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ARTICLE

Hormone Replacement Therapy and Breast Cancer: Heterogeneous Risks by Race, Weight, and Breast Density

Ningqi Hou, Susan Hong, Wenli Wang, Olufunmilayo I. Olopade, James J. Dignam, Dezheng Huo

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Correspondence to: Dezheng Huo, MD, PhD, University of Chicago, Health Studies, 5841 S. Maryland Ave, MC 2007, Chicago, IL 60637 (e-mail: dhuo@uchicago.edu).

Background Although studies have demonstrated a positive association between hormone replacement therapy (HRT) and breast cancer risk, this association may vary by patient factors.

Methods We analyzed 1 642 824 screening mammograms with 9300 breast cancer cases in postmenopausal women aged 45 years or older derived from the Breast Cancer Surveillance Consortium, a longitudinal registry of mammography screening in the United States. Multiple imputation methods were used to accommodate missing data for HRT use (14%) and other covariables. We performed logistic regression to estimate odds ratios (ORs) for breast cancer associated with HRT use within strata of race/ethnicity, age, body mass index (BMI), and breast density, with two-way interaction terms between HRT use and each key covariable of interest. *P* values for assessing possible interactions were computed from Wald *z* statistics. All statistical tests were two-sided.

Results HRT use was associated with greater than 20% increased risk in white (OR = 1.21; 95% CI = 1.14 to 1.28), Asian (OR = 1.58; 95% CI = 1.18 to 2.11), and Hispanic women (OR = 1.35; 95% CI = 1.09 to 1.67) but not black women (OR = 0.91; 95% CI = 0.72 to 1.14; $P_{interaction}$ = .04). In women with low/normal BMI and extremely dense breasts, HRT use was associated with the highest breast cancer risk (OR = 1.49; 95% CI = 1.21 to 1.83), compared with nonusers. In overweight/obese women with less-dense breasts, no excess risk was associated with HRT use (adjusted ORs = 0.96 to 1.03).

Conclusions The impact of HRT use on breast cancer risk varies according to race/ethnicity, BMI, and breast density. This risk stratification could help in advising HRT use for the relief of menopausal symptoms.

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Although estrogen is the most effective treatment available for the relief of menopausal symptoms (1), multiple observational studies have shown an increase in breast cancer risk with hormone replacement therapy (HRT) use (2–4). The Women's Health Initiative (WHI) study showed a 24% increase in invasive breast cancer risk with the use of estrogen–progestin therapy (5). After the initial WHI publication in 2002, HRT prescriptions in the United States decreased by 38% in 2003 (6). Although other explanations cannot be entirely ruled out, the concurrent decrease in breast cancer incidence in women aged 50 years and older between 2002 and 2003 has been attributed to the reduced use of HRT since July 2002 (7–11). Despite this, it is unclear whether the increase in breast cancer risk with HRT use is seen in all women. Some women may receive considerable benefit with little harm (12). Thus a better understanding of the differential risks associated with HRT use is needed to better assess each individual's risk vs benefit (13).

The risk of breast cancer with HRT use may vary with age or timing of therapy initiation. Studies have shown breast cancer risk is greater if therapy is initiated around the time of menopause (14–16). Breast density is a strong and independent risk factor for breast cancer. Women with high breast density are at higher breast cancer risk regardless of HRT use (17). Moreover, the association of breast cancer with HRT use is stronger for leaner compared with heavier women (18). The effect of HRT in black women is limited and inconsistent. Although the WHI trial (6.8% black) found no interaction by race (5), the Black Women's Health Study reported no association for less than 10 years of HRT use and an increase in risk for 10 or more years of use (18). The biracial Carolina Breast Cancer Study found HRT use was not associated with breast cancer in black women aged 20 to 49 years and protective for women aged 50 to 74 years (19). Considering the substantial heterogeneity in breast cancer risk among HRT users, accurately assessing an individual's risk could help clinicians evaluate the risk vs benefit of treating menopausal symptoms with HRT (20). To date, few studies have examined the interactions of age, race, body mass index (BMI), and breast density together on HRT and breast cancer risk.

We used data from the National Cancer Institute's Breast Cancer Surveillance Consortium (BCSC), consisting of 1 642 824 screening mammograms and 9300 breast cancer cases to investigate whether low- and high-risk groups could be identified.

Methods

The BCSC was established in 1994 and collected participant characteristics at the time of each mammography screening exam and confirmed cancer outcomes for all women. Details of the data collection and confidentiality procedures of BCSC are described elsewhere (21). Each mammography registry had institutional review board approval, and all registries have strict procedures for deidentification of patient information and protection of confidentiality (22). Main variables of interest included age group, mammographic breast density, race/ethnicity, BMI, HRT use, and diagnosis of cancer. Breast density was collected from the technologist and radiologist at the time of mammography (23). We used the publicly available dataset that Barlow et al. aggregated and deidentified (24), which included women aged 35 to 84 years who underwent screening mammography between 1996 and 2002 from seven community-based registries: Colorado; New Hampshire; New Mexico; North Carolina; San Francisco, California; Vermont; and Washington.

