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ORIGINAL PAPER

Breast cancer risk factors in relation to breast density (United States)

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Abstract
Objectives Evaluate known breast cancer risk factors in relation to breast density.
Methods We examined factors in relation to breast density in 144,018 New Hampshire (NH) women with at least one mammogram recorded in a statewide mammography registry. Mammographic breast density was measured by radiologists using the BI-RADS classification; risk factors of interest were obtained from patient intake forms and questionnaires.
Results Initial analyses showed a strong inverse influence of age and body mass index (BMI) on breast density. In addition, women with late age at menarche, late age at first birth, premenopausal women, and those currently using hormone therapy (HT) tended to have higher breast density, while those with greater parity tended to have less dense breasts. Analyses stratified on age and BMI suggested interactions, which were formally assessed in a multivariable model. The impact of current HT use, relative to nonuse, differed across age groups, with an inverse association in younger women, and a positive association in older women ($p < 0.0001$ for the interaction). The positive effects of age at menarche and age at first birth, and the inverse influence of parity were less apparent in women with low BMI than in those with high BMI ($p = 0.04$, $p < 0.0001$ and $p = 0.01$, respectively, for the interactions). We also noted stronger positive effects for age at first birth in postmenopausal women ($p = 0.004$ for the interaction). The multivariable model indicated a slight positive influence of family history of breast cancer.
Conclusions The influence of age at menarche and reproductive factors on breast density is less evident in women with high BMI. Density is reduced in young women using HT, but increased in HT users of age 50 or more.

Keywords Hormone replacement therapy · Reproductive history · Mammographic breast density

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Introduction

Numerous studies have shown that breast density, as assessed through mammography, is an important breast cancer risk factor [1–5]. Relative to the lowest classification of breast density (fatty tissue), women with the highest classification (extreme density) may have a 2- to 6-fold increased risk of breast cancer [5–8]. In addition to its role in breast cancer risk, breast density reduces mammographic accuracy [9–12], potentially increasing the risk of a later stage breast cancer diagnosis.

Previous studies indicate that established breast cancer risk factors, including family history of breast cancer, age at first birth, parity, and postmenopausal hormone use, have similar associations with breast density. In contrast, the influence of age at menarche, which in most studies is inversely related to breast cancer risk [e.g., 13–15], remains uncertain. Some studies have found positive associations [6, 16, 17], at least one suggests an inverse association [18], and others found no relation between age at menarche on breast density [19, 20].

In an effort to clarify inconsistent results from previous studies, we evaluated established breast cancer risk factors in relation to breast density in a large population of women enrolled in a statewide mammography registry. Our intention was to determine whether characteristics associated with breast cancer risk were also related to breast density, a finding that would be consistent with the notion that density mediates breast cancer risk. We were particularly interested in assessing the influence of menarcheal age.

Methods

The New Hampshire Mammography Network (NHMN) registers all consenting women who undergo mammography at participating mammographic facilities in our state. Details of the registry have been described previously [21, 22]. For the present study, potentially eligible women were NH residents of ages 30–89, who had at least one mammogram registered in the NHMN from 1 May 1996 to 20 June 2002.

The epidemiological data used in this analysis arose from three sources: a self-administered questionnaire completed by the patient, a patient intake form administered face-to-face by the radiologic technologist, and a standardized clinical assessment form completed by the radiologist. The questionnaire collected height, weight, place of birth, ethnicity, marital status, education, insurance coverage, reason for the current visit, past history of clinical breast examinations and mammography, age at menarche, parity, and age at first birth. The questionnaire also queried women regarding the date of their last menstrual period and history of gynecological surgery. This information was used to classify women as premenopausal (still having periods naturally) or postmenopausal (periods had stopped permanently) either naturally, because of chemotherapy/radiation, or surgery). The patient intake form obtained date of birth, family history of breast cancer (in the subject's mother, sister, daughter, or other relative), personal history of breast cancer, history of breast procedures, type of exam conducted at current visit, examination outcomes, recommendation for further work-up or follow-up, and current use of postmenopausal hormone therapy (HT). The clinical assessment form obtained the type of exam conducted at current visit, breast density, examination outcomes and recommendation for further work-up or follow-up. All three forms are completed during the woman's first NHMN mammography visit. Patient intake and clinical assessment forms are also completed at subsequent mammography visits, and the questionnaire is updated as possible.

