Race May Not Impact Endocrine Therapy–Related Changes in Breast Density

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ABSTRACT

Background: Reduction in breast density may be a biomarker of endocrine therapy (ET) efficacy. Our objective was to assess the impact of race on ET-related changes in volumetric breast density (VBD).

Methods: This retrospective cohort study assessed longitudinal changes in VBD measures in women with estrogen receptor–positive invasive breast cancer treated with ET. VBD, the ratio of fibroglandular volume (FGV) to breast volume (BV), was measured using Volpara software. Changes in measurements were evaluated using a multivariable linear mixed effects model.

Results: Compared with white women ($n = 191$), black women ($n = 107$) had higher rates of obesity [mean ± SD body mass index (BMI) 34.5 ± 9.1 kg/m^2 vs. 30.6 ± 7.0 kg/m^2, $P < 0.001$] and premenopausal status (32.7% vs. 16.7%, $P = 0.002$). Age- and BMI-adjusted baseline FGV, BV, and VBD were similar between groups. Modeled longitudinal changes were also similar: During a follow-up of 30.7 ± 15.0 months (mean ± SD), FGV decreased over time in premenopausal women (slope = −0.323 cm^3; SE = 0.093; $P = 0.001$), BV increased overall (slope = 2.475 cm^3; SE = 0.483; $P < 0.0001$), and VBD decreased (premenopausal slope = −0.063%, SE = 0.011; postmenopausal slope = −0.016%, SE = 0.004; $P < 0.0001$). Race was not significantly associated with these longitudinal changes, nor did race modify the effect of time on these changes. Higher BMI was associated with lower baseline VBD ($P < 0.0001$). Among premenopausal women, VBD declined more steeply for women with lower BMI (time × BMI, $P = 0.0098$).

Conclusions: Race does not appear to impact ET-related longitudinal changes in VBD.

Impact: Racial disparities in estrogen receptor–positive breast cancer recurrence and mortality may not be explained by differential declines in breast density due to ET.

Introduction

Mammographic breast density is a measure of the relative amounts of radiopaque epithelial and stromal tissue compared with radiolucent adipose tissue (1). Higher baseline breast density is an independent risk factor for breast cancer (2–4), and changes in breast density positively correlate with changes in breast cancer risk (5, 6). Furthermore, reduction in density after breast cancer diagnosis is associated with improved survival (7–10). Longitudinal changes in density may therefore be a surrogate for the effectiveness of risk reductive therapies.

Adjuvant endocrine therapy (ET) is an essential component of multimodality therapy for estrogen receptor (ER)–positive breast cancer. Treatment with selective estrogen receptor modulators (SERM) such as tamoxifen or with aromatase inhibitors (AI) reduces the risk of recurrence and prolongs disease-free survival (11, 12). Mounting evidence supports reduction in breast density as a biomarker for ET efficacy (8–10, 13–16).

Variability in ET efficacy may contribute to differences in outcomes between different patient populations. Even when controlling for clinical variables such as stage and variations in treatment, compared with white women, black women with ER$^+$ breast cancer suffer from higher rates of recurrence and breast cancer–specific mortality (17–22). Because baseline breast density may differ by race (23–25), ET-related changes in breast density—an emerging biomarker of treatment efficacy—may also be affected by race. Although there are several published studies on longitudinal changes in density in white women with ET treatment, the data on longitudinal changes in breast density in black women are sparse with black patients comprising <3% of prior cohorts (8–10, 13–16).

We sought to examine the impact of race on longitudinal changes in volumetric breast density (VBD) in women with ER$^+$ invasive breast cancer treated with ET. Because black women with ER$^+$ breast cancer have poorer outcomes than white women and because steeper longitudinal declines in breast density are associated with improved outcomes, we hypothesized that black women experience less acute declines in density in response to ET.

Materials and Methods

Data sources

We performed a retrospective cohort study of women diagnosed with ER$^+$ invasive breast cancer at our institution. Demographic and clinical characteristics were obtained via our institutional cancer registry and/or independent review of electronic medical records. Raw, for-processing mammographic data necessary for VBD calculations on the contralateral normal breast were obtained from the breast imaging center.

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Cohort selection

The study was restricted to women diagnosed with ER^+ invasive breast cancer between 2009 and 2013 as raw mammographic data were available for these years. Among 1,952 women diagnosed with breast cancer during this time-period, 818 were excluded for reasons stated in Supplementary Fig. S1. ET treatment was determined from institutional cancer registry data and prescription was confirmed via medical record review. In four cases, the exact date of ET initiation was unknown, so the first day of the known month was used. Menopausal status was based on age at diagnosis, with patients over 50 years of age classified as postmenopausal.

Pending availability of mammographic data, 1,134 women (325 black, 809 white) were eligible for inclusion. Mammographic data were individually reviewed to ensure that raw data for the noncancerous breast were available for at least two timepoints: around diagnosis and after ET initiation. Baseline mammogram was defined as a screening or diagnostic mammogram performed within 2 years prior to diagnosis or up to several months postdiagnosis provided that the patient had not yet initiated ET. If multiple mammograms met these criteria for an individual patient, the mammogram closest to the date of diagnosis was utilized. Follow-up mammograms were defined as any screening or diagnostic mammogram performed at least 6 months after diagnosis. Women who did not meet these mammographic criteria were excluded ($n = 836$). A total of 298 women (107 black, 191 white) were included in the study.

Quantitative breast density measurements

Raw mammographic data for the noncancerous breast were processed by Volpara version 1.5.12 (Volpara Health Technologies Limited, Rochester, NY). Volpara is a fully-automated, FDA-cleared, clinically-validated software that utilizes proprietary algorithms to calculate three-dimensional, volume-based density measurements from digital mammograms (26). Calculations are made for each mammographic view on a per-pixel basis and are reported in the following measurements: breast volume (BV) in cubic centimeters (cm^3), fibroglandular volume (FGV) in cm^3, VBD (the ratio of FGV to BV), and breast thickness (BT) in millimeters (26). For each measurement, the mean of the values for the two mammographic views at each timepoint was utilized in our analyses.

