.3	19.6[d]	0.001
21–40	51.8	61.3	
41–60	16.4	15.4	
61–80	5.8	3.3	
81–100	0.7	0.4	
Relationship to breast cancer proband			
Sister	1.8	1.3	0.001
Daughter	6.9	5.6	
Granddaughter	18.6	16.9	
Niece	32.5	27.2	
Marry-in	40.2	49.0	
Lifestyle variables			
Alcohol consumption			
Never	14.6	15.9	0.51
Monthly	62.4	62.0	
Weekly	18.3	18.0	
Daily	4.7	4.1	
Smoking history			
Never	58.0	52.4	0.001
Former, ≤20 pack-years	18.3	16.4	
Former, >20 pack-years	11.6	10.6	
Current, ≤20 pack-years	2.6	5.0	
Current, >20 pack-years	9.5	15.6	
Exercise			
Low	33.2	38.9	0.001
Moderate	41.2	37.8	
High	25.6	23.3	

[a] Total *n* for study sample includes those women who were included in the study sample ($n = 1508$) and the additional 92 that were excluded from analyses because of incomplete food frequency questionnaires and 79 women excluded because of breast cancer.
[b] Includes those who responded to the mammogram component only, the food frequency component only, or neither component.
[c] *P* for χ^2 test or *t* test.
[d] Mammographic density was computed at the time of the study for those "nonrespondents" who returned a mammogram.

Table 3 Multivariate-adjusted[a] mean value (95% CI) of percent breast density by quartiles of total caloric, fat, and cholesterol intake

	All[b,c] (n = 1508)		Premenopausal (n = 283)			Postmenopausal (n = 1225)		
	Mean[a]	95% CI	n	Mean[a]	95% CI	n	Mean[a]	95% CI
Total caloric intake (kcal)								
≤1460.9	36	(34–38)	66	44	(38–50)	311	33	(30–35)
>1460.9–1829.2	35	(33–38)	70	40	(34–46)	307	32	(30–35)
>1829.2–2314.2	34	(32–37)	82	38	(33–43)	295	31	(29–34)
>2314.2	35	(35–37)	65	42	(36–49)	312	31	(29–34)
P_{trend}[d]	0.08			0.35			0.17	
Type of fat								
Total fat (g)								
≤56.8	35	(33–37)	49	41	(35–47)	328	32	(30–34)
>56.8–64.7	36	(33–38)	70	42	(36–48)	307	33	(31–35)
>64.7–73.1	34	(32–37)	80	39	(33–45)	297	32	(29–34)
>73.1	35	(33–37)	84	40	(35–45)	293	32	(29–34)
P_{trend}[d]	0.78			0.55			0.73	
Saturated fat (%)[e]								
≤0.31	35	(33–38)	38	44	(37–51)	339	32	(30–34)
>0.31–0.33	35	(32–37)	75	42	(36–48)	302	31	(29–34)
>0.33–0.36	36	(34–38)	73	42	(36–48)	304	33	(31–35)
>0.36	34	(32–37)	97	37	(32–43)	280	32	(30–34)
P_{trend}[d]	0.5			0.03			0.8	
Monounsaturated fat (%)[e]								
≤0.37	35	(32–37)	81	38	(32–44)	296	32	(30–34)
>0.37–0.38	36	(33–38)	76	43	(37–49)	301	32	(30–34)
>0.38–0.39	35	(33–37)	82	39	(33–45)	295	32	(30–34)
>0.39	35	(32–37)	44	42	(36–48)	333	32	(30–34)
P_{trend}[d]	0.11			0.27			0.62	
Polyunsaturated fat (%)[e]								
≤0.17	35	(32–38)	94	38	(33–44)	283	32	(30–35)
>0.17–0.19	35	(33–37)	67	39	(34–45)	310	32	(30–34)
>0.19–0.22	35	(33–37)	68	43	(38–50)	309	31	(29–34)
>0.22	35	(33–38)	54	42	(35–49)	323	32	(30–34)
P_{trend}[d]	0.99			0.05			0.64	
P:S ratio								
≤0.48	35	(32–37)	100	38	(32–44)	277	32	(30–34)
>0.48–0.57	35	(33–38)	67	40	(34–47)	310	32	(30–34)
>0.57–0.69	35	(32–37)	65	43	(36–50)	312	31	(29–33)
>0.69	35	(33–38)	51	43	(36–50)	326	32	(30–34)
P_{trend}[d]	0.6			0.03			0.74	
ω-3 FA (g)								
≤0.11	35	(33–38)	75	40	(34–45)	302	33	(30–35)
>0.11–0.17	35	(33–37)	79	40	(35–46)	298	32	(30–34)
>0.17–0.26	35	(33–38)	69	40	(35–46)	308	32	(30–34)
>0.26	35	(32–37)	60	42	(35–48)	317	31	(29–34)
P_{trend}[d]	0.58			0.48			0.3	
Cholesterol (mg)								
≤187.0	35	(32–37)	51	40	(33–46)	326	32	(30–34)
>187.0–225.7	36	(33–38)	72	41	(34–47)	305	33	(31–35)
>225.7–273.5	36	(33–38)	82	39	(34–44)	295	33	(31–35)
>273.5	34	(32–37)	78	42	(36–47)	299	31	(28–33)
P_{trend}[d]	0.58			0.56			0.22	

