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ORIGINAL REPORT

Breast Cancer Risk by Breast Density, Menopause, and Postmenopausal Hormone Therapy Use

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ABSTRACT

Purpose
We determined whether the association between breast density and breast cancer risk and cancer severity differs according to menopausal status and postmenopausal hormone therapy (HT) use.

Methods
We collected data on 587,369 women who underwent 1,349,027 screening mammography examinations; 14,090 women were diagnosed with breast cancer. We calculated 5-year breast cancer risk from a survival model for subgroups of women classified by their Breast Imaging Reporting and Data System (BIRADS) breast density, age, menopausal status, and current HT use, assuming a body mass index of 25 kg/m^2. Odds of advanced (ie, IIb, III, IV) versus early (ie, I, IIa) stage invasive cancer was calculated according to BIRADS density.

Results
Breast cancer risk was low among women with low density (BIRADS-1): women age 55 to 59 years, 5-year risk was 0.8% (95% CI, 0.6 to 0.9%) for non-HT users and 0.9% (95% CI, 0.7% to 1.1%) for estrogen and estrogen plus progestin users. Breast cancer risk was high among women with very high density (BIRADS-4), particularly estrogen plus progestin users: women age 55 to 59 years, 5-year risk was 2.4% (95% CI, 2.0% to 2.8%) for non-HT users, 3.0% (95% CI, 2.6% to 3.5%) for estrogen users, and 4.2% (95% CI, 3.7% to 4.6%) for estrogen plus progestin users. Advanced-stage breast cancer risk was increased 1.7-fold for postmenopausal HT users who had very high density (BIRADS-4) compared to those with average density (BIRADS-2).

Conclusion
Postmenopausal women with high breast density are at increased risk of breast cancer and should be aware of the added risk of taking HT, especially estrogen plus progestin.

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INTRODUCTION

High breast density is a prevalent and strong risk factor for breast cancer.[1] Postmenopausal hormone therapy (HT), in particular estrogen plus progestin, increases breast density[2-4] and breast cancer risk.[5] Whether breast density has a greater impact on breast cancer risk for some subgroups of women defined by menopausal status and postmenopausal HT use is unknown.

Few studies have shown tumors in dense breasts may progress more rapidly than those in fatty breasts.[6,7] Studies also have shown high breast density is associated with larger tumor size among screen-detected cancers[6,8,9] and with positive lymph nodes.[6,7,10] Postmenopausal estrogen and progestin use for 5 years or more increases the likelihood of developing breast cancer that is diagnosed at an advanced stage.[5,11] It is not known if breast cancer severity is increased even more in women with dense breasts who use postmenopausal HT.

Our study aimed to extend the literature by reporting whether the association between breast density and breast cancer risk and cancer severity differs according to menopausal status and postmenopausal HT use. Our hypothesis is high breast density will increase risk of breast cancer and advanced-stage disease most among postmenopausal women taking HT, and low breast density will result in a low risk of breast cancer and advanced-staged disease regardless of menopausal status or HT use.

METHODS

Data Source

Data were pooled from seven mammography registries that participate in the Breast Cancer Surveillance

Consortium[12] (http://breastscreening.cancer.gov). These registries collect information on mammography examinations performed in their defined catchment areas. Each mammography registry annually links women in its registry to a state tumor registry or regional Surveillance, Epidemiology, and End Results program that collects population-based cancer data. Each registry obtains annual approval from its institutional review board for consenting processes or a waiver of consent, enrollment of participants, and ongoing data linkages for research purposes. All registries have received Federal Certificates of Confidentiality that protect the identities of research subjects.

Subjects

The study sample included bilateral screening mammography examinations between January 1, 1996, and December 31, 2006, with a recorded Breast Imaging Reporting and Data System (BIRADS)[13] breast density measurement among women age 30 years or older who completed a self-administered questionnaire at the time of each examination and did not have a history of breast cancer or breast implants. We excluded mammography examinations among women with missing body mass index (BMI; 13.7%), HT use (2.9%), or menopausal status (3.1%). Of eligible examinations, 19.7% were excluded because of missing data. Mammography examinations that occurred after December 31, 2006, were not included, to ensure at least 12 months for reporting cancers to tumor registries. Cancer ascertainment from cancer registries is estimated to be more than 94.3% complete during the study time period.[14]

