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Research Article

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Oral Contraceptive Use and Estrogen/Progesterone Receptor–Negative Breast Cancer among African American Women

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Abstract

Background: Oral contraceptive formulations have changed over time, making it relevant to assess the effect of more recent formulations on breast cancer risk. In addition, some studies have found stronger positive associations of oral contraceptive use with estrogen receptor–negative (ER^-) than with ER-positive (ER^+) breast cancer. We carried out the first assessment of the effect of oral contraceptive use on the incidence of breast cancer classified by receptor status among African American women, a group disproportionately affected by ER^- cancer.

Methods: We followed 53,848 Black Women's Health Study participants from 1995 to 2007 through biennial health questionnaires, in which participants reported information about incident breast cancer, oral contraceptive use, and breast cancer risk factors. Pathology information was obtained on receptor status for 789 incident cases. Incidence rate ratios (IRR) with 95% confidence intervals (95% CI) were derived from Cox regression models with control for confounding factors.

Results: Ever use of oral contraceptives was more strongly associated with ER^-PR^- breast cancer (279 cases; IRR, 1.65; 95% CI, 1.19-2.30) than with ER^+PR^+ cancer (386 cases; IRR, 1.11; 95% CI, 0.86-1.42). The risk of ER^-PR^- breast cancer increased with increasing duration of use among recent users.

Conclusions: These results indicate that the oral contraceptive formulations used in recent decades increase breast cancer risk in African American women, with a greater effect for ER^- than ER^+ cancer.

Impact: Mechanisms to explain the adverse influence of oral contraceptive use on ER^- breast cancer need to be elucidated. *Cancer Epidemiol Biomarkers Prev; 19(8); 2073–9. ©2010 AACR.*

Introduction

Numerous epidemiologic studies, many completed at least two decades ago, have assessed the influence of oral contraceptive use on the incidence of breast cancer. A combined analysis of data from most of those earlier studies, which included more than 50,000 women with breast cancer and 100,000 unaffected women, estimated a 25% increase in breast cancer risk among current users of oral contraceptives, with the increase largely dissipating by 10 years after use ended; there was a nonsignificant trend of increasing risk with increasing duration of use (1, 2). Results of more recent studies are mixed (3-10).

Some studies have found stronger associations of oral contraceptive use with estrogen receptor–negative (ER^-) breast cancer than with ER-positive (ER^+) cancer (7, 11-14), but others have found little or no difference (4, 15-19). A stronger association of oral contraceptive use with ER^- breast cancer would be important because ER^- tumors have a worse prognosis than ER^+ tumors (20).

Oral contraceptive preparations have changed over time (21-24), and it therefore remains relevant to assess the influence of more recent preparations on the risk of breast cancer. In view of the possibility that oral contraceptive use may more strongly influence the risk of ER^- tumors than ER^+ tumors and the fact that African American women are more often diagnosed with ER^- tumors than white women (25), we assessed the influence of oral contraceptive use on breast cancer risk in African American women according to receptor status. To do so, we used data collected in a follow-up study of African American women, the Black Women's Health Study (BWHS).

Materials and Methods

Study population and data

The BWHS began in 1995 when 59,027 African American women, ages 21 to 69 years, from across the United

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States completed health questionnaires. Subsequently, participants completed biennially mailed follow-up questionnaires. Data collected through completion of the 2007 questionnaire cycle were used in this report. Follow-up of the baseline cohort (i.e., the proportion of the baseline cohort who completed a questionnaire or is known to be deceased) has exceeded 80% in each follow-up cycle and was 81% in 2007. The Institutional Review Board of Boston University approved the protocol and reviewed the study annually.

At baseline in 1995, participants were asked about the duration of use of "birth control pills" at various ages. Baseline information was also collected on height and current weight, weight at age 18 years, age at menarche, parity, breast cancer in first-degree relatives, hours per week of vigorous physical activity, alcohol consumption, menopausal status, age at menopause, supplemental female hormone use, and years of education. The biennial follow-up questionnaires collected information on the incidence of breast cancer and updated information on birth control pill use, weight, vigorous physical activity, alcohol consumption, menopausal status, and supplemental female hormone use and also asked about the use of Depo-Provera and Norplant. We calculated the body mass index (BMI) as weight in kilograms divided by height in square meters.