Breast cancer case subjects were identified by linking mammography registries to cancer registries or pathology data. Diagnoses of invasive cancers and ductal carcinoma in situ (DCIS) within 1 year of the screening mammogram were recorded. A 1-year interval was used because women were encouraged to be screened every 1 to 2 years and the observation period was truncated by a new screening examination. HRT was recorded as currently using or not using. Although HRT use may be longer than 1 year, duration of HRT use was not available. There were a total of 2 392 998 eligible screening mammograms for women without a prior history of breast cancer who had undergone a mammogram within the preceding 5 years. We included only postmenopausal women (aged ≥55 years or aged 45–54 years who reported the absence of menses for at least 1 year, either surgical or natural) in this analysis.

Statistical Analysis

In the BCSC dataset, HRT information was available for 86% of women with screening mammograms. A number of other key variables were also missing. In statistical modeling, a large portion of missing data can be a major source of bias, in addition to causing reduced precision. Multiple imputation is becoming a common approach to account for the missing values of all covariables (25,26). We employed the imputation by chained equation program developed by Royston and colleagues, which is based on each conditional density of a variable given all other variables (27). Advantages of imputation by chained equation include 1) no multivariable joint distribution assumption (and specifically no normality assumption), 2) the allowing of different types of variables to be imputed together, and 3) the ability to use different kinds of weights. A probabilistic rule based on regression models for each covariable with the other covariables serving as predictors was used to impute possible values for individual missing covariable values. For binary variables such as HRT use, we used logistic regression; for categorical variables such as race, we used multinomial logistic regression; and for ordinal categorical variables such as BMI and breast density, we used ordinal logistic regression. This process was repeated to randomly produce multiple complete datasets (n = 20), which were then analyzed in standard fashion, followed by application of the Rubin's rule to combine the parameter estimates from each analysis and compute appropriate standard errors (28). As in the analytical models described below, interaction terms were taken into consideration during the imputation phase by including all the necessary interaction terms in the imputation model. The observed distribution of variables with missing data was compared with that after the imputation.

With the original dataset before imputation, we summarized the distribution of demographic characteristics, breast cancer incidences, and proportion of missing values, stratified by HRT use. Using the imputed datasets, crude and multiple logistic regressions were performed to estimate the association between breast cancer risk and HRT use. Two-way interaction terms between HRT use and each of the key covariables of interest (age, race/ethnicity, BMI, and breast density) were included in the model. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for each subgroup were obtained by model stratification. *P* values for assessing possible interactions were computed from Wald *z* statistics, for which order of categories was taken into consideration for the ordinal BMI and breast density. Because leaner women tend to have denser breasts, we included both the HRT-by-BMI and HRT-by–breast density interaction terms in the same model to assess if the heterogeneity effect is confounded between BMI and breast density. All statistical tests were two-sided. A *P* value of less than .05 was considered statistically significant.

Complete Case Analysis and Sensitivity Analyses

As a benchmark, we restricted the analysis to complete cases in the original dataset before imputation. Furthermore, we conducted sensitivity analyses to examine whether results remain under mechanism of not missing at random. Because BMI has the highest proportion of missing values and known possibility of underreporting among overweight or obese women, we focused the sensitivity analyses on BMI. Specifically, we randomly simulated BMI values 20 times for patients with missing BMI under a multinomial distribution toward higher BMI (35.0% normal weight, 25.0% overweight, 22.0% obese I, and 18.0% obese II). This is equivalent to assuming that women with missing BMI have 1.9-fold higher odds of being in overweight or obese BMI categories in an ordinal logistic model.

Of the 2 362 998 screening mammograms included in the original breast cancer risk model (24), we included 1 642 824 (68.7%) from postmenopausal women aged 45 years or older in the analysis. The racial/ethnic composition was 62.7% non-Hispanic white, 4.8% non-Hispanic black, 3.2% Asian/Pacific Islander, 6.3% Hispanic, 1.2% other or mixed racial/ethnic background, and 21.9% unknown.