Measurements and Definitions

Demographic and breast health history information were obtained on a self-administered questionnaire (http://breastscreening.cancer.gov) and information was allowed to change each time a questionnaire was completed at a screening examination. Women were considered to have a family history of breast cancer if they reported having at least one first-degree relative (ie, mother, sister, or daughter) with breast cancer. Current HT users were those who reported using prescription HT at the time of a screening examination. Postmenopausal women were defined as those with both ovaries removed, reported their periods had stopped naturally, currently using postmenopausal HT, or age 55 or older. Women were considered to have missing menopausal status if they had a hysterectomy without bilateral oophorectomy and were not using HT or menopause status could not be determined based on available information. Postmenopausal women with hysterectomy information (53%) were included in analyses by hormone type. Women with a uterus using HT were considered to be using estrogen plus progestin, whereas women without a uterus using HT were considered to be using estrogen only, as previously described.[5] Self-reported height and weight were used to calculate BMI by dividing weight in kilograms by height in meters squared (kg/m^2). We used self-reported race and ethnicity data to categorize women as non-Hispanic white, non-Hispanic black, Hispanic, Asian/Native Hawaiian/Pacific Islander, Native American/Native Alaskan, or other/mixed race.

Mammographic breast density was categorized from each bilateral screening examination using BIRADS breast density categories: 1 = almost entirely fat (low density); 2 = scattered fibroglandular densities (average density); 3 = heterogeneously dense (high density); 4 = extremely dense (very high density).

Women were considered to have breast cancer if reports from a breast pathology database, Surveillance, Epidemiology, and End Results program, or state tumor registry showed any invasive carcinoma or ductal carcinoma in situ. Women with lobular carcinoma in situ only were not considered to have cancer. Stage at diagnosis was classified according to the TNM system based on the criteria of the American Joint Committee on Cancer as stage 0, I, II, III, or IV.[15] Early-stage invasive cancer was defined as stage I or IIA and late stage as IIB, III, or IV.

Statistical Analysis

Frequency distributions of risk factors at first breast density measurement were determined for women with and without breast cancer. All other analyses were performed using each available breast density measurement assigned at a screening examination as the unit of analysis unless otherwise specified.

We used the partly conditional Cox proportional hazard survival model[16] to assess the association between breast density and breast cancer risk by age, menopausal status, and HT use to allow for multiple breast density and HT measurements per woman. Follow-up time was taken to be the time from each breast density measurement to cancer diagnosis or censoring (at death or end of follow-up period). To evaluate the inter-relationship between breast density, menopausal status, and current HT use, we included all-way interaction terms between these factors. We then performed analyses to assess if the relationship between breast density, menopausal status, and current HT use changed by age group. We used BIRADS-2 density as the referent group for all models since this density was the most prevalent. SEs were calculated using a robust sandwich estimator proposed for repeated measured survival data.[17]

Table 1. Characteristics of Study Women With and Without Breast Cancer Obtained at the First Breast Density Measurement

Characteristic	Women: No Breast Cancer No.	%	Women: Breast Cancer No.	%
No.	573,279		14,090	
Age, years				
30-39	43,534	8	512	4
40-49	201,810	35	3,538	25
50-59	155,262	27	4,090	29
60-69	95,193	17	3,194	23
70-79	59,651	10	2,228	16
80+	17,829	3	528	4
Race/ethnicity				
Non-Hispanic white	434,626	76	11,345	81
Non-Hispanic black	11,494	2	212	2
Asian or Pacific Islander	22,749	4	387	3
American Indian or Alaskan Native	6,029	1	75	1
Other/mixed/unknown	35,293	6	1,125	8
Hispanic	63,088	12	946	7
First degree family history of breast cancer*				
Yes	76,641	14	2,889	21
No	480,044	86	10,924	79
Current hormone therapy				
Yes	146,579	26	4,534	32
No	426,700	74	9,556	68
Menopausal status				
Premenopausal	220,389	38	3,856	27
Postmenopausal and no hormone therapy use	206,311	36	5,700	40
Postmenopausal and hormone therapy use	146,579	26	4,534	32
BIRADS breast density†				
1	57,127	10	834	6
2	253,072	44	5,946	42
3	210,644	37	5,751	41
4	52,436	9	1,559	11
Median body mass index, kg/m^2	26.8		26.8	
Standard deviation	6.0		5.7	
Median follow-up time, years‡	6.4		3.7	

Abbreviation: BIRADS, Breast Imaging Reporting and Data System.
*Missing family history included 2.9% for women without breast cancer and 2.0% with breast cancer.
†BIRADS density 1 = almost entirely fat (low breast density); 2 = scattered fibroglandular densities (average breast density); 3 = heterogeneously dense (high breast density); 4 = extremely dense (very high breast density).
‡Median follow-up time is shorter for those with cancer compared to those without because follow-up time is censored at the time of breast cancer diagnosis.