In the present analyses based on follow-up from 1995 through 2007, we excluded 1,478 women who reported breast cancer or another cancer at baseline and 3,098 women who reported use of injected or implanted progestogen contraceptives. Among the remaining women, 1,392 women reported incident breast cancer; we have obtained pathology data to date from hospital pathology records or cancer registry data for 1,202 cases, of which 789 had information on receptor status and 413 did not. The proportion of the hospital or cancer registry records obtained on BWHS participants that contained information on ER/PR status increased from 47% in 1997 to 88% in 2007, reflecting the increasing ascertainment of ER/PR status in U.S. hospitals over time. We excluded cases for which receptor status was unknown, which left 53,848 women.

The present analyses are based on the 789 incident breast cancer cases with known receptor status. The proportions with ER^+PR^+, ER^+PR^-, PR^+ER^-, and ER^-PR^- tumors were similar to the proportions for African American women observed elsewhere (26-28). The characteristics of the 789 cases with known receptor status were similar to those of the excluded cases for which receptor status was unavailable ($n = 603$). Baseline values of risk factors for breast cancer were 35.2% and 35.2% for ≥50 years of age in included and excluded cases, respectively; 47.8% and 45.9% for 16 or more years of education; 30.5% and 31.1% for menarche before age 12 years; 24.5% and 22.2% for nulliparity; 50.3% and 53.2% for BMI ≥20 kg/m^2 at age 18 years; 31.3% and 33.2% for current BMI ≥30 kg/m^2; 13.6% and 12.3% for family history of breast cancer; 59.4% and 56.6% for premenopausal; 12.9% and 11.0% for oral contraceptive use within the previous 5 years; 26.3% and 25.9% for ever use of female hormone supplements; 37.0% and 38.9% for nonparticipation in vigorous exercise; and 25.6% and 27.8% for current alcohol consumption.

Data analysis

Each participant contributed person-time from March 1995 until the diagnosis of breast cancer, death, loss to follow-up, or the end of follow-up, whichever came first. We used Cox regression models (29), stratified by age in 1-year intervals and questionnaire cycle, to estimate multivariable incidence rate ratios (IRR) for breast cancer and 95% confidence intervals (95% CI) for categories of oral contraceptive use relative to never use, with control for age at menarche (<12, 12-13, ≥14 years), parity (0, 1, 2, ≥3 births), age at first birth (<20, 20-24, ≥25 years), BMI at age 18 years (<20, 20-24, ≥25 kg/m^2), family history of breast cancer, education (≤12, 13-15, ≥16 years), vigorous exercise (none, <5, ≥5 hours/wk), current alcohol consumption (<1, 1-6, ≥7 drinks/wk), age at menopause (premenopausal, <45, 45-49, ≥50 years), and menopausal female hormone use (never, <5 years of use, ≥5 years of use). BMI at age 18 years was included in the regression model because it is a risk factor for both premenopausal and postmenopausal breast cancers in our data; current BMI was not controlled because it is a weaker risk factor for breast cancer in the BWHS than BMI at age 18 years and controlling for it had no effect on the IRR estimates (30). Women who reported a hysterectomy but retained one or both ovaries were classified as premenopausal if their current age was less than the 10th percentile of age at natural menopause in the BWHS (<43 years), as postmenopausal if their age was greater than the 90th percentile of age at natural menopause in the cohort (≥57 years), and as having unknown age at menopause if their age was 43 to 56 years. Control for other factors such as breast-feeding had little effect on the IRRs. The Anderson-Gill data structure was used to update all time-varying covariates and exact methods were used to handle tied events (31).

To assess whether associations with oral contraceptive use were modified by other risk factors, we included a cross-product term between the exposure and potential effect modifier in the multivariable model. Two-sided P values for tests of interaction were obtained from a likelihood ratio test with the degrees of freedom equal to the difference in the number of parameters between the null and alternative models. To test for trend across categories of duration of oral contraceptive use, we entered the categories into an ordinal term in the regression. Tests for trend according to recency of oral contraceptive use included users only. Departures from the proportional hazards assumption (i.e., a constant IRR across age and time) were tested by the likelihood ratio test comparing models with and without interaction terms for age and calendar time with the main exposure variables.

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Results

Women who used oral contraceptives were younger, had lower BMI, and were more likely to be parous, have a later age at first birth, have higher levels of education, and drink alcohol than women who never used oral contraceptives (Table 1).

