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Postmenopausal Female Hormone Use and Estrogen Receptor–Positive and –Negative Breast Cancer in African American Women

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Abstract

Background: Use of estrogen with progestin (combination therapy) is associated with increased incidence of estrogen receptor–positive (ER+) breast cancer in observational studies and randomized trials among postmenopausal white women. Whether this is also the case among African American women is not established.

Methods: Using data from the AMBER consortium collected from 1993 to 2013, we assessed use of estrogen alone and of combination therapy in relation to ER+ and ER-negative (ER-) breast cancer risk in postmenopausal African American women, based on 1132 ER+ case patients, 512 ER- case patients, and 6693 control patients. Odds ratios (ORs) and confidence intervals (CIs) were estimated using multinomial logistic regression with control for breast cancer risk factors.

Results: Forty-seven percent of control patients had used estrogen alone, combination therapy, or both. The odds ratio for ER+ breast cancer associated with combination use, relative to never use of either estrogen alone or combination therapy, was 1.50 (95% CI = 1.25 to 1.79). The increase was greater for recent (OR = 1.55, 95% CI = 1.21 to 1.99) and long-term use (OR = 1.75, 95% CI = 1.13 to 2.73) and among nonobese women (OR = 1.91, 95% CI = 1.29 to 2.83). Breast cancer risk was increased regardless of the interval between onset of menopause and initiation of combination use (OR = 1.43, 95% CI = 1.11 to 1.85, for <5 year interval; OR = 1.78, 95% CI = 1.34 to 2.37, for ≥5 year interval). Combination use was not associated with risk of ER- breast cancer, and use of estrogen alone was not associated with risk of either ER+ or ER- breast cancer.

Conclusion: Use of estrogen with progestin increases risk of ER+ breast cancer in African American women. A decrease in use would be expected to reduce the number of ER+ cancers.

Observational studies (1–9) and randomized trials (10–12) indicate that use of supplements of estrogen together with progestin ("combination" use) increases the incidence of breast cancer, largely estrogen receptor–positive (ER+) cancer, among white postmenopausal women. The increase declines after cessation of use (1,7,13), but how long it persists is unclear (6). Users of estrogen alone in the Women's Health Initiative (WHI) randomized trial had a lower incidence of breast cancer than nonusers (14), but some observational studies suggest that long-term use increases risk (1,7,15). The relative increase in risk

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associated with female hormone use has been greater among leaner women in some studies (1,7,9,16,17). The timing of use in relation to onset of menopause may also modify an effect: In WHI (12) and the British Million Women's follow-up study (18), the increase in risk was greater for use begun within five years of onset of menopause than for use begun later.

Only a few studies have assessed African American women specifically. In the Black Women's Health Study (BWHS), estrogen alone and combination use were associated with increased breast cancer incidence (19). In the Nashville Breast Health Study (20), a follow-up study based on mammography registries (17), and the Carolina Breast Cancer Study (CBCS) (21), hormone use was not associated with increased risk of breast cancer among African American women, but all types of hormone use were grouped together, limiting interpretation of the findings. In a multicenter case-control study of white and African American women, continuous combined estrogen with progestin was associated with increased risk while estrogen alone was not, and race reportedly did not modify the associations (22).

To assess estrogen alone and combination use in relation to ER+ and ER- cancer in African American women and the potential modifying effects of body mass index and timing of use relative to menopause onset, we analyzed data from the African American Breast Cancer Epidemiology and Risk (AMBER) Consortium (23).