Breast density, the outcome variable, estimates the proportion of fibroglandular tissue in the breast, relative to fat. Breast density was recorded on the standardized clinical assessment form by interpreting radiologists using the American College of Radiology Breast Imaging Reporting and Data System® (BI-RADS®) classification (1 = fatty, 2 = scattered density, 3 = heterogeneously dense, and 4 = extremely dense) [23]. In the event of discordance in the density of the right and left breast, the woman was classified according to the higher density classification. Breast density readings were available for 162,933 (95.4%) of the 170,815 women who had at least one mammogram recorded in the registry.

To optimize temporal correspondence between the women's characteristics and the classification of breast density, the statistical analyses were, when possible, based on the woman's breast density on the date of the first recorded mammogram. When data for variables (other than HT use) were unavailable for the date of the mammogram, we searched forward in the NHMN records to retrieve replacement information corresponding to a subsequent mammography visit. Informative forward searches retrieved information from subsequent mammographic encounters occurring, on average, within 24 months of the index mammogram, and reduced missing values by 3–9%.

Current body mass index (BMI; kg/m^2) was missing for 18,195 women, and the analyses were confined to 144,018 women for whom this measure was available. Included in the analytic sample were 131,480 (91%) women with a screening mammogram, 10,885 (8%) with a diagnostic mammogram, and 1,653 (1%) for whom the reason for the mammogram was not recorded. The majority of women, 136,283 (95%) had no personal history of breast cancer, 6,033 (4%) had a prior history of breast cancer based on NHMN records or the patient intake form, and 1,702 (1%) had unknown breast cancer status.

We used unconditional logistic regression analyses to generate odds ratios (OR) and 95% confidence intervals (CI) [24] for the association between factors and breast density, dichotomized as heterogeneously/extremely dense (dense) or fatty/scattered density (not dense). Statistical significance required a probability value of <0.05 (two-sided test). OR were computed using the cutpoints shown in the tables. Tests of trend and the corresponding OR were based on the categorical (age at menarche) or the continuous form of the variable (age, BMI, age at first birth, parity), in accordance with the method of data collection.

Because breast density was inversely associated with age (p for trend <0.0001) and current BMI (p for trend <0.0001), terms for these variables, using the continuous form, were included in all models. We found no evidence of confounding by the other variables shown in Table 1 (fully adjusted OR were within 10% of those adjusted for age and BMI). Model building began with terms representing the main effects, and included interaction terms involving age, BMI, and menopausal status as suggested by visual inspection of the stratified analyses. The presence of statistical interactions was formally tested using likelihood ratio tests. The interaction term representing BMI was defined as BMI ≥30 (high BMI), versus <30 (low BMI). The final multivariable model, based on all women, contained terms for age and BMI in their continuous form, BMI (high, low), family history of breast cancer, age at menarche, age at first birth, parity, menopausal status, current use of HT, and terms for the interactions involving BMI (high, low) and age at menarche, age at first birth, and parity, a term for the interaction involving age and current HT use, and a term for the interaction between age at first birth and menopausal status. We repeated the analyses in parous women, in

Table 1 Distribution of women's characteristics by breast density, dichotomized as dense versus not dense

Characteristics of study sample (n = 144,018)	Not dense		Dense	
	n	%	*n*	%
Age (years)				
30–39	6,728	8	10,011	16
40–49	24,970	31	29,954	48
50–59	21,537	27	13,597	22
60–69	15,160	19	5,433	9
70–79	10,349	13	3,039	5
80–89	2,476	3	774	1
All women	81,220	56	62,798	44
Education				
<High school	6,887	8	2,703	4
High school graduate	27,485	34	17,291	28
College graduate	35,270	43	31,113	50
Post graduate	9,971	12	10,681	17
Missing	1,607	2	1,010	2
Marital status				
Not married	25,235	31	16,905	27
Married	54,181	67	44,598	71
Missing	1,804	2	1,295	2
Current BMI				
<20	2,640	3	6,479	10
20–22.49	9,848	12	16,570	26
22.5–24.99	15,480	19	16,060	26
25–27.49	14,266	18	9,812	16
27.5–29.99	12,689	16	6,353	10
30–34.99	15,197	19	5,326	8
35+	11,100	14	2,198	4