As shown in Table 2, the multivariable IRR for ever oral contraceptive use relative to never use was elevated for ER⁻PR⁻ breast cancer (IRR, 1.65; 95% CI, 1.19-2.30) and compatible with 1.00 for ER⁺PR⁺ and ER⁺PR⁻ cancers. The multivariable estimates were closely similar to estimates controlled for age and questionnaire cycle only (data not shown). There were 15 cases of ER⁻PR⁺ cancer: the IRR for ever oral contraceptive use, based on 4 never users and 11 users among the cases, was 0.72 (95% CI, 0.22-2.34).

Table 1. Baseline characteristics (age standardized) according to oral contraceptive use in the BWHS

	Oral contraceptive use			
	Never	Ever	<5 y ago	≥10-y duration
n	13,186	40,662	13,552	6,538
Age (y), mean	42.1	38.3	30.1	39.4
Age at menarche (y), mean	12.3	12.4	12.6	12.3
BMI at age 18 y (kg/m^2), mean	22.0	21.3	21.2	20.9
BMI (kg/m^2), mean	28.8	27.8	27.3	27.2
Education (y), %				
≤12	24.0	17.5	20.8	13.4
13-15	34.5	35.9	32.1	33.4
≥16	41.3	46.5	46.9	53.1
Family history of breast cancer, %	6.8	6.5	7.6	6.5
Parity, %				
Nulliparous	42.1	33.4	38.5	41.5
1	17.2	22.5	25.3	25.3
2	19.0	23.8	14.3	21.1
≥3	21.4	20.1	21.8	12.1
Age at first birth (y), parous only, %				
<20	37.6	33.5	25.3	32.3
20-24	37.6	35.6	35.1	31.5
≥25	23.8	29.9	34.6	35.0
Premenopausal, %	74.6	75.8	80.8	77.2
Ever FH use, %	14.8	16.7	9.7	16.9
Vigorous activity (h/wk), %				
None	34.1	31.5	29.3	31.1
<5	48.0	51.5	54.2	52.3
≥5	13.0	13.2	12.0	13.6
Alcohol (drinks/wk), %				
<1	78.9	73.3	73.9	70.2
1-6	14.9	20.2	19.5	22.9
≥7	5.1	5.9	6.0	6.2

Abbreviation: FH, female hormones.

The association with ever oral contraceptive use differed significantly between ER⁺PR⁺ and ER⁻PR⁻ cancers: In a case-only Cox regression analysis that compared ER⁻PR⁻ cancer to ER⁺PR⁺ cancer, the IRR for ever oral contraceptive use was 1.57 (95% CI, 1.27-1.92). A comparison of ER⁻ cancer with ER⁺ cancer yielded an IRR of 1.53 (95% CI, 1.25-1.88).

With regard to the relation of years since last oral contraceptive use to ER⁻PR⁻ cancer (Table 2), the IRR was highest for recent use [use that extended into the previous 5 years; IRR, 1.97 (95% CI, 1.21-3.20); *P*-trend = 0.45]. With regard to duration of use, the IRR for ER⁻PR⁻ cancer was largest for the longest duration category considered, 15+ years (IRR, 2.25; 95% CI, 1.23-4.11; *P*-trend = 0.013). For ER⁺PR⁺ cancer, the IRR for use of oral contraceptives was increased, 1.45 (95% CI, 1.02-2.07), for the 10-14 year duration category, but the IRR for 15+ years of use did not increase further (IRR, 1.24; 95% CI, 0.74-2.09). There were no other notable associations of categories of interval since last use or duration of use with ER⁺PR⁺ or ER⁺PR⁻ cancer.

The duration of use and the interval since last use are considered jointly in Table 3. The IRR for ER⁻PR⁻ cancer among recent users increased with increasing duration of use to 2.52 (95% CI, 1.43-4.45) for use that lasted at least 10 years (*P*-trend = 0.001). There were also significant associations of ER⁻PR⁻ cancer with use that ended at least 10 years previously and was of duration <5 years (IRR, 1.72, 95% CI1.21-2.44) or duration 10+ years (IRR, 1.69; 95% CI, 1.01-2.83). For ER⁺PR⁺ cancer, there was a significant association with recent long-duration use (IRR, 1.66; 95% CI, 1.01-2.74; *P*-trend = 0.10) and with <5 years of use that ended 5 to 9 years previously (IRR, 2.13; 95% CI, 1.13-4.03). For ER⁺PR⁻ cancer, all estimates were compatible with 1.00.