Methods

Participating Studies

The AMBER Consortium pools data from four studies of breast cancer subtypes in African American women (23). The BWHS is a cohort study of 59 000 African American women age 21 to 69 years at baseline in 1995, followed through biennial health questionnaires (19). Incident breast cancer were self-reported; case patients were confirmed by pathology data from hospitals and from cancer registries in 24 states covering 95% of participants. A nested case-control dataset was created: For each case patient, control patients selected from BWHS participants who had not developed breast cancer at the case patient's diagnosis date (index date) were matched on five-year age group, geographic region, and most recent questionnaire completed before the index date. The CBCS is a population-based case-control study of breast cancer among women age 20 to 74 years in North Carolina (24); we used data collected from 1993 to 2011. Case patients were identified through the North Carolina Central Cancer Registry, with oversampling of younger and African American case patients. Control patients younger than age 65 years, identified from Division of Motor Vehicle lists, and older control patients, identified from Health Care Financing Administration lists, were frequency-matched to case patients on race and five-year age group. Exposure and covariate data with reference to the year before diagnosis (case patients) or interview date (control patients) were collected through in-person interviews. The Multiethnic Cohort Study (MEC) is a prospective study that included 16 594 African American women age 45 to 75 years at baseline from 1993 to 1996 (25). Participants were identified through driver's license files for Hawaii and Los Angeles County in California. Case patients were ascertained through the Hawaii Tumor Registry, Cancer Surveillance Program for Los Angeles County, and California State Cancer Registry. A nested case-control dataset was created: Case patients were matched with control patients according to five-year age group and questionnaire completed before the case diagnosis. The Women's Circle of Health Study (WCHS) is a case-control study begun in 2003 of women age 20 to 75 years in New York and New Jersey (26,27). Breast cancer case patients were identified through major hospitals in New York and the New Jersey Cancer Registry. Control patients were identified through random digit dialing and community-based recruitment and were frequency matched to case patients on five-year age group. Exposure and covariate data were collected through in-person interviews with reference to the year before diagnosis (cases patient) or interview date (control patients). Each study obtained informed consent and was approved by the relevant institutional review boards. The data from the two case-control studies and the nested case-control datasets from the follow-up studies were harmonized and pooled at the AMBER Consortium's data coordinating center with input from each study.

Study Population

The present study was based on data collected between 1993 and 2013 from women age 40 to 75 years who reported their periods had stopped because of natural causes for at least a year or because of surgery (hysterectomy with bilateral oophorectomy or bilateral oophorectomy alone).

Case Patients

Potential case patients were incident cases of invasive breast cancer (91.4%) or ductal carcinoma in situ (8.6%). Immunohistochemistry data from hospital and cancer registry records were used to classify case patients as ER+ or ER- (73.7% of potential case patients). When human epidermal growth factor receptor 2 (HER2) data were available for ER- case patients (61.7%), they were classified according to triple-negative status (TN: ER-, PR-, HER2-). The distribution of case patients by subtype (Table 1) was as expected for African American women (28–31).

Exposure and Covariate Data

Each study asked about menopause, female hormone use for menopause, types of hormones used, age started, and duration. Information on breast cancer risk factors included breast cancer in mother, sister, or daughter, reproductive factors, weight, education, and use of oral contraceptives, alcohol, and cigarettes.

Data Analysis

We used multinomial logistic regression models to calculate odds ratios (ORs) and confidence intervals (CIs) for the relation of estrogen alone and combination use to risk of ER+ and ER- breast cancer; the reference category was never use of either estrogen alone or combination therapy. We controlled for five-year age group, study, index date (continuous), geographic region (New Jersey, other Northeast, South, Midwest, West), educational attainment (<12, 12, 13–15, 16, >16 years), family history of breast cancer (yes, no), age at menarche (<11, 11–12, 13–14, 15–16, ≥17), parity (nulliparous, parous), age at first birth (<25, ≥25), age at menopause (<45, 45–49, 50–54, ≥55), type of menopause (natural menopause, bilateral oophorectomy), body mass index (<25, 25–29, ≥30 kg/m^2), alcohol consumption (current, other), and cigarette smoking (<10, ≥10 pack-years). Control for lactation and mammography use did not alter the estimates. We used indicator variables for missing data (<2% for each variable). Effect modification was assessed in strata of age, body mass index, type of menopause, and interval between menopause and female hormone initiation; interaction on the multiplicative

Table 1. Control patients and case patients by study and use of estrogen alone and estrogen plus progestin by case-control status, postmenopausal women age 40 to 75 y

