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Race, Menopausal Hormone Therapy, and Invasive Breast Cancer in the Carolina Breast Cancer Study

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Abstract

Purpose: The use of combined estrogen-progestin menopausal hormone therapy (MHT) has been shown to increase the risk of breast cancer, however, recent observational studies have suggested that the association between MHT and breast cancer may be modified by race. The objective of this study was to investigate the association between MHT use and incidence of invasive breast cancer in Black and White women aged ≥40 years at diagnosis after accounting for racial differences in patterns of MHT use and formulation.
Methods: Data from the Carolina Breast Cancer Study, a population-based case–control study of Black and White women in North Carolina conducted between 1993 and 2001, was used to analyze 1474 invasive breast cancer cases and 1339 controls using unconditional logistic regression.
Results: Black women were less likely than White women to use any MHT and were more likely to use an unopposed-estrogen formulation. Combined estrogen-progestin MHT use was associated with a greater odds of breast cancer in White (adjusted odds ratio [OR] 1.48, 95% confidence interval [CI]: 1.03–2.13) and Black (OR 1.43, 95% CI: 0.76–2.70) women, although the estimate in Black women was imprecise. In contrast, use of unopposed-estrogen MHT among women with prior hysterectomy was not associated with breast cancer in women of either race.
Conclusion: The association between MHT and invasive breast cancer appears to be similar in both Black and White women after accounting for differences in formulation and prior hysterectomy. These findings emphasize the importance of accounting for MHT formulation in race-stratified analyses of breast cancer risk.

Keywords: breast cancer, African American, hormone therapy, menopause, hysterectomy

Introduction

Menopausal hormone therapy (MHT) is a treatment for menopausal symptoms and for health consequences of early onset of menopause, such as osteoporosis and depression.[1] However, many observational studies have indicated an increased risk of breast cancer associated with the use of MHT, particularly combined estrogen plus progestin therapy. Results from a large randomized trial of the Women's Health Initiative (WHI) indicated a 24% increase in invasive breast cancer risk among postmenopausal women treated with combined estrogen-progestin after a mean of 5.2 years of follow-up [hazard ratio (HR) 1.24, 95% confidence interval (CI): 1.01–1.54],[2] although no significant association with breast cancer was found in the unopposed-estrogen trial among women with prior hysterectomy when the intervention phase was stopped (HR 0.77, 95% CI: 0.59–1.01).[3,4] The use of MHT in the United States has declined dramatically since the results of the WHI trial were published in 2003, and subsequent reductions in the incidence of breast cancer in the population have been documented.[5–8]

Despite overall declines in MHT use, much of what is known about the effect of hormone therapy on breast cancer risk in postmenopausal women has originated from studies conducted in predominantly White study populations. Evidence concerning the effect of MHT among Black women is limited and inconsistent. Results from an analysis of a large number of postmenopausal women in the Breast Cancer Surveillance Consortium, a longitudinal registry of 1.6 million screening mammograms, reported a positive association between any

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hormone therapy use and breast cancer among White women, but no association among Black women.[9] Among women with natural menopause in the Nashville Breast Health Study, ever use of any hormone therapy was positively associated with estrogen receptor positive breast cancer in White women but inversely associated in Black women.[10] Results from an early phase of the Carolina Breast Cancer Study also showed an inverse association between combined estrogen-progestin MHT use and breast cancer in Black women.[11]

In contrast, the original WHI combined estrogen-progestin trial reported no significant modification of the reported association by race, although Black women comprised only 6.8% of the study population.[2] A later reanalysis of both WHI trials with a greater number of breast cancer cases showed the same result, indicating no significant modification of reported associations between either estrogen-only or estrogen plus progestin therapy and breast cancer according to race.[12] An analysis of 32,559 women aged 40 years and older in the Black Women's Health Study indicated estrogen plus progestin MHT use for ≥5 years was associated with a greater incidence rate of breast cancer compared to never use (incidence rate ratio [IRR] 1.45, 95% CI: 0.94–2.23).[13]

To elucidate inconsistencies in previous findings of the MHT-breast cancer risk relationship in Black women, we sought to evaluate racial differences in the association between MHT and breast cancer risk after accounting for differences in patterns of MHT use, formulation, and prior hysterectomy. We investigated the association between MHT and the incidence of invasive breast cancer overall and according to tumor subtype and hysterectomy status among Black and White women in Phase 1 and 2 of the Carolina Breast Cancer Study from 1993 to 2001.