We explored the associations of ever oral contraceptive use with ER⁻PR⁻ and ER⁺PR⁺ cancers according to categories of breast cancer risk factors (Table 4). There were no significant interactions.

The 789 cases with known ER/PR status considered in the above analyses are a subset of the 1,392 BWHS breast cancer cases ascertained during follow-up. For purposes of comparison with studies that considered all cases regardless of ER/PR status, we calculated the multivariable IRR for ever oral contraceptive use relative to never use in the overall sample: 1.09 (95% CI, 0.96-1.24).

Discussion

In this follow-up study of African American women, oral contraceptive use was more strongly associated with an increased risk of ER⁻PR⁻ breast cancer than of ER⁺PR⁺ breast cancer. The incidence of ER⁻PR⁻ breast cancer increased significantly among recent users as the duration

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Table 2. Years since last use and duration of use of oral contraceptives in relation to breast cancer incidence by receptor status

Use	Person-years	ER^+/PR^+		ER^+/PR^-		ER^-/PR^-	
		No. cases	IRR (95% CI)	No. cases	IRR (95% CI)	No. cases	IRR (95% CI)
Never used	128,768	102	1.00 (reference)*	29	1.00 (reference)	46	1.00 (reference)
Ever used	445,824	284	1.11 (0.86-1.42)	80	0.97 (0.61-1.54)	233	1.65 (1.19-2.30)
Years since last use							
<5	139,891	44	1.29 (0.85-1.96)	12	1.42 (0.63-3.21)	43	1.97 (1.21-3.20)
5-9	49,283	24	1.53 (0.94-2.50)	4	0.99 (0.32-3.04)	12	1.23 (0.63-2.41)
10+	256,649	216	1.07 (0.83-1.37)	64	0.94 (0.59-1.50)	178	1.64 (1.17-2.29)
Duration (y)							
<5	250,648	150	1.03 (0.79-1.35)	43	0.91 (0.55-1.49)	139	1.67 (1.18-2.36)
5-9	110,142	64	1.09 (0.78-1.52)	25	1.31 (0.74-2.33)	44	1.37 (0.89-2.11)
10-14	63,348	52	1.45 (1.02-2.07)	9	0.82 (0.37-1.78)	35	1.83 (1.11-2.90)
15+	21,686	18	1.24 (0.74-2.09)	3	0.75 (0.22-2.54)	15	2.25 (1.23-4.11)

*Never use of oral contraceptives is the reference category; IRRs are adjusted for age, questionnaire cycle, age at menarche, BMI at age 18 y, family history of breast cancer, years of education, parity, age at first birth, age at menopause, menopausal hormone use, vigorous activity, and alcohol intake.

of use increased, with the largest increase (2.5-fold) among recent users whose duration of use was 10 or more years. However, there were some inconsistencies in that the incidence of ER^-PR^- cancer was also significantly increased for some shorter-duration and nonrecent categories of use. For ER^+PR^+ cancer, results were null for most categories of interval since last use and duration but there was a significant increase (1.66-fold) for recent users with 10 or more years of use. Results for ER^+PR^- tumors were null, but the numbers were small.

The present results strengthen the evidence that there is a stronger association of oral contraceptive use with ER^- cancer than with ER^+ cancer (32). In several case-control studies, odds ratios for oral contraceptive use have been greater for ER^- cancer than for ER^+ cancer (7, 11-14). Specifically, the odds ratio for 20 or more years of oral contraceptive use was 2.23 for ER^- cancer and 1.39 for ER^+ cancer (7); for recent use, 3.1 for ER^- cancer and 1.6 for ER^+ cancer (11); for ever use, 1.33 for ER^- cancer and 0.88 for ER^+ cancer (12); for ever use, 2.0 for ER^-

Table 3. Joint relation of years since last use and duration of use to breast cancer incidence by receptor status