Table 1 continued

Characteristics of study sample (n = 144,018)	Not dense		Dense	
	n	%	*n*	%
Family history breast cancer				
No	55,591	68	41,234	66
Yes	25,629	32	21,564	34
Age at menarche				
<11	6,130	8	3,094	5
11	14,028	17	9,328	15
12	20,928	26	15,833	25
13	22,024	27	18,281	29
14	9,430	12	8,534	14
15+	7,413	9	6,830	11
Missing	1,267	2	898	1
Age at first birth[a]				
<20	15,537	21	8,554	15
20–24	30,574	41	18,674	34
25–29	16,694	22	14,276	26
30–34	6,038	8	6,705	12
35+	1,972	3	2,478	4
Missing	4,526	6	5,026	9
Parity				
0	5,879	8	7,085	11
1	7,023	9	7,665	12
2	19,791	24	18,262	29
3	17,652	22	13,032	21
4	11,723	14	6,905	11
5+	13,795	17	5,896	9
Missing	5,357	7	3,953	6
Menopausal status				
Premenopausal	29,132	36	37,554	60
Postmenopausal	46,874	58	21,895	35
Missing	5,214	6	3,349	5
HT use[b]				
No	32,829	63	12,867	51
Yes	16,338	31	10,722	42
Missing	2,921	6	1,655	7

[a] Age at first birth in parous women

[b] A small proportion of women (5.5%) who reported whether they used HT did not give their menopausal status

women with a screening mammogram, and in women who did not have a personal history of breast cancer.

Results

In all women, scattered density (45%) was most frequently recorded, followed by heterogeneous density (34%), fatty breasts (12%), and extremely dense breasts (10%). The distribution of factors by breast density, classified as not dense versus dense, is shown in Table 1. In general, based on the cutpoints shown, there was a tendency for younger women, those with higher education, and married women to have denser breasts. Women with lower BMI also had greater breast density, consistent with our use of BI-RADS categories, which assess the proportion of fibroglandular tissue (versus fat) in the breast. Women with a family history of breast cancer, later menarcheal age, later age at first birth, and low parity had a tendency toward higher breast density. High breast density was more common in premenopausal than in postmenopausal women, and in women currently using HT compared to nonusers.

Age-stratified analyses, adjusted for age and BMI, showed a weak, positive influence of family history of breast cancer across all age groups assessed (Table 2). A small positive association between age at menarche and breast density appeared to vary by age, with weaker effects in the older and youngest age groups. There were no clear age-related patterns for either the positive effect of age at first birth or the inverse effect of parity or menopausal status. Current HT use, compared to nonuse, was inversely associated with breast density in the younger age groups, and positively associated in women of age 50 or more. In women of age 70 or more, those using HT, compared to nonusers, had twice the odds of having dense breasts.

Analyses stratified on BMI suggested that the influence of some factors was less evident in women of BMI ≥30 (high BMI) than in those of BMI <30 (low BMI) (Table 3). In particular, the positive influence of age at menarche and age at first birth, and the inverse influence of parity were least apparent in the highest BMI group. The data suggested an inverse effect of being postmenopausal, relative to premenopausal, which decreased consistently across the BMI groupings, but the change in OR from the lowest to the highest BMI group was slight. Although the influence of current HT use fluctuated somewhat over BMI groups, there were no obvious patterns.

Analyses stratified by menopausal status revealed largely similar results for most variables, but the relationship between age at first birth and breast density was stronger in the postmenopausal women (Table 4).

We assessed risk factors and potential interactions in a multivariable model (Table 5). Only one factor, family history of breast cancer, which showed a weak but significant positive effect (OR 1.09; 95% CI 1.05–1.14) on breast density, was not involved in an interaction. The possible interaction involving age and age at menarche, suggested by the age-stratified analyses, was not statistically significant ($p = 0.10$). A statistically significant interaction was found between current HT use and age ($p < 0.0001$). Interactions were also present between BMI and age at menarche ($p = 0.04$), age at first birth ($p < 0.0001$), and parity ($p = 0.01$). We also noted a significant interaction between menopausal status and age at first birth ($p = 0.004$), but the coefficients were inconsistent across categories of age at first birth. When the interaction between menopausal status and age at first birth was omitted from the multivariable model, results for the remaining terms were essentially unchanged. A possible interaction involving age, menopausal status, and HT was not significant ($p = 0.10$).

We repeated the analyses in the subgroup of women who did not have a personal history of breast cancer, and found similar results (Table 5). The findings were also comparable when the analyses were confined to parous women, or to those with a screening mammogram (data not shown).