Among the postmenopausal women, 44.4% of them reported being HRT users, 41.6% reported being HRT nonusers, and 14.0% were unknown. Using the original (ie, without imputation) data, Table 1 shows breast cancer incidence by patient characteristics, stratified by HRT use. More than half (52.7%) of the mammograms were performed among patients aged 50 to 65 years. Overall, HRT users had a higher incidence of breast cancer compared with nonusers (5.78 vs 5.46 per 1000). The incidence rates differed by patients' characteristics, particularly by BMI and breast density. Among HRT users, women with higher BMI had lower

Table 1. Postmenopausal breast cancer incidence rates by selected characteristics and hormone replacement therapy use*

	HRT users			HRT nonusers			Unknown HRT use		
Characteristic	**No. (%)**	**Cases**	**Rate (95% CI)†**	**No. (%)**	**Cases**	**Rate (95% CI)†**	**No. (%)**	**Cases**	**Rate (95% CI)†**
Age, y									
45–49	72 347 (10.6%)	197	2.72 (2.34 to 3.10)	45 587 (6.3%)	141	3.09 (2.58 to 3.60)	8834 (3.8%)	23	2.60 (1.54 to 3.67)
50–54	162 930 (23.8%)	659	4.04 (3.74 to 4.35)	86 389 (11.9%)	296	3.42 (3.04 to 3.82)	19 336 (8.4%)	67	3.47 (2.64 to 4.29)
55–59	157 028 (23.0%)	945	6.02 (5.64 to 6.40)	124 741 (17.1%)	654	4.52 (4.15 to 4.89)	52 363 (22.7%)	286	5.46 (4.83 to 6.09)
60–64	110 409 (16.2%)	753	6.82 (6.33 to 7.31)	110 863 (15.2%)	582	5.25 (4.82 to 5.68)	42 249 (18.4%)	241	5.70 (4.83 to 6.09)
65–69	79 196 (11.6%)	564	7.12 (6.54 to 7.31)	114 636 (15.7%)	671	5.85 (5.41 to 6.29)	38 072 (16.5%)	232	6.09 (5.31 to 6.88)
70–75	56 042 (8.2%)	449	8.01 (7.27 to 8.75)	113 304 (15.5%)	754	6.65 (6.18 to 7.13)	33 760 (14.7%)	217	6.43 (5.58 to 7.28)
75–79	32 976 (4.8%)	262	7.95 (6.99 to 8.90)	87 955 (12.1%)	634	7.21 (6.65 to 7.77)	24 171 (10.5%)	193	7.98 (6.86 to 9.11)
80–84	12 422 (1.8%)	121	9.74 (8.01 to 11.5)	45 721 (6.3%)	343	7.50 (6.71 to 8.29)	11 493 (7.8%)	106	9.22 (7.48 to 11.0)
Race/ethnicity									
Non-Hispanic white	468 059 (68.5%)	2851	6.09 (5.87 to 6.31)	444 141 (60.9%)	2546	5.73 (5.51 to 5.95)	117 671 (51.0%)	757	6.43 (5.98 to 6.89)
Non-Hispanic black	21 836 (3.2%)	95	4.35 (3.48 to 5.22)	50 071 (6.9%)	307	6.13 (5.44 to 6.82)	6571 (2.9%)	41	6.24 (4.34 to 8.14)
Asian/Pacific Islander	17 291 (2.5%)	112	6.48 (5.28 to 7.67)	29 477 (4.0%)	122	4.14 (3.41 to 4.87)	5789 (2.5%)	27	4.66 (2.91 to 6.42)
Hispanic	42 623 (6.2%)	195	4.58 (3.93 to 5.22)	47 360 (6.5%)	171	3.61 (3.07 to 4.15)	13 699 (6.0%)	73	5.33 (4.11 to 6.55)
Other/mixed	5990 (0.9%)	29	4.84 (3.08 to 6.60)	8975 (1.2%)	41	4.57 (3.17 to 5.96)	3975 (1.7%)	15	3.78 (1.87 to 5.68)
Unknown	127 551 (18.7%)	668	5.24 (4.84 to 5.63)	149 172 (20.5)	798	5.35 (4.98 to 5.72)	82 573 (35.9%)	452	5.47 (4.98 to 5.98)
Body mass index									
<25 kg/m^2	157 295 (23.0%)	976	6.20 (5.82 to 6.59)	146 881 (20.1%)	679	4.62 (4.28 to 4.97)	28 079 (12.2%)	209	7.44 (6.44 to 8.45)
25–29.99 kg/m^2	103 375 (15.1%)	608	5.89 (5.42 to 6.35)	115 053 (15.8%)	663	5.76 (5.33 to 6.20)	18 850 (8.2%)	137	7.27 (6.06 to 8.48)
30–34.99 kg/m^2	43 250 (6.3%)	239	5.53 (4.83 to 6.22)	54 759 (7.5%)	350	6.39 (5.72 to 7.06)	7589 (3.3%)	54	7.12 (5.22 to 9.01)
≥35 kg/m^2	21 150 (3.1%)	125	5.91 (4.88 to 6.94)	29 504 (4.1%)	187	6.34 (5.43 to 7.24)	3344 (1.5%)	22	6.58 (3.84 to 9.32)
Unknown	358 280 (52.4%)	2002	5.59 (5.34 to 5.83)	382 999 (52.5%)	2106	5.50 (5.26 to 5.73)	172 416 (74.9%)	943	5.47 (5.12 to 5.82)
Breast density									
Almost entirely fat	36 522 (5.3%)	63	1.73 (1.30 to 2.15)	71 013 (9.7%)	199	2.80 (2.41 to 3.19)	16 942 (7.4%)	44	2.60 (1.83 to 3.36)
Scattered fibroglandualar densities	226 175 (33.1%)	996	4.40 (4.13 to 4.68)	302 745 (41.5%)	1571	5.19 (4.93 to 5.45)	68 439 (29.7%)	390	5.70 (5.13 to 6.26)
Heterogeneously dense	211 285 (30.9%)	1429	6.76 (6.41 to 7.11)	179 651 (24.6%)	1147	6.38 (6.02 to 6.75)	42 122 (18.3%)	308	7.31 (6.50 to 8.13)
Extremely dense	35 726 (5.2%)	253	7.08 (6.21 to 7.95)	23 718 (3.3%)	136	5.73 (4.77 to 6.70)	5823 (2.5%)	45	7.73 (5.48 to 9.98)
Unknown	173 642 (25.4%)	1209	6.96 (6.57 to 7.35)	152 069 (20.9%)	932	6.13 (5.74 to 6.52)	96 952 (42.1%)	578	5.96 (5.48 to 6.45)
Total, No.	683 350	3950	5.78 (5.60 to 5.96)	729 196	3985	5.46 (5.30 to 5.63)	230 278	1365	5.93 (5.61 to 6.24)