[a] All analyses (except total caloric intake) are adjusted for caloric intake, age, age^2, body mass index, WHR, physical activity, age at menarche, age at first birth and number of births combined, self-reported alcohol intake, smoking, family history of breast cancer, hormone replacement usage (all and postmenopausal women), and oral contraceptive usage (premenopausal women).
[b] The analyses for all women are performed on quartiles of the energy-adjusted dietary variable.
[c] Analyses for all women combined are also adjusted for menopausal status.
[d] Test for trend is an F test of the linear contrast.
[e] Fat variables are a percentage of total fat intake.

(P_{trend} = 0.08) and postmenopausal women (P_{trend} = 0.09). In premenopausal women, women who were never drinkers over the previous 12 months had a multivariate-adjusted mean breast density of 39% (95% CI, 34–43), whereas those who consumed ≤3.9 g/day had a breast density of 45% (95% CI, 40–50) and those consuming >3.9 g/day had a breast density of 42% (95% CI, 38–46). In postmenopausal women, the multivariate-adjusted densities (and 95% CI) were 31% (26–30), 32% (27–31), and 33% (28–31, 32) for increasing categories of alcohol intake.

The association of breast density with source of alcohol by menopausal status is presented in Table 7. When all sources of alcohol were entered simultaneously in a single model, only wine intake among postmenopausal women was significant.

Table 4 Multivariate-adjusted[a] mean value (95% CI) of percent breast density by categories of dairy and meat food groups and margarine intake in premenopausal women (n = 283)