Use		Person-years	ER^+/PR^+		ER^+/PR^-		ER^-/PR^-	
Years since last use	Duration (y)		No. cases	IRR (95% CI)	No. cases	IRR (95% CI)	No. cases	IRR (95% CI)
Never used		128,768	102	1.00 (reference)*	29	1.00 (reference)	46	1.00 (reference)
<5	<5	54,784	10	0.89 (0.45-1.77)	5	1.77 (0.63-4.99)	12	1.54 (0.78-3.05)
	5-9	42,284	10	1.19 (0.59-2.40)	4	1.92 (0.60-6.19)	9	1.58 (0.73-3.42)
	10+	42,824	24	1.66 (1.01-2.74)	3	0.84 (0.23-13.03)	22	2.52 (1.43-4.45)
5-9	<5	24,427	12	2.13 (1.13-4.03)	1	0.72 (0.09-5.50)	4	1.03 (0.36-2.94)
	5-9	12,574	4	1.03 (0.37-2.89)	0	-	3	1.15 (0.35-3.80)
	10+	12,283	8	1.31 (0.62-2.77)	3	1.85 (0.53-6.47)	32	1.50 (0.58-3.86)
10+	<5	171,437	128	1.00 (0.76-1.32)	37	0.86 (0.52-1.44)	123	1.72 (1.21-2.44)
	5-9	55,285	50	1.10 (0.77-1.57)	21	1.35 (0.75-2.46)	32	1.35 (0.85-2.15)
	10+	29,927	38	1.33 (0.90-1.95)	6	0.64 (0.26-1.58)	23	1.69 (1.01-2.83)

*Never use of oral contraceptives is the reference category; IRRs are adjusted for age, age at menarche, BMI at age 18 y, family history of breast cancer, education, parity, age at first birth, menopausal status, age at menopause, menopausal hormone use, vigorous activity, and alcohol intake.

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Table 4. Ever oral contraceptive use in relation to ER^+PR^+ and ER^-PR^- cancers according to categories of breast cancer risk factors

Risk factor	ER^+PR^+			ER^-PR^-		
	OC use ever/never (no. cases)	IRR* (95% CI)	$P^\dagger$	OC use ever/never (no. cases)	IRR* (95% CI)	$P^\dagger$
Age (y)						
<50	144/23	1.28 (0.82-2.00)	0.07	119/14	1.80 (1.03-3.15)	0.87
50+	140/70	1.04 (0.77-1.41)		114/32	1.59 (1.05-2.41)	
Premenopausal	130/19	1.36 (0.84-2.21)	0.14	106/15	1.49 (0.86-2.57)	0.75
Postmenopausal	112/27	0.95 (0.69-1.31)		90/27	1.66 (1.05-2.62)	
BMI at age 18 y (kg/m^2)						
<20	134/43	0.89 (0.61-1.29)	0.55	116/25	1.43 (0.91-2.25)	0.42
20+	146/57	1.10 (0.79-1.54)		116/21	1.85 (1.14-3.01)	
Current BMI (kg/m^2)						
<25	69/19	0.94 (0.55-1.61)	0.35	62/11	1.53 (0.78-2.98)	0.97
25+	214/83	1.13 (0.85-1.49)		171/35	1.67 (1.14-2.44)	
Age at menarche (y)						
<12	77/28	1.05 (0.65-1.69)	0.90	77/18	1.41 (0.82-2.44)	0.41
12+	206/74	1.10 (0.82-1.47)		156/28	1.79 (1.18-2.73)	
Age at first birth (y)						
<20	62/29	0.99 (0.61-1.61)	0.44	57/14	1.56 (0.84-2.90)	0.25
20+	150/47	1.02 (0.71-1.46)		140/18	2.18 (1.31-3.62)	
Parity						
0	72/24	1.54 (0.91-2.61)	0.33	34/14	1.00 (0.50-1.98)	0.06
1+	212/78	0.99 (0.75-1.32)		198/32	1.92 (1.30-2.83)	
Female hormone use						
Never	184/51	1.19 (0.85-1.66)	0.29	165/24	2.05 (1.32-3.19)	0.12
Ever	98/49	1.04 (0.69-1.45)		68/21	1.26 (0.74-2.14	
Family history						
No	229/85	1.39 (0.77-2.54)	0.24	194/39	2.15 (0.93-4.98)	0.55
Yes	55/17	1.04 (0.79-1.37)		39/7	1.59 (1.10-2.28)	
Cigarette smoking						
Never	170/54	1.23 (0.88-1.72)	0.59	141/26	1.53 (0.99-2.35)	0.75
Ever	114/47	1.01 (0.69-1.47)		92/20	1.83 (1.09-3.08)	
Alcohol (drinks/wk)						
<1	207/78	1.08 (0.81-1.43)	0.82	169/38	1.42 (0.98-2.05)	0.49
1+	77/24	1.16 (0.69-1.94)		64/8	2.81 (1.29-6.09)	
Vigorous exercise						
No	159/59	1.25 (0.90-1.74)	0.24	131/30	1.59 (1.05-2.42)	0.72
Yes	122/41	0.89 (0.61-1.31)		101/15	1.82 (1.04-3.21)	
Education (y)						
<16	143/49	1.39 (0.97-1.99)	0.15	139/29	1.77 (1.16-2.70)	0.44
16+	141/53	0.87 (0.62-1.23)		102/17	1.55 (1.07-2.31)	