Statistical analysis

Continuous variables were summarized overall and by race (black vs. white) by presenting the number of nonmissing observations, mean, SD, median, and 25th and 75th percentiles. Categorical variables were summarized overall and by race by presenting the number of patients and percentage for each category. Continuous variables were compared between race using the standard two-sample t test while categorical variables were compared by Pearson chi-square test or Fisher exact test, where applicable. Missing demographic and baseline data were treated as missing; no method for imputation was utilized.

Observed breast density measurements were graphically displayed using locally weighted scatterplot smoothing (LOWESS) curves with 95% confidence limits (CIs). The LOWESS is a nonparametric regression method that uses local weighted regression to fit a smooth curve through points in a scatter plot (27). The main advantage of this method is that it makes very little assumptions about the form of the relationship between the biomarker and time. Plots were used as a general guideline to assess the functional relationship of breast density measures over time for modeling purposes.

Change in breast density measurements across time were modeled using a linear mixed effects (LME) model with patient included as a random effect (random intercept-slope). When combined with the fixed effects, the random effects describe the mean breast density profile for any woman. The random intercept-slope model postulates that each woman's breast density measurements vary randomly about an underlying linear trajectory, described by an intercept (initial breast density value at baseline) and a single slope (rate of change over time). The random effects are assumed to have a multivariate normal distribution with mean zero and unstructured variance–covariance matrix. This model is flexible in that one need not have the same number of observations per subject and time can be continuous, rather than a fixed set of time points.

Covariates were selected for the following reasons: variable of interest (race), established associations with breast density measurements [body mass index (BMI), age at diagnosis, menopausal status, chemotherapy], and established associations with prognosis (stage, PR status, HER2 status, grade). All covariates were included as fixed effects. Consideration was given to whether chemotherapy, ET, and menopausal status should be included as time-dependent covariates. However, because no woman received chemotherapy or ET at the time of diagnosis or prior to the first breast density measurement, and because the majority of women were either premenopausal or postmenopausal over the entire time course of their breast density measurements, these variables were included as time-independent factors (fixed effects).

Two-way interaction terms were incorporated in each of the LME models to test whether the rates of change in breast density measurements over time (i.e., slope) were differentially affected by race, chemotherapy, or menopausal status. Two-way interactions were evaluated sequentially and simultaneously. If a significant interaction was observed for a specific variable ($P < 0.05$), models were stratified by subgroups of that variable; in the absence of significant effect modification, variables were included as fixed effects. Multicollinearity was assessed using the variance inflation factor (VIF; ref. 28). A variable with a VIF greater than 5 was considered problematic (29). Residual diagnostics were used to assess model fit, including misspecification of the mean response structure. Further analyses were performed by type of ET prescribed (tamoxifen or AI). Analyses were performed using SAS statistical software (v9.4). A P value of less than 0.05 was considered statistically significant.

Results

Description of cohort

Demographic and clinical characteristics are summarized overall and by race in **Table 1**. Compared with white women, black women were younger (mean age at diagnosis 55.8 $\pm$ 10.8 years vs. 62.3 $\pm$ 12.1 years; $P < 0.001$). Relatedly, the black group had a significantly higher proportion of premenopausal patients (32.7% vs. 16.7%; $P = 0.002$) and a higher rate of tamoxifen use (33.6% vs. 13.1%; $P < 0.001$). On average, black women had significantly higher BMI than white women (34.5 $\pm$ 9.3 vs. 30.6 $\pm$ 7.5; $P < 0.001$). BMI remained relatively constant over time on a patient-level basis (Supplementary Fig. S2; $P = 0.727$). There were no significant differences between racial groups with respect to stage, tumor grade, PR status, or HER2 status. However, black women were more likely to receive chemotherapy than whites (49.5% vs. 30.9%; $P = 0.002$).

Figure 1 illustrates the typical timeline of treatment events and mammographic investigations for the average woman in the cohort. The median number of follow-up mammograms was 2 (range 1–6) and the median time from diagnosis to last mammogram was 802 days.

Table 1. Demographic and clinical characteristics of the study population overall and by race.

Variable	Statistic or category	Overall ($N = 298$)	Race		P
			White ($n = 191$[a])	Black ($n = 107$)	
Age at diagnosis (year)	Mean (SD)	59.9 (12.0)	62.3 (12.1)	55.8 (10.8)	<0.001
	Median (IQR)	60.0 (51.3–68.8)	62.9 (53.8–71.2)	54.7 (47.5–64.0)	
Postmenopausal	No	67 (22.4%)	32 (16.7%)	35 (32.7%)	0.002
	Yes	231 (77.5%)	159 (83.3%)	72 (67.3%)	
Body mass index (kg/m^2)[b]	Mean (SD)	32.1 (8.4)	30.6 (7.5)	34.5 (9.3)	<0.001
	Median (IQR)	30.7 (25.9–36.5)	29.1 (25.2–34.3)	33.8 (29.0–38.3)	
Grade	I	54 (18.1%)	34 (17.8%)	20 (18.7%)	0.094
	II	167 (56.0%)	115 (60.2%)	52 (48.6%)	
	III	77 (25.8%)	42 (22.0%)	35 (32.7%)	
PR status	Negative	252 (84.6%)	164 (85.9%)	88 (82.2%)	0.407
	Positive	46 (15.4%)	27 (14.1%)	19 (17.8%)	
HER2 status	Negative	269 (90.3%)	176 (92.2%)	93 (86.9%)	0.157
	Positive	29 (9.7%)	15 (7.8%)	14 (13.1%)	
Stage	I	156 (52.3%)	106 (55.5%)	50 (46.7%)	0.193
	II	104 (34.9%)	66 (34.0%)	39 (36.4%)	
	III/IV	38 (12.7%)	20 (10.5%)	18 (16.8%)	
Endocrine therapy	Tamoxifen	61 (20.5%)	25 (13.1%)	36 (33.6%)	<0.001
	AI	236 (79.5%)	165 (86.8%)	71 (66.4%)	
Chemotherapy	No	186 (62.4%)	132 (69.1%)	54 (50.5%)	0.002
	Yes	112 (37.6%)	59 (30.9%)	53 (49.5%)	

Abbreviations: IQR, Interquartile range; PR, progesterone receptor; SD, standard deviation.
[a]Endocrine therapy type missing for one patient.
[b]BMI at the time of baseline mammogram was not available for 27 patients, but was available at later timepoints in treatment.