	Servings/week			P_{trend}[b]	
Dairy food groups					
Total dairy intake	0–8.5	9–18.5	≥19		
Mean[a]	44	40	38	0.01	
95% CI	(37–51)	(33–46)	(32–44)		
n	76	105	102		
High fat dairy	0–4	4.5–9	≥9.5		
Mean[a]	42	43	38	0.08	
95% CI	(35–48)	(37–49)	(32–44)		
n	85	89	109		
Low fat dairy	0–3	3.5–8	≥8.5		
Mean[a]	42	40	38	0.14	
95% CI	(35–48)	(34–46)	(32–45)		
n	98	87	98		
Fermented dairy	0–2.5	3–5	≥5.5		
Mean[a]	38	40	41	0.25	
95% CI	(32–45)	(34–46)	(35–48)		
n	89	92	102		
Cheese intake	0–1	1.5–3	≥3.5		
Mean[a]	40	40	40	0.86	
95% CI	(32–48)	(34–46)	(34–46)		
n	102	84	97		
Meat food groups					
Total meat intake	0–9	9.5–13.5	≥14		
Mean[a]	41	39	40	0.90	
95% CI	(34–48)	(33–46)	(34–47)		
n	81	97	105		
High fat meat intake	0–5	5.5–9	≥9.5		
Mean[a]	42	38	41	0.76	
95% CI	(35–49)	(32–44)	(34–47)		
n	85	89	109		
Low fat meat intake	0–1.5	2–3.5	≥3.75		
Mean[a]	41	39	41	0.90	
95% CI	(34–47)	(33–45)	(35–47)		
n	108	89	86		
Fish intake	0–0.5	1–1.5	≥2		
Mean[a]	39	41	41	0.50	
95% CI	(33–45)	(34–47)	(34–47)		
n	59	121	103		
White meat intake	0–2.5	3–4.5	≥5		
Mean[a]	37	41	41	0.11	
95% CI	(31–44)	(35–47)	(35–47)		
n	88	95	100		
Red meat intake	0–2.5	3–5	≥5.5		
Mean[a]	41	40	40	0.47	
95% CI	(35–48)	(34–47)	(33–46)		
n	74	101	108		
Margarine alone	0–0.5	1–3	5.5–7	≥8	
Mean[a]	39	41	40	43	
95% CI	(32–45)	(35–47)	(33–47)	(36–50)	0.14
n	97	66	72	48	

[a] All analyses are adjusted for caloric intake, age, age^2, body mass index, WHR, physical activity, age at menarche, age at first birth and number of births combined, self-reported alcohol intake, smoking, family history of breast cancer, and oral contraceptive use.
[b] Test for trend is an F test of the linear contrast.

The trend of increasing multivariate-adjusted breast density with increasing white wine intake (29, 31, and 34%; $P_{trend} < 0.01$) was opposite of the observed trend with red wine intake (34, 32, and 28%; $P_{trend} = 0.02$).

Other Dietary Factors. Total carbohydrates, crude and dietary fiber, animal protein, total protein, calcium, and caffeine intake were also examined with breast density in multivariate analyses. None of these dietary factors were significantly associated with breast density in analyses for all women combined or stratified by menopausal status (data not shown).

Discussion

Results of this study suggest that increased breast density is associated with decreased intakes of saturated fat in premenopausal women, potentially through intake of dairy foods. Intake of polyunsaturated fat, as well as the P:S ratio, are linearly associated with increased breast density in premenopausal women. Intakes of vitamins C and E are associated with increased density, also among premenopausal women, and there was a linear trend of increasing breast density with increasing vitamin B_{12} intake among postmenopausal women only. Finally, among both premenopausal and postmenopausal women, alcohol and breast density were linearly associated, although the trends were of borderline significance. Examinations of sources of alcohol revealed that red and white wine were both associated with breast density among postmenopausal women, but the associations were in opposite directions.

Few studies have examined the association of dietary factors with percent or total area of breast density (10, 12, 14, 15) or mammographic parenchymal pattern (11, 13), and the results are not consistent. For example, in the current study, greater intakes of saturated fat were associated with lower mean breast density among premenopausal women. Others have observed positive (10, 12) associations or no association (11, 13, 14). Our findings on polyunsaturated fat agree with one study in which premenopausal breast cancer cases with a DY (or dysplasia classification) parenchymal pattern had higher levels of polyunsaturated fat (11) but not with others that showed no association with breast densities (10, 12) or mammographic dysplasia (13). We observed the P:S ratio to be positively associated with breast density among premenopausal women, but Boyd *et al.* (13) found no association. Boyd *et al.* (15) performed a dietary intervention with a low-fat, high-fiber diet and noted a significant reduction in total area of density for the intervention compared with the control group, primarily among the premenopausal women, but no reduction in percent density. A dietary analysis of macronutrient intake in the perimenopausal women (n = 78) in this intervention study showed that the decrease in total area of percent density seen in the intervention group could be best explained by reductions in dietary cholesterol, although reductions in saturated fat were of borderline significance (12). We were not able to examine the perimenopausal women separately in our analysis.