Materials and Methods

Study population

The Carolina Breast Cancer Study (CBCS) is a population-based, case–control study of incident breast cancer among women in 24 counties in central and eastern North Carolina. Cases were identified from the North Carolina Central Cancer registry. Eligible cases were aged 20–74 years and were diagnosed with a first primary breast cancer between 1993 and 2000. Figure 1 presents the contact and enrollment proportions according to case/control status. Younger (<50 years) and Black cases were oversampled to provide sufficient sample sizes for racially stratified analyses. Controls were selected during the same time period and from the same geographic area as cases using North Carolina Driver's License and Medicare beneficiary lists. Controls were frequency-matched to cases using randomized recruitment according to race and 5-year age group. Details on overall study response rates have been published previously.[14,15] Participants were interviewed in-person by trained nurses using a standardized questionnaire to obtain information on demographics and potential risk factors for breast cancer. The interview was conducted within 1 year of diagnosis date for 95% of cases. Detailed information on hormone use, family history of cancer, reproductive and menstrual history, socioeconomic status, occupational exposures, and behavioral risk factors for breast cancer was collected. Race was self-reported. Anthropometric measurements were taken by trained nurses at the time of interview to obtain body mass index (BMI).

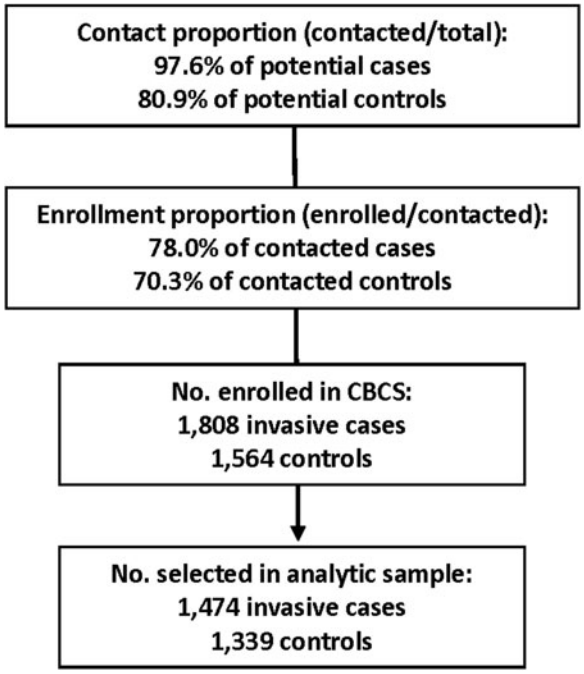

FIG. 1. Contact and enrollment in the Carolina Breast Cancer Study (Phase 1 and 2) for invasive breast cancer cases and controls.

The present analysis includes invasive cases and controls who were aged ≥40 at the time of selection into the study. This age cut point was chosen to include women who used MHT before menopause onset. Among ever MHT users in our sample, 31% began therapy while premenopausal, indicating a significant number of users were prescribed MHT prophylactically for suspected health benefits or for perimenopausal symptoms occurring gradually before the cessation of ovarian function. Including premenopausal women in our study allowed for the investigation of associations between timing of MHT initiation or cessation and breast cancer.

The study sample was also restricted to women who self-identified as Black/African American or White. Women who had undergone natural menopause (ceased menstruation in the absence of hysterectomy) or bilateral oophorectomy by the time of selection/diagnosis were considered postmenopausal. Age at menopause was equal to the age at surgery for women who underwent bilateral oophorectomy and age at cessation of menstruation for women with no history of gynecologic surgery. Women who underwent hysterectomy alone or in conjunction with unilateral oophorectomy before natural menopause were considered postmenopausal at age 50 years and assigned an age at menopause equal to 50. This imputation method was shown to yield similar results to a more precise method in an analysis of risk factors for breast cancer using data from the Nurse's Health Study.[16] Women with chemotherapy or radiation induced menopause were excluded ($n=24$). The final analytical sample consisted of 1474 cases and 1339 controls.

Exposure assessment

MHT use was ascertained during the interview with a photo card of commonly prescribed therapies to help

participants accurately recall history of use and formulation. Information on type of hormone, dose, duration of use, and age at first/last use was collected. Ever MHT use was defined as treatment with any formulation of hormone therapy for ≥3 months at any point before the time of selection or diagnosis. For analyses examining timing and duration of use, ever users were grouped into multiple categories: recency of initiation (<5 to ≥5 years), recency of last use (Current user, <5 to ≥5 years), and total duration of use (<5 to 5–10, >10 years). Type of therapy was also grouped into three categories of formulation use: unopposed estrogen only, estrogen always with progestin, and estrogen sometimes with progestin. Other combinations of estrogen and progestin use were rare and excluded from analyses of formulation due to insufficient sample sizes. Recency of initiation was analyzed as a joint exposure with MHT formulation when sample size was sufficient.

Outcome assessment

The primary outcome of interest was incident invasive breast cancer. The secondary outcome was incident subtype-specific invasive breast cancer. For subtype-specific analyses, cases were categorized as having either: (1) estrogen receptor (ER) or progesterone receptor (PR) positive (ER+/PR−, ER−/PR+, ER+/PR+) or (2) estrogen and progesterone receptor negative (ER−/PR−) tumors. Controls were the comparison group. Tumor subtypes were abstracted from medical records for 80% of cases and determined using immunohistochemistry assays for others. Cases with missing information for ER or PR status were excluded from subtype-specific analyses ($n = 65$).