Adjusted 5-year breast cancer risk was calculated based on the product-limit estimate of the survival function for each age, menopausal status, breast density, and HT group, fixing BMI at 25 kg/m^2. There was no differential effect of BMI on the relationship between breast density and menopausal status with or without HT and cancer risk ($P = .3$), thus we present 5-year risks for normal weight women (Appendix Tables A1 and A2 show risk estimates fixing BMI at 18.5 and 30 kg/m^2).

To evaluate whether tumor stage at diagnosis is associated with most recent breast density measurement before diagnosis or menopausal status, we fit four separate logistic regression models according to menopause status and HT use restricting to breast cancer cases with cancer stage as the outcome (advanced *v* early stage). We adjusted for age, BMI as linear and quadratic terms, HT use, menopause status (all breast cancers only) and registry. We performed a sensitivity analysis by further restricting to screened-detected cancers defined as those cancers identified within 12 months of an abnormal screening result[13,18] to see whether this altered the results.

All data analyses were conducted using SAS software, version 9.1 of the SAS system for Windows (SAS Institute Inc, Cary, NC). Two-sided statistical tests resulting in *P* values less than .05 were considered statistically significant.

RESULTS

Among 587,369 women who were ≥ 30 years (mean, 56.4 years), 1,349,027 screening mammography examinations were performed (median, 2.0 exams/woman; range, 1 to 11), and 14,090 women were diagnosed with breast cancer. Women subsequently diagnosed with breast cancer compared with women not diagnosed with breast cancer were more likely to be older than 50 years (71% *v* 57%), white (81% *v* 76%), postmenopausal (73% *v* 62%), currently using HT (32% *v* 26%), and have a first-degree relative with breast cancer (21% *v* 14%), respectively (Table 1). A total of 52% of women with breast cancer had BIRADS-3 (high breast density) or BIRADS-4 (very high breast density) at first density measure compared to 46% of women without breast cancer.

The strength of the association between BIRADS-3 or BIRADS-4 density and breast cancer was strongest for premenopausal women and postmenopausal HT users and did not vary by type of HT use (Table 2). Women with BIRADS-1 density (low breast density) were at low breast cancer risk irrespective of menopausal status and HT use.

There was a differential relationship between high breast density and breast cancer for postmenopausal HT users compared to non-HT users (*P* for interaction < .001). Among postmenopausal women with the same breast density measure, HT users compared with non-HT users had higher breast cancer risk for those with BIRADS-4 density (hazard ratio [HR], 1.38; 95% CI, 1.25 to 1.50; $P < .001$) and BIRADS-3 density (HR, 1.22; 95% CI, 1.16 to 1.27; $P < .001$), but not among women with BIRADS-2 density (average breast density; HR, 1.03; 95% CI, 0.97 to 1.08; $P = .32$) or BIRADS-1 density (low breast density; HR, 0.91; 95% CI, 0.76 to 1.05; $P = .19$).

We estimated breast cancer risk according to breast density, age, menopausal status, and HT use fixing BMI at 25 kg/m^2. Postmenopausal HT users with BIRADS-3 or BIRADS-4 density had a higher breast cancer risk at a younger age than nonusers; postmenopausal HT users age 55 to 59 years or older had a 5-year breast cancer risk of higher than 3%, while postmenopausal non-HT users did not achieve this risk until age 65 years or older (Table 3). Notably, postmenopausal HT use had no or little influence on breast cancer risk among women with BIRADS-1 or BIRADS-2 density. Women age 35 to 69 years with low breast density had a low 5-year breast cancer risk (range, 0.1% to 1.6%), irrespective of menopausal status and HT use. Premenopausal women age 50 to 54 years with BIRADS-4 density had a 5-year breast risk of 3.1% similar to postmenopausal non-HT users age 65 to 69 years with BIRADS-3 density.