Discussion

Evidence accumulating for nearly 30 years supports the association between breast density and breast cancer [1–5]. Although the notion remains controversial, breast density may be a biomarker of risk [25]. In addition to its influence on breast cancer risk, breast density reduces the accuracy of screening mammography [11, 12, 26, 27], particularly in younger women [9] who tend to have denser breasts [28]. Perhaps as a direct consequence of reduced screening accuracy, breast density is associated with increased risk of interval breast cancers [11], with an adverse impact on breast cancer prognosis.

Most studies of breast cancer risk have shown an inverse effect of age at menarche [13–15, 29], but previous studies of the relationship between age at menarche and breast density have produced inconsistent results. A positive association was seen in two studies [16, 18], including a large HMO population of nearly 30,000 women in Seattle [16]. Studies of breast

Table 2 Odds ratios (OR) and 95% confidence intervals (CI) for the association with breast density according to age group

Characteristic[a]	Age group				
	<40 n = 16,739 OR (95% CI)	40–49 n = 54,924 OR (95% CI)	50–59 n = 35,134 OR (95% CI)	60–69 n = 20,593 OR (95% CI)	70+ n = 16,628 OR (95% CI)
Family history breast cancer					
No	Reference	Reference	Reference	Reference	Reference
Yes	1.06 (0.99, 1.13)	1.10 (1.06, 1.14)	1.07 (1.02, 1.13)	1.10 (1.03, 1.18)	1.11 (1.02, 1.20)
Age at menarche					
Overall OR (95% CI)[b]	1.04 (1.01, 1.06)	1.06 (1.05, 1.08)	1.03 (1.02, 1.05)	1.01 (0.99, 1.03)	1.01 (0.98, 1.03)
p for trend[b]	0.002	<0.0001	0.0001	0.31	0.70
<11	Reference	Reference	Reference	Reference	Reference
11	0.99 (0.85, 1.18)	1.14 (1.04, 1.24)	1.28 (1.15, 1.42)	1.06 (0.90, 1.24)	1.11 (0.89, 1.38)
12	1.04 (0.89, 1.21)	1.15 (1.06, 1.25)	1.26 (1.15, 1.39)	1.12 (0.96, 1.30)	1.18 (0.96, 1.45)
13	1.15 (0.98, 1.35)	1.25 (1.16, 1.36)	1.27 (1.15, 1.40)	1.20 (1.03, 1.39)	1.00 (0.82, 1.23)
14	1.21 (1.02, 1.44)	1.34 (1.22, 1.46)	1.37 (1.23, 1.53)	1.23 (1.05, 1.46)	1.22 (0.99, 1.51)
15+	1.29 (1.08, 1.55)	1.45 (1.32, 1.60)	1.36 (1.21, 1.52)	1.05 (0.89, 1.25)	1.15 (0.92, 1.43)
Age at first birth[c]					
Overall OR (95% CI)[d]	1.08 (1.06, 1.10)	1.05 (1.04, 1.06)	1.07 (1.06, 1.08)	1.07 (1.05, 1.09)	1.06 (1.05, 1.08)
p for trend[d]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
<20	Reference	Reference	Reference	Reference	Reference
20–24	1.06 (0.95, 1.19)	1.14 (1.08, 1.21)	1.21 (1.14, 1.29)	1.23 (1.12, 1.34)	1.07 (0.93, 1.24)
25–29	1.09 (0.98, 1.22)	1.19 (1.12, 1.26)	1.40 (1.30, 1.51)	1.51 (1.36, 1.68)	1.28 (1.11, 1.49)
30–34	1.35 (1.18, 1.53)	1.23 (1.15, 1.36)	1.58 (1.42, 1.76)	1.64 (1.39, 1.95)	1.42 (1.18, 1.70)
35+	1.67 (1.30, 2.16)	1.48 (1.35, 1.63)	1.85 (1.58, 2.17)	1.90 (1.44, 2.49)	1.47 (1.14, 1.91)
Parity					
Overall OR (95% CI)[d]	0.86 (0.84, 0.88)	0.91 (0.90, 0.93)	0.90 (0.86, 0.91)	0.89 (0.87, 0.90)	0.87 (0.85, 0.89)
p for trend[d]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
0	Reference	Reference	Reference	Reference	Reference
1	0.74 (0.65, 0.86)	0.90 (0.83, 0.87)	0.87 (0.79, 0.97)	0.87 (0.73, 1.05)	0.88 (0.73, 1.05)
2	0.58 (0.52, 0.66)	0.73 (0.69, 0.78)	0.77 (0.71, 0.85)	0.77 (0.67, 0.89)	0.66 (0.57, 0.78)
3	0.48 (0.42, 0.55)	0.69 (0.65, 0.74)	0.67 (0.61, 0.73)	0.65 (0.57, 0.76)	0.59 (0.51, 0.69)
4	0.49 (0.42, 0.57)	0.61 (0.57, 0.66)	0.61 (0.55, 0.67)	0.55 (0.48, 0.64)	0.49 (0.42, 0.58)
5+	0.38 (0.33, 0.45)	0.60 (0.55, 0.66)	0.52 (0.47, 0.58)	0.49 (0.42, 0.56)	0.39 (0.33, 0.46)
Menopausal status					
Premenopausal	Reference	Reference	Reference		
Postmenopausal	0.69 (0.60 , 0.79)	0.71 (0.68, 0.75)	0.71 (0.67, 0.75)	N/A	N/A
HT use					
No	Reference	Reference	Reference	Reference	Reference
Yes	0.69 (0.57, 0.84)	0.80 (0.75, 0.86)	1.39 (1.32, 1.46)	1.82 (1.70, 1.95)	2.02 (1.84, 2.22)