Compared with white women, black women initiated ET significantly later after diagnosis (median 168.5 days vs. 95 days; $P = 0.001$).

Observed baseline breast density measurements

LOWESS scatter plots for each observed quantitative breast density measurement are presented in **Fig. 2**. As depicted in the plots, black women had relatively higher BV not only at baseline but also throughout ET treatment, whereas VBD and BT were consistently similar between racial groups. Black women had relatively higher FGV at baseline and for the first several years of ET therapy. Longitudinal trends appeared similar between groups: BV and BT increased over time whereas VBD and FGV decreased over time.

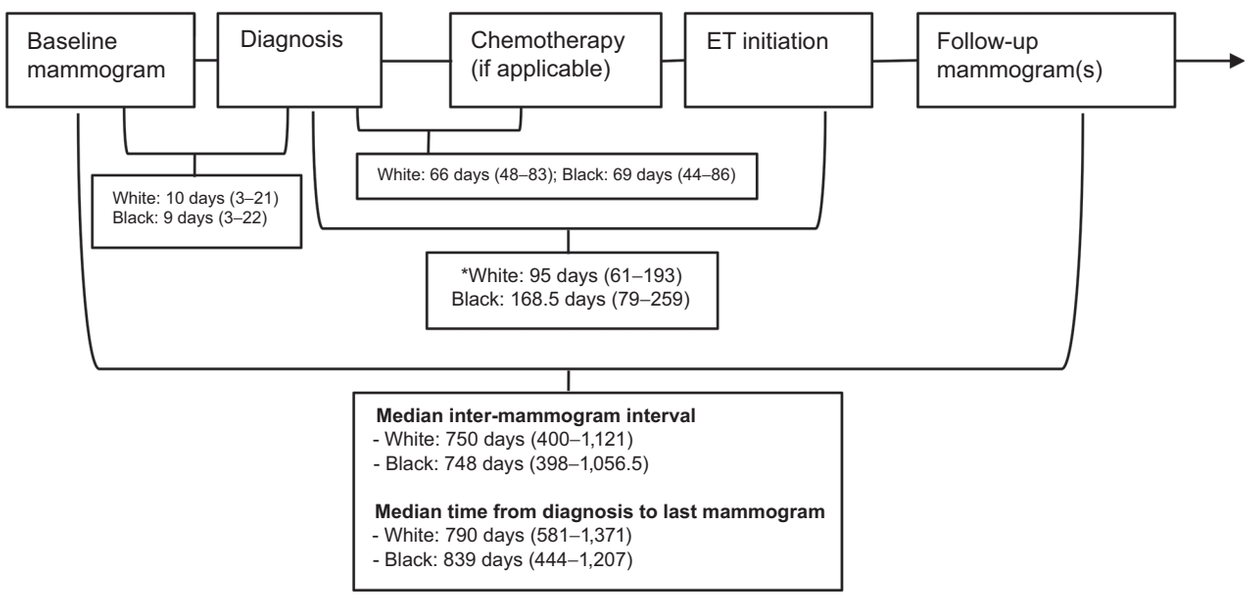

Figure 1.
Timeline of treatment events and mammographic examinations relative to date of diagnosis. Values presented are medians, with interquartile range noted in parentheses. *, Denotes statistical significance.

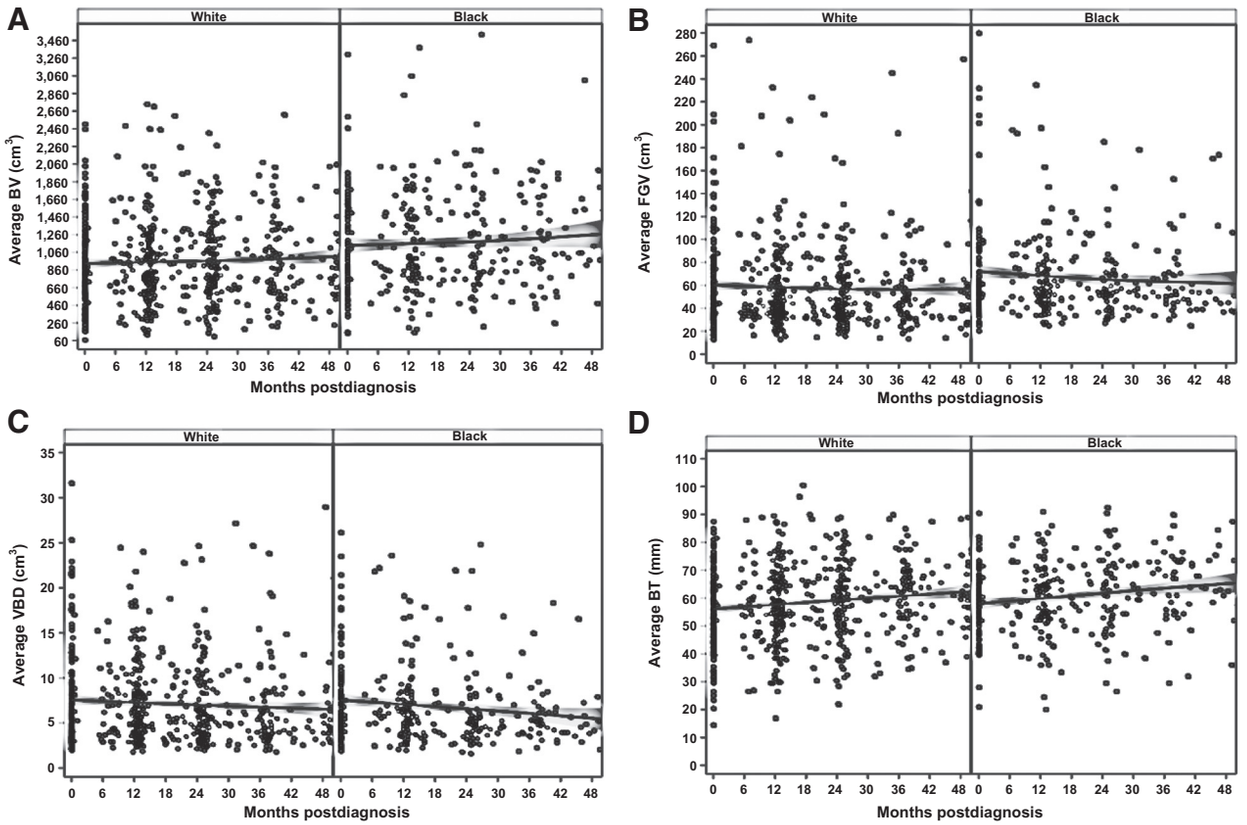

Figure 2.