We also estimated 5-year breast cancer risk according to breast density and type of HT use among postmenopausal women fixing BMI at 25 kg/m^2. Five-year breast cancer risk was higher among postmenopausal women age 55 to 59 years who had BIRADS-4 density, particularly among estrogen plus progestin users; estrogen users (3.0%) and estrogen plus progestin users (4.2%; Table 4). Similar

Table 2. Association Between Breast Density and Breast Cancer Risk by Menopausal Status and HT Use

	BIRADS Breast Density*							
	1		2	3		4		
Variable	HR	95% CI		HR	95% CI	HR	95% CI	
Premenopausal†	0.46	0.37 to 0.58	Reference	1.62	1.51 to 1.75	2.04	1.84 to 2.26	
Postmenopausal no HT†	0.57	0.53 to 0.62	Reference	1.35	1.28 to 1.42	1.51	1.35 to 1.68	
Postmenopausal HT†	0.50	0.44 to 0.57	Reference	1.59	1.51 to 1.69	2.02	1.83 to 2.22	
Postmenopausal E use‡	0.61	0.48 to 0.78	Reference	1.60	1.42 to 1.80	1.99	1.61 to 2.46	
Postmenopausal E + P‡	0.45	0.34 to 0.59	Reference	1.58	1.44 to 1.74	2.09	1.79 to 2.43	

Abbreviations: HT, hormone therapy; BIRADS, Breast Imaging Reporting and Data System; HR, hazard ratio; E, estrogen; E + P, estrogen + progesterone; BMI, body mass index.

*BIRADS density 1 = almost entirely fat (low breast density); 2 = scattered fibroglandular densities (average breast density); 3 = heterogeneously dense (high breast density); 4 = extremely dense (very high breast density).

†HRs for entire cohort come from partly conditional Cox proportional hazards models assuming interactions between HT use, menopausal status, and breast density using robust sandwich variance estimates to account for multiple mammography estimations per woman adjusting for age category, BMI, BMI^2, interactions between BMI and BMI^2 with menopausal status (since they were significant $P = .001$ and $P = .025$, respectively) and registry. Interaction terms use a hierarchical algorithm in which all lower order main effects or interactions are included in the model regardless of statistical significance. Risk estimates were calculated for women with a BMI = 25 kg/m^2 (approximate average BMI in population) and average registry (proportions of mammography examinations from each registry).

‡HRs for women with known hysterectomy status come from partly conditional Cox proportional hazards models assuming interactions between type of HT use, menopausal status, and breast density using robust sandwich variance estimates to account for multiple mammography estimations per woman adjusting for age category, BMI, BMI^2, interactions between BMI and BMI^2 with menopausal status (since they were significant ($P = .002$ and $P = .017$, respectively), E, E + P, and registry. Interaction terms use a hierarchical algorithm in which all lower order main effects or interactions are included in the model regardless of statistical significance. Risk estimates were calculated for women with a BMI = 25 kg/m^2 (approximate average BMI in population) and average registry (proportions of mammography examinations from each registry).

Table 3. Five-Year Cancer Risk Estimates After a Screening Mammography Examination by Breast Density, Age, Menopausal Status, and HT Use Assuming BMI = 25 kg/m^2