	All studies		BWHS		CBCS		MEC		WCHS	
Study subjects	N		N		N		N		N	
Control patients	6693		3348		309		2638		398	
Breast cancer case patients										
ER+	1132		325		217		386		204	
ER-	512		167		133		132		80	
	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases
Female hormone use	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Never used female hormones*	3509 (52.4)	949 (57.7)	1504 (44.9)	207 (42.1)	192 (62.1)	251 (71.7)	1477 (56.0)	260 (50.2)	336 (84.4)	231 (81.3)
Used estrogen alone										
Ever use	2318 (34.6)	475 (28.9)	1328 (39.7)	182 (37.0)	100 (32.4)	76 (21.7)	851 (32.3)	178 (34.4)	39 (9.8)	39 (13.7)
Duration of use, y										
<5	1397 (62.8)	276 (60.3)	755 (58.8)	111 (62.4)	55 (55.0)	40 (53.3)	559 (69.7)	110 (10.2)	28 (71.8)	15 (39.5)
≥5	828 (37.2)	182 (39.7)	529 (41.2)	67 (37.6)	45 (45.0)	35 (46.7)	243 (30.3)	57 (89.8)	11 (28.2)	23 (60.5)
Time since last use, y										
<5	1200 (53.4)	235 (51.1)	1048 (79.3)	144 (79.1)	71 (74.0)	57 (76.0)	70 (8.9)	17 (10.2)	11 (28.2)	17 (46.0)
≥5	1046 (46.6)	225 (48.9)	274 (20.7)	38 (20.9)	25 (26.0)	18 (24.0)	719 (91.1)	149 (89.8)	28 (71.8)	20 (54.0)
Used estrogen with progestin										
Ever use	1293 (19.3)	321 (19.5)	821 (24.5)	159 (32.3)	25 (8.1)	26 (7.4)	423 (16.0)	118 (22.8)	24 (6.0)	18 (6.3)
Duration of use, y										
<5	893 (75.4)	212 (71.9)	551 (72.9)	100 (69.9)	19 (79.2)	19 (73.1)	305 (80.1)	80 (73.4)	18 (78.3)	13 (76.5)
≥5	291 (24.6)	83 (28.1)	205 (27.1)	43 (30.1)	5 (20.8)	7 (26.9)	76 (19.9)	29 (26.6)	5 (21.7)	4 (23.5)
Time since last use, y										
<5	634 (50.9)	154 (49.8)	531 (64.8)	105 (66.0)	17 (70.8)	22 (84.6)	73 (19.3)	18 (16.7)	13 (54.2)	9 (56.3)
≥5	612 (49.1)	155 (50.2)	288 (35.2)	54 (34.0)	7 (29.2)	4 (15.4)	306 (80.7)	90 (83.3)	11 (45.8)	7 (43.7)

* Never used estrogen alone or estrogen with progestin. BWHS = Black Women's Health Study; CBCS = Carolina Breast Cancer Study; ER = estrogen receptor; MEC = multiethnic cohort; WCHS = Women's Circle of Health Study.

scale was tested by the likelihood ratio test, comparing models with and without interaction terms. Statistical tests were two-sided. SAS 9.2 statistical software (SAS Institute Inc., Cary, NC) was used. A *P* value of less than .05 was considered statistically significant.

Results

There were 1132 ER+ case patients, 512 ER- case patients (including 219 TN), and 6693 control patients. Among the control patients, 47.6% had used some form of hormone therapy: 28.3% used estrogen alone, 12.9% used combination therapy, and 6.4% used both. Combination use was lower in CBCS and WCHS than in BWHS and MEC (Table 1), and use of estrogen alone or combination therapy in the previous five years was lowest in MEC.

For ER+ breast cancer, odds ratios for ever use of estrogen alone, use within the previous five years, and use lasting 10 years or more were close to the null (Table 2). The odds ratio for use lasting 20 years or more was 1.20 (95% CI = 0.73 to 1.96), and the odds ratio for such use that continued until less than five years previously was 0.69 (95% CI = 0.33 to 1.43) (data not shown). For ER- breast cancer, odds ratios for estrogen alone were compatible with the null (Table 2). For TN cancer, the odds ratio for use of estrogen alone was 1.14 (95% CI = 0.77 to 1.69) (data not shown).

Combination use was associated with increased risk of ER+ cancer, with an odds ratio of 1.50 (95% CI = 1.25 to 1.79) for ever use (Table 2). Risk increased with duration of use to 1.75 (95% CI = 1.13 to 2.73) for 10 years or more. Ten or more years after cessation, the odds ratio for ever use was 1.34 (95% CI = 0.99 to 1.82); the decline following cessation was not monotonic, as the odds ratio for last use five to nine years ago, 1.80 (95% CI = 1.32 to 2.45), was greater than the odds ratio, 1.55 (95% CI = 1.21 to 1.99), for last use less than five years previously. Use of combination therapy was not associated with increased risk of ER- cancer (Table 2). For TN cancer, the odds ratio for combination use was 1.32 (95% CI = 0.88 to 1.98), and estimates for last use less than five years previously and duration of use 10 or more years were also compatible with the null (data not shown). Control for duration of use in analyses of time since last use, time since last use in analyses of duration, and use of estrogen alone resulted in little change in the odds ratios for combination use. The results were unchanged when in situ cases were excluded.