* Among patients with known hormone replacement therapy (HRT) use. CI = confidence interval.

† Rate is presented as number per 1000 screening mammograms.

breast cancer incidence, whereas among HRT nonusers, women with higher BMI had higher breast cancer incidence.

Results

Two-Way Effect Modifications

As shown in Table 1, considerable percentages of data are missing for the main risk factors. After multiple imputations, the distributions of BMI, HRT use, race, and breast density were very similar to those before imputations (Supplementary Table 1, available online). Thus for multivariable analysis, we used the imputed data. The effect of HRT in subgroups of age, race/ethnicity, BMI, and breast density are shown in Table 2. The associations between HRT use and breast cancer risk were mostly positive in women aged 50 years and older, yet there was no statistically significant association for younger women aged 45 to 49 years. The heterogeneity effect, however, was not statistically significant ($P_{interaction}$ = .72). The association was positive in non-Hispanic whites (OR = 1.21; 95% CI = 1.14 to 1.28), Asian/Pacific Islanders (OR = 1.58; 95% CI = 1.18 to 2.11), and Hispanics (OR = 1.35; 95% CI = 1.09 to 1.67), but not in non-Hispanic blacks (OR = 0.91; 95% CI = 0.72 to 1.14; $P_{interaction}$ = .04). As for BMI, HRT was more strongly associated with breast cancer risk in leaner women than overweight women, whereas no association was observed in obese women ($P_{interaction}$ = .01). This association also varied by mammographic breast density: Women with denser breasts had higher odds ratios for breast cancer associated with HRT use than women with less-dense breasts ($P_{interaction}$ = .004).

In Table 3, we further stratified the analysis by race/ethnicity, focusing on BMI and breast density, both of which appear to be strong modifiers. By interacting with HRT separately, the trends of heterogeneity effects by BMI or by breast density remained in the same direction as in Table 2. Despite this, the heterogeneity effects by BMI or by breast density were statistically significant in non-Hispanic whites only, possibly because of the large sample size in this racial group. We estimated the statistical power to detect such interaction by race/ethnicity: with an odds ratio of 1.20 for marginal effect of HRT, an odds ratio of 1.50 for marginal effect of BMI, and a theta of 1.35 for HRT-by-BMI interactive effect, a sample size of 454 000 is required for 80% power at an alpha of 0.05, suggesting that the study has sufficient power in whites only.

Effect Modifications by Both BMI and Breast Density

Because breast density was inversely correlated with BMI (Spearman ρ = –0.26; P < .001) and each modified the association between HRT and breast cancer risk, we wondered whether the heterogeneity effects of HRT by BMI and by breast density confounded each other. Therefore, we fit a multivariable logistic regression model, including both HRT-by-BMI and HRT-by–breast density interaction terms. We found that both interactions remained statistically significant in this model. Table 4 shows the adjusted odds ratios for HRT users versus nonusers in each BMI

Table 2. Association between hormone replacement therapy use and breast cancer risk among postmenopausal women, according to age group, race/ethnicity, body mass index, or breast density, respectively