Scatterplots of observed breast density measurements, by race, for BV (**A**), FGV (**B**), VBD (**C**), and BT (**D**). LOWESS plots are superimposed. Shaded area represents the 95% confidence limits for the predicted LOWESS mean values.

Breast volume

Observed baseline BV was significantly higher among black women than white women (mean 1131 ± 549 cm^3 vs. 944 ± 468 cm^3, $P = 0.003$). However, this did not remain significant after adjustment for age and BMI ($P = 0.082$). Mean age- and BMI-adjusted BV for black women was 1,660 cm^3 (SE = 67 cm^3) compared with 1,570 cm^3 (SE = 66 cm^3) for white women.

Results of the final multivariable linear mixed effects models for BV are shown in **Table 2**. BV significantly increased over time ($P < 0.0001$). The change in BV was not differentially affected by

Table 2. Results of the final multivariable mixed effects model for BV.

Variable[a]	Effect	Estimate	SE	*P*
Time	Per month change	2.475	0.483	<0.0001
Race	African American vs. white	97.811	52.325	0.062
Menopausal status	Postmenopausal vs. premenopausal	−2.280	49.397	0.963
Age at diagnosis	Per year increase	−2.083	2.779	0.454
Stage	II vs. I	11.092	60.729	0.855
	III/IV vs. I	−139.300	88.661	0.117
PR status	Positive vs. negative	42.703	66.890	0.524
HER2 status	Positive vs. negative	5.093	88.830	0.954
Grade	II vs. I	−90.698	65.663	0.168
	III vs. I	−118.540	83.266	0.155
Chemotherapy	Yes vs. no	2.309	73.954	0.975
BMI	Per kg/m^2 increase	35.753	3.032	<0.0001
Endocrine therapy	Tamoxifen vs. AI	−107.540	79.774	0.178

Abbreviation: PR, progesterone receptor.

[a]Two-way interaction results: time*chemotherapy, $P = 0.7773$; time*menopausal status, $P = 0.64036$; time*race, $P = 0.46544$.

Table 3. Results of the final multivariable mixed effects models for FGV.

		Premenopausal			Postmenopausal		
Variable[a]	**Effect**	**Estimate**	**SE**	***P* value**	**Estimate**	**SE**	***P* value**
Time	Per month change	−0.323	0.093	0.001	−0.019	0.035	0.580
Race	African American vs. white	4.071	9.502	0.669	7.918	5.258	0.133
Age at diagnosis	Per year increase	−0.013	0.811	0.987	−0.072	0.283	0.798
Stage	II vs. I	7.083	12.197	0.563	5.042	5.998	0.401
	III/IV vs. I	6.292	15.410	0.684	8.060	9.164	0.380
PR status	Positive vs. negative	−3.122	13.483	0.817	4.209	6.501	0.518
HER2 status	Positive vs. negative	12.301	12.943	0.344	−7.238	9.985	0.469
Grade	II versus I	44.851	18.749	0.019	−5.149	6.000	0.391
	III vs. I	62.363	20.791	0.003	−10.023	7.871	0.204
Chemotherapy	Yes vs. no	−33.837	13.595	0.014	1.438	7.544	0.849
BMI	Per kg/m^2 increase	−0.808	0.633	0.205	0.620	0.289	0.033
Endocrine therapy	Tamoxifen vs. AI	6.469	11.525	0.576	5.540	11.668	0.635

Abbreviation: PR, progesterone receptor.
[a]Two-way interaction results: time*race, $P = 0.8298$ premenopausal, $P = 0.7038$ postmenopausal; time*chemotherapy, $P = 0.4514$ premenopausal, $P = 0.8242$ postmenopausal.

race, chemotherapy, or menopausal status. For white women, the change in BV was 2.52 cm^3 per month (95% CI, 1.54–3.50 cm^3) and for black women, 2.36 cm^3 per month (95% CI, 0.33–4.38 cm^3). Race was not significantly associated with longitudinal changes in BV. Higher BMI was significantly associated with increased BV at baseline ($P < 0.0001$); however, BMI did not affect the change in BV over time (time × BMI: $P = 0.4272$).

Fibroglandular volume

Observed baseline FGV was significantly higher among black women than white women (mean 71.7 ± 45.1 cm^3 vs. 59.5 ± 38.1 cm^3, $P = 0.017$). However, age- and BMI-adjusted baseline FGV was not significantly different between races ($P = 0.103$). Mean adjusted FGV for black women was 77.4 cm^3 (SE = 6.0 cm^3) compared with 69.9 cm^3 (SE = 5.9 cm^3) for white women.

Results of the final multivariable linear mixed effects models for FGV are shown in **Table 3**. Change in FGV over time was differentially affected by menopausal status (time × menopausal status: $P = 0.0036$); therefore, modeling results are presented by pre- and postmenopausal subgroups. Race was not significantly associated with longitudinal changes in FGV for either subgroup.

For postmenopausal women, there was no evidence of a significant change in FGV over time (slope = −0.019 cm^3 per month; $P = 0.580$); nor was the change differentially affected by chemotherapy ($P = 0.8242$) or by race ($P = 0.7038$). For postmenopausal white women, the slope was −0.006 cm^3 per month (95% CI, −0.067–0.055) and for postmenopausal black women, slope was −0.053 cm^3 per month (95% CI, −0.211–0.106). In contrast, FGV significantly decreased over time for premenopausal women (slope −0.32 cm^3 per month; $P < 0.0001$). This decrease was not differentially affected by chemotherapy ($P = 0.4514$) or by race ($P = 0.8298$). For premenopausal white women, FGV decreased by 0.36 cm^3 per month (95% CI, −0.65–0.07) and for premenopausal black women, by 0.28 cm^3 per month (95% CI, −0.51–0.05).