[a] Adjusted for age and current BMI as continuous variables

[b] Based on the cutpoints shown

[c] Among parous women

[d] Based on the continuous form of the variable

cancer family members [17], Singaporean women [20], and Hispanic women [19] found no association between menarcheal age and breast density. Findings from the HMO-based study suggested the positive effect of age at menarche was stronger in the youngest and oldest age groups [16], whereas a study of nearly 5,000 women in Guernsey found significant positive effects only in postmenopausal women [6]. In contrast, our age-stratified analyses suggested weaker effects in the oldest age groups, although the interaction involving age and age at menarche was not statistically significant. Also in this study, analyses stratified on BMI suggested that age at menarche was positively associated with breast density in most BMI groups, but the association was tenuous in women with high BMI, and the interaction involving age at menarche and high BMI was statistically significant. A positive association between age at menarche and breast density, even if confined to women with lower BMI, seems paradoxical, given the usual inverse association between age at menarche and breast cancer and the strong positive association between breast density and breast cancer risk.

Consistent with some [16–18, 20, 30, 31], but not all [6, 19] previous efforts, our findings show that age at first birth and parity are generally associated with

Table 3 Odds ratios (OR) and 95% confidence intervals (CI) for the association with breast density according to BMI group

Characteristic[a]	Current BMI				
	<22.5 *n* = 35,547 OR (95% CI)	22.5–25.49 *n* = 37,153 OR (95% CI)	25.5–27.49 *n* = 18,744 OR (95% CI)	27.5–29.99 *n* = 18,775 OR (95% CI)	≥30 *n* = 33,799 OR (95% CI)
Family history of breast cancer					
No	Reference	Reference	Reference	Reference	Reference
Yes	1.09 (1.03, 1.14)	1.03 (0.99, 1.08)	1.08 (1.01, 1.15)	1.15 (1.08, 1.23)	1.09 (1.03, 1.15)
Age at menarche					
Overall OR (95% CI)[b]	1.04 (1.03, 1.06)	1.05 (1.03, 1.06)	1.04 (1.02, 1.06)	1.03 (1.01, 1.05)	1.01 (0.99, 1.03)
p for trend[b]	<0.001	0.001	0.001	0.004	0.25
<11	Reference	Reference	Reference	Reference	Reference
11	1.25 (1.09, 1.43)	1.17 (1.05, 1.31)	1.13 (0.98, 1.31)	1.20 (1.05, 1.38)	1.10 (0.99, 1.22)
12	1.36 (1.20, 1.55)	1.26 (1.13, 1.40)	1.10 (0.96, 1.27)	1.16 (1.01, 1.32)	1.09 (0.98, 1.21)
13	1.43 (1.26, 1.63)	1.33 (1.20, 1.48)	1.16 (1.01, 1.33)	1.21 (1.06, 1.38)	1.06 (0.94, 1.16)
14	1.54 (1.34, 1.75)	1.44 (1.28, 1.61)	1.25 (1.08, 1.45)	1.19 (1.02, 1.38)	1.16 (1.02, 1.31)
15+	1.52 (1.32, 1.75)	1.43 (1.27, 1.61)	1.26 (1.07, 1.48)	1.33 (1.13, 1.56)	1.06 (0.93, 1.21)
Age at first birth[c]					
Overall OR (95% CI)[d]	1.08 (1.07, 1.09)	1.07 (1.06, 1.08)	1.07 (1.06, 1.09)	1.06 (1.04, 1.07)	1.03 (1.02, 1.04)