	BIRADS Breast Density*							
	1		2		3		4	
Age	5 Year Risk %†	95% CI	5-Year Risk %†	95% CI	5-Year Risk %†	95% CI	5-Year Risk %†	95% CI
Premenopausal‡								
30-34	0.3	0.0 to 0.9	0.5	0.2 to 0.7	0.9	0.6 to 1.3	0.7	0.2 to 1.1
35-39	0.1	0.0 to 0.3	0.7	0.6 to 0.9	1.1	0.9 to 1.2	1.5	1.2 to 1.7
40-44	0.4	0.2 to 0.5	0.9	0.8 to 0.9	1.5	1.4 to 1.6	1.8	1.7 to 2.0
45-49	0.7	0.5 to 0.9	1.3	1.2 to 1.4	2.1	1.9 to 2.2	2.5	2.3 to 2.7
50-54	0.8	0.4 to 1.1	1.5	1.4 to 1.7	2.3	2.1 to 2.5	**3.1**	**2.7 to 3.5**
Postmenopausal and no HT use‡								
30-45	0.2	0.1 to 0.5	0.7	0.5 to 1.0	1.1	0.7 to 1.4	1.2	0.5 to 1.9
45-49	0.5	0.2 to 0.7	0.8	0.7 to 1.0	1.6	1.3 to 1.8	2.2	1.6 to 2.7
50-54	0.6	0.5 to 0.8	1.3	1.2 to 1.4	1.8	1.6 to 1.9	2.2	1.8 to 2.6
55-59	0.8	0.6 to 0.9	1.7	1.6 to 1.8	2.4	2.3 to 2.6	2.4	2.0 to 2.8
60-64	1.1	1.0 to 1.3	2.0	1.9 to 2.1	2.7	2.5 to 2.9	2.8	2.2 to 3.4
65-69	1.2	1.1 to 1.4	2.3	2.2 to 2.5	**3.2**	**3.0 to 3.4**	**3.4**	**2.7 to 4.2**
70-79	1.7	1.5 to 1.9	2.6	2.5 to 2.7	**3.4**	**3.0 to 3.6**	**3.4**	**2.8 to 4.1**
80+	1.5	1.2 to 1.7	2.6	2.4 to 2.8	2.6	2.3 to 2.9	**3.5**	**2.4 to 4.5**
Postmenopausal and HT use‡								
30-45	0.3	0.1 to 0.5	0.6	0.4 to 0.7	1.1	0.8 to 1.3	1.1	0.7 to 1.6
45-49	0.5	0.3 to 0.8	0.9	0.8 to 1.1	1.5	1.3 to 1.7	2.2	1.8 to 2.7
50-54	0.6	0.4 to 0.8	1.3	1.2 to 1.4	2.3	2.1 to 2.4	2.8	2.5 to 3.2
55-59	0.8	0.6 to 1.0	1.8	1.7 to 2.0	**3.1**	**2.9 to 3.3**	**4.3**	**3.8 to 4.8**
60-64	1.0	0.7 to 1.2	2.0	1.9 to 2.2	**3.4**	**3.2 to 3.7**	**4.1**	**3.5 to 4.8**
65-69	1.6	1.2 to 2.0	2.3	2.1 to 2.5	**3.6**	**3.3 to 3.9**	**3.6**	**2.8 to 4.4**
70-79	1.5	1.2 to 1.9	2.9	2.6 to 3.1	**3.3**	**3.1 to 3.6**	**4.2**	**3.5 to 5.0**
80+	1.3	0.5 to 2.2	2.5	2.0 to 3.0	**4.3**	**3.6 to 5.0**	**4.4**	**2.5 to 6.2**

Abbreviations: HT, hormone therapy; BMI, body mass index; BIRADS, Breast Imaging Reporting and Data System.

*BIRADS density 1 = almost entirely fat (low breast density); 2 = scattered fibroglandular densities (average breast density); 3 = heterogeneously dense (high breast density); 4 = extremely dense (very high breast density).

†Risk estimates come from the partly conditional Cox proportional hazards models assuming interactions between HT use, menopausal status, and breast density using robust sandwich variance estimates to account for multiple mammography estimations per woman adjusting for age category, BMI, BMI2, interactions between BMI and BMI2 with menopausal status (since they were significant $P = .002$ and $P = .017$, respectively), E, E + P, and registry. Interaction terms use a hierarchical algorithm in which all lower order main effects or interactions are included in the model regardless of statistical significance. Risk estimates were calculated for women with a BMI = 25 kg/m^2 (approximate average BMI in population) and average registry (proportions of mammography examinations from each registry).

‡Premenopausal group with n = 3,856 breast cancers; postmenopausal no HT group with n = 5,700 breast cancers; postmenopausal HT group with n = 4,534 breast cancers.

patterns of risk were observed for other age groups with very high breast density except risks were lower among women in their thirties and forties (range, 1.3% to 2.5% across groups) and higher among women in their sixties (range, 3.6% to 5.8% across groups) than among women in their fifties (range, 2.3% to 4.2% across groups). Five-year breast cancer risk was low and the same among women age 55 to 59 years with BIRADS-1 density whether they were postmenopausal estrogen users or estrogen plus progestin users (0.9%; Table 4). Similar low-risk patterns were observed for women in other age groups with BIRADS-1 density (BIRADS-1). Five-year risk was slightly lower among postmenopausal women age 50 to 79 years with BIRADS-2 density that were estrogen users (Table 4) compared to nonusers (Table 3).