For premenopausal women, grades II and III tumors and chemotherapy were statistically associated with higher FGV at baseline. None of these factors differentially affected change in FGV over time. For postmenopausal women, the only factor significantly associated with higher FGV at baseline was higher BMI ($P = 0.033$); however, change in FGV over time was not differentially affected by BMI (time × BMI: $P = 0.1000$).

Volumetric breast density

Observed baseline VBD was not significantly different between races, either before ($P = 0.833$) or after adjustment for age and BMI ($P = 0.368$). For black women, mean unadjusted VBD was 7.6% ± 4.9% and adjusted VBD was 4.6% (SE = 0.7%). For white women, mean unadjusted VBD was 7.5% ± 5.1% and adjusted VBD was 4.1% (SE = 0.7%).

Results of the final multivariable linear mixed effects models for VBD are shown in **Table 4**. Change in VBD over time was differentially affected by menopausal status (time × menopausal status: $P < 0.0001$); therefore, modeling results are presented by pre- and postmenopausal subgroups. No significant association was observed between race and longitudinal changes in VBD for either subgroup.

VBD significantly decreased over time for both menopausal subgroups ($P < 0.0001$), although the decline was more pronounced in premenopausal women than postmenopausal women (slope = −0.063% per month vs. −0.017% per month, respectively). Neither chemotherapy nor race differentially affected change in VBD over time. For premenopausal women, the rate of change in VBD was −0.074% per month (95% CI, −0.101%–0.047%) for white women and −0.057% per month (95% CI, −0.086%–0.028%) for black women. For postmenopausal women, the rate of change in VBD was −0.019% per month (95% CI, −0.029%–0.009%) for white women and −0.009% per month (95% CI, −0.021%–0.003%) for black women. Higher BMI was significantly associated with lower VBD at baseline for both pre- and postmenopausal subgroups ($P < 0.0001$). In addition, premenopausal women with lower BMI had a steeper decline in VBD compared with women with a higher BMI (time × BMI; $P = 0.0098$).

Breast thickness

Observed baseline BT was not significantly different between races, either before ($P = 0.243$) or after adjustment for age and BMI ($P = 0.305$). For black women, mean unadjusted BT was 57.9 ± 12.1 mm and adjusted BT was 67.3 mm (SE = 1.8 mm). For white women, mean unadjusted BT was 56.0 ± 13.4 and adjusted BT was 68.8 mm (SE = 1.8 mm).

Results of the final multivariable linear mixed effects model for BT are shown in Supplementary Table S1. BT significantly increased over time ($P < 0.0001$); this change was not differentially affected by race, chemotherapy, or menopausal status. For white women, the slope was 0.136 mm per month (95% CI, 0.097–0.175 mm) and for black women,

Table 4. Results of the final multivariable mixed effects models for VBD.

Variable[a]	Effect	Premenopausal			Postmenopausal		
		Estimate	SE	*P*	Estimate	SE	*P*
Time	Per month change	−0.063	0.011	<0.0001	−0.016	0.004	<0.0001
Race	African American vs. white	−0.207	1.023	0.840	0.384	0.580	0.508
Age at diagnosis	Per year increase	0.079	0.087	0.365	−0.019	0.031	0.540
Stage	II vs. I	1.527	1.315	0.248	0.710	0.660	0.283
	III/IV vs. I	3.235	1.654	0.053	1.623	1.011	0.109
PR status	Positive vs. negative	−2.014	1.445	0.166	0.347	0.717	0.629
HER2 status	Positive vs. negative	−1.577	1.394	0.261	−0.657	1.103	0.552
Grade	II vs. I	4.071	2.007	0.045	0.578	0.662	0.384
	III vs. I	7.498	2.226	0.001	0.243	0.868	0.780
Chemotherapy	Yes vs. no	−2.772	1.456	0.060	−0.621	0.832	0.456
BMI	Per kg/m^2 increase	−0.414	0.068	<0.0001	−0.164	0.032	<0.0001
Endocrine therapy	Tamoxifen vs. AI	−0.397	1.246	0.751	1.567	1.282	0.222

Abbreviation: PR, progesterone receptor.
[a]Two-way interaction results: time*race, $P = 0.4390$ premenopausal, $P = 0.2182$ postmenopausal; time*chemotherapy, $P = 0.9439$ premenopausal, $P = 0.5132$ postmenopausal.

0.155 mm per month (95% CI, 0.100–0.210 mm). Higher BMI was significantly associated with increased BT at baseline ($P < 0.0001$). Change in BT over time, however, was not differentially affected by BMI (BMI × time: $P = 0.9881$).

Analyses stratified by ET type

For each breast density measurement, separate analyses were performed for women who were prescribed tamoxifen and for women who were prescribed an AI. Results were consistent with observations from models that included ET type as a covariate. For example, race did not significantly modify the change in BV over time (tamoxifen: $P = 0.2124$; AI: $P = 0.8468$). The change in BV was 3.57 cm^3 per month (SE = 0.87) for patients who were prescribed tamoxifen, and 2.00 cm^3 per month (SE = 0.55) for patients who were prescribed an AI.

Discussion

We observed an overall longitudinal decrease in Volpara-calculated VBD in women treated with ET; this change was not impacted by race. This is the largest study to assess longitudinal changes in breast density in black women treated with ET. Prior cohorts included <3% black women (8–10, 13–16). With black women representing over one-third of our cohort, our study has substantially greater power to detect differences in ET-associated density changes between races.