p for trend[d]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
<20	Reference	Reference	Reference	Reference	Reference
20–24	1.21 (1.13, 1.31)	1.20 (1.13, 1.28)	1.15 (1.05, 1.26)	1.13 (1.03, 1.23)	1.04 (0.96, 1.11)
25–29	1.39 (1.29, 1.51)	1.34 (1.25, 1.44)	1.21 (1.10, 1.34)	1.31 (1.19, 1.45)	1.10 (1.01, 1.19)
30–34	1.45 (1.32, 1.60)	1.55 (1.42, 1.70)	1.40 (1.23, 1.59)	1.42 (1.25, 1.63)	1.11 (0.99, 1.24)
35+	1.79 (1.56, 2.06)	1.84 (1.61, 2.09)	1.88 (1.56, 2.28)	1.62 (1.33, 1.97)	1.29 (1.08, 1.53)
Parity					
Overall OR (95% CI)[d]	0.86 (0.85, 0.87)	0.88 (0.87, 0.89)	0.90 (0.88, 0.92)	0.91 (0.89, 0.93)	0.93 (0.92, 0.95)
p for trend[d]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
0	Reference	Reference	Reference	Reference	Reference
1	0.75 (0.67, 0.84)	0.80 (0.73, 0.89)	0.93 (0.81, 1.08)	1.13 (0.98, 1.30)	0.95 (0.85, 1.07)
2	0.61 (0.55, 0.66)	0.67 (0.62, 0.73)	0.74 (0.66, 0.84)	0.90 (0.79, 1.02)	0.85 (0.78, 0.94)
3	0.52 (0.48, 0.58)	0.58 (0.53, 0.63)	0.68 (0.60, 0.77)	0.80 (0.71, 0.91)	0.81 (0.73, 0.89)
4	0.44 (0.39, 0.48)	0.52 (0.47, 0.57)	0.60 (0.52, 0.69)	0.71 (0.62, 0.81)	0.75 (0.68, 0.84)
5+	0.37 (0.34, 0.41)	0.44 (0.40, 0.48)	0.52 (0.45, 0.60)	0.64 (0.56, 0.74)	0.66 (0.59, 0.74)
Menopausal status					
Premenopausal	Reference	Reference	Reference	Reference	Reference
Postmenopausal	0.67 (0.63, 0.72)	0.68 (0.64, 0.72)	0.71 (0.65, 0.77)	0.73 (0.67, 0.79)	0.75 (0.70, 0.80)
HT use					
No	Reference	Reference	Reference	Reference	Reference
Yes	1.23 (1.15, 1.31)	1.33 (1.26, 1.42)	1.34 (1.23, 1.46)	1.41 (1.30, 1.55)	1.34 (1.25, 1.45)

[a] Adjusted for age and current BMI as continuous variables

[b] Based on the cutpoints shown

[c] Among parous women

[d] Based on the continuous form of the variable

breast density in a pattern resembling known associations with breast cancer risk. However, our stratified analyses indicate that the influence of the reproductive variables is less pronounced in women with high BMI, and our modeling results confirmed interactions involving BMI and both variables. These findings, along with our findings for age at menarche, are consistent with the possibility that hormonal or reproductive events are less influential in heavier women, whose circulating hormone levels may be influenced by conversion in peripheral adipose tissue. We also noted a stronger positive influence of age at first birth in postmenopausal women, although a previous study of Native American women found stronger effects in premenopausal women [30]. Our sample was large, and the multivariable results were inconsistent across categories of age at first birth; thus, it is possible the interaction between menopausal status and age at first birth was due to statistical artifact rather than true effect modification.