As shown in Table 3, the odds ratio of ER+ cancer associated with combination use was most increased among leaner women (BMI < 25 kg/m^2, OR = 1.91, 95% CI = 1.29 to 2.83), less increased among overweight women (BMI = 25–29 kg/m^2, OR = 1.69, 95% CI = 0.83 to 1.64), and closest to the null among obese women (BMI ≥ 30 kg/m^2, OR = 1.24, 95% CI = 0.93 to 1.64) ($P_{interaction}$ = .17). Within strata of age (Table 3), the odds ratios for combination use were elevated among women age 60 to 69 years and 70 years or older but not among women age 40 to 59 years ($P_{interaction}$ = .58). In subanalyses among women age 40 to 59 years, the odds ratios for combination use were elevated among leaner women (OR = 2.17, 95% CI = 1.05 to 4.46) and overweight women (OR = 1.69, 95% CI = 1.23 to 2.31) but not among obese women (OR =1.24, 95% CI = 0.93 to 1.65) (data not shown). The odds ratios for combination use were increased approximately 50% among women menopausal because of natural causes and among women menopausal because of bilateral oophorectomy ($P_{interaction}$ = .82) (Table 3).

A statistically significant increase in risk of ER+ cancer associated with combination use was observed regardless of the interval between onset of menopause and initiation of use (Table 4): Odds ratios were 1.43 (95% CI = 1.11 to 1.85) for intervals of less than five years and 1.78 (95% CI = 1.34 to 2.37) for longer intervals. There were no increases in ER- cancer risk for combination use regardless of timing of initiation, nor were there increases in risk of ER+ or ER- cancer associated with use of estrogen alone.

Results for combination use were similar in the two studies that included most users: The odds ratio for ER+ cancer associated with ever use was 1.64 (95% CI = 1.25 to 2.16) in BWHS and 1.58 (95% CI = 1.18 to 2.12) in MEC.

Discussion

The present study indicates that an appreciable proportion of African American women have used menopausal female hormone supplements: 47.6% of control patients in our four studies conducted in several areas of the United States from 1993 to 2013 reported use. The lower use of female hormones in CBCS, a study whose participants had lower educational levels, reflects that women of higher socioeconomic status tend to more commonly use these drugs (32). The low prevalence of use in WCHS, a study initiated in 2003, reflects the nationwide decline in use following publication of results from WHI documenting higher breast cancer risk in users of combination therapy (11,33–35).

Based on data collected prospectively in two follow-up studies and data from two case-control studies, we found that use of estrogen with progestin is associated with increased risk of ER+ cancer in African American women. This finding agrees with results from the WHI randomized trial of combination use (11) and case-control (1,4,5) and follow-up studies (1–3,7–9) that were based largely on white women. In the E3N follow-up study in France, estrogen taken with a progestagen other than dydrogesterone was associated with increased breast cancer risk (36); the high-risk progestin category included medroxyprogesterone acetate, which is widely used in the United States (9). As in many previous studies, we also found that breast cancer risk was greater for more recent and long-term use and that there was little evidence of an association of combination use with risk of ER- cancer (1–5,7–9).

In the WHI randomized trial, a statistically significant increased risk of breast cancer was observed for participants in the combination use group relative to the placebo group up to more than eight years following the end of the intervention study (11,37,38). In the Million Women's follow-up study (7), risk declined within a few years after cessation of hormone use, but risk after cessation was not assessed for past use of estrogen alone and combination therapy separately. Risk of breast cancer associated with combination use was still increased 10 years after cessation in the present study, and the increased incidence for women in the E3N study with at least five years of use persisted for up to 10 years after cessation (6).

The few studies that have assessed a potential modifying effect of timing of use in relation to onset of menopause on the association with combination use yielded differing results. In the present study, combination use was associated with a statistically significant increased risk of ER+ breast cancer regardless of when use began, and the odds ratio for use begun close to menopause was smaller than that for use begun later. In contrast, the Million Women's Study (18) and WHI (12) found that combination use begun within five years of menopause onset increased risk of breast cancer appreciably more than use begun later. The E3N follow-up study's results were mixed: There were increases in risk of similar magnitude for women who had used combination therapy for at least two years regardless of when use started, but for shorter-term users the risk estimate was greater for use that began within three years of menopause (36).