Among women with ER$^+$ breast cancer, both recurrence rates and cancer-specific mortality are higher for black women than white women (17–22). Although black women often present with adverse prognostic features and have relatively lower rates of ET adherence (30, 31), adjusted analyses suggest that disparities in outcome cannot be fully explained by these factors (17–22). Strong retrospective evidence suggests that density declines in white and Asian women correlate with improved cancer outcomes (8–10, 13–16). If decline in breast density is an accurate biomarker for ET efficacy in women of all races, our observation that black and white women experience similar density declines suggests that differences in outcomes cannot be attributed to race-related variability in ET efficacy. The causes of the disparate outcomes of black women with ER$^+$ breast cancer are likely multifactorial and influenced by factors such as genetics, structural racism, and social determinants of health (32, 33). Our negative results underscore the importance of directing attention to these areas in future disparities research.

Another strength of our study is the use of a robust tool for measuring breast density. Breast density can be assessed qualitatively or quantitatively, through either area-based or volume-based calculations (34). All methodologies generate broadly consistent results (34–37), but automated volumetric measurements such as Volpara demonstrate the least variability and highest reproducibility (38). In addition, Volpara may be superior to other methods in the detection of interracial differences in breast density. As previously reported, baseline breast density among black versus white women may not be apparent by qualitative visual assessment method, but are detectable by quantitative methods (23).

Most prior studies on ET-associated longitudinal changes in breast density utilized either qualitative (14, 15) or area-based quantitative methods (8–10, 13, 16), precluding direct comparisons with our results. Our observations are broadly consistent with those of Engmann and colleagues, who compared longitudinal changes in density in women with ER$^+$ breast cancer treated with ET relative to healthy controls (39). Concordant with our results, menopausal status significantly impacted longitudinal changes in Volpara-calculated VBD. Among women treated with ET with a baseline VBD <10%, they observed an adjusted absolute annual decline in VBD of 0.38% for premenopausal women and 0.03% to 0.07% for postmenopausal women. We observed similar absolute annual declines in VBD of 0.76% and 0.19%, respectively, in a cohort in which over 75% of women had unadjusted baseline VBD <10%. Volpara offers a density grading system that correlates with the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS) Breast Composition Categories, with 7.5% as the cutoff between categories b and c. As the median unadjusted baseline VBD in our cohort was 6.0%, over half of the women had baseline density corresponding to BI-RADS categories a or b. Based on the correlation between Volpara density grade and BI-RADS categories, the magnitude of decline observed in our study is less than that observed previously (15). Ko and colleagues found that among women receiving adjuvant tamoxifen, those whose breast density declined significantly enough to downgrade

them to a lower BI-RADS category had lower rates of recurrence (15); such a downgrade would require an absolute decrease in VBD on the order of 4%, well above our observed declines. It remains to be determined whether less dramatic declines are prognostically meaningful.

Like Engmann and colleagues, we also observed a significant impact of menopausal status on longitudinal changes in Volpara-calculated FGV. Both studies found that FGV remained relatively stable over time among postmenopausal women, with an annual change of -0.23 cm^3 per year in our cohort versus -0.79 or $+0.14$ cm^3 per year among women with baseline VBD <10% treated with tamoxifen or an AI, respectively (39). However, we observed a lesser predicted annual decline in FGV for premenopausal women: 3.88 cm^3 versus 6.38 cm^3 per year for women with VBD <10% (39). Differences in unadjusted baseline FGV, which was relatively higher in our cohort (60–72 cm^3 vs. 47–76 cm^3), may impact the magnitude of the change in FGV over time. In addition, rates of ET adherence may be dissimilar between cohorts. As black women have been reported to have lower rates of ET adherence than white women (30, 31), it is possible that a disproportionately greater proportion of the women in our cohort had shallower declines in density due to noninitiation and/or shorter duration of ET.

Our observation that BMI significantly impacts ET-associated longitudinal changes in breast density is unique. Although several prior studies controlled for BMI (8, 14, 39), only one specifically examined the relationship between BMI and ET-related density changes (9). Nyante and colleagues found no significant association between BMI and longitudinal changes in percent density in women treated with tamoxifen (9). In contrast, we observed a significant association between higher BMI and longitudinal declines in VBD among premenopausal women, which appears to be primarily driven by concomitant longitudinal increases in BV. Our cohorts had notable differences in baseline BMI, with both a higher mean and wider range in our study. Because BMI has an inverse relationship with baseline breast density (4) and women with higher baseline breast density have greater ET-associated density declines (8–10, 14–16), it is unclear why a significant association between BMI and longitudinal density reduction was not observed in Nyante's cohort, which had a comparatively lower baseline BMI. Methodologic differences may also contribute to our discordant findings. Area-based measures, such as those used by Nyante and colleagues, and volumetric measures may capture distinct aspects of breast density (40–42).

Chemotherapy has been shown to reduce breast density in several studies, perhaps through mechanisms related to induction of menopause (43, 44). In our cohort, both rates of premenopausal status and chemotherapy receipt were higher among black women. However, no difference in longitudinal FGV changes was observed in multivariable analyses that controlled for race and other variables. It should be noted that it is difficult to disentangle the effects of chemotherapy from the effects of ET, as in clinical practice follow-up mammograms are not routinely obtained after chemotherapy completion and ET initiation. Therefore, changes in density measurements observed between the baseline mammogram and first follow-up mammogram may be impacted by not only ET-related changes but also chemotherapy-related changes. A prospective study of longitudinal changes in density in which subjects undergo mammography after completion of chemotherapy and before ET initiation would allow for more accurate determinations of longitudinal changes in breast density measurements due to each individual therapy.

Our data add to the current knowledge about race-related differences in baseline breast density measurements. Only one prior study has reported volumetric baseline measurements in black women (23). McCarthy and colleagues used Quantra software to analyze screening mammograms of healthy black and white women with no history of breast cancer. Although we observed no significant differences in age- and BMI-adjusted baseline FGV and VBD between races, they observed significantly higher FGV among black women with BMI ≥ 30 kg/m^2 and significantly higher VBD among black women overall when adjusting for the same variables. Algorithmic differences between Quantra and Volpara may affect our contrasting results. In addition, differences between healthy women and women with breast cancer may contribute, as women with breast cancer have relatively higher baseline Volpara-calculated VBD compared with healthy controls (45). On the other hand, black women had lower baseline breast density than their white counterparts in studies that utilized qualitative assessments according to the BI-RADS Breast Composition Categories (24, 25). Further studies are needed to clarify the association between race and baseline VBD measures among both healthy women and women with breast cancer; simultaneous evaluation of breast density by multiple software programs may be particularly informative.