Vitamin A, retinol, vitamin C, carotenoids, and α-tocopherol have been studied in association with breast density (10) or the parenchymal pattern (11, 13). Of these studies, the only significant association was seen with increased carotene intake (10, 11). Results from the current study do not support these earlier observations. The initial positive linear associations that we observed with breast density and vitamin C in premenopausal women and B_{12} in postmenopausal women remained for supplements but not for food intake. For vitamin E, the increasing trend in density was suggestive among both food and supplement intakes, suggesting that vitamin E, as both food and

Table 5 Multivariate-adjusted[a] mean value (95% CI) of percent breast density by quartiles of vitamin intakes

Vitamin	All[b,c] (n = 1508)		Premenopausal (n = 283)			Postmenopausal (n = 1225)		
	Mean[a]	95% CI	n	Mean[a]	95% CI	n	Mean[a]	95% CI
Vitamin A (IU)								
≤9826.4	35	(29–34)	103	39	(35–47)	274	32	(33–37)
>9,826.4–14,347.7	36	(31–35)	70	44	(36–48)	307	33	(33–38)
>14,347.7–21,012.0	35	(30–34)	60	40	(33–45)	317	32	(32–37)
>21,012.0	35	(29–34)	50	40	(35–45)	327	31	(33–37)
P_{trend}[d]	0.61			0.66			0.45	
Retinol (IU)								
≤1487.2	35	(33–38)	75	41	(37–51)	302	32	(29–34)
>1,487.2–2,616.0	35	(32–37)	79	39	(36–48)	298	32	(34–45)
>2,616.0–5,308.0	35	(34–38)	73	41	(36–48)	304	32	(35–47)
>5,308.0	35	(32–37)	56	41	(32–43)	321	32	(35–47)
P_{trend}[d]	0.35			0.61			0.5	
Carotene (IU)								
≤6796.7	35	(32–37)	106	40	(32–44)	271	31	(29–33)
>6796.7–10,492.4	36	(33–38)	72	41	(37–49)	305	33	(31–35)
>10,492.4–15,998.7	35	(33–37)	50	42	(33–45)	327	32	(30–35)
>15,998.7	34	(32–37)	55	38	(36–48)	322	31	(29–33)
P_{trend}[d]	0.77			0.56			0.77	
Vitamin C (mg)								
≤146.6	34	(32–38)	96	38	(33–44)	281	31	(29–33)
>146.6–217.3	36	(33–37)	78	40	(34–45)	299	33	(31–36)
>217.3–385.2	36	(33–37)	43	41	(38–50)	334	33	(31–35)
>385.2	35	(33–38)	66	43	(35–49)	311	32	(30–34)
P_{trend}[d]	0.23			0.03			0.68	
Vitamin D (IU)								
≤188.7	35	(33–38)	86	40	(34–45)	291	32	(30–35)
>188.7–328.4	34	(33–37)	75	40	(35–46)	302	31	(29–33)
>328.4–562.8	35	(33–38)	76	41	(35–46)	301	32	(30–35)
>562.8	35	(32–37)	46	42	(35–48)	331	32	(30–34)
P_{trend}[d]	0.68			0.55			0.96	
Vitamin E (IU)								
≤6.9	35	(32–37)	87	38	(33–46)	290	33	(30–35)
>6.9–12.4	34	(33–38)	77	39	(34–47)	300	31	(29–33)
>12.4–51.7	35	(33–38)	75	43	(34–44)	302	32	(29–34)
>51.7	36	(32–37)	44	42	(36–47)	333	32	(30–35)
P_{trend}[d]	0.2			0.05			0.88	
Vitamin B_{12} (mg)								
≤5.2	34	(34–38)	63	40	(38–50)	314	31	(29–33)
>5.2–7.1	34	(33–38)	88	38	(34–46)	289	31	(29–34)
>7.1–12.1	36	(32–37)	82	42	(33–43)	295	33	(31–35)
>12.1	36	(35–37)	50	43	(36–49)	327	33	(30–35)
P_{trend}[d]	<0.01			0.14			0.03	
Folate (mg)								
≤294.7	35	(34–38)	93	40	(38–50)	284	32	(29–34)
>294.7–378.1	34	(33–38)	61	40	(34–46)	316	31	(29–34)
>378.1–627.3	36	(32–37)	67	42	(33–43)	310	33	(30–35)
>627.3	36	(35–37)	62	41	(36–49)	315	33	(30–35)
P_{trend}[d]	0.1			0.32			0.27	