Among women diagnosed with breast cancer, premenopausal women who had BIRADS-4 density were more likely to be diagnosed with advanced stage disease (stages IIB, III, or IV) than women with BIRADS-2 density (Table 5) and this pattern was similar among postmenopausal HT users. Postmenopausal non-HT users with BIRADS-3 density were slightly more likely to be diagnosed with advanced-stage disease compared to those with BIRADS-2 density and there was a trend toward non-HT users with BIRADS-4 density to be diagnosed with advanced-stage disease. When we examined only tumors detected by screening mammography (true-positive cancers), the same associations remained as reported in Table 5 (data not shown).

DISCUSSION

We found use of postmenopausal HT, in particular, estrogen plus progestin therapy, is associated with higher breast cancer risk among women with high breast density compared to postmenopausal women with high breast density that do not take HT. Studies have shown postmenopausal estrogen use alone does not result in an increase in breast cancer incidence.[5,19] In our study, estrogen alone was associated with higher breast cancer risk among women with high breast density compared to postmenopausal women with high breast density that did not take HT, but to a lesser extent than estrogen plus progestin therapy, and no increase or a slightly lower breast cancer risk among postmenopausal women with average breast density. We also

Table 4. Association Between Breast Density and Breast Cancer Risk by Type of HT Use Among Postmenopausal Women With Known Hysterectomy Status and 5-Year Breast Cancer Risk After a Screening Mammography Examination Across Age Groups for Women With a BMI of 25 kg/m^2

	BIRADS Breast Density*							
	1		2		3		4	
Variable	5-Year Risk %†	95% CI	5-Year Risk %†	95% CI	5-Year Risk %†	95% CI	5-Year Risk %†	95% CI
Postmenopausal E use‡								
30-45	0.4	0.3 to 0.5	0.7	0.6 to 0.7	1.1	1.0 to 1.2	1.3	1.1 to 1.6
45-49	0.6	0.4 to 0.7	0.9	0.8 to 1.0	1.4	1.3 to 1.6	1.8	1.5 to 2.1
50-54	0.7	0.6 to 0.9	1.2	1.1 to 1.3	1.8	1.7 to 2.0	2.3	1.9 to 2.6
55-59	0.9	0.7 to 1.1	1.5	1.4 to 1.7	2.4	2.3 to 2.6	3.0	2.6 to 3.5
60-64	1.1	0.9 to 1.4	1.9	1.7 to 2.0	2.9	2.7 to 3.2	3.6	3.1 to 4.2
65-69	1.3	1.0 to 1.6	2.1	2.0 to 2.3	3.4	3.1 to 3.6	4.2	3.5 to 4.8
70-79	1.4	1.1 to 1.7	2.3	2.1 to 2.5	3.6	3.4 to 3.9	4.5	3.8 to 5.2
80+	1.3	1.0 to 1.6	2.1	1.9 to 2.3	3.3	3.0 to 3.7	4.1	3.4 to 4.8
Postmenopausal E + P‡								
30-45	0.4	0.3 to 0.5	0.9	0.8 to 1.0	1.4	1.3 to 1.5	1.9	1.6 to 2.1
45-49	0.5	0.4 to 0.7	1.2	1.1 to 1.3	1.9	1.7 to 2.0	2.5	2.2 to 2.8
50-54	0.7	0.5 to 0.9	1.5	1.4 to 1.6	2.4	2.2 to 2.6	3.2	2.8 to 3.5
55-59	0.9	0.7 to 1.1	2.0	1.9 to 2.2	3.2	3.0 to 3.4	4.2	3.7 to 4.6
60-64	1.1	0.8 to 1.4	2.4	2.3 to 2.6	3.8	3.6 to 4.1	5.0	4.5 to 5.6
65-69	1.3	1.0 to 1.6	2.8	2.6 to 3.0	4.4	4.1 to 4.7	5.8	5.1 to 6.4
70-79	1.4	1.0 to 1.7	3.0	2.8 to 3.2	4.7	4.4 to 5.0	6.2	5.5 to 6.9
80+	1.2	0.9 to 1.6	2.8	2.5 to 3.0	4.3	3.9 to 4.7	5.7	5.0 to 6.4