Our data are subject to several limitations, including those inherent to retrospective analyses such as missing data and selection bias. Rates of patient exclusion due to lack of sufficient raw mammographic data differed by race, and it is unknown whether this had an impact on our results. Although we were able to control for BMI and chemotherapy, we were unable to account for other factors which may affect density such as parity and hormone replacement therapy use (4). As previously mentioned, we were also unable to verify compliance with ET. It is therefore possible that some women discontinued therapy prior to their follow-up mammogram, which would bias our results towards not observing an effect.

In addition, the menopausal status of an individual patient may have changed during the course of the study. Although we stratified analyses by premenopausal and postmenopausal subgroups in cases of significant interaction between menopausal status and time, it is possible that some women who were premenopausal at diagnosis converted to postmenopausal status over the course of treatment. In women without breast cancer, FGV declines across the perimenopausal transition, with steeper declines observed among women with higher baseline density (46). Whether similar trends occur in women receiving ET is unknown.

Given the complex interactions between race, BMI, menopausal status, and other factors with baseline breast density, validation of our results through prospective studies is warranted. A case–control design would enable robust analyses and improve our understanding of the impact of race, if any, on longitudinal changes in breast density. Prospective studies should also enable determination of whether ET-associated declines in density correlate with improved outcomes in women of all races. As we gain a deeper understanding of this complex biomarker of ET efficacy, careful attention should be paid to ensuring that ET algorithms are applicable to a diverse population.

In summary, race does not appear to impact ET-related longitudinal changes in VBD, and racial disparities in ER^+ breast cancer recurrence and mortality may not be explained by differential declines in breast density due to ET.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H.M. Johnson, H. Shivalingappa, W. Irish, J.H. Wong, K. Verbanac, N.A. Vohra
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References

1. Li T, Sun L, Miller N, Nicklee T, Woo J, Hulse-Smith L, et al. The association of measured breast tissue characteristics with mammographic density and other risk factors for breast cancer. Cancer Epidemiol Biomarkers Prev 2005; 14:343–9.
2. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2006;15:1159–69.
3. Vachon CM, van Gils CH, Sellers TA, Ghosh K, Pruthi S, Brandt KR, et al. Mammographic density, breast cancer risk and risk prediction. Breast Cancer Res 2007;9:217.
4. Huo CW, Chew GL, Britt KL, Ingman WV, Henderson MA, Hopper JL, et al. Mammographic density-a review on the current understanding of its association with breast cancer. Breast Cancer Res Treat 2014;144:479–502.
5. Kerlikowske K, Ichikawa L, Miglioretti DL, Buist DSM, Vacek PM, Smith-Bindman R, et al. Longitudinal measurement of clinical mammographic breast density to improve estimation of breast cancer risk. J Natl Cancer Inst 2007;99: 386–95.
6. Byrne C, Ursin G, Martin CF, Peck JD, Cole EB, Zeng D, et al. Mammographic density change with estrogen and progestin therapy and breast cancer risk. J Natl Cancer Inst 2017;109. doi: 10.1093/jnci/djx001.
7. Andersson TM, Crowther MJ, Czene K, Hall P, Humphreys K. Mammographic density reduction as a prognostic marker for postmenopausal breast cancer: results using a joint longitudinal-survival modeling approach. Am J Epidemiol 2017;186:1065–73.
8. Li J, Humphreys K, Eriksson L, Edgren G, Czene K, Hall P. Mammographic density reduction is a prognostic marker of response to adjuvant tamoxifen therapy in postmenopausal patients with breast cancer. J Clin Oncol 2013;31: 2249–56.
9. Nyante SJ, Sherman ME, Pfeiffer RM, Berrington de Gonzalez A, Brinton LA, Aiello Bowles EJ, et al. Prognostic significance of mammographic density change after initiation of tamoxifen for ER-positive breast cancer. J Natl Cancer Inst 2015;107. doi: 10.1093/jnci/dju425.
10. Nyante SJ, Sherman ME, Pfeiffer RM, de Gonzalez AB, Brinton LA, Bowles EJA, et al. Longitudinal change in mammographic density among ER-positive breast cancer patients using tamoxifen. Cancer Epidemiol Biomarkers Prev 2016;25: 212–6.
11. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, Gray R, Clarke M, Cutter D, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011;378:771–84.
12. Early Breast Cancer Trialists' Collaborative Group. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015;386:1341–52.
13. Mullooly M, Pfeiffer RM, Nyante SJ, Heckman-Stoddard BM, Perloff M, Jatoi I, et al. Mammographic density as a biosensor of tamoxifen effectiveness in adjuvant endocrine treatment of breast cancer: opportunities and implications. J Clin Oncol 2016;34:2093–7.
14. Cuzick J, Warwick J, Pinney E, Duffy SW, Cawthorn S, Howell A, et al. Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. J Natl Cancer Inst 2011;103:744–52.
15. Ko KL, Shin IS, You JY, Jung SY, Ro J, Lee ES. Adjuvant tamoxifen-induced mammographic breast density reduction as a predictor for recurrence in estrogen receptor-positive premenopausal breast cancer patients. Breast Cancer Res Treat 2013;142:559–67.
16. Kim J, Han W, Moon HG, Ahn SK, Shin H-C, You J-M, et al. Breast density change as a predictive surrogate for response to adjuvant endocrine therapy in hormone receptor positive breast cancer. Breast Cancer Res 2012;14:R102.
17. Arciero CA, Yang J, Peng L, Ward KC, O'Regan R, Sahin AA, et al. African American patients with breast cancer have worse prognosis than white patients in certain subtypes and stages. Breast Cancer Res Treat 2017;166:743–55.
18. Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA. Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States. JAMA 2015;313:165–73.
19. O'Brien KM, Cole SR, Tse CK, Perou CM, Carey LA, Foulkes WD, et al. Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study. Clin Cancer Res 2010;16:6100–10.
20. Rauscher GH, Silva A, Pauls H, Frasor J, Bonini MG, Hoskins K. Racial disparity in survival from estrogen and progesterone receptor-positive breast cancer: implications for reducing breast cancer mortality disparities. Breast Cancer Res Treat 2017;163:321–30.
21. Wright JL, Reis IM, Zhao W, Panoff JE, Takita C, Sujoy V, et al. Racial disparity in estrogen receptor positive breast cancer patients receiving trimodality therapy. Breast 2012;21:276–83.
22. Warner ET, Tamimi RM, Hughes ME, Ottesen RA, Wong YN, Edge SB, et al. Racial and ethnic differences in breast cancer survival: mediating effect of tumor characteristics and sociodemographic and treatment factors. J Clin Oncol 2015; 33:2254–61.
23. McCarthy AM, Keller BM, Pantalone LM, Hsieh MK, Synnestvedt M, Conant EF, et al. Racial differences in quantitative measures of area and volumetric breast density. J Natl Cancer Inst 2016;108. doi: 10.1093/jnci/djw104.
24. Razzaghi H, Troester MA, Gierach GL, Olshan AF, Yankaskas BC, Millikan RC. Mammographic density and breast cancer risk in White and African American Women. Breast Cancer Res Treat 2012;135:571–80.
25. del Carmen MG, Hughes KS, Halpern E, Rafferty E, Kopans D, Parisky YR, et al. Racial differences in mammographic breast density. Cancer 2003;98:590–6.
26. Highnam R, Brady SM, Yaffe MJ, Karssemeijer N, Harvey J. Robust breast composition measurement - Volpara. In: Marti J, Oliver A, Freixenet J, Marti R, editors. Digital mammography. IWDM 2010. Lecture notes in computer science, vol. 6136. Berlin, Heidelberg: Springer; 2010. p. 342–49.
27. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc 1979;74:829–36.
28. Cheng J, Edwards LJ, Maldonado-Molina MM, Komro KA, Muller KE. Real longitudinal data analysis for real people: building a good enough mixed model. Stat Med 2010;29:504–20.
29. Sheather SJ. A modern approach to regression with R. New York, NY: Springer; 2009.
30. Roberts MC, Wheeler SB, Reeder-Hayes K. Racial/Ethnic and socioeconomic disparities in endocrine therapy adherence in breast cancer: a systematic review. Am J Public Health 2015;105:e4–e15.
31. Wheeler SB, Spencer J, Pinheiro LC, Murphy CC, Earp JA, Carey L, et al. Endocrine therapy nonadherence and discontinuation in black and white women. J Natl Cancer Inst 2019;111:498–508.
32. Newman LA, Mason J, Cote D, Vin Y, Carolin K, Bouwman D, et al. African-American ethnicity, socioeconomic status, and breast cancer survival: a meta-analysis of 14 studies involving over 10,000 African-American and 40,000 White American patients with carcinoma of the breast. Cancer 2002;94: 2844–54.