Stratification

Analysis of the relationship between MHT and breast cancer was stratified by race to compare measures of association in Black and White women separately. The subtype-specific analysis was not stratified by race due to insufficient sample size. Analyses were also stratified by hysterectomy status to minimize confounding by indication for this surgery, since hysterectomy is an indication for unopposed estrogen MHT and is independently associated with decreased breast cancer risk.[17–19] Women with hysterectomy may not be comparable to women without surgery when attempting to make inferences about hormonal risk factors for breast cancer given differences in timing of menopause, endogenous estrogen exposure, duration and formulation of MHT, and indications for surgery that may confer differences in breast cancer risk independent of MHT. Women were classified as having undergone hysterectomy if they reported having their uterus surgically removed before study selection. Analyses not stratified by hysterectomy status were adjusted for gynecologic surgery status (no surgery, hysterectomy alone, any oophorectomy with or without hysterectomy) using model adjustment for comparison with stratified analyses.

Statistical analysis

Percentages for descriptive characteristics among controls were weighted by the inverse of their sampling probability to obtain prevalence estimates in the source population in central and eastern North Carolina. Unconditional logistic regression was used to estimate odds ratios (OR) and 95% CI as measures of association between MHT use and case status. All tests of association (other than likelihood ratio tests for the evaluation of modification) were evaluated at a significance level of $\alpha = 0.05$. Never MHT users were the referent group for all analyses. An offset term was incorporated in all models to account for the sampling probabilities used to select cases and controls in the CBCS design.

All models were adjusted for confounders of age at selection/diagnosis, age at menopause, and educational attainment based on a minimally sufficient adjustment set identified a priori using a directed acyclic graph.[20] Estimates in the hysterectomy group were adjusted for history of bilateral oophorectomy, which was identified a priori as a potential confounder. Subtype-specific analyses were also adjusted for race. Additional covariates including BMI, age at menarche, smoking history, first degree family history of breast cancer, parity, and age at first full-term pregnancy were adjusted for in separate models but adjustment for these variables resulted in similar estimates (results not shown). Likelihood ratio tests were used to evaluate the presence of modification by race and obesity status (BMI ≥30) separately. Tests were conducted in nested models with the addition of an interaction term between ever use of any MHT and the variable of interest. All likelihood ratio tests were evaluated at a significance level of $\alpha = 0.1$.

All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). The study protocol was approved by the Institutional Review Board of the University of North Carolina at Chapel Hill.

Results

Descriptive characteristics

Table 1 presents distributions of characteristics among cases and controls stratified by ever versus never MHT use, with weighted proportions for controls as estimates of prevalence in the source population. Among controls, the proportion of women who ever used MHT was 35%. These women were more likely to be White, possess some college-level education, have leaner BMI <25, and be postmenopausal. Controls who ever used MHT were also more likely to have undergone any gynecologic surgery (68%) than never users (24%). The most common surgery among never users was hysterectomy without oophorectomy (14%). Among postmenopausal controls, ever users were more likely to have an earlier age at menopause.

Among both cases and controls, the median duration of total hormone therapy use was 60 months for White and 36 months for Black users, but the median age at first use was similar for both Black and White users (45 and 46 years, respectively). Unopposed estrogen was the most common MHT formulation used, although the proportion of women using estrogen plus progestin was higher among cases than controls. Among ever users, the prevalence of estrogen-only MHT use was greater among Black than White women (75% vs. 50%). Likelihood ratio tests did not indicate the presence of modification by race in the overall sample or by obesity status (BMI ≥30) in Black or White women ($p > 0.1$). There was also no indication of modification by these variables within strata of hysterectomy status ($p > 0.1$).

Hormone therapy and breast cancer

Table 2 presents associations between MHT and breast cancer. Estrogen always with progestin MHT use was

Table 1. Characteristics of Cases and Controls by Menopausal Hormone Therapy use in Phase 1 and 2 of the Carolina Breast Cancer Study, 1993–2001 ($N = 2813$)