Table 2. Female hormone use in relation to breast cancer subtypes, postmenopausal women age ≥40 y

		ER+			ER-		
Female hormone use	Control patients	Case patients	OR (95% CI)*	OR (95% CI)†	Case patients	OR (95% CI)*	OR (95% CI)†
Never used‡	3509	649	1.00 (referent)	1.00 (referent)	300	1.00 (referent)	1.00 (referent)
Estrogen alone							
Ever use	2318	322	1.03 (0.89 to 1.21)	1.07 (0.89 to 1.28)	153	1.00 (0.80 to 1.24)	1.10 (0.85 to 1.42)
Duration of use, y							
<5	1397	190	1.04 (0.86 to 1.25)	1.05 (0.86 to 1.28)	86	0.95 (0.73 to 1.23)	1.01 (0.76 to 1.34)
5–9	329	45	1.01 (0.72 to 1.41)	1.07 (0.74 to 1.54)	32	1.29 (0.86 to 1.92)	1.51 (0.96 to 2.36)
≥10	499	77	1.06 (0.82 to 1.39)	1.18 (0.87 to 1.61)	28	0.85 (0.56 to 1.28)	1.03 (0.65 to 1.65)
Time since last use, y							
<5	1200	144	1.01 (0.82 to 1.23)	1.05 (0.82 to 1.35)	90	1.03 (0.78 to 1.36)	1.15 (0.83 to 1.58)
5–9	332	51	1.16 (0.84 to 1.59)	1.14 (0.81 to 1.59)	22	1.09 (0.69 to 1.72)	1.15 (0.71 to 1.86)
≥10	714	115	1.01 (0.80 to 1.27)	1.05 (0.82 to 1.34)	37	0.90 (0.62 to 1.31)	1.00 (0.68 to 1.48)
Estrogen plus progestin							
Ever use	1,293	235	1.54 (1.29 to 1.83)	1.50 (1.25 to 1.79)	86	1.13 (0.87 to 1.47)	1.09 (0.83 to 1.43)
Duration of use, y							
<5	893	153	1.45 (1.18 to 1.78)	1.42 (1.15 to 1.74)	59	1.10 (0.81 to 1.49)	1.06 (0.78 to 1.45)
5–9	174	36	1.84 (1.25 to 2.69)	1.77 (1.20 to 2.62)	15	1.45 (0.83 to 2.53)	1.39 (0.79 to 2.45)
≥10	117	28	1.81 (1.17 to 2.79)	1.75 (1.13 to 2.73)	4	0.65 (0.24 to 1.79)	0.62 (0.22 to 1.71)
Time since last use, y							
<5	634	108	1.61 (1.27 to 2.06)	1.55 (1.21 to 1.99)	46	1.12 (0.80 to 1.58)	1.04 (0.73 to 1.47)
5–9	323	61	1.84 (1.36 to 2.49)	1.80 (1.32 to 2.45)	15	0.94 (0.54 to 1.61)	0.93 (0.54 to 1.61)
≥10	403	61	1.37 (1.02 to 1.84)	1.34 (0.99 to 1.82)	18	1.09 (0.66 to 1.80)	1.11 (0.67 to 1.86)

* Adjusted for age, study, year, and geographic region. CI = confidence interval; ER = estrogen receptor; OR = odds ratio.

† Adjusted for age, study, year, geographic region, education, parity, age at first birth, age at menopause, type of menopause, age at menarche, body mass index, oral contraceptive use, family history of breast cancer, alcohol use, and smoking.

‡ Never used estrogen alone or estrogen plus progestin.

Table 3. Use of estrogen plus progestin in relation to ER+ breast cancer, postmenopausal women age ≥40 y, stratified by body mass index, age, and type of menopause

Characteristic	Never used*		Ever used		P†
	Case patients/ Control patients	OR (95% CI) ‡	Case patients/ Control patients	OR (95% CI) ‡	
Body mass index, kg/m^2					.17
<25	98/721	1.00 (referent)	62/317	1.91 (1.29 to 2.83)	
25–29	192/1179	1.00 (referent)	83/448	1.69 (0.83 to 1.64)	
≥30	326/1501	1.00 (referent)	86/501	1.24 (0.93 to 1.65)	
Age, y					.58
40–59	218/1147	1.00 (referent)	75/510	1.29 (0.93 to 1.78)	
60–69	228/1199	1.00 (referent)	101/516	1.60 (1.19 to 2.15)	
≥70	203/1163	1.00 (referent)	59/267	1.72 (1.22 to 2.44)	
Type of menopause					
Natural	521/2779	1.00 (referent)	178/942	1.55 (1.26 to 1.91)	
Bilateral oophorectomy	77/510	1.00 (referent)	48/302	1.51 (0.98 to 2.31)	.82

* Never used estrogen alone or estrogen plus progestin. CI = confidence interval; OR = odds ratio.