[a] All analyses are adjusted for caloric intake, age, age^2, body mass index, WHR, physical activity, age at menarche, age at first birth and number of births combined, self-reported alcohol intake, smoking, family history of breast cancer, hormone replacement usage (all and postmenopausal women), and oral contraceptive usage (premenopausal women).
[b] Analyses for all women combined are also adjusted for menopausal status.
[c] The analyses for all women are performed on quartiles of the energy-adjusted dietary variable.
[d] Test for trend is an F test of the linear contrast.

supplement, should be investigated more closely in premenopausal women.

Our findings on total alcohol intake were consistent with some studies (13, 14, 16) but not others (10, 26). However, the source of alcohol, to our knowledge, has not been examined with breast density in any published studies. The observed association between total alcohol intake and percent breast density in both menopausal groups is in the same direction as the literature on alcohol intake and breast cancer risk (27, 28). Of seven recent prospective studies, the five largest studies that also controlled for other breast cancer risk factors found increased relative risks of 1.2–3.3, comparing the highest category of intake to never drinkers (33). A pooled analysis of six studies (including the five mentioned above) also found an increase in breast cancer risk (relative risk, 1.09 for an increment of 10 g/day) for women consuming ≤60 g/day *versus* never drinkers (34). Breast density could potentially be on the pathway between alcohol intake and cancer.

Table 6 Multivariate-adjusted[a] mean percent breast density (95% CI) by categories of food and supplement intakes of Vitamins C, E, and B_{12}

Vitamin intake	Menopausal status	Category of intake[b]				P_{trend}[c]
		1	2	3	4	
Vitamin C (mg)	Pre[d]					
	Food only	39 (32–50)	42 (35–49)	40 (37–47)	40 (33–47)	0.99
	Supplement only	37 (32–43)	39 (32–46)	43 (37–50)	42 (36–49)	0.02
	Post[e]					
	Food only	32 (30–35)	33 (30–35)	31 (29–34)	31 (29–33)	0.22
	Supplement only	31 (29–33)	33 (31–36)	32 (29–34)	32 (29–34)	0.98
Vitamin E (mg TE)	Pre[d]					
	Food only	38 (32–45)	38 (32–45)	42 (35–48)	44 (37–52)	0.12
	Supplement only	39 (32–45)	42 (35–49)	40 (33–46)	43 (35–50)	0.31
	Post[e]					
	Food only	32 (29–35)	33 (31–35)	31 (29–33)	31 (29–34)	0.54
	Supplement only	31 (29–33)	32 (30–35)	33 (30–35)	32 (30–35)	0.31
Vitamin B_{12} (mg)	Pre[d]					
	Food only	44 (36–51)	39 (33–45)	39 (32–46)	42 (35–48)	0.55
	Supplement only	39 (33–45)	42 (35–39)	42 (35–50)	41 (34–48)	0.55
	Post[e]					
	Food only	31 (29–34)	31 (29–33)	33 (30–36)	31 (29–34)	0.48
	Supplement only	32 (30–34)	31 (29–33)	32 (29–34)	34 (31–36)	0.05

[a] All analyses are adjusted for caloric intake, age, age^2, body mass index, WHR, physical activity, age at menarche, age at first birth and number of births combined, self-reported alcohol intake, smoking, family history of breast cancer, hormone replacement usage (postmenopausal women), and oral contraceptive usage (premenopausal women).
[b] For food source, categories are quartiles. For supplement use, non-users make up category 1. Categories 2–4 are tertiles of supplement intake.
[c] Test for trend is an F test of the linear contrast.
[d] $n = 283$.
[e] $n = 1225$.