	Ever users (n = 943)			*Never users (n = 1870)*		
	Cases	*Controls*		*Cases*	*Controls*	
	No.	*No.*	*Weighted %*[a]	*No.*	*No.*	*Weighted %*[a]
Median age (IQR)	59 (11)	55 (13)		53 (20)	48 (14)	
Race						
White	322	304	(86)	504	422	(74)
Black	151	166	(14)	497	447	(26)
Education						
≤High school	194	218	(39)	514	421	(41)
Some college	147	161	(39)	233	210	(26)
≥College	132	91	(21)	254	237	(34)
Missing					1	
Measured BMI						
≤24	171	150	(40)	297	240	(36)
25–29	158	161	(33)	282	248	(29)
≥30	138	150	(28)	395	362	(35)
Missing	6	9		27	19	
Median BMI (IQR)	27 (24–32)			28 (24–34)		
Parity						
0	72	54	(11)	136	78	(10)
1	82	78	(16)	146	152	(19)
2	147	147	(34)	304	271	(36)
≥3	172	191	(38)	415	368	(36)
Age at first birth						
Nulliparous	72	54	(11)	142	81	(10)
<20	126	154	(28)	317	283	(25)
20–24	163	169	(38)	292	278	(34)
>24	112	93	(23)	250	227	(31)
Age at menopause						
Premenopausal	35	31	(7)	441	386	(53)
≤39	51	76	(16)	39	40	(4)
40–44	54	56	(13)	54	41	(4)
45–49	104	80	(18)	121	94	(10)
50–54	199	187	(43)	292	268	(28)
≥55	23	22	(4)	41	25	(2)
Missing	7	18		13	15	
Type of gynecologic surgery						
None	205	139	(32)	767	633	(76)
Hysterectomy + Bilat. oophorectomy	118	145	(27)	30	40	(3)
Hysterectomy + Unilat. oophorectomy	31	42	(8)	45	38	(4)
Hysterectomy only	86	103	(23)	125	134	(14)
Bilateral oophorectomy only	2	3	(1)	3	0	(0)
Other[b]	31	37	(10)	31	24	(4)
Missing		1				
Age at menarche						
<13	247	215	(46)	498	395	(44)
≥13	225	252	(54)	502	470	(56)
Missing	1	3		1	4	
Oral contraceptive use						
Never	175	186	(35)	406	339	(30)
Ever	293	278	(65)	594	525	(70)
Missing	5	6		1	5	
Hormone therapy formulation						
Unopposed estrogen only	253	299	(58)			
Estrogen always with progestin	143	95	(24)			
Estrogen sometimes with progestin	45	50	(12)			
Estrogen and progestin never together	11	6	(2)			
Progestin only	21	20	(4)			
Duration of hormone therapy use (years)						
<5	243	241	(49)			
5–10	104	91	(22)			
>10	119	135	(29)			
Missing	7	3				

Includes White and Black women aged ≥40 years. Excludes women with chemotherapy/radiation induced menopause.

[a]Percentages are weighted by the inverse of the sampling probability and reflect estimated prevalence in the source population in North Carolina.

[b]Women who had gynecologic surgery but specific procedure is unknown.

BMI, body mass index.

Table 2. Odds Ratios and 95% Confidence Interval for the Association Between Hormone Therapy and Invasive Breast Cancer Among Black and White Women in the Carolina Breast Cancer Study, 1993–2001 (N=2813)

	Black (n=*1261*)		*White* (n=*1552*)	
Hormone therapy use	*Cases/controls*	*OR*[a] *(95% CI)*	*Cases/ controls*	*OR*[a] *(95% CI)*
Never (ref)	488/438	1.00	500/415	1.00
Ever	147/164	0.82 (0.61–1.10)	319/288	1.19 (0.93–1.52)
Formulation[b]				
Unopposed estrogen only	106/130	0.75 (0.53–1.05)	145/169	1.02 (0.73–1.44)
Progestin always with estrogen	31/16	1.43 (0.76–2.70)	108/64	1.48 (1.03–2.13)
Progestin sometimes with estrogen	5/10	0.45 (0.15–1.36)	39/37	1.03 (0.63–1.68)
Recency of initiation				
<5 years	54/55	0.82 (0.54–1.25)	95/79	1.12 (0.79–1.58)
≥5 years	92/104	0.88 (0.62–1.26)	218/209	1.20 (0.90–1.58)
Recency of initiation and Formulation				
<5 years and Unopposed estrogen only	35/41	0.73 (0.44–1.21)	38/34	1.14 (0.66–1.95)
<5 years and Progestin always with estrogen	17/8	1.36 (0.56–3.29)	39/32	1.04 (0.62–1.73)
Recency of last use				
Current	88/94	0.86 (0.60–1.23)	229/203	1.24 (0.94–1.62)
<5 years	26/25	0.94 (0.52–1.69)	45/39	1.13 (0.71–1.80)
≥5 years	32/39	0.83 (0.50–1.39)	43/45	1.02 (0.63–1.63)
Duration				
<5 years	90/96	0.83 (0.59–1.17)	151/133	1.10 (0.82–1.47)
5 to <10 years	31/30	0.98 (0.57–1.69)	69/59	1.26 (0.84–1.88)
≥10 years	25/37	0.67 (0.38–1.17)	93/95	1.25 (0.86–1.82)