† Two-sided *P* value for interaction.

‡ Adjusted for age, study, year, geographic region, education, parity, age at first birth, age at menopause, type of menopause, age at menarche, body mass index, oral contraceptive use, family history of breast cancer, alcohol use, and smoking.

In several large follow-up studies, associations of female hormone use with increased risk of breast cancer were strongest among lean women and weakest among obese women (1,9,16–18). In the present study, the increase in the odds ratio for ER+ cancer associated with combination use was also largest among the leaner women and smallest among obese women. In the WHI randomized trial (39), the hazard ratio for combination use was 1.29 (95% CI = 0.94 to 1.79) in lean women, 1.34 (95% CI = 1.04 to 1.75) in overweight women, and 1.14 (95% CI = 0.90 to 1.44) in obese women. While not entirely consistent with the observational data, the WHI results are consistent with a smaller effect in obese women. If an effect is indeed smaller in obese women, it may reflect that the relative contribution of female hormone supplements to endogenous estrogen levels from body fat among postmenopausal obese women may be small in comparison with the relative contribution among thinner women, making it difficult to detect an increased risk because of hormone use among heavier women.

The incidence of breast cancer, especially ER+ cancer, declined in the United States in 2002 and 2003, a decrease that has been attributed to the decline in use of combination therapy that followed publicity about the WHI results (35,40,41). The rapid decline suggests that combination use promotes already-existing cancers. However, the association with longer-duration use is compatible with a carcinogenic initiating effect (39).

Results on the association of use of estrogen alone with breast cancer risk differ among the various studies. Among women assigned to estrogen alone in the WHI randomized trial, incidence of breast cancer was 23% lower than in the placebo group (14); the statistically significant decreased incidence among users persisted several years post trial (42) but was no longer present when follow-up after the end of the trial had continued for more than eight years (38). In the present study, use of estrogen alone, even for durations up to 20 years among recent users, was not associated with risk of breast cancer. In the Nurses' Health Study, a 50% increase in risk of ER+ cancer associated with current estrogen use became apparent after 15 years of use (15), and an increase of more than 20% in overall breast cancer risk was found for more than 15 years of use in a case-control study in Los Angeles (5). In the collaborative analysis published in 1997 (1) and the Million Women's Study (7), current long-term use of estrogen alone was also associated with increases in risk of breast cancer.

The WHI and observational studies of hormone use and breast cancer have answered somewhat different questions. The WHI assessed a combination regimen and an estrogen regimen that were commonly used in the United States, and the participants randomly assigned to these treatments or placebo were in their 50s, 60s, and 70s. The observational studies assessed whatever preparations study participants had chosen to use, and most women had begun use at the time of menopause. Well-conducted randomized trials and observational studies have different strengths and limitations (43). Case-control studies are susceptible to selection and reporting bias related to female hormone use, and follow-up studies are susceptible to selection bias related to female hormone use. Random assignment eliminates these biases, and standardized and thorough follow-up, as in WHI, minimizes biases related to case ascertainment. The WHI had sufficient statistical power to assess whether incidence of several conditions differed between treated women and the placebo group but was not well-powered to assess incidence within smaller subgroups. The large observational studies have had sufficient statistical power for assessment of hormone effects within subgroups, and they have been able to assess much longer durations of use than the WHI. Despite differences in design and populations, the WHI and observational studies are in agreement that certain regimens of combination use increase the risk of breast cancer and that the risk remains elevated for some time after use ceases. Results on estrogen alone, which likely has a smaller effect if any than combination use (1–9), have been variable. After the end of the WHI estrogen alone randomized trial, a decreased risk of breast cancer in users noted at the end of the intervention phase (14) had disappeared after longer follow-up (38,42). The observational study results have varied from no association to positive associations (1–9), but a large control study (5) and a large follow-up study (15) suggest that risk increases only after 15 to 20 years of use. Additional data on estrogen use for very long durations and other unsettled questions, such as whether the timing of use in relation to menopause matters, will come from observational studies. Judgements about the totality of the evidence