The associations of breast cancer risk and individual sources of alcohol consumed are not consistent among studies. Some studies suggest hard liquor and beer as sources associated with a greater risk of breast cancer (29, 30, 35). Some case-control studies in Italy and Latin America have found increased odds of breast cancer with red wine intake (31, 32), whereas others suggest a decreased risk with wine intake (36, 37). Still others show no clear involvement of any specific type of alcoholic beverage (28). The pooled analysis of six large prospective studies mentioned above found statistically significant increases in breast cancer risk for beer and liquor intake (1.11–95% CI, 1.04–1.19; and 1.05–95% CI, 1.01–1.10, respectively) and a non-statistically significant increase in risk with red and white wine combined (1.05–95% CI, 0.98–1.12; Ref. 34).

Wine is a major source of polyphenols. Red wine is richer in polyphenols than white wine because the skins and seeds are not removed from red wine when the grapes are crushed. Recently, red wine solids have been reported to delay spontaneous tumor onset in transgenic mice (38). In particular, the polyphenol resveratrol appears to possess antiproliferative properties (39), phytoestrogen properties (40), and potentially cancer chemopreventive activity (41). It is tempting to speculate that perhaps the polyphenols in red wine also influence percent breast density.

If the associations of fat or alcohol with breast density (or both) are indeed true, then one must resolve the fact that these differences do not consistently parallel breast cancer risk across epidemiological studies. One possible explanation is that the differences in percent densities across the high *versus* low categories of these dietary factors may not be large enough to result in changes in breast cancer risk. For example, the differences in breast density seen in our study for highest *versus* lowest quartiles or tertiles of any single factor were generally on the order of magnitude of 5–8%. However, the estimates of increased risk for breast cancer are consistently seen across larger categories of breast density, on the order of 20–25% (2, 4, 5). Byrne *et al.* (4) found odds ratios of 1.0, 1.6, 2.5, 2.8, and 4.4, for the corresponding categories of density: 0%, 1–24%, 25–49%, 50–74%, and ≥75%. Boyd *et al.* (2) showed similar estimates of risk (relative risk, 1.0, 1.2, 2.2, 2.4, 3.4, and 5.3) across the categories: 0% density, 1–10%, 10–24%, 25–49%, 50–74%, and ≥75%. The results from Saftlas *et al.* (5) are also consistent with these two studies. Thus, there is an increasing trend in breast cancer risk with increasing density for these and other studies using a quantitative breast density measure (6, 42); however, these increases in breast cancer risk may only be seen with large differences in density.

The mechanisms by which diet may affect breast density are not known. Dietary factors could potentially alter density through their effect on sex hormones (9, 15). Plasma lipoproteins could increase the hormone level in breast tissue by acting as carriers for steroid hormones, thereby increasing breast density and ultimately

Table 7 Multivariate-adjusted[a] mean value (95% CI) of percent breast density according to types of alcohol intake

Type of alcohol	Servings/week[b]			P_{trend}[d]
	Nondrinkers[c]	≤1	≥2–4	
Beer				
Pre				
Mean[a]	44	48	44	0.82
95% CI	(37–50)	(42–55)	(37–51)	
n	186	66	31	
Post				
Mean[a]	32	30	32	0.63
95% CI	(29–34)	(27–33)	(29–36)	
n	1012	139	64	
Red wine				
Pre				
Mean[a]	44	43	48	0.42
95% CI	(39–49)	(38–49)	(35–62)	
n	218	56	9	
Post				
Mean[a]	34	32	28	0.02
95% CI	(31–36)	(29–34)	(24–33)	
n	1044	138	36	
White wine				
Pre				
Mean[a]	45	44	47	0.62
95% CI	(38–52)	(37–51)	(39–55)	
n	196	67	19	
Post				
Mean[a]	29	31	34	<0.01
95% CI	(26–32)	(28–33)	(30–37)	
n	930	226	63	
Liquor				
Pre				
Mean[a]	44	47	45	0.60
95% CI	(38–50)	(40–54)	(38–52)	
n	188	53	42	
Post				
Mean[a]	31	32	31	0.77
95% CI	(28–33)	(29–35)	(28–34)	
n	929	157	133	