[a]Odds ratios were adjusted for age at selection/diagnosis, age at menopause, gynecologic surgery, and education. An offset term was incorporated into the model to account for the CBCS sampling design.
[b]Results for women taking progestin only and estrogen in addition to progestin but never simultaneously are not shown due to sparse data, but these women are included in the ever/never, recency of first/last use, and duration models.
CI, confidence interval; OR, odds ratio.

associated with a greater odds of breast cancer in White women (OR 1.48 95% CI: 1.03–2.13) and appeared similarly associated in Black women (OR 1.43, 95% CI: 0.76–2.70), although the estimate for Black women was imprecise due to a smaller population of Black ever users. Recency of initiation of MHT was not associated with breast cancer in either Black or White women. Estimates for current and longer term (>5 years) MHT use were suggestive of a positive association in White users only. Black women using MHT for 10 or more years exhibited an inverse association with breast cancer (OR 0.67, 95% CI: 0.38–1.17), although the estimate was imprecise.

Table 3 presents results for the evaluation of MHT and breast cancer stratified by hysterectomy status. Among women with an intact uterus, current use was positively associated with breast cancer among White women (OR 1.49, 95% CI: 1.03–2.14). There was also a suggestion of a positive association for ever use of progestin always with estrogen (OR 1.40, 95% CI: 0.95–2.05) and initiation of any MHT ≥5 years before selection/diagnosis (OR 1.40, 95% CI: 0.96–2.02). For Black women, estimates were generally null and imprecise as MHT use was less common. Unopposed estrogen-only use appeared inversely associated with breast cancer in Black women (OR 0.48, 95% CI: 0.23–0.97), although this estimate describes a small sample of women with potentially unique clinical characteristics given that this formulation is contraindicated in women with an intact uterus.

Among women with prior hysterectomy, use of unopposed estrogen-only accounted for 87% of total MHT use, which was expected given this formulation increases the risk of endometrial cancer and is contraindicated in women with an intact uterus.[6,21] Unopposed estrogen-only use was not associated with the odds of breast cancer in White (OR 0.97, 95% CI: 0.62–1.50) or Black (OR 0.87, 95% CI: 0.58–1.31) women. Estimates for the combined estrogen and progestin formulation were too imprecise to draw inferences for either race group. Alternative categorizations of gynecologic surgery, such as the inclusion of bilateral or unilateral oophorectomy, were analyzed but resulted in similar estimates (results not shown).

Hormone therapy and breast cancer subtypes

Table 4 presents associations between MHT and hormone receptor status of breast tumors. Among women with an intact uterus, estrogen always with progestin MHT use appeared to be associated with a greater odds of ER+ or PR+ breast cancer (OR 1.36, 95% CI: 0.95–1.94), as did current MHT use (OR 1.39, 95% CI: 1.00–1.93) and use for 5 to <10 years (OR 1.83, 95% CI: 1.09–3.06). There were no associations between MHT use and ER− and PR− breast cancer. Among women with prior hysterectomy, there was no evidence of an association between ever use of unopposed estrogen-only MHT and either ER+ or PR+, or ER− and PR−, tumors. Recent use (<5 years) appeared to be associated with the odds of ER+ or PR+ breast cancer (OR 1.42, 95% CI: 0.74–2.69), although this result was imprecise and inconsistent with null findings for ever use, recency of initiation, and duration of use.

TABLE 3. ODDS RATIOS AND 95% CONFIDENCE INTERVAL FOR THE ASSOCIATION BETWEEN HORMONE THERAPY AND INVASIVE BREAST CANCER AMONG BLACK AND WHITE WOMEN ACCORDING TO HYSTERECTOMY STATUS IN THE CAROLINA BREAST CANCER STUDY, 1993–2001 ($N = 2813$)