*Never use of oral contraceptives is the reference category; IRRs adjusted for age, age at menarche, BMI at age 18 y, family history of breast cancer, education, parity, age at first birth, menopausal status, age at menopause, menopausal hormone use, vigorous activity, and alcohol intake.

†*P* value for interaction.

cancer and 1.11 for ER^+ cancer (13); and for 10 or more years of use, 1.27 for ER^-PR^- cancer and 0.76 for ER^+PR^+ cancer (14). The Carolina Breast Cancer Study found odds ratios for ever oral contraceptive use to be greater for basal-like breast cancer (which is a major component of ER^-PR^- cancer) than for luminal A breast cancer (which is a major component of ER^+PR^+ breast cancer; ref. 33). Other studies of ER^+ and ER^- breast cancer have not shown differing relations of oral contraceptive use by receptor status (15-19). Our study of oral

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contraceptive use and receptor subtypes is the only study to report separately on black women, and it is also the first follow-up study of the association.

The present results suggest that the oral contraceptive preparations used in the last several decades increase the risk of breast cancer in African American women. Recent formulations have lower doses of estrogen and progestin and different types of progestin than earlier oral contraceptives (21-24). In studies of oral contraceptive use and breast cancer diagnosed in the last 15 years, there were positive associations with recent or long-term use in a Scandinavian follow-up study (3), in the Carolina Breast Cancer Study among African American women but not among white women (34), in a hospital-based case-control study in the northeastern United States among both African American and white women (4), in the Long Island Breast Cancer Study among premenopausal women (5), in a hospital-based case-control study of nonwhite women in South Africa among women under the age of 35 years (6), and in a case-control study in the southwestern United States (7). There were no associations with breast cancer overall in a study of white women in Los Angeles (14) or in the largest case-control study of all conducted in several regions of the United States (9).

Most studies of oral contraceptive use and breast cancer have focused on white women. Among five studies that reported on African American and white women separately (4, 9, 10, 35, 36), all but one (9) reported point estimates of relative risk for breast cancer overall that were greater for African American women. The higher estimates for African American women may reflect the greater proportion of ER^- cancer in that ethnic group.

Because the prevalence of oral contraceptive use is similar or perhaps even lower among African American women than white women (9, 10, 34, 37), oral contraceptive use by itself is unlikely to explain the higher proportion of ER^- breast cancers among African American women. Some hormone-related factors, such as nulliparity, delayed childbearing, and early age at menarche, have been associated more strongly with increased risk of ER^+PR^+ breast cancer than of ER^-PR^- breast cancer (8, 32). Higher current BMI (32, 38) and use of menopausal female hormone supplements (39, 40) have also been associated with increased risk of postmenopausal ER^+ cancer. If these effects were mediated through hormonal mechanisms that involve the amounts of estrogen and progesterone and their specific receptors (40), one might also expect oral contraceptive use to be more strongly associated with ER^+ cancer than with ER^- cancer. However, the estrogens and progestins in oral contraceptives differ in type and concentration from those in postmenopausal female hormone supplements. It is also possible that nonhormonal mechanisms might be involved (39).

A strength of the present study is its focus on African American women, a group disproportionately affected by ER^- breast cancer. The prospective data collection will have eliminated biased recall of oral contraceptive use. Important risk factors for breast cancer were controlled in the analyses. Follow-up rates were sufficiently high to make bias from selective losses an unlikely explanation of the findings. Bias could have resulted from the exclusion of breast cancer cases from the analysis because of lack of information on receptor status. However, the prevalences of breast cancer risk factors were similar in the included and excluded cases.

In summary, the present results strengthen the evidence that the oral contraceptive preparations used in recent decades increase the risk of breast cancer and are the first evidence that the increase is larger for ER^-PR^- than for ER^+PR^+ cancer among African American women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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