Abbreviations: HT, hormone therapy; BMI, body mass index; BIRADS, Breast Imaging Reporting and Data System; E, estrogen; E + P, estrogen plus progestin.
*BIRADS density 1 = almost entirely fat (low breast density); 2 = scattered fibroglandular densities (average breast density); 3 = heterogeneously dense (high breast density); 4 = extremely dense (very high breast density).
†Risk estimates come from the partly conditional Cox proportional hazards models assuming interactions between HT use, menopausal status, and breast density using robust sandwich variance estimates to account for multiple mammography estimations per woman adjusting for age category, BMI, BMI^2, interactions between BMI and BMI^2 with menopausal status (since they were significant $P = .002$ and $P = .017$, respectively), E, E + P, and registry. Interaction terms use a hierarchical algorithm in which all lower order main effects or interactions are included in the model regardless of statistical significance. Risk estimates were calculated for women with a BMI = 25 kg/m^2 (approximate average BMI in population) and average registry (proportions of mammography examinations from each registry).
‡E group with n = 977 breast cancers and E + P group with n = 1,438 breast cancers.

found premenopausal women age 50 to 54 years with high breast density were at higher risk of breast cancer and advanced cancer similar to postmenopausal HT users with high breast density of similar age. Low breast density is associated with a low risk of breast cancer for premenopausal and postmenopausal women of all ages regardless of HT use.

The mechanism(s) responsible for high breast density and HT's influence to increase breast cancer risk are unknown. HT use among postmenopausal women, in particular estrogen plus a progestin,[20] could slow the normal process of breast involution that occurs with aging[21,22] resulting in sustained high breast density and increased breast cancer risk. Alternatively, or in addition to, presence of extensive or high breast densities together with endogenous estrogen and progesterone in premenopausal women and exogenous estrogen and progestin therapy in postmenopausal women may stimulate proliferation of the greater numbers of epithelial and stromal cells in the breast associated with high breast density[23] to promote tumorigenesis and increase breast cancer risk. This hypothesis of an additive influence of hormones and breast density on tumor growth is supported by the observed highest increased risk of advanced disease in premenopausal women and postmenopausal HT users with high breast density.

Taking HT for longer than 1 year has been shown to increase mammographic breast density in approximately 16% to 20% of women,[2,24] with average increases in mammographic density of 3% to 5% over 12 months associated with estrogen and progestin use and 1.6% with estrogen.[2-4,25] A cross-sectional study has examined the influence of HT and breast density on breast cancer risk.[26] Their findings show the relationship of HT and breast cancer risk is not mediated solely by HT increasing breast density, which indirectly supports our hypothesis of an additive influence of HT and breast density on breast cancer risk rather than HT simply increasing breast density to increase breast cancer risk.[26] Findings from the International Breast Cancer Intervention Study I (IBIS-I) also indirectly suggest a role for estrogens in the regulation of breast epithelial and stromal proliferation and promotion of tumorgenesis.[27] The IBIS-I has reported for women on tamoxifen that had a reduction in breast density of 10% or greater, the risk of breast cancer was significantly reduced 52% relative to controls. Women on tamoxifen that had a reduction in breast density of lower than 10% had a small, nonsignificant 8% reduction in breast cancer incidence.[28]

We found women were at low breast cancer risk if they had low breast density, regardless of age, menopausal status, and HT use. This suggests the same factors that lead women to have low breast density, may also lead to a permanent change in breast density structure that lasts throughout life and is not influenced by exogenous factors such as HT. Pregnancy, in particular early age at first birth, early age at menopause, and inheritance of low breast density are all factors that could contribute to a permanent low breast density.[29,30] A recently published risk model based on BIRADS density found women with low breast density rarely had high breast cancer risk, regardless of age,

Table 5. Tumor Stage of Invasive Cancers by BIRADS Density Dependent on Menopausal Status