	HRT users vs nonusers		
Characteristic	**Crude OR (95% CI)**	**Adjusted OR* (95% CI)**	**$P_{interaction}$**
Age, y			.72
45–49	0.89 (0.72 to 1.11)	0.91 (0.73 to 1.12)	
50–54	1.18 (1.03 to 1.35)	1.19 (1.03 to 1.37)	
55–59	1.34 (1.19 to 1.51)	1.33 (1.19 to 1.49)	
60–64	1.30 (1.16 to 1.44)	1.27 (1.14 to 1.43)	
65–69	1.22 (1.08 to 1.38)	1.19 (1.05 to 1.35)	
70–75	1.21 (1.05 to 1.39)	1.18 (1.02 to 1.36)	
75–79	1.13 (0.97 to 1.31)	1.09 (0.94 to 1.27)	
80–84	1.32 (1.05 to 1.65)	1.28 (1.02 to 1.59)	
Race/ethnicity			.04
Non-Hispanic white	1.05 (1.00 to 1.11)	1.21 (1.14 to 1.28)	
Non-Hispanic black	0.77 (0.61 to 0.97)	0.91 (0.72 to 1.14)	
Asian/Pacific Islander	1.46 (1.10 to 1.94)	1.58 (1.18 to 2.11)	
Hispanic	1.19 (0.95 to 1.47)	1.35 (1.09 to 1.67)	
Other/mixed	1.09 (0.67 to 1.75)	1.23 (0.76 to 1.99)	
Body mass index, kg/m^2			.01
<25	1.19 (1.08 to 1.31)	1.35 (1.22 to 1.49)	
25–29.99	1.01 (0.91 to 1.14)	1.15 (1.02 to 1.29)	
30–34.99	0.95 (0.79 to 1.15)	1.08 (0.88 to 1.32)	
≥35	0.95 (0.72 to 1.25)	1.05 (0.80 to 1.38)	
Breast density			.004
Almost entirely fat	0.82 (0.62 to 1.10)	1.03 (0.77 to 1.37)	
Scattered fibroglandular densities	0.91 (0.84 to 0.98)	1.12 (1.02 to 1.23)	
Heterogeneously dense	1.08 (0.99 to 1.16)	1.29 (1.19 to 1.40)	
Extremely dense	1.22 (0.99 to 1.50)	1.41 (1.15 to 1.74)	

* Adjusted odds ratios (ORs) of hormone replacement therapy (HRT) users versus nonusers were estimated from logistic regression models, adjusting for age, race/ethnicity, body mass index, breast density, age at first birth, previous breast procedure, number of first-degree relatives with breast cancer, surgical menopause, and result of last mammogram before the index mammogram (negative or false positive), using data after missing data imputation. *P* values for assessing possible interactions were computed from Wald *z* statistics in logistic regressions. All statistical tests were two-sided. CI = confidence interval.

Table 3. Association between hormone replacement therapy use and breast cancer risk among postmenopausal women according to breast density and body mass index, stratified by race/ethnicity*

	Breast cancer risk: HRT users vs nonusers							
	Non-Hispanic white (n = 1 318 151)		Non-Hispanic black (n = 99 921)		Asian/Pacific Islander (n = 66 695)		Hispanic (n = 133 732)	
Characteristic	**OR (95% CI)**	**%**	**OR (95% CI)**	**%**	**OR (95% CI)**	**%**	**OR (95% CI)**	**%**
Breast density†	*P*§ = .008		*P*§ = .83		*P*§ = .85		*P*§ = .32	
Almost entirely fat	1.08 (0.79 to 1.47)	8.0	0.71 (0.19 to 2.74)	0.7	1.13 (0.13 to 9.53)	0.3	0.78 (0.27 to 2.29)	1.1
Scattered fibro-glandualar densities	1.12 (1.02 to 1.23)	39.6	0.91 (0.62 to 1.35)	3.1	1.48 (0.77 to 2.86)	1.6	1.26 (0.90 to 176)	4.2
Heterogeneously dense	1.29 (1.17 to 1.42)	29.6	0.85 (0.59 to 1.21)	2.2	1.53 (1.05 to 2.23)	1.8	1.53 (1.02 to 2.31)	2.5
Extremely dense	1.46 (1.16 to 1.84)	4.4	0.77 (0.31 to 1.90)	0.3	1.53 (0.55 to 4.27)	0.4	1.35 (0.52 to 3.51)	0.4
Body mass index, kg/m^2‡	*P*§ = .04		*P*§ = .77		*P*§ = .99		*P*§ = .12	
<25	1.33 (1.19 to 1.50)	37.8	0.92 (0.50 to 1.70)	1.4	1.52 (1.07 to 2.16)	2.7	1.67 (1.14 to 1.81)	3.5
25–29.99	1.14 (0.88 to 1.41)	26.3	0.87 (0.51 to 1.49)	2.1	1.49 (0.77 to 2.88)	1.0	1.27 (0.85 to 1.92)	3.0
30–34.99	1.11 (0.87 to 1.41)	11.5	0.83 (0.46 to 1.50)	1.5	1.06 (0.25 to 4.48)	0.3	0.91 (0.46 to 1.81)	1.3
≥35	1.08 (0.78 to 1.51)	5.9	0.81 (0.40 to 1.64)	1.1	2.74 (0.34 to 21.9)	0.1	1.07 (0.42 to 2.77)	0.5

* Adjusted odds ratios (ORs) of hormone replacement therapy (HRT) users vs nonusers were estimated from logistic regression models, stratified by race/ethnicity, adjusting for age, body mass index, breast density, age at first birth, previous breast procedure, number of first-degree relatives with breast cancer, surgical menopause, and result of last mammogram before the index mammogram (negative or false positive), using data after missing data imputation. CI = confidence interval.