Only one variable, family history of breast cancer, was not involved in interactions with age, BMI, or menopausal status. Although previous studies have not shown an effect of family history on breast density [3, 6, 19], this is likely due to limited power to detect a weak association. The modest inverse effect of menopausal status has been noted previously [19, 20, 30]. Most previous reports, although not all [20], found a

Table 4 Odds ratios (OR) and 95% confidence intervals (CI) for the association with breast density according to menopausal status

Characteristic[a]	Menopausal status	
	Premenopausal n = 66,686 OR (95% CI)	Postmenopausal n = 68,769 OR (95% CI)
Family history of breast cancer		
No	Reference	Reference
Yes	1.09 (1.05, 1.13)	1.08 (1.04, 1.12)
Age at first birth		
Overall OR (95% CI)	1.05 (1.04, 1.06)	1.03 (1.02, 1.04)
p for trend	<0.0001	<0.0001
<11	Reference	Reference
11	1.12 (1.03, 1.21)	1.15 (1.06, 1.25)
12	1.12 (1.04, 1.22)	1.20 (1.12, 1.30)
13	1.22 (1.13, 1.32)	1.21 (1.12, 1.31)
14	1.31 (1.21, 1.43)	1.29 (1.18, 1.40)
≥15	1.40 (1.28, 1.53)	1.25 (1.15, 1.36)
Age at first birth[b]		
Overall OR (95% CI)[c]	1.05 (1.05, 1.06)	1.07 (1.06, 1.08)
p for trend[c]	<0.0001	<0.0001
<20	Reference	Reference
20–24	1.07 (1.01, 1.13)	1.21 (1.15, 1.27)
25–29	1.11 (1.05, 1.17)	1.41 (1.33, 1.49)
30–34	1.21 (1.13, 1.29)	1.57 (1.45, 1.71)
≥35	1.48 (1.35, 1.62)	1.77 (1.57, 2.00)
Parity		
Overall OR (95% CI)[c]	0.90 (0.87, 0.91)	0.88 (0.88, 0.89)
p for trend[c]	<0.0001	<0.0001
0	Reference	Reference
1	0.87 (0.81, 0.93)	0.86 (0.79, 0.93)
2	0.70 (0.66, 0.74)	0.72 (0.68, 0.77)
3	0.63 (0.60, 0.68)	0.62 (0.58, 0.67)
4	0.57 (0.53, 0.62)	0.55 (0.51, 0.59)
≥5	0.52 (0.49, 0.57)	0.46 (0.43, 0.50)
HT use		
No	NA	Reference
Yes	NA	1.47 (1.41, 1.52)

[a] Adjusted for age and current BMI as continuous variables

[b] Among parous women

[c] Based on the continuous form of the variable

positive association between use of HT and breast density [16, 17, 19, 30, 32, 33], resembling the well-known association between use of these hormones and breast cancer risk. The large size of our study allowed an assessment of HT use in young postmenopausal women, and these analyses showed a modest but significant inverse effect in postmenopausal women less than 50 years of age, a phenomenon that has no clear explanation. In women of age 50 or more, the positive effect of HT on density increased with age, perhaps reflecting a corresponding decrease in density in untreated women in the same age group. Consistent with our findings, at least two previous studies of breast density showed an increasing effect of HT use when examined over increasing age groups [16, 32]. A prospective study of breast cancer risk also noted stronger HT effects in older women [37], although this is not always seen [36]. The age-related increase observed in our study could potentially reflect a longer duration of HT use, but at least two studies have shown that most of the increase in breast density occurs soon after HT initiation [33, 34], and duration of use was not associated with increased breast density in the HMO study [16]. In contrast, the positive influence of HT on breast cancer risk is usually observed for current/recent and long-term use [35–40]. While speculative, it is possible that sustained breast density associated with long term HT use mediates the relationship between HT and breast cancer risk. Finally, our data did not indicate a stronger effect of HT on breast density in leaner woman, but a few studies [38–40], including a collaborative analysis of 51 studies [38], suggested a stronger association between HT and breast cancer risk in leaner women.

Although the type of HT used (estrogen alone or estrogen combined with progesterone) was not assessed in our study, a possible role of progesterone is suggested by reports that breast density is greater during the luteal phase of the menstrual cycle [41–43]. In addition, at least two studies have found substan-

Table 5 Betas (β) and standard errors (SE) for the association between factors and breast density in all women and in subgroups[a]