Variable	No.	%	Tumor Stage*				Analysis Comparing Advance to Early Stage Cancer†	
			I	IIA	IIB	III or IV	OR	95% CI
All women								
No.	10,514		6,262	4,645	1,045	916		
BIRADS‡								
1	664	6.3	68.9	17.5	6.0	7.6	0.74	0.57 to 0.94
2	4,645	44.2	62.6	20.3	8.9	8.1	1.00	
3	4,799	45.6	57.1	23.2	10.8	8.9	1.25	1.11 to 1.40
4	1,075	10.2	51.6	24.1	12.9	11.4	1.60	1.33 to 1.91
Premenopausal								
No.	2,277		1,145	636	310	236		
BIRADS‡								
1	36	1.6	54.5	30.3	6.1	9.1	0.47	0.17 to 1.26
2	636	27.9	50.4	26.0	13.6	10.1	1.00	
3	1,256	55.2	51.4	25.8	13.1	9.8	1.18	0.92 to 1.50
4	503	22.1	47.1	25.1	15.5	12.3	1.71	1.26 to 2.31
Postmenopausal and no HT								
No.	4,980		3,139	2,717	423	412		
BIRADS‡								
1	504	10.1	68.5	17.4	6.2	7.9	0.81	0.61 to 1.08
2	2,717	54.6	65.0	18.9	8.1	8.0	1.00	
3	1,848	37.1	59.3	22.7	9.6	8.5	1.21	1.02 to 1.44
4	251	5.0	58.8	21.8	9.7	9.7	1.32	0.93 to 1.88
Postmenopausal and HT								
No.	3,257		1,978	1,292	312	268		
BIRADS‡								
1	124	3.8	74.6	14.4	5.1	5.9	0.60	0.33 to 1.10
2	1,292	39.7	63.7	20.7	8.5	7.2	1.00	
3	1,695	52.0	59.0	22.0	10.4	8.6	1.37	1.12 to 1.69
4	321	9.9	52.9	24.4	11.4	11.4	1.75	1.27 to 2.42

Abbreviations: BIRADS, Breast Imaging Reporting and Data System; OR, odds ratio; HT, hormone therapy; BMI, body mass index.

*Row percentages.

†Four separate logistic regression models for the binary outcome advanced stage cancer (IIB, III, or IV) versus early stage (I and IIA) adjusted for age, BMI, BMI^2, HT, menopausal status (for All Women model only), and registry. All predictors were measured at the most recent screening examination prior to breast cancer diagnosis.

‡BIRADS density 1 = almost entirely fat (low breast density); 2 = scattered fibroglandular densities (average breast density); 3 = heterogeneously dense (high breast density); 4 = extremely dense (very high breast density).

family history of breast cancer, and history of prior breast biopsy.[31] Our study supports these findings by showing menopausal status and postmenopausal HT use did not result in higher breast cancer risk among women with low breast density. Moreover, women with low breast density were not at higher risk of advanced-stage disease.

Studies have reported the strength of the association between breast density and breast cancer does not vary by menopausal status.[32-34] We extend the literature by examining the strength of the association among postmenopausal women by HT use. We found risk of breast cancer and advanced disease is higher among postmenopausal HT users only if they have high breast density and the strength of the association between breasts density and breast cancer is weaker among postmenopausal non-HT users than among premenopausal women.

This study has several strengths, including the large, population-based study sample and large number of outcomes. We examined the association of breast density and breast cancer separately by menopausal status and among postmenopausal women by HT use. Importantly, we included multiple measurements of breast density and HT use over time, enhancing the statistical power of our study and accounting for the modest proportion of women that can have an increase (20%) or decrease (19%) in BIRADS category within 3 years.[35]

We collected self-reported information on HT use at the time of mammography, lessening the possibility of recall bias, but perhaps leading to some misclassification due to self-report. Any misclassification is likely to have been random, leading to an underestimation of the association between HT use and breast cancer. We inferred women on HT with a uterus were taking estrogen and progestin and women without a uterus were taking estrogen only, consistent with recommended clinical guidelines.[36] We acknowledge there may be some misclassification of HT type. However, the magnitude of enhanced breast cancer risk among estrogen and progestin users compared with nonusers we report is consistent with other studies.[5,11] BIRADS density categories were assigned as part of routine clinical practice. Inter-rater agreement of the BIRADS density measure is moderate.[37,38] Misclassification of BIRADS categories may have influenced our results, so some of the associations we observed could be an under- or overestimation. We report results for normal weight women to better examine the influence of HT and menopause on breast density, thus results may not be generalizable to obese women.

In summary, women with low breast density are at low breast cancer risk regardless of age, menopause status, and HT use. Future research should explore whether women with low breast density are appropriate candidates for less intensive screening strategies. Approximately 50% of postmenopausal women have high or very high breast density, are at high breast cancer risk, and may be considering or using HT.[35] Postmenopausal women with high breast density may want to consider the added risk of breast cancer when deciding on whether to start or stop HT, especially estrogen plus progestin.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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