† Percentages of sample by race and breast density.

‡ Percentages of sample by race and body mass index.

§ *P* values for assessing possible interactions were computed from Wald *z* statistics in logistic regressions. All statistical tests were two-sided.

Table 4. Association between hormone replacement therapy use and breast cancer risk distribution of study population according to both breast density and body mass index

	Breast cancer risk: HRT users vs nonusers				
Characteristic	**Under/Normal weight (BMI = 10–24.99 kg/m^2) OR (95% CI), % of population**	**Overweight (BMI = 25–29.99 kg/m^2) OR (95% CI), % of population**	**Obese I (BMI = 30–34.99 kg/m^2) OR (95% CI), % of population**	**Obese II (BMI ≥ 35 kg/m^2) OR (95% CI), % of population**	***P* for HRT × breast density**
Breast density					.03
Almost entirely fat	1.18 (0.86 to 1.43)	1.02 (0.77 to 1.36)	0.97 (0.67 to 1.41)	0.96 (0.67 to 1.39)	
	2.4%	3.5%	2.4%	1.7%	
Scattered fibro-glandular densities	1.25 (1.09 to 1.43)	1.08 (0.93 to 1.25	1.03 (0.85 to 1.25)	1.02 (0.76 to 1.36)	
	19.0%	17.1%	8.2%	4.2%	
Heterogeneously dense	1.40 (1.25 to 1.57)	1.21 (1.06 to 1.39)	1.16 (0.92 to 1.46)	1.14 (0.87 to 1.50)	
	19.9%	10.7%	3.8%	1.6%	
Extremely dense	1.49 (1.21 to 1.83)	1.29 (1.01 to 1.66)	1.23 (0.90 to 1.69)	1.22 (0.87 to 1.71)	
	3.9%	1.1%	0.3%	0.1%	
P for HRT × BMI interaction		.04			

* Adjusted odds ratios (ORs) of hormone replacement therapy (HRT) users ves non-users in a logistic regression model, including age, race/ethnicity, body mass index (BMI), breast density, age at first birth, previous breast procedure, number of first-degree relatives with breast cancer, surgical menopause, result of last mammogram before the index mammogram (negative or false positive), as well as two interaction terms (HRT × BMI and HRT × breast density), using data after missing data imputation. *P* values for assessing possible interactions were computed from Wald *z* statistics in a logistic regression. All statistical tests were two-sided. Colored cells: green = no elevated risk; pink = elevated risk with statistical significance; white = elevated risk without statistical significance. CI = confidence interval.

and breast density combination. The association between HRT use and breast cancer risk was strongest for underweight/normal weight women who had extremely dense breasts (adjusted OR = 1.49; 95% CI = 1.21 to 1.83). Approximately 55% of the study population experienced an increased risk of breast cancer due to HRT use (pink color cells in Table 4). Overweight and obese women with less-dense breasts consisted of 20% of the study population (green color cells in Table 4). For these women, the association between HRT use and breast cancer risk was essentially absent (adjusted ORs = 0.96–1.03). The remaining 25% of the study population had an elevated risk of breast cancer due to HRT use, but statistical significance was not reached (white color cells in Table 4).

In the analysis by tumor behavior (DCIS vs invasive), we found similar patterns of associations for invasive breast cancer despite some attenuation (Supplementary Table 2, available online), and null associations in the majority of the BMI/breast density combinations for DCIS, possibly because of limited sample size in subgroups (Supplementary Table 3, available online). In models without these interaction terms, the overall effect of HRT use on DCIS tended to be positive but did not reach statistical significance (OR = 1.11; P = .07), and the the overall effect of HRT use on invasive breast cancer was more profound (OR = 1.23; P < .001).

Supplementary Table 4 (available online) shows results by complete case analysis (original data). Although only 12.0% of the observations can be included in this multivariable analysis, the overall patterns and trends of associations are similar to the ones with imputed data. Supplementary Table 5 (available online) shows results of sensitivity analysis under assumption of not missing at random (eg, participants who had missing BMIs were more likely to be overweight or obese). Although individual point estimates and confidence intervals changed, the overall patterns and trends of associations remained.