[a] All analyses are adjusted for caloric intake, age, age^2, body mass index, WHR, physical activity, age at menarche, age at first birth and number of births combined, smoking, family history of breast cancer, hormone replacement usage (postmenopausal women) and oral contraceptive usage (premenopausal women), and other sources of alcohol.
[b] Servings are glasses/week for beer, white and red wine, and shots/week for liquor.
[c] Nondrinkers of type of alcohol.
[d] Test for trend is an *F* test of the linear contrast.

breast cancer risk (14). Diet may also influence breast density through a direct effect of the nutrient on breast tissue (10). For example, in the female rat, ductal branching and end bud proliferation is reduced with ingestion of retinol analogues (43). We (16) recently provided evidence for a major gene influence on breast density. According to that analysis, roughly 30% of the variability of breast density could be explained by a putative major gene. This raises the possibility of a diet-gene interaction. A certain genotype might increase susceptibility to the effects of nutrients on breast tissue, resulting in increased proliferation of breast stroma for those women. This is an important area of investigation in future studies.

The results from this study should be viewed as hypothesis generating. Because several tests were performed, it is plausible that some associations reflect chance. Additionally, this study is prone to the error inherent in dietary assessment in large epidemiological studies. However, our 153-item semiquantitative food frequency questionnaire was adapted from Willett *et al.* (21), who demonstrated reasonable levels of reliability and validity of the instrument in the Nurse's Health Study. In addition, the Iowa Women's Health Study, whose semiquantitative food frequency questionnaire was similar to the instrument used in the current study, was evaluated over the 3 years of administration. They found reasonable estimates of reproducibility and validity (44) in a similar Midwestern population.

Another potential limitation for our study is that the measure of breast density was subjectively determined by one radiologist. However, the reliability of the measure of breast density was shown to be high. Also, two studies were performed by our radiologist (C. C. K.) on samples of individuals with breast density readings to evaluate the correlation of our subjective estimate with other quantitative density estimates, including a magnetic resonance imaging measure and a measure from a computerized thresholding technique. The subjective estimate used in our study was highly correlated with the magnetic resonance imaging estimates ($r = 0.95$)[5] and the thresholding measure estimates of breast density ($r = 0.89$).[6] Other studies have generated similar results (45, 46). Despite the high reliability, potential misclassification of breast density may have occurred, most likely resulting in attenuated associations.

It is interesting to note that this study used mammograms from the mediolateral oblique view to estimate breast density, whereas most studies have used the craniocaudal projection. Byng *et al.* (47) have shown that estimates of breast density from the mediolateral view are systematically lower than those from the craniocaudal view (by a scale factor of 0.86), although the two are highly correlated (0.92–0.96). Consequently, we have a smaller proportion of women (17%) with estimates of breast density that are 50% and greater than those of other studies (28%–32%; Refs. 2, 4).

This study was cross-sectional in nature and did not allow us to determine temporal associations. However, it is unlikely that an unmeasured characteristic (breast density) influences dietary intake. Also, there was evidence for participation bias in the mammography and dietary components of this study; women returning mammograms differed on several dietary factors. However, the differences were generally small in magnitude. Taken together with the differences in breast cancer risk factor information between the study group and the other women in the cohort, it appears that our study group of women may have been somewhat more health conscious than the other women in the cohort. In any case, the internal validity of the comparisons being made should not be compromised.

Because of the importance of the association of breast density and breast cancer, our initial findings should be further investigated. The association with red wine is especially interesting, in light of the favorable associations reported with red wine and other diseases.

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