33. Pallok K, De Maio F, Ansell DA. Structural racism - a 60-year-old black woman with breast cancer. N Engl J Med 2019;380:1489–93.
34. Jeffers AM, Sieh W, Lipson JA, Rothstein JH, McGuire V, Whittemore AS, et al. Breast cancer risk and mammographic density assessed with semiautomated and fully automated methods and BI-RADS. Radiology 2017;282:348–55.
35. Brandt KR, Scott CG, Ma L, Mahmoudzadeh AP, Jensen MR, Whaley DH, et al. Comparison of clinical and automated breast density measurements: implications for risk prediction and supplemental screening. Radiology 2016; 279:710–9.
36. Eng A, Gallant Z, Shepherd J, McCormack V, Li J, Dowsett M, et al. Digital mammographic density and breast cancer risk: a case-control study of six alternative density assessment methods. Breast Cancer Res 2014;16:439.
37. Astley SM, Harkness EF, Sergeant JC, Warwick J, Stavrinos P, Warren R, et al. A comparison of five methods of measuring mammographic density: a case-control study. Breast Cancer Res 2018;20:10.
38. Alonzo-Proulx O, Mawdsley GE, Patrie JT, Yaffe MJ, Harvey JA. Reliability of automated breast density measurements. Radiology 2015;275:366–76.
39. Engmann NJ, Scott CG, Jensen MR, Ma L, Brandt KR, Mahmoudzadeh AP, et al. Longitudinal changes in volumetric breast density with tamoxifen and aromatase inhibitors. Cancer Epidemiol Biomarkers Prev 2017;26:930–7.
40. Brand JS, Czene K, Shepherd JA, Leifland K, Heddson B, Sundbom A, et al. Automated measurement of volumetric mammographic density: a tool for widespread breast cancer risk assessment. Cancer Epidemiol Biomarkers Prev 2014;23:1764–72.
41. Cheddad A, Czene K, Eriksson M, Li J, Easton D, Hall P, et al. Area and volumetric density estimation in processed full-field digital mammograms for risk assessment of breast cancer. PLoS One 2014;9:e110690.
42. Lokate M, Kallenberg MG, Karssemeijer N, Van den Bosch MA, Peeters PH, Van Gils CH. Volumetric breast density from full-field digital mammograms and its association with breast cancer risk factors: a comparison with a threshold method. Cancer Epidemiol Biomarkers Prev 2010;19:3096–105.
43. Knight JA, Blackmore KM, Fan J, Malone KE, John EM, Lynch CF, et al. The association of mammographic density with risk of contralateral breast cancer and change in density with treatment in the WECARE study. Breast Cancer Res 2018;20:23.
44. Eriksson L, He W, Eriksson M, Humphreys K, Bergh J, Hall P, et al. Adjuvant therapy and mammographic density changes in women with breast cancer. JNCI Cancer Spectr 2018;2:pky071.
45. Engmann NJ, Scott CG, Jensen MR, Winham S, Miglioretti DL, Ma L, et al. Combined effect of volumetric breast density and body mass index on breast cancer risk. Breast Cancer Res Treat 2019;177:165–73.
46. Engmann NJ, Scott C, Jensen MR, Winham SJ, Ma L, Brandt KR, et al. Longitudinal changes in volumetric breast density in healthy women across the menopausal transition. Cancer Epidemiol Biomarkers Prev 2019;28: 1324–30.