	Intact uterus (n = *1844*)				*Hysterectomy* (n = *968*)			
	Black		*White*		*Black*		*White*	
Hormone therapy use	*Cases/controls*	*OR*[a] *(95% CI)*	*Cases/controls*	*OR*[a] *(95% CI)*	*Cases/controls*	*OR*[a] *(95% CI)*	*Cases/controls*	*OR*[a] *(95% CI)*
Never (ref)	353/297	1.00	427/337	1.00	135/141	1.00	73/78	1.00
Ever	50/42	0.77 (0.48–1.24)	177/117	1.23 (0.91–1.68)	97/122	0.88 (0.59–1.32)	142/171	0.98 (0.64–1.51)
Formulation[b]								
Unopposed estrogen only	17/21	0.48 (0.23–0.97)	25/22	1.01 (0.54–1.89)	89/109	0.87 (0.58–1.31)	120/147	0.97 (0.62–1.50)
Progestin always with estrogen	26/14	1.18 (0.58–2.37)	104/62	1.40 (0.95–2.05)	5/2	2.32 (0.43–12.45)	4/2	2.85 (0.48–17.07)
Progestin sometimes with estrogen	2/3	0.50 (0.08–3.21)	31/20	1.24 (0.67–2.28)	3/7	0.50 (0.12–2.12)	8/17	0.56 (0.21–1.48)
Recency of initiation								
<5 years	25/19	0.78 (0.41–1.49)	62/48	0.97 (0.63–1.49)	29/36	0.88 (0.49–1.58)	33/31	1.13 (0.62–2.08)
≥5 years	25/20	0.90 (0.47–1.70)	111/69	1.40 (0.96–2.02)	67/84	0.92 (0.59–1.44)	107/140	0.91 (0.58–1.45)
Recency of last use								
Current	33/20	1.04 (0.57–1.92)	124/68	1.49 (1.03–2.14)	55/74	0.84 (0.53–1.34)	105/135	0.93 (0.60–1.45)
<5 years	7/11	0.43 (0.16–1.18)	27/24	0.89 (0.49–1.60)	19/14	1.58 (0.72–3.47)	18/15	1.42 (0.65–3.11)
≥5 years	10/7	1.02 (0.37–2.80)	25/25	0.87 (0.48–1.59)	22/32	0.82 (0.44–1.52)	18/20	1.12 (0.51–2.47)
Duration								
<5 years	37/29	0.82 (0.48–1.41)	96/80	0.95 (0.67–1.36)	53/67	0.89 (0.56–1.42)	55/53	1.16 (0.69–1.97)
5 to <10 years	9/9	0.65 (0.24–1.72)	46/18	2.18 (1.21–3.95)	22/21	1.22 (0.61–2.42)	23/41	0.65 (0.35–1.22)
≥10 years	4/4	0.68 (0.16–2.87)	31/19	1.52 (0.81–2.84)	21/33	0.71 (0.37–1.33)	62/76	1.05 (0.62–1.76)

[a]Odds ratios were adjusted for age at selection/diagnosis, age at menopause, education, and bilateral oophorectomy status. An offset term was incorporated into the model to account for the CBCS sampling design.

[b]Results for women taking progestin only and estrogen in addition to progestin but never simultaneously are not shown due to sparse data, but these observations are included in the ever/never, recency, and duration models.

TABLE 4. ODDS RATIOS AND 95% CONFIDENCE INTERVAL FOR THE ASSOCIATION BETWEEN HORMONE THERAPY AND BREAST CANCER SUBTYPE IN THE CAROLINA BREAST CANCER STUDY, 1993–2001 (N=2,813)

	Intact uterus (n=*1844*)				*Hysterectomy* (n=*968*)			
	ER+ or PR+		*ER– and PR–*		*ER+ or PR+*		*ER– and PR–*	
Hormone therapy use	*Cases/Controls*	*OR*[a] *(95% CI)*	*Cases/Controls*	*OR*[a] *(95% CI)*	*Cases/Controls*	*OR*[a] *(95% CI)*	*Cases/Controls*	*OR*[a] *(95% CI)*
Never (ref)	489/634	1.00	239/634	1.00	120/219	1.00	69/219	1.00
Ever	161/159	1.08 (0.82–1.43)	53/159	0.95 (0.65–1.40)	151/293	0.95 (0.68–1.33)	71/293	1.04 (0.68–1.60)
Formulation[b]								
Unopposed estrogen only	23/43	0.57 (0.33–0.99)	17/43	1.19 (0.63–2.27)	132/256	0.93 (0.66–1.31)	61/256	1.04 (0.67–1.61)
Progestin always with estrogen	96/76	1.36 (0.95–1.94)	24/76	0.90 (0.53–1.52)	6/4	2.76 (0.73–9.49)	3/4	2.83 (0.59–13.57)
Progestin sometimes with estrogen	26/23	1.20 (0.66–2.18)	6/23	0.79 (0.31–2.03)	8/24	0.68 (0.28–1.67)	2/24	0.41 (0.09–1.92)
Recency of initiation								
<5 years	54/67	0.86 (0.58–1.28)	27/67	0.96 (0.58–1.59)	32/67	0.91 (0.55–1.50)	24/67	1.27 (0.70–2.28)
≥5 years	105/89	1.28 (0.91–1.79)	25/89	0.95 (0.57–1.59)	117/224	0.97 (0.67–1.40)	46/224	0.96 (0.60–1.55)
Recency of last use								
Current	115/88	1.39 (1.00–1.93)	35/88	1.16 (0.73–1.84)	103/209	0.90 (0.62–1.30)	46/209	0.96 (0.60–1.54)
<5 years	24/35	0.78 (0.45–1.36)	8/35	0.57 (0.25–1.28)	21/29	1.42 (0.75–2.69)	14/29	2.08 (0.99–4.38)
≥5 years	21/32	0.72 (0.40–1.30)	10/32	1.06 (0.49–2.28)	26/52	1.01 (0.58–1.77)	10/52	0.83 (0.38–1.80)
Duration								
<5 years	85/109	0.86 (0.62–1.19)	40/109	0.97 (0.63–1.48)	63/120	0.98 (0.65–1.46)	34/120	1.10 (0.66–1.82)
5 to <10 years	46/27	1.83 (1.09–3.06)	7/27	0.76 (0.31–1.82)	32/62	0.94 (0.56–1.58)	12/62	0.82 (0.40–1.68)
≥10 years	28/23	1.27 (0.71–2.30)	5/23	0.97 (0.34–2.71)	54/109	0.87 (0.55–1.37)	24/109	1.13 (0.63–2.03)