Table 4. Female hormone use in relation to breast cancer subtypes, postmenopausal women age ≥40 y, stratified by time between menopause and initiation of female hormone use

Time between menopause and initiation of female hormone use	Control patients	ER+		ER-	
		Case patients	OR (95% CI)*	Case patients	OR (95% CI)*
Never used†	3509	649	1.00 (referent)	300	1.00 (referent)
Estrogen alone					
<5-y interval					
Ever use	983	164	1.14 (0.90 to 1.45)	76	1.06 (0.75 to 1.49)
Duration of use, y					
<5	611	97	1.16 (0.86 to 1.48)	36	0.85 (0.56 to 1.29)
≥5	358	66	1.18 (0.84 to 1.68)	38	1.45 (0.91 to 2.32)
Time since last use, y					
<5	524	73	1.01 (0.72 to 1.41)	46	1.02 (0.66 to 1.58)
≥5	457	90	1.23 (0.93 to 1.64)	29	1.05 (0.67 to 1.65)
≥5-y interval					
Ever use	711	83	1.17 (0.87 to 1.56)	40	1.21 (0.80 to 1.82)
Duration of use, y					
<5	468	56	1.12 (0.81 to 1.55)	32	1.34 (0.87 to 2.05)
≥5	211	25	1.38 (0.84 to 2.26)	6	0.70 (0.29 to 1.69)
Time since last use, y					
<5	445	52	1.32 (0.92 to 1.91)	23	1.05 (0.63 to 1.76)
≥5	255	30	1.01 (0.66 to 1.53)	17	1.56 (0.90 to 2.71)
Estrogen plus progestin					
<5-y interval					
Ever use	568	988	1.43 (1.11 to 1.85)	28	0.69 (0.45 to 1.05)
Duration of use, y					
<5	406	68	1.37 (1.02 to 1.84)	19	0.62 (0.38 to 1.03)
≥5	142	24	1.39 (0.87 to 2.23)	7	0.79 (0.36 to 1.75)
Time since last use, y					
<5	313	47	1.33 (0.93 to 1.89)	17	0.65 (0.38 to 1.11)
≥5	254	51	1.54 (1.09 to 2.16)	11	0.75 (0.39 to 1.42)
≥5-y interval					
Ever use	412	78	1.78 (1.34 to 2.37)	23	1.15 (0.72 to 1.84)
Duration of use, y					
<5	116	58	1.69 (1.23 to 2.33)	19	1.21 (0.73 to 2.02)
≥5	53	13	2.18 (1.14 to 4.17)	3	1.25 (0.38 to 4.14)
Time since last use, y					
<5	203	36	1.72 (1.15 to 2.55)	13	1.15 (0.62 to 2.10)
≥5	207	42	1.86 (1.28 to 2.68)	10	1.16 (0.59 to 2.28)

* Adjusted for age, study, year, geographic region, education, parity, age at first birth, age at menopause, type of menopause, age at menarche, body mass index, oral contraceptive use, family history of breast cancer, alcohol use, and smoking. CI = confidence interval; OR = odds ratio.
† Never used estrogen alone or estrogen plus progestin.

will need to weigh the quality of the studies and their statistical power.

Our study is the largest to date of female hormone supplements and breast cancer risk in African American women and the first to informatively assess ER+ and ER- cancer separately in this group, but numbers in some subanalyses were small. While BWHS and CBCS published results on female hormones and breast cancer previously (19,21), the present analyses included larger numbers of users as well as participants from two other studies. However, our study is not without limitations. Classification of breast cancer subtype was based on results from numerous hospital pathology laboratories, which may have resulted in nondifferential misclassification of ER status. There will also have been misclassification of use of estrogen with progestin and estrogen alone because of errors in self-report. However, self-report of female hormone use, especially of recent and long-duration use, has been found to be sufficiently accurate for use in epidemiologic studies (44). We lacked appropriate data for assessment of the dose and type of estrogen or progestin used.

In conclusion, our results provide strong evidence that combination use is an important risk factor for ER+ cancer in African American women. It is well recognized that use of menopausal female hormone supplements was high among white women for many years, and the present data indicate that use has been common in postmenopausal African American women as well, although less so than among white women (9,17,21). As in white women, a reduction in combination use by African American women would be expected to reduce the number of ER+ breast cancers.

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