Discussion

Using BCSC data, we examined the association between HRT use and breast cancer risk among postmenopausal women by age, race/ethnicity, BMI, and mammographic breast density. For both black women and overweight/obese women with breasts composed almost entirely of fat, HRT use was not associated with an increased risk for breast cancer. On the other hand, underweight/normal weight women with dense breasts were found to be more sensitive to the detrimental effects of HRT on breast cancer risk. If these findings are confirmed in other studies, HRT use may be reasonable for some women.

Current literature on breast cancer risk and HRT use in black women is limited and inconsistent (5,18,19). In BCSC, we observed no association between HRT and breast cancer risk in non-Hispanic black women. There was, however, a 20% to 60% increased risk for non-Hispanic whites, Asian/Pacific Islanders, and Hispanics. Our study provides additional evidence that HRT use may not impact breast cancer risk among black women. Additionally, based on secular trends of breast cancer incidence from Surveillance Epidemiology and End Results (SEER) registries, the decline in breast cancer incidence after the 2002 WHI trial dissemination occurred with statistical significance in whites but not in blacks, echoing the finding of no effect of HRT in blacks (29). This cannot be explained by mammography screening because the screening prevalence remained constant during those years (30,31).

A novelty of this study is the investigation of BMI and breast density together regarding their effect modification on HRT and breast cancer risk. The WHI randomized trial reported no effect modification by BMI (5,15). However, observational studies have suggested a higher risk of breast cancer with HRT use for women of normal weight compared with overweight or obese women (2,3,32–34), particularly in those women with higher breast density (17). Although BMI and breast density are correlated and should be considered together, no study has concurrently examined both. The mechanisms underlying breast density or obesity's modification of HRT's effect on breast cancer risk are largely unknown or lack consensus. As body weight increases, the amount of fat in the breast tissue also increases (35). Obesity is positively associated with breast cancer risk in postmenopausal women, and adipose tissue is a major source of endogenous estrogens after menopause. It is possible that obese women are less sensitive to the exogenous source of circulating hormones introduced by HRT. In our study, we found an interaction of breast density and HRT independent of BMI, suggesting the underlying mechanism for breast density–HRT interaction may be beyond endogenous estrogen sensitivity. Additionally, HRT use (especially combined estrogen and progesterone therapy) may increase breast density (36,37). Although women with high breast density are at higher breast cancer risk regardless of HRT use (17), controlling for breast density may be partially controlling for a variable in the causal pathway.

By studying breast density and body weight simultaneously, we were able to identify low and high risk subgroups. In the BCSC cohort, we found no elevated breast cancer risk associated with HRT use for overweight and obese women with low breast density (approximately 20% of the study population), suggesting a large subgroup of women may not be at elevated risk for breast cancer with HRT use.

Despite several strengths of this study, including the use of a large database, careful multiple imputation to properly handle missing data, and robust results demonstrated in complete case analysis and sensitivity analysis, there are several limitations. First, the lack of information on type of HRT may have attenuated the null association seen in black women. Unlike combined HRT, estrogen alone has been reported to be associated with a lower risk for invasive breast cancer (38). Black women may be more likely to have undergone a hysterectomy and use estrogen alone. This was noted in both the WHI [where proportionally more blacks were included in the estrogen alone trial (34) than in the estrogen plus progesterone trial (12): 15.1% vs 6.8%, respectively] and the Black Women's Health Study, where twice as many HRT users reported using estrogen alone compared with estrogen plus progesterone (18). However, in the Black Women's Health Study, the observed associations did not dramatically differ by HRT type (estrogen alone or estrogen plus progesterone), suggesting that type of HRT may not be as sensitive for black women (18). Second, duration of HRT use is unknown, and only current HRT use was captured in the database. Thus the study can only examine the short-term effect of current HRT use, and the true effect of long-term HRT use on breast cancer risk might be higher than observed, especially in subgroups of women identified to be sensitive to HRT. Although longer use of HRT

has been associated with higher risk, breast cancer incidence rates declined rapidly after cessation of therapy, with no risk elevation for most previous users (4,11). Lastly, the absence of information on breast cancer subtypes prevents us from assessing whether or not the lack of association between HRT and breast cancer risk in black women is linked to higher rates of hormone receptor–negative breast cancers in black women.

Our study investigated the heterogeneous association of HRT use on breast cancer risk. Black women, obese women, and women with breast tissue composed largely of fat may benefit from HRT use with minimal excess breast cancer risk. Confirmatory studies with more detailed information about other risk factors, including duration of HRT, use are needed to more accurately assess the risk vs benefit of postmenopausal HRT use.