Characteristic	All women n = 144,018 β (SE)	Women without breast cancer n = 136,283 β (SE)
Intercept	4.82 (0.17)	4.88 (0.17)
Age	–0.04 (0.001)	–0.04 (0.001)
Current BMI	–0.12 (0.003)	–0.12 (0.003)
Family history of breast cancer	0.09 (0.02)	0.09 (0.02)
BMI <30	–0.53 (0.11)	–0.53 (0.11)
Postmenopausal	–0.43 (0.09)	–0.43 (0.09)
HT use	–1.22 (0.11)	–1.25 (0.11)
Age at menarche		
15+	–0.01 (0.10)	–0.03 (0.11)
14	0.04 (0.10)	0.01 (0.10)
13	–0.01 (0.08)	–0.03 (0.08)
12	0.08 (0.08)	0.06 (0.08)
11	0.04 (0.08)	0.02 (0.08)
BMI <30 * Age at menarche		
15+	0.30 (0.12)	0.32 (0.12)
14	0.24 (0.11)	0.28 (0.11)
13	0.22 (0.09)	0.24 (0.10)
12	0.12 (0.09)	0.15 (0.10)
11	0.11 (0.10)	0.14 (0.10)
Age at first birth		
Nulliparous	0.38 (0.16)	0.13 (0.17)
35+	0.19 (0.22)	0.25 (0.23)
30–34	–0.19 (0.15)	–0.18 (0.15)
25–29	–0.11 (0.12)	–0.12 (0.12)
20–24	0.14 (0.11)	0.13 (0.11)
BMI <30 * Age at first birth		
Nulliparous	0.57 (0.10)	0.59 (0.11)
35+	0.41 (0.18)	0.40 (0.18)
30–34	0.31 (0.11)	0.32 (0.12)
25–29	0.12 (0.08)	0.15 (0.08)
20–24	0.06 (0.06)	0.06 (0.06)
Postmenopausal * Age at first birth		
Nulliparous	0.09 (0.15)	0.10 (0.15)
35+	–0.08 (0.19)	–0.14 (0.19)
30–34	0.27 (0.13)	0.26 (0.13)
25–29	0.25 (0.11)	0.23 (0.11)
20–24	–0.05 (0.10)	–0.04 (0.11)
Parity[a]		
1	0.29 (0.09)	0.28 (0.09)
2	0.22 (0.07)	0.23 (0.07)
3	0.14 (0.07)	0.17 (0.07)
4	0.09 (0.07)	0.11 (0.08)
BMI <30 * Parity[b]		
1	0.30 (0.10)	0.30 (0.10)
2	0.22 (0.07)	0.20 (0.08)
3	0.18 (0.08)	0.15 (0.08)
4	0.09 (0.08)	0.07 (0.09)
Age * HT use	0.03 (0.002)	0.03 (0.002)

[a] Based on a multivariable model containing all terms shown in the table

[b] The nulliparous parameter and its interaction with BMI were set to 0, since these variables were linear combinations of other variables

tially greater changes in parenchymal patterns in women initiating use of a combined estrogen plus progesterone hormone regimen, as opposed to single agent estrogen [33, 34]. Results from the Women's Health Initiative randomized clinical trials of postmenopausal hormones also indicate that the increased risk of breast cancer is due to the combined regimen [44] rather than single agent estrogen [45].

Strengths of our study include the large size of our sample, allowing analyses stratified by relatively refined age and BMI groups, which has not been possible in most previous studies, and good representation of the underlying population. Epidemiologic data were obtained on the time of the mammographic visit, ensuring updated information, and importantly, a high level of correspondence between use of hormone replacement therapy and the assessment of breast density. Limitations of our study include 11% of women for whom BMI is missing, reliance of self-report for BMI, and a lack of information regarding the type and duration of HT use. Our definition of family history of breast cancer included second degree relatives, which may have attenuated the effect of this variable. Also, the BI-RADS scores are qualitative, as opposed to digital quantification of density, and were applied by community radiologists, who despite being trained to use this system, may apply it differently. Nevertheless, our general findings in terms of the direction of effects for reproductive factors and HT use were compatible with those of most previous studies.

In conclusion, our results, based on the largest study to date, confirm earlier findings that most established breast cancer risk factors behave similarly in relation to breast density, consistent with the notion that breast density mediates breast cancer risk. However, our data indicated an inverse effect of HT in younger women, and a positive influence in older women, which has not been reported previously. We also noted effect modification by BMI, in which the positive effects of age at menarche and age at first birth, and the inverse effects of parity were less apparent in heavier women. Further investigation, including biological studies, may elucidate the complex interrelationships of hormones, BMI, breast density, and breast cancer and potentially offer opportunities for breast cancer prevention.

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