Cases with missing subtype information were excluded (N=65).

[a]Odds ratios were adjusted for age at selection/diagnosis, age at menopause, education, and race. An offset term was incorporated into the model to account for the CBCS sampling design.

[b]Results for women taking progestin only and estrogen in addition to progestin but never simultaneously are not shown due to sparse data, but these observations are included in the ever/never, recency, and duration models.

ER, estrogen receptor; PR, progesterone receptor.

Discussion

Results from previous studies have suggested a possible racial difference in the association between combined estrogen and progestin MHT and breast cancer, with estimates in Black women tending to be either null or inversely associated[9–11,22,23] and results from the predominantly White WHI trial indicating elevated risk. We found that estrogen always with progestin MHT use was associated with an increased odds of breast cancer in White women and suggestive of a similar association in Black women. The estimate for Black women was imprecise due to a substantially smaller number of Black MHT users in the CBCS compared to White users. Women with prior hysterectomy used unopposed estrogen almost exclusively, and use of this formulation was not associated with breast cancer in either Black or White women. Ours is one of few studies in Black women to examine different formulations of therapy, particularly among those with and without prior hysterectomy.

Previously reported racial differences in the MHT-breast cancer relationship may reflect differences in indications for therapy and in formulations used between Black and White women. Hysterectomy is generally associated with a reduced risk of breast cancer,[17–19] and prior hysterectomy is an indication for unopposed estrogen use given that progestin is typically needed only to oppose estrogen's effect on endometrial cancer.[3] In our study, women with hysterectomy primarily used unopposed estrogen, which can be considered a wholly different exposure than combined estrogen plus progestin therapy in terms of its association with breast cancer risk. Results from the WHI estrogen-only trial of previously hysterectomized women showed that the risk of breast cancer was not increased with use of estrogen alone.[3] There were also proportionally more Black women in the estrogen alone trial (15.1%) than the estrogen plus progestin trial (6.8%), as prior hysterectomy was a criterion for inclusion. Black women in the United States experience a considerably higher incidence of hysterectomy than White women, and rates vary by geographic region with the highest rates occurring in the United States South.[24–27] Consistent with this trend, our study showed that the prevalence of hysterectomy was greater among Black (40%) compared to White (30%) women. Black women were also much more likely to receive estrogen-only therapy, as 75% of Black ever users received this formulation compared to just 50% of White ever users. Our results showed no association between unopposed estrogen use and breast cancer among women with prior hysterectomy. Results from previous studies reporting a weak or inverse association between hormone therapy and breast cancer in Black women could be explained by neglecting to adequately account for the disproportionate use of the estrogen-only formulation in this population.

Our results showed that ever use of any MHT was not associated with either hormone receptor positive or ER−/PR− breast cancer. Results from an analysis of White women in the Nashville Breast Health Study indicate that among those who underwent hysterectomy without bilateral oophorectomy, ever use of any hormone therapy was positively associated with both ER+/PR+ and ER−/PR− breast cancer, but inverse associations for both subtypes were observed for women with hysterectomy and bilateral oophorectomy, suggesting a potential role for oophorectomy in modifying the risk of these subtypes compared to hysterectomy alone.[28] In our study, we did not investigate whether oophorectomy modified the risk of specific subtypes. Examining results by formulation, our results indicate a positive association between use of estrogen always with progestin and hormone receptor positive tumors. This result has been shown by others in populations of women with and without gynecologic surgery.[10,28–32] Among women with hysterectomy, use of estrogen-only was not associated with hormone receptor positive or ER−/PR− tumors, suggesting that, in women with surgical menopause, incidence of these subtypes are not influenced by use of estrogen-only MHT.

Results from several large observational studies have shown current or recent (1–4 years) estrogen plus progestin MHT use to be associated with an increased breast cancer risk among postmenopausal women.[33–35] Analyses from the Million Women's Study indicated estrogen plus progestin MHT use initiated <5 versus ≥5 years after menopause was associated with a greater risk of breast cancer (risk ratio [RR] 2.04, 95% CI: 1.95–2.14 vs. RR 1.53, 95% CI: 1.38–1.70).[34] Results from the WHI observational cohort study also indicate the association between estrogen plus progestin MHT and breast cancer to be highest for women initiating therapy at the time of menopause onset (HR 1.68, 95% CI: 1.52–1.86), with the association decreasing linearly with increasing time between menopause and MHT initiation.[35] Similarly, results from the WHI estrogen plus progestin randomized trial among postmenopausal women indicated an elevated breast cancer risk in women who initiated therapy <5 versus ≥5 years after menopause (HR 1.41, 95% CI: 1.14–1.74 vs. HR 1.15, 95% CI: 0.96–1.37).[36] In our study, current use and initiation of MHT ≥5 years before study enrollment was associated with a greater odds of breast cancer only in White women without prior hysterectomy. Results from the two Sisters study of MHT in young women showed that adjustment for recency of last use, age at first use, and menopausal status at first use did not modify observed associations, suggesting that timing of MHT initiation is most critical for breast cancer risk after menopause.[37]

With respect to unopposed estrogen MHT use among women with hysterectomy, previous observational and experimental studies have yielded inconsistent results for its association with breast cancer risk.[3,33,38–40] Current hypotheses on the risk of unopposed estrogen use pertain to the timing of therapy initiation after menopause onset, whereby women initiating therapy within 5 years of menopause tend to exhibit a greater breast cancer risk compared to those who initiate after this period.[34,41,42] Conversely, an antitumor effect of unopposed estrogen therapy in estrogen-deprived postmenopausal women has been proposed as a biological mechanism for explaining reductions in breast cancer risk.[43] In our study, use of unopposed estrogen therapy was not associated with an increased breast cancer risk among women who underwent hysterectomy. Although the timing of MHT initiation relative to menopause onset among women with hysterectomy was not examined in this study, the median age at first use for Black and White women in this group was the same (44 years), suggesting that timing did not play a substantial role in comparing results by race.

The Carolina Breast Cancer Study is a population-based sample representative of Black and White women in the

United States South where the majority of Black Americans reside. Detailed information on menopausal history and gynecologic surgery reduced the potential for misclassification of menopausal status and type of menopause. We used a similar method for imputing age at menopause in our sample as that shown in the Nurse's Health Study. Our imputation method is less biased than assigning age at menopause equal to age at hysterectomy.[16,44] Race-specific changes in the patterns and prevalence of hormone therapy after the publication of the WHI results could bias subsequent observational studies of racial differences in the association between MHT and breast cancer risk. In particular, White, educated women may have benefitted more from the change in MHT treatment guidelines relative to nonWhite women.[7] This study avoids such bias given the pre-2003 data collection period. However, our results may not reflect risk for women using MHT according to current clinical guidelines that emphasize low-dose, short-term treatment, rather than long-term treatment for prevention of chronic diseases that was more common during the CBCS study period.

Recall bias may have led to misclassification of MHT use, particularly if use was intermittent or if formulation varied frequently. Older participants may also have had difficulty recalling usage history correctly. However, the use of a photo card with commonly prescribed hormone therapy products during the interview likely enhanced recall of MHT formulation and duration. MHT users may have better access to or be more likely to utilize healthcare resources compared to nonusers, which may have introduced detection bias.[45] This potential bias may have led to elevated estimates for associations between MHT and breast cancer. It also may affect interpretations of racial differences in associations if Black women experience greater barriers to medical care. While we adjusted all models for educational attainment to account for potential bias related to access to care, the availability of additional information pertaining to socioeconomic status and uptake of medical services may have improved the validity of our estimates. Our study was limited by a small sample size of Black compared to White ever MHT users, which affected the precision of estimates of association in Black women. Despite this, our representative sample revealed important differences in the uptake of MHT, formulation used, and hysterectomy prevalence in Black versus White women that should inform future work on this topic.

The association between estrogen plus progestin therapy and invasive breast cancer is biologically plausible given the established links between endogenous sex hormone exposure and breast cancer risk at critical periods over a woman's lifetime.[46] The increased risk associated with estrogen plus progestin therapy has been attributed to progestin's role in stimulating a higher mitotic rate and cell proliferation in breast tissue compared to estrogen alone.[47] Although progestin is added to estrogen-only formulations to oppose estrogen's effect on endometrial cancer risk, explorations into use of lower doses and nonsynthetic sources of progesterone could improve the safety profile of conjugated hormone therapy while conferring the same benefits for managing menopausal symptoms.[6]

In summary, our results emphasize that use of estrogen always with progestin appears to be similarly associated with greater risk of breast cancer in White and Black women. Unopposed estrogen therapy was not associated with breast cancer risk in either race group. Our findings could help explain conflicting results from previous studies of Black women that did not account for racial differences in MHT formulation and surgical indications for use.

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Author Disclosure Statement

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