References

1. Belchetz PE. Hormonal treatment of postmenopausal women. *N Engl J Med*. 1994;330(15):1062–1071.
2. Ross RK, Paganini-Hill A, Wan PC, et al. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst*. 2000;92(4):328–332.
3. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet*. 1997;350(9084):1047–1059.
4. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*. 2003;362(9382):419–427.
5. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA*. 2003;289(24):3243–3253.
6. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA*. 2004;291(1):47–53.
7. Jemal A, Ward E, Thun MJ. Recent trends in breast cancer incidence rates by age and tumor characteristics among U.S. women. *Breast Cancer Res*. 2007;9(3):R28.
8. Katalinic A, Rawal R. Decline in breast cancer incidence after decrease in utilisation of hormone replacement therapy. *Breast Cancer Res Treat*. 2008;107(3):427–430.
9. Li CI, Daling JR. Changes in breast cancer incidence rates in the United States by histologic subtype and race/ethnicity, 1995 to 2004. *Cancer Epidemiol Biomarkers Prev*. 2007;16(12):2773–80.
10. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med*. 2007;356(16):1670–1674.
11. Chlebowski RT, Kuller LH, Prentice RL, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med*. 2009;360(6):573–587.
12. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321–333.
13. Shoupe D. Individualizing hormone therapy to minimize risk: accurate assessment of risks and benefits. *Womens Health (Lond Engl)*. 2011;7(4):475–485.
14. Beral V, Reeves G, Bull D, et al. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. *J Natl Cancer Inst*. 2011;103(4):296–305.
15. Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA*. 2010;304(15):1684–1692.
16. Fournier A, Mesrine S, Boutron-Ruault MC, et al. Estrogen-progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? *J Clin Oncol*. 2009;27(31):5138–5143.
17. Kerlikowske K, Cook AJ, Buist DS, et al. Breast cancer risk by breast density, menopause, and postmenopausal hormone therapy use. *J Clin Oncol*. 2010;28(24):3830–3837.
18. Rosenberg L, Palmer JR, Wise LA, et al. A prospective study of female hormone use and breast cancer among black women. *Arch Intern Med*. 2006;166(7):760–765.
19. Hall IJ, Moorman PG, Millikan RC, et al. Comparative analysis of breast cancer risk factors among African-American women and white women. *AmJ Epidemiol*. 2005;161(1):40–51.
20. Martin KA, Manson JE. Approach to the patient with menopausal symptoms. *J Clin Endocrinol Metab*. 2008;93(12):4567–4575.
21. Ballard-Barbash R, Taplin SH, Yankaskas BC, et al. Breast Cancer Surveillance Consortium: a national mammography screening and outcomes database. *Am J Roentgenol*. 1997;169(4):1001–1008.
22. Carney PA, Geller BM, Moffett H, et al. Current medicolegal and confidentiality issues in large, multicenter research programs. *Am J Epidemio.l* 2000;152(4):371–378.
23. Carney PA, Miglioretti DL, Yankaskas BC, et al. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. *Ann Intern Med*. 2003;138(3):168–175.
24. Barlow WE, White E, Ballard-Barbash R, et al. Prospective breast cancer risk prediction model for women undergoing screening mammography. *J Natl Cancer Inst*. 2006;98(17):1204–1214.
25. Van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med*. 1999;18(6):681–694.
26. Royston P. Multiple imputation of missing values. *Stata J*. 2004;4(3):227–241.
27. Royston P. Multiple imputation of missing values: further update of ice, with an emphasis on categorical variables. *Stata J*. 2009;9(3):466–477.
28. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30(4):377–399.
29. Hou N, Huo D. A trend analysis of breast cancer incidence rates in the United States from 2000 to 2009 shows a recent increase. *Breast Cancer Res Treat*. 2013;138(2):633–641.
30. Breen N, K AC, Meissner HI, et al. Reported drop in mammography: is this cause for concern? *Cancer*. 2007;109(12):2405–2409.
31. Ryerson AB, Miller JW, Eheman CR, et al. Recent trends in U.S. mammography use from 2000–2006: a population-based analysis. *Prev Med*. 2008;47(5):477–482.
32. Reeves GK, Beral V, Green J, et al. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. *Lancet Oncol*. 2006;7(11):910–918.
33. Schairer C, Lubin J, Troisi R, et al. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA*. 2000;283(4):485–491.
34. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291(14):1701–1712.
35. Brisson J, Morrison AS, Kopans DB, et al. Height and weight, mammographic features of breast tissue, and breast cancer risk. *Am J Epidemiol*. 1984;119(3):371–381.
36. Greendale GA, Reboussin BA, Slone S, et al. Postmenopausal hormone therapy and change in mammographic density. *J Natl Cancer Inst*. 2003;95(1):30–37.
37. McTiernan A, Martin CF, Peck JD, et al. Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial. *J Natl Cancer Inst*. 2005;97(18):1366–1376.
38. LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA*. 2011;305(13):1305–1314.

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Affiliations of authors: Department of Health Studies (NH, JJD, DH) and Department of Medicine and Center for Clinical Cancer Genetics (SH, OIO), University of Chicago, Chicago, IL; Center for Injury Research and Prevention, Children's Hospital of Philadelphia, Philadelphia